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CONTEMPORARY TRENDS IN SCHOOL RECONSTRUCTION

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Introduction. At the beginning of the 21st century, the reconstruction of existing school buildings became one of the priority directions in the development of educational infrastructure. In many countries, a significant part of the school building stock was formed in the second half of the twentieth century and no longer meets contemporary requirements for the organization of the educational process, comfort, energy efficiency, and safety. At the same time, pedagogical approaches are changing, focusing on the development of communication, creativity, teamwork, and individual educational trajectories [1–3]. Additional factors in the transformation of the school environment include the dissemination of the principles of inclusiveness, environmental sustainability, and sustainable development, as well as the need to improve the sanitary and hygienic characteristics of buildings, which became particularly relevant during the COVID-19 pandemic.

The aim of the study is to identify contemporary trends in the reconstruction of school complexes. The analysis of international architectural practice made it possible to identify the following trends in school reconstruction (Fig. 1).

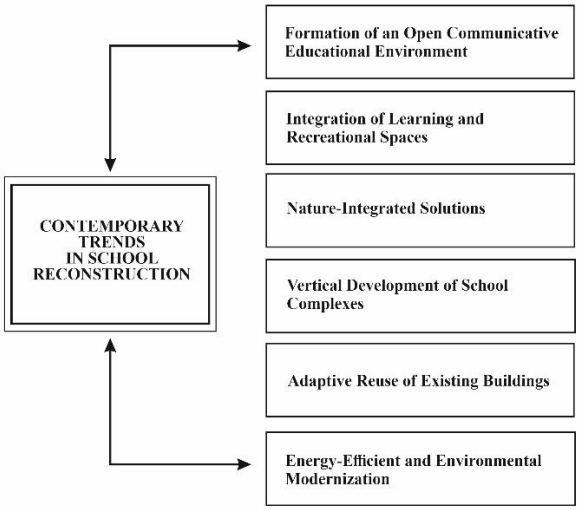

Figure 1. Contemporary trends in school reconstruction

Formation of an Open Communicative Educational Environment. One of the most characteristic trends in contemporary school reconstruction is the transition from the traditional system of isolated classrooms and corridors to an open educational environment that encourages communication, collaboration, and informal learning. In

reconstructed schools, the role of atriums, multifunctional recreational areas, collaborative workspaces, and visually open circulation zones is increasing.

A representative example is the reconstruction of Vienna West High School in Vienna (2018), where a former military barracks was transformed into a contemporary educational complex with an internal courtyard around which open learning and communication spaces were organized [4]. The central courtyard became a kind of social core of the school, while the transparency of the internal connections embodies the concept of the "open school". Similar approaches were implemented during the reconstruction of DSSI Elementary School in Seoul [5], where spatial transformations were aimed at creating shared learning areas that can be reconfigured according to the needs of the educational process.

Integration of Learning and Recreational Spaces. The contemporary school is increasingly viewed as a holistic educational environment in which learning takes place not only in classrooms but also in recreational areas, internal courtyards, galleries, and open public spaces. As a result of reconstruction, the traditional boundaries between educational and recreational functions are gradually becoming blurred.

In the Vienna West High School project, the terraced internal courtyard is used as a space for learning, recreation, and social interaction among students [4]. A similar approach can be observed in the reconstruction of Longjiang Foreign Language School in China, where sports and recreational functions are integrated into a multi-level campus structure [6].

Nature-Integrated Solutions involve strengthening the interaction between the educational environment and nature. Learning gardens, outdoor classrooms, green roofs, internal courtyards, and terraces are actively employed, with the natural environment being regarded as an integral component of the educational process. In many contemporary projects, learning activities are partially transferred beyond traditional indoor spaces, while natural elements are integrated into the architectural structure of the school. This approach contributes to improving students' psychological well-being, fostering environmental awareness, and creating a healthier educational environment.

A particularly illustrative example is the reconstruction of Fuwen Primary School in China (2018), where the reconstructed school is conceived as an environment that is as closely connected to nature as possible [7]. The architectural concept is aimed at creating a space that is perceived by children not as an institutional building but as a comfortable living environment that is open to interaction with nature.

Vertical Development of School Complexes. The increasing density of urban development and the limited availability of land resources encourage the active use of vertical space in school reconstruction projects. This is manifested through the vertical extension of existing buildings, the use of roofs as functional spaces, the creation of multi-level sports facilities, and the development of underground levels.

A striking example is the reconstruction of Longjiang Foreign Language School in China (2022), where, due to the shortage of available land, a multi-level campus was created with a sports field on the roof and additional functional spaces underneath it [6]. As a result, the number of classrooms increased from 22 to 42 without expanding

the boundaries of the site. A similar approach was applied in the reconstruction of Svetozar Marković Primary School in Belgrade, where an increase in capacity was achieved through the addition of a new floor and the conversion of the attic space [8].

Adaptive Reuse of Existing Buildings. Adaptive reuse involves the adaptation of existing buildings to meet new educational needs. This approach makes it possible to preserve material resources, reduce the environmental impact of construction, and simultaneously create a qualitatively new educational environment.

An example of this approach is the reconstruction of Vienna West High School, where a former military barracks was transformed into a contemporary school through partial demolition, the addition of new building volumes, and the creation of an open internal courtyard [4]. Another important direction is the modernization of existing school buildings while preserving their architectural identity to the greatest extent possible and, at the same time, adapting them to contemporary functional requirements.

Energy-Efficient and Environmental Modernization. Another characteristic trend is the comprehensive modernization of engineering systems and the improvement of the energy performance of school buildings. Contemporary reconstruction projects widely employ façade thermal insulation, heat recovery systems, automated ventilation systems, the use of renewable energy sources, and intelligent building management systems.

A representative example is the reconstruction of Emil Belluš Secondary Vocational School in Slovakia (2017–2018) [9], where a comprehensive package of thermal modernization measures was implemented, including the installation of heat recovery systems, solar thermal and photovoltaic systems, as well as automated control of ventilation and lighting.

Conclusions. The conducted analysis of contemporary school reconstruction projects made it possible to identify the main directions of transformation of the educational environment in the twenty-first century. These include the formation of open communicative spaces, the integration of educational and recreational functions, the active implementation of nature-integrated solutions, the vertical development of school complexes, the adaptive reuse of existing buildings, and comprehensive energy-efficient modernization.

These trends indicate a gradual transition from the traditional model of the school building to a multifunctional educational environment oriented toward students' needs, the flexibility of the educational process, environmental responsibility, and the efficient use of available resources. Of particular importance is the integration of architectural, pedagogical, social, and environmental approaches, which defines the main directions of school reconstruction development in the coming decades.

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ТРАНСФОРМАЦІЯ ПУБЛІЧНИХ ПРОСТОРІВ МІСТ З УРАХУВАННЯМ БЕЗПЕКОВИХ ВИМОГ ТА ІНКЛЮЗИВНОСТІ

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ВСТУП

Сучасне містобудування перебуває на етапі фундаментального переосмислення парадигми розвитку міського середовища. Довгий час ключовими орієнтирами для архітекторів та урбаністів слугували економічна доцільність, естетична виразність та комерційна привабливість локацій. Однак глобальні та локальні кризи початку XXI століття — пандемії, кліматичні зміни, а головне, збройні конфлікти та загрози техногенного та воєнного характеру — висунули на перший план інші пріоритети. Безпека та інклюзивність стали базовими критеріями життєздатності будь-якого міського простору.

Для України питання трансформації публічних просторів має екзистенційне значення. Масштабні руйнування міської інфраструктури, значне збільшення кількості людей із тривкими порушеннями здоров’я, хронічний стрес населення та перманентна загроза обстрілів вимагають негайної зміни нормативно-правової бази, методологічних підходів та практичних інструментів проектування. Публічний простір сьогодні більше не може бути просто транзитною зоною або місцем декоративного відпочинку; він має виконувати захисну, адаптивну та інтеграційну функції.

Метою цих тез є комплексне дослідження теоретико-методологічних та практичних засад трансформації публічних просторів міст в умовах криз, що дозволяє забезпечити гармонійне поєднання жорстких безпекових вимог із принципами універсального дизайну та безбар'єрності. Досягнення цієї мети передбачає перехід від концепції «декоративного урбанізму» до концепції «стійкого, безпечного та людиноцентричного містобудування»[1]

ТЕОРЕТИКО-МЕТОДОЛОГІЧНІ ЗАСАДИ ПРОЕКТУВАННЯ БЕЗПЕЧНОГО ТА ІНКЛЮЗИВНОГО СЕРЕДОВИЩА

Теоретичний базис дослідження спирається на інтеграцію двох ключових урбаністичних концепцій: теорії захисного середовища через архітектурне

проектування (зокрема, концепція CPTED — Crime Prevention Through Environmental Design) та концепції Універсального дизайну (Universal Design). Традиційно ці підходи розвивалися паралельно, а іноді навіть вступали в суперечність. Наприклад, елементи фізичного захисту (масивні блоки, лабіринтові проходи) створювали серйозні перешкоди для маломобільних груп населення (МГН).

Сучасна архітектурна наука вимагає синергії цих підходів. Простір має бути спроектований таким чином, щоб захисні властивості були імплементовані в його структуру природно, без створення візуального тиску чи відчуття «фортеці», при цьому повністю задовольняючи потреби всіх категорій користувачів.

КРИТЕРІЇ ОЦІНКИ ПУБЛІЧНОГО ПРОСТОРУ НОВОГО ТИПУ

Для детального аналізу трансформаційних процесів доцільно запровадити комплексну систему критеріїв, що поєднують інклюзивний та безпековий виміри. Кожен елемент простору оцінюється через призму доступності, захищеності та психологічного комфорту[2,4].

Категорія оцінки	Параметри безпеки (Security)	Параметри інклюзивності (Inclusion)	Інтеграційні рішення (Синтез)
Просторова доступність	Наявність чітких евакуаційних шляхів, відсутність тупикових зон.	Відсутність порогів, ухил пандусів не більше 8%, тактильна навігація.	Широкі евакуаційні безбар'єрні алеї, підсвічені в темний час доби на рівні покриття.
Фізичний захист	Стримування транспортних засобів (антитаранні пристрої).	Вільний простір для маневрування крісел колісних та дитячих візків.	Використання масивних вуличних меблів, бетонних кашпо з озелененням як захисних бар'єрів.
Візуальний контроль	Освітленість 100% площі, відсутність«сліпих зон» для відеонагляду.	Контрастне маркування елементів, читабельність шрифтів на рівні очей.	Інтелектуальні системи освітлення, інтегровані в елементи інклюзивної навігації.

Цивільний захист	Швидкий доступ до сертифікованих укриттів.	Доступність укриттів для осіб з інвалідністю (ліфти, підйомники, герметичні пандуси).	Створення підземних паркінгів подвійного призначення під площами з інклюзивними входами.

Процес трансформації описується узагальненою функцією просторової стійкості ***Sp***, яка максимізує рівень безпеки та доступності при мінімізації витрат та просторової ізоляції:

$$Sp = \int (B(x) \times I(x)) / R(x)\, dx \rightarrow max$$

де ***B(x)*** — коефіцієнт безпекової захищеності зони ***x***, ***I(x)*** — індекс інклюзивної доступності, а ***R(x)*** — рівень просторової рестрикції (обмежень, які накладаються захисними елементами на свободу пересування).

БЕЗПЕКОВІ ВИМОГИ ЯК ДРАЙВЕР ПРОСТОРОВИХ ЗМІН

В умовах постійних загроз безпекові вимоги перестають бути додатком до проекту, вони стають його структурною основою. Першочерговим завданням архітектора є зонування простору за рівнями вразливості. Необхідно диференціювати транзитні потоки, зони тривалого перебування людей та сервісні під'їзди[4,5].

Важливим аспектом є інтеграція елементів інженерно-технічного захисту в ландшафтну архітектуру. Замість неестетичних металевих парканів чи тимчасових залізобетонних блоків, що створюють депресивний візуальний ефект та сигналізують про постійну небезпеку, архітектура містобудування має використовувати методи «невидимого захисту». Геопластика (створення штучного рельєфу, терас, підпірних стінок оптимальної висоти) дозволяє заблокувати несанкціонований в'їзд транспорту, виступає як захисний екран від вибухової хвилі та уламків, і водночас слугує амфітеатром чи зоною відпочинку для містян.

Крім того, критично важливим є проектування підземного та напівпідземного простору міських площ та парків. Будь-яка реконструкція чи створення нового

публічного простору повинна супроводжуватися аналізом близькості об'єктів укриття. Мова йде про споруди подвійного призначення: підземні комерційні галереї, паркінги чи амфітеатри, які в разі оголошення тривоги протягом 3–5 хвилин можуть прийняти розрахункову кількість відвідувачів простору, забезпечуючи при цьому безперешкодний безбар'єрний спуск для людей на кріслах колісних та батьків із візками.

ІНКЛЮЗИВНІСТЬ ТА УНІВЕРСАЛЬНИЙ ДИЗАЙН В АРХІТЕКТУРНОМУ СЕРЕДОВИЩІ

Інклюзивність у контексті трансформації публічних просторів — це не лише наявність пандуса біля входу до будівлі. Це створення безперервного ланцюжка

доступності, що охоплює транспортні вузли, пішохідні комунікації, зони відпочинку та санітарні вузли. Принципи Універсального дизайну вимагають, щоб простір був однаково зручним, зрозумілим та безпечним для дитини, літньої людини, ветерана на протезах, особи з порушеннями зору чи слуху[3,4].

Важливою складовою інклюзивності є тактильна та візуальна навігація. Тактильна плитка (направляюча та застережна) має бути інтегрована в мощення таким чином, щоб чітко вказувати безпечні напрямки руху та попереджати про наближення до небезпечних зон (край тротуару, сходи, велодоріжка). Колористика простору повинна уникати хаотичності, натомість використовувати контрастні поєднання для виділення функціональних зон та потенційних перешкод.

Особливу увагу слід приділити місцям відпочинку. Вуличні меблі (лави, столи) мають розроблятися з урахуванням антропометричних характеристик різних груп населення. Лави повинні мати зручні спинки та підлокітники (що полегшує підйом літнім людям), а поруч із ними обов'язково передбачаються вільні кишені для крісел колісних, щоб людина з інвалідністю не залишалася на проході, а була повноцінно інтегрована в групу тих, хто відпочиває[4,5].

СВІТОВИЙ ДОСВІД ТА УКРАЇНСЬКІ РЕАЛІЇ: ПОРІВНЯЛЬНИЙ АНАЛІЗ

Аналіз світової практики показує, що країни, які стикалися з хронічними безпековими викликами (наприклад, Ізраїль, Велика Британія, країни Близького Сходу), давно перейшли до стратегії гнучкого містобудування (Resilient Urbanism). В Ізраїлі стандарти захищеності публічних просторів інтегровані в будівельні коди вже кілька десятиліть. Кожен сквер чи бульвар має чітко визначені часові ізохрони доступності до захисних споруд.

У Великій Британії після терактів початку 2000-х років було розроблено концепцію «безпечних вулиць», де акцент зроблено на стримуванні автомобільних таранних атак за допомогою інтегрованих малих архітектурних форм (МАФів) — посилених ліхтарних стовпів, міцних гранітних лав, масивних вазонів. При цьому всі ці елементи не перешкоджають руху пішоходів та відповідають вимогам доступності[7,8].

Україна сьогодні формує унікальний досвід, адже масштаб викликів перевищує більшість відомих світових аналогів. Вітчизняні архітектори змушені працювати в умовах обмежених фінансових ресурсів та жорсткого дефіциту часу. Це зумовлює розвиток методів тактильного урбанізму — швидких, недорогих, але ефективних трансформацій (наприклад, використання модульних бетонних конструкцій, які одночасно захищають від уламків та слугують вуличними меблями й елементами вертикального озеленення).

ПРАКТИЧНІ КЕЙСИ ТА АРХІТЕКТУРНО-МІСТОБУДІВНІ РІШЕННЯ

Розглянемо практичні підходи до ревіталізації типової міської площі в українському місті з метою її адаптації до нових вимог. Традиційна площа є відкритим, замощеним простором, повністю вразливим до повітряних загроз та небезпек з боку дорожнього руху, часто з багатьма бар'єрами у вигляді бордюрів

та сходинок.

Запропоноване архітектурне рішення передбачає наступні кроки:

1. **Зміна рельєфу (Геопластика):** Створення штучних пологих пагорбів по периметру площі з ухилом, що не перевищує 4–5%. Це дозволяє створити природні безбар'єрні пандуси для прогулянок, захистити центральну зону від шуму та візуального впливу транспорту, а також утворити захисний вал.

2. **Дисперсне розташування малих архітектурних форм:** Лави та зони очікування інтегруються безпосередньо в підпірні стінки цих пагорбів. Матеріал — монолітний залізобетон із дерев'яним покриттям сидінь. Такі конструкції здатні витримувати значні механічні навантаження та виконувати роль уловлювачів осколків на рівні людського зросту.

3. **Трансформація системи водовідведення та мощення:** Використання тактильного мощення як елемента дизайну. Дренажні решітки встановлюються врівень із покриттям, ширина прорізів у них не перевищує 10 мм, що унеможливлює застрягання підборів, палиць для ходьби чи коліс[8].

4. **Інтегровані наземно-підземні комунікації:** Існуючий підземний перехід або підвал під суміжною будівлею реконструюється під інклюзивне сховище подвійного призначення, а входи до нього обладнуються панорамними ліфтами та пологими серпантинними спусками, інтегрованими в загальний ландшафт площі.

ПСИХОЛОГІЧНИЙ АСПЕКТ АРХІТЕКТУРНОГО СЕРЕДОВИЩА В КРИЗОВИЙ ПЕРІОД

Простір міст має значний вплив на психоемоційний стан населення. Тривалий розсогласований простір, наповнений елементами руйнації або агресивного військового захисту, посилює симптоми посттравматичного стресового розладу (ПТСР) та загальний рівень тривожності. Тому архітектура містобудування повинна використовувати інструменти терапевтичного дизайну[9].

Озеленення грає ключову роль у стабілізації психіки. Використання багаторічних трав, кущів та дерев із розлогими кронами створює відчуття затишку, природного захисту та повернення до мирного життя. Звукові ландшафти (штучні безбар'єрні фонтани, сухі фонтани, що не мають відкритої чаші води і є повністю безпечними для дітей та МГН) допомагають маскувати міський шум та створюють заспокійливий звуковий фон.

Окрім того, важливим є уникнення монотонності в забудові та мощенні. Використання природних матеріалів (дерево, камінь) із приємною тактильною текстурою на рівні людського дотику (поручні, підлокітники, елементи фасадів) знижує рівень відчуження та агресії, які часто генерує мегаполіс.

ВИСНОВКИ

Трансформація публічних просторів міст із урахуванням безпекових вимог та інклюзивності — це не тимчасовий тренд, а довгострокова стратегія розвитку архітектури та містобудування. Безпека та безбар'єрність не повинні конкурувати між собою чи обмежувати архітектурну виразність об'єктів. Сучасний підхід до проектування доводить, що найкращі захисні рішення є

непомітними, інтегрованими в ландшафт і максимально корисними для всіх верств населення.

Для успішної реалізації цієї стратегії в Україні необхідно вжити ряд системних кроків:

• Оновити державні будівельні норми (ДБН) у сферах містобудування, благоустрою та захисних споруд, закріпивши обов'язковість синергетичного проектування безпеки та універсального дизайну.

• Впроваджувати обов'язкову партисипацію (залучення громад, ветеранів, людей з інвалідністю) на ранніх етапах проектування будь-якого публічного простору.

• Сприяти розвитку вітчизняного виробництва спеціалізованих елементів благоустрою (армованих МАФів, систем тактильної навігації, інклюзивного обладнання).

• Орієнтувати навчальні програми підготовки архітекторів та містобудівників на вивчення методів гнучкого урбанізму, CPTED та терапевтичного дизайну середовища.

Впровадження запропонованих підходів дозволить перетворити українські міста на зразки стійкості, де кожен мешканець почуватиметься захищеним, визнаним та залученим до активного соціального життя.

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BIOPHYSICAL MECHANISMS OF DRUG TRANSPORT THROUGH THE CELL MEMBRANE

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The cytoplasmic membrane operates as a highly dynamic, selective barrier consisting of a phospholipid bilayer embedded with functional proteins. Understanding how pharmacological agents cross this barrier is a fundamental challenge in molecular biophysics and drug design. Generally, cellular influx of therapeutic compounds occurs via four primary routes: passive transbilayer diffusion, carrier-mediated facilitated diffusion, primary/secondary active transport, and vesicular endocytosis. Low-molecular-weight lipophilic drugs cross the hydrophobic core of the membrane spontaneously, driven by concentration gradients in accordance with Fick's laws. Conversely, hydrophilic molecules and macromolecular structures rely heavily on specialized transmembrane proteins, such as ion channels and active transporters. The overall kinetics of these transport processes are strictly governed by the physical state of the lipid matrix, transmembrane voltage gradients, and ambient thermodynamic conditions [1-3]. To evaluate the permeation dynamics, a comparative biophysical modeling approach was applied to various model drugs with distinct molecular weights and partition coefficients (logP). The calculated kinetic parameters representing these diverse transport pathways are summarized in Table 1.

Table 1.
Biophysical parameters governing the permeation kinetics of model drug compounds

Compound Group	Molecular Mass (Da)	Partition Coefficient (logP)	Primary Transport Mechanism	Membrane Permeability (P·10−6 cm/s)
Group A (Lipophilic)	< 300	> 2.0	Passive lipid diffusion	24.5
Group B (Hydrophilic)	< 200	< 0.5	Facilitated (Channel-mediated)	12.2
Group C (Charged Ions)	< 100	Negative	Active transport / Ion pumps	3.1
Group D (Macromolecules)	> 1000	Neutral	Endocytosis / Vesicular	0.4

Continuation of Table 1.

Compound Group	Temperature Dependence	Energy (ATP) Requirement	pH Sensitivity	Voltage-Gated Dependence
Group A (Lipophilic)	Weak	None	Negligible	Independent
Group B (Hydrophilic)	Moderate	None	High	Partially dependent
Group C (Charged Ions)	High	Required	High	Fully dependent
Group D (Macromolecules)	Very High	Required	Moderate	Independent

As demonstrated by the quantitative data, molecules displaying high lipophilicity (logP > 2.0) exhibit accelerated transbilayer partition rates, reaching a permeability coefficient of P = 24.5x10^-6sm/s. This passive thermodynamic flux (J) through the lipid matrix is mathematically defined by Fick's first law of diffusion.

In conclusion, deciphering the biophysical forces that control drug transport across cellular membranes provides critical insights for modern biopharmaceutics. Factors such as molecular mass, charge density, and lipophilicity serve as the primary physical determinants of a drug's entry mechanism. Quantitative mathematical and biophysical modeling of these membrane-molecule interactions establishes a predictive framework for optimizing targeted drug delivery systems and enhancing the overall therapeutic efficacy of novel pharmaceuticals [4-6].

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STUDY OF THE MECHANISMS OF THE EFFECT OF UV-B RAYS ON THE PHOTOSYNTHETIC ELECTRON CHAIN OF PLANTS

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Sunlight forms a complex spectrum of ultraviolet (UV), visible light, and infrared wavelengths. Each wavelength has a different effect on plant growth and development [1].

Various studies have shown that UV-B radiation induces a variety of phenotypic responses in plants, including inhibition of hypocotyl growth, cotyledon expansion, phototropic curvature, and induction of UV-B-protective pigmentation. Whole-genome expression profiling over the past decade has identified specific pathways activated in response to low levels of UV-B [2].

Excessive use of halogen-containing compounds has led to a decrease in the ozone layer, and as a result, the amount of ultraviolet (UV) radiation reaching the Earth's surface has increased. UV rays are one of the factors that seriously affect the development and physiological activity of plants. An increase in the amount of malondialdehyde (MDA) and other aldehydes during UV radiation indicates that free radicals increase, the plant's defense system cannot fully compensate for this, and as a result, biological membranes are damaged.

Although the effect of UV-A rays increases the level of malonaldehyde in leaves, the damage it causes to cell membranes is weaker than that of UV-B and UV-C rays. Plants develop various protective and adaptive mechanisms to adapt to such stress factors.

Compounds such as ascorbic acid (vitamin C), dehydroascorbic acid, proline, and antioxidant enzymes — catalase, peroxidase, glutathione reductase, and ascorbate peroxidase — play an important role in reducing the damage caused by UV rays. In addition, reactive oxygen species (ROS), UVR8 protein, as well as photoreceptors such as phytochrome and cryptochrome are considered to be key elements of the UV signal transduction mechanism.

The text, while noting that UV rays can negatively affect the photosynthesis process and plant growth, also highlights certain positive aspects of it. Thus, UV light can increase the stress resistance of plants by stimulating the synthesis of various pigments such as flavonoids and carotenoids. The study of these defense mechanisms is of great importance in terms of healthy plant development and maintaining the stability of ecosystems.Specifically, the molecular mechanism of UV-B induced damage focuses on the disruption of the oxygen-evolving complex (OEC) and the degradation of D1 and D2 core proteins within the Photosystem II reaction center. This biophysical lesion uncouples the excitation energy transfer from light-harvesting complexes, driving a significant reduction in linear electron transport. To mitigate this photon-induced inhibition, the plant's metabolic network upregulates the

phenylpropanoid pathway, transforming simple phenylalanine into complex polyphenolic structures. These UV-absorbing compounds accumulate in the adaxial epidermal layer, acting as an internal optical shield that truncates the destructive ultraviolet flux before it reaches the vulnerable mesophyll chloroplasts. [3].

Wheat and corn plants were used as the research objects. Wheat is one of the most consumed cereals and undergoes major changes in its physicochemical properties due to pre- and post-harvest operations [4].

Plant samples were grown under optimal conditions prior to the study. The plants were maintained under standard light and temperature conditions and irradiated for a certain period of time in a special irradiation device designed for UV-B rays. Then, leaf sections were taken from the samples and prepared for analysis. The PAM (pulse-amplitude modulated) fluorometry method was used to assess the activity of the electron transport chain of photosynthesis. This method allows to determine the photochemical efficiency (Fv/Fm) of photosystem II (PSII), the degree of photoinhibition, and the rate of electron transport.

Delayed light emission has been used to assess short-term energy storage in the electron transport chain of photosynthesis.

The physiological effects of UV-B irradiation on the structural and functional properties of wheat seedlings were studied. During the study, it was determined that as the irradiation dose increased, the height of the plants decreased, the size of the leaf surface and the amount of photosynthetic pigments decreased. At the same time, a weakening of photosynthesis indicators was observed, but the amount of low molecular weight antioxidants increased.

These results indicate that pretreatment of wheat seedlings with UV-B irradiation should be carried out at lower doses than those used in the experiments [5].

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ADAMANTYLGLYCINE AS A SYNTHON FOR NITROGENOUS HETEROCYLES. SYNTHESIS OF 5-(ADAMANTAN-1-YL)-3-METHYL-4,5-DIHYDRO-1,2,4-TRIAZIN-6(1H)-ONE AND 4-(ADAMANTAN-1-YL)-2-METHYL-1H-IMIDAZOL-5(4H)-ONE

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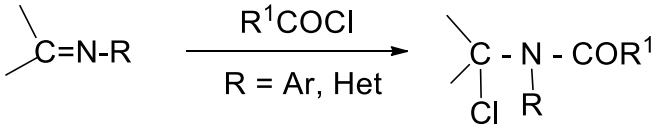
It is known that many heterocyclic compounds, even relatively simple ones, are difficult to obtain, significantly limiting their scope of application. Therefore, the search for new regioselective heterocyclizations based on readily available reagents is highly relevant. Various amidoalkylating agents, in particular those obtained fromSchiff bases according to the general scheme, are among such promising reagents.



The preparation of reagents using this scheme is only briefly mentioned in the literature [1-3].

The use of such amidoalkylating reagents obtained from cage ketones would allow the preparation of unique spiro derivatives of nitrogen heterocycles. There are no reports of such syntheses in the literature.

The aim of this study is to attempt to synthesize 1-(Spiro[adamantane-2,1'-isoindolin]-2'-yl)ethanone (4) starting from adamantan-2-one (1).

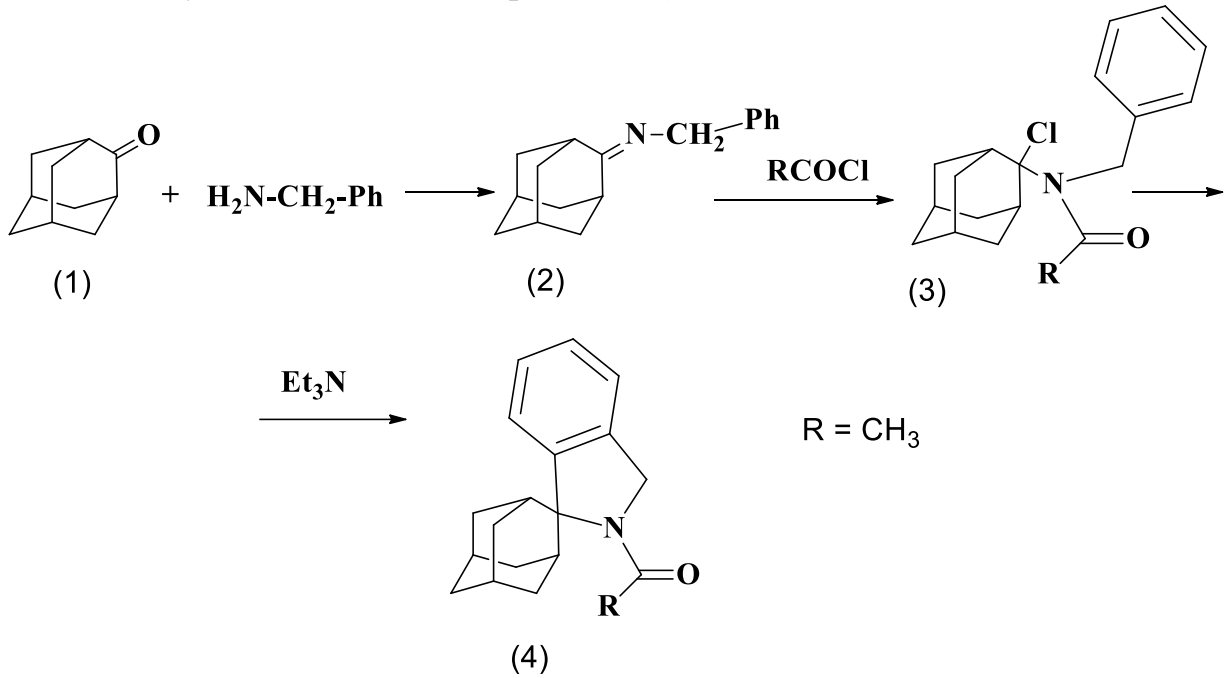
General synthesis procedure.

1) Synthesis of the Schiff base. N-((5R,7S)-adamantan-2-ylidene)-1-phenylmethanamine (2). An equivolic amount of benzylamine was added to a solution of 0.05 mol of adamantanone (1) in dry toluene, and the mixture was refluxed with a Dean-Stark trap until the calculated amount of water was released.

2) Synthesis of the amidoalkylating reagent. N-benzyl-N-(2-chloroadamantan-2-yl)acetamide (3). 0.05 mol of acetyl chloride was added to a solution of the resulting compound (2), and the mixture was left at room temperature for 24 hours.

3) Synthesis of 1-(Spiro[adamantane-2,1'-isoindolin]-2'-yl)ethanone (4). An equimolar amount of triethylamine was added to a solution of compound (3), and the mixture was refluxed for 7 hours. Toluene was removed under vacuum. The residue was crystallized from ethanol-hexane. Yield 78%. M.p. 243-245 °C.

The synthesis of compound (4) is shown in the scheme:



The structure of compound (4) was confirmed based on 1H and 13C NMR, IR and mass spectra.

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ФІЗИКО-МЕХАНІЧНІ ТА ЕЛЕКТРОДИНАМІЧНІ ВЛАСТИВОСТІ ПОЛІМЕР-НЕОРГАНІЧНИХ КОМПОЗИЦІЙНИХ МАТЕРІАЛІВ

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Поширення композиційних матеріалів для поглинання електромагнітного випромінювання тісно пов’язане з розвитком інформаційних технологій та виникненням електромагнітного забруднення, такого як електромагнітні перешкоди та випромінювання, радіочастотні глушіння тощо [1–6]. В теперішній час досліджуються та розробляються новітні матеріали для поглинання електромагнітного випромінювання з малою товщиною, низькою щільністю, широким діапазоном частот поглинання, які становлять великий інтерес для вирішення проблем поглинання електромагнітного випромінювання [7, 8].

Сучасна наукова література демонструє значний інтерес до конструювання радіопоглинаючих матеріалів. Зокрема, більшість робіт зосереджена на розробці високопродуктивних композиційних матеріалів, що поєднують магнітні наповнювачі (ферити [9, 10], метали [11–13]) з різноманітними діелектричними матрицями — керамічними [14], полімерними тощо [15, 16]. Полімерні композиційні матеріали, що містять карбід кремнію [17], вуглецеві волокна [18,

19], сажу [20] та вуглецеві нанотрубки [21, 22], також на сьогоднішній день мають широке поширення.

МАТЕРІАЛИ ТА МЕТОДИ

Метою роботи є дослідження полімер-неорганічних композиційних матеріалів для поглинання електромагнітного випромінювання.

Вирішувалися наступні завдання:

– дослідити вплив наповнювачів на властивості епоксидних полімер-неорганічних композиційних матеріалів;

– визначити характеристики поглинання електромагнітного випромінювання епоксидними полімер-неорганічними композиційними матеріалами.

Для отримання полімерних композиційних матеріалів для поглинання електромагнітного випромінювання були використані наступні матеріали:

– епоксидна смола на основі Epikote Resin MGS LR 285 (США);

– порошок карбіду кремнію SiC марки 64C F1500 M3 (Україна) з розміром частинок 50–65 мкм, температурою плавлення 2700 °C та коефіцієнтом лінійного теплового розширення α від 5×10^6 до 7×10^6 K^{-1};

– порошок оксиду хрому Cr_2O_3 марки Klebrig (Китай) з розміром частинок 2–5 мкм, температурою плавлення 2435 °C, температурою кипіння близько 4000 °C);

– графітовий порошок (розмір частинок 20–25 мкм), який отримували зі стандартних графітових заготовок. Графітові заготовки подрібнювали до класу менше 0,2 мм за допомогою вальцьової дробарки. Аналітичні показники вологості, зольності, водню та вуглецю визначалися в отриманому зразку графіту відповідно до чинної нормативної документації: ISO 589:2015, ДСТУ 8995:2020, ISO 1171:2010, ISO 625:1996. Далі зразок графіту додатково подрібнювали до 100% вмісту фракції менше 0,075 мм за допомогою циліндричного млина та на розсіювачі на ситах з розміром отворів 0,02 мм;

- наночастинки титанату калію отримували спіканням шихти, що містить TiO_2, K_2CO_3 та KCl. TiO_2:K_2O використовували у співвідношенні (у молях) від 4:1 до 7:1 з додаванням від маси S TiO_2:K_2O 20 % мас. KCl.

Полімер-неорганічні композиційні матеріали були отримані шляхом змішування епоксидної смоли з порошком карбіду кремнію SiC, порошком оксиду хрому Cr_2O_3, порошком графіту та наночастинками титанату калію (у кількостях 10-20% мас.) та затвердіння при 60 °C протягом 2 годин. Для кожного досліджуваного складу було отримано 10 тестових зразків.

Вимірювання електродинамічних характеристик зразків полімер-неорганічних композитів проводилися за допомогою мікрохвильового векторного мережевого аналізатора (VNA) Keysight Technologies PNA N5227A, що має діапазон вимірювання частот від 10 МГц до 67 ГГц. Зразки мали форму порожнистих циліндрів із зовнішнім діаметром 1,84 мм і щільно входили в коаксіальну вимірювальну комірку. Комірка мала внутрішній діаметр 0,03164 дюйма (0,80 мм) та зовнішній діаметр 0,0728 дюйма (1,85 мм). Довжина зразка вздовж коаксіального хвилеводу становила 3,4 мм. Спочатку на тестовій установці було виконано повне двопортове калібрування, щоб усунути похибки,

спричинені спрямованістю, узгодженням джерела, узгодженням навантаження, ізоляцією та частотною характеристикою.

РЕЗУЛЬТАТИ ТА ОБГОВОРЕННЯ

Основні дослідження були спрямовані на вивчення впливу введення наночастинок карбіду кремнію SiC, оксиду хрому Cr_2O_3, графіту та титанату калію на міцність та технологічні властивості полімер-неорганічних композитів з метою оптимізації складу та кількості наповнювача полімер-неорганічних композитів. Введення наночастинок карбіду кремнію SiC та титанату калію до епоксидної смоли збільшує щільність матеріалу, тоді як наповнювачі з графіту та оксиду хрому Cr_2O_3 зменшують щільність. Додавання наночастинок SiC, Cr_2O_3, графіту та титанату калію до епоксидної смоли з вмістом наповнювача до 20 мас.% збільшує ударну в'язкість композиту та міцність на розрив під час згинання. Фактично, було встановлено, що полімер-неорганічні композити з вмістом титанату калію 20 мас.% мають найкращий набір міцнісних характеристик.

Для полімер-неорганічних композиційних матеріалів з оптимальними міцнісними характеристиками вимірювали мікрохвильове пропускання та відбиття за допомогою векторного аналізу нуклеотидів (VNA) у діапазоні частот 1–67 ГГц. Під час випробувань демонструвалися глибокі мінімуми пропускання електромагнітних хвиль через зразки полімер-неорганічних композиційних матеріалів. Мінімальне основне відбиття спостерігалося для полімер-неорганічних композиційних матеріалів на основі епоксидної смоли з 20% мас. SiC та 20% мас. титанатів калію. Різкі зміни спостерігаються поблизу певних частот, де електромагнітна півхвилі в матеріалі зразка стає аліквотною частиною довжини зразка. На таких частотах зразок проявляє себе як резонатор з багаторазовими внутрішніми відбиттями, що призводить до різкого зростання поглинання. Водночас вхідний коефіцієнт відбиття падає. Це можна використовувати для максимізації поглинання у вузькій смузі частот. Також мінімальні спостережувані значення (пропускання) є типовими для полімер-неорганічних композитів на основі епоксидної смоли з 20% мас. SiC та 10% мас. графіту + 10% мас. Cr_2O_3. Такі результати свідчать про перевагу комплексної системи наповнювачів у розробці ефективних матеріалів для поглинання електромагнітного випромінювання.

ВИСНОВКИ

Отримано полімер-неорганічні композиційні матеріали на основі епоксидної смоли, модифікованої неорганічними графіто-феромагнітними наповнювачами (карбід кремнію SiC, оксид хрому Cr_2O_3, графіт та титанат калію). Було досліджено комплекс міцнісних характеристик та вивчено склади з вищим вмістом карбіду кремнію SiC - 10% мас., а також оптимізовано вміст графіту оксиду хрому Cr_2O_3 та графіту в діапазоні 5-25% мас. Було виявлено, що введення наночастинок карбіду кремнію SiC та титанату калію до епоксидної смоли збільшує щільність матеріалу, тоді як наповнювачі з графіту та оксиду хрому Cr_2O_3 зменшують щільність. Також дослідження показують, що додавання карбіду кремнію SiC, оксиду хрому Cr_2O_3, графіту та наночастинок титанату

калію до епоксидної смоли до 20 мас.% наповнювача збільшує ударну міцність композиту та міцність на розрив під час згинання.

Визначено, що мінімальне відбиття спостерігається для полімер-неорганічних епоксидних композитів з 20 мас.% SiC та 20 мас.% титанатів калію. Мінімальне пропускання спостерігається для полімер-неорганічних епоксидних композитів з 20 мас.% SiC та 10 мас.% графіту + 10 мас.% Cr_2O_3. Перевага застосування комплексної системи наповнювачів була доведена дослідженням впливу модифікації полімер-неорганічних композитів на поглинання електромагнітного випромінювання.

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ANALYSIS OF DEVELOPMENT TRENDS IN FOURTH-GENERATION DISTRICT HEATING SYSTEMS IN UKRAINE

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Introductions. District heating systems constitute a fundamental component of the energy infrastructure of cities and buildings. Their development is closely associated with changes in energy policy, heat generation technologies, and contemporary requirements for energy efficiency and environmental safety. Current trends are driving the transition from conventional centralized solutions to intelligent, low-temperature, and decentralized systems, referred to as fourth-generation district heating (4GDH) and fifth-generation district heating (5GDH). A detailed analysis of the evolution and operating characteristics of these systems is presented in studies [1–5].

First generation (1GDH). The earliest district heating systems operated using steam as the heat transfer medium. They were characterized by extremely high operating temperatures and pressures, substantial heat losses, and a low level of operational safety. Coal combustion served as the primary energy source.

Second generation (2GDH). The subsequent stage of development was associated with the transition to hot water as the heat transfer medium. Operating temperatures remained high (above 100 °C); however, these systems became more reliable and safer. Fossil fuels, primarily coal and natural gas, continued to serve as the main sources of thermal energy.

Third generation (3GDH). Third-generation district heating systems became widely adopted in the late twentieth and early twenty-first centuries. Their distinguishing features included the use of pre-insulated pipelines, a reduction in supply temperatures to 90–125 °C, and the widespread implementation of combined heat and power (CHP) plants. Third-generation district heating systems established the foundation of modern district heating networks in many countries. Most district heating systems in Ukraine also belong to this stage of development and are currently classified as third-generation systems.

Fourth generation (4GDH). Fourth-generation district heating systems are designed to integrate renewable energy sources, improve energy efficiency, and reduce operating temperature levels. They represent a key instrument in the transition toward sustainable energy systems. These systems widely employ high-efficiency combined heat and power (CHP) plants, large-scale heat pumps, seasonal and daily thermal energy storage, as well as intelligent control systems. Digitalization and predictive thermal load management also play an important role. Their principal advantages include reduced network heat losses, lower CO_2 emissions, and enhanced integration of renewable energy sources. At the same time, their implementation is constrained by

the need to modernize buildings and district heating networks, as well as by significant initial investment costs.

Fifth generation (5GDHC). Fifth-generation district heating and cooling (5th Generation District Heating and Cooling, 5GDHC) represents the next stage in the evolution of district energy systems. It is based on the use of ultra-low-temperature heat transfer media while combining heating and cooling functions within a single network. Such systems provide maximum operational flexibility, enable the integration of diverse energy sources, and comply with contemporary requirements for climate neutrality.

Aim. The aim of this study is to analyze the development trends of fourth-generation district heating systems in Ukraine, taking into account the environmental, energy-related, and social aspects of their implementation, to assess the technical potential for modernizing existing district heating systems, and to determine the readiness of infrastructure and consumers for the transition to a new district heating model. Particular attention is given to identifying investment barriers, institutional challenges, and the key factors affecting the effective integration of fourth-generation district heating technologies into Ukraine's energy sector.

Materials and methods. An analytical approach was employed in this study. System analysis was used to examine the interrelationships among the technical, environmental, economic, and social factors influencing the development of fourth-generation district heating systems. Comparative analysis was applied to compare the current state of district heating in Ukraine with international experience in the implementation of 4GDH technologies, while methods of analysis and synthesis were used to identify industry trends, determine the opportunities for modernizing district heating networks, and assess the potential for integrating renewable and waste heat energy sources.

To evaluate the prospects for implementing 4GDH systems, a review of the scientific literature and an analysis of current practices were conducted. This made it possible to identify the main investment barriers, institutional and regulatory constraints, and to assess the readiness of engineering infrastructure and the residential building stock for the transition to low-temperature district heating systems. This approach ensured a comprehensive assessment of current trends and provided a sound basis for drawing well-founded conclusions regarding the prospects for the development of 4GDH technologies in Ukraine.

Results and discussion. International experience in the implementation of fourth-generation (4GDH) and fifth-generation (5GDH) district heating systems demonstrates that their development is determined by a combination of factors, among which government policy, innovative technologies, regulatory and legal frameworks, and investment support play a key role. Implemented projects in the European Union, North America, and Asia confirm that the successful deployment of such systems is possible only through the integration of technical solutions with long-term strategic programmes for the modernization of the energy sector. Practical experience provides the basis for developing recommendations on district heating infrastructure planning, the integration of renewable energy sources, and the creation of conditions for scaling

up the 4GDH and 5GDH concepts. The potential, technical prerequisites, and organizational conditions for the implementation of fourth-generation district heating systems in Ukraine are presented in [6].

In Ukraine, the need to transform district heating systems is driven not only by global trends toward decarbonization and improved energy efficiency but also by the ongoing martial law, which creates additional risks for critical energy infrastructure. Prior to the full-scale war, most district heating systems corresponded to the third-generation concept, relying on large-scale heat sources, including combined heat and power (CHP) plants and district boiler houses operating with high-temperature hot-water networks. Such a configuration exhibited limited flexibility, significant dependence on the operation of individual large facilities, and high vulnerability to missile attacks and physical damage. The failure of a single heat source could result in the interruption of heat supply to entire districts or cities.

Under current conditions, a new concept for district heating development is emerging, based on the gradual transition from centralized heat generation to decentralized energy production. The main components of this approach include the deployment of modular boiler plants, small- and medium-scale combined heat and power (CHP) units, heat pumps, thermal energy storage systems, and the integration of renewable energy sources. Such a structure enhances energy security, reduces dependence on individual large heat sources, and ensures a more reliable heat supply even under crisis conditions. A representative example is the city of Kharkiv, where modular boiler plants and CHP units are being introduced alongside conventional heat sources to provide heat supply for individual residential districts. The prospects for the utilization of renewable energy sources in Ukraine's district heating systems are discussed in [7–9].

Fourth-generation district heating systems provide a number of environmental and energy-related benefits. They contribute to reducing greenhouse gas emissions by decreasing the use of fossil fuels and integrating renewable energy sources, waste heat, and heat pumps. The application of low-temperature operating regimes significantly reduces heat losses during energy transmission, which is particularly important for extensive urban district heating networks. The further evolution toward fifth-generation systems operating at ultra-low temperatures enables even greater reductions in heat losses and further improvements in overall system efficiency.

An important characteristic of these systems is their increased operational flexibility. Through the use of thermal energy storage, the combination of multiple heat sources, and integration with the electricity system, such networks are capable of adapting to the variable output of renewable energy sources. This transforms district heating into an active component of an integrated energy system, contributing to the balancing of energy supply and demand.

The economic advantages of 4GDH systems include lower long-term operating costs, the gradual reduction of heat production and distribution costs, decreased dependence on imported energy resources, and improved energy independence. The utilization of local energy resources and waste heat reduces the impact of price fluctuations in global energy markets. Furthermore, the integration of district heating

networks with electricity supply systems, water supply infrastructure, and digital management platforms creates opportunities for comprehensive urban infrastructure planning, thereby optimizing the use of utility networks and reducing capital expenditures.

The development of 4GDH technologies also stimulates the emergence of new market segments and the creation of employment opportunities. Demand is increasing for the production of heat pumps, thermal energy storage equipment, automation systems, and digital management platforms. This contributes to industrial development, innovation, and enhanced economic competitiveness.

Another important aspect is the increased resilience of local communities. The decentralized structure of heat generation reduces dependence on large heat sources and enables continued system operation even under emergency conditions. The use of low-temperature operating regimes also contributes to improving the quality of life by reducing local emissions, lowering noise levels, and increasing the reliability of heat supply.

A further distinguishing feature is the changing role of the end user. Modern buildings equipped with heat pumps or solar thermal installations can not only consume heat but also supply surplus thermal energy to the network. This creates new models of interaction between network operators and consumers, stimulates the development of energy communities, and enhances public energy awareness.

At the same time, the implementation of 4GDH systems requires comprehensive building energy renovation, modernization of internal heating systems, the installation of individual substations with weather-compensated control, and the automation of heat consumption processes. The management of district heating networks becomes increasingly complex due to the simultaneous operation of multiple heat sources, thermal energy storage systems, and digital monitoring technologies. The main constraints remain the high capital costs associated with the reconstruction of networks and equipment, as well as shortcomings in the regulatory framework, which requires the revision of standards, tariff models, and mechanisms for promoting the utilization of waste heat resources.

Conclusions. The conducted analysis demonstrated that the development of fourth-generation district heating (4GDH) systems is one of the key directions for the modernization of Ukraine's district heating infrastructure. This is particularly relevant in the context of the decarbonization of the energy sector, post-war recovery, and integration into the European energy market. The 4GDH concept envisages the transition to low-temperature district heating networks, the extensive use of renewable energy sources, waste heat, heat pumps, thermal energy storage systems, and advanced digital control technologies, thereby ensuring a comprehensive transformation of the sector.

Military actions have significantly increased the urgency of transitioning to more decentralized district heating systems. The utilization of local heat sources, small- and medium-scale combined heat and power (CHP) units, modular boiler plants, and renewable energy sources contributes to improving the reliability of heat supply, enhancing energy security, and strengthening the resilience of critical energy

infrastructure. This approach reduces dependence on large centralized heat sources, which are the most vulnerable to damage, while ensuring more flexible and stable system operation.

The transition to 4GDH systems provides comprehensive environmental, energy-related, economic, and social benefits. These include reduced heat losses in district heating networks, lower greenhouse gas emissions through the integration of renewable energy sources and waste heat, improved energy efficiency, and the possibility of coupling different energy sectors. Equally important are the promotion of innovative technologies, advanced digital control systems, and the automation of heat demand management, which create new opportunities for optimizing urban infrastructure. The social benefits are reflected in improved reliability of heat supply, enhanced quality of life, and the establishment of new models of interaction between consumers and district heating network operators.

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ЧАСОВИЙ АНАЛІЗ КЛАСТЕРНИХ СТРУКТУР, ОТРИМАНИХ МЕТОДОМ НЕКОНТРОЛЬОВАНОЇ КЛАСИФІКАЦІЇ, ДЛЯ МОНІТОРИНГУ ДИНАМІКИ ЗАПЛАВИ ПІСЛЯ КАТАСТРОФІЧНОЇ ПОВЕНІ: ПРИКЛАД ОСТРОВА ХОРТИЦЯ

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Дистанційне зондування Землі дає змогу аналізувати динаміку ландшафтів, однак катастрофічні порушення формують нові стани земної поверхні, які не можуть бути адекватно відображені за допомогою класів земного покриву, визначених на основі ретроспективних даних [1]. Дослідження присвячене розробленню підходу до часового узгодження результатів неконтрольованої класифікації для моніторингу динаміки заплави острова Хортиця після руйнування Каховського водосховища. Багаточасові супутникові дані Sentinel-2 Level-2A за 2022–2025 роки були оброблені із застосуванням спектральних індексів, стандартизовані в межах єдиного простору предикторів і класифіковані методом неконтрольованої кластеризації. Отримані для окремих дат кластерні структури були узгоджені на основі спектральної подібності та просторової безперервності, а їх інтерпретація здійснювалася з використанням концепцій ландшафтної пам'яті та ландшафтного розпізнавання. На наступному етапі шляхом контекстної суперкластеризації було сформовано просторово-часові одиниці вищого рівня організації. У результаті аналізу за весь період дослідження виділено 16 кластерів, тоді як для окремих часових зрізів їхня кількість становила від 4 до 12. Їхнє часове узгодження дозволило виокремити суперкластери, що характеризуються різними типами динаміки — спрямованою, сезонною та змішаною. Запропонована методологія забезпечує виявлення новоутворених станів поверхні, їх часову інтеграцію та включення до ієрархічної просторово-часової моделі посткатастрофічної трансформації ландшафтів [2].

Неконтрольована класифікація даних дистанційного зондування дає змогу виділяти кластери як феноменологічно визначені, умовно дискретні категорії, придатні для аналізу просторової неоднорідності ландшафтів [3]. Їхнє значення істотно зростає в межах ієрархічної інтерпретації. Первинні кластери відображають спектрально однорідні стани растрового поля. Суперкластери першого порядку формуються шляхом часового узгодження первинних кластерів на основі спектральної подібності та просторової безперервності, тоді як суперкластери другого порядку репрезентують інваріантні просторово-часові мозаїки. Такий підхід дозволяє використовувати єдину формальну конструкцію

— кластер — для опису різних рівнів природної організації: від локальних типів середовищ існування та екотопів до хорологічних одиниць вищого рангу.

Принциповою особливістю запропонованої методології є збереження растрової парадигми на всіх рівнях аналізу. Нарощування ієрархічної складності досягається не шляхом переходу до полігонального представлення, а завдяки зміні семантики номінального ідентифікатора, критерію класифікації, екологічної та ландшафтної інтерпретації, а також урахуванню механізмів ландшафтної пам'яті та розпізнавання. Це забезпечує можливість виявлення закономірностей вищого рівня організації в межах тієї самої піксельної онтології, як і первинні кластери.

Важливим методологічним аспектом є використання повної сукупності суперкластерів першого порядку як єдиної основи для оцінювання профілів просторової спорідненості. Такий підхід забезпечує порівнянність локальних просторових конфігурацій на масштабі всієї досліджуваної території. Водночас екологічні та ландшафтні аналоги кластерів існують лише як наближені відповідності. Це зумовлено відносною автономністю рослинного покриву, ґрунтових і гідрологічних процесів, а також градієнтним і мозаїчним характером природних меж [4]. Тому ієрархію кластерів доцільно розглядати як систему операційних просторових сурогатів, що відображають природні об'єкти з різним ступенем точності [5]. Таким чином, запропонований підхід поєднує формальну математичну диференціацію із можливістю екологічної та ландшафтної інтерпретації отриманих результатів.

Для ландшафтів, що зазнали катастрофічних змін, особливого значення набувають концепції ландшафтної пам'яті та ландшафтного розпізнавання. Ландшафтна пам'ять забезпечує зв'язок між послідовними станами ландшафту, зберігаючи інформацію про попередні конфігурації, тоді як розпізнавання дає змогу ідентифікувати як успадковані, так і новоутворені просторові структури.

На рівні первинного кластера ландшафтна пам'ять відповідає фіксації поточного спектрального стану як репрезентативного шаблону без механізму його порівняння з іншими часовими зрізами. На рівні суперкластера першого порядку пам'ять і розпізнавання охоплюють процеси збереження, трансформації, забування та появи нових структур. На рівні суперкластерів другого порядку об'єктом аналізу стають інваріантні просторово-часові мозаїки, що відображають довготривалу організацію ландшафту. Це відкриває можливість виявлення успадкованих структур, простеження їхніх трансформацій та ідентифікації якісно нових утворень, сформованих унаслідок катастрофічних подій. Для заплавних ландшафтів, які перебувають у стані посткатастрофічної перебудови, такий підхід створює концептуальну основу для дослідження просторової організації з позицій ландшафтної пам'яті, а також для розпізнавання та формування нових структурних станів.

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РОЗВИТОК АРТИКУЛЯЦІЙНОЇ ТОЧНОСТІ ТА ЇЇ ЗВ'ЯЗОК ІЗ МОТОРНИМ ПЛАНУВАННЯМ У ДІТЕЙ ДОШКІЛЬНОГО ВІКУ З ДИСЛАЛІЄЮ

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На сучасному етапі розвитку спеціальної педагогіки та логопедії проблема порушень звуковимови у дітей дошкільного віку залишається однією з найбільш актуальних. Особливе місце серед мовленнєвих порушень займає дислалія, яка характеризується неправильним відтворенням звуків за умови нормального слуху та збереженої іннервації мовленнєвого апарату. Дислалія залишається одним із найпоширеніших мовленнєвих порушень у дітей дошкільного віку [5]. Попри те, що традиційно дислалія розглядається як порушення звуковимови при нормальному слуху та збереженій іннервації мовленнєвого апарату, сучасні дослідження в галузі нейропсихології та логопедії вказують на глибші механізми цієї проблеми. Зокрема, все частіше дефекти звуковимови пов’язують із недостатністю моторного планування (праксису). Багато дітей з дислалією демонструють здатність виконати артикуляційний уклад ізольовано, проте зазнають значних труднощів при спробі автоматизувати звук у мовленнєвому потоці або при переключенні з одного звука на інший. Це актуалізує необхідність вивчення зв’язку між моторним плануванням та артикуляційною точністю.

Моторне планування (або праксис) – це здатність мозку задумати, організувати та виконати послідовність незвичних рухів [2]. У мовленнєвому акті цей процес трансформується в артикуляційну праксію. Згідно з концепцією М. Бернштейна про рівні побудови рухів, мовлення є одним із найскладніших моторних актів, що вимагає ідеальної координації десятків м’язів у мілісекундному діапазоні.

Дослідження у галузі нейропсихології та логопедії свідчать про тісний взаємозв’язок між рівнем розвитку моторного планування та артикуляційною точністю у дітей дошкільного віку з дислалією. Недостатня сформованість

механізмів програмування та контролю рухів негативно впливає на здатність дитини виконувати точні артикуляційні рухи, що проявляється у різноманітних порушеннях звуковимови.

Однією з характерних особливостей дітей із низьким рівнем моторного планування є порушення переключення між артикуляційними позиціями. У таких випадках дитина може правильно виконувати окремі артикуляційні рухи або вимовляти ізольовані звуки, проте відчувати труднощі під час їх поєднання у склади чи слова. Наприклад, дитина правильно вимовляє звуки [с] та [а] окремо, але при переході до складу «са» втрачає точність артикуляції, оскільки не встигає перебудувати моторну програму відповідно до нової артикуляційної позиції [1]. Це свідчить про недостатню сформованість механізмів послідовної організації рухів та їх автоматизації.

Іншим проявом порушення моторного планування є так званий «пошук артикуляції». Під час вимови певного звука дитина здійснює множинні хаотичні рухи язиком, губами або нижньою щелепою, намагаючись знайти правильну артикуляційну позицію. Така поведінка вважається ознакою недостатньої сформованості аферентного праксису, тобто порушення здатності до точного кінестетичного контролю положення органів мовлення. У результаті дитина не може швидко та впевнено відтворити необхідний артикуляційний уклад, що негативно впливає на якість звуковимови.

Ще однією характерною особливістю є спрощення звукової структури слова. Діти дошкільного віку з порушеннями моторного планування часто пропускають окремі звуки або спрощують складні звукосполучення, особливо у словах зі збігом приголосних. Наприклад, слово «стрибати» може вимовлятися як «тибати», а слово «квітка» — як «кітка». Подібні помилки пояснюються тим, що центральна нервова система не встигає спланувати та реалізувати складну послідовність артикуляційних рухів, необхідних для правильної вимови всіх звуків слова.

Враховуючи зазначені особливості, розвиток артикуляційної точності повинен ґрунтуватися на комплексному підході до формування моторного планування. Аналіз наукових джерел дозволяє виокремити три основні компоненти цього процесу: орієнтацію, послідовність та автоматизацію рухів.

Першим компонентом є орієнтація, яка передбачає формування у дитини уявлення про положення та рухи органів артикуляційного апарату. Для розвитку цього компонента широко використовуються вправи із дзеркалом, що допомагають дитині візуально контролювати власні рухи та співвідносити їх зі зразком, запропонованим логопедом. Ефективним засобом також є зондовий масаж та вправи на розвиток кінестетичних відчуттів, які сприяють усвідомленню положення язика, губ і нижньої щелепи під час виконання артикуляційних вправ [1].

Другим компонентом є розвиток послідовності рухів, який полягає у формуванні здатності виконувати серії артикуляційних дій у визначеному порядку. На цьому етапі доцільно використовувати динамічні артикуляційні вправи, що передбачають швидке переключення між різними артикуляційними

позами. Наприклад, послідовне виконання вправ «Лопаточка», «Голочка» та «Чашечка» у різному темпі сприяє розвитку координації рухів, покращенню переключення між артикуляційними укладами та формуванню стійких моторних програм.

Третім компонентом є автоматизація, яка забезпечує перехід від свідомого контролю артикуляційних рухів до їх автоматизованого виконання. На цьому етапі дитина поступово навчається відтворювати звуки та звукосполучення без постійного контролю з боку дорослого, що сприяє закріпленню правильної звуковимови у спонтанному мовленні [4].

З метою підвищення ефективності корекційної роботи традиційну артикуляційну гімнастику доцільно поєднувати з вправами на розвиток загального праксису та нейропсихологічними іграми. Одним із перспективних напрямів є використання нейродинамічних вправ, які передбачають одночасне виконання рухових і мовленнєвих дій. Наприклад, дитина може ритмічно натискати пальцями на кнопки або торкатися поверхні столу під час вимови цільового звука чи складу. Такі вправи сприяють розвитку міжсистемної координації, активізують роботу різних відділів головного мозку та покращують програмування мовленнєвих рухів.

Важливе місце у розвитку артикуляційної точності займає ритмізація мовлення. Використання метронома або ритмічних музичних супроводів під час автоматизації звуків допомагає дитині узгоджувати артикуляційні рухи з часовою структурою мовлення. Чіткий ритм сприяє формуванню стійких моторних програм та покращує плавність мовленнєвих рухів.

Ефективним засобом розвитку моторного планування є також використання перехресних рухів, які стимулюють міжпівкульну взаємодію та сприяють покращенню загального моторного контролю. До таких вправ належать почергові дотики правою рукою до лівого коліна, одночасне виконання асиметричних рухів руками, вправи на координацію рухів очей, рук та мовлення. Регулярне використання подібних вправ позитивно впливає на розвиток праксису, координації рухів та підвищує ефективність формування правильної звуковимови у дітей дошкільного віку з дислалією [5].

Включення вправ і завдань, спрямованих на розвиток моторного планування, у систему корекційної роботи при дислалії має суттєвий позитивний вплив на динаміку формування правильної звуковимови. Практичні спостереження та результати нейропсихологічних досліджень свідчать, що така інтеграція дозволяє значно скоротити тривалість етапу автоматизації звуків, у середньому у 1,5–2 рази, порівняно з традиційними логопедичними підходами.

Підвищення ефективності пояснюється тим, що дитина поступово опановує універсальний алгоритм моторної діяльності «планування — виконання – контроль», який спочатку формується на рівні загальної моторики, а згодом переноситься у сферу мовленнєвих рухів. У результаті мовленнєвий апарат стає більш пластичним, а артикуляційні дії – гнучкими та керованими. Це сприяє стабілізації артикуляційної точності та зменшенню варіативності помилок у процесі мовлення.

Важливим ефектом є зниження кількості випадків так званого «мовленнєвого розпаду», який проявляється у втраті правильної вимови при збільшенні темпу мовлення або ускладненні лексичного матеріалу. Діти, які систематично виконують вправи на розвиток моторного планування, демонструють більш стійке збереження правильної артикуляційної позиції навіть у складних мовленнєвих умовах, що свідчить про сформованість внутрішніх механізмів контролю мовленнєвої діяльності [3].

Артикуляційна точність при дислалії має безпосередній зв'язок із рівнем розвитку моторного планування. Порушення звуковимови у більшості випадків є наслідком недостатньої сформованості артикуляційного праксису та механізмів програмування рухів, а не лише ізольованим артикуляційним дефектом.

У зв'язку з цим корекційна робота при дислалії повинна мати комплексний характер і бути спрямована не лише на постановку та автоматизацію звуків, але й на розвиток здатності дитини до швидкого формування, зміни та утримання моторних програм. Такий підхід забезпечує більш стійкі результати логопедичної корекції та сприяє загальному розвитку мовленнєвої системи.

Перспективним напрямом подальших досліджень є інтеграція методів сенсорної інтеграції та нейрокорекції у класичну систему подолання дислалії. Застосування міждисциплінарного підходу дозволяє не лише підвищити ефективність корекційного процесу, але й створити умови для профілактики вторинних порушень писемного мовлення, зокрема дисграфії, у подальшому шкільному навчанні дітей.

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ДЕЯКІ ОСОБЛИВОСТІ ФОРМУВАННЯ РИТОРИЧНОЇ КОМПЕТЕНТНОСТІ СТУДЕНТІВ-ФІЛОЛОГІВ

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У сучасному глобалізованому світі за умов інтеграції різних країн в економічній, політичній, військовій, природоохоронній, науково-технічній, освітній, культурній сферах, а також за умов запровадження європейських стандартів вищої освіти значно зросли вимоги до рівня професійної підготовки фахівців практично всіх профілів, зокрема до філологів. Науковці активно розробляють зміст професійних компетентностей працівників різних галузей людської життєдіяльності для того, щоб чітко визначити вимоги до знань, умінь, навичок та особистісних якостей фахівця, необхідних для ефективного виконання професійних обов'язків.

Сучасні мовознавці й педагоги (Н. Бабич, Н. Голуб, О. Горошкіна, Д. Даценко, Н. Дудник, С. Караман, Г. Клочек, Н. Колотілова, Т. Конівіцька, З. Куньч, О. Кучерук, Л. Мамчур, Л. Мацько, В. Нищета, Г. Онуфрієнко, М. Пентилюк, О. Ранюк, Л. Ткаченко, ін.) плідно працюють над удосконаленням принципів, методів і прийомів підготовки майбутніх філологів. Окрім питання про шляхи вдосконалення предметних компетентностей, пов'язаних зі знаннями певної професії та відповідними вміннями й навичками, дослідники доволі активно обговорюють проблеми формування мовної, мовленнєвої, комунікативної, риторичної компетентностей майбутніх фахівців. Науковці зауважують, що питання про досконалі мовні знання, володіння технікою мовлення, уміння здійснювати комунікацію в різних ситуаціях спілкування і в різноманітних форматах (від діалогу до масової та міжкультурної комунікації), переконливо доносити думки й впливати на співрозмовників у період дистанційного навчання, у часи суцільної інформатизації і комп'ютеризації, засилля мультимедійної комунікації, поширення тестових технологій оцінювання якості освіти й у зв'язку із цим обмеження повноцінних усних опитувань набувають особливої *актуальності* [1, с. 49; 2, с. 18-23].

Проблеми викладання риторики філологам-перекладачам порушували такі науковці й педагоги, як Г. Адамова, О. Ничко, М. Рудіна, І. Стецько, Л. Таланова Т. Юрчишин та деякі ін. Однак, на нашу думку, ще недостатньо розроблено питання про шляхи, методи, прийоми формування й розвитку риторичної компетентності саме майбутніх перекладачів.

Мета нашої праці – з'ясувати деякі особливості формування риторичної компетентності студентів закладів вищої освіти – майбутніх перекладачів.

Кожен із науковців розуміє «риторичну компетентність» по-своєму, вкладаючи дещо різний зміст в це поняття. У зв'язку із цим маємо навіть різні найменування для цієї компетентності: *риторична* (Д. Даценко, Т. Коніцівіцька, Т. Симоненко), *мовленнєво-риторична* (Г. Бондаренко), *лінгвориторична* (Н. Краснопольська, С. Шестакова), *мовно-риторична* (Л. Мамчур) тощо.

Поняття «риторична компетентність» у сучасній лінгводидактиці досі не здобуло остаточного визначення, хоча питання про це неодноразово порушувалося в науковій літературі. До обговорення сутності цього поняття долучалися Л. Башманівська, Г. Бондаренко, Н. Голуб, С. Горобець, М. Ковалик, О. Кучерук, Л. Мамчур, В. Нищета, Г. Онуфрієнко, Н. Подлевська, О. Ранюк, Т. Симоненко, С. Толочко та ін. На основі дефініцій, поданих дослідниками (С. Горобець, М. Ковалик, Л. Мамчур, С. Толочко), риторичну компетентність майбутнього перекладача визначаємо як здатність усвідомлено сприймати повідомлення, створювати, ефективно виголошувати й аргументовано передавати інформацію засобами рідної та інших мов, впливати на співрозмовників, переконувати їх, утверджувати вищі морально-етичні й патріотичні ідеали суспільства. До складу риторичної компетентності науковці зараховують мовні, мовленнєві, комунікативні, риторичні, організаційно-управлінські знання, уміння й навички, світоглядні погляди й цінності, інтелектуальні й творчі здібності, критичне мислення, особистісні якості тощо (С. Горобець, М. Ковалик, В. Нищета).

На нашу думку, риторична компетентність ґрунтується на мовній і мовленнєвій компетентностях (знаннях мов і їхніх норм, уміннях будувати усні висловлення з дотриманням цих норм), і ми погоджуємося з тими науковцями, які визнають її вищим рівнем комунікативної майстерності (С. Горобець, О. Кучерук). Дослідниця Т. Симоненко виокремлює психологічний, культурологічний, мотиваційний, соціальний чинники, що впливають на процес засвоєння мовних норм риторичною особистістю, серед яких соціальний називає одним з найважливіших [3, с. 134].

Слід відзначити, що проблему розвитку риторичної компетентності майбутніх філологів науковці розглядають здебільшого на прикладі викладання мовознавчих дисциплін (С. Глущук, С. Горобець, І. Циганок), що, безсумнівно, є виправданим, оскільки науковці вказують на потребу збагачення словникового складу здобувачів освіти, працю зі словниками, роботу з текстом, підготовку доповідей, виконання проєктів тощо. Уважаємо, що формування риторичної майстерності майбутнього філолога доцільно здійснювати під час вивчення всіх лінгвістичних дисциплін, завдяки яким студенти ознайомлюються з новими лексичними засобами певної мови й опановують їх. Проте варто було б глибше дослідити особливості розвитку риторичної компетентності на заняттях з літератури та інших гуманітарних дисциплін (серед яких логіка, психологія, соціолінгвістика та ін.), оскільки на цих заняттях досить активно можна вдосконалювати риторичні вміння й навички майбутніх філологів, що сприяло б комплексному розвитку риторичної особистості.

На нашу думку, важливо вибудувати певну траєкторію формування риторичних умінь і навичок у ЗВО. Логічним буде, якщо спочатку студенти ЗВО оволодіють деякими риторичними знаннями, уміннями й навичками на заняттях зі вступу до мовознавства, теоретичних і практичних курсів мов, що вивчаються, де викладачі розвивають мовну, мовленнєву й комунікативну компетентності, без яких опанування риторичними навичками практично неможливе. Паралельно на заняттях з історії зарубіжної літератури під час застосування, наприклад, таких видів завдань, як аналіз сюжетно-композиційних особливостей художніх творів, обговорення проблематики текстів, характеристика вжитих лексичних засобів, тропів і стилістичних фігур, виразне читання напам'ять (і не тільки) віршів та уривків з інших творів, підготовка доповідей, написання рецензій на художні твори, проведення круглих столів і дискусій тощо, можна звертати увагу на розвиток навичок з красномовства.

Згодом на заняттях з риторики, де, крім удосконалення вже здобутих знань і вмінь, студенти дізнаються про принципи риторичної діяльності, засади логіки, правила побудови публічного виступу, риторичні прийоми активізації уваги слухачів та впливу на них, етикетні норми, аналізують аудіо- та відеоматеріали з виступами видатних осіб минулого й сучасності, характеризують вербальні й невербальні особливості виступів, поведінки ораторів, і тоді в здобувачів освіти формується цілісне уявлення про риторичну поведінку.

Після опанування цих навчальних дисциплін уважаємо виправданим викладання курсів з основ міжкультурної комунікації, лінгвістики тексту, лінгвокраїнознавства та ін., які поглиблюють знання студентів про правила створення досконалого тексту, особливості спілкування й поведінки з представниками інших культур, і покращують уміння й навички переконливої комунікації. Зрештою, підготовка доповідей про власні здобутки у результаті виконання наукових досліджень і виступи на захистах кваліфікаційних робіт продемонструють, на нашу думку, рівень риторичної компетентності майбутніх перекладачів. Можемо твердити, що формування риторичних умінь і навичок відбуватиметься в такий спосіб не лише на заняттях з красномовства, буде більш ефективним, корелюватиметься за змістом з іншими комунікативно орієнтованими та гуманітарними дисциплінами і триватиме протягом усього періоду навчання в закладі вищої освіти.

Під час викладання риторики та інших фахових дисциплін майбутнім перекладачам будуть корисними такі завдання, що сприяють формуванню риторичної компетентності: праця з текстами (перекладання текстів різних стилів, компаративний аналіз перекладів того самого тексту, проєктні (підготовка доповідей і презентацій, виголошення текстів різних стилів) та інші креативні завдання (написання есе, творчих робіт), проведення конференцій і круглих столів, дискусій на задані теми, кейс-стаді, праця зі словниками, логічні й мнемотехнічні завдання, трансформаційні вправи, вправи на аналіз аудіовізуальних матеріалів, змагання ораторів, методика спонтанних виступів, вправи на розвиток техніки мовлення (постановка голосу, тренування дикції, техніки дихання, передання інтонаційних відтінків), рефлексивний аналіз тощо.

Деякі науковці висувають до риторичної вправності майбутнього фахівця певні критерії, серед яких, наприклад, розвинені комунікативні навички; морально-етичні переконання, соціокультурна компетентність і загальна ерудиція особистості; високий рівень культури мовлення; прагнення до мовленнєвої взаємодії та вдосконалення; саморефлексія; оволодіння засобами виразності й техніки мовлення, експресією комунікації [3, с. 135]. Варто, на нашу думку, додати ще фахову обізнаність у певній галузі людської діяльності, володіння критичним мисленням, що додасть упевненості перекладачам.

Ми переконані, що формування риторичної компетентності є обов'язковим складником фахової підготовки майбутніх перекладачів. У зв'язку із цим актуальною залишається проблема визначення шляхів підвищення риторичної майстерності майбутніх філологів на заняттях з перекладознавчих дисциплін. Уважаємо за доцільне викладачам ЗВО на заняттях зі спеціальних дисциплін не лише дбати про формування перекладацьких умінь і навичок, але й продовжувати підвищувати риторичну культуру майбутніх філологів під час виконання підготовчих, тренувальних, аналітичних завдань.

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РОЗВИТОК ЛОГОПЕДОМ ФОНЕТИКО-ФОНЕМАТИЧНИХ ПРОЦЕСІВ У МОЛОДШИХ ШКОЛЯРІВ З ПОРУШЕННЯМ СЛУХУ

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Однією з актуальних проблем сучасної спеціальної педагогіки та логопедії є розвиток мовлення дітей з порушеннями слуху. Слух відіграє провідну роль у формуванні мовленнєвої функції, оскільки забезпечує сприймання, розрізнення та контроль власного мовлення. Порушення слухового аналізатора негативно впливає на формування всіх компонентів мовленнєвої системи, зокрема фонетико-фонематичних процесів, які є основою правильної звуковимови та оволодіння навичками читання і письма [5].

У молодшому шкільному віці відбувається активне вдосконалення фонематичного сприймання, формуються навички звукового аналізу та синтезу, удосконалюється звуковимова. Однак у дітей з порушенням слуху цей процес має специфічні особливості та потребує цілеспрямованого логопедичного супроводу.

Проблема мовленнєвого розвитку дітей з порушеннями слуху знайшла відображення у працях українських і зарубіжних науковців. Питання формування фонетико-фонематичної сторони мовлення висвітлено у дослідженнях, присвячених розвитку фонематичного слуху, звуковимови та мовленнєвого сприймання дітей з особливими освітніми потребами. Науковці наголошують, що своєчасна логопедична допомога сприяє подоланню вторинних мовленнєвих порушень та забезпечує успішну соціалізацію дитини.

Фонетико-фонематичні процеси є складною системою, що охоплює фонематичний слух, фонематичне сприймання, звуковимову, а також навички фонематичного аналізу і синтезу. Їх розвиток у дітей з порушенням слуху відбувається в умовах обмеженого або спотвореного сприймання мовленнєвих звуків, що зумовлює виникнення вторинних мовленнєвих порушень.

Розвиток фонетико-фонематичних процесів у молодших школярів з порушенням слуху є складним, багатоетапним процесом, який потребує системної та послідовної логопедичної роботи. Організація корекційно-

розвиткової діяльності повинна враховувати ступінь втрати слуху, рівень мовленнєвого розвитку, наявність слухопротезування та індивідуальні особливості дитини. У науковій та методичній літературі виокремлюють кілька взаємопов'язаних етапів розвитку фонетико-фонематичних процесів: підготовчий етап, етап формування фонематичного сприймання, етап корекції звуковимови та етап розвитку навичок фонематичного аналізу і синтезу [4].

Підготовчий етап є фундаментом для подальшого розвитку фонетико-фонематичних процесів. Його основною метою є формування слухової уваги, розвиток уміння реагувати на звуки навколишнього середовища та створення передумов для сприймання мовлення [2].

На цьому етапі логопед спрямовує роботу на розвиток здатності дитини помічати наявність або відсутність звуку, визначати його гучність, тривалість, висоту та тембр. Особливе значення має формування інтересу до звукового світу та розвиток орієнтування у звуковому середовищі.

Для реалізації зазначених завдань використовуються вправи на розпізнавання та диференціацію немовленнєвих звуків. Зокрема, дитині пропонується визначити, який музичний інструмент звучить – барабан, дзвіночок, бубон чи металофон. Поступово вправи ускладнюються: дитина повинна не лише розпізнати звук, а й визначити його силу, тривалість або послідовність.

Значна увага приділяється диференціації побутових шумів. Логопед використовує аудіозаписи або реальні предмети, пропонуючи дитині впізнати звук дверей, що зачиняються, дзвінка телефону, шуму води, кроків, шелесту паперу чи стуку олівця. Такі вправи сприяють розвитку слухової уваги та формуванню первинних навичок слухового аналізу.

Поступово до роботи включаються мовленнєві звуки: дитина вчиться реагувати на голос логопеда, розрізняти довгі та короткі звуки, визначати зміни сили голосу та інтонації [1]. Таким чином створюються передумови для формування фонематичного сприймання.

Наступним етапом є формування фонематичного сприймання, яке у дітей з порушенням слуху базується не лише на слуховому, а й на слухо-зоровому сприйманні мовлення. У зв'язку з обмеженими можливостями слухового аналізатора важливого значення набуває використання зорового каналу, зокрема читання з губ та спостереження за артикуляцією співрозмовника.

На початковому етапі роботи логопед формує вміння диференціювати голосні звуки. Найдоступнішими для сприймання є голосні [а], [о], [у], оскільки вони мають чітко виражену та візуально помітну артикуляцію. Логопед демонструє правильне положення губ і язика, використовуючи дзеркало, малюнки, артикуляційні схеми та відеоматеріали. Дитина навчається співвідносити почутий звук із його артикуляційним образом [3].

Після засвоєння голосних здійснюється перехід до диференціації приголосних. Особлива увага приділяється розрізненню фонем, близьких за акустичними та артикуляційними характеристиками. З цією метою використовуються пари слів-квазіомонімів, наприклад: коза – коса, будка – утка,

жук – звук, миска – мишка. Дитині пропонується уважно спостерігати за артикуляцією логопеда, сприймати звуковий сигнал та співвідносити його із відповідною картинкою.

Ефективним методом є використання тактильно-вібраційного контролю. При диференціації дзвінких та глухих приголосних дитина кладе руку на гортань логопеда, а потім на власну гортань, відчуваючи наявність або відсутність вібрації голосових зв'язок. Це допомагає сформувати уявлення про механізм утворення звуків та сприяє розвитку фонематичного слуху.

Поступово ускладнюються завдання: дитина вчиться визначати однакові та різні звуки, знаходити заданий звук у слові, розрізняти слова, які відрізняються лише однією фонемою.

Після формування базових навичок фонематичного сприймання розпочинається цілеспрямована робота над корекцією звуковимови [1]. У дітей з порушенням слуху цей процес має свої особливості, оскільки відсутність або недостатність слухового контролю ускладнює самостійне оволодіння правильною артикуляцією.

Постановка звуків здійснюється переважно механічним способом або за допомогою наслідування. Логопед використовує артикуляційні вправи, спеціальні зонди, шпателі, а також дзеркало, яке дозволяє дитині контролювати власні артикуляційні рухи.

Важливе місце посідає візуалізація артикуляційних процесів. Для цього застосовуються графічні схеми, профілі звуків, артикуляційні таблиці та мультимедійні засоби. Ефективними є комп'ютерні програми, у яких дитина отримує візуальний зворотний зв'язок щодо правильності вимови. Наприклад, при правильному відтворенні звука на екрані з'являється певний сигнал або анімаційний ефект, що підвищує мотивацію до занять [3].

Корекція звуковимови передбачає не лише постановку окремих звуків, а й їх автоматизацію у складах, словах, реченнях та зв'язному мовленні. Особлива увага приділяється формуванню чіткої артикуляції, координації рухів органів мовлення та розвитку мовленнєвого самоконтролю.

Важливим напрямом роботи є розвиток просодичної сторони мовлення. У дітей з порушенням слуху мовлення часто є монотонним, позбавленим логічних наголосів та інтонаційної виразності [4]. Для подолання цих труднощів логопед використовує диригування, рухи руками, ритмічні вправи, плескання в долоні, музичний супровід. Такі прийоми допомагають дитині засвоїти ритм, темп і мелодику мовлення та зробити його більш природним і виразним.

Заключним і надзвичайно важливим етапом є розвиток навичок фонематичного аналізу та синтезу, які є основою успішного оволодіння читанням і письмом.

На цьому етапі логопед формує вміння визначати кількість звуків у слові, встановлювати їх послідовність, характеризувати звуки за основними ознаками та поєднувати їх у слова.

Широко використовуються кольорові фішки, які допомагають візуалізувати звуковий склад слова. Наприклад, голосні позначаються червоним кольором,

тверді приголосні – синім, м'які – зеленим. Дитина викладає схему слова, аналізує його звукову структуру та співвідносить звук із відповідною буквою.

Ефективними є вправи на визначення позиції звука у слові: на початку, в середині або в кінці. Дитині пропонується знайти заданий звук у словах, порівняти слова за звуковим складом, замінити один звук іншим та пояснити, як змінилося значення слова.

Особливе значення має робота з розрізною азбукою. Після слухо-зорового сприйняття слова дитина складає його з окремих букв, що сприяє формуванню стійких графемно-фонемних зв'язків та розвитку навичок читання і письма.

Таким чином, поетапна організація логопедичної роботи забезпечує послідовне формування фонетико-фонематичних процесів у молодших школярів з порушенням слуху та створює передумови для успішного мовленнєвого і навчального розвитку дітей цієї категорії.

Подальші дослідження мають бути спрямовані на розробку індивідуальних стратегій навчання для дітей із кохлеарними імплантами в умовах інклюзивної освіти. Таким чином, порушення слухового сприймання різних частотних характеристик мовлення безпосередньо впливає на формування фонематичного слуху, що визначає специфіку мовленнєвого розвитку дітей з порушенням слуху та потребує цілеспрямованої корекційно-розвиткової роботи.

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ВПЛИВ «ЗЕЛЕНОГО КУРСУ» НА СТРАТЕГІЧНЕ УПРАВЛІННЯ ЕКСПОРТНОЮ ДІЯЛЬНІСТЮ ПІДПРИЄМСТВ

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Сучасний етап розвитку світового господарства характеризується глобальним зміщенням акцентів у бік сталого розвитку та кліматичної нейтральності. Європейський «Зелений курс», маючи на меті перетворення Європи на перший кліматично нейтральний континент до 2050 року, виступає не просто локальною екологічною ініціативою, а потужним драйвером трансформації всієї системи міжнародної торгівлі.

Для підприємств-експортерів, особливо з країн, що розвиваються або перебувають на етапі євроінтеграції, це означає фундаментальну зміну правил гри. Екологічні стандарти та вимоги декарбонізації стрімко еволюціонують із категорії інструментів корпоративної соціальної відповідальності (добровільних ініціатив) у жорсткі, законодавчо закріплені регуляторні бар'єри. Як наслідок, традиційні чинники міжнародної конкурентоспроможності (низька вартість робочої сили чи сировини) втрачають свою домінуючу роль, поступаючись критеріям екологічної місткості виробництва та продукту.

Найбільш відчутним та практичним інструментом «Зеленого курсу» для зовнішньоекономічної діяльності є Механізм прикордонного вуглецевого коригування (CBAM — Carbon Border Adjustment Mechanism). CBAM фактично вирівнює умови для європейських виробників, які сплачують за викиди в межах системи ETS, та імпортерів із третіх країн, де екологічне законодавство є менш суворим.

Для вітчизняних експортерів, чия продукція орієнтована на ринки ЄС (зокрема, у секторах чорної металургії, цементу, добрив, електроенергії, алюмінію та водню), впровадження CBAM створює прямі фінансові та операційні загрози. Високий рівень вуглецевої місткості традиційного виробництва призводить до додаткового фінансового навантаження на кордоні, що автоматично знижує цінову конкурентоспроможність продукції [3]. Отже, стратегічне управління експортом більше не може ігнорувати «вуглецевий слід»; оцінка екологічних ризиків стає обов'язковим елементом калькуляції експортної собівартості.

Адаптація до вимог «Зеленого курсу» вимагає від топ-менеджменту підприємств докорінного перегляду підходів до формування експортних стратегій. Традиційна реактивна модель (адаптація «постфактум» під конкретні вимоги покупця) є неефективною і загрожує повною втратою зовнішніх ринків збуту. Натомість необхідне впровадження проактивної моделі управління.

Основою такої трансформації є інтеграція ESG-критеріїв (Environmental, Social, Governance) у загальну корпоративну та експортну стратегію підприємства. Це передбачає:

– диверсифікацію експортного портфеля з фокусом на низьковуглецеві товари;

– переоцінку та реконфігурацію цільових ринків збуту з урахуванням темпів впровадження екологічного регулювання;

– зміну філософії позиціонування компанії на міжнародній арені — від «постачальника дешевої продукції» до «екологічно відповідального партнера».

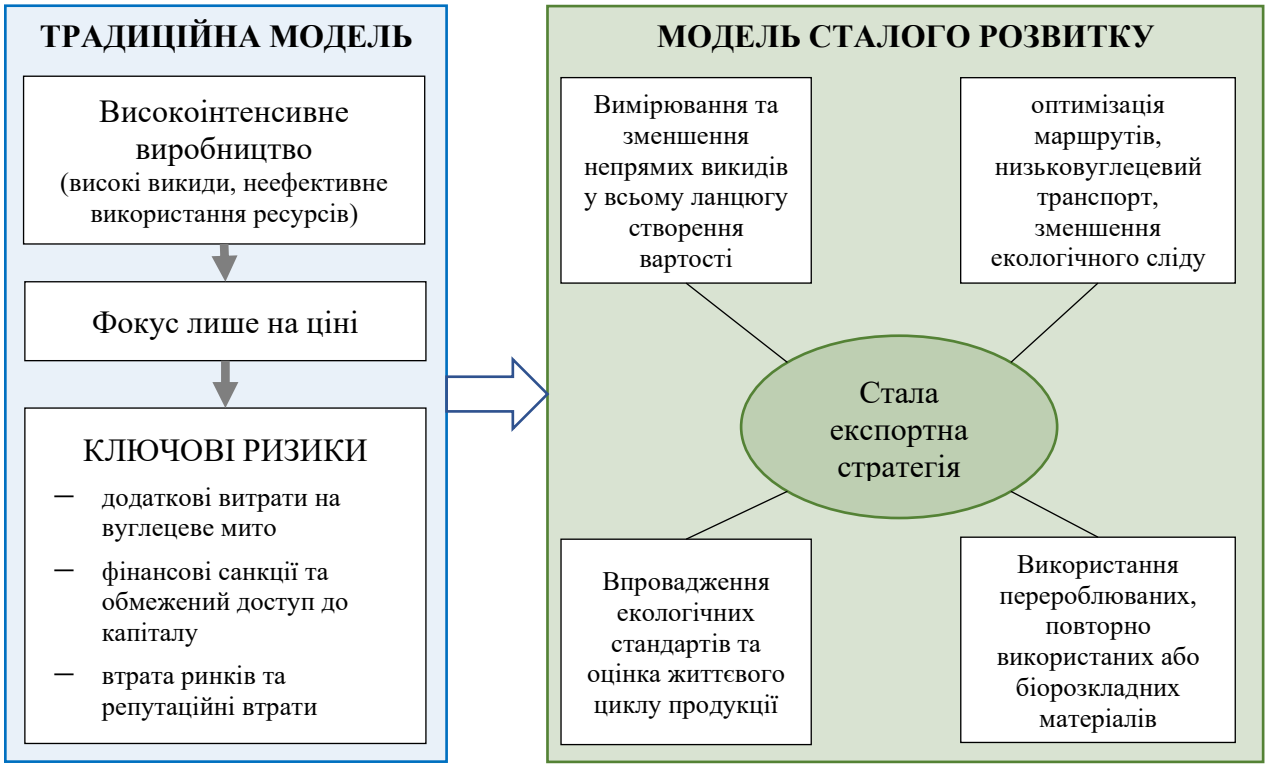

Рисунок 1 Стратегічна трансформація експортної діяльності в умовах «зеленого курсу»

Джерело: створено на основі [2,4,5]

Запропонована модель трансформації наочно демонструє, що вибір підприємства на користь того чи іншого стратегічного підходу призводить до принципово різних фінансово-економічних та ринкових наслідків.

Інерційне дотримання традиційної моделі, яка орієнтована виключно на цінову конкуренцію та ігнорування екологічних стандартів, у довгостроковій перспективі деструктивно впливає на бізнес. Через необхідність сплати

додаткових вуглецевих мит в межах CBAM та подорожчання традиційних енергоресурсів собівартість продукції зростає, що повністю нівелює колишні цінові переваги. Невідповідність екологічним вимогам створює жорсткі нетарифні бар'єри й фактично блокує експорт до преміальних географічних сегментів. Крім того, міжнародні фінансові інституції та банки дедалі частіше відмовляють у кредитуванні проектам, які не відповідають ESG-критеріям, а статус екологічно невідповідального виробника руйнує партнерські зв'язки з міжнародними брендами та веде до втрати конкурентоспроможності.

Натомість проактивна модернізація бізнес-процесів і перехід до сталої моделі управління експортом відкривають перед підприємством нові стратегічні можливості. Наявність еко-сертифікатів та низький вуглецевий слід перетворюють експортера на пріоритетного партнера для європейських контрагентів, забезпечуючи стабільний доступ до преміальних ринків ЄС та глобальних ланцюгів постачання [1]. Підприємство отримує можливість залучати спеціалізовані міжнародні гранти, пільгові зелені кредити та капітал інвесторів, орієнтованих на сталий розвиток. Екологічність та циркулярність товару дозволяють формувати вищу ринкову ціну, успішно конкурувати в нецінових параметрах, а також створювати стійку репутацію бренду, що гарантує життєздатність бізнесу в умовах жорсткого кліматичного регулювання майбутнього.

Практична реалізація оновленої експортної стратегії вимагає глибокої перебудови внутрішніх та зовнішніх бізнес-процесів підприємства. Ключовими напрямами еко-модернізації є:

- управління ланцюгами постачань;
- «зелена» логістика;
- екологічна сертифікація та маркування
- циркулярні моделі продукту

Управління ланцюгами постачань передбачає, що експортер повинен контролювати екологічність не лише власного виробництва, а й оцінювати викиди та стандарти своїх постачальників сировини й матеріалів (Scope 3 emissions)

Зелена логістика включає оптимізацію транспортних маршрутів, перехід на більш екологічні види транспорту, наприклад залізничний чи річковий замість автомобільного, а також мінімізацію порожніх пробігів з метою скорочення викидів CO_2 під час транспортування експортних вантажів

Екологічна сертифікація та маркування означає отримання міжнародно визнаних сертифікатів (ISO 14001, інвентаризація парникових газів за ISO 14064, оцінка життєвого циклу LCA), що є перепусткою на високомаржинальні ринки розвинених країн

Циркулярні моделі продукту базуються на перегляді дизайну пакування (використання біорозкладних чи придатних до вторинної переробки матеріалів) та врахуванні вимог до утилізації продукту після завершення його життєвого циклу

Підсумовуючи, можна стверджувати, що «Зелений курс» — це не тимчасовий тренд, а довгостроковий вектор розвитку світової економіки, який незворотно змінює архітектуру міжнародного менеджменту. Для підприємств-експортерів жорсткі екологічні вимоги імпортерів є водночас і кризовим викликом, і стратегічним вікном можливостей.

Підприємства, які зможуть першими модернізувати свої виробничі та логістичні потужності, впровадити системи моніторингу викидів і переорієнтувати стратегічне управління на принципи сталого розвитку, отримають суттєві конкурентні переваги. Вони не лише збережуть доступ до преміальних ринків (зокрема ЄС), а й зможуть претендувати на вигідні умови «зеленого» фінансування та залучення міжнародних інвестицій. Своєчасна екологічна трансформація експортної діяльності є єдиним можливим шляхом забезпечення довгострокової життєздатності бізнесу в умовах нової кліматичної реальності.

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HELICOBACTER PYLORI INFECTION AND IRON DEFICIENCY ANEMIA: CURRENT INSIGHTS INTO THE PATHOGENETIC RELATIONSHIP

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Abstract. *Helicobacter pylori* infection remains one of the most prevalent chronic bacterial infections worldwide and is increasingly recognized as an important extra-gastric contributor to iron deficiency anemia. Although gastrointestinal blood loss and nutritional iron deficiency are well-established causes of anemia, accumulating evidence indicates that persistent *H. pylori* infection may impair systemic iron homeostasis through multiple mechanisms, including chronic gastric inflammation, reduced gastric acid secretion, increased hepcidin expression, altered iron absorption, and bacterial competition for available iron. These complex interactions have expanded the clinical significance of *H. pylori* beyond gastroduodenal disease and have highlighted its potential role in patients with unexplained or refractory iron deficiency anemia.

This systematic literature review summarizes current evidence regarding the pathogenetic relationship between *Helicobacter pylori* infection and iron deficiency anemia and evaluates contemporary approaches to diagnosis and management. Particular attention is given to the molecular mechanisms of iron dysregulation, the influence of bacterial virulence factors, the role of gastric mucosal pathology, and the clinical effects of eradication therapy on hematological outcomes. The review also examines current international recommendations concerning *H. pylori* testing in patients with unexplained iron deficiency anemia and discusses emerging biomarkers and personalized therapeutic strategies. The available evidence supports routine consideration of *H. pylori* infection as a potentially reversible cause of iron deficiency

anemia, particularly in patients without an identifiable source of blood loss or inadequate dietary iron intake.

Keywords: *Helicobacter pylori; iron deficiency anemia; iron metabolism; hepcidin; chronic gastritis; gastric atrophy; eradication therapy; iron absorption; extra-gastric manifestations; inflammation.*

Introduction

Helicobacter pylori infection affects nearly half of the world's population and remains one of the most common chronic bacterial infections in clinical practice. Although its pathogenic role in chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma is well established, increasing attention has been directed toward its extra-gastric manifestations. Among these, iron deficiency anemia has emerged as one of the most clinically relevant conditions because of the growing body of evidence linking persistent *H. pylori* infection with impaired iron metabolism and reduced hematological recovery, particularly in patients without an identifiable source of gastrointestinal blood loss [1–3].

The relationship between *H. pylori* infection and iron deficiency anemia appears to be multifactorial. Chronic gastric inflammation may impair gastric acid secretion and reduce the bioavailability of dietary iron, while progressive atrophic gastritis further compromises iron absorption within the upper gastrointestinal tract. In addition, inflammatory activation promotes increased hepcidin production, limiting intestinal iron uptake and macrophage iron release. Experimental studies also suggest that *H. pylori* competes directly with the host for available iron and that highly virulent bacterial strains may intensify disturbances in systemic iron homeostasis through enhanced inflammatory activity and increased metabolic demand [2–5].

Recent investigations have expanded understanding of the molecular mechanisms underlying this association. Virulence factors such as cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) have been implicated in persistent mucosal inflammation, epithelial injury, and alterations of iron transport pathways. At the same time, advances in molecular microbiology and gastroenterology have demonstrated that eradication of *H. pylori* frequently results in significant improvement of hemoglobin concentration, serum ferritin, and transferrin saturation, particularly when combined with appropriate iron supplementation. These observations have strengthened the concept that persistent *H. pylori* infection should be considered among the potentially reversible causes of unexplained or refractory iron deficiency anemia [4–7].

Recognition of the pathogenetic relationship between *H. pylori* infection and iron deficiency anemia has important implications for contemporary gastroenterological practice. International clinical guidelines increasingly recommend investigation for *H. pylori* in selected patients with unexplained iron deficiency, while growing interest in personalized medicine has stimulated research into biomarkers capable of identifying individuals most likely to benefit from eradication therapy. Nevertheless, important uncertainties remain regarding the relative contribution of bacterial, host, and environmental factors to iron dysregulation across different patient populations. The

aim of the study was to summarize current evidence regarding the pathogenetic relationship between *Helicobacter pylori* infection and iron deficiency anemia and to evaluate contemporary concepts of diagnosis and clinical management.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding the pathogenetic relationship between *Helicobacter pylori* infection and iron deficiency anemia. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier international consensus reports and landmark studies were included only when they provided essential evidence concerning the mechanisms of iron metabolism, *H. pylori* pathogenesis, or clinical management of iron deficiency anemia.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, and evidence-based clinical practice guidelines addressing *Helicobacter pylori*, iron metabolism, chronic gastritis, iron deficiency anemia, and eradication therapy. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on pathogenetic mechanisms, diagnostic approaches, hematological outcomes, and the effectiveness of eradication therapy in restoring iron homeostasis.

Results

Accumulating evidence supports a clinically significant association between *Helicobacter pylori* infection and iron deficiency anemia, particularly in patients without identifiable gastrointestinal bleeding or other established causes of iron deficiency. Multiple systematic reviews and meta-analyses have demonstrated a higher prevalence of *H. pylori* infection among individuals with unexplained iron deficiency anemia compared with healthy controls, while successful eradication has been associated with significant improvements in hemoglobin concentration, serum ferritin, transferrin saturation, and other hematological indices. These observations have established *H. pylori* infection as an important reversible contributor to iron deficiency in both adult and pediatric populations [8–10].

The mechanisms linking *H. pylori* infection with iron deficiency are multifactorial and involve complex interactions between bacterial virulence, chronic inflammation, and host iron metabolism. Persistent gastric colonization induces chronic active gastritis, stimulates inflammatory cytokine production, and increases hepatic hepcidin synthesis, thereby suppressing intestinal iron absorption and reducing iron release from macrophage stores. Simultaneously, chronic inflammation disrupts the expression of iron transport proteins, including ferroportin and divalent metal transporter-1, further impairing systemic iron homeostasis. These mechanisms may persist even in the absence of overt gastrointestinal bleeding [9–12].

Direct bacterial competition for iron represents another important pathogenic mechanism. *Helicobacter pylori* requires iron for survival and expresses multiple outer membrane proteins, iron-binding proteins, and transport systems that facilitate

acquisition of host iron. Experimental studies have demonstrated that highly virulent strains possess enhanced capacity for iron uptake, allowing bacterial persistence under conditions of limited iron availability. Consequently, infection may contribute to progressive depletion of iron stores, particularly in individuals with marginal dietary iron intake, increased physiological requirements, or impaired gastrointestinal absorption [10–13].

Increasing evidence also implicates bacterial virulence factors in the development of iron deficiency. Strains expressing cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) induce more severe gastric inflammation, greater epithelial injury, and accelerated progression toward multifocal atrophic gastritis. Progressive loss of acid-secreting parietal cells results in hypochlorhydria, impaired solubilization of dietary non-heme iron, and reduced intestinal iron absorption. Chronic gastric mucosal injury may therefore amplify the metabolic consequences of persistent infection while further compromising restoration of normal iron balance [11–15].

From a gastroenterological perspective, evaluation of patients with unexplained or refractory iron deficiency anemia increasingly includes investigation for *H. pylori* infection. Current international recommendations support non-invasive testing using the urea breath test or stool antigen test in appropriate clinical settings, while upper gastrointestinal endoscopy with gastric biopsy remains indicated in selected patients with alarm symptoms, suspected premalignant gastric lesions, recurrent anemia, or treatment-resistant disease. Histopathological assessment additionally provides valuable information regarding the severity of gastritis, the presence of atrophic changes, intestinal metaplasia, and bacterial colonization, all of which may influence clinical management [12–16].

Eradication therapy has demonstrated consistent hematological benefits across numerous clinical studies. Combined eradication treatment and iron supplementation generally produce greater improvements in hemoglobin concentration and ferritin levels than iron replacement alone, particularly in patients with persistent infection and depleted iron stores. In many individuals, normalization of iron metabolism continues after successful bacterial eradication, suggesting that elimination of the underlying inflammatory stimulus restores physiological mechanisms of iron absorption and utilization. These findings reinforce the importance of identifying *H. pylori* as a potentially reversible cause of iron deficiency anemia [13–18].

Recent investigations have explored novel biomarkers capable of improving diagnostic accuracy and monitoring therapeutic response. Hepcidin, serum ferritin, soluble transferrin receptor, reticulocyte hemoglobin content, inflammatory cytokines, and markers of gastric mucosal injury have shown promising associations with disease activity and treatment outcomes. Molecular techniques for detection of bacterial virulence genes and antimicrobial resistance may further facilitate individualized therapeutic strategies, particularly in regions with high rates of antibiotic resistance and recurrent treatment failure [15–19].

Despite substantial advances, several important challenges remain. Considerable heterogeneity exists regarding patient age, severity of gastritis, nutritional status, geographic variation, bacterial strain characteristics, and diagnostic criteria used across

published studies. Furthermore, iron deficiency frequently results from multiple interacting mechanisms, making it difficult to determine the precise contribution of *H. pylori* infection in individual patients. Nevertheless, current evidence consistently supports incorporation of *H. pylori* testing into the diagnostic evaluation of unexplained or recurrent iron deficiency anemia and highlights the importance of timely eradication therapy as part of a comprehensive gastroenterological management strategy [16–20].

Discussion

The findings of the present review indicate that *Helicobacter pylori* infection should be considered an important and potentially reversible contributor to iron deficiency anemia, particularly in patients without overt gastrointestinal bleeding or other identifiable causes of iron depletion. Contemporary evidence suggests that the relationship between persistent *H. pylori* infection and iron deficiency extends beyond chronic gastritis alone and involves a complex interaction of inflammatory, metabolic, and microbiological mechanisms. This broader understanding has strengthened recognition of *H. pylori* infection as an extra-gastric disorder with clinically significant hematological consequences [8–11].

A consistent observation across recent investigations is that disruption of systemic iron homeostasis results from several complementary pathogenic pathways. Chronic gastric inflammation impairs gastric acid secretion and reduces dietary iron bioavailability, while inflammatory activation promotes increased hepcidin production, limiting intestinal iron absorption and iron mobilization from tissue stores. Simultaneously, bacterial competition for iron and the effects of highly virulent strains further aggravate iron depletion. These mechanisms help explain why iron deficiency may persist despite adequate dietary intake or oral iron supplementation when the underlying infection remains untreated [10–14].

From a gastroenterological perspective, growing evidence supports broader consideration of *H. pylori* testing in the evaluation of unexplained or refractory iron deficiency anemia. The diagnostic value of non-invasive testing, including the urea breath test and stool antigen testing, has increased substantially because these methods provide high diagnostic accuracy while avoiding unnecessary endoscopic procedures in appropriately selected patients. Conversely, upper gastrointestinal endoscopy remains essential when alarm symptoms, recurrent anemia, advanced age, or suspected premalignant gastric pathology warrant direct assessment of the gastric mucosa. Such an individualized diagnostic strategy improves both diagnostic efficiency and therapeutic decision-making [12–16].

Another important finding is the consistent hematological benefit observed following successful eradication therapy. Numerous studies demonstrate that eradication combined with iron supplementation achieves greater improvement in hemoglobin concentration and restoration of iron stores than iron therapy alone, particularly in patients with persistent infection and chronic gastritis. These observations indicate that correction of iron deficiency requires not only replacement of depleted iron stores but also elimination of the underlying pathological process responsible for impaired iron metabolism. Consequently, eradication therapy should be

regarded as an integral component of management in appropriately selected patients with *H. pylori*-associated iron deficiency anemia [14–18].

Despite substantial progress, several important limitations remain within the available evidence. Considerable variability exists among published studies regarding patient demographics, nutritional status, prevalence of atrophic gastritis, bacterial virulence profiles, antimicrobial resistance, and definitions of iron deficiency anemia. Furthermore, iron metabolism is influenced by numerous physiological and pathological factors, making it difficult to determine the precise contribution of *H. pylori* infection in every clinical setting. Additional well-designed prospective studies are therefore required to clarify the relative importance of individual pathogenetic mechanisms and to identify patients who derive the greatest benefit from eradication therapy [15–19].

Future research should focus on integrating molecular microbiology, host inflammatory biomarkers, gastric mucosal assessment, and personalized therapeutic approaches to improve diagnostic accuracy and treatment outcomes. Greater understanding of bacterial virulence factors, host genetic susceptibility, hepcidin regulation, and the gastric microbiome may facilitate development of precision medicine strategies for patients with *H. pylori*-associated iron deficiency anemia. Such advances are expected to optimize patient selection for eradication therapy, improve restoration of iron homeostasis, and reduce the long-term burden of recurrent or treatment-resistant iron deficiency [17–20].

CONCLUSION

Helicobacter pylori infection is increasingly recognized as a clinically significant and potentially reversible cause of iron deficiency anemia through its effects on gastric physiology, systemic inflammation, and iron metabolism. Current evidence demonstrates that chronic gastric inflammation, impaired iron absorption, increased hepcidin activity, and bacterial competition for iron collectively contribute to the development and persistence of iron deficiency, particularly in patients with unexplained or refractory anemia. Recognition of these pathogenetic mechanisms supports routine consideration of *H. pylori* infection during the diagnostic evaluation of iron deficiency anemia when common causes have been excluded.

Future research should focus on improving risk stratification through the identification of reliable biomarkers of iron dysregulation, characterization of bacterial virulence profiles, and refinement of personalized treatment strategies. Integration of modern diagnostic methods with timely eradication therapy and appropriate iron replacement may improve hematological recovery, reduce recurrence of iron deficiency, and optimize long-term clinical outcomes in patients with *Helicobacter pylori*-associated iron deficiency anemia.

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LONG-TERM CARDIOVASCULAR CONSEQUENCES OF HYPERTENSIVE DISORDERS OF PREGNANCY: CONTEMPORARY PERSPECTIVE

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Abstract. Hypertensive disorders of pregnancy are among the leading causes of maternal and perinatal morbidity worldwide and are increasingly recognized as important predictors of future cardiovascular disease in women. Although clinical manifestations often resolve after delivery, accumulating evidence indicates that pregnancy complicated by gestational hypertension or preeclampsia may reveal an underlying predisposition to long-term vascular dysfunction and adverse cardiometabolic remodeling. Women with a history of hypertensive disorders of pregnancy demonstrate substantially higher risks of chronic hypertension, ischemic heart disease, heart failure, stroke, atrial fibrillation, chronic kidney disease, and premature cardiovascular mortality compared with those who experience normotensive pregnancies. These observations have shifted the perception of hypertensive pregnancy complications from transient obstetric disorders to early indicators of lifelong cardiovascular risk.

This systematic literature review summarizes current evidence regarding the long-term cardiovascular consequences of hypertensive disorders of pregnancy and examines contemporary approaches to risk assessment, long-term surveillance, and preventive management. Particular attention is given to the mechanisms of endothelial dysfunction, persistent vascular injury, myocardial remodeling, chronic inflammation, and metabolic alterations that contribute to future cardiovascular disease. The review also evaluates the role of cardiovascular imaging, circulating biomarkers, and multidisciplinary postpartum follow-up in identifying women at increased risk. The available evidence supports the integration of pregnancy history into routine

cardiovascular risk assessment and highlights the importance of individualized preventive strategies aimed at reducing long-term cardiovascular morbidity and mortality in women with previous hypertensive disorders of pregnancy.

Keywords: *hypertensive disorders of pregnancy; preeclampsia; gestational hypertension; cardiovascular disease; endothelial dysfunction; myocardial remodeling; cardiovascular risk; postpartum follow-up; cardiovascular prevention; women's cardiovascular health.*

Introduction

Hypertensive disorders of pregnancy (HDP) affect approximately 5–10% of pregnancies worldwide and remain one of the leading causes of maternal and perinatal morbidity and mortality. This group of conditions includes gestational hypertension, preeclampsia, eclampsia, and chronic hypertension with superimposed preeclampsia, all of which are associated with significant obstetric complications and adverse fetal outcomes. Traditionally, these disorders were regarded as pregnancy-specific conditions that resolved after delivery; however, growing evidence demonstrates that their clinical significance extends well beyond the postpartum period, with important implications for long-term maternal cardiovascular health [1–3].

Accumulating epidemiological data indicate that women with a history of HDP experience substantially higher risks of chronic hypertension, ischemic heart disease, heart failure, atrial fibrillation, stroke, chronic kidney disease, and premature cardiovascular mortality later in life. Although the precise mechanisms underlying these associations remain incompletely understood, persistent endothelial dysfunction, vascular inflammation, metabolic dysregulation, oxidative stress, and adverse cardiac remodeling are believed to play central roles. Pregnancy has therefore been increasingly recognized as a physiological stress test capable of revealing an underlying predisposition to future cardiovascular disease years before conventional risk factors become clinically apparent [2–5].

Recent advances in cardiovascular medicine have expanded understanding of the structural and functional cardiac changes that persist following hypertensive pregnancy disorders. Echocardiography, cardiac magnetic resonance imaging, arterial stiffness assessment, and circulating biomarkers have demonstrated evidence of sustained myocardial remodeling, impaired vascular function, and subclinical cardiac dysfunction long after delivery. These findings have strengthened the concept that pregnancy history should be incorporated into cardiovascular risk assessment and have prompted increasing collaboration between obstetricians, cardiologists, and primary care physicians in the long-term follow-up of affected women [4–7].

Recognition of hypertensive disorders of pregnancy as early markers of future cardiovascular disease has important implications for preventive medicine. Timely postpartum risk assessment, aggressive modification of cardiovascular risk factors, and structured long-term surveillance may provide opportunities to reduce the incidence of major cardiovascular events in this high-risk population. Nevertheless, important questions remain regarding optimal screening strategies, duration of follow-up, and implementation of individualized preventive interventions. The aim of the study was to summarize current evidence regarding the long-term cardiovascular consequences

of hypertensive disorders of pregnancy and to evaluate contemporary approaches to cardiovascular risk assessment, surveillance, and prevention in women with previous hypertensive pregnancy complications.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding the long-term cardiovascular consequences of hypertensive disorders of pregnancy and current approaches to risk assessment, surveillance, and prevention. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier international guidelines and landmark studies were included only when they provided essential evidence concerning the pathophysiology or long-term cardiovascular implications of hypertensive disorders of pregnancy.

Eligible publications included systematic reviews, meta-analyses, randomized and non-randomized clinical studies, prospective and retrospective cohort studies, observational investigations, and evidence-based clinical practice guidelines addressing cardiovascular outcomes following gestational hypertension, preeclampsia, and related hypertensive pregnancy disorders. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on cardiovascular risk, myocardial and vascular remodeling, diagnostic assessment, prognostic biomarkers, and preventive strategies during long-term postpartum follow-up.

Results

Hypertensive disorders of pregnancy (HDP) are now recognized as independent predictors of future cardiovascular disease rather than transient obstetric complications confined to pregnancy. Large population-based cohort studies and meta-analyses consistently demonstrate that women with previous gestational hypertension or preeclampsia have a substantially increased lifetime risk of chronic hypertension, ischemic heart disease, heart failure, stroke, atrial fibrillation, and cardiovascular mortality compared with women who experienced normotensive pregnancies. The magnitude of risk is greatest following early-onset or severe preeclampsia, recurrent hypertensive disorders, and pregnancies complicated by fetal growth restriction or preterm delivery, suggesting that disease severity is closely associated with subsequent cardiovascular outcomes [8–10].

Persistent endothelial dysfunction represents one of the principal biological mechanisms linking HDP with long-term cardiovascular disease. Pregnancy complicated by placental malperfusion is associated with sustained activation of inflammatory pathways, oxidative stress, impaired nitric oxide bioavailability, and persistent vascular injury that may continue for years after delivery. These alterations contribute to progressive arterial stiffness, microvascular dysfunction, accelerated atherosclerosis, and impaired vascular repair, thereby increasing susceptibility to future cardiovascular events even in relatively young women without conventional cardiovascular risk factors [9–12].

Structural and functional cardiac remodeling has been increasingly documented following hypertensive pregnancy disorders. Echocardiographic studies demonstrate persistent left ventricular hypertrophy, impaired diastolic relaxation, subtle systolic dysfunction identified by global longitudinal strain analysis, and increased left atrial volume long after pregnancy. Cardiac magnetic resonance imaging has further identified diffuse myocardial fibrosis, altered ventricular geometry, and evidence of persistent myocardial remodeling in selected high-risk populations. These findings indicate that cardiovascular alterations frequently persist beyond the resolution of pregnancy-related hypertension and may precede symptomatic cardiovascular disease by many years [10–13].

Long-term cardiovascular risk after HDP extends beyond the heart and vasculature to include a broad spectrum of cardiometabolic disorders. Women with previous preeclampsia demonstrate increased incidence of chronic kidney disease, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, and obesity, all of which further amplify cardiovascular risk throughout later life. Contemporary evidence therefore supports the concept that hypertensive pregnancy disorders should be regarded as markers of generalized vascular and metabolic susceptibility rather than isolated obstetric events [11–15].

From a cardiological perspective, pregnancy provides a unique opportunity to identify women who may benefit from early cardiovascular prevention. Current recommendations increasingly advocate systematic postpartum cardiovascular evaluation, including regular blood pressure monitoring, assessment of body mass index, lipid profile, glucose metabolism, renal function, and lifestyle-related risk factors. In selected patients, echocardiography, assessment of arterial stiffness, coronary artery calcium scoring, or advanced cardiovascular imaging may provide additional information regarding subclinical cardiovascular injury and facilitate individualized risk stratification [12–17].

Recent advances in cardiovascular imaging and biomarker research have substantially improved the detection of early myocardial and vascular abnormalities after hypertensive pregnancy disorders. Speckle-tracking echocardiography enables identification of subtle myocardial dysfunction despite preserved ejection fraction, while cardiac magnetic resonance imaging provides detailed characterization of myocardial fibrosis and ventricular remodeling. Circulating biomarkers including high-sensitivity cardiac troponins, N-terminal pro-B-type natriuretic peptide, soluble fms-like tyrosine kinase-1, placental growth factor, and markers of endothelial dysfunction have shown promising associations with long-term cardiovascular risk, although their routine clinical application requires further validation [13–18].

Prevention has become a central component of long-term cardiovascular care following HDP. Lifestyle modification, optimization of blood pressure, weight management, regular physical activity, smoking cessation, dietary counseling, and early treatment of dyslipidemia and impaired glucose metabolism contribute to reducing future cardiovascular risk. Increasing attention has also been directed toward structured cardio-obstetric follow-up programs that facilitate coordinated care between

obstetricians, cardiologists, primary care physicians, and other specialists during the years following pregnancy [15–19].

Despite growing recognition of HDP as a major cardiovascular risk factor, several important challenges remain. Awareness among both healthcare professionals and patients remains suboptimal, resulting in inadequate long-term surveillance after delivery. Considerable variability persists regarding the timing, frequency, and intensity of postpartum cardiovascular assessment across healthcare systems, and standardized follow-up pathways have not yet been universally adopted. Nevertheless, the current body of evidence consistently supports the integration of pregnancy history into cardiovascular risk assessment and reinforces the importance of early multidisciplinary prevention strategies aimed at reducing long-term cardiovascular morbidity and mortality in women with previous hypertensive disorders of pregnancy [16–20].

Discussion

The findings of the present review reinforce the concept that hypertensive disorders of pregnancy should be regarded as early manifestations of future cardiovascular vulnerability rather than isolated obstetric complications. Accumulating evidence demonstrates that women who develop gestational hypertension or preeclampsia experience persistent vascular and myocardial alterations that substantially increase their lifetime risk of cardiovascular disease. These observations support the transition from a pregnancy-centered approach to a life-course model of cardiovascular prevention in women, in which pregnancy history serves as an important determinant of long-term cardiovascular risk [8–11].

A consistent finding across contemporary studies is the persistence of endothelial dysfunction and adverse cardiovascular remodeling long after delivery. Although blood pressure frequently normalizes during the postpartum period, many women continue to exhibit impaired vascular function, increased arterial stiffness, subclinical myocardial dysfunction, and chronic low-grade inflammation. These abnormalities may explain why cardiovascular events occur years or even decades after the index pregnancy and emphasize that clinical recovery following delivery does not necessarily indicate complete restoration of cardiovascular health [10–14].

From a cardiological perspective, pregnancy complicated by hypertensive disorders offers a valuable opportunity for early identification of women at increased cardiovascular risk before the development of overt cardiovascular disease. Contemporary imaging techniques, including speckle-tracking echocardiography and cardiac magnetic resonance imaging, have improved the detection of subclinical myocardial abnormalities, while circulating biomarkers may further refine individual risk assessment. Integration of these diagnostic tools into postpartum cardiovascular evaluation has the potential to identify high-risk women who may benefit from earlier preventive intervention and closer longitudinal surveillance [12–16].

Equally important is the role of multidisciplinary postpartum care. Long-term management should not conclude with resolution of pregnancy-related hypertension but should include structured collaboration between obstetricians, cardiologists, primary care physicians, endocrinologists, and nephrologists when appropriate.

Regular assessment of blood pressure, metabolic status, renal function, body weight, and lifestyle-related risk factors allows implementation of individualized preventive measures before irreversible cardiovascular damage develops. Such coordinated follow-up represents one of the most promising strategies for reducing future cardiovascular morbidity in this population [14–18].

Despite considerable advances, several limitations remain within the available evidence. Published studies differ with respect to diagnostic criteria, duration of follow-up, severity of hypertensive disorders, adjustment for traditional cardiovascular risk factors, and definitions of long-term outcomes, limiting direct comparison between investigations. Furthermore, although observational evidence consistently demonstrates strong associations between hypertensive pregnancy disorders and future cardiovascular disease, prospective interventional studies evaluating optimal surveillance strategies and preventive interventions remain comparatively limited [15–19].

Future research should focus on developing standardized postpartum cardiovascular follow-up protocols, validating multimodal risk prediction models, and identifying biomarkers capable of improving individualized risk stratification. Greater integration of cardiovascular imaging, molecular biomarkers, artificial intelligence, and digital health technologies may facilitate earlier detection of subclinical cardiovascular disease and support precision prevention. Continued collaboration between cardiology and obstetrics will be essential for translating current evidence into effective long-term clinical strategies that improve cardiovascular outcomes for women with previous hypertensive disorders of pregnancy [17–20].

CONCLUSION

Hypertensive disorders of pregnancy are now recognized as important early indicators of future cardiovascular disease rather than complications limited to the gestational period. The available evidence demonstrates that women with a history of gestational hypertension or preeclampsia have a substantially increased long-term risk of chronic hypertension, ischemic heart disease, heart failure, stroke, chronic kidney disease, and other cardiometabolic disorders. Persistent endothelial dysfunction, vascular injury, and myocardial remodeling appear to represent the principal biological mechanisms underlying this increased cardiovascular susceptibility. Recognition of pregnancy history as an integral component of cardiovascular risk assessment provides an opportunity for earlier identification of high-risk women and implementation of timely preventive strategies.

Future efforts should focus on establishing standardized postpartum cardiovascular surveillance programs, improving multidisciplinary collaboration between obstetricians and cardiologists, and validating novel imaging and molecular biomarkers for individualized risk prediction. Integration of pregnancy history into routine cardiovascular prevention, together with early lifestyle modification and targeted management of modifiable risk factors, may reduce long-term cardiovascular morbidity and improve lifelong cardiovascular health in women with previous hypertensive disorders of pregnancy.

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OBSTRUCTIVE SLEEP APNEA AND CARDIOVASCULAR RISK: CURRENT EVIDENCE, PATHOPHYSIOLOGICAL MECHANISMS, AND CLINICAL IMPLICATIONS

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Abstract. Obstructive sleep apnea (OSA) is one of the most common sleep-related breathing disorders and has emerged as an independent risk factor for cardiovascular morbidity and mortality. Recurrent episodes of upper airway obstruction during sleep result in intermittent hypoxia, sleep fragmentation, sympathetic nervous system activation, oxidative stress, systemic inflammation, endothelial dysfunction, and metabolic disturbances that collectively promote cardiovascular injury. Growing evidence demonstrates that OSA is strongly associated with arterial hypertension, coronary artery disease, heart failure, atrial fibrillation, stroke, pulmonary hypertension, and sudden cardiac death. Early recognition of OSA has therefore become an important component of cardiovascular risk assessment and long-term prevention strategies.

This systematic literature review summarizes current evidence regarding the pathophysiological mechanisms linking obstructive sleep apnea with cardiovascular disease, the clinical consequences of untreated OSA, contemporary diagnostic approaches, and evidence-based therapeutic interventions. Particular attention is given to multimodal cardiovascular assessment, polysomnography, advanced cardiac imaging, circulating biomarkers, continuous positive airway pressure therapy, and emerging applications of artificial intelligence and digital health technologies for individualized risk stratification. Current evidence supports routine screening for OSA in patients at high cardiovascular risk and emphasizes multidisciplinary management to reduce cardiovascular complications and improve long-term clinical outcomes.

Keywords: *obstructive sleep apnea; cardiovascular disease; intermittent hypoxia; arterial hypertension; atrial fibrillation; heart failure; endothelial dysfunction; continuous positive airway pressure; cardiovascular risk; polysomnography.*

Introduction

Obstructive sleep apnea (OSA) is one of the most prevalent chronic sleep-related breathing disorders and has become an important public health concern owing to its high prevalence and significant cardiovascular consequences. Current epidemiological studies estimate that moderate-to-severe OSA affects hundreds of millions of adults worldwide, while a substantial proportion of cases remain undiagnosed. Delayed diagnosis contributes to persistent intermittent hypoxia, recurrent nocturnal arousals, and progressive systemic complications that substantially increase cardiovascular morbidity, mortality, and healthcare utilization. Consequently, OSA is now recognized not only as a respiratory disorder but also as an independent cardiovascular risk factor requiring multidisciplinary management [1–3].

From the perspective of otorhinolaryngology, OSA develops primarily because of recurrent collapse of the upper airway during sleep. Anatomical narrowing of the pharyngeal airway caused by obesity, adenotonsillar hypertrophy, macroglossia, elongated soft palate, nasal obstruction, craniofacial abnormalities, and reduced neuromuscular tone plays a central role in airway instability. Chronic nasal obstruction, septal deviation, inferior turbinate hypertrophy, chronic rhinosinusitis, and other upper airway disorders may further increase airway resistance and aggravate nocturnal respiratory events. Modern otorhinolaryngological assessment therefore extends beyond identification of anatomical abnormalities and includes dynamic evaluation of upper airway collapse to determine the most appropriate therapeutic strategy, including continuous positive airway pressure therapy, oral appliances, or upper airway surgery [2–5].

From a cardiovascular perspective, recurrent episodes of apnea and hypopnea initiate a complex cascade of pathophysiological responses characterized by intermittent hypoxia, oxidative stress, sympathetic nervous system activation, endothelial dysfunction, systemic inflammation, intrathoracic pressure fluctuations, and metabolic dysregulation. These mechanisms contribute to persistent arterial hypertension, vascular remodeling, accelerated atherosclerosis, myocardial remodeling, electrical instability, and impaired cardiac function. Numerous prospective studies have demonstrated that untreated OSA is independently associated with resistant hypertension, coronary artery disease, atrial fibrillation, chronic heart failure, pulmonary hypertension, ischemic stroke, and sudden cardiac death. The severity of cardiovascular risk increases progressively with higher apnea–hypopnea index values, greater nocturnal oxygen desaturation, and prolonged cumulative hypoxic burden [4–7].

Growing recognition of the close interaction between upper airway pathology and cardiovascular disease has shifted clinical practice toward integrated multidisciplinary management involving otorhinolaryngologists, cardiologists, sleep medicine specialists, pulmonologists, and neurologists. Advances in polysomnography, drug-induced sleep endoscopy, ambulatory cardiorespiratory monitoring, echocardiography,

cardiac magnetic resonance imaging, and circulating biomarkers have substantially improved risk stratification and individualized treatment planning. The aim of the study was to summarize current evidence regarding the pathophysiological mechanisms linking obstructive sleep apnea with cardiovascular disease and to evaluate contemporary diagnostic and therapeutic approaches from the perspectives of otorhinolaryngology and cardiology.

Materials and Methods

This study was conducted as a systematic literature review to evaluate current evidence regarding the relationship between obstructive sleep apnea and cardiovascular risk, with particular emphasis on pathophysiological mechanisms, clinical manifestations, and contemporary diagnostic and therapeutic approaches. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies were included only when they established fundamental concepts regarding obstructive sleep apnea or cardiovascular pathophysiology.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, clinical practice guidelines, and international consensus statements addressing obstructive sleep apnea, cardiovascular disease, polysomnography, cardiac imaging, continuous positive airway pressure therapy, and cardiovascular outcomes. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance were excluded. The selected literature was critically analyzed with emphasis on pathophysiological mechanisms, cardiovascular complications, diagnostic methods, treatment effectiveness, and long-term clinical outcomes.

Results

Obstructive sleep apnea (OSA) develops as a consequence of recurrent collapse of the upper airway during sleep and represents one of the most important disorders encountered in contemporary otorhinolaryngology. The anatomical substrate of airway obstruction differs considerably among patients and frequently includes septal deviation, inferior turbinate hypertrophy, chronic rhinosinusitis, adenoid or tonsillar hypertrophy, elongated soft palate, macroglossia, enlarged tongue base, and craniofacial abnormalities. Obesity further aggravates airway narrowing through fat deposition within the parapharyngeal tissues, while age-related reduction in pharyngeal muscle tone increases airway collapsibility. Endoscopic studies demonstrate that obstruction may occur at multiple anatomical levels simultaneously, emphasizing the heterogeneous nature of OSA and the need for individualized anatomical assessment before treatment selection [8–10].

Comprehensive otorhinolaryngological evaluation has become an essential component of OSA diagnosis because identification of the predominant site of airway collapse directly influences therapeutic strategy. Drug-induced sleep endoscopy (DISE) has emerged as the reference method for dynamic visualization of upper airway obstruction during pharmacologically induced sleep, allowing classification of collapse

at the velum, oropharynx, tongue base, and epiglottis. In combination with flexible nasopharyngoscopy, nasal endoscopy, cephalometric analysis, cone-beam computed tomography, and upper airway magnetic resonance imaging, DISE significantly improves patient selection for surgical intervention and predicts postoperative outcomes more accurately than awake examination alone [9–12].

The severity of upper airway obstruction is quantified using overnight polysomnography, which remains the diagnostic gold standard for OSA. The apnea–hypopnea index (AHI), oxygen desaturation index (ODI), cumulative hypoxic burden, minimum nocturnal oxygen saturation, arousal index, and sleep architecture provide objective assessment of disease severity. Current classifications define mild OSA as AHI 5–14 events/hour, moderate OSA as 15–29 events/hour, and severe OSA as ≥30 events/hour. Recent investigations suggest that cumulative nocturnal hypoxic burden and oxygen desaturation metrics correlate more closely with cardiovascular outcomes than AHI alone, indicating that physiological consequences of apnea may be more important than event frequency [10–13].

Treatment strategies in otorhinolaryngology are increasingly individualized according to anatomical characteristics and disease severity. Continuous positive airway pressure (CPAP) remains the first-line treatment for moderate and severe OSA; however, upper airway surgery plays a crucial role in selected patients with correctable anatomical obstruction. Septoplasty, turbinate reduction, adenotonsillectomy, uvulopalatopharyngoplasty, expansion sphincter pharyngoplasty, transoral robotic surgery, tongue-base reduction, maxillomandibular advancement, and hypoglossal nerve stimulation have demonstrated favorable outcomes in carefully selected patients. Weight reduction, positional therapy, oral mandibular advancement devices, and combined multimodal treatment further improve long-term airway patency and treatment adherence [11–15].

The cardiovascular consequences of OSA arise from repetitive cycles of intermittent hypoxia and reoxygenation that initiate persistent sympathetic activation, oxidative stress, systemic inflammation, endothelial dysfunction, platelet activation, and vascular remodeling. These mechanisms promote increased arterial stiffness, impaired nitric oxide bioavailability, activation of the renin–angiotensin–aldosterone system, myocardial fibrosis, and accelerated atherosclerosis. Recurrent negative intrathoracic pressure during obstructive events further increases left ventricular afterload and myocardial oxygen demand, contributing to progressive structural and functional cardiac remodeling [12–16].

Strong evidence now supports OSA as an independent risk factor for multiple cardiovascular diseases. Patients with moderate-to-severe OSA demonstrate significantly higher rates of arterial hypertension, particularly resistant hypertension, coronary artery disease, heart failure, atrial fibrillation, ventricular arrhythmias, pulmonary hypertension, ischemic stroke, and cardiovascular mortality. Severe OSA has been associated with a two- to threefold increase in the risk of atrial fibrillation recurrence after catheter ablation and a substantially greater likelihood of recurrent cardiovascular events following myocardial infarction or ischemic stroke. The magnitude of cardiovascular risk closely correlates with nocturnal hypoxic burden,

oxygen desaturation severity, and cumulative duration of sleep-disordered breathing [13–17].

Modern cardiovascular evaluation of patients with OSA extends beyond routine clinical assessment. Echocardiography frequently demonstrates left ventricular hypertrophy, diastolic dysfunction, right ventricular remodeling, pulmonary artery pressure elevation, and left atrial enlargement. Cardiac magnetic resonance imaging provides highly accurate assessment of myocardial fibrosis and ventricular remodeling, while ambulatory blood pressure monitoring identifies nocturnal hypertension and non-dipping blood pressure patterns that are highly prevalent among patients with OSA. Biomarkers including high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-α, NT-proBNP, high-sensitivity cardiac troponins, and markers of oxidative stress further contribute to cardiovascular risk stratification [15–19].

Accumulating evidence indicates that effective treatment of OSA favorably influences cardiovascular health. Continuous positive airway pressure therapy improves nocturnal oxygenation, reduces sympathetic activity, lowers blood pressure, decreases atrial fibrillation recurrence, improves endothelial function, and partially reverses cardiac remodeling in adherent patients. Combined management incorporating weight reduction, optimization of cardiometabolic risk factors, and treatment of upper airway obstruction produces the greatest cardiovascular benefit. Emerging artificial intelligence algorithms integrating polysomnographic parameters, cardiovascular imaging, wearable sensor data, and electronic health records are expected to enhance individualized cardiovascular risk prediction and optimize long-term management of patients with obstructive sleep apnea [17–20].

Discussion

The findings of the present review demonstrate that obstructive sleep apnea should be regarded as a systemic disorder with substantial cardiovascular consequences rather than an isolated disease of the upper airway. Although recurrent pharyngeal collapse represents the initiating event, the resulting intermittent hypoxia, sleep fragmentation, sympathetic overactivity, oxidative stress, and systemic inflammation trigger complex pathophysiological processes affecting the cardiovascular system. These mechanisms explain the strong association between untreated OSA, and arterial hypertension, coronary artery disease, heart failure, cardiac arrhythmias, stroke, and cardiovascular mortality reported in contemporary clinical studies [8–11].

From an otorhinolaryngological perspective, detailed evaluation of upper airway anatomy remains fundamental for successful management of OSA. Contemporary evidence indicates that airway obstruction is frequently multilevel, involving the nasal cavity, soft palate, lateral pharyngeal walls, tongue base, and epiglottis. Consequently, routine clinical examination alone is often insufficient for treatment planning. Drug-induced sleep endoscopy, together with advanced imaging techniques, has substantially improved identification of the predominant site of airway collapse and allows selection of patients who are most likely to benefit from upper airway surgery or other targeted interventions. This individualized anatomical approach has significantly increased the effectiveness of surgical treatment compared with traditional procedure selection based solely on awake examination [10–14].

From the cardiology perspective, OSA is now recognized as an independent and potentially modifiable cardiovascular risk factor. Persistent nocturnal hypoxia contributes to endothelial dysfunction, vascular stiffness, activation of the renin–angiotensin–aldosterone system, myocardial remodeling, and electrical instability of the myocardium. Numerous longitudinal studies have demonstrated that the severity of nocturnal oxygen desaturation and cumulative hypoxic burden predict adverse cardiovascular outcomes more accurately than the apnea–hypopnea index alone. These findings suggest that future cardiovascular risk assessment should incorporate physiological measures of nocturnal hypoxia in addition to conventional polysomnographic indices [12–16].

Current evidence also highlights the importance of early cardiovascular screening in patients with confirmed OSA. Comprehensive evaluation including ambulatory blood pressure monitoring, echocardiography, electrocardiographic assessment, and laboratory biomarkers allows earlier identification of subclinical cardiovascular involvement before irreversible structural changes occur. Conversely, patients presenting with resistant hypertension, atrial fibrillation, chronic heart failure, pulmonary hypertension, or recurrent ischemic stroke should be actively screened for previously undiagnosed OSA, as treatment of sleep-disordered breathing may improve cardiovascular prognosis and reduce disease progression [14–18].

Although continuous positive airway pressure remains the most effective treatment for moderate and severe OSA, clinical outcomes largely depend on long-term adherence. Several randomized studies have shown that regular CPAP use improves endothelial function, lowers blood pressure, reduces sympathetic activation, and decreases recurrence of atrial fibrillation following catheter ablation. Nevertheless, poor treatment adherence remains a major clinical challenge. For this reason, individualized management combining weight reduction, treatment of nasal obstruction, oral appliance therapy, upper airway surgery when indicated, and optimization of cardiovascular risk factors appears to provide greater long-term benefit than reliance on a single therapeutic modality [15–19].

Despite substantial advances in sleep medicine and cardiovascular research, several important questions remain unresolved. Considerable heterogeneity exists among published studies regarding patient selection, definitions of disease severity, cardiovascular endpoints, and treatment adherence, limiting direct comparison of outcomes. Future multicenter prospective investigations integrating advanced upper airway imaging, polysomnography, multimodal cardiovascular assessment, molecular biomarkers, wearable monitoring technologies, and artificial intelligence–based prediction models are expected to improve individualized risk stratification and facilitate precision management of patients with obstructive sleep apnea at increased cardiovascular risk [17–20].

CONCLUSION

Obstructive sleep apnea is a multifactorial disorder that extends beyond upper airway obstruction and represents an independent contributor to cardiovascular morbidity and mortality. Current evidence demonstrates that recurrent nocturnal airway collapse initiates a cascade of intermittent hypoxia, sympathetic nervous system

activation, oxidative stress, endothelial dysfunction, and chronic inflammation, ultimately promoting the development of arterial hypertension, coronary artery disease, heart failure, cardiac arrhythmias, stroke, and other major cardiovascular complications. Early recognition of anatomical abnormalities of the upper airway together with comprehensive cardiovascular assessment is therefore essential for timely diagnosis and effective risk reduction.

Optimal management of patients with obstructive sleep apnea requires close collaboration between otorhinolaryngologists, cardiologists, sleep medicine specialists, pulmonologists, and primary care physicians. Individualized treatment strategies based on upper airway anatomy, disease severity, and cardiovascular risk profile including continuous positive airway pressure therapy, weight reduction, surgical correction of anatomical obstruction when indicated, and aggressive management of cardiovascular risk factors provide the greatest potential for improving long-term outcomes. Future integration of advanced imaging techniques, wearable monitoring systems, artificial intelligence–based diagnostic algorithms, and precision medicine approaches is expected to further enhance early detection, personalized treatment, and prevention of cardiovascular complications associated with obstructive sleep apnea.

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IMPACT OF BIOLOGIC THERAPY ON FERTILITY AND PREGNANCY OUTCOMES IN WOMEN WITH RHEUMATIC DISEASES

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Abstract. Biologic therapy has fundamentally changed the management of rheumatic diseases by improving disease control, reducing irreversible organ damage, and enhancing quality of life in women of reproductive age. As an increasing number of patients plan pregnancy while receiving biologic agents, questions regarding their effects on female fertility, pregnancy outcomes, and fetal safety have become an important focus of contemporary clinical research. Current evidence suggests that uncontrolled inflammatory activity has a greater adverse impact on reproductive outcomes than appropriately selected biologic therapy, highlighting the importance of maintaining disease remission before conception and throughout pregnancy.

This review summarizes current evidence regarding the impact of biologic therapy on fertility and pregnancy outcomes in women with rheumatic diseases. Particular attention is given to the influence of biologic agents on ovarian function, assisted reproductive technologies, pregnancy planning, maternal disease activity, placental transfer, fetal development, neonatal outcomes, and breastfeeding. Recent studies and international recommendations indicate that several biologic agents, particularly tumor necrosis factor inhibitors, can be safely continued during selected stages of pregnancy and lactation when clinically indicated. Individualized treatment strategies based on disease activity, reproductive planning, and multidisciplinary collaboration between rheumatologists, obstetricians, and reproductive specialists remain essential for optimizing maternal and neonatal outcomes.

Keywords: *biologic therapy; rheumatic diseases; fertility; pregnancy outcomes; tumor necrosis factor inhibitors; reproductive health; pregnancy; breastfeeding.*

Introduction. Rheumatic diseases frequently affect women during their reproductive years, creating significant challenges for fertility preservation, pregnancy planning, and long-term maternal health. Chronic systemic inflammation, autoimmune dysregulation, and cumulative organ damage may impair reproductive function and increase the risk of infertility, adverse pregnancy outcomes, and pregnancy-related complications. Historically, concerns regarding potential teratogenicity and fetal safety often resulted in discontinuation of effective immunosuppressive therapy before conception, increasing the likelihood of disease flares and unfavorable obstetric outcomes. Contemporary evidence has shifted this paradigm by demonstrating that sustained disease remission before and during pregnancy is one of the strongest determinants of successful maternal and neonatal outcomes [1–3].

The introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) has substantially improved the management of rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, systemic juvenile inflammatory disorders, and selected connective tissue diseases. By selectively targeting key inflammatory pathways, biologic agents provide effective suppression of disease activity while reducing the need for prolonged glucocorticoid exposure. Growing clinical experience has demonstrated that, for several biologic agents, continuation of treatment during conception and selected stages of pregnancy may be associated with better maternal disease control without increasing the risk of major congenital malformations or serious neonatal complications when appropriately prescribed [3–5].

Preservation of reproductive function has become an increasingly important component of comprehensive rheumatologic care. Beyond controlling inflammation, biologic therapy may indirectly improve fertility by restoring ovulatory function, reducing systemic inflammatory burden, improving sexual health, and facilitating successful conception. Simultaneously, increasing attention has been directed toward placental transfer of biologic agents, fetal immune development, neonatal vaccination strategies, breastfeeding safety, and the long-term health of children exposed to biologic therapy during intrauterine life. These issues have become particularly relevant following the publication of updated international recommendations regarding reproductive health in women with rheumatic diseases [5–7].

Despite substantial advances in reproductive rheumatology, important questions remain regarding the comparative safety of individual biologists, their influence on assisted reproductive technologies, optimal timing of treatment discontinuation or continuation during pregnancy, and individualized therapeutic strategies according to disease phenotype and reproductive plans. Continuous accumulation of clinical evidence and long-term observational data has refined current recommendations, while emphasizing the importance of multidisciplinary management involving rheumatologists, obstetricians, maternal-fetal medicine specialists, and reproductive endocrinologists [7].

The aim of this review was to summarize current evidence regarding the impact of biologic therapy on fertility and pregnancy outcomes in women with rheumatic diseases, with particular emphasis on reproductive function, maternal disease control, fetal safety, and contemporary evidence-based management strategies.

Materials and Methods

This study was conducted as a systematic literature review. A comprehensive search of the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases was performed to identify relevant publications published between 2020 and 2026. Priority was given to international clinical guidelines, systematic reviews, meta-analyses, randomized clinical trials, prospective cohort studies, and large observational investigations evaluating the effects of biologic therapy on fertility, pregnancy, and neonatal outcomes in women with rheumatic diseases.

Studies investigating biologic disease-modifying antirheumatic drugs, reproductive function, ovarian reserve, assisted reproductive technologies, pregnancy planning, maternal disease activity, placental transfer, fetal development, pregnancy complications, neonatal outcomes, and breastfeeding were included. Conference abstracts, case reports, duplicate publications, studies with insufficient methodological quality, and reports lacking clinically relevant reproductive or obstetric outcomes were excluded. The selected evidence was critically analyzed and synthesized to evaluate the safety and effectiveness of biologic therapy throughout the reproductive continuum, from preconception counseling to postpartum management and lactation.

Results

Biologic therapy has substantially transformed the management of rheumatic diseases in women of reproductive age by enabling sustained disease remission while reducing cumulative inflammatory burden. Current evidence indicates that disease activity itself exerts a greater negative influence on fertility and pregnancy outcomes than appropriately selected biologic treatment. Persistent systemic inflammation has been associated with impaired ovarian function, menstrual disturbances, reduced fecundity, delayed conception, and increased risks of miscarriage and obstetric complications. Consequently, achievement of stable remission before conception has become a principal therapeutic objective in reproductive rheumatology [8,9].

Female fertility is influenced by multiple disease-related and treatment-related factors. Chronic inflammation may impair ovarian reserve through accelerated follicular depletion, endocrine dysregulation, and altered hypothalamic-pituitary-ovarian function. Effective suppression of inflammatory activity with biologic disease-modifying antirheumatic drugs has been associated with restoration of ovulatory cycles, improved reproductive endocrine function, enhanced sexual health, and shorter time to pregnancy in women with well-controlled disease. Available studies indicate that biologic therapy itself does not appear to adversely affect ovarian reserve or natural fertility when used according to current recommendations [9,10].

The increasing use of assisted reproductive technologies has generated considerable interest regarding the influence of biologic therapy on reproductive outcomes. Contemporary studies demonstrate that continuation of biologic treatment during ovarian stimulation and in vitro fertilization may improve implantation potential by maintaining low disease activity and reducing systemic inflammation. Women achieving stable remission before assisted reproduction generally demonstrate higher clinical pregnancy rates and lower risks of treatment interruption compared with patients experiencing active disease at the time of conception [10–12].

Tumor necrosis factor inhibitors remain the most extensively investigated biologic agents during pregnancy. Accumulating evidence supports the favorable safety profile of certolizumab pegol, adalimumab, etanercept, infliximab, and golimumab when prescribed according to current international recommendations. Certolizumab pegol demonstrates minimal placental transfer because of the absence of an Fc fragment and may be continued throughout pregnancy when clinically indicated. Other TNF inhibitors exhibit increasing placental passage during the third trimester, requiring individualized treatment decisions based on maternal disease activity and fetal considerations [12–14].

Evidence regarding non-TNF biologic agents continues to expand. Although clinical experience with rituximab, abatacept, tocilizumab, secukinumab, ustekinumab, and other targeted biologic therapies remains more limited than with TNF inhibitors, recent observational studies have not demonstrated substantial increases in the incidence of major congenital malformations following appropriately selected treatment. Nevertheless, because long-term safety data remain limited for several agents, individualized risk-benefit assessment before conception remains essential, particularly when continuation of therapy during pregnancy is considered [14–16].

Maintenance of adequate disease control throughout pregnancy has consistently been associated with improved maternal outcomes. Women receiving effective biologic therapy demonstrate lower frequencies of disease flares, reduced glucocorticoid requirements, and better physical function during gestation. Stable inflammatory control also contributes to lower rates of preeclampsia, preterm delivery, fetal growth restriction, and cesarean section compared with pregnancies complicated by uncontrolled rheumatic disease. These findings emphasize that prevention of disease exacerbation represents a major determinant of favorable obstetric outcomes [15–17].

Neonatal outcomes are influenced by both maternal disease activity and placental exposure to biologic agents. Current evidence indicates that biologic therapy compatible with pregnancy is not associated with significant increases in congenital anomalies, neonatal mortality, or severe early childhood infections. However, infants exposed to IgG-based biologic agents during late pregnancy may retain detectable circulating drug concentrations for several months after birth, influencing recommendations regarding administration of live vaccines during early infancy. Breastfeeding is considered compatible with several biologic agents because only minimal quantities are transferred into breast milk and systemic absorption by the infant is negligible [17–19].

Recent international recommendations increasingly support individualized management strategies based on disease phenotype, biologic agent characteristics, reproductive plans, and maternal preferences. Multidisciplinary collaboration between rheumatologists, maternal-fetal medicine specialists, obstetricians, and reproductive endocrinologists facilitates optimization of treatment before conception, continuation of appropriate therapy during pregnancy, and coordinated postpartum follow-up. Ongoing prospective registries and long-term observational studies are expected to

further refine evidence-based recommendations regarding biologic therapy across the entire reproductive continuum in women with rheumatic diseases [19,20].

Discussion

The present review demonstrates that the management of reproductive health in women with rheumatic diseases has undergone substantial changes over the past decade. Pregnancy is no longer considered contraindicated for the majority of patients receiving biologic therapy, provided that conception occurs during a period of stable disease control and treatment is selected according to current evidence-based recommendations. Increasing clinical experience indicates that active inflammatory disease represents a considerably greater threat to maternal and fetal health than the continuation of appropriately chosen biologic agents. Consequently, achievement and maintenance of remission before conception have become fundamental objectives of contemporary reproductive rheumatology [8–10].

An important finding emerging from recent studies is that chronic systemic inflammation itself adversely affects female reproductive potential. Persistent immune activation may impair ovarian function, interfere with ovulation, alter endometrial receptivity, and reduce the likelihood of successful conception. Effective suppression of inflammatory activity with biologic disease-modifying antirheumatic drugs appears to improve reproductive function primarily through restoration of physiological immune homeostasis rather than by directly influencing ovarian reserve. This concept explains why improvements in fertility observed during biologic treatment are generally attributed to optimal disease control rather than to a specific pharmacological effect on reproductive tissues [9–12].

Among currently available biologic agents, tumor necrosis factor inhibitors possess the strongest evidence supporting their use during pregnancy. Multiple prospective registries and observational studies have consistently demonstrated favorable maternal and fetal safety profiles, particularly for certolizumab pegol, which exhibits minimal placental transfer. Nevertheless, therapeutic decisions should remain individualized because placental transport varies among biologic agents and increases considerably during the third trimester for monoclonal antibodies containing the Fc fragment. Careful consideration of maternal disease activity anticipated obstetric risks, and fetal exposure therefore remains essential when determining treatment continuation throughout pregnancy [12–15].

The available evidence regarding non-TNF biologic therapies remains less robust but continues to expand. Although published observational studies have not identified a substantial increase in congenital malformations or serious neonatal complications associated with several newer biologic agents, the relatively limited duration of follow-up and smaller patient populations require cautious interpretation. Until more comprehensive long-term safety data become available, treatment decisions involving rituximab, abatacept, tocilizumab, interleukin inhibitors, and other targeted biologic therapies should continue to rely on individualized assessment of maternal benefit and potential fetal risk [14–17].

Another important aspect concerns neonatal management following intrauterine exposure to biologic therapy. Current recommendations increasingly recognize that

neonatal outcomes depend not only on fetal drug exposure but also on the degree of maternal inflammatory control throughout pregnancy. Stable disease activity contributes to improved placental function, reduced obstetric complications, and more favorable neonatal adaptation. At the same time, knowledge of placental pharmacokinetics remains essential for planning infant vaccination schedules, particularly following exposure to biologic agents capable of significant transplacental transfer during late gestation. These considerations further emphasize the importance of coordinated communication between rheumatologists, obstetricians, neonatologists, and primary care physicians [16–19].

Despite considerable progress, several unresolved questions remain. Evidence regarding long-term immune development in children exposed to biologic therapy during fetal life, comparative safety among newer biologic agents, and the influence of biologic treatment on assisted reproductive technologies continues to evolve. Future multicenter prospective studies and international pregnancy registries will be essential for strengthening the evidence base, refining clinical recommendations, and supporting increasingly personalized therapeutic strategies. Such advances are expected to further improve reproductive outcomes while maintaining optimal disease control in women with rheumatic diseases throughout pregnancy and the postpartum period [18–20].

CONCLUSION

Current evidence indicates that biologic therapy has significantly improved reproductive outcomes in women with rheumatic diseases by enabling sustained disease remission before conception and throughout pregnancy. Available data consistently demonstrate that uncontrolled inflammatory activity poses a greater risk to fertility, pregnancy progression, and perinatal outcomes than appropriately selected biologic treatment. Tumor necrosis factor inhibitors remain the best-studied biologic agents and have accumulated substantial evidence supporting their use during pregnancy when clinically indicated, whereas the safety profile of newer biologic therapies continues to be refined through ongoing observational studies and international pregnancy registries.

Optimal reproductive outcomes require individualized treatment planning based on disease activity, reproductive goals, and the pharmacological characteristics of each biologic agent. Comprehensive preconception counseling, maintenance of disease control, multidisciplinary collaboration, and careful maternal and fetal monitoring throughout pregnancy remain the cornerstones of clinical management. Further prospective multicenter investigations with long-term follow-up of both mothers and offspring are needed to strengthen the evidence base, clarify the safety of emerging biologic therapies, and support the development of increasingly personalized approaches to reproductive care in women with rheumatic diseases.

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THE RETINA AS A BIOMARKER OF NEURODEGENERATIVE DISEASES: THE ROLE OF OCT AND OCT ANGIOGRAPHY IN THE EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

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Abstract. Neurodegenerative diseases, particularly Alzheimer's disease and Parkinson's disease, remain among the leading causes of disability and cognitive decline worldwide, creating an urgent need for reliable biomarkers capable of identifying pathological changes before the onset of irreversible neurological impairment. The retina, as an embryological extension of the central nervous system, has emerged as a promising non-invasive window into neurodegenerative processes. Recent advances in optical coherence tomography (OCT) and OCT angiography (OCTA) have enabled detailed assessment of retinal neuronal and microvascular alterations, revealing structural and vascular abnormalities that may precede the development of overt clinical manifestations. Growing evidence suggests that retinal imaging could complement conventional neurological biomarkers and contribute to earlier detection of neurodegenerative disorders.

This systematic literature review summarizes current evidence regarding the role of retinal structural and microvascular changes as biomarkers of Alzheimer's disease and Parkinson's disease and evaluates the clinical utility of OCT and OCTA in early diagnosis. Particular attention is given to retinal nerve fiber layer thinning, ganglion cell complex alterations, retinal microvascular impairment, correlations with cognitive and motor dysfunction, and the emerging application of artificial intelligence in retinal image analysis. The available evidence indicates that integration of OCT and OCTA

into multidisciplinary diagnostic pathways may improve early identification of neurodegenerative diseases, facilitate individualized risk stratification, and support timely therapeutic intervention before substantial neurological deterioration occurs.

Keywords: *retina; neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; optical coherence tomography; OCT angiography; retinal biomarkers; retinal nerve fiber layer; ganglion cell complex; artificial intelligence.*

Introduction

Neurodegenerative diseases represent one of the greatest challenges facing modern medicine because of their increasing prevalence, progressive clinical course, and profound socioeconomic impact. Alzheimer's disease and Parkinson's disease account for the majority of age-related neurodegenerative disorders and are characterized by gradual neuronal loss, irreversible functional decline, and the absence of curative treatment. Since disease-modifying therapies are expected to provide the greatest benefit during the earliest stages of neurodegeneration, considerable attention has been directed toward identifying accessible and reliable biomarkers capable of detecting pathological changes before the onset of overt neurological symptoms [1–3].

The retina has attracted growing interest as a potential biomarker of neurodegeneration because of its shared embryological origin, structural organization, and microvascular characteristics with the central nervous system. Degeneration of retinal ganglion cells, thinning of the retinal nerve fiber layer, alterations of the ganglion cell-inner plexiform layer complex, and retinal microvascular dysfunction have all been reported in patients with Alzheimer's disease and Parkinson's disease. These findings suggest that retinal abnormalities may reflect cerebral neurodegenerative processes and provide measurable indicators of disease progression through non-invasive ophthalmic imaging [2–5].

Recent advances in ophthalmic imaging have substantially expanded the diagnostic potential of retinal biomarkers. Optical coherence tomography enables high-resolution quantitative assessment of individual retinal layers, whereas OCT angiography provides detailed visualization of retinal and choroidal microcirculation without the need for intravenous contrast administration. Numerous studies have demonstrated significant associations between retinal structural and vascular abnormalities and established neurological biomarkers, including cognitive performance, motor impairment, magnetic resonance imaging findings, cerebrospinal fluid biomarkers, and positron emission tomography. These observations have strengthened the concept that retinal imaging may complement conventional neurological investigations in the early diagnosis of neurodegenerative disorders [4–7].

Despite encouraging results, several important questions remain regarding the diagnostic accuracy, reproducibility, and clinical applicability of retinal biomarkers across different neurodegenerative diseases and disease stages. Variability in imaging protocols, patient characteristics, and analytical methods continues to limit the widespread implementation of OCT and OCT angiography in routine neurological practice. At the same time, rapid advances in artificial intelligence, automated image analysis, and multimodal biomarker integration are creating new opportunities for precision diagnostics. The aim of the study was to summarize current evidence

regarding the role of the retina as a biomarker of neurodegenerative diseases and to evaluate the contribution of OCT and OCT angiography to the early diagnosis of Alzheimer's disease and Parkinson's disease.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding the role of retinal biomarkers in the early diagnosis of neurodegenerative diseases, with particular emphasis on Alzheimer's disease and Parkinson's disease. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies and international consensus documents were included only when they provided essential evidence concerning retinal imaging, neurodegenerative mechanisms, or diagnostic approaches.

Eligible publications included systematic reviews, meta-analyses, prospective and retrospective cohort studies, observational investigations, diagnostic accuracy studies, and evidence-based clinical guidelines addressing retinal structural and microvascular alterations assessed by optical coherence tomography and OCT angiography. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on retinal biomarkers, imaging characteristics, diagnostic performance, associations with neurological outcomes, and emerging applications of artificial intelligence in retinal image analysis.

Results

The retina has emerged as one of the most promising non-invasive biomarkers of neurodegenerative diseases because of its anatomical continuity with the central nervous system and its accessibility to high-resolution imaging. Numerous clinical studies have demonstrated that retinal structural and microvascular alterations occur during the early stages of Alzheimer's disease and Parkinson's disease, often preceding clinically significant neurological impairment. These findings support the concept that retinal imaging may provide objective biomarkers reflecting ongoing neurodegenerative processes while complementing conventional neurological investigations [8–10].

Optical coherence tomography has consistently demonstrated thinning of the peripapillary retinal nerve fiber layer (pRNFL), ganglion cell layer (GCL), and ganglion cell-inner plexiform layer (GCIPL) in patients with Alzheimer's disease. Structural abnormalities are particularly pronounced within the superior and inferior retinal quadrants and become progressively more evident with disease severity. Several longitudinal studies have reported significant correlations between retinal layer thickness and cognitive performance assessed by the Mini-Mental State Examination, suggesting that retinal degeneration parallels cerebral neuronal loss and may reflect disease progression [9–12].

Patients with Parkinson's disease exhibit a distinct pattern of retinal alterations characterized by progressive thinning of the inner retinal layers, particularly the ganglion cell complex and retinal nerve fiber layer. Degeneration of dopaminergic

amacrine cells, impaired retinal neurotransmission, and progressive neuronal loss contribute to abnormalities in contrast sensitivity, color vision, and visual processing that frequently precede advanced motor manifestations. Increasing evidence suggests that retinal structural measurements may correlate with disease duration, motor severity, and non-motor symptoms, supporting their potential role as biomarkers of disease progression [10–13].

Optical coherence tomography angiography has expanded the diagnostic capabilities of retinal imaging by enabling non-invasive visualization of retinal and choroidal microcirculation. Multiple studies have demonstrated reductions in superficial and deep capillary plexus vessel density, enlargement of the foveal avascular zone, and impaired retinal perfusion in both Alzheimer's disease and Parkinson's disease. These vascular abnormalities appear to reflect microvascular dysfunction accompanying neurodegeneration and may provide additional diagnostic information beyond structural retinal measurements obtained with conventional OCT [11–15].

From an ophthalmological perspective, OCT has become an indispensable imaging modality because of its excellent reproducibility, rapid acquisition time, and ability to quantify subtle structural changes that are undetectable during routine fundus examination. Automated segmentation of retinal layers allows objective evaluation of the retinal nerve fiber layer, ganglion cell complex, macular thickness, and optic nerve head morphology, facilitating standardized longitudinal follow-up. The widespread availability of OCT in ophthalmic practice creates opportunities for incorporating retinal biomarkers into routine clinical assessment of patients at increased risk of neurodegenerative disease [12–16].

The introduction of OCT angiography has further strengthened the role of ophthalmology in the early detection of neurodegenerative disorders. Unlike fluorescein angiography, OCTA provides detailed visualization of retinal microvascular networks without intravenous contrast administration, making repeated examinations safe and well suited for longitudinal monitoring. Quantitative assessment of vessel density, perfusion indices, and foveal avascular zone morphology has demonstrated encouraging diagnostic performance, particularly when combined with structural OCT measurements and comprehensive ophthalmological examination [13–18].

Artificial intelligence and machine learning are increasingly being integrated into ophthalmic imaging analysis. Deep learning algorithms trained on OCT and OCTA datasets have demonstrated high accuracy in distinguishing patients with Alzheimer's disease or Parkinson's disease from healthy controls while identifying imaging patterns that may be imperceptible to human observers. Integration of automated retinal image analysis with clinical, neurological, and neuroimaging data has the potential to improve diagnostic precision and facilitate large-scale screening programs for neurodegenerative diseases [15–19].

Despite substantial advances, several challenges remain before retinal biomarkers can be routinely incorporated into neurological practice. Variability in imaging devices, segmentation algorithms, acquisition protocols, and patient selection contributes to

heterogeneity across published studies. In addition, retinal changes associated with aging, glaucoma, diabetic retinopathy, and other ocular diseases may reduce diagnostic specificity. Nevertheless, the current body of evidence consistently indicates that OCT and OCT angiography represent valuable complementary tools for the early detection and monitoring of neurodegenerative diseases, particularly when integrated with established neurological biomarkers and multidisciplinary clinical assessment [16–20].

Discussion

The findings of the present review support the concept that the retina represents a biologically relevant extension of the central nervous system and may serve as a readily accessible biomarker of neurodegenerative disease. Structural retinal alterations and microvascular abnormalities detected by OCT and OCT angiography demonstrate significant associations with pathological processes occurring within the brain, suggesting that retinal imaging may provide valuable information regarding neuronal degeneration before the appearance of advanced clinical manifestations. This relationship has stimulated increasing interest in incorporating ophthalmic biomarkers into the diagnostic evaluation of Alzheimer's disease and Parkinson's disease [8–11].

One of the most important observations emerging from recent investigations is that retinal abnormalities are detectable during the early phases of neurodegeneration, when conventional neurological symptoms may still be subtle or absent. Progressive thinning of the retinal nerve fiber layer and ganglion cell complex, together with impairment of retinal microvascular perfusion, has been consistently associated with cognitive decline in Alzheimer's disease and with motor and non-motor dysfunction in Parkinson's disease. These findings indicate that OCT and OCT angiography may contribute not only to diagnosis but also to longitudinal monitoring of disease progression and therapeutic response [10–14].

From an ophthalmological perspective, OCT and OCT angiography have transformed retinal imaging by providing highly reproducible, quantitative, and non-invasive assessment of neuronal and vascular integrity. Their widespread availability in routine ophthalmic practice makes these technologies particularly attractive for large-scale clinical implementation. Nevertheless, retinal imaging should not be interpreted in isolation. Age-related ocular changes, glaucoma, diabetic retinopathy, age-related macular degeneration, and high myopia may influence retinal measurements and reduce diagnostic specificity. Careful ophthalmological examination therefore remains essential for appropriate interpretation of imaging findings and exclusion of competing ocular pathology [12–16].

Another important consideration is the growing role of multidisciplinary collaboration between ophthalmologists, neurologists, neuroradiologists, and cognitive specialists. Retinal biomarkers appear to provide the greatest diagnostic value when integrated with established neurological assessments, magnetic resonance imaging, positron emission tomography, cerebrospinal fluid biomarkers, and neuropsychological testing. Such multimodal diagnostic strategies are likely to improve risk stratification, facilitate earlier diagnosis, and support individualized clinical decision-making, particularly in patients with mild cognitive impairment or prodromal Parkinson's disease [13–18].

Despite encouraging results, several limitations continue to affect the current evidence base. Published studies vary considerably with respect to imaging platforms, segmentation algorithms, diagnostic criteria, disease stage, and outcome measures, limiting direct comparison between investigations. Many studies also involve relatively small cohorts and cross-sectional designs, restricting the ability to determine the temporal relationship between retinal alterations and progressive neurodegeneration. Standardization of imaging protocols and validation across diverse populations remain essential prerequisites for widespread clinical adoption [15–19].

Future research should focus on prospective multicenter studies evaluating the prognostic value of retinal biomarkers throughout the course of neurodegenerative disease. Integration of artificial intelligence, automated image analysis, multimodal retinal imaging, and molecular biomarkers may substantially improve diagnostic accuracy while enabling personalized prediction of disease progression. Continued collaboration between ophthalmology and neurology is expected to accelerate the translation of retinal imaging from an investigational tool to an established component of precision diagnostics for Alzheimer's disease and Parkinson's disease [17–20].

CONCLUSION

The available evidence indicates that the retina has considerable potential as a non-invasive biomarker of neurodegenerative diseases, reflecting both structural neuronal loss and microvascular dysfunction associated with Alzheimer's disease and Parkinson's disease. Optical coherence tomography and OCT angiography enable objective detection of retinal alterations that may precede clinically apparent neurological impairment, thereby expanding opportunities for earlier diagnosis and improved risk stratification. Integration of retinal imaging into multidisciplinary diagnostic pathways may complement established neurological biomarkers and contribute to more timely identification of patients at risk for progressive neurodegeneration.

Future advances will depend on the standardization of imaging protocols, validation of retinal biomarkers in large prospective multicenter studies, and broader implementation of artificial intelligence–assisted image analysis. Combining OCT and OCT angiography with neuroimaging, molecular biomarkers, and comprehensive neurological assessment may enhance diagnostic accuracy, facilitate personalized monitoring of disease progression, and improve clinical decision-making. Such an integrated approach has the potential to establish retinal imaging as an important component of precision diagnostics for Alzheimer's disease and Parkinson's disease.

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NOVEL TARGETED THERAPIES FOR ATOPIC DERMATITIS: JANUS KINASE INHIBITORS AND MONOCLONAL ANTIBODIES

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Abstract. Targeted systemic therapies have fundamentally transformed the management of moderate-to-severe atopic dermatitis by providing more selective and effective control of type 2 inflammation than conventional immunosuppressive agents. Advances in the understanding of disease immunopathogenesis have identified multiple therapeutic targets, particularly cytokine signaling mediated by interleukin-4, interleukin-13, interleukin-31, and the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. These discoveries have led to the development of monoclonal antibodies and selective JAK inhibitors that offer rapid symptom control, substantial improvement in skin lesions and pruritus, and sustained disease remission with favorable safety profiles. Consequently, targeted therapy has become a cornerstone of contemporary treatment algorithms for patients with inadequately controlled atopic dermatitis.

This review summarizes current evidence regarding the efficacy, safety, and clinical application of monoclonal antibodies and JAK inhibitors in the treatment of atopic dermatitis. Particular attention is given to their mechanisms of action, comparative clinical performance, patient selection, long-term treatment outcomes, and emerging precision medicine strategies. Recent evidence indicates that biologic agents and JAK inhibitors provide complementary therapeutic options with distinct efficacy profiles, speed of clinical response, safety considerations, and monitoring requirements. Individualized treatment selection based on disease phenotype, comorbidities, patient preferences, and risk–benefit assessment is expected to further

optimize long-term disease control and improve quality of life for patients with moderate-to-severe atopic dermatitis.

Keywords: *atopic dermatitis; targeted therapy; Janus kinase inhibitors; monoclonal antibodies; biologic therapy; dupilumab; tralokinumab; lebrikizumab; upadacitinib; abrocitinib.*

Introduction

Atopic dermatitis is a chronic relapsing inflammatory skin disease characterized by persistent pruritus, epidermal barrier dysfunction, and marked heterogeneity in clinical presentation. Affecting both children and adults, it represents one of the most prevalent immune-mediated dermatological disorders worldwide and is associated with substantial impairment in quality of life, sleep disturbance, psychological distress, and increased healthcare utilization. Conventional treatment with topical corticosteroids, calcineurin inhibitors, phototherapy, and systemic immunosuppressive agents has improved disease control for many patients; however, a considerable proportion continue to experience inadequate clinical response, frequent relapses, or treatment-limiting adverse effects, highlighting the need for more effective and targeted therapeutic approaches [1–3].

Advances in the understanding of disease immunopathogenesis have fundamentally changed the therapeutic landscape of atopic dermatitis. The disease is now recognized because of complex interactions among epidermal barrier dysfunction, genetic susceptibility, environmental factors, and dysregulated immune responses dominated by type 2 inflammation. Cytokines including interleukin-4, interleukin-13, interleukin-31, thymic stromal lymphopoietin, and additional inflammatory mediators play central roles in maintaining chronic inflammation, promoting epidermal barrier disruption, and amplifying pruritus. These discoveries have provided the biological rationale for the development of highly selective therapies targeting specific inflammatory pathways rather than broadly suppressing the immune system [3–5].

Monoclonal antibodies and Janus kinase (JAK) inhibitors have emerged as major therapeutic advances for patients with moderate-to-severe atopic dermatitis requiring systemic treatment. Monoclonal antibodies selectively inhibit extracellular cytokines or their receptors, whereas JAK inhibitors interfere with intracellular signaling pathways responsible for transmitting multiple inflammatory cytokine signals. Clinical trials and real-world studies have consistently demonstrated substantial improvements in disease severity, pruritus, quality of life, and long-term disease control with these targeted therapies. Their introduction has expanded treatment options and enabled more individualized management strategies based on disease phenotype, comorbidities, patient characteristics, and therapeutic goals [5–7].

Despite these advances, important questions remain regarding optimal treatment sequencing, comparative effectiveness, long-term safety, biomarker-guided patient selection, and the positioning of targeted therapies within evolving clinical practice guidelines. Ongoing clinical trials and real-world evidence continue to refine current treatment algorithms while supporting the transition toward precision medicine in atopic dermatitis. As the number of available targeted agents continues to increase,

comprehensive evaluation of their clinical performance has become essential for evidence-based therapeutic decision-making [7].

Aim of the study was to review current evidence regarding the efficacy, safety, mechanisms of action, and clinical application of Janus kinase inhibitors and monoclonal antibodies in the treatment of atopic dermatitis, with emphasis on their role in personalized therapeutic strategies and long-term disease management.

Materials and Methods

This study was conducted as a systematic literature review. A comprehensive search of the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases was performed to identify relevant publications published between 2020 and 2026. Priority was given to international clinical practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, prospective cohort studies, and real-world investigations evaluating targeted therapies for moderate-to-severe atopic dermatitis.

Studies assessing the efficacy, safety, mechanisms of action, and long-term outcomes of monoclonal antibodies and Janus kinase (JAK) inhibitors were included. Particular attention was given to dupilumab, tralokinumab, lebrikizumab, nemolizumab, upadacitinib, abrocitinib, baricitinib, and topical ruxolitinib, as well as comparative studies evaluating treatment response, disease severity, pruritus, quality of life, and safety profiles. Case reports, conference abstracts, duplicate publications, and studies lacking clinically relevant therapeutic outcomes were excluded. The selected evidence was critically synthesized to evaluate the current role of targeted therapies in the personalized management of atopic dermatitis.

Results

The therapeutic landscape of atopic dermatitis has changed substantially over the past decade following advances in the understanding of disease immunopathogenesis. Conventional systemic therapies, including cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil, have demonstrated clinical efficacy but remain limited by non-selective immunosuppression, cumulative toxicity, frequent adverse events, and variable long-term effectiveness. These limitations have accelerated the development of targeted therapies capable of selectively inhibiting key inflammatory pathways while providing sustained disease control with improved safety profiles. Current international guidelines increasingly recommend biologic agents and Janus kinase (JAK) inhibitors for patients with moderate-to-severe disease inadequately controlled by topical therapy or conventional systemic treatment [8,9].

The rationale for targeted therapy is based on the central role of type 2 immune inflammation in the pathogenesis of atopic dermatitis. Interleukin-4 (IL-4) and interleukin-13 (IL-13) promote epidermal barrier dysfunction, suppress structural protein synthesis, impair antimicrobial defense, and amplify chronic inflammation. Additional cytokines, including IL-31, thymic stromal lymphopoietin (TSLP), IL-22, and IL-33, contribute to pruritus, epithelial injury, and persistent immune activation. Intracellular transmission of multiple cytokine signals through the JAK-STAT pathway provides an additional therapeutic target capable of simultaneously modulating several inflammatory cascades involved in disease progression [9–11].

Monoclonal antibodies have become a cornerstone of systemic treatment for moderate-to-severe atopic dermatitis. Dupilumab, the first biologic approved for this indication, selectively blocks the IL-4 receptor α subunit, thereby inhibiting signaling of both IL-4 and IL-13. Numerous randomized clinical trials and real-world studies have demonstrated sustained reductions in disease severity, rapid improvement in pruritus, restoration of skin barrier function, and significant enhancement of quality of life. More recently, IL-13-specific monoclonal antibodies, including tralokinumab and lebrikizumab, have shown comparable long-term efficacy while maintaining favorable safety profiles, further expanding therapeutic options for individualized patient management [10–13].

Selective inhibition of additional inflammatory mediators has also broadened the biologic treatment spectrum. Nemolizumab, targeting the IL-31 receptor, has demonstrated marked antipruritic activity and clinically meaningful reductions in eczema severity, particularly in patients with severe itch that remains inadequately controlled despite conventional therapy. Ongoing clinical investigations evaluating inhibitors of OX40, IL-22, IL-33, TSLP, and other immune pathways continue to expand the range of biologic therapies and may provide new opportunities for precision treatment according to specific disease endotypes [12–15].

Janus kinase inhibitors represent a second major class of targeted systemic therapies. Upadacitinib, abrocitinib, and baricitinib inhibit intracellular cytokine signaling responsible for multiple inflammatory pathways implicated in atopic dermatitis. Clinical trials consistently demonstrate rapid reduction of pruritus, often within the first days of treatment, accompanied by substantial improvements in Eczema Area and Severity Index (EASI) scores, Investigator's Global Assessment (IGA), sleep quality, and patient-reported outcomes. Topical ruxolitinib has also demonstrated significant efficacy in patients with mild-to-moderate disease while minimizing systemic drug exposure [13–16].

Comparative clinical studies have highlighted important differences between biologic agents and JAK inhibitors. Monoclonal antibodies generally demonstrate excellent long-term safety, sustained efficacy, and favorable tolerability with relatively limited laboratory monitoring requirements. In contrast, JAK inhibitors frequently provide more rapid onset of clinical response and greater early reductions in pruritus but require careful assessment of cardiovascular risk factors, thromboembolic events, serious infections, and laboratory abnormalities. Consequently, treatment selection increasingly relies on individualized evaluation of patient age, comorbidities, disease phenotype, previous therapeutic response, and overall benefit-risk profile [15–18].

Long-term extension studies and real-world registries have confirmed durable efficacy of targeted therapies in routine clinical practice. Sustained improvements in disease severity, reduction in flare frequency, decreased reliance on systemic corticosteroids, restoration of work productivity, and significant enhancement of health-related quality of life have been consistently reported. Drug persistence remains high for both biologic agents and JAK inhibitors, although treatment continuation is influenced by clinical response, adverse events, patient preference, and healthcare

accessibility. These findings support the long-term integration of targeted therapies into standard management algorithms for chronic atopic dermatitis [17–19].

Current research is increasingly directed toward precision medicine approaches that integrate molecular biomarkers, immune profiling, pharmacogenomics, and real-world clinical data to optimize therapeutic selection. Advances in artificial intelligence, machine learning, and multi-omics technologies are expected to improve prediction of treatment response, identify disease endotypes, and facilitate personalized therapeutic strategies. The development of next-generation biologic agents and highly selective kinase inhibitors is likely to further expand treatment options and refine individualized management of atopic dermatitis in the coming years [19,20].

Discussion

The findings of this review demonstrate that targeted therapies have fundamentally transformed the management of moderate-to-severe atopic dermatitis by shifting treatment from broad immunosuppression to selective modulation of disease-specific inflammatory pathways. Improved understanding of type 2 immune responses has enabled the development of biologic agents and Janus kinase (JAK) inhibitors that provide substantial clinical benefit while minimizing many of the limitations associated with conventional systemic therapies. Current evidence consistently shows that targeted treatment not only reduces disease activity but also improves long-term disease control, decreases the frequency of exacerbations, and enhances health-related quality of life [8–10].

One of the principal observations emerging from contemporary clinical studies is that monoclonal antibodies and JAK inhibitors should not be regarded as competing therapeutic options but rather as complementary treatment strategies with distinct clinical advantages. Monoclonal antibodies targeting IL-4, IL-13, and IL-31 provide highly selective immune modulation with excellent long-term safety and durable efficacy, making them particularly suitable for prolonged maintenance therapy. In contrast, JAK inhibitors suppress multiple inflammatory signaling pathways simultaneously and are characterized by a rapid onset of action, especially with regard to pruritus relief and early improvement of skin inflammation. These pharmacological differences have become increasingly important when selecting individualized treatment strategies for patients with diverse clinical phenotypes [10–13].

The review also highlights the growing importance of personalized therapeutic decision-making. Contemporary management of atopic dermatitis extends beyond disease severity alone and increasingly incorporates patient age, comorbid allergic diseases, previous treatment response, cardiovascular risk profile, infection history, pregnancy planning, laboratory monitoring requirements, and patient preferences. Such an individualized approach allows clinicians to balance efficacy with long-term safety while optimizing treatment adherence and overall patient satisfaction. Recent international guidelines increasingly emphasize shared decision-making and individualized risk-benefit assessment when selecting targeted therapies [12–15].

Accumulating real-world evidence has further strengthened confidence in the long-term effectiveness of targeted agents. Registry studies and extension trials have demonstrated sustained improvements in disease severity, sleep quality, productivity,

and quality of life, together with prolonged treatment persistence in routine clinical practice. Importantly, successful disease control has also been associated with restoration of epidermal barrier function and partial normalization of the skin microbiome, supporting the concept that effective targeted therapy influences multiple pathogenic mechanisms beyond suppression of inflammatory cytokines alone [14–17].

Despite these advances, several challenges remain. Direct head-to-head comparative studies between individual biologic agents and JAK inhibitors remain relatively limited, and long-term safety data continue to accumulate, particularly for prolonged JAK inhibitor therapy. Careful patient selection, continuous safety monitoring, and individualized benefit-risk evaluation therefore remain essential components of clinical practice. In addition, biomarkers capable of accurately predicting therapeutic response have not yet been fully validated for routine clinical use, limiting the ability to optimize first-line targeted therapy for individual patients [16–19].

Future progress in the management of atopic dermatitis is expected to be driven by precision medicine approaches integrating molecular biomarkers, pharmacogenomics, multi-omics technologies, artificial intelligence-assisted prediction models, and real-world clinical data. The development of next-generation biologic agents, more selective kinase inhibitors, and biomarker-guided therapeutic algorithms is likely to further improve treatment efficacy while reducing unnecessary therapeutic switching. As the understanding of disease heterogeneity continues to expand, targeted therapy is expected to become increasingly individualized, allowing more precise selection of treatment according to the underlying biological mechanisms responsible for each patient's disease [18–20].

CONCLUSION

Targeted therapies have redefined the treatment paradigm for moderate-to-severe atopic dermatitis by providing selective modulation of the key immunological pathways responsible for disease development and persistence. Monoclonal antibodies and Janus kinase inhibitors have demonstrated superior efficacy compared with conventional systemic therapies in reducing disease severity, controlling pruritus, improving skin barrier function, and enhancing health-related quality of life. Their distinct mechanisms of action provide complementary therapeutic opportunities, allowing treatment strategies to be tailored according to individual clinical characteristics, comorbidities, and patient preferences.

Current evidence supports the integration of targeted therapies into personalized management algorithms for atopic dermatitis, with treatment selection based on a comprehensive assessment of efficacy, safety, long-term disease control, and individual risk profiles. Ongoing advances in molecular immunology, biomarker discovery, pharmacogenomics, and precision medicine are expected to further optimize patient stratification and therapeutic decision-making. Continued development of next-generation biologic agents and highly selective JAK inhibitors will likely expand available treatment options and contribute to more durable disease remission, improved long-term outcomes, and higher quality of life for patients with atopic dermatitis.

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OPHTHALMIC COMPLICATIONS OF LONG-TERM GLUCOCORTICOID THERAPY: CURRENT EVIDENCE, RISK FACTORS, AND PREVENTION STRATEGIES

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Abstract. Long-term glucocorticoid therapy remains an essential component of treatment for numerous autoimmune, inflammatory, respiratory, dermatological, neurological, and ophthalmic disorders. However, prolonged exposure to systemic, topical, inhaled, or intraocular glucocorticoids is associated with a broad spectrum of ocular complications that may lead to irreversible visual impairment if not recognized at an early stage. Steroid-induced ocular hypertension, secondary open-angle glaucoma, posterior subcapsular cataract, central serous chorioretinopathy, delayed corneal epithelial healing, ocular surface disease, and increased susceptibility to infectious keratitis represent the most clinically significant adverse effects. The incidence and severity of these complications depend on treatment duration, cumulative dose, route of administration, individual susceptibility, and pre-existing ocular comorbidities.

This systematic literature review summarizes current evidence regarding the pathophysiological mechanisms, risk factors, diagnostic approaches, prevention strategies, and contemporary management of ophthalmic complications associated with long-term glucocorticoid therapy. Particular attention is given to advances in multimodal ocular imaging, including optical coherence tomography, OCT angiography, anterior segment imaging, and automated glaucoma assessment, as well as evidence-based recommendations for patient monitoring and individualized risk stratification. Current data support regular ophthalmological surveillance and timely intervention as key components in preventing irreversible vision loss among patients receiving prolonged glucocorticoid treatment.

Keywords: *glucocorticoids; steroid-induced glaucoma; posterior subcapsular cataract; ocular hypertension; central serous chorioretinopathy; optical coherence tomography; OCT angiography; ocular surface disease; ophthalmic complications; long-term glucocorticoid therapy.*

Introduction

Glucocorticoids remain among the most widely prescribed medications in modern clinical practice because of their potent anti-inflammatory and immunosuppressive properties. They are routinely used in the management of autoimmune diseases, rheumatological disorders, chronic respiratory diseases, inflammatory bowel disease, dermatological conditions, neurological disorders, organ transplantation, and numerous ophthalmic diseases. Although these agents have substantially improved clinical outcomes across multiple medical specialties, prolonged glucocorticoid therapy is associated with a broad spectrum of systemic and ocular adverse effects that may significantly compromise visual function and quality of life. As the number of patients requiring long-term corticosteroid treatment continues to increase, prevention and early recognition of ophthalmic complications have become increasingly important in routine clinical practice [1–3].

From an ophthalmological perspective, glucocorticoids affect virtually every anatomical structure of the eye. Persistent corticosteroid exposure alters aqueous humor dynamics through structural and biochemical changes within the trabecular meshwork, resulting in steroid-induced ocular hypertension and secondary open-angle glaucoma. In addition, prolonged therapy promotes posterior subcapsular cataract formation, impairs corneal epithelial regeneration, disrupts tear film homeostasis, suppresses local immune responses, and increases susceptibility to bacterial, viral, and fungal ocular infections. Recent studies have also demonstrated an association between corticosteroid use and central serous chorioretinopathy, suggesting that glucocorticoids may influence choroidal circulation, retinal pigment epithelium function, and retinal homeostasis [2–5].

The risk of developing ophthalmic complications depends on multiple factors, including cumulative glucocorticoid dose, duration of treatment, route of administration, patient age, genetic susceptibility, and pre-existing ocular disease. Systemic therapy is associated with a higher incidence of cataract and glaucoma during prolonged treatment, whereas topical ophthalmic corticosteroids may induce rapid elevations in intraocular pressure, particularly in genetically predisposed individuals. Advances in optical coherence tomography, OCT angiography, anterior segment imaging, corneal biomechanics, and automated visual field analysis have substantially improved the ability to detect early structural and functional changes before irreversible vision loss occurs, supporting the implementation of regular ophthalmological monitoring in patients receiving chronic corticosteroid therapy [4–7].

Growing recognition of steroid-induced ocular toxicity has shifted clinical practice toward individualized risk assessment, early diagnosis, and preventive management strategies. Contemporary recommendations emphasize interdisciplinary collaboration between ophthalmologists and physicians prescribing glucocorticoids to optimize

treatment while minimizing vision-threatening complications. The aim of the study was to summarize current evidence regarding the pathophysiological mechanisms, risk factors, diagnostic approaches, prevention strategies, and contemporary management of ophthalmic complications associated with long-term glucocorticoid therapy.

Materials and Methods

This study was conducted as a systematic literature review to evaluate current evidence regarding ophthalmic complications associated with long-term glucocorticoid therapy. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies were included only when they established fundamental concepts regarding steroid-induced ocular disease or the mechanisms of glucocorticoid-related eye injury.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, clinical practice guidelines, and international consensus statements addressing glucocorticoid therapy, steroid-induced glaucoma, cataract, central serous chorioretinopathy, ocular surface disease, diagnostic imaging, and preventive strategies. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance were excluded. The selected literature was critically analyzed with emphasis on pathogenic mechanisms, risk factors, diagnostic methods, prevention, treatment approaches, and long-term ophthalmological outcomes.

Results

Long-term glucocorticoid therapy affects multiple ocular tissues through complex molecular and cellular mechanisms that involve alterations in extracellular matrix metabolism, suppression of physiological immune responses, oxidative stress, mitochondrial dysfunction, and impaired tissue repair. The likelihood of ophthalmic complications depends on the cumulative dose, duration of treatment, route of administration, and individual susceptibility. Patients receiving systemic therapy for more than 3–6 months, repeated intravitreal corticosteroid injections, or prolonged topical ophthalmic corticosteroids demonstrate the highest incidence of clinically significant ocular adverse events. Age, diabetes mellitus, high myopia, pre-existing glaucoma, connective tissue diseases, and a positive family history of glaucoma further increase the probability of vision-threatening complications [8–10].

Steroid-induced ocular hypertension and secondary open-angle glaucoma represent the most extensively studied complications of chronic glucocorticoid exposure. Glucocorticoids stimulate accumulation of extracellular matrix proteins, fibronectin, elastin, and glycosaminoglycans within the trabecular meshwork while simultaneously reducing phagocytic activity and altering cytoskeletal organization of trabecular cells. These changes impair aqueous humor outflow and progressively elevate intraocular pressure. Approximately 30–40% of the general population demonstrate a measurable steroid response, whereas 5–8% develop marked intraocular pressure elevation. Patients with primary open-angle glaucoma, diabetes mellitus, or a family history of

glaucoma exhibit substantially greater susceptibility and may develop irreversible optic nerve damage if treatment continues without ophthalmological monitoring [9–12].

Posterior subcapsular cataract is another major complication associated with prolonged glucocorticoid therapy. Oxidative injury, disruption of lens epithelial cell differentiation, altered crystallin protein metabolism, and impaired antioxidant defense mechanisms contribute to progressive lens opacification. The risk increases with higher cumulative corticosteroid exposure and prolonged treatment duration and is particularly pronounced among patients with autoimmune diseases requiring chronic systemic therapy. Clinical studies indicate that posterior subcapsular cataracts progress more rapidly than age-related cortical cataracts and are associated with early deterioration of near vision, glare sensitivity, and contrast perception, frequently necessitating cataract surgery at a younger age than expected in the general population [10–13].

Advances in ophthalmic imaging have substantially improved early detection of steroid-related ocular injury. Goldmann applanation tonometry remains the reference standard for intraocular pressure measurement, while pachymetry allows correction for central corneal thickness. Optical coherence tomography (OCT) enables quantitative assessment of retinal nerve fiber layer (RNFL) and ganglion cell complex thickness, facilitating identification of early glaucomatous neurodegeneration before detectable visual field loss. OCT angiography further demonstrates reductions in peripapillary, and macular vessel density associated with chronic intraocular pressure elevation, providing additional biomarkers of early optic nerve damage. Automated perimetry remains indispensable for functional assessment and longitudinal monitoring of glaucomatous progression [11–15].

Modern imaging also plays an essential role in identifying retinal and choroidal complications associated with glucocorticoid therapy. Central serous chorioretinopathy is characterized by increased choroidal thickness, hyperpermeability of the choroidal circulation, dysfunction of the retinal pigment epithelium, and accumulation of subretinal fluid. Spectral-domain OCT accurately detects neurosensory retinal detachment, pigment epithelial detachments, and subtle structural abnormalities, while OCT angiography and enhanced-depth imaging provide detailed visualization of choroidal vascular alterations. Fluorescein and indocyanine green angiography remain valuable in selected cases requiring differentiation from inflammatory or neovascular retinal diseases [12–16].

Evaluation of the ocular surface has likewise become increasingly sophisticated. Chronic glucocorticoid exposure may suppress epithelial regeneration, destabilize the tear film, reduce goblet cell density, and impair local immune defense, increasing susceptibility to bacterial, fungal, and herpetic keratitis. Contemporary assessment combines slit-lamp biomicroscopy, fluorescein and lissamine green staining, tear break-up time, Schirmer testing, corneal topography, anterior segment OCT, and in vivo confocal microscopy to detect epithelial defects, corneal nerve alterations, inflammatory changes, and early infectious complications before irreversible tissue damage develops [13–17].

Current preventive strategies emphasize individualized ophthalmological surveillance according to the route and duration of glucocorticoid therapy. Baseline comprehensive ophthalmic examination followed by periodic intraocular pressure measurement, optic nerve assessment, OCT imaging, visual field testing, and lens evaluation allows earlier identification of steroid responders and timely modification of treatment. When clinically feasible, reduction of corticosteroid exposure or transition to steroid-sparing immunomodulatory therapy decreases the incidence of progressive ocular complications. In patients with steroid-induced glaucoma, topical hypotensive medications remain first-line treatment, whereas selective laser trabeculoplasty or glaucoma surgery may be required in refractory cases. Cataract extraction continues to provide excellent visual rehabilitation once visually significant lens opacity develops [15–19].

Recent advances in artificial intelligence and precision ophthalmology are expected to further improve monitoring of patients receiving long-term glucocorticoids. Deep learning algorithms applied to OCT, OCT angiography, fundus photography, and visual field analysis demonstrate high accuracy for detecting early glaucomatous damage and predicting disease progression before clinically apparent visual impairment occurs. Integration of automated image analysis with clinical risk factors, genetic susceptibility, and electronic health record data may facilitate personalized screening strategies and optimize prevention of irreversible vision loss in high-risk patients requiring prolonged glucocorticoid therapy [17–20].

Discussion

The findings of the present review demonstrate that ophthalmic complications remain among the most clinically significant adverse effects of long-term glucocorticoid therapy. Although glucocorticoids are indispensable in the management of numerous inflammatory and autoimmune diseases, prolonged exposure may induce irreversible structural and functional changes affecting the trabecular meshwork, crystalline lens, retina, choroid, cornea, and ocular surface. Importantly, many of these complications develop gradually and remain asymptomatic during the early stages, emphasizing the need for regular ophthalmological surveillance throughout the course of corticosteroid treatment rather than only after visual symptoms become apparent [8–11].

Steroid-induced ocular hypertension and secondary open-angle glaucoma continue to represent the leading causes of irreversible vision loss associated with chronic glucocorticoid use. Current evidence indicates that individual susceptibility to corticosteroid-induced intraocular pressure elevation varies considerably and is influenced by genetic background, pre-existing glaucoma, diabetes mellitus, high myopia, connective tissue disorders, and cumulative corticosteroid exposure. These observations support individualized risk stratification and highlight the importance of baseline ophthalmological assessment before initiating prolonged glucocorticoid therapy, particularly in patients with known risk factors [10–13].

Advances in ophthalmic imaging have substantially improved the early diagnosis of steroid-related ocular injury. Optical coherence tomography, OCT angiography, anterior segment imaging, and automated visual field analysis now permit detection of

subtle structural and functional abnormalities before irreversible optic nerve damage or clinically significant visual field loss develops. Similarly, high-resolution retinal imaging has enhanced recognition of central serous chorioretinopathy and other corticosteroid-associated retinal disorders, allowing earlier therapeutic intervention and closer monitoring of disease progression. These technologies have shifted clinical practice toward proactive detection rather than management of advanced ocular complications [12–16].

An important aspect highlighted by contemporary studies is the cumulative effect of prolonged glucocorticoid exposure on multiple ocular structures. Patients frequently develop more than one steroid-related complication simultaneously, such as ocular hypertension combined with posterior subcapsular cataract or ocular surface disease accompanied by recurrent infectious keratitis. Consequently, isolated assessment of intraocular pressure alone is insufficient for comprehensive follow-up. Long-term monitoring should include evaluation of the optic nerve, retinal nerve fiber layer, macular structure, crystalline lens, corneal integrity, tear film stability, and visual function to identify early pathological changes affecting different components of the visual system [13–17].

Prevention remains the most effective strategy for reducing vision-threatening complications associated with long-term glucocorticoid therapy. Current international recommendations emphasize prescribing the lowest effective corticosteroid dose for the shortest possible duration, consideration of steroid-sparing therapeutic alternatives whenever clinically appropriate, and implementation of structured ophthalmological follow-up protocols. Close communication between ophthalmologists and specialists responsible for glucocorticoid therapy—including rheumatologists, pulmonologists, neurologists, nephrologists, dermatologists, and gastroenterologists—is essential for balancing therapeutic efficacy with ocular safety and minimizing unnecessary corticosteroid exposure [15–19].

Despite substantial progress, several important challenges remain. Published studies differ regarding corticosteroid dose thresholds, duration of exposure, follow-up intervals, and diagnostic criteria for steroid-induced ocular disease, limiting direct comparison between investigations. Future multicenter prospective studies integrating multimodal imaging, genetic susceptibility markers, artificial intelligence–based image analysis, and individualized risk prediction models are expected to improve early identification of steroid responders and facilitate personalized preventive strategies. Such an approach may substantially reduce irreversible visual impairment and improve long-term outcomes in patients requiring chronic glucocorticoid therapy [17–20].

CONCLUSION

Long-term glucocorticoid therapy is associated with a broad spectrum of ophthalmic complications that may affect virtually every ocular structure and, if left undetected, lead to irreversible visual impairment. Current evidence demonstrates that steroid-induced ocular hypertension, secondary open-angle glaucoma, posterior subcapsular cataract, central serous chorioretinopathy, ocular surface disorders, and infectious complications develop through complex mechanisms involving impaired aqueous humor outflow, oxidative stress, immune dysregulation, and structural

remodeling of ocular tissues. Early recognition of these changes is essential for preserving visual function and preventing permanent vision loss.

Comprehensive ophthalmological monitoring should be considered an integral component of long-term glucocorticoid therapy, particularly in patients with prolonged treatment, high cumulative doses, or pre-existing ocular risk factors. Regular assessment using intraocular pressure measurement, optical coherence tomography, visual field testing, and slit-lamp examination enables timely diagnosis and appropriate intervention before advanced structural damage occurs. Future integration of multimodal ocular imaging, artificial intelligence–based diagnostic systems, and personalized risk assessment models is expected to improve prevention strategies and optimize long-term visual outcomes in patients requiring chronic glucocorticoid treatment.

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ENHANCED RECOVERY AFTER SURGERY (ERAS) PROTOCOLS IN ONCOLOGIC SURGERY: CURRENT EVIDENCE AND OPPORTUNITIES TO REDUCE POSTOPERATIVE COMPLICATIONS

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Abstract. Enhanced Recovery After Surgery (ERAS) protocols have become an integral component of modern perioperative care and are increasingly implemented in oncologic surgery to reduce postoperative morbidity, accelerate functional recovery, and improve overall treatment outcomes. Patients undergoing major cancer surgery are particularly susceptible to postoperative complications because of advanced age, malnutrition, sarcopenia, systemic inflammation, immunosuppression, and the physiological stress associated with extensive surgical procedures. Contemporary evidence indicates that multimodal ERAS pathways effectively attenuate the surgical stress response, preserve physiological function, decrease complication rates, shorten hospital stay, and facilitate earlier initiation of adjuvant oncological therapy without compromising surgical safety.

This systematic literature review summarizes current evidence regarding the effectiveness of ERAS protocols in oncologic surgery, with emphasis on their pathophysiological rationale, principal perioperative components, impact on postoperative complications, and implementation across different oncological specialties. Particular attention is given to prehabilitation, minimally invasive surgical techniques, multimodal analgesia, early mobilization, nutritional optimization, compliance with ERAS pathways, and emerging applications of digital health technologies and artificial intelligence for perioperative management. Current evidence supports ERAS as a cornerstone of contemporary oncologic surgery, contributing to improved postoperative recovery, reduced healthcare utilization, and enhanced long-term patient outcomes.

Keywords: *enhanced recovery after surgery; ERAS; oncologic surgery; postoperative complications; prehabilitation; multimodal analgesia; minimally invasive surgery; perioperative care; postoperative recovery; cancer surgery.*

Introduction

Surgical treatment remains the cornerstone of curative therapy for most solid malignancies despite substantial advances in systemic treatment and radiation oncology. However, major oncologic procedures are frequently associated with considerable physiological stress, prolonged hospitalization, and a high incidence of postoperative complications that may delay recovery, postpone adjuvant therapy, increase healthcare costs, and adversely affect long-term oncological outcomes. Patients with cancer often present with malnutrition, sarcopenia, anemia, chronic inflammation, frailty, and multiple comorbidities, making them particularly vulnerable to perioperative morbidity. Consequently, optimization of perioperative management has become a major priority in contemporary oncologic surgery [1–3].

From the perspective of surgical physiology, tissue injury initiates a complex neuroendocrine and inflammatory stress response characterized by activation of the hypothalamic–pituitary–adrenal axis, sympathetic nervous system stimulation, insulin resistance, protein catabolism, cytokine release, and transient immunosuppression. Excessive perioperative stress contributes to impaired wound healing, infectious complications, postoperative ileus, thromboembolic events, pulmonary dysfunction, prolonged immobilization, and delayed functional recovery. Traditional perioperative practices, including prolonged fasting, liberal intravenous fluid administration, delayed oral nutrition, and extended bed rest, may further amplify these adverse physiological responses and negatively influence postoperative outcomes [2–5].

From the perspective of oncologic surgery, rapid postoperative recovery has clinical importance extending beyond early discharge. Delayed recovery and postoperative complications frequently postpone initiation of adjuvant chemotherapy or radiotherapy, reducing treatment adherence and potentially compromising long-term disease control in selected malignancies. Enhanced Recovery After Surgery (ERAS) protocols were developed to minimize the physiological consequences of surgery through evidence-based multimodal perioperative care incorporating prehabilitation, nutritional optimization, minimally invasive surgical techniques, multimodal opioid-sparing analgesia, goal-directed fluid therapy, early mobilization, and early enteral nutrition. Increasing evidence demonstrates that high compliance with ERAS pathways is associated with lower complication rates, shorter hospital stay, improved quality of life, and earlier return to planned oncological treatment across multiple surgical specialties [4–7].

Growing experience with ERAS implementation has transformed perioperative management from procedure-centered care to patient-centered multidisciplinary treatment involving surgeons, anesthesiologists, oncologists, nurses, dietitians, physiotherapists, and rehabilitation specialists. Continuous refinement of ERAS protocols, together with advances in minimally invasive surgery, digital perioperative monitoring, and individualized risk assessment, has further expanded their role in modern cancer care. The aim of the study was to summarize current evidence regarding

the effectiveness of ERAS protocols in oncologic surgery, their impact on postoperative complications, and contemporary opportunities for improving perioperative and oncological outcomes.

Materials and Methods

This study was conducted as a systematic literature review to evaluate current evidence regarding the effectiveness of Enhanced Recovery After Surgery (ERAS) protocols in reducing postoperative complications among patients undergoing oncologic surgery. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies were included only when they established the fundamental principles of ERAS or significantly influenced contemporary perioperative management in oncologic surgery.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, ERAS Society guidelines, and international consensus statements addressing perioperative care, enhanced recovery pathways, prehabilitation, postoperative complications, minimally invasive surgery, and multimodal perioperative management in patients with malignant diseases. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on perioperative outcomes, postoperative morbidity, ERAS protocol compliance, length of hospital stay, recovery of gastrointestinal function, timing of adjuvant therapy, and overall clinical effectiveness.

Results

Enhanced Recovery After Surgery (ERAS) protocols are based on the principle that postoperative complications arise not only from the surgical procedure itself but also from the physiological stress response induced by tissue injury. Activation of the hypothalamic–pituitary–adrenal axis, sympathetic nervous system stimulation, systemic inflammatory response, insulin resistance, protein catabolism, and transient immunosuppression contribute to delayed gastrointestinal recovery, impaired wound healing, increased susceptibility to infection, and prolonged hospitalization. Contemporary studies demonstrate that multimodal ERAS pathways significantly attenuate these responses through coordinated perioperative interventions, resulting in faster restoration of physiological homeostasis and improved postoperative recovery [8–10].

Prehabilitation has become one of the most important components of modern ERAS protocols in oncologic surgery. Comprehensive preoperative optimization includes nutritional assessment, correction of anemia, respiratory rehabilitation, physical exercise, smoking cessation, optimization of glycemic control, and psychological preparation. Recent meta-analyses demonstrate that structured prehabilitation programs improve functional capacity before surgery, reduce postoperative pulmonary complications by approximately 25–35%, decrease overall postoperative morbidity by nearly 20%, and shorten recovery time, particularly among

elderly patients and individuals with sarcopenia or frailty. Assessment of nutritional status and skeletal muscle mass has become increasingly important because preoperative sarcopenia is consistently associated with higher rates of postoperative complications and delayed functional recovery [9–12].

Implementation of evidence-based perioperative measures further enhances postoperative outcomes. Modern ERAS pathways recommend avoidance of prolonged fasting, preoperative carbohydrate loading, goal-directed fluid therapy, maintenance of normothermia, minimally invasive surgical techniques, multimodal opioid-sparing analgesia, early enteral nutrition, and mobilization within the first postoperative day whenever clinically feasible. High protocol adherence has consistently been associated with fewer postoperative complications, earlier return of bowel function, reduced opioid consumption, shorter duration of intravenous fluid administration, and earlier hospital discharge. Several multicenter studies have shown that patients achieving ERAS compliance above 70–80% experience significantly lower morbidity than those managed with partial protocol implementation [10–13].

The benefits of ERAS have been consistently demonstrated across multiple oncological specialties. In colorectal cancer surgery, adherence to ERAS protocols reduces postoperative ileus, surgical site infections, anastomotic complications, and overall hospital stay while facilitating earlier initiation of adjuvant chemotherapy. Similar improvements have been reported following gastric, esophageal, hepatobiliary, pancreatic, urological, thoracic, and gynecological oncologic procedures. Contemporary meta-analyses indicate reductions in overall postoperative complications ranging from approximately 20% to 40%, depending on surgical complexity and protocol compliance, without increasing rates of readmission, reoperation, or postoperative mortality [11–15].

Minimally invasive surgical approaches substantially enhance the effectiveness of ERAS pathways. Laparoscopic and robotic techniques reduce operative blood loss, postoperative pain, inflammatory cytokine release, and tissue trauma while facilitating earlier ambulation and recovery of gastrointestinal function. When combined with ERAS principles, minimally invasive surgery has been associated with shorter hospitalization, lower rates of pulmonary complications, faster return to oral nutrition, and improved postoperative quality of life. These benefits are particularly evident in colorectal, gastric, prostate, and gynecological cancer surgery, where rapid functional recovery allows timely continuation of multidisciplinary oncological treatment [12–16].

One of the most clinically relevant advantages of ERAS implementation is its influence on continuation of cancer therapy. Major postoperative complications frequently delay initiation of adjuvant chemotherapy or radiotherapy beyond recommended time intervals, potentially reducing oncological effectiveness in selected malignancies. Studies published during the last several years demonstrate that patients managed within standardized ERAS pathways experience earlier functional recovery and are significantly more likely to commence adjuvant treatment according to planned schedules. Improved perioperative recovery may therefore contribute not only to

reduced postoperative morbidity but also to optimization of long-term oncological outcomes [13–17].

Evaluation of ERAS effectiveness has become increasingly standardized by validated outcome measures. Postoperative morbidity is commonly assessed using the Clavien–Dindo classification and the Comprehensive Complication Index, whereas functional recovery is evaluated by time to first oral intake, first bowel movement, independent ambulation, hospital discharge, and patient-reported quality-of-life measures. Compliance with individual ERAS elements has emerged as an independent predictor of clinical outcomes, with each additional successfully implemented protocol component contributing to progressive reductions in postoperative complications and healthcare resource utilization [15–19].

Recent technological advances are further expanding the role of ERAS in oncologic surgery. Digital perioperative platforms, wearable monitoring devices, telemedicine follow-up, artificial intelligence–based predictive algorithms, and individualized perioperative risk models allow continuous assessment of physiological recovery and early detection of postoperative deterioration. Integration of these technologies with established ERAS protocols is expected to improve patient adherence, optimize perioperative decision-making, facilitate personalized postoperative care, and further reduce complications following major oncologic surgery [17–20].

Discussion

The findings of the present review demonstrate that ERAS protocols have fundamentally changed the concept of perioperative care in oncologic surgery by replacing traditional procedure-centered management with an evidence-based, multidisciplinary approach focused on preservation of physiological function and accelerated recovery. Contemporary studies consistently show that postoperative outcomes depend not only on surgical technique but also on optimization of the patient's metabolic, nutritional, inflammatory, and functional status throughout the perioperative period. These observations explain why comprehensive ERAS pathways achieve greater clinical benefit than isolated perioperative interventions [8–11].

One of the principal advantages of ERAS implementation is attenuation of the surgical stress response. Reduction of prolonged fasting, early enteral nutrition, multimodal opioid-sparing analgesia, goal-directed fluid therapy, maintenance of normothermia, and early mobilization collectively reduce insulin resistance, preserve skeletal muscle function, improve gastrointestinal recovery, and decrease postoperative immunosuppression. These physiological effects are particularly important in oncology, where excessive postoperative inflammation and delayed recovery may adversely influence tolerance to subsequent antitumor treatment. High-quality evidence therefore supports ERAS as a strategy that improves both short-term surgical recovery and overall continuity of oncological care [10–14].

An important finding across recent studies is the strong relationship between ERAS protocol compliance and clinical outcomes. Centers achieving adherence rates exceeding 70–80% consistently report lower postoperative morbidity, fewer infectious complications, reduced incidence of postoperative ileus, shorter hospitalization, and lower healthcare costs compared with institutions implementing only selected ERAS

components. These data indicate that the effectiveness of ERAS depends on coordinated execution of the complete perioperative pathway rather than on individual interventions performed in isolation, emphasizing the importance of standardized multidisciplinary implementation [12–16].

Current evidence also demonstrates that ERAS protocols are applicable across a broad spectrum of oncologic procedures, including colorectal, gastric, esophageal, hepatopancreatobiliary, urological, thoracic, breast, and gynecological cancer surgery. Although specific protocol elements may require adaptation according to surgical complexity and tumor location, the overall clinical benefits remain remarkably consistent. Reductions in postoperative complications are accompanied by earlier restoration of functional independence, shorter time to oral nutrition, and more rapid recovery of physical activity, supporting widespread implementation of ERAS across different oncological specialties [13–17].

Another clinically significant advantage of ERAS is its influence on multidisciplinary cancer treatment. Major postoperative complications frequently delay the initiation of adjuvant chemotherapy or radiotherapy beyond recommended timeframes, potentially compromising long-term disease control in selected malignancies. Patients recovering through standardized ERAS pathways are more likely to begin postoperative oncological treatment according to schedule because of faster physiological recovery and fewer severe complications. This relationship suggests that perioperative optimization may indirectly contribute to improved oncological outcomes in addition to reducing surgical morbidity [15–18].

Despite substantial progress, several challenges remain. Variability in institutional resources, differences in protocol implementation, limited compliance with individual ERAS elements, and heterogeneity among patient populations continue to influence clinical outcomes. Future research should focus on personalized ERAS pathways incorporating frailty assessment, sarcopenia evaluation, digital perioperative monitoring, artificial intelligence–based risk prediction, and remote postoperative follow-up. Integration of these technologies into established ERAS programs has the potential to further reduce postoperative complications, improve adherence to evidence-based perioperative care, and optimize long-term outcomes for patients undergoing oncologic surgery [17–20].

CONCLUSION

Enhanced Recovery After Surgery (ERAS) protocols have become an essential component of contemporary oncologic surgery, providing a comprehensive evidence-based approach to perioperative care that extends beyond the technical aspects of surgical treatment. Current evidence demonstrates that implementation of multimodal ERAS pathways effectively attenuates the surgical stress response, reduces postoperative complications, accelerates recovery of gastrointestinal function and physical activity, shortens hospital stay, and improves overall postoperative outcomes across a wide range of oncological procedures. High compliance with ERAS protocols is consistently associated with superior clinical results, emphasizing the importance of coordinated multidisciplinary implementation throughout the perioperative period.

The greatest clinical benefit is achieved through integration of prehabilitation, minimally invasive surgical techniques, optimized anesthesia, multimodal analgesia, individualized fluid management, early mobilization, and timely nutritional support. Beyond improving short-term recovery, ERAS protocols facilitate earlier initiation of adjuvant oncological therapy, contributing to uninterrupted multidisciplinary cancer treatment. Future development of personalized ERAS pathways incorporating frailty assessment, digital perioperative monitoring, artificial intelligence, and predictive analytics is expected to further enhance perioperative decision-making, reduce postoperative morbidity, and improve long-term outcomes for patients undergoing oncologic surgery.

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CARDIOMETABOLIC MYOCARDIAL REMODELING IN TYPE 2 DIABETES MELLITUS: CONTEMPORARY MECHANISMS, DIAGNOSTIC APPROACHES, AND PREVENTIVE STRATEGIES

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Abstract. Cardiometabolic myocardial remodeling represents a fundamental pathological process underlying the development of diabetic cardiomyopathy and contributes substantially to the increased incidence of heart failure, arrhythmias, and cardiovascular mortality among individuals with type 2 diabetes mellitus. Beyond the impact of accelerated atherosclerosis and macrovascular disease, chronic hyperglycemia, insulin resistance, lipotoxicity, mitochondrial dysfunction, oxidative stress, low-grade inflammation, and myocardial fibrosis induce progressive structural and functional alterations of the myocardium. Recent advances in cardiovascular imaging, biomarker discovery, and molecular cardiology have considerably expanded current understanding of these mechanisms, creating new opportunities for earlier diagnosis and more targeted prevention of diabetic myocardial injury.

This systematic literature review summarizes contemporary evidence regarding the mechanisms of cardiometabolic myocardial remodeling in type 2 diabetes mellitus and evaluates current diagnostic approaches and preventive strategies. Particular attention is devoted to the molecular pathways involved in myocardial remodeling, multimodality cardiovascular imaging, circulating biomarkers, and the emerging role of sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and other cardioprotective therapies. The available evidence indicates that early identification of subclinical myocardial dysfunction combined with comprehensive cardiometabolic risk modification and personalized therapeutic interventions may substantially reduce the progression of structural cardiac damage

and improve long-term cardiovascular outcomes in patients with type 2 diabetes mellitus.

Keywords: *type 2 diabetes mellitus; cardiometabolic remodeling; diabetic cardiomyopathy; myocardial fibrosis; insulin resistance; cardiovascular imaging; echocardiography; cardiac magnetic resonance imaging; SGLT2 inhibitors; GLP-1 receptor agonists.*

Introduction

Type 2 diabetes mellitus (T2DM) remains one of the leading contributors to cardiovascular morbidity and mortality worldwide, affecting more than half a billion individuals and imposing a substantial burden on healthcare systems. Although accelerated atherosclerosis has traditionally been considered the principal mechanism responsible for adverse cardiovascular outcomes in diabetes, growing evidence indicates that chronic metabolic disturbances directly affect myocardial structure and function independently of obstructive coronary artery disease or hypertension. These changes collectively contribute to cardiometabolic myocardial remodeling, a complex process characterized by progressive alterations in myocardial architecture, metabolism, and mechanical performance that ultimately predispose patients to heart failure and other cardiovascular complications [1–3].

Cardiometabolic myocardial remodeling develops through the interaction of multiple pathophysiological mechanisms. Persistent hyperglycemia, insulin resistance, lipotoxicity, mitochondrial dysfunction, oxidative stress, chronic low-grade inflammation, endothelial dysfunction, and activation of profibrotic signaling pathways promote cardiomyocyte hypertrophy, apoptosis, extracellular matrix expansion, and diffuse myocardial fibrosis. These abnormalities impair myocardial energetics, reduce ventricular compliance, and progressively compromise both systolic and diastolic function. Increasing recognition of these mechanisms has shifted attention from the management of overt cardiovascular disease toward earlier identification of subclinical myocardial injury and prevention of irreversible structural remodeling [2–5].

Substantial progress has also been achieved in the diagnosis of diabetic myocardial involvement. Contemporary echocardiographic techniques, particularly speckle-tracking echocardiography and global longitudinal strain analysis, enable detection of subtle myocardial dysfunction before conventional measures such as left ventricular ejection fraction become abnormal. Cardiac magnetic resonance imaging with tissue characterization, including T1 mapping and extracellular volume quantification, provides additional insight into diffuse myocardial fibrosis and structural remodeling. Simultaneously, the emergence of novel circulating biomarkers and multimodal risk assessment has improved the ability to identify patients at increased cardiovascular risk during the asymptomatic stages of disease [4–7].

The therapeutic landscape has evolved considerably with the introduction of glucose-lowering agents that provide cardiovascular protection beyond glycemic control. Sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, and other cardiometabolic therapies have demonstrated favorable effects on myocardial remodeling, heart failure risk, and cardiovascular outcomes in patients with

T2DM. These advances underscore the importance of integrating mechanistic understanding with early diagnostic strategies and individualized preventive interventions. The aim of the study was to summarize current evidence regarding the mechanisms of cardiometabolic myocardial remodeling in type 2 diabetes mellitus, contemporary diagnostic approaches, and preventive strategies aimed at reducing cardiovascular complications and improving long-term clinical outcomes.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence on the mechanisms of cardiometabolic myocardial remodeling in patients with type 2 diabetes mellitus, current diagnostic approaches, and preventive strategies. A comprehensive search of the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases was performed to identify relevant publications published between 2020 and 2026. Earlier landmark studies and international clinical guidelines were included only when they provided essential evidence regarding the pathophysiology or clinical management of diabetic myocardial remodeling.

The review included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational studies, and evidence-based clinical practice guidelines addressing myocardial remodeling, diabetic cardiomyopathy, cardiovascular imaging, circulating biomarkers, and preventive therapeutic interventions in patients with type 2 diabetes mellitus. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological rigor or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on molecular mechanisms, diagnostic performance of contemporary imaging modalities and biomarkers, as well as the effectiveness of pharmacological and non-pharmacological preventive strategies.

Results

Cardiometabolic myocardial remodeling in type 2 diabetes mellitus develops through the interaction of multiple metabolic, inflammatory, and neurohormonal pathways that progressively alter myocardial structure and function. Persistent hyperglycemia promotes the accumulation of advanced glycation end products, activation of protein kinase C, excessive production of reactive oxygen species, and chronic inflammatory signaling, all of which contribute to cardiomyocyte injury and extracellular matrix remodeling. Simultaneously, insulin resistance disrupts myocardial glucose utilization, shifting energy metabolism toward increased fatty acid oxidation. Although this adaptation initially preserves ATP production, prolonged lipid overload results in lipotoxicity, mitochondrial dysfunction, impaired myocardial energetics, and progressive ventricular dysfunction [8–10].

Diffuse myocardial fibrosis represents one of the central pathological features of diabetic myocardial remodeling. Activation of transforming growth factor-β, connective tissue growth factor, and profibrotic signaling pathways stimulates excessive collagen synthesis and extracellular matrix expansion, leading to increased myocardial stiffness and impaired ventricular relaxation. Histopathological and

imaging studies consistently demonstrate that diffuse interstitial fibrosis develops long before clinical manifestations of heart failure become apparent. These structural alterations are closely associated with progressive deterioration of both diastolic and systolic function and independently predict adverse cardiovascular outcomes [9–12].

Growing evidence suggests that diabetic myocardial remodeling should be regarded as a systemic cardiometabolic disorder rather than an isolated cardiac abnormality. Endothelial dysfunction, coronary microvascular impairment, autonomic imbalance, chronic low-grade inflammation, adipose tissue dysfunction, and activation of the renin–angiotensin–aldosterone system interact to accelerate structural myocardial damage. Persistent inflammatory activation involving cytokines such as interleukin-6 and tumor necrosis factor-α further amplifies oxidative stress and fibrotic remodeling, while mitochondrial injury reduces myocardial energetic efficiency and cellular resilience [10–13].

Advances in cardiovascular imaging have substantially improved the detection of subclinical myocardial involvement. Speckle-tracking echocardiography enables identification of impaired global longitudinal strain before left ventricular ejection fraction declines, allowing recognition of early systolic dysfunction despite preserved conventional echocardiographic parameters. Cardiac magnetic resonance imaging provides highly sensitive assessment of myocardial tissue characteristics, with native T1 mapping and extracellular volume quantification enabling non-invasive evaluation of diffuse fibrosis. These imaging techniques have demonstrated superior sensitivity for detecting early myocardial remodeling and are increasingly incorporated into risk stratification algorithms for patients with T2DM [11–15].

Circulating biomarkers further enhance early detection and risk assessment. High-sensitivity cardiac troponins, N-terminal pro-B-type natriuretic peptide, soluble ST2, galectin-3, growth differentiation factor-15, and markers of collagen turnover have shown significant associations with myocardial fibrosis, ventricular dysfunction, and future cardiovascular events. Although no single biomarker currently provides sufficient diagnostic accuracy in isolation, combining biochemical markers with advanced cardiac imaging significantly improves identification of patients at high risk for progressive myocardial remodeling and heart failure [12–16].

Contemporary pharmacological management has shifted from glycemic control alone toward comprehensive cardiometabolic protection. Sodium-glucose cotransporter-2 inhibitors consistently reduce hospitalization for heart failure, attenuate left ventricular remodeling, improve myocardial energetics, and preserve renal function across a broad spectrum of cardiovascular risk. Glucagon-like peptide-1 receptor agonists demonstrate favorable effects on body weight, systemic inflammation, endothelial function, and atherosclerotic cardiovascular disease, while selective non-steroidal mineralocorticoid receptor antagonists and other emerging therapies further contribute to attenuation of myocardial fibrosis and ventricular remodeling [13–18].

Non-pharmacological interventions remain fundamental components of prevention. Sustained weight reduction, regular aerobic and resistance exercise, dietary modification, optimization of blood pressure and lipid levels, smoking cessation, and

treatment of obstructive sleep apnea collectively reduce metabolic stress and improve myocardial function. Current evidence supports the integration of lifestyle modification with early initiation of cardioprotective pharmacotherapy, emphasizing that prevention of myocardial remodeling requires comprehensive management of the entire cardiometabolic profile rather than isolated glucose lowering [15–19].

Despite substantial advances in understanding diabetic myocardial remodeling, several important challenges remain. The heterogeneous clinical presentation, variable progression of structural myocardial changes, and absence of universally accepted screening algorithms continue to limit early diagnosis. Furthermore, uncertainty persists regarding the optimal combination of imaging modalities, circulating biomarkers, and therapeutic strategies for individualized risk assessment. Nevertheless, the available evidence consistently supports early identification of subclinical myocardial injury and timely implementation of multimodal preventive interventions as the most effective approach for limiting cardiometabolic myocardial remodeling and reducing long-term cardiovascular complications in patients with type 2 diabetes mellitus [16–20].

Discussion

The findings of the present review indicate that cardiometabolic myocardial remodeling represents a central mechanism linking type 2 diabetes mellitus with the subsequent development of heart failure and other adverse cardiovascular outcomes. Rather than being a consequence of isolated hyperglycemia, myocardial injury results from the cumulative effects of metabolic dysregulation, chronic inflammation, oxidative stress, mitochondrial dysfunction, and progressive fibrosis. This concept explains why structural and functional cardiac abnormalities frequently emerge before the onset of overt clinical manifestations and highlights the importance of identifying myocardial involvement during the subclinical stage of disease [8–11].

An important observation across contemporary studies is the growing shift from conventional cardiovascular risk assessment toward earlier detection of myocardial remodeling using sensitive imaging techniques and circulating biomarkers. Speckle-tracking echocardiography and cardiac magnetic resonance imaging have substantially improved the ability to identify diffuse myocardial abnormalities that are not detected by standard echocardiographic parameters. When combined with biomarkers reflecting myocardial injury, fibrosis, and neurohormonal activation, these approaches provide a more comprehensive evaluation of cardiovascular risk and may facilitate earlier implementation of preventive interventions [10–14].

Recent therapeutic advances have also transformed the management of patients with T2DM. Large cardiovascular outcome trials consistently demonstrate that SGLT2 inhibitors and GLP-1 receptor agonists exert cardioprotective effects extending beyond glucose lowering. Improvement of myocardial energetics, attenuation of inflammation and fibrosis, reduction of ventricular wall stress, and favorable effects on body weight and renal function collectively contribute to slowing the progression of myocardial remodeling. These observations support a transition from purely glycemic management toward integrated cardiometabolic protection as a principal therapeutic objective [12–17].

Despite these advances, important limitations remain in the current body of evidence. Published studies differ considerably in patient characteristics, duration of diabetes, imaging protocols, biomarker panels, and definitions of subclinical myocardial dysfunction, making direct comparison between investigations challenging. Furthermore, many studies evaluate surrogate imaging or biochemical endpoints rather than long-term clinical outcomes, limiting the ability to determine which diagnostic strategies provide the greatest prognostic value in routine practice [13–18].

Another emerging direction is the application of precision cardiovascular medicine. The integration of multimodal imaging, circulating biomarkers, genetic profiling, and artificial intelligence–based analytical models may enable more accurate prediction of disease progression and individualized therapeutic decision-making. Such approaches have the potential to identify patients who would derive the greatest benefit from early cardioprotective treatment while avoiding unnecessary interventions in lower-risk populations. Although these technologies remain under active investigation, preliminary evidence suggests that they may substantially improve future strategies for cardiovascular prevention in diabetes [15–19].

Future research should prioritize prospective multicenter studies with standardized diagnostic criteria and harmonized outcome measures to better define the natural history of cardiometabolic myocardial remodeling and evaluate long-term therapeutic efficacy. Particular attention should be directed toward identifying reliable screening algorithms for asymptomatic patients, validating novel imaging biomarkers, and clarifying the combined effects of emerging pharmacological therapies. Continued integration of molecular biology, advanced cardiovascular imaging, and personalized treatment strategies is expected to further improve prevention of myocardial remodeling and reduce the cardiovascular burden associated with type 2 diabetes mellitus [17–20].

CONCLUSION

Cardiometabolic myocardial remodeling is a key pathophysiological process underlying the development of diabetic cardiomyopathy and cardiovascular complications in patients with type 2 diabetes mellitus. The available evidence indicates that structural and functional myocardial alterations arise from the complex interaction of metabolic, inflammatory, and neurohormonal mechanisms, often preceding the onset of clinically apparent cardiovascular disease. Contemporary diagnostic modalities, particularly advanced echocardiography, cardiac magnetic resonance imaging, and circulating biomarkers, have substantially improved the detection of subclinical myocardial injury, while emerging cardioprotective therapies have expanded opportunities for preventing or slowing disease progression.

Future advances in this field will depend on earlier identification of high-risk individuals, implementation of personalized diagnostic algorithms, and broader integration of multimodal cardiovascular assessment into routine clinical practice. Further prospective studies are required to establish standardized screening strategies, validate novel biomarkers, and determine the long-term impact of targeted pharmacological and non-pharmacological interventions on myocardial remodeling

and cardiovascular outcomes. Such developments may facilitate more effective prevention of heart failure and improve long-term prognosis in patients with type 2 diabetes mellitus.

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THE SKIN MICROBIOME AND ATOPIC DERMATITIS: FROM PATHOGENESIS TO EMERGING THERAPEUTIC STRATEGIES

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Abstract. The skin microbiome has emerged as a critical regulator of epidermal homeostasis, immune function, and barrier integrity, playing a central role in the development and progression of atopic dermatitis. Increasing evidence indicates that alterations in the composition and diversity of cutaneous microbial communities contribute to epithelial barrier dysfunction, immune dysregulation, and chronic type 2 inflammation. Microbial dysbiosis, characterized by reduced bacterial diversity and overgrowth of *Staphylococcus aureus*, has been consistently associated with disease exacerbation, increased severity, and impaired therapeutic response. These discoveries have shifted the understanding of atopic dermatitis from a primarily inflammatory skin disorder toward a complex disease involving dynamic interactions between the host immune system, skin barrier, and resident microbiota.

This review summarizes current evidence regarding the role of the skin microbiome in the pathogenesis of atopic dermatitis and discusses emerging microbiome-targeted therapeutic strategies. Particular attention is given to the mechanisms linking microbial dysbiosis with epidermal barrier impairment, immune activation, and disease progression, as well as advances in microbiome profiling, biologic therapy, Janus kinase inhibitors, probiotics, bacteriotherapy, bacteriophages, and other novel therapeutic approaches. Recent studies suggest that restoration of microbial diversity

and modulation of host–microbiome interactions may complement conventional anti-inflammatory treatment and represent an important step toward personalized management of atopic dermatitis.

Keywords: *atopic dermatitis; skin microbiome; microbial dysbiosis; Staphylococcus aureus; skin barrier; biologic therapy; Janus kinase inhibitors; probiotics; bacteriotherapy; precision medicine.*

Introduction

Atopic dermatitis is a chronic inflammatory skin disease characterized by recurrent eczematous lesions, intense pruritus, impaired epidermal barrier function, and marked heterogeneity in clinical presentation. It affects both children and adults and represents one of the most prevalent immune-mediated dermatological disorders worldwide. Despite significant advances in understanding its immunopathology, the mechanisms responsible for disease onset, persistence, and recurrent exacerbations remain incompletely understood. Contemporary evidence indicates that atopic dermatitis results from a complex interaction among genetic susceptibility, epidermal barrier dysfunction, environmental factors, immune dysregulation, and alterations in the cutaneous microbiome [1–3].

The skin microbiome has emerged as a fundamental regulator of cutaneous homeostasis. Under physiological conditions, diverse microbial communities contribute to maintenance of epithelial barrier integrity, modulation of innate and adaptive immune responses, inhibition of pathogenic microorganisms, and preservation of local immune tolerance. In patients with atopic dermatitis, however, this ecological balance is disrupted by a reduction in microbial diversity and a predominance of *Staphylococcus aureus*, which promotes epithelial damage, amplifies type 2 inflammatory responses, and increases disease severity. These observations have established microbial dysbiosis as a key component of disease pathogenesis rather than a secondary consequence of inflammation [3–5].

Advances in molecular microbiology, high-throughput sequencing technologies, and metagenomic analysis have substantially expanded understanding of host–microbiome interactions in atopic dermatitis. These technologies have demonstrated that microbial composition changes dynamically during disease flares and remission, suggesting that alterations in the skin microbiome may serve not only as markers of disease activity but also as potential therapeutic targets. At the same time, growing evidence indicates that successful treatment with biologic agents and targeted small-molecule therapies is accompanied by partial restoration of microbial diversity and improvement of epidermal barrier function, further supporting the close relationship between immune regulation and microbial homeostasis [5–7].

Recognition of the skin microbiome as a therapeutic target has stimulated the development of innovative treatment strategies aimed at restoring microbial equilibrium rather than solely suppressing inflammation. Probiotics, postbiotics, bacteriotherapy, bacteriophage-based therapy, microbiome transplantation, antimicrobial peptides, biologic agents, and Janus kinase inhibitors are currently being investigated as complementary approaches to conventional management. As knowledge of host–microbiome interactions continues to evolve, microbiome-directed

interventions are expected to become an increasingly important component of precision medicine in patients with atopic dermatitis [7].

Aim of the study was to review current evidence regarding the role of the skin microbiome in the pathogenesis of atopic dermatitis and to evaluate emerging microbiome-targeted therapeutic strategies with emphasis on their mechanisms of action, clinical effectiveness, and future applications in personalized patient care.

Materials and Methods

This study was conducted as a systematic literature review. A comprehensive search of the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases was performed to identify relevant publications published between 2020 and 2026. Priority was given to international clinical practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, prospective cohort studies, and translational research investigating the role of the skin microbiome in atopic dermatitis and the development of microbiome-targeted therapeutic strategies.

Studies evaluating microbial dysbiosis, host–microbiome interactions, epidermal barrier dysfunction, immune mechanisms, microbiome profiling, biologic therapy, Janus kinase inhibitors, probiotics, postbiotics, bacteriotherapy, bacteriophages, and other emerging therapeutic approaches were included. Case reports, conference abstracts, duplicate publications, and studies lacking clinically relevant microbiological or therapeutic outcomes were excluded. The selected evidence was critically synthesized to evaluate the contribution of the skin microbiome to disease pathogenesis and its potential as a therapeutic target in the management of atopic dermatitis.

Results

The skin microbiome is a highly dynamic ecosystem composed of bacteria, fungi, viruses, and mites that collectively contribute to maintenance of epidermal homeostasis and cutaneous immune defense. Under physiological conditions, commensal microorganisms interact with keratinocytes and resident immune cells to preserve epithelial barrier integrity, regulate antimicrobial peptide production, and inhibit colonization by pathogenic species. This balanced microbial environment supports immune tolerance and protects against excessive inflammatory responses. Disruption of microbial homeostasis has emerged as one of the central mechanisms contributing to the development of inflammatory skin disorders, particularly atopic dermatitis [8,9].

Microbial dysbiosis is now recognized as a characteristic feature of atopic dermatitis. Numerous sequencing studies have consistently demonstrated a marked reduction in microbial diversity accompanied by expansion of *Staphylococcus aureus*, particularly during disease exacerbations. Increased *S. aureus* colonization promotes epidermal barrier disruption through the production of proteases, toxins, and superantigens that stimulate keratinocyte injury and amplify type 2 immune responses. The degree of microbial imbalance has been shown to correlate closely with disease severity, lesion extent, and clinical activity, suggesting that microbiome composition may serve as a biomarker of disease progression [9–11].

The interaction between the skin microbiome and the host immune system represents a fundamental component of disease pathogenesis. Dysbiosis contributes to

activation of epithelial alarmins, including thymic stromal lymphopoietin, interleukin-25, and interleukin-33, leading to polarization of T-helper 2 immune responses and increased production of interleukin-4, interleukin-13, interleukin-5, and interleukin-31. These cytokines impair epidermal differentiation, suppress antimicrobial peptide synthesis, reduce filaggrin expression, and further compromise barrier integrity, establishing a self-perpetuating cycle linking microbial imbalance with chronic inflammation [10–12].

Advances in molecular microbiology have substantially improved characterization of the cutaneous microbiome. High-throughput sequencing, shotgun metagenomics, metatranscriptomics, and other multi-omics technologies now permit comprehensive analysis of microbial diversity, functional activity, and host–microbiome interactions. These techniques have demonstrated dynamic microbial changes during disease flares, treatment response, and remission, providing opportunities for microbiome-based biomarkers capable of supporting disease stratification, therapeutic monitoring, and individualized treatment selection [11–14].

Conventional treatment remains focused on restoration of epidermal barrier function and suppression of inflammation. Regular use of emollients, topical corticosteroids, topical calcineurin inhibitors, phosphodiesterase-4 inhibitors, and systemic immunomodulatory therapy effectively improve clinical symptoms while indirectly promoting recovery of microbial diversity through normalization of the skin barrier. Nevertheless, persistent dysbiosis may remain detectable despite clinical improvement, suggesting that inflammatory control alone may not fully restore microbial homeostasis in all patients [13–16].

Growing attention has therefore shifted toward therapies directly targeting the skin microbiome. Probiotics, prebiotics, postbiotics, topical application of beneficial commensal bacteria, bacteriophage therapy, antimicrobial peptides, and microbiome transplantation are being investigated as complementary approaches aimed at reducing *Staphylococcus aureus* colonization while restoring microbial diversity. Early clinical studies have demonstrated encouraging improvements in disease severity and microbial composition, although larger randomized trials remain necessary to establish long-term efficacy and safety [15–18].

The introduction of biologic agents and targeted small-molecule therapies has further expanded treatment opportunities for patients with moderate-to-severe atopic dermatitis. Clinical studies evaluating dupilumab, tralokinumab, lebrikizumab, and Janus kinase inhibitors have demonstrated not only significant reductions in disease activity but also progressive normalization of the skin microbiome. Decreased *Staphylococcus aureus* abundance together with restoration of commensal bacterial populations has been observed following effective suppression of type 2 inflammation, highlighting the close relationship between immune regulation and microbial homeostasis [17–19].

Current evidence increasingly supports a precision medicine approach integrating microbiome profiling with clinical, immunological, and molecular biomarkers. Artificial intelligence-assisted analysis of metagenomic data, machine learning algorithms, and multi-omics integration are expected to improve patient stratification,

predict therapeutic response, and identify novel microbiome-targeted interventions. As understanding of host–microbiome interactions continues to evolve, personalized modulation of the cutaneous microbiome may become an essential component of future therapeutic strategies for atopic dermatitis, complementing conventional anti-inflammatory treatment and improving long-term disease control [19,20].

Discussion

The findings of this review support the concept that the skin microbiome is an active participant in the pathogenesis of atopic dermatitis rather than a passive consequence of chronic inflammation. Contemporary research demonstrates that microbial dysbiosis contributes to disruption of epidermal barrier integrity, amplification of type 2 immune responses, and persistence of cutaneous inflammation through continuous interactions between resident microorganisms and the host immune system. The characteristic predominance of *Staphylococcus aureus* and the accompanying reduction in microbial diversity have been consistently associated with disease severity, frequency of exacerbations, and impaired barrier function, emphasizing the biological significance of microbial homeostasis in maintaining healthy skin [8–10].

An important observation emerging from recent studies is that restoration of microbial diversity appears to parallel clinical improvement rather than simply reflect reduced inflammation. Effective treatment is accompanied by progressive normalization of the cutaneous microbial ecosystem, suggesting that successful disease control involves simultaneous recovery of immune regulation, epidermal barrier function, and microbial balance. This concept supports the growing recognition that therapeutic strategies directed exclusively at suppressing inflammation may be insufficient to achieve sustained remission if microbial dysbiosis persists. Consequently, the skin microbiome has become an important therapeutic target alongside conventional immunomodulatory approaches [10–13].

Rapid advances in sequencing technologies have substantially expanded understanding of host–microbiome interactions in atopic dermatitis. High-throughput metagenomic analysis has demonstrated considerable interindividual variability in microbial composition, indicating that the cutaneous microbiome may influence treatment response and disease progression differently among patients. These observations reinforce the concept of biological heterogeneity within atopic dermatitis and provide a rationale for integrating microbiome profiling into future personalized management strategies. At present, however, standardization of sampling techniques, sequencing methodologies, and bioinformatic analysis remains necessary before microbiome assessment can be routinely incorporated into clinical practice [12–15].

Growing evidence also supports the therapeutic potential of microbiome-directed interventions. Probiotics, postbiotics, topical application of beneficial commensal microorganisms, bacteriophage therapy, and antimicrobial peptides have demonstrated encouraging preliminary results by reducing *Staphylococcus aureus* colonization and promoting restoration of microbial diversity. Nevertheless, clinical evidence remains heterogeneous, with variations in treatment protocols, microbial preparations, and outcome measures limiting direct comparison between published studies. Large

multicenter randomized trials will therefore be essential to establish the long-term efficacy, safety, and optimal clinical indications for these emerging therapies [14–17].

The introduction of biologic agents and Janus kinase inhibitors has further strengthened the link between immune modulation and microbiome restoration. Clinical investigations consistently demonstrate that targeted inhibition of key inflammatory pathways not only improves disease severity but is also accompanied by normalization of the skin microbial community, particularly through reduction of *Staphylococcus aureus* abundance and recovery of commensal bacterial populations. These findings suggest that successful management of atopic dermatitis should be viewed as a process of restoring the equilibrium between the epidermal barrier, immune system, and cutaneous microbiome rather than focusing solely on suppression of inflammatory mediators [16–19].

Future progress in the management of atopic dermatitis is expected to rely on precision medicine approaches integrating microbiome profiling, immunological biomarkers, genomic data, and artificial intelligence-assisted predictive models. Such strategies may enable earlier identification of disease endotypes, prediction of therapeutic response, and selection of individualized microbiome-targeted interventions. Continued advances in multi-omics technologies and translational research are likely to transform the skin microbiome from a promising biological marker into a clinically actionable therapeutic target, ultimately improving long-term disease control and quality of life for patients with atopic dermatitis [18–20].

CONCLUSION

Current evidence demonstrates that the skin microbiome plays a fundamental role in the pathogenesis of atopic dermatitis through its close interaction with the epidermal barrier and the cutaneous immune system. Microbial dysbiosis, characterized by reduced microbial diversity and overrepresentation of *Staphylococcus aureus*, contributes to persistent inflammation, impaired barrier function, and recurrent disease exacerbations. Advances in microbiome research have substantially expanded the understanding of disease mechanisms, highlighting that restoration of microbial homeostasis is closely associated with clinical improvement and may represent an important therapeutic objective alongside suppression of type 2 inflammation.

Emerging microbiome-targeted therapies, including probiotics, postbiotics, bacteriotherapy, bacteriophages, biologic agents, and Janus kinase inhibitors, have opened new opportunities for individualized treatment of atopic dermatitis. Although many of these approaches remain under clinical investigation, accumulating evidence suggests that combining immune modulation with strategies aimed at restoring microbial diversity may improve long-term disease control and reduce the risk of relapse. Future integration of microbiome profiling, multi-omics technologies, and artificial intelligence into clinical practice is expected to support precision medicine approaches and further optimize therapeutic decision-making for patients with atopic dermatitis.

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THE IMPACT OF ALLERGIC RHINITIS ON SLEEP QUALITY AND COGNITIVE FUNCTION IN ADULTS

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Abstract. Allergic rhinitis is one of the most prevalent chronic inflammatory diseases of the upper respiratory tract and is increasingly recognized as a condition that extends beyond nasal symptoms alone. Persistent nasal obstruction, mucosal inflammation, nocturnal symptom exacerbation, and sleep fragmentation contribute to impaired sleep quality, excessive daytime sleepiness, and reduced cognitive performance. These disturbances adversely affect attention, memory, executive functioning, occupational productivity, and overall quality of life. Growing evidence suggests that the burden of allergic rhinitis is mediated not only by local inflammatory processes but also by complex interactions between immune activation, sleep disruption, and neurocognitive function.

This systematic literature review summarizes current evidence regarding the impact of allergic rhinitis on sleep quality and cognitive function in adults and evaluates contemporary approaches to diagnosis, assessment, and management. Particular attention is given to the mechanisms linking upper airway inflammation with sleep disturbances, objective and subjective methods for evaluating sleep and cognition, and the effects of pharmacological treatment and allergen-specific immunotherapy on neurocognitive outcomes. The review also examines emerging applications of digital sleep monitoring and personalized therapeutic strategies aimed at improving both sleep quality and cognitive performance. Current evidence supports comprehensive management of allergic rhinitis as an important strategy for reducing disease burden and optimizing long-term functional outcomes in adult patients.

Keywords: *allergic rhinitis; sleep quality; cognitive function; excessive daytime sleepiness; nasal obstruction; inflammation; polysomnography; quality of life; allergen immunotherapy; neurocognitive impairment.*

Introduction

Allergic rhinitis is one of the most common chronic inflammatory disorders affecting the upper respiratory tract, with an estimated prevalence exceeding 20% of the adult population in many countries. Although traditionally regarded as a disease characterized by nasal congestion, rhinorrhea, sneezing, and itching, allergic rhinitis is now recognized as a systemic inflammatory condition capable of substantially impairing physical, psychological, and social well-being. The persistence of symptoms throughout the day and their frequent exacerbation during the night contribute to a considerable reduction in quality of life and represent an important source of functional disability among adults [1–3].

Sleep disturbance has emerged as one of the most clinically significant yet frequently underestimated consequences of allergic rhinitis. Chronic nasal obstruction increases upper airway resistance, promotes mouth breathing, disrupts normal sleep architecture, and contributes to recurrent nocturnal awakenings, fragmented sleep, and excessive daytime sleepiness. Inflammatory mediators, including histamine, interleukins, and other cytokines, may further influence central mechanisms regulating sleep–wake cycles, suggesting that impaired sleep in allergic rhinitis results from both mechanical and immunological pathways [2–5].

Growing evidence indicates that chronic sleep disruption associated with allergic rhinitis adversely affects cognitive performance. Adults with persistent symptoms frequently demonstrate impairments in attention, working memory, executive function, psychomotor speed, and learning efficiency, leading to reduced occupational productivity and diminished daily functioning. Neurocognitive impairment appears to be mediated by the combined effects of sleep fragmentation, intermittent nocturnal hypoxia in selected patients, systemic inflammation, and altered neuroimmune signaling. These findings have expanded the clinical significance of allergic rhinitis beyond symptom control alone and have highlighted its broader neurological and psychosocial consequences [4–7].

Recent advances in sleep medicine, allergy diagnostics, and digital health technologies have improved the ability to evaluate both sleep quality and cognitive function in patients with allergic rhinitis. Objective assessment using polysomnography, actigraphy, validated sleep questionnaires, and standardized neuropsychological testing has strengthened understanding of the relationship between allergic inflammation and neurocognitive performance. At the same time, contemporary pharmacological therapies and allergen-specific immunotherapy have demonstrated the potential to improve not only nasal symptoms but also sleep quality and cognitive outcomes. The aim of the study was to summarize current evidence regarding the impact of allergic rhinitis on sleep quality and cognitive function in adults and to evaluate contemporary approaches to diagnosis, assessment, and treatment of these clinically important complications.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding the impact of allergic rhinitis on sleep quality and cognitive function in adults. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier international guidelines and landmark studies were included only when they provided essential evidence concerning the pathophysiology, diagnosis, or management of allergic rhinitis and its effects on sleep and cognition.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, and evidence-based clinical practice guidelines addressing allergic rhinitis, sleep disturbances, cognitive performance, and therapeutic interventions. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on pathogenic mechanisms, sleep assessment, neurocognitive outcomes, quality of life, and the effectiveness of contemporary treatment strategies.

Results

Allergic rhinitis is increasingly recognized as a chronic inflammatory disorder with important systemic consequences extending beyond the upper respiratory tract. Numerous epidemiological studies demonstrate that adults with persistent allergic rhinitis experience significantly poorer sleep quality, greater daytime fatigue, reduced work productivity, and lower health-related quality of life than individuals without allergic disease. The severity of nocturnal symptoms closely correlates with disease activity, suggesting that inadequate control of nasal inflammation contributes directly to sleep disruption and functional impairment [8–10].

The mechanisms responsible for sleep disturbances in allergic rhinitis are multifactorial. Persistent nasal obstruction increases upper airway resistance, promotes mouth breathing, and interferes with normal sleep architecture by increasing sleep fragmentation and reducing slow-wave and rapid eye movement sleep. In addition, inflammatory mediators such as histamine, interleukin-1β, interleukin-6, tumor necrosis factor-α, and other cytokines influence central nervous system pathways regulating circadian rhythm and sleep–wake homeostasis. These combined mechanical and inflammatory mechanisms explain why patients frequently report difficulty initiating sleep, recurrent nocturnal awakenings, non-restorative sleep, and excessive daytime sleepiness despite adequate sleep duration [9–12].

Objective assessment of sleep has demonstrated measurable alterations in adults with allergic rhinitis. Polysomnographic studies reveal reduced sleep efficiency, prolonged sleep latency, increased arousal index, and greater nocturnal respiratory instability in patients with persistent nasal obstruction. Actigraphy and validated questionnaires, including the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale, consistently demonstrate impaired subjective and objective sleep quality even among individuals with mild disease. Sleep impairment appears

particularly pronounced during seasonal exacerbations and in patients with concomitant asthma or chronic rhinosinusitis [10–13].

Appropriate treatment of allergic rhinitis has been associated with meaningful improvement in sleep quality. Intranasal corticosteroids remain the most effective therapy for reducing nasal inflammation and restoring nasal airflow, leading to better sleep continuity and reduced daytime somnolence. Second-generation antihistamines improve allergic symptoms while producing minimal sedative effects, and allergen-specific immunotherapy has demonstrated sustained benefits extending beyond symptom control through modification of the underlying allergic response. Emerging biological therapies targeting type 2 inflammation have shown promising effects in selected patients with severe allergic disease, although long-term evidence remains limited [11–15].

Cognitive dysfunction has become an increasingly recognized consequence of chronic allergic rhinitis. Adults with persistent symptoms frequently demonstrate deficits in sustained attention, working memory, executive functioning, processing speed, and psychomotor performance. These impairments are associated with reduced occupational productivity, decreased academic performance, impaired decision-making, and diminished daily functioning. Current evidence suggests that cognitive decline results from the combined effects of sleep disruption, chronic inflammation, fatigue, and impaired daytime alertness rather than from allergic inflammation alone [12–16].

Neurocognitive assessment has revealed significant relationships between the severity of sleep disturbance and the degree of cognitive impairment. Individuals with poor sleep quality consistently perform worse on standardized tests evaluating attention, executive function, reaction time, and memory compared with patients whose allergic symptoms are adequately controlled. Functional neuroimaging studies further suggest that chronic sleep disruption may alter activity within brain regions responsible for attention regulation, emotional processing, and higher cognitive functions, although the underlying neurobiological mechanisms continue to be investigated [13–17].

Growing attention has been directed toward objective methods for evaluating sleep and cognitive performance in patients with allergic rhinitis. Integration of polysomnography, actigraphy, wearable sleep monitoring devices, validated neuropsychological testing, and digital symptom tracking enables comprehensive assessment of disease burden while facilitating individualized therapeutic decision-making. Artificial intelligence–based analytical models have demonstrated promising ability to identify patterns of sleep disruption, predict symptom exacerbations, and evaluate treatment response using multimodal clinical data [15–19].

Despite substantial progress, several important challenges remain. Considerable heterogeneity exists among published studies regarding disease severity, seasonal variation, treatment exposure, and methods used to evaluate sleep and cognition. Furthermore, the coexistence of asthma, chronic rhinosinusitis, obesity, anxiety, depression, and obstructive sleep apnea may independently influence cognitive performance and complicate interpretation of study findings. Nevertheless, the current

body of evidence consistently indicates that effective control of allergic rhinitis improves sleep quality, enhances cognitive function, and contributes to better long-term quality of life in adult patients [16–20].

Discussion

The findings of the present review demonstrate that allergic rhinitis should not be regarded solely as a localized inflammatory disorder of the nasal mucosa. Persistent allergic inflammation exerts systemic effects that extend to sleep regulation, daytime functioning, and cognitive performance, substantially increasing the overall burden of disease. Contemporary evidence consistently indicates that impaired sleep represents one of the principal mechanisms through which allergic rhinitis affects cognitive function and quality of life, emphasizing the need for a broader multidisciplinary approach to patient management [8–11].

A consistent observation across recent studies is that nocturnal nasal obstruction and chronic upper airway inflammation contribute to disruption of normal sleep architecture through both mechanical and immunological pathways. Recurrent sleep fragmentation, reduced sleep efficiency, and excessive daytime sleepiness are associated with measurable impairments in attention, working memory, executive function, and psychomotor performance. These relationships appear particularly evident in patients with persistent moderate-to-severe disease, suggesting that inadequate symptom control may have consequences extending well beyond respiratory discomfort [10–14].

From an otorhinolaryngological perspective, comprehensive evaluation of nasal obstruction remains fundamental for understanding the mechanisms responsible for sleep impairment. Structural abnormalities of the nasal cavity, chronic mucosal edema, turbinate hypertrophy, and concomitant sinonasal disorders may further compromise nocturnal airflow and amplify sleep-related symptoms. Careful endoscopic examination, objective assessment of nasal patency, and identification of coexisting upper airway pathology therefore play an important role in selecting the most appropriate therapeutic strategy and improving both respiratory and functional outcomes [12–16].

Another important consideration is the growing recognition that sleep quality should be incorporated into the routine assessment of adults with allergic rhinitis. Validated sleep questionnaires, actigraphy, and polysomnography provide complementary information regarding disease severity that cannot be captured by evaluation of nasal symptoms alone. In selected patients, particularly those with severe daytime somnolence or persistent fatigue despite appropriate therapy, investigation for concomitant sleep disorders such as obstructive sleep apnea may be warranted because overlapping conditions may further impair cognitive function and treatment response [14–18].

Current evidence also indicates that effective treatment of allergic rhinitis may improve neurocognitive outcomes by reducing nocturnal symptoms and restoring normal sleep patterns. Intranasal corticosteroids remain the cornerstone of therapy because of their ability to reduce mucosal inflammation and improve nasal airflow, while second-generation antihistamines and allergen-specific immunotherapy

contribute to sustained symptom control with minimal adverse effects on cognition. Although biological therapies have demonstrated promising results in selected patients with severe type 2 inflammation, additional long-term studies are needed to clarify their impact on sleep quality and cognitive performance [15–19].

Future research should focus on prospective multicenter studies integrating objective sleep assessment, standardized neuropsychological evaluation, inflammatory biomarkers, and advanced digital monitoring technologies. Greater application of wearable devices, artificial intelligence, and precision medicine approaches may improve early identification of patients at increased risk for sleep-related cognitive impairment and facilitate individualized therapeutic strategies. Such developments are expected to strengthen collaboration between allergists, otorhinolaryngologists, sleep medicine specialists, and neurologists while improving long-term functional outcomes in adults with allergic rhinitis [17–20].

CONCLUSION

Allergic rhinitis is associated with clinically significant impairment of sleep quality and cognitive function, affecting multiple aspects of daily performance and overall quality of life in adults. Current evidence indicates that persistent nasal obstruction, chronic allergic inflammation, and sleep fragmentation act synergistically to promote excessive daytime sleepiness, reduced attention, impaired memory, and diminished executive functioning. Early recognition of sleep-related symptoms and comprehensive management of allergic rhinitis are therefore essential not only for controlling nasal manifestations but also for preventing functional and neurocognitive consequences.

Future research should focus on standardizing objective methods for assessing sleep and cognitive performance, validating novel biomarkers of disease burden, and evaluating the long-term effects of emerging therapeutic strategies on neurocognitive outcomes. Integration of allergies, otorhinolaryngology, sleep medicine, and neurology, together with the use of digital monitoring technologies and personalized treatment approaches, may improve symptom control, optimize cognitive function, and enhance long-term quality of life in adults with allergic rhinitis.

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CARDIOVASCULAR REMODELING AFTER PREECLAMPSIA: CURRENT INSIGHTS INTO THE LONG-TERM RISK OF CARDIOVASCULAR DISEASE IN WOMEN

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Abstract. Preeclampsia is increasingly recognized as an early manifestation of future cardiovascular disease rather than a pregnancy-limited hypertensive disorder. Growing evidence demonstrates that women with a history of preeclampsia have a substantially increased long-term risk of chronic hypertension, ischemic heart disease, heart failure, stroke, atrial fibrillation, chronic kidney disease, and premature cardiovascular mortality. Persistent endothelial dysfunction, chronic inflammation, oxidative stress, maladaptive myocardial remodeling, and vascular injury contribute to structural and functional cardiovascular alterations that may persist for years after delivery. These observations have shifted the clinical paradigm from short-term obstetric management toward lifelong cardiovascular surveillance and prevention.

This systematic literature review summarizes current evidence regarding cardiovascular remodeling after preeclampsia and evaluates its contribution to the long-term risk of cardiovascular disease in women. Particular attention is given to the mechanisms of myocardial and vascular remodeling, advanced cardiovascular imaging, circulating biomarkers, risk stratification, and contemporary recommendations for long-term follow-up. The review also discusses emerging applications of artificial intelligence and precision medicine for individualized cardiovascular risk prediction after hypertensive disorders of pregnancy. Current evidence supports the integration of obstetric history into cardiovascular risk assessment and highlights the importance of early preventive interventions to reduce future cardiovascular morbidity and mortality in women with previous preeclampsia.

Keywords: *preeclampsia; cardiovascular remodeling; cardiovascular disease; endothelial dysfunction; left ventricular remodeling; arterial stiffness; echocardiography; pregnancy complications; women's cardiovascular health; precision medicine.*

Introduction

Hypertensive disorders of pregnancy remain one of the leading causes of maternal morbidity and mortality worldwide, with preeclampsia affecting approximately 2–8% of all pregnancies. Despite substantial advances in obstetric care, preeclampsia continues to account for a considerable proportion of severe maternal complications, preterm birth, fetal growth restriction, and perinatal mortality. During the past decade, however, growing attention has shifted beyond the immediate obstetric consequences of the disease toward its long-term impact on women's cardiovascular health. Increasing evidence demonstrates that pregnancy functions as a physiological cardiovascular stress test, and the development of preeclampsia frequently identifies women with an underlying predisposition to future cardiovascular disease. Consequently, preeclampsia is no longer regarded solely as a pregnancy-specific complication but as one of the earliest clinically identifiable markers of lifelong cardiovascular risk [1–3].

Large population-based cohort studies and meta-analyses consistently demonstrate that women with previous preeclampsia have a two- to fourfold higher risk of chronic hypertension, ischemic heart disease, heart failure, stroke, atrial fibrillation, and cardiovascular mortality compared with women who experienced normotensive pregnancies. This increased risk often becomes apparent within the first decade after delivery and may persist for several decades. Moreover, recurrent preeclampsia, early-onset disease, and severe maternal manifestations are associated with an even greater likelihood of adverse cardiovascular outcomes, emphasizing the need for early identification of high-risk individuals and implementation of long-term preventive strategies [2–5].

The biological mechanisms underlying this association are complex and involve persistent endothelial dysfunction, chronic low-grade inflammation, oxidative stress, vascular stiffness, impaired coronary microvascular function, myocardial remodeling, and metabolic dysregulation. Advanced cardiovascular imaging has demonstrated that structural and functional abnormalities of the myocardium, left ventricular geometry, diastolic function, and arterial elasticity may persist long after pregnancy, even in women without overt cardiovascular disease. These findings support the concept that cardiovascular remodeling initiated during preeclampsia may continue after delivery and contribute to progressive cardiovascular dysfunction throughout later life [4–7].

Recognition of pregnancy history as an integral component of cardiovascular risk assessment has become an important priority in contemporary cardiology and cardio-obstetrics. International scientific societies increasingly recommend long-term cardiovascular follow-up, aggressive modification of cardiovascular risk factors, and multidisciplinary care for women with previous hypertensive disorders of pregnancy. At the same time, advances in cardiovascular imaging, circulating biomarkers, and artificial intelligence–based risk prediction models have created new opportunities for

earlier detection of subclinical cardiovascular disease and personalized prevention. The aim of the study was to summarize current evidence regarding cardiovascular remodeling after preeclampsia and to evaluate its contribution to the long-term risk of cardiovascular disease in women.

Materials and Methods

This study was conducted as a systematic literature review to evaluate current evidence regarding cardiovascular remodeling after preeclampsia and its association with long-term cardiovascular disease in women. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark investigations and international consensus statements were included only when they provided fundamental evidence concerning the pathophysiology of preeclampsia, cardiovascular remodeling, or long-term cardiovascular outcomes.

Eligible publications included systematic reviews, meta-analyses, randomized and non-randomized clinical studies, prospective and retrospective cohort studies, observational investigations, and evidence-based clinical practice guidelines addressing hypertensive disorders of pregnancy, myocardial remodeling, vascular dysfunction, cardiovascular imaging, biomarkers, and long-term cardiovascular risk after preeclampsia. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on the mechanisms of cardiovascular remodeling, structural and functional cardiac alterations, vascular changes, diagnostic modalities, long-term clinical outcomes, and strategies for cardiovascular prevention and follow-up in women with a history of preeclampsia.

Results

Preeclampsia is currently regarded as one of the strongest female-specific predictors of future cardiovascular disease. Large population-based cohort studies and recent meta-analyses consistently demonstrate that women with previous preeclampsia have an approximately 2-fold higher risk of composite cardiovascular disease, 2-fold higher risk of ischemic heart disease, 1.8–2.2-fold higher risk of stroke, 2-fold higher risk of cardiovascular mortality, and the greatest relative increase in the risk of heart failure, which ranges from 2.5 to more than 4-fold compared with women after normotensive pregnancies. The probability of adverse cardiovascular outcomes is further amplified in women with recurrent, early-onset, or severe preeclampsia, indicating a dose-response relationship between disease severity and subsequent cardiovascular risk. Importantly, epidemiological evidence demonstrates that excess cardiovascular risk becomes detectable within the first years after delivery and persists for several decades, emphasizing that preeclampsia should be considered an early marker of accelerated cardiovascular aging rather than an isolated obstetric complication.

Persistent endothelial dysfunction represents the central mechanism responsible for long-term cardiovascular remodeling after preeclampsia. Histopathological and molecular studies demonstrate sustained impairment of nitric oxide bioavailability,

increased endothelin-1 activity, chronic oxidative stress, complement activation, persistent low-grade inflammation, and prolonged imbalance between proangiogenic and antiangiogenic mediators, including vascular endothelial growth factor, placental growth factor, and soluble fms-like tyrosine kinase-1. These abnormalities promote progressive arterial stiffness, vascular fibrosis, impaired coronary microvascular function, and accelerated atherosclerotic remodeling. In addition, elevated concentrations of inflammatory cytokines, C-reactive protein, interleukin-6, tumor necrosis factor-α, and adhesion molecules have been detected years after the index pregnancy, supporting the concept of ongoing vascular injury long after clinical resolution of preeclampsia [8–11].

Cardiac remodeling after preeclampsia is characterized by persistent structural and functional myocardial abnormalities. Echocardiographic studies consistently demonstrate increased left ventricular mass index, concentric remodeling, impaired global longitudinal strain, diastolic dysfunction, left atrial enlargement, and reduced myocardial reserve in women with previous preeclampsia. Cardiac magnetic resonance imaging has further identified diffuse myocardial fibrosis, altered extracellular volume fraction, impaired ventricular relaxation, and subtle reductions in myocardial contractile performance despite preserved left ventricular ejection fraction. Women with early-onset or preterm preeclampsia exhibit the greatest degree of persistent myocardial remodeling, suggesting that pregnancy-related myocardial injury may contribute directly to future development of heart failure with preserved ejection fraction [10–14].

Progressive vascular remodeling constitutes another important component of the long-term cardiovascular phenotype. Women with previous preeclampsia demonstrate significantly increased carotid intima-media thickness, higher pulse wave velocity, impaired flow-mediated dilation, increased augmentation index, coronary microvascular dysfunction, and greater coronary artery calcification compared with women after uncomplicated pregnancies. These abnormalities indicate accelerated vascular aging and reduced arterial compliance, both of which independently predict future hypertension, coronary artery disease, and cerebrovascular events. Microvascular dysfunction has also been demonstrated within the renal, retinal, and coronary circulations, suggesting that generalized endothelial injury extends beyond the systemic arterial tree [11–15].

Long-term clinical follow-up studies demonstrate accelerated accumulation of conventional cardiovascular risk factors after preeclampsia. Chronic hypertension develops approximately 3–4 times more frequently than after normotensive pregnancies, while type 2 diabetes mellitus, dyslipidemia, obesity, metabolic syndrome, and chronic kidney disease also occur at substantially higher rates. Recent prospective data indicate that hypertension, diabetes, and hypercholesterolemia appear, on average, about eight years earlier in women with a history of preeclampsia than in women following uncomplicated pregnancies. These observations suggest that pregnancy identifies a population predisposed to premature cardiometabolic disease, creating an opportunity for earlier preventive intervention.

Contemporary cardiovascular imaging has considerably improved detection of subclinical disease in this population. Speckle-tracking echocardiography identifies reductions in global longitudinal strain before conventional systolic dysfunction becomes evident, whereas cardiac magnetic resonance imaging provides accurate assessment of myocardial fibrosis, ventricular geometry, extracellular matrix expansion, and diffuse myocardial injury. Coronary computed tomography angiography, vascular ultrasound, pulse wave analysis, endothelial function testing, and circulating biomarkers including high-sensitivity troponin, N-terminal pro-B-type natriuretic peptide, growth differentiation factor-15, galectin-3, and angiogenic markers have demonstrated potential value for early cardiovascular risk stratification before clinically overt disease develops [13–18].

Current international recommendations increasingly recognize previous preeclampsia as an independent female-specific cardiovascular risk factor requiring structured long-term follow-up. Contemporary cardio-obstetric strategies recommend regular assessment of blood pressure, body mass index, lipid profile, glucose metabolism, renal function, and global cardiovascular risk beginning in early adulthood. Lifestyle modification, weight management, blood pressure optimization, promotion of physical activity, smoking cessation, and aggressive management of modifiable cardiovascular risk factors are now considered essential components of postpartum care. Increasing emphasis has also been placed on multidisciplinary collaboration between obstetricians, cardiologists, internists, nephrologists, and primary care physicians to ensure continuity of cardiovascular prevention after complicated pregnancies [14–19].

Rapid advances in precision cardiology are creating new opportunities for individualized prediction of long-term cardiovascular outcomes after preeclampsia. Machine learning algorithms integrating pregnancy characteristics, echocardiographic parameters, vascular imaging, laboratory biomarkers, and electronic health record data have demonstrated encouraging predictive performance for future hypertension, heart failure, and major adverse cardiovascular events. Integration of obstetric history with multimodal cardiovascular phenotyping may substantially improve individualized risk assessment and facilitate earlier implementation of preventive strategies, representing one of the most promising future directions in women's cardiovascular medicine and cardio-obstetrics.

Discussion

The findings of the present review reinforce the concept that preeclampsia represents an early manifestation of future cardiovascular disease rather than a transient pregnancy-specific disorder. Accumulating evidence demonstrates that cardiovascular remodeling initiated during pregnancy frequently persists long after delivery, affecting both myocardial structure and vascular function. Persistent endothelial dysfunction, chronic inflammation, oxidative stress, and maladaptive cardiac remodeling create a biological substrate that substantially increases susceptibility to hypertension, ischemic heart disease, heart failure, cerebrovascular disease, and chronic kidney disease. These observations support the growing recognition of pregnancy as a unique cardiovascular stress test capable of revealing women at increased lifetime cardiovascular risk [8–11].

One of the most important findings emerging from contemporary studies is that cardiovascular injury following preeclampsia extends beyond conventional cardiovascular risk factors. Structural abnormalities of the left ventricle, impaired myocardial deformation, diffuse myocardial fibrosis, increased arterial stiffness, and coronary microvascular dysfunction have been demonstrated in otherwise asymptomatic women years after pregnancy. Importantly, many of these abnormalities are detectable before the development of clinically overt cardiovascular disease, suggesting that preeclampsia initiates a prolonged process of cardiovascular remodeling rather than simply identifying women with pre-existing susceptibility. This distinction has significant implications for both early diagnosis and preventive intervention [10–14].

From a cardiological perspective, advances in cardiovascular imaging have considerably improved the detection of subclinical remodeling after hypertensive disorders of pregnancy. Speckle-tracking echocardiography, cardiac magnetic resonance imaging, coronary computed tomography, and vascular ultrasound provide complementary assessment of myocardial mechanics, extracellular fibrosis, arterial stiffness, and endothelial dysfunction. These techniques have consistently demonstrated greater sensitivity than conventional cardiovascular assessment and may facilitate identification of women who would benefit from intensified surveillance before irreversible myocardial dysfunction develops. Nevertheless, standardized imaging algorithms and validated risk thresholds remain insufficiently defined for routine clinical practice [12–16].

An equally important development is the increasing incorporation of pregnancy history into cardiovascular risk assessment. International cardiovascular societies now recognize previous preeclampsia as an independent female-specific cardiovascular risk factor, emphasizing that reproductive history should become an integral component of cardiovascular evaluation throughout adult life. Earlier identification of women with previous hypertensive disorders of pregnancy provides an opportunity to initiate aggressive modification of blood pressure, body weight, lipid abnormalities, glucose metabolism, and other modifiable risk factors at a stage when cardiovascular remodeling may still be partially reversible. Such preventive strategies have the potential to reduce long-term cardiovascular morbidity substantially [14–18].

Despite considerable progress, several important limitations remain. Published studies differ regarding diagnostic criteria for preeclampsia, duration of follow-up, cardiovascular endpoints, imaging protocols, and adjustment for traditional cardiovascular risk factors. Furthermore, the relative contributions of persistent pregnancy-induced vascular injury and pre-existing cardiometabolic susceptibility remain incompletely understood. Additional large prospective multicenter studies with standardized cardiovascular phenotyping are required to clarify the natural history of post-preeclampsia cardiovascular remodeling and identify the most effective preventive interventions [15–19].

Future research should focus on integrating multimodal cardiovascular imaging, circulating biomarkers, genomics, proteomics, and artificial intelligence into personalized risk prediction models. Such approaches may allow earlier identification

of women at highest risk for progressive cardiovascular disease and facilitate individualized follow-up strategies after complicated pregnancies. Strengthening collaboration between cardiologists, obstetricians, maternal-fetal medicine specialists, nephrologists, and primary care physicians will be essential for translating emerging scientific evidence into routine clinical practice and improving long-term cardiovascular health in women with a history of preeclampsia [17–20].

CONCLUSION

Preeclampsia is now recognized as an important female-specific cardiovascular risk factor that identifies women with an increased likelihood of developing long-term cardiovascular disease. Current evidence demonstrates that persistent cardiovascular remodeling following preeclampsia involves structural and functional myocardial alterations, endothelial dysfunction, arterial stiffening, and chronic vascular injury, which collectively contribute to the subsequent development of hypertension, ischemic heart disease, heart failure, stroke, and chronic kidney disease. These findings indicate that the cardiovascular consequences of preeclampsia extend well beyond the postpartum period and should be considered throughout a woman's lifetime.

Contemporary management should therefore extend beyond obstetric care and include structured long-term cardiovascular surveillance, comprehensive assessment of modifiable risk factors, and timely implementation of preventive strategies. Integration of obstetric history with advanced cardiovascular imaging, circulating biomarkers, and individualized risk prediction models may facilitate earlier detection of subclinical cardiovascular disease and improve long-term outcomes. Continued development of multidisciplinary cardio-obstetric care and precision prevention strategies is expected to play a central role in reducing the future burden of cardiovascular disease among women with a history of preeclampsia.

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OBSTRUCTIVE SLEEP APNEA IN PREGNANCY: IMPACT ON MATERNAL AND PERINATAL OUTCOMES

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Abstract. Obstructive sleep apnea has emerged as an increasingly recognized medical complication of pregnancy owing to the rising prevalence of maternal obesity, advanced maternal age, and metabolic disorders. Physiological changes occurring during pregnancy, including upper airway edema, weight gain, hormonal influences, and alterations in respiratory physiology, predispose susceptible women to sleep-disordered breathing or exacerbate pre-existing disease. Growing evidence indicates that obstructive sleep apnea is associated with an increased risk of gestational hypertension, preeclampsia, gestational diabetes mellitus, cesarean delivery, and cardiovascular complications, while also adversely affecting placental function and fetal development. Despite these associations, the condition remains substantially underdiagnosed because many symptoms overlap with normal physiological changes during pregnancy.

This systematic literature review summarizes current evidence regarding the impact of obstructive sleep apnea on maternal and perinatal outcomes and discusses contemporary approaches to screening, diagnosis, and clinical management. Particular attention is given to the pathophysiological mechanisms linking intermittent hypoxia and sleep fragmentation with placental dysfunction, endothelial injury, systemic inflammation, and adverse pregnancy outcomes. The review also examines the role of polysomnography, validated screening tools, continuous positive airway pressure therapy, and multidisciplinary antenatal care. The available evidence suggests that early recognition and timely treatment of obstructive sleep apnea may reduce maternal morbidity, improve placental function, and contribute to more favorable perinatal

outcomes, supporting the integration of sleep medicine into routine obstetric practice for women at increased risk.

Keywords: *obstructive sleep apnea; pregnancy; sleep-disordered breathing; preeclampsia; gestational diabetes mellitus; maternal outcomes; perinatal outcomes; continuous positive airway pressure; polysomnography; placental dysfunction.*

Introduction

Obstructive sleep apnea (OSA) is increasingly recognized as an important contributor to adverse maternal and fetal health during pregnancy. Once considered relatively uncommon among women of reproductive age, OSA is now diagnosed with growing frequency owing to the global rise in obesity, advanced maternal age, pre-existing metabolic disorders, and improved awareness of sleep-disordered breathing. Physiological adaptations of pregnancy, including progressive weight gain, upper airway edema, hormonal changes, reduced functional residual lung capacity, and increased oxygen consumption, may promote upper airway collapse during sleep and aggravate previously unrecognized disease. Consequently, OSA has become an important component of modern obstetric medicine because of its potential influence on both maternal well-being and pregnancy outcomes [1–3].

The pathophysiological effects of OSA extend beyond recurrent upper airway obstruction. Repetitive episodes of intermittent hypoxia, sleep fragmentation, sympathetic nervous system activation, oxidative stress, endothelial dysfunction, and systemic inflammation contribute to widespread cardiovascular and metabolic disturbances. During pregnancy, these mechanisms may impair placental perfusion, disrupt normal vascular adaptation, and alter maternal hemodynamics, thereby increasing susceptibility to hypertensive disorders, gestational diabetes mellitus, fetal growth abnormalities, and preterm birth. The close interaction between sleep-disordered breathing and pregnancy-related physiological changes has prompted increasing interest in the role of OSA as a potentially modifiable obstetric risk factor [2–5].

Recent evidence has strengthened the association between maternal OSA and a broad spectrum of adverse pregnancy outcomes. Large cohort studies and systematic reviews have reported higher rates of gestational hypertension, preeclampsia, cesarean delivery, intensive care admission, and cardiovascular complications among affected women. In addition, maternal OSA has been linked to placental dysfunction, fetal growth restriction, low birth weight, neonatal intensive care unit admission, and other unfavorable perinatal outcomes. Nevertheless, the condition remains substantially underdiagnosed because common symptoms, including fatigue, daytime sleepiness, and poor sleep quality, frequently overlap with normal physiological changes during pregnancy, limiting timely identification and treatment [4–7].

Recognition of OSA during pregnancy has important clinical implications because effective treatment, particularly continuous positive airway pressure therapy, may improve maternal oxygenation, reduce cardiovascular stress, and potentially decrease the risk of adverse obstetric outcomes. At the same time, uncertainty remains regarding optimal screening strategies, diagnostic algorithms, and patient selection for treatment, highlighting the need for continued evaluation of contemporary evidence. The aim of

the study was to summarize current evidence regarding the impact of obstructive sleep apnea on maternal and perinatal outcomes, with emphasis on underlying pathophysiological mechanisms, modern diagnostic approaches, and current management strategies during pregnancy.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding the impact of obstructive sleep apnea during pregnancy on maternal and perinatal outcomes. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier international guidelines and landmark studies were included only when they provided essential evidence concerning the diagnosis, pathophysiology, or management of obstructive sleep apnea in pregnancy.

Eligible publications included systematic reviews, meta-analyses, randomized and non-randomized clinical studies, prospective and retrospective cohort studies, observational investigations, and evidence-based clinical practice guidelines addressing maternal complications, fetal and neonatal outcomes, diagnostic methods, and therapeutic interventions for obstructive sleep apnea during pregnancy. Conference abstracts, case reports, duplicate publications, editorials, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on pathophysiological mechanisms, diagnostic accuracy, maternal and perinatal outcomes, and the effectiveness of contemporary management strategies.

Results

Obstructive sleep apnea (OSA) during pregnancy has emerged as an increasingly important obstetric condition because of its association with a broad spectrum of maternal and fetal complications. The reported prevalence varies considerably according to the diagnostic method, gestational age, and baseline maternal characteristics, ranging from less than 5% in low-risk pregnancies to more than 30% among women with obesity, chronic hypertension, or pre-existing diabetes mellitus. Disease severity frequently increases as pregnancy progresses due to physiological weight gain, upper airway edema, reduced functional residual capacity, and progressive alterations in respiratory mechanics, particularly during the third trimester [8–10].

The pathophysiological effects of OSA extend well beyond nocturnal respiratory disturbances. Recurrent episodes of intermittent hypoxia and sleep fragmentation activate the sympathetic nervous system, increase oxidative stress, promote systemic inflammation, and impair endothelial function. These mechanisms contribute to abnormal placental vascular remodeling, reduced uteroplacental perfusion, and disturbances in angiogenic signaling, thereby creating conditions that favor the development of hypertensive disorders of pregnancy and placental insufficiency. Elevated circulating concentrations of inflammatory cytokines, endothelin-1, and antiangiogenic factors have been consistently reported in pregnant women with moderate to severe OSA [9–12].

Among maternal complications, hypertensive disorders represent the most consistently documented adverse outcomes. Multiple cohort studies and meta-analyses demonstrate significantly increased risks of gestational hypertension and preeclampsia in women with OSA, even after adjustment for maternal obesity and other confounding variables. In addition, OSA has been associated with gestational diabetes mellitus, impaired glucose metabolism, excessive gestational weight gain, cardiac arrhythmias, pulmonary hypertension, thromboembolic events, cesarean delivery, postpartum hemorrhage, prolonged hospitalization, and admission to intensive care units in severe cases [10–14].

Adverse fetal and neonatal outcomes have also been reported with increasing consistency. Chronic maternal intermittent hypoxia and placental dysfunction may impair fetal oxygen delivery and restrict intrauterine growth. Several large observational studies have demonstrated associations between maternal OSA and fetal growth restriction, low birth weight, preterm birth, small-for-gestational-age infants, lower Apgar scores, neonatal respiratory complications, and increased rates of neonatal intensive care unit admission. Although residual confounding cannot be completely excluded, the overall evidence supports an unfavorable effect of untreated maternal OSA on perinatal health [11–15].

From an otorhinolaryngological perspective, pregnancy induces a series of anatomical and physiological alterations that increase susceptibility to upper airway obstruction during sleep. Elevated concentrations of estrogen and progesterone promote mucosal hyperemia and edema of the nasal cavity and pharynx, while gestational weight gain contributes to soft tissue enlargement and narrowing of the upper airway lumen. These physiological adaptations are particularly relevant in women with obesity, allergic rhinitis, chronic rhinosinusitis, adenotonsillar hypertrophy, nasal septal deviation, or craniofacial abnormalities, all of which further increase upper airway collapsibility. Consequently, otorhinolaryngological assessment represents an important component of risk stratification in pregnant women presenting with habitual snoring, witnessed apneas, or excessive daytime sleepiness [12–16].

Contemporary evaluation of pregnant women with suspected OSA increasingly incorporates detailed examination of the upper airway. Nasal endoscopy, assessment of septal deviation, inferior turbinate hypertrophy, pharyngeal anatomy, tongue base position, Mallampati classification, and Friedman tongue position help identify potential anatomical contributors to airway obstruction. Recognition of these abnormalities facilitates individualized management, particularly through optimization of nasal patency and treatment of pregnancy-related rhinitis, which may improve nocturnal breathing and enhance adherence to continuous positive airway pressure therapy. These findings underscore the complementary role of otorhinolaryngological examination alongside sleep studies and obstetric assessment [13–18].

Management of OSA during pregnancy requires close collaboration between obstetricians, otorhinolaryngologists, sleep medicine specialists, anesthesiologists, and neonatologists. Because elective upper airway surgery is generally postponed until after delivery, treatment primarily relies on conservative measures, including positional therapy, optimization of nasal airflow, management of inflammatory upper airway

disorders, body weight control, and timely initiation of continuous positive airway pressure in women with moderate or severe disease. Postpartum follow-up remains equally important, as pregnancy may unmask previously undiagnosed chronic OSA requiring definitive otorhinolaryngological evaluation and long-term treatment after childbirth [14–20].

Despite growing recognition of OSA as an important obstetric disorder, several challenges remain. Considerable heterogeneity persists in diagnostic criteria, screening algorithms, definitions of disease severity, and outcome measures across published studies. Furthermore, high-quality randomized clinical trials evaluating the effects of continuous positive airway pressure therapy on maternal and neonatal outcomes remain limited. Nevertheless, the current body of evidence consistently indicates that early multidisciplinary assessment involving both obstetric and otorhinolaryngological specialists, combined with timely diagnosis and individualized management, represents the most effective strategy for reducing maternal morbidity and improving perinatal outcomes in pregnancies complicated by obstructive sleep apnea [16–20].

Discussion

The findings of the present review indicate that obstructive sleep apnea should be regarded as an important component of contemporary obstetric care rather than solely as a sleep-related breathing disorder. Accumulating evidence demonstrates that recurrent nocturnal hypoxia, sleep fragmentation, and sympathetic overactivity contribute to endothelial dysfunction, placental hypoperfusion, and metabolic disturbances that adversely affect both maternal and fetal health. The consistent association between OSA and hypertensupportorders of pregnancy, gestational diabetes mellitus, preterm birth, and impaired fetal growth supports the growing recognition of sleep-disordered breathing as a clinically significant and potentially modifiable obstetric risk factor [8–11].

A notable finding across recent studies is the increasing emphasis on early identification of women at high risk for OSA. Routine antenatal care has traditionally focused on cardiovascular and metabolic risk assessment, whereas evaluation of sleep-related symptoms has received comparatively little attention. Contemporary evidence suggests that incorporation of targeted screening for habitual snoring, witnessed apneas, excessive daytime sleepiness, obesity, chronic hypertension, and previous hypertensive pregnancy disorders may facilitate earlier diagnosis and allow timely implementation of preventive measures before irreversible maternal or placental complications develop [10–13].

From an otorhinolaryngological perspective, pregnancy creates unique anatomical and physiological conditions that predispose women to upper airway obstruction. Hormone-induced mucosal edema increased nasal resistance, gestational weight gain, and changes in pharyngeal soft tissues may substantially reduce upper airway patency, particularly in women with pre-existing nasal or pharyngeal abnormalities. These observations highlight that structural evaluation of the upper airway should not be considered a secondary investigation but rather an integral component of multidisciplinary assessment. Careful otorhinolaryngological examination allows

identification of anatomical factors that may aggravate sleep-disordered breathing and influence the selection of individualized therapeutic strategies [12–16].

Another important aspect is the contribution of otorhinolaryngologists to the conservative management of pregnant women with OSA. Although surgical correction of upper airway abnormalities is generally postponed until the postpartum period, optimization of nasal breathing through treatment of pregnancy-related rhinitis, inflammatory upper airway disease, or reversible nasal obstruction may improve nocturnal ventilation and enhance tolerance to continuous positive airway pressure therapy. Close collaboration between obstetricians, sleep medicine specialists, and otorhinolaryngologists therefore represents an important prerequisite for achieving optimal maternal and fetal outcomes [13–18].

Despite substantial advances in understanding OSA during pregnancy, several limitations continue to affect the available evidence. Published studies differ in diagnostic criteria, methods of sleep assessment, definitions of disease severity, and adjustment for important confounding factors such as obesity and pre-existing metabolic disease. Furthermore, randomized controlled trials evaluating the influence of CPAP therapy on perinatal outcomes remain limited, making it difficult to establish definitive recommendations regarding the magnitude of treatment benefit beyond improvements in maternal respiratory physiology and blood pressure control [15–19].

Future investigations should focus on developing pregnancy-specific screening algorithms, validating diagnostic tools suitable for routine antenatal practice, and determining the optimal timing of intervention in women at different levels of risk. Attention should also be directed toward integrated obstetric and otorhinolaryngological care pathways, advanced assessment of upper airway anatomy, and long-term follow-up of women diagnosed with OSA during pregnancy. Such multidisciplinary strategies may improve early detection, optimize individualized treatment, and ultimately reduce both maternal morbidity and adverse perinatal outcomes associated with obstructive sleep apnea [17–20].

CONCLUSION

Obstructive sleep apnea is increasingly recognized as a significant medical disorder during pregnancy that adversely affects both maternal and perinatal outcomes. The available evidence indicates that intermittent hypoxia, sleep fragmentation, endothelial dysfunction, and placental impairment contribute to the development of hypertensive disorders of pregnancy, gestational diabetes mellitus, fetal growth abnormalities, and other obstetric complications. Early recognition of women at increased risk, together with comprehensive assessment of upper airway anatomy and timely initiation of appropriate therapy, may reduce pregnancy-related morbidity and improve neonatal outcomes. These findings highlight the importance of incorporating both obstetric and otorhinolaryngological evaluation into the routine management of pregnant women with suspected sleep-disordered breathing.

Further progress in this field will depend on the development of standardized screening strategies specifically adapted for pregnancy, validation of reliable diagnostic algorithms, and implementation of prospective multicenter studies evaluating the long-term effectiveness of therapeutic interventions. Greater integration

of sleep medicine, otorhinolaryngology, and obstetric care has the potential to improve early diagnosis, optimize individualized treatment, and enhance both maternal and perinatal prognosis in pregnancies complicated by obstructive sleep apnea.

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NOVEL STRATEGIES FOR THE TREATMENT OF OBESITY IN ENDOCRINOLOGY: EFFICACY AND SAFETY OF SEMAGLUTIDE AND TIRZEPATIDE

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Abstract. Obesity is currently recognized as a chronic, relapsing, multifactorial endocrine and metabolic disease associated with substantial morbidity, premature mortality, and escalating healthcare costs worldwide. Conventional lifestyle interventions frequently provide insufficient long-term weight reduction because of complex neuroendocrine mechanisms regulating appetite, energy expenditure, and body weight homeostasis. The development of incretin-based pharmacotherapy has fundamentally changed the therapeutic landscape of obesity management. Semaglutide, a glucagon-like peptide-1 receptor agonist, and tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, have demonstrated unprecedented efficacy in achieving sustained weight loss while simultaneously improving multiple cardiometabolic risk factors. These advances have established pharmacological treatment as a central component of comprehensive obesity management in modern endocrinology.

This systematic literature review summarizes current evidence regarding the efficacy and safety of semaglutide and tirzepatide in the treatment of obesity and evaluates their role within contemporary endocrine practice. Particular attention is given to the mechanisms of action of incretin-based therapies, evidence from major clinical trials, effects on body composition, insulin resistance, cardiovascular and renal outcomes, metabolic dysfunction-associated steatotic liver disease, and long-term safety. The review also discusses current international clinical recommendations and emerging therapeutic strategies involving next-generation incretin agents and personalized obesity management. Available evidence indicates that semaglutide and

tirzepatide have substantially expanded therapeutic opportunities for obesity and are redefining standards of medical treatment for this chronic disease.

Keywords: *obesity; semaglutide; tirzepatide; GLP-1 receptor agonist; GIP/GLP-1 receptor agonist; incretin therapy; weight loss; cardiometabolic risk; endocrine therapy; precision medicine.*

Introduction

Obesity has become one of the most pressing global health challenges of the twenty-first century, with its prevalence increasing at an unprecedented rate across all age groups and geographic regions. According to recent international estimates, more than one billion people worldwide are living with obesity, and the burden of obesity-related complications continues to rise despite ongoing public health interventions. The disease is associated with substantially increased risks of type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnea, several malignancies, and premature mortality. Beyond its clinical consequences, obesity imposes considerable economic costs on healthcare systems and contributes to reduced quality of life, impaired physical functioning, and long-term disability. These observations have established obesity as a chronic endocrine and metabolic disease requiring comprehensive long-term management rather than a consequence of lifestyle factors alone [1–3].

Traditional approaches based on dietary modification, increased physical activity, and behavioral interventions remain essential components of obesity management but frequently fail to achieve durable weight reduction because of complex physiological mechanisms regulating appetite and energy balance. Adaptive neuroendocrine responses following weight loss promote increased hunger, reduced energy expenditure, and progressive weight regain, limiting the long-term effectiveness of lifestyle interventions in many patients. Recognition of these biological mechanisms has transformed current understanding of obesity pathophysiology and stimulated the development of targeted pharmacological therapies capable of modifying central appetite regulation and metabolic homeostasis [2–5].

The introduction of incretin-based medications has fundamentally changed the therapeutic landscape of obesity treatment. Semaglutide, a glucagon-like peptide-1 receptor agonist, and tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, have demonstrated unprecedented efficacy in producing clinically meaningful and sustained weight reduction while simultaneously improving glycemic control, insulin sensitivity, blood pressure, lipid metabolism, and cardiovascular risk profiles. Results from the STEP and SURMOUNT clinical trial programs have shifted expectations regarding pharmacological treatment, positioning these agents among the most effective non-surgical interventions currently available for obesity management [4–7].

Rapid expansion of clinical evidence has also raised important questions regarding optimal patient selection, long-term safety, treatment duration, maintenance of weight loss after therapy discontinuation, and integration of incretin-based agents into comprehensive endocrine care. At the same time, novel multi-receptor agonists and personalized therapeutic strategies are emerging as promising directions for future

obesity management. The aim of the study was to summarize current evidence regarding the efficacy and safety of semaglutide and tirzepatide and to evaluate their role within contemporary strategies for the treatment of obesity in endocrinology.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding the efficacy and safety of semaglutide and tirzepatide in the treatment of obesity. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies and international clinical guidelines were included only when they provided essential evidence concerning obesity pathophysiology, incretin biology, or the development of pharmacological obesity management.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, and evidence-based clinical practice guidelines addressing obesity pharmacotherapy, glucagon-like peptide-1 receptor agonists, dual GIP/GLP-1 receptor agonists, cardiometabolic outcomes, and treatment safety. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on therapeutic efficacy, body weight reduction, metabolic outcomes, cardiovascular and renal effects, adverse events, and emerging strategies for personalized obesity treatment.

Results

Obesity is increasingly recognized as a chronic neuroendocrine disease characterized by dysregulation of central appetite pathways, altered energy homeostasis, adipose tissue dysfunction, chronic low-grade inflammation, and insulin resistance. Excess adiposity is accompanied by increased secretion of pro-inflammatory cytokines, including tumor necrosis factor-α, interleukin-6, and monocyte chemoattractant protein-1, together with reduced adiponectin concentrations and progressive leptin resistance. These abnormalities promote ectopic lipid deposition, hepatic steatosis, endothelial dysfunction, β-cell stress, and accelerated cardiometabolic disease progression. Consequently, pharmacological treatment has shifted from achieving modest weight reduction toward modifying the biological mechanisms responsible for obesity persistence and recurrence [8–10].

Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist that suppresses appetite through activation of hypothalamic proopiomelanocortin/cocaine- and amphetamine-regulated transcript neurons while inhibiting orexigenic neuropeptide Y/agouti-related peptide pathways. In addition, semaglutide delays gastric emptying, enhances postprandial satiety, reduces energy intake by approximately 25–35%, improves insulin sensitivity, and decreases hepatic glucose production. Beyond glycemic regulation, treatment is associated with reductions in visceral adipose tissue, inflammatory biomarkers, systolic blood pressure, triglyceride concentrations, and hepatic fat content, indicating broad metabolic effects extending beyond weight loss alone [9–12].

Tirzepatide exerts complementary actions through simultaneous activation of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Dual incretin receptor stimulation enhances insulin secretion in a glucose-dependent manner, suppresses glucagon release, improves adipocyte metabolism, increases postprandial satiety, and produces greater reductions in energy intake than selective GLP-1 receptor agonism. Experimental studies further demonstrate favorable effects on adipose tissue remodeling, mitochondrial function, lipid oxidation, and inflammatory signaling, providing a biological explanation for the superior weight reduction observed in clinical trials [10–13].

Evidence from randomized clinical trials has fundamentally changed expectations regarding pharmacological obesity treatment. In the STEP 1 trial, adults receiving semaglutide 2.4 mg once weekly achieved a mean body weight reduction of 14.9% after 68 weeks compared with 2.4% in the placebo group, while more than 86% of participants achieved at least 5% weight loss, approximately 69% achieved ≥10%, and nearly 50% achieved ≥15% weight reduction. Subsequent STEP studies confirmed sustained improvements in waist circumference, blood pressure, glycated hemoglobin, lipid profile, physical functioning, and health-related quality of life, with continued treatment associated with maintenance of weight reduction over longer follow-up periods [11–15].

The SURMOUNT clinical program demonstrated even greater efficacy with tirzepatide. In SURMOUNT-1, participants receiving the 15 mg dose experienced a mean body weight reduction approaching 21% after 72 weeks, while more than half achieved ≥20% weight loss. The recently published head-to-head SURMOUNT-5 trial further demonstrated superior efficacy of tirzepatide compared with semaglutide, with greater reductions in both body weight and waist circumference after 72 weeks of treatment. Participants treated with tirzepatide were significantly more likely to achieve clinically meaningful weight reductions of 10%, 15%, 20%, and 25%, confirming the enhanced therapeutic potential of dual GIP/GLP-1 receptor agonism.

Beyond weight reduction, both agents produce clinically important improvements in cardiometabolic health. Semaglutide has demonstrated significant reductions in major adverse cardiovascular events among adults with overweight or obesity and established cardiovascular disease, independent of diabetes status, while tirzepatide consistently improves insulin resistance, blood pressure, atherogenic lipid profiles, hepatic steatosis, inflammatory biomarkers, and renal risk factors. Increasing evidence also supports beneficial effects on metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnea, heart failure with preserved ejection fraction, and progression toward type 2 diabetes, highlighting the pleiotropic actions of incretin-based therapies.

Safety analyses demonstrate that both semaglutide and tirzepatide possess favorable benefit-risk profiles. Gastrointestinal adverse events, including nausea, vomiting, diarrhea, constipation, and dyspepsia, remain the most frequently reported complications and occur predominantly during dose escalation. The majority are mild to moderate in severity and rarely require permanent treatment discontinuation. Serious adverse events, including pancreatitis, gallbladder disease, severe dehydration, and

clinically significant hypoglycemia in non-diabetic patients, are uncommon. Across the SURMOUNT trials, gastrointestinal symptoms explained only a small proportion of the observed weight loss, indicating that therapeutic efficacy is primarily mediated through neuroendocrine mechanisms rather than treatment intolerance.

The therapeutic paradigm for obesity is therefore undergoing a profound transformation. Contemporary international recommendations increasingly position incretin-based pharmacotherapy alongside lifestyle intervention as an essential component of long-term obesity management rather than a secondary option after treatment failure. Current research is focused on triple agonists targeting GLP-1, GIP, and glucagon receptors, combination pharmacotherapy, precision medicine approaches, and artificial intelligence–assisted prediction of therapeutic response. These developments are expected to further individualize obesity treatment and improve long-term maintenance of weight reduction while reducing obesity-related cardiovascular and metabolic complications.

Discussion

The findings of the present review demonstrate that incretin-based pharmacotherapy has fundamentally transformed the management of obesity by targeting the biological mechanisms responsible for weight gain rather than solely reducing caloric intake. Contemporary evidence consistently shows that semaglutide and tirzepatide produce weight reductions that were previously achievable primarily through bariatric surgery, while simultaneously improving multiple cardiometabolic risk factors. These observations support the current concept of obesity as a chronic endocrine disease requiring long-term pharmacological management in appropriately selected patients rather than short-term intervention aimed exclusively at body weight reduction [8–11].

One of the most important developments in recent years has been the recognition that clinically meaningful weight loss is accompanied by broad metabolic improvements extending beyond adipose tissue reduction. Both semaglutide and tirzepatide consistently improve insulin sensitivity, decrease visceral and ectopic fat accumulation, reduce systemic inflammation, normalize adipokine secretion, and improve endothelial function. These biological effects contribute to reductions in blood pressure, improvements in lipid metabolism, attenuation of hepatic steatosis, and lower progression toward type 2 diabetes. Consequently, the therapeutic value of incretin-based agents should be assessed within the broader context of cardiometabolic risk modification rather than body mass reduction alone [10–14].

Comparison of currently available agents indicates important differences in therapeutic efficacy. Across contemporary randomized clinical trials, tirzepatide has consistently demonstrated greater reductions in body weight and waist circumference than semaglutide, reflecting the synergistic metabolic effects of dual GIP and GLP-1 receptor activation. Nevertheless, semaglutide remains supported by extensive cardiovascular outcome data and has established efficacy across a broad spectrum of patients with obesity and overweight. Therefore, treatment selection should not rely exclusively on the magnitude of weight loss but should also consider cardiovascular

risk profile, glycemic status, comorbid conditions, patient preferences, treatment accessibility, and long-term therapeutic objectives [12–16].

Long-term treatment adherence remains one of the principal challenges in obesity management. Available evidence indicates that discontinuation of incretin-based therapy is frequently followed by partial recovery of lost body weight, emphasizing that obesity should be managed similarly to other chronic endocrine disorders requiring sustained treatment. These observations reinforce the importance of combining pharmacotherapy with structured lifestyle modification, nutritional counseling, physical activity, and behavioral interventions to maximize durability of therapeutic response and improve long-term metabolic outcomes [14–18].

The overall safety profile of semaglutide and tirzepatide appears favorable and supports their expanding role in endocrine practice. Gastrointestinal adverse events remain the predominant treatment-related complications but are generally transient, dose-dependent, and manageable through gradual dose escalation. Current evidence has not identified major unexpected long-term safety concerns; however, continued pharmacovigilance and real-world observational studies remain necessary to evaluate rare adverse events, prolonged treatment exposure, and safety in populations underrepresented in randomized clinical trials, including older adults, individuals with advanced chronic kidney disease, and patients with multiple endocrine disorders [15–19].

Future research is expected to redefine obesity treatment through the development of next-generation incretin therapies, combination receptor agonists, precision medicine strategies, and biomarker-guided therapeutic selection. Integration of genomic, metabolomic, and digital health data with artificial intelligence may facilitate prediction of individual treatment response and optimization of long-term management. Such advances are likely to further improve clinical outcomes while supporting a transition toward personalized endocrine care in patients with obesity and complex cardiometabolic disease [17–20].

CONCLUSION

Semaglutide and tirzepatide have substantially expanded the therapeutic possibilities for obesity by providing sustained and clinically meaningful weight reduction together with significant improvements in glycemic control, insulin resistance, cardiovascular risk factors, and other obesity-related comorbidities. Current evidence demonstrates that incretin-based pharmacotherapy modifies the underlying neuroendocrine and metabolic mechanisms of obesity rather than simply reducing energy intake, supporting its role as a cornerstone of contemporary endocrine management. The accumulated data from large randomized clinical trials and cardiovascular outcome studies confirm that these agents offer favorable efficacy and safety profiles when integrated into comprehensive long-term treatment strategies.

Future progress in obesity management will depend on individualized treatment selection, optimization of long-term adherence, and integration of pharmacotherapy with lifestyle intervention, digital health technologies, and precision medicine approaches. Further prospective studies evaluating long-term cardiovascular, renal, hepatic, and overall clinical outcomes, together with the development of next-

generation multi-receptor agonists, are expected to further refine therapeutic algorithms and improve long-term management of patients with obesity in endocrinological practice.

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CLINICAL, NEUROIMAGING, AND ELECTROENCEPHALOGRAPHIC PREDICTORS OF POST-TRAUMATIC EPILEPSY FOLLOWING TRAUMATIC BRAIN INJURY: CURRENT EVIDENCE AND FUTURE PERSPECTIVES

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Abstract. Post-traumatic epilepsy is one of the most serious long-term neurological complications of traumatic brain injury and accounts for a substantial proportion of acquired epilepsies in adolescents and adults. The risk of epilepsy is determined by the severity and characteristics of brain injury and is associated with a complex process of post-traumatic epileptogenesis involving neuroinflammation, blood–brain barrier disruption, neuronal loss, axonal injury, gliosis, and persistent alterations in neuronal network excitability. Despite advances in neurocritical care, accurate identification of patients at high risk of developing post-traumatic epilepsy remains a major clinical challenge. Increasing evidence indicates that the integration of clinical characteristics with neuroimaging and electroencephalographic findings may significantly improve early risk stratification and facilitate timely implementation of individualized preventive strategies.

This systematic literature review summarizes current evidence regarding clinical, neuroimaging, and electroencephalographic predictors of post-traumatic epilepsy following traumatic brain injury. Particular attention is given to structural and functional neuroimaging markers, electroencephalographic abnormalities, emerging circulating biomarkers, and artificial intelligence–based prediction models that enhance individualized assessment of epileptogenesis. Current evidence supports a multimodal diagnostic approach combining clinical evaluation, advanced neuroimaging, electroencephalography, and biomarker analysis to improve prediction of post-traumatic epilepsy and optimize long-term management of patients after traumatic brain injury.

Keywords: *post-traumatic epilepsy; traumatic brain injury; electroencephalography; magnetic resonance imaging; computed tomography; epileptogenesis; neuroimaging; biomarkers; artificial intelligence; risk prediction.*

Introduction

Traumatic brain injury (TBI) remains one of the leading causes of mortality and long-term neurological disability worldwide, affecting millions of individuals each year. Improvements in emergency medicine, neurosurgical techniques, and intensive care have substantially increased survival after moderate and severe TBI, resulting in a growing population of patients living with chronic neurological sequelae. Among these, post-traumatic epilepsy (PTE) represents one of the most disabling complications because it contributes to recurrent seizures, cognitive impairment, psychiatric disorders, reduced functional independence, and diminished quality of life. PTE accounts for a considerable proportion of acquired epilepsies in adults and is associated with increased healthcare utilization and long-term socioeconomic burden [1–3].

The development of post-traumatic epilepsy is a dynamic biological process rather than an immediate consequence of brain injury. Following trauma, a cascade of molecular and cellular events—including blood–brain barrier disruption, neuroinflammation, excitotoxicity, oxidative stress, neuronal apoptosis, synaptic reorganization, and reactive gliosis—promotes progressive epileptogenesis. Although only a subset of patients ultimately develop epilepsy, the risk increases substantially after severe traumatic brain injury, penetrating injuries, intracerebral hemorrhage, depressed skull fractures, and early post-traumatic seizures. These observations indicate that timely identification of individuals at highest risk remains a major priority in contemporary neurology and neurotraumatology [2–5].

Recent advances in diagnostic technologies have considerably improved understanding of the mechanisms underlying post-traumatic epileptogenesis. High-resolution computed tomography, advanced magnetic resonance imaging techniques, tensor diffusion imaging, susceptibility-weighted imaging, functional MRI, and electroencephalography provide complementary information regarding structural brain injury, white matter integrity, cortical network dysfunction, and abnormal neuronal activity. Simultaneously, increasing evidence supports the prognostic value of circulating biomarkers, quantitative electroencephalography, and artificial intelligence–based prediction models for identifying patients with an elevated probability of developing chronic epilepsy after traumatic brain injury [4–7].

Despite these advances, reliable prediction of post-traumatic epilepsy remains challenging because no single clinical, neuroimaging, or electrophysiological marker demonstrates sufficient predictive accuracy when used in isolation. Current research therefore focuses on multimodal risk assessment that integrates clinical characteristics with neuroimaging findings, electroencephalographic abnormalities, and biological markers to improve individualized prognostic evaluation. The aim of the study was to summarize current evidence regarding clinical, neuroimaging, and electroencephalographic predictors of post-traumatic epilepsy following traumatic

brain injury and to evaluate their role in early risk stratification and personalized patient management.

Materials and Methods

This study was conducted as a systematic literature review to evaluate current evidence regarding the clinical, neuroimaging, and electroencephalographic predictors of post-traumatic epilepsy following traumatic brain injury. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies were included only when they provided fundamental evidence regarding post-traumatic epileptogenesis or established diagnostic principles for post-traumatic epilepsy.

Eligible publications included systematic reviews, meta-analyses, randomized and non-randomized clinical studies, prospective and retrospective cohort studies, observational investigations, clinical practice guidelines, and international consensus statements addressing post-traumatic epilepsy, traumatic brain injury, neuroimaging, electroencephalography, biomarkers, and risk prediction. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on clinical risk factors, neuroimaging and electroencephalographic findings, diagnostic performance of emerging biomarkers, and contemporary multimodal approaches to predicting post-traumatic epilepsy.

Results

Clinical characteristics remain the primary determinants of post-traumatic epilepsy (PTE) risk following traumatic brain injury. Large prospective cohort studies consistently demonstrate that the incidence of PTE increases proportionally with injury severity, ranging from 1–3% after mild TBI, 4–8% after moderate TBI, and 10–25% following severe TBI, while patients with penetrating cranial injuries may develop epilepsy in 30–50% of cases. Early post-traumatic seizures occurring within the first seven days after injury represent one of the strongest independent predictors of subsequent epilepsy, increasing the long-term risk by approximately 2–4-fold. Additional clinical predictors include depressed skull fractures, intracerebral hematomas, cortical contusions, prolonged post-traumatic amnesia, low admission Glasgow Coma Scale scores, neurosurgical intervention, advanced age, and persistent neurological deficits [8–10].

The process of post-traumatic epileptogenesis develops over months or years through progressive molecular and cellular alterations rather than as a direct consequence of the initial injury. Blood–brain barrier disruption permits infiltration of inflammatory mediators into the cerebral parenchyma, while activation of microglia and astrocytes results in sustained production of interleukin-1β, interleukin-6, tumor necrosis factor-α, and transforming growth factor-β. These inflammatory cascades promote neuronal hyperexcitability, synaptic remodeling, axonal degeneration, oxidative stress, and reactive gliosis, ultimately leading to persistent reorganization of cortical neuronal networks. Recent experimental and clinical investigations further

indicate that chronic neuroinflammation may continue for several years after traumatic brain injury, providing a biological substrate for delayed seizure development [9–12].

Increasing attention has been directed toward circulating biomarkers capable of identifying patients at increased risk before clinical epilepsy develops. Elevated serum concentrations of glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase-L1 (UCH-L1), neurofilament light chain (NfL), total tau protein, S100B, inflammatory cytokines, and several microRNA profiles have demonstrated significant associations with injury severity and subsequent epileptogenesis. Although none of these biomarkers currently possesses sufficient diagnostic accuracy for independent clinical use, multimarker approaches combined with imaging and electroencephalographic findings have consistently demonstrated superior predictive performance compared with isolated laboratory parameters [10–13].

Neuroimaging has become an essential component of risk stratification for post-traumatic epilepsy. Computed tomography performed during the acute phase accurately identifies intracerebral hemorrhage, cortical contusions, depressed skull fractures, subdural and epidural hematomas, diffuse cerebral edema, and penetrating injuries, all of which are independently associated with increased seizure risk. Among these findings, cortical hemorrhagic contusions, multiple intracerebral hemorrhages, temporal lobe injuries, and retained intracranial metallic fragments demonstrate the strongest association with subsequent epilepsy. Serial CT examinations also provide valuable information regarding lesion progression and secondary brain injury during the early post-traumatic period [11–14].

Advanced magnetic resonance imaging offers greater sensitivity for detecting structural abnormalities associated with epileptogenesis. High-resolution T1- and T2-weighted imaging, fluid-attenuated inversion recovery sequences, susceptibility-weighted imaging, diffusion tensor imaging, and functional MRI identify diffuse axonal injury, microhemorrhages, hippocampal atrophy, cortical gliosis, white matter disruption, and abnormalities of functional brain connectivity that may remain undetected on conventional CT. Several longitudinal studies have demonstrated that reduced fractional anisotropy, extensive diffuse axonal injury, mesial temporal structural damage, and persistent cortical network disruption independently predict subsequent development of post-traumatic epilepsy, even after adjustment for conventional clinical risk factors [12–16].

Electroencephalography remains the most informative functional tool for assessing cortical excitability after traumatic brain injury. Continuous EEG monitoring performed during the acute phase frequently detects non-convulsive seizures, periodic discharges, focal slowing, epileptiform spikes, rhythmic delta activity, and high-frequency oscillations that are not clinically apparent. Quantitative EEG analysis has further demonstrated alterations in spectral power distribution, functional connectivity, and network synchronization before clinical seizure onset. Persistent epileptiform discharges and abnormal background activity during long-term follow-up have consistently been associated with significantly increased risk of chronic epilepsy, supporting the prognostic value of EEG beyond seizure detection alone [13–17].

Recent advances in artificial intelligence and machine learning have enabled integration of multidimensional clinical information into predictive models for post-traumatic epilepsy. Algorithms combining demographic characteristics, Glasgow Coma Scale scores, neuroimaging findings, quantitative EEG parameters, serum biomarkers, and electronic health record data have demonstrated higher predictive accuracy than conventional statistical models. Deep learning applied to MRI and CT imaging has shown particular promise for automated identification of subtle structural abnormalities associated with epileptogenesis, while multimodal prediction models may facilitate individualized risk stratification and selection of patients for preventive clinical trials [15–19].

Current evidence increasingly supports a multimodal approach to predicting post-traumatic epilepsy rather than reliance on any single diagnostic modality. Integration of clinical variables with advanced neuroimaging, electroencephalographic findings, circulating biomarkers, and computational prediction models provide the highest diagnostic performance for identifying patients at elevated long-term risk. Such individualized assessment has the potential to optimize neurological surveillance, improve patient selection for antiepileptogenic interventions, and facilitate precision medicine strategies aimed at reducing the long-term burden of epilepsy following traumatic brain injury [17–20].

Discussion

The findings of the present review demonstrate that post-traumatic epilepsy remains one of the most important long-term neurological complications of traumatic brain injury despite substantial advances in neurocritical care and neurosurgical management. Contemporary evidence indicates that epileptogenesis is a prolonged and multifactorial process driven by structural brain injury, persistent neuroinflammation, synaptic reorganization, and progressive alterations in neuronal network excitability. Consequently, the development of epilepsy cannot be explained solely by the severity of the initial trauma, emphasizing the need for comprehensive longitudinal assessment of patients after traumatic brain injury [8–11].

Clinical predictors continue to provide the foundation for risk stratification, particularly injury severity, early post-traumatic seizures, intracranial hemorrhage, penetrating traumas, depressed skull fractures, and prolonged post-traumatic unconsciousness. However, these factors alone demonstrate only moderate predictive accuracy because many patients with severe traumatic brain injury never develop epilepsy, whereas seizures may occur after apparently less extensive injuries. This variability highlights the biological heterogeneity of post-traumatic epileptogenesis and supports the integration of additional diagnostic modalities into contemporary prognostic models [9–13].

Neuroimaging has emerged as one of the most valuable tools for identifying structural substrates associated with future epilepsy. Conventional computed tomography remains indispensable during the acute stage for detecting hemorrhage, cortical contusions, and mass lesions requiring urgent intervention, whereas advanced magnetic resonance imaging provides greater sensitivity for diffuse axonal injury, hippocampal damage, microhemorrhages, gliosis, and abnormalities of structural

connectivity. Recent studies suggest that quantitative MRI metrics and diffusion tensor imaging may identify epileptogenic changes before clinical seizure onset, providing opportunities for earlier recognition of patients at particularly high risk [11–15].

Electroencephalography complements neuroimaging by providing direct functional assessment of cortical excitability. Persistent epileptiform discharges, periodic patterns, pathological slowing, and high-frequency oscillations have consistently been associated with increased risk of post-traumatic epilepsy. At the same time, quantitative EEG and long-term video-EEG monitoring have improved the detection of subclinical epileptiform activity that cannot be identified by routine neurological examination. The combination of EEG abnormalities with neuroimaging findings appears to provide substantially greater prognostic value than either modality alone, supporting their complementary role in multimodal diagnostic algorithms [13–17].

Another important direction in current research is the development of integrated prediction models combining clinical variables, neuroimaging characteristics, electroencephalographic findings, and circulating biomarkers. Artificial intelligence and machine learning algorithms have demonstrated encouraging predictive performance by identifying complex interactions among multiple risk factors that are difficult to detect using conventional statistical methods. Although these approaches remain under clinical validation, they represent a promising step toward individualized prediction of post-traumatic epilepsy and more rational selection of patients for prolonged neurological monitoring and future antiepileptogenic interventions [15–19].

Despite substantial progress, important limitations remain. Published studies differ regarding definitions of post-traumatic epilepsy, duration of follow-up, imaging protocols, EEG methodology, and outcome measures, limiting direct comparison between investigations. Furthermore, no individual biomarker or diagnostic modality currently demonstrates sufficient sensitivity and specificity for routine independent clinical use. Future large prospective multicenter studies integrating standardized neuroimaging, quantitative electroencephalography, molecular biomarkers, and artificial intelligence–based analytical methods are expected to improve prediction accuracy and facilitate the development of personalized strategies for preventing post-traumatic epilepsy after traumatic brain injury [17–20].

CONCLUSION

Post-traumatic epilepsy is a multifactorial consequence of traumatic brain injury that develops through complex interactions between structural brain damage, persistent neuroinflammation, neuronal network remodeling, and individual biological susceptibility. Current evidence indicates that reliable prediction of epilepsy cannot be achieved using isolated clinical characteristics alone. Instead, the highest prognostic accuracy is obtained through the integration of clinical risk factors with neuroimaging findings and electroencephalographic abnormalities, allowing earlier identification of patients at increased risk of epileptogenesis and long-term neurological complications.

Contemporary multimodal assessment combining advanced magnetic resonance imaging, computed tomography, electroencephalography, circulating biomarkers, and emerging artificial intelligence–based prediction models represent the most promising

strategy for individualized risk stratification after traumatic brain injury. Further prospective multicenter studies are needed to standardize diagnostic algorithms, validate integrated prognostic models, and optimize preventive interventions aimed at reducing the incidence of post-traumatic epilepsy and improving long-term neurological outcomes.

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PREDICTORS OF ADVERSE OUTCOMES IN NEONATES REQUIRING PROLONGED MECHANICAL VENTILATION IN THE NEONATAL INTENSIVE CARE UNIT

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Abstract. Prolonged mechanical ventilation remains one of the most challenging aspects of neonatal intensive care and is frequently required in critically ill preterm and term infants with severe respiratory, neurological, or cardiovascular disorders. Although advances in neonatal respiratory support have significantly improved survival, extended dependence on mechanical ventilation continues to be associated with increased risks of bronchopulmonary dysplasia, ventilator-associated complications, neurodevelopmental impairment, prolonged hospitalization, and mortality. Early identification of clinical and biological predictors of adverse outcomes is therefore essential for optimizing respiratory management, guiding individualized therapeutic strategies, and improving both short- and long-term prognosis.

This review summarizes current evidence regarding predictors of adverse outcomes in neonates requiring prolonged mechanical ventilation in the neonatal intensive care unit. Particular attention is given to prenatal and perinatal risk factors, respiratory and hemodynamic characteristics, neurological injury, inflammatory and laboratory biomarkers, ventilator-associated complications, and emerging predictive technologies. Recent studies indicate that integration of clinical parameters with advanced monitoring techniques, validated severity scoring systems, lung ultrasound, and artificial intelligence-based predictive models may improve risk stratification and support personalized respiratory care. Early recognition of high-risk neonates offers opportunities to optimize ventilation strategies, reduce preventable complications, facilitate successful weaning, and improve long-term clinical outcomes.

Keywords: *neonates; prolonged mechanical ventilation; neonatal intensive care unit; adverse outcomes; bronchopulmonary dysplasia; respiratory failure; predictive factors; lung ultrasound; artificial intelligence; neonatal critical care.*

Introduction

Mechanical ventilation remains an essential component of intensive care for critically ill neonates with severe respiratory insufficiency, extreme prematurity, congenital anomalies, perinatal asphyxia, and other life-threatening conditions. Over recent decades, advances in neonatal respiratory support, surfactant therapy, antenatal corticosteroid administration, and perinatal care have significantly improved survival rates among high-risk infants. Nevertheless, a substantial proportion of neonates continue to require prolonged mechanical ventilation, which remains associated with increased morbidity, prolonged hospitalization, and adverse long-term outcomes despite ongoing improvements in neonatal intensive care [1–3].

Prolonged dependence on invasive respiratory support contributes to the development of numerous pulmonary and extrapulmonary complications. Ventilator-induced lung injury, bronchopulmonary dysplasia, ventilator-associated infections, pulmonary hypertension, airway trauma, intraventricular hemorrhage, retinopathy of prematurity, impaired postnatal growth, and neurodevelopmental disorders represent some of the most significant complications observed in ventilated neonates. The risk of these adverse outcomes is influenced by multiple prenatal, perinatal, and postnatal factors, including gestational age, birth weight, severity of respiratory disease, cardiovascular instability, inflammatory response, and duration of respiratory support [3–5].

Growing evidence indicates that prediction of adverse outcomes should not rely on a single clinical variable but instead requires comprehensive assessment of multiple physiological, laboratory, and imaging parameters. Modern neonatal intensive care increasingly incorporates validated severity scoring systems, lung ultrasound, electrical impedance tomography, continuous cardiorespiratory monitoring, and biomarkers of inflammation and lung injury to improve early risk stratification. Recent advances in artificial intelligence and machine learning have further expanded opportunities for individualized prediction of respiratory outcomes and optimization of ventilatory management [5–7].

Despite considerable progress in respiratory support technologies, prolonged mechanical ventilation remains a major determinant of both short-term complications and long-term neurodevelopmental outcomes in neonatal intensive care units. Identification of reliable prognostic factors is therefore essential for optimizing ventilation strategies, guiding timely weaning, reducing preventable complications, and improving survival without severe disability. Continued refinement of predictive models may contribute to more individualized respiratory care and better long-term outcomes for critically ill neonates [7].

Aim of the study was to review current evidence regarding predictors of adverse outcomes in neonates requiring prolonged mechanical ventilation in the neonatal intensive care unit, with emphasis on clinical, respiratory, hemodynamic, laboratory,

and imaging factors that may improve early risk stratification and support individualized management strategies.

Materials and Methods

This study was conducted as a systematic literature review. A comprehensive search of the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases was performed to identify relevant publications published between 2019 and 2026. Priority was given to international clinical practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, prospective cohort studies, and multicenter observational investigations evaluating prolonged mechanical ventilation and predictors of adverse outcomes in critically ill neonates.

Studies assessing prenatal and perinatal risk factors, respiratory and hemodynamic parameters, neurological injury, laboratory biomarkers, ventilator-associated complications, severity scoring systems, lung ultrasound, artificial intelligence-based prediction models, and strategies for optimizing respiratory support were included. Case reports, conference abstracts, duplicate publications, and studies lacking clinically relevant outcome measures were excluded. The selected evidence was critically synthesized to evaluate predictors of adverse outcomes and their role in improving risk stratification and individualized respiratory management in the neonatal intensive care unit.

Results

Prolonged mechanical ventilation remains one of the strongest indicators of disease severity among critically ill neonates admitted to the neonatal intensive care unit (NICU). Although advances in neonatal respiratory support have substantially improved survival, prolonged dependence on invasive ventilation continues to be associated with increased risks of bronchopulmonary dysplasia, ventilator-induced lung injury, nosocomial infection, prolonged hospitalization, neurodevelopmental impairment, and mortality. Current evidence demonstrates that adverse outcomes are determined not by ventilation duration alone but by a complex interaction between prenatal characteristics, disease severity, inflammatory response, and the effectiveness of respiratory management [8,9].

Prenatal and perinatal characteristics are among the earliest predictors of prolonged ventilatory support and unfavorable clinical outcomes. Extremely low gestational age, very low birth weight, fetal growth restriction, maternal hypertensive disorders, chorioamnionitis, antenatal infection, inadequate antenatal corticosteroid exposure, perinatal asphyxia, and low Apgar scores have consistently been associated with increased risks of prolonged mechanical ventilation and respiratory complications. These factors contribute to structural and functional pulmonary immaturity, impaired postnatal adaptation, and increased susceptibility to chronic lung injury during intensive care [9–11].

Respiratory disorders remain the principal determinants of prolonged ventilator dependence. Severe respiratory distress syndrome, evolving bronchopulmonary dysplasia, persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, pulmonary hypoplasia, meconium aspiration syndrome, and severe neonatal pneumonia frequently require extended invasive respiratory support.

Several studies have demonstrated that high oxygen requirements, elevated oxygenation index, prolonged exposure to high airway pressures, reduced pulmonary compliance, and repeated failure of extubation are independently associated with adverse respiratory and survival outcomes [10–13].

Cardiovascular instability and neurological injury further increase the likelihood of poor prognosis in ventilated neonates. Hemodynamically significant patent ductus arteriosus, systemic hypotension requiring vasoactive support, pulmonary hypertension, impaired tissue perfusion, intraventricular hemorrhage, periventricular leukomalacia, hypoxic-ischemic encephalopathy, and neonatal seizures have all been associated with prolonged respiratory support and increased mortality. These conditions frequently coexist with severe respiratory disease, complicating ventilatory management and delaying successful weaning [12–15].

Inflammatory and laboratory biomarkers have gained increasing importance in prognostic assessment. Elevated concentrations of C-reactive protein, procalcitonin, interleukin-6, interleukin-8, lactate, abnormal blood gas parameters, persistent metabolic acidosis, and biomarkers of oxidative stress have been associated with severe pulmonary inflammation, ventilator-associated complications, and adverse clinical outcomes. Although no single biomarker has demonstrated sufficient predictive accuracy when used in isolation, combined biomarker panels integrated with clinical variables have shown improved prognostic performance in critically ill neonates [14–17].

Prolonged invasive ventilation itself contributes to multiple secondary complications that adversely affect both short-term recovery and long-term development. Ventilator-associated pneumonia, ventilator-induced lung injury, bronchopulmonary dysplasia, airway trauma, subglottic stenosis, retinopathy of prematurity, feeding difficulties, impaired somatic growth, and long-term neurodevelopmental impairment occur more frequently among infants requiring extended respiratory support. The cumulative burden of these complications emphasizes the importance of minimizing unnecessary ventilator exposure while maintaining adequate respiratory stability [15–18].

Recent advances in neonatal monitoring have improved early identification of infants at high risk for adverse outcomes. Clinical severity scores such as CRIB II and SNAPPE-II, together with lung ultrasound, electrical impedance tomography, near-infrared spectroscopy, and continuous physiological monitoring, provide valuable information regarding pulmonary function, cardiovascular stability, and disease progression. Machine learning algorithms and artificial intelligence-based prediction models have demonstrated promising accuracy in estimating extubation success, predicting bronchopulmonary dysplasia, and identifying neonates at increased risk of prolonged mechanical ventilation before irreversible complications develop [17–19].

Current evidence supports individualized respiratory management as the most effective strategy for reducing adverse outcomes in mechanically ventilated neonates. Lung-protective ventilation, optimization of positive end-expiratory pressure, permissive hypercapnia when clinically appropriate, early caffeine therapy, minimally invasive surfactant administration, timely transition to non-invasive respiratory

support, standardized weaning protocols, and multidisciplinary neonatal care have all been associated with improved survival and reduced incidence of ventilation-related complications. Future integration of predictive biomarkers with advanced monitoring technologies and artificial intelligence may further enhance precision-based respiratory care and improve both immediate and long-term outcomes in this vulnerable population [19,20].

Discussion

The findings of this review demonstrate that adverse outcomes in neonates requiring prolonged mechanical ventilation result from a complex interaction of prenatal vulnerability, severity of the underlying disease, physiological instability, and complications developing during intensive care. Prolonged ventilatory support should therefore be regarded not only as a life-sustaining intervention but also as a marker of critical illness associated with an increased risk of pulmonary, neurological, and systemic complications. Contemporary evidence indicates that outcome prediction is most accurate when multiple clinical, laboratory, and physiological parameters are evaluated simultaneously rather than relying on ventilation duration alone [8–10].

One of the principal observations emerging from recent studies is the dominant influence of gestational age and birth weight on both respiratory recovery and long-term prognosis. Extremely preterm infants possess structurally immature lungs, deficient surfactant production, impaired pulmonary vascular development, and limited physiological reserve, making them particularly susceptible to ventilator-induced lung injury and bronchopulmonary dysplasia. However, current evidence also suggests that the severity of respiratory disease, effectiveness of ventilatory management, and occurrence of secondary complications may ultimately modify outcomes independently of prematurity itself. This emphasizes the importance of continuous reassessment throughout the course of intensive care rather than relying exclusively on baseline perinatal characteristics [10–13].

The review further highlights the close relationship between respiratory and cardiovascular dysfunction in critically ill neonates. Persistent pulmonary hypertension, hemodynamically significant patent ductus arteriosus, systemic hypotension, and impaired tissue perfusion frequently coexist with severe respiratory failure and complicate ventilatory management. Simultaneously, neurological complications, including intraventricular hemorrhage and hypoxic-ischemic brain injury, substantially influence both survival and long-term neurodevelopment. These findings reinforce the need for integrated cardiopulmonary and neurological assessment throughout mechanical ventilation rather than isolated evaluation of pulmonary function alone [12–15].

Another important observation is the increasing value of multimodal monitoring and predictive technologies in neonatal intensive care. Lung ultrasound, electrical impedance tomography, near-infrared spectroscopy, continuous physiological monitoring, and validated neonatal severity scores provide dynamic information regarding disease progression and response to treatment. More recently, artificial intelligence and machine learning algorithms have demonstrated promising ability to predict extubation readiness, bronchopulmonary dysplasia, and other clinically

relevant outcomes. Although these technologies require further prospective validation, they represent an important step toward individualized respiratory management based on continuous risk assessment rather than static clinical variables [15–18].

Current evidence also supports lung-protective ventilation as a fundamental strategy for improving neonatal outcomes. Avoidance of excessive tidal volumes, optimization of positive end-expiratory pressure, minimization of oxygen toxicity, timely surfactant administration, standardized weaning protocols, and early transition to non-invasive respiratory support have consistently been associated with lower rates of ventilator-induced lung injury and bronchopulmonary dysplasia. Successful implementation of these approaches depends on close collaboration among neonatologists, respiratory therapists, nurses, neurologists, cardiologists, and other multidisciplinary team members responsible for the comprehensive management of critically ill newborns [17–19].

Despite substantial advances in neonatal intensive care, important challenges remain. Predictive models continue to differ in the variables included, timing of assessment, and reported predictive accuracy, limiting their universal application across neonatal populations. Future multicenter studies should focus on integrating clinical characteristics, biomarkers, imaging findings, genomic information, and artificial intelligence-assisted prediction models into standardized risk stratification systems. Such an approach has the potential to facilitate earlier identification of high-risk infants, optimize individualized respiratory strategies, reduce ventilation-related complications, and improve both survival and long-term neurodevelopmental outcomes in neonates requiring prolonged mechanical ventilation [18–20].

CONCLUSION

Prolonged mechanical ventilation remains a major determinant of adverse outcomes in critically ill neonates despite substantial advances in neonatal intensive care and respiratory support. Current evidence demonstrates that unfavorable prognosis is influenced by a combination of prenatal and perinatal characteristics, severity of respiratory disease, cardiovascular instability, neurological injury, inflammatory response, and ventilation-associated complications. Early identification of these predictors enables more accurate risk stratification, supports timely clinical decision-making, and facilitates individualized respiratory management aimed at reducing preventable morbidity and mortality.

Contemporary neonatal care increasingly relies on integrated assessment combining clinical evaluation, laboratory biomarkers, advanced imaging techniques, validated severity scoring systems, and continuous physiological monitoring. Emerging technologies, including artificial intelligence and machine learning, offer promising opportunities to improve prediction of adverse outcomes and optimize ventilatory strategies for individual patients. Further multicenter prospective studies are needed to validate comprehensive predictive models and establish standardized evidence-based approaches that enhance survival while minimizing long-term pulmonary and neurodevelopmental complications in neonates requiring prolonged mechanical ventilation.

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CT RADIOMICS FOR PREOPERATIVE PREDICTION OF SURGICAL OUTCOMES IN PANCREATIC TUMORS

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Abstract. Computed tomography (CT)-based radiomics has emerged as a promising quantitative imaging approach capable of extracting high-dimensional information that is not appreciable through conventional visual image interpretation. In pancreatic tumors, radiomic analysis provides objective characterization of intratumoral heterogeneity, tissue architecture, vascular involvement, and biological behavior, offering opportunities to improve preoperative risk stratification. Growing evidence suggests that CT radiomics may predict tumor aggressiveness, lymph node metastasis, margin-negative (R0) resection, early postoperative recurrence, treatment response, and long-term survival. These advances have positioned radiomics as a key component of precision imaging and an important complement to traditional radiological assessment in pancreatic oncology.

This systematic literature review summarizes current evidence regarding the application of CT radiomics for preoperative prediction of surgical outcomes in pancreatic tumors and evaluates emerging developments in radiomics-driven clinical decision support. Particular attention is given to image acquisition and feature extraction, radiomics-based prediction models, integration with clinical variables, laboratory biomarkers, and artificial intelligence algorithms. The review also discusses current limitations related to image standardization, segmentation, model reproducibility, and external validation, together with future directions involving radiogenomics and personalized surgical planning. Available evidence indicates that CT radiomics has considerable potential to improve patient selection, optimize surgical strategies, and support individualized management of pancreatic tumors before operative intervention.

Keywords: *CT radiomics; pancreatic tumors; pancreatic cancer; preoperative prediction; surgical outcomes; artificial intelligence; machine learning; radiogenomics; precision medicine; computed tomography.*

Introduction

Pancreatic tumors remain among the most challenging malignancies in contemporary oncology because of their aggressive biological behavior, late clinical presentation, and limited long-term survival despite advances in surgical and systemic treatment. Curative-intent resection remains the cornerstone of management for resectable disease; however, postoperative recurrence is common even after margin-negative surgery. Consequently, accurate preoperative assessment of tumor biology and prediction of surgical outcomes have become essential components of individualized treatment planning, extending beyond conventional evaluation of anatomical resectability alone [1–3].

Contrast-enhanced computed tomography is the primary imaging modality for staging pancreatic tumors and assessing vascular involvement, metastatic spread, and surgical feasibility. Nevertheless, conventional radiological interpretation relies predominantly on qualitative image assessment and may not adequately reflect the underlying biological heterogeneity of the tumor. Radiomics has emerged as an advanced quantitative imaging technique capable of extracting hundreds of imaging features that characterize tumor texture, intensity, morphology, and spatial heterogeneity. These quantitative biomarkers provide additional information regarding tumor phenotype that cannot be appreciated through routine visual interpretation [2–5].

Recent studies have demonstrated that CT-derived radiomic signatures are associated with numerous clinically relevant outcomes, including histological grade, lymph node metastasis, microvascular invasion, response to neoadjuvant therapy, postoperative complications, recurrence risk, and overall survival. Integration of radiomic features with clinical variables, serum biomarkers such as carbohydrate antigen 19-9, and machine learning algorithms have further improved the predictive performance of preoperative models. Growing interest in radiogenomics has additionally strengthened the relationship between imaging phenotypes and molecular characteristics of pancreatic tumors, creating new opportunities for precision oncology and personalized surgical decision-making [4–7].

Despite these promising developments, several challenges continue to limit widespread clinical implementation of CT radiomics. Variability in imaging protocols, tumor segmentation methods, feature extraction techniques, and model validation affects reproducibility and generalizability across institutions. Moreover, standardized methodological frameworks and prospective multicenter validation remain necessary before radiomics can be routinely incorporated into clinical practice. The aim of the study was to summarize current evidence regarding the role of CT radiomics in the preoperative prediction of surgical outcomes in pancreatic tumors and to evaluate contemporary advances, methodological limitations, and future perspectives for clinical implementation.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding the role of computed tomography (CT) radiomics in the preoperative prediction of surgical outcomes in pancreatic tumors. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies were included only when they established fundamental principles of radiomics, artificial intelligence, or pancreatic tumor imaging.

Eligible publications included systematic reviews, meta-analyses, prospective and retrospective cohort studies, observational investigations, methodological studies, and international consensus statements addressing CT radiomics, pancreatic tumors, surgical prediction models, artificial intelligence, and radiogenomics. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on radiomic feature extraction, predictive model development, clinical validation, surgical outcomes, and emerging applications in precision oncology.

Results

Computed tomography (CT)-based radiomics has become one of the most rapidly evolving applications of artificial intelligence in abdominal imaging. Unlike conventional radiological assessment, radiomics enables extraction of hundreds to thousands of quantitative imaging features that characterize tumor intensity, texture, shape, spatial complexity, and intratumoral heterogeneity. These features provide imaging biomarkers that reflect biological characteristics of pancreatic tumors and substantially expand the diagnostic value of routine contrast-enhanced CT examinations. Recent studies consistently demonstrate that radiomic analysis improves preoperative characterization of pancreatic neoplasms beyond conventional morphological interpretation alone [8–10].

The biological significance of radiomic features has been increasingly clarified through correlations with histopathological and molecular findings. Texture heterogeneity, entropy, gray-level co-occurrence matrix parameters, first-order histogram features, and higher-order wavelet characteristics have been associated with tumor cellularity, stromal desmoplasia, necrosis, angiogenesis, fibrosis, and proliferative activity. Radiogenomic investigations further suggest that specific radiomic signatures correlate with alterations in KRAS, TP53, SMAD4, and CDKN2A, as well as with molecular subtypes of pancreatic ductal adenocarcinoma, supporting the concept that quantitative imaging can serve as a non-invasive surrogate for tumor biology [9–12].

Image acquisition and segmentation remain critical determinants of radiomics performance. Differences in scanner type, reconstruction algorithms, slice thickness, contrast enhancement phases, and segmentation methodology significantly influence feature reproducibility. Manual segmentation remains the most commonly applied approach, although semi-automated and fully automated segmentation algorithms

based on deep learning have demonstrated increasing accuracy and substantially improved efficiency. Current standardization initiatives seek to reduce technical variability and improve external reproducibility across institutions [10–13].

Recent advances in artificial intelligence have further enhanced the predictive performance of CT radiomics. Machine learning algorithms, including random forests, support vector machines, gradient boosting methods, and deep neural networks, enable selection of the most informative radiomic features while integrating clinical variables, laboratory biomarkers, and conventional imaging findings. These multimodal predictive models consistently outperform single-parameter approaches and have demonstrated promising accuracy for individualized risk stratification before surgical intervention [11–15].

From a surgical perspective, CT radiomics has shown considerable value in predicting clinically meaningful operative outcomes. Numerous studies have reported significant associations between preoperative radiomic signatures and the probability of margin-negative (R0) resection, vascular invasion, lymph node metastasis, perineural invasion, and pathological tumor stage. Quantitative assessment of tumor heterogeneity also contributes to estimation of technical resectability and may assist multidisciplinary teams in selecting patients who are more likely to benefit from primary surgery or neoadjuvant treatment [12–16].

Radiomics has also demonstrated important prognostic utility following surgical treatment. Several predictive models accurately estimate the risk of early postoperative recurrence, disease-free survival, overall survival, and response to adjuvant therapy. Integration of radiomic features with serum carbohydrate antigen 19-9 concentrations, inflammatory biomarkers, and clinicopathological variables further improves prognostic performance and facilitates individualized postoperative surveillance strategies. Such multimodal approaches support more precise prediction of long-term oncological outcomes than conventional staging systems alone [13–18].

Radiogenomics has emerged as one of the most promising developments within pancreatic imaging research. Correlations between quantitative imaging phenotypes and genomic, transcriptomic, and proteomic profiles enable non-invasive characterization of tumor biology and provide opportunities for personalized oncological management. Integration of CT radiomics with molecular profiling may improve patient selection for targeted therapies, identify aggressive biological subtypes before surgery, and facilitate individualized treatment planning within multidisciplinary pancreatic cancer programs [15–19].

Despite substantial progress, important challenges continue to limit widespread clinical implementation of CT radiomics. Considerable heterogeneity persists regarding image acquisition protocols, feature extraction software, segmentation techniques, statistical methodology, and external validation across published studies. Many predictive models remain based on relatively small retrospective cohorts and lack independent multicenter validation. Nevertheless, current evidence consistently indicates that CT radiomics represents a highly promising decision-support tool capable of improving preoperative risk assessment, optimizing surgical strategy, and advancing precision medicine in patients with pancreatic tumors [16–20].

Discussion

The findings of the present review demonstrate that CT radiomics has evolved from an experimental image analysis technique into a promising decision-support tool for the preoperative evaluation of pancreatic tumors. By converting routine imaging data into quantitative biomarkers, radiomics provides clinically relevant information regarding tumor heterogeneity, biological aggressiveness, and the likelihood of favorable surgical outcomes. Contemporary evidence indicates that radiomic analysis complements conventional radiological assessment and has the potential to improve individualized treatment planning before operative intervention [8–11].

A consistent observation across recent studies is the close relationship between radiomic features and the underlying biological characteristics of pancreatic tumors. Quantitative texture parameters, measures of intratumoral heterogeneity, and higher-order imaging features have demonstrated meaningful associations with histological grade, stromal composition, vascular invasion, lymph node metastasis, and molecular alterations. These findings suggest that radiomics may serve as a non-invasive imaging biomarker capable of providing information that traditionally requires postoperative pathological examination, thereby supporting earlier and more informed clinical decision-making [10–14].

From a surgical perspective, the greatest clinical value of CT radiomics lies in its ability to improve preoperative risk stratification. Prediction of margin-negative resection, assessment of vascular involvement, estimation of recurrence risk, and identification of biologically aggressive tumors may influence decisions regarding primary surgery, neoadjuvant therapy, or alternative treatment strategies. Rather than replacing established radiological criteria, radiomics enhances existing preoperative evaluation by incorporating quantitative information that is not appreciable through visual image interpretation alone. Such integration is particularly valuable for patients with borderline resectable disease, where treatment decisions frequently require careful multidisciplinary consideration [12–16].

Another important development is the increasing integration of radiomics with artificial intelligence and multimodal predictive models. Machine learning algorithms capable of combining radiomic features with clinical characteristics, laboratory biomarkers such as carbohydrate antigen 19-9, and conventional imaging findings have consistently demonstrated superior predictive performance compared with isolated parameters. Furthermore, emerging radiogenomic approaches strengthen the biological interpretability of radiomic signatures and may facilitate non-invasive prediction of molecular tumor subtypes, supporting the transition toward precision oncology and individualized surgical planning [14–18].

Despite encouraging progress, several methodological limitations continue to restrict routine clinical implementation. Published studies remain heterogeneous with respect to CT acquisition protocols, segmentation techniques, feature extraction software, model construction, and statistical validation. Many predictive algorithms have been developed using retrospective single-center datasets with limited external validation, raising concerns regarding reproducibility and generalizability across different healthcare settings. Standardization of radiomics methodology,

harmonization of imaging protocols, and prospective multicenter validation therefore remain essential prerequisites for widespread clinical adoption [15–19].

Future research should focus on the development of robust, externally validated radiomics models that can be seamlessly integrated into routine radiological workflows. Greater collaboration between radiologists, pancreatic surgeons, oncologists, pathologists, and data scientists will be necessary to establish clinically applicable decision-support systems. Integration of radiomics with radiogenomics, liquid biopsy, digital pathology, and advanced artificial intelligence algorithms may substantially improve preoperative prediction of surgical outcomes and facilitate more personalized management of patients with pancreatic tumors, ultimately enhancing both oncological outcomes and surgical decision-making [17–20].

CONCLUSION

CT radiomics has emerged as a promising non-invasive imaging approach capable of improving preoperative evaluation of pancreatic tumors by providing quantitative information on tumor heterogeneity, biological behavior, and surgical risk. Current evidence indicates that radiomic models can enhance prediction of margin-negative resection, vascular invasion, lymph node metastasis, postoperative recurrence, and long-term survival when integrated with conventional imaging, clinical variables, and laboratory biomarkers. These advances support the growing role of radiomics as an important component of precision imaging and individualized surgical decision-making in pancreatic oncology.

Future progress will depend on the standardization of imaging protocols, optimization of tumor segmentation and feature extraction, and validation of predictive models in large prospective multicenter studies. Integration of CT radiomics with artificial intelligence, radiogenomics, and other multimodal biomarkers has the potential to further improve patient selection, optimize treatment strategies, and facilitate personalized perioperative management. Continued development of robust and clinically applicable radiomics models may substantially strengthen the role of quantitative imaging in the multidisciplinary care of patients with pancreatic tumors.

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CONTEMPORARY APPROACHES TO REHABILITATION AFTER FACIAL RECONSTRUCTIVE SURGERY: IMPACT ON FUNCTIONAL AND AESTHETIC OUTCOMES

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Abstract. Facial reconstructive surgery plays a pivotal role in restoring anatomical integrity and functional capacity following trauma, oncologic resection, congenital malformations, and complex head and neck procedures. Although substantial advances in microsurgical reconstruction, virtual surgical planning, and tissue transfer techniques have improved surgical outcomes, postoperative rehabilitation remains a critical determinant of long-term functional recovery and aesthetic success. Contemporary rehabilitation extends beyond wound healing and encompasses restoration of facial expression, mastication, swallowing, speech, nasal breathing, sensory function, cervical mobility, and psychosocial well-being. In patients undergoing reconstruction involving otolaryngological structures, multidisciplinary rehabilitation is particularly important because functional impairment frequently affects multiple physiological systems simultaneously.

This review summarizes current evidence regarding contemporary rehabilitation strategies following facial reconstructive surgery, with particular emphasis on functional and aesthetic outcomes. The review discusses rehabilitation after reconstruction of facial soft tissues, craniofacial structures, and head and neck defects, including procedures involving the oral cavity, pharynx, larynx, nose, and auricle. Current evidence demonstrates that early multidisciplinary rehabilitation integrating physical therapy, speech and swallowing therapy, neuromuscular retraining, scar management, nutritional support, and psychological care significantly improves postoperative recovery, quality of life, and patient-reported outcomes. Emerging

technologies, including three-dimensional surgical planning, digital outcome assessment, regenerative medicine, and artificial intelligence-assisted rehabilitation, are expected to further optimize individualized postoperative care and enhance both functional restoration and aesthetic rehabilitation.

Keywords: *facial reconstructive surgery; rehabilitation; head and neck reconstruction; otolaryngology; functional outcomes; aesthetic outcomes; microsurgery; speech rehabilitation; swallowing rehabilitation; quality of life.*

Introduction

Facial reconstructive surgery represents one of the most challenging fields of contemporary reconstructive medicine because successful treatment requires restoration of both anatomical appearance and complex physiological functions. Surgical reconstruction is frequently performed following traumatic injuries, oncologic resections, congenital craniofacial anomalies, severe infections, and extensive defects involving the oral cavity, nose, pharynx, larynx, and other structures of the head and neck. While advances in microsurgical techniques, free tissue transfer, and virtual surgical planning have substantially improved reconstructive outcomes, surgery alone rarely ensures complete functional recovery. Long-term postoperative rehabilitation has therefore become an essential component of comprehensive patient management, directly influencing functional performance, aesthetic restoration, and overall quality of life [1–3].

Functional impairment after facial reconstruction often extends beyond cosmetic concerns and may involve mastication, swallowing, speech production, nasal breathing, facial expression, sensory perception, and cervical mobility. Patients undergoing reconstruction after head and neck cancer surgery are particularly vulnerable because resection frequently affects multiple anatomical structures simultaneously, resulting in complex functional deficits that require coordinated multidisciplinary rehabilitation. Current evidence indicates that delayed or inadequate rehabilitation is associated with prolonged disability, poorer nutritional status, impaired communication, reduced social reintegration, and diminished patient-reported quality of life, even when surgical reconstruction is technically successful [3–5].

Recent years have witnessed substantial progress in rehabilitation strategies following facial and head and neck reconstruction. Early mobilization, structured physiotherapy, facial neuromuscular retraining, speech and swallowing rehabilitation, scar management, nutritional optimization, and psychosocial support have become integral elements of enhanced recovery protocols. At the same time, digital technologies—including three-dimensional surgical planning, objective facial movement analysis, virtual rehabilitation platforms, and standardized patient-reported outcome measures—have expanded opportunities for individualized postoperative care and more precise assessment of treatment effectiveness [5–7].

Despite these advances, considerable heterogeneity persists in rehabilitation protocols, timing of intervention, outcome assessment, and long-term follow-up across reconstructive centers. Furthermore, rehabilitation requirements differ substantially according to the location and extent of reconstruction, particularly in patients undergoing procedures involving otolaryngological structures, where restoration of

airway protection, phonation, swallowing, and facial function represents a major therapeutic priority. Continuous refinement of multidisciplinary rehabilitation pathways therefore remains essential for maximizing both functional recovery and aesthetic outcomes following facial reconstructive surgery [7].

Aim of the study was to review current evidence regarding contemporary rehabilitation strategies after facial reconstructive surgery and to evaluate their impact on functional recovery, aesthetic outcomes, and quality of life, with particular emphasis on patients undergoing reconstruction involving head and neck and otolaryngological structures.

Materials and Methods

This study was conducted as a systematic literature review. A comprehensive search of the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases was performed to identify relevant publications published between 2020 and 2026. Priority was given to international clinical practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, prospective cohort studies, and multicenter observational investigations evaluating postoperative rehabilitation following facial reconstructive surgery and head and neck reconstruction.

Studies investigating rehabilitation after reconstructive procedures involving the face and head and neck, including restoration of facial nerve function, mastication, swallowing, speech, airway function, and aesthetic outcomes, were included. Publications evaluating physical therapy, speech and swallowing rehabilitation, neuromuscular retraining, scar management, digital rehabilitation technologies, and multidisciplinary treatment protocols were also considered. Case reports, conference abstracts, duplicate publications, and studies lacking clinically relevant functional or aesthetic outcomes were excluded. The selected evidence was critically synthesized to evaluate the effectiveness of contemporary rehabilitation strategies following facial reconstructive surgery.

Results

Successful rehabilitation following facial reconstructive surgery extends far beyond restoration of anatomical continuity and has become an essential determinant of long-term functional and aesthetic outcomes. Contemporary reconstructive procedures are performed after facial trauma, oncologic resection, congenital craniofacial anomalies, severe infections, and complex defects involving the head and neck. Although advances in microsurgery and reconstructive techniques have markedly improved surgical success, postoperative functional recovery depends largely on structured rehabilitation initiated during the early postoperative period. Current evidence consistently demonstrates that early multidisciplinary rehabilitation reduces long-term disability, accelerates functional recovery, and improves patient-reported quality of life [8,9].

From the perspective of reconstructive and plastic surgery, rehabilitation primarily focuses on restoring facial symmetry, soft tissue mobility, muscular function, scar maturation, and aesthetic appearance. Early physiotherapy, lymphatic drainage, facial massage, neuromuscular retraining, scar modulation, and individualized exercise programs reduce postoperative edema, prevent fibrosis, improve tissue elasticity, and

facilitate recovery of facial expression. Modern rehabilitation protocols increasingly incorporate objective assessment of facial movement using digital image analysis and standardized outcome instruments, allowing clinicians to monitor functional improvement throughout the recovery process [9–11].

Restoration of facial nerve function represents one of the principal challenges following reconstructive procedures involving the parotid region, temporal bone, midface, or extensive oncologic resections. Persistent facial paralysis substantially affects eye protection, oral competence, speech articulation, mastication, and emotional expression. Current rehabilitation strategies combine targeted facial exercises, electromyographic biofeedback, mirror therapy, neuromuscular electrical stimulation in selected patients, and psychological support. These interventions have been associated with improved facial symmetry, reduction of synkinesis, enhanced voluntary muscle activation, and better long-term functional outcomes when initiated during the early stages of recovery [10–12].

Rehabilitation assumes additional complexity following reconstruction of otolaryngological structures, particularly after surgery involving the oral cavity, pharynx, larynx, and hypopharynx. Patients undergoing treatment for head and neck malignancies frequently experience dysphagia, impaired phonation, reduced airway protection, aspiration, altered respiratory function, and nutritional compromise. Contemporary evidence supports early involvement of speech-language pathologists and swallowing specialists to restore safe oral intake, improve communication, minimize aspiration risk, and facilitate functional reintegration. Early rehabilitation has been consistently associated with shorter dependence on enteral feeding, improved nutritional status, and better health-related quality of life [12–14].

Rehabilitation following laryngectomy and complex laryngeal reconstruction represents another major component of postoperative management in otolaryngology. Recovery extends beyond wound healing and includes restoration of communication, optimization of respiratory function, tracheostomy care, pulmonary rehabilitation, and psychosocial adaptation. Voice rehabilitation through tracheoesophageal prostheses, electrolarynx training, or esophageal speech remains fundamental for social reintegration. Current multidisciplinary rehabilitation programs have demonstrated significant improvements in communication ability, social participation, emotional well-being, and long-term patient satisfaction after total or partial laryngectomy [13–16].

Functional recovery after reconstruction of the nose, auricle, maxilla, and midfacial skeleton also require specialized rehabilitation strategies. Beyond aesthetic restoration, these procedures aim to preserve nasal airflow, olfactory function, hearing support, mastication, ocular protection, and craniofacial stability. Three-dimensional surgical planning, patient-specific implants, virtual surgical simulation, and postoperative functional assessment have substantially improved reconstructive precision while facilitating individualized rehabilitation. Close collaboration between plastic surgeons, otolaryngologists, maxillofacial surgeons, ophthalmologists, and rehabilitation specialists has become increasingly important in optimizing both functional and cosmetic outcomes [15–18].

Patient-reported outcome measures have become central to evaluating rehabilitation success after facial reconstruction. Contemporary assessment extends beyond objective measurements of facial movement or wound healing and incorporates quality of life, social reintegration, emotional well-being, body image, speech intelligibility, swallowing function, and satisfaction with facial appearance. Instruments such as FACE-Q, EORTC QLQ-H&N35, UW-QOL, and FACE Disability Index provide standardized evaluation of treatment effectiveness and support individualized rehabilitation planning. Increasing evidence indicates that successful functional recovery strongly correlates with improved psychosocial adaptation and overall patient satisfaction [17–19].

Emerging technologies continue to reshape postoperative rehabilitation after facial and head and neck reconstruction. Artificial intelligence-assisted facial motion analysis, wearable rehabilitation devices, tele-rehabilitation platforms, three-dimensional motion tracking, regenerative medicine, tissue engineering, and virtual reality-based rehabilitation are expanding opportunities for personalized postoperative care. These innovations enable continuous functional monitoring, earlier detection of recovery deficits, and individualized adjustment of rehabilitation programs. Current evidence suggests that integration of advanced digital technologies with multidisciplinary rehabilitation pathways may further enhance functional restoration, aesthetic recovery, and long-term quality of life following complex facial reconstructive procedures [19,20].

Discussion

The available evidence indicates that postoperative rehabilitation has become an integral component of facial reconstructive surgery rather than a secondary stage following successful anatomical reconstruction. Contemporary reconstructive techniques can restore facial continuity and structural integrity with high reliability; however, restoration of appearance alone does not guarantee recovery of essential physiological functions. Functional outcomes largely depend on the timely initiation of rehabilitation aimed at improving facial movement, speech, swallowing, mastication, airway function, and psychosocial adaptation. Current literature consistently demonstrates that delayed rehabilitation is associated with prolonged functional impairment, reduced quality of life, and lower patient satisfaction despite technically successful surgical reconstruction [8–10].

One of the most important observations emerging from recent studies is the growing importance of multidisciplinary rehabilitation. Recovery following facial reconstruction frequently requires coordinated management by plastic surgeons, otolaryngologists, maxillofacial surgeons, rehabilitation physicians, speech-language pathologists, physiotherapists, nutrition specialists, psychologists, and specialized nursing teams. Such collaboration is particularly important after extensive head and neck oncologic surgery, where impairment of several physiological functions often occurs simultaneously. Comprehensive rehabilitation programs addressing both functional recovery and psychosocial well-being have demonstrated superior long-term outcomes compared with isolated rehabilitation interventions [10–13].

The review also highlights the distinct rehabilitation challenges encountered after reconstructive procedures involving otolaryngological structures. Surgical treatment of tumors affecting the oral cavity, pharynx, larynx, and related anatomical regions frequently results in complex disturbances of swallowing, phonation, airway protection, and nutritional status. Restoration of these functions requires individualized rehabilitation protocols initiated during the early postoperative period. Published studies consistently report that structured swallowing therapy, speech rehabilitation, respiratory training, and tracheostomy management reduce aspiration-related complications, shorten dependence on enteral nutrition, improve communication, and facilitate earlier return to daily activities [12–15].

From the perspective of reconstructive and plastic surgery, optimization of aesthetic outcomes remains inseparable from functional rehabilitation. Scar maturation, restoration of facial symmetry, preservation of soft tissue mobility, and recovery of facial expression directly influence psychological recovery and social reintegration. Increasing evidence suggests that objective functional improvement and patient satisfaction with facial appearance are closely interconnected, emphasizing that successful rehabilitation should address both physical and aesthetic dimensions of recovery. Consequently, patient-reported outcome measures have become indispensable tools for evaluating the effectiveness of reconstructive treatment and guiding individualized rehabilitation strategies [14–17].

Technological innovation has substantially expanded the possibilities for postoperative rehabilitation. Three-dimensional surgical planning, objective facial motion analysis, digital imaging, wearable monitoring systems, tele-rehabilitation, and artificial intelligence-assisted assessment allow more accurate evaluation of recovery while supporting personalized rehabilitation programs. Although many of these technologies remain under active clinical investigation, preliminary evidence suggests that their integration into routine practice may improve functional monitoring, optimize therapeutic decision-making, and increase long-term rehabilitation efficiency. Future advances in regenerative medicine and tissue engineering are also expected to further enhance recovery following complex facial reconstruction [16–19].

Despite considerable progress, important challenges remain. Rehabilitation protocols continue to vary among institutions with respect to timing, duration, therapeutic intensity, and outcome assessment, limiting direct comparison between published studies. In addition, long-term prospective data evaluating functional recovery after different reconstructive techniques remain relatively limited, particularly for patients undergoing combined plastic and otolaryngological reconstruction. Future multicenter studies should focus on developing standardized rehabilitation pathways, validating objective functional assessment tools, and defining evidence-based rehabilitation protocols tailored to specific anatomical defects and reconstructive procedures. Such efforts will contribute to more consistent clinical practice and further improve both functional and aesthetic outcomes following facial reconstructive surgery [18–20].

CONCLUSION

Contemporary evidence demonstrates that successful outcomes after facial reconstructive surgery depend not only on accurate anatomical reconstruction but also on the quality and timing of postoperative rehabilitation. Early multidisciplinary rehabilitation plays a central role in restoring facial movement, mastication, swallowing, speech, airway function, and aesthetic appearance while facilitating psychosocial recovery and improving overall quality of life. Patients undergoing reconstruction involving head and neck and otolaryngological structures particularly benefit from coordinated rehabilitation programs integrating plastic surgeons, otolaryngologists, rehabilitation specialists, speech-language pathologists, physiotherapists, nutritionists, and psychologists. Such an approach promotes more complete functional recovery and reduces the long-term impact of postoperative disability.

Current rehabilitation strategies are increasingly supported by advances in digital medicine, three-dimensional surgical planning, objective functional assessment, tele-rehabilitation, and artificial intelligence-assisted technologies, enabling more personalized postoperative care. Nevertheless, considerable variability persists in rehabilitation protocols, outcome measures, and long-term follow-up across reconstructive centers. Further prospective multicenter studies are required to establish standardized evidence-based rehabilitation pathways and to evaluate the long-term effectiveness of emerging technologies. Their implementation is expected to further optimize functional restoration, improve aesthetic outcomes, and enhance patient-reported quality of life following facial reconstructive surgery.

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ANTIBIOTIC RESISTANCE IN HELICOBACTER PYLORI: CONTEMPORARY CHALLENGES IN DIAGNOSIS AND SELECTION OF ERADICATION THERAPY

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Abstract. Antibiotic resistance in *Helicobacter pylori* has become one of the major challenges limiting the effectiveness of eradication therapy worldwide. The progressive increase in resistance to clarithromycin, levofloxacin, and metronidazole has resulted in declining eradication rates for conventional empirical treatment regimens and has prompted substantial revisions of international clinical guidelines. At the same time, marked regional variation in antimicrobial susceptibility patterns complicates therapeutic decision-making and underscores the need for individualized treatment strategies. Advances in molecular diagnostics and antimicrobial susceptibility testing have expanded opportunities for selecting optimized eradication regimens while reducing the risk of treatment failure and repeated antibiotic exposure.

This systematic literature review summarizes current evidence regarding the epidemiology and molecular mechanisms of antibiotic resistance in *Helicobacter pylori* and evaluates contemporary diagnostic approaches and strategies for selecting eradication therapy. Particular attention is given to phenotypic and molecular methods of resistance detection, regional resistance patterns, evidence-based treatment algorithms, and the role of bismuth-containing regimens, potassium-competitive acid blockers, and susceptibility-guided therapy. The available evidence indicates that integrating antimicrobial susceptibility testing with personalized treatment selection may improve eradication success, limit the further spread of antibiotic resistance, and optimize long-term clinical outcomes in patients with *Helicobacter pylori* infection.

Keywords: *Helicobacter pylori; antibiotic resistance; eradication therapy; antimicrobial susceptibility testing; molecular diagnostics; clarithromycin resistance; bismuth quadruple therapy; vonoprazan; personalized treatment.*

Introduction

Helicobacter pylori infection remains one of the most prevalent chronic bacterial infections worldwide, affecting approximately half of the global population. Persistent colonization of the gastric mucosa is closely associated with chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma, making *H. pylori* an important target for both therapeutic intervention and gastric cancer prevention. Successful eradication substantially reduces the risk of disease progression and recurrence; however, treatment effectiveness has declined considerably over the past decade because of the rapid global emergence of antibiotic-resistant strains [1–3].

Antibiotic resistance has become the principal factor limiting eradication success. Resistance to clarithromycin, levofloxacin, and metronidazole has increased in many regions, while resistance patterns vary substantially across countries and even within individual populations. These geographical differences have reduced the effectiveness of empirical treatment regimens and prompted international societies to recommend region-specific therapeutic strategies whenever local antimicrobial susceptibility data are available. Consequently, selection of eradication therapy has evolved from a standardized empirical approach toward individualized treatment based on resistance profiles and previous antibiotic exposure [2–5].

Advances in diagnostic technology have significantly improved the detection of antimicrobial resistance in *H. pylori*. In addition to conventional culture-based susceptibility testing, molecular techniques such as polymerase chain reaction, real-time PCR, fluorescence in situ hybridization, and next-generation sequencing enable rapid identification of genetic mutations associated with antibiotic resistance. These methods facilitate earlier optimization of treatment, reduce unnecessary antibiotic exposure, and improve eradication rates, particularly in regions where antimicrobial resistance is highly prevalent. At the same time, widespread implementation of molecular diagnostics remains limited by cost, laboratory infrastructure, and regional differences in healthcare resources [4–7].

Recent international guidelines emphasize that successful management of *H. pylori* infection increasingly depends on integrating antimicrobial susceptibility testing, regional epidemiological data, and individualized therapeutic decision-making. The introduction of bismuth-containing quadruple therapy, potassium-competitive acid blocker–based regimens, rifabutin-containing rescue therapy, and susceptibility-guided treatment algorithms has expanded therapeutic options for patients with resistant infection. The aim of the study was to summarize current evidence regarding antibiotic resistance in *Helicobacter pylori*, contemporary diagnostic approaches, and evidence-based strategies for selecting eradication therapy in the era of increasing antimicrobial resistance.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding antibiotic resistance in *Helicobacter pylori*, current diagnostic approaches, and strategies for selecting eradication therapy. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier international consensus reports and clinical guidelines were included only when they provided essential recommendations relevant to the diagnosis or management of *H. pylori* infection.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational studies, and international clinical practice guidelines addressing antimicrobial resistance, susceptibility testing, molecular diagnostics, and eradication therapy for *Helicobacter pylori*. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on resistance mechanisms, regional epidemiological patterns, diagnostic accuracy, and the effectiveness of contemporary empirical and susceptibility-guided eradication strategies.

Results

Antibiotic resistance has become the principal determinant of unsuccessful *Helicobacter pylori* eradication worldwide. Recent epidemiological studies demonstrate a continuous increase in resistance to clarithromycin, levofloxacin, and metronidazole, with substantial geographical variability in antimicrobial susceptibility patterns. In many countries, clarithromycin resistance now exceeds the threshold at which empirical clarithromycin-based triple therapy is no longer recommended as first-line treatment. Previous exposure to macrolides or fluoroquinolones remains one of the strongest predictors of treatment failure, emphasizing the importance of considering individual antibiotic history before initiating eradication therapy [8–10].

The molecular basis of antibiotic resistance in *H. pylori* has been extensively characterized. Clarithromycin resistance is primarily associated with point mutations within the 23S rRNA gene, whereas fluoroquinolone resistance results predominantly from mutations affecting the *gyrA* gene. Resistance to metronidazole involves alterations in oxygen-sensitive nitroreductase pathways, while resistance to amoxicillin and tetracycline remains comparatively uncommon but has been reported with increasing frequency in several regions. The progressive accumulation of multiple resistance mechanisms has contributed to the emergence of multidrug-resistant strains, significantly complicating therapeutic decision-making [9–12].

Accurate identification of antimicrobial resistance has become an essential component of contemporary *H. pylori* management. Conventional culture with antimicrobial susceptibility testing remains the reference standard but is limited by technical complexity and restricted availability. Molecular diagnostic techniques, including polymerase chain reaction, real-time PCR, fluorescence in situ hybridization, and next-generation sequencing, enable rapid detection of resistance-associated mutations directly from gastric biopsy specimens or stool samples. These technologies

facilitate individualized treatment selection and improve eradication success, particularly in populations with high resistance rates [10–14].

Current international guidelines increasingly recommend individualized eradication strategies based on regional resistance patterns and antimicrobial susceptibility testing whenever feasible. Bismuth-containing quadruple therapy remains the preferred empirical first-line regimen in areas with high clarithromycin resistance, whereas potassium-competitive acid blocker–based regimens and susceptibility-guided treatment have demonstrated superior eradication rates in selected populations. Rifabutin-containing rescue therapy and other alternative regimens provide additional options for patients with multiple previous treatment failures or multidrug-resistant infection [11–16].

From a gastroenterological perspective, successful eradication of *H. pylori* extends beyond bacterial elimination and represents a fundamental strategy for preventing chronic gastroduodenal disease. Persistent infection maintains chronic active gastritis, promotes progressive mucosal inflammation, and contributes to the development of gastric and duodenal ulcers, gastric mucosal atrophy, intestinal metaplasia, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma. Numerous longitudinal studies demonstrate that timely eradication interrupts the inflammatory cascade, reduces ulcer recurrence, and lowers the long-term risk of gastric malignancy, particularly when treatment is initiated before irreversible precancerous changes have developed [12–17].

Endoscopic evaluation remains central to the gastroenterological management of patients with *H. pylori* infection, particularly in individuals presenting with alarm symptoms, peptic ulcer disease, iron deficiency anemia, or suspected premalignant gastric lesions. Modern endoscopic techniques, including high-definition white-light endoscopy, image-enhanced endoscopy, narrow-band imaging, and targeted biopsy protocols, improve the detection of gastric atrophy, intestinal metaplasia, dysplasia, and early gastric cancer. Histopathological assessment continues to provide valuable information regarding the severity of gastritis and the extent of mucosal damage while also allowing tissue acquisition for culture and molecular resistance testing when indicated [13–18].

Confirmation of successful eradication has become an essential component of contemporary gastroenterological practice. Current international recommendations advise routine post-treatment testing using the urea breath test or stool antigen test after completion of therapy, whereas serological testing is not suitable for confirming bacterial clearance. Verification of eradication allows early recognition of treatment failure, facilitates timely implementation of second-line therapy, and reduces the risk of persistent inflammation and disease progression. This test-of-cure strategy has become increasingly important in the era of rising antimicrobial resistance and declining efficacy of empirical treatment regimens [14–19].

Despite major therapeutic advances, several clinical challenges remain. Regional differences in resistance patterns, limited availability of susceptibility testing, inappropriate antibiotic prescribing, and poor treatment adherence continue to compromise eradication success in routine practice. Future gastroenterological

management is expected to rely increasingly on precision medicine, integrating molecular resistance profiling, individualized therapeutic algorithms, novel acid-suppressive agents, and continuous regional surveillance of antimicrobial resistance. Such strategies have the potential to improve eradication rates while limiting the further spread of antibiotic-resistant *H. pylori* strains and reducing the global burden of gastroduodenal disease [15–20].

Discussion

The findings of the present review demonstrate that antibiotic resistance has become the principal factor limiting the effectiveness of *Helicobacter pylori* eradication worldwide. The widespread increase in resistance to clarithromycin, levofloxacin, and metronidazole has substantially reduced the efficacy of conventional empirical treatment regimens that were previously considered standard first-line therapy. Contemporary evidence indicates that successful eradication increasingly depends on understanding regional resistance patterns and selecting treatment strategies that reflect local epidemiological characteristics rather than relying on uniform empirical protocols [8–11].

An important development in recent years has been the transition from empirical treatment toward personalized eradication therapy. International guidelines increasingly advocate antimicrobial susceptibility testing whenever available, particularly after treatment failure or in regions with high clarithromycin resistance. Molecular diagnostic techniques have significantly shortened the time required to identify resistance-associated mutations and provide clinically relevant information before treatment initiation. Although these methods are not yet universally accessible, their broader implementation has the potential to improve eradication success while reducing unnecessary exposure to ineffective antibiotics [10–14].

From a gastroenterological perspective, the clinical significance of successful *H. pylori* eradication extends far beyond symptom control. Elimination of the infection interrupts the chronic inflammatory process responsible for progressive gastric mucosal injury and reduces the incidence of peptic ulcer recurrence, gastric mucosal atrophy, intestinal metaplasia, and gastric malignancy. Consequently, eradication therapy should be regarded as an integral component of gastric cancer prevention rather than solely as antimicrobial treatment. This concept has become increasingly important in countries with a high prevalence of gastric cancer, where early identification and treatment of *H. pylori* infection may substantially reduce long-term disease burden [12–16].

Another important aspect concerns the role of endoscopy in the comprehensive management of infected patients. Modern endoscopic imaging allows detailed assessment of gastric mucosal abnormalities while providing tissue samples for histopathological examination and, when appropriate, antimicrobial susceptibility testing. In patients with premalignant lesions or previous unsuccessful eradication attempts, integration of advanced endoscopic assessment with microbiological and molecular diagnostic techniques facilitates more accurate risk stratification and individualized therapeutic planning. Such an approach reflects the growing convergence of diagnostic endoscopy and precision gastroenterology [13–17].

Despite considerable progress, important limitations remain. Access to culture-based susceptibility testing and molecular diagnostics varies substantially between healthcare systems, limiting the widespread implementation of personalized treatment strategies. Furthermore, resistance surveillance programs remain insufficient in many regions, resulting in limited availability of reliable local epidemiological data. Differences in study design, definitions of treatment success, and regional antimicrobial prescribing practices also contribute to heterogeneity among published investigations, complicating direct comparison of therapeutic outcomes [15–19].

Future management of *H. pylori* infection is expected to incorporate broader use of molecular resistance testing, continuous regional surveillance, and individualized treatment algorithms supported by advances in microbiology and artificial intelligence. Further research should focus on validating rapid point-of-care diagnostic technologies, evaluating novel antimicrobial combinations, and optimizing susceptibility-guided therapeutic strategies capable of maintaining high eradication rates despite the continued evolution of antibiotic resistance. Such developments are likely to strengthen antimicrobial stewardship while improving long-term gastroenterological outcomes for patients with *H. pylori* infection [16–20].

CONCLUSION

Antibiotic resistance has become the major obstacle to successful *Helicobacter pylori* eradication and represents one of the most important challenges in contemporary gastroenterology. The continuous increase in resistance to commonly used antimicrobial agents has reduced the effectiveness of empirical treatment regimens and necessitated a transition toward evidence-based, individualized therapeutic approaches. Advances in molecular diagnostics, antimicrobial susceptibility testing, and optimized eradication protocols have substantially improved the ability to select appropriate treatment strategies, while confirmation of eradication remains an essential component of long-term gastroenterological management and gastric cancer prevention.

Future progress will depend on expanding access to rapid susceptibility testing, strengthening regional surveillance of antimicrobial resistance, and integrating precision medicine into routine clinical practice. Continued development of novel antimicrobial regimens, potassium-competitive acid blocker–based therapies, and molecular diagnostic technologies is expected to improve eradication success while reducing unnecessary antibiotic exposure. The implementation of personalized treatment algorithms based on local epidemiological data and individual resistance profiles may contribute to more effective infection control and better long-term outcomes for patients with *Helicobacter pylori* infection.

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CARDIORENAL-METABOLIC SYNDROME: A NEW CONCEPT FOR THE MANAGEMENT OF PATIENTS AT HIGH CARDIOVASCULAR RISK

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Abstract. Cardiorenal-metabolic syndrome (CKM syndrome) has emerged as an integrated clinical concept reflecting the close interplay between cardiovascular disease, chronic kidney disease, obesity, type 2 diabetes mellitus, and metabolic dysfunction. Rather than representing isolated disorders, these conditions form a continuum driven by shared pathophysiological mechanisms, including insulin resistance, chronic low-grade inflammation, endothelial dysfunction, oxidative stress, neurohormonal activation, and progressive organ remodeling. The growing prevalence of obesity and metabolic diseases has substantially increased the number of patients simultaneously affected by cardiac and renal impairment, emphasizing the need for coordinated approaches to risk assessment and long-term management. Recent international recommendations have proposed CKM syndrome as a framework for earlier identification of individuals at increased cardiovascular risk and for implementing preventive strategies before irreversible organ damage develops.

This review summarizes current evidence on the pathophysiology, clinical staging, diagnostic principles, and treatment of cardiorenal-metabolic syndrome in patients at high cardiovascular risk. It highlights contemporary strategies that combine lifestyle modification with pharmacological therapies offering cardiovascular and renal protection, including sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, nonsteroidal mineralocorticoid receptor antagonists, and optimized lipid-lowering therapy. Available evidence suggests that early detection of CKM syndrome, comprehensive evaluation of cardiovascular, renal, and metabolic status, and multidisciplinary care can improve clinical outcomes and substantially reduce major adverse cardiovascular and renal events.

Keywords: *cardiorenal-metabolic syndrome; cardiovascular risk; chronic kidney disease; sodium-glucose cotransporter-2 inhibitors; glucagon-like peptide-1 receptor agonists; cardiovascular prevention.*

Introduction. Cardiovascular diseases remain the leading cause of mortality worldwide despite significant advances in prevention, diagnostics, and pharmacological treatment. At the same time, the global prevalence of obesity, type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD), and metabolic dysfunction continue to increase, resulting in a growing population of patients with multiple interrelated chronic conditions. Accumulating epidemiological evidence indicates that these disorders rarely occur in isolation. Instead, they share common biological mechanisms and mutually accelerate the progression of cardiovascular and renal injury, substantially increasing the risk of myocardial infarction, stroke, heart failure, end-

stage kidney disease, and premature death [1–3]. Conventional disease-oriented management frequently fails to capture this complex interaction, emphasizing the need for a more integrated clinical framework.

Recognition of these interconnected processes has led to the introduction of the Cardiovascular-Kidney-Metabolic (CKM) syndrome concept by the American Heart Association in 2023. This framework defines CKM syndrome as a continuum encompassing metabolic risk factors, obesity, impaired glucose metabolism, chronic kidney disease, and cardiovascular pathology, while emphasizing their bidirectional pathophysiological relationships rather than considering them as separate clinical entities [4]. The proposed staging system shifts clinical attention toward earlier identification of patients at increased lifetime cardiovascular risk, even before overt cardiovascular disease becomes clinically apparent. Such an approach reflects current understanding that cardiovascular injury often develops over many years through cumulative exposure to metabolic and renal dysfunction.

The biological basis of CKM syndrome is multifactorial and involves persistent low-grade inflammation, insulin resistance, endothelial dysfunction, oxidative stress, adipose tissue remodeling, activation of the renin–angiotensin–aldosterone system, sympathetic overactivity, and progressive myocardial and renal fibrosis [5–7]. These mechanisms create a self-perpetuating cycle in which deterioration of one organ system contributes to dysfunction of the others. During the last decade, several large randomized clinical trials have demonstrated that therapies initially developed for glycemic control, particularly sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors) and glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists), significantly reduce cardiovascular events, hospitalization for heart failure, and progression of chronic kidney disease irrespective of glucose-lowering effects alone [8]. These findings have fundamentally changed contemporary strategies for cardiovascular prevention and support the transition from isolated treatment of individual diseases toward integrated cardiorenal-metabolic care.

Despite substantial progress in therapeutic options, implementation of the CKM concept in routine clinical practice remains inconsistent. Many patients continue to receive fragmented care from different specialists, while opportunities for early intervention, comprehensive risk stratification, and coordinated management are often missed. In addition, rapid expansion of evidence has led to continuous updates in international recommendations, creating the need for an up-to-date synthesis of available data. The aim of this review was to summarize current evidence regarding the epidemiology, pathophysiological mechanisms, clinical staging, diagnostic approaches, and contemporary management strategies for cardiorenal-metabolic syndrome in patients at high cardiovascular risk.

Materials and methods. This study was conducted as a systematic literature review. Publications indexed in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library were searched to identify studies evaluating the epidemiology, pathophysiology, clinical staging, diagnosis, and management of cardiorenal-metabolic syndrome. The search included articles published between 2020 and 2026,

together with current international clinical practice guidelines and scientific statements relevant to cardiovascular, renal, and metabolic diseases.

Priority was given to systematic reviews, meta-analyses, randomized controlled trials, large prospective cohort studies, and evidence-based recommendations from international professional societies. Publications with insufficient methodological quality, duplicate reports, conference abstracts without full-text availability, and studies not directly related to the objectives of the review were excluded. The collected evidence was synthesized using a narrative analytical approach with emphasis on clinically relevant findings and contemporary therapeutic strategies for patients at high cardiovascular risk.

Results. The reviewed literature demonstrates that cardiorenal-metabolic syndrome should be considered not as a simple coexistence of cardiovascular disease, chronic kidney disease, obesity, and type 2 diabetes mellitus, but as a progressive clinical continuum with shared mechanisms of organ injury. The American Heart Association presidential advisory defined CKM syndrome as a systemic disorder caused by interactions between metabolic risk factors, chronic kidney disease, and the cardiovascular system, and proposed staged assessment from the absence of risk factors to clinically manifest cardiovascular disease [9]. This approach is clinically important because patients with obesity, insulin resistance, albuminuria, reduced estimated glomerular filtration rate, hypertension, and dyslipidemia frequently move across risk categories long before myocardial infarction, stroke, heart failure, or end-stage kidney disease becomes evident. The available evidence therefore supports a shift from narrow diagnosis-based management toward earlier detection of combined cardiovascular, renal, and metabolic risk.

A key finding of recent studies is that renal involvement has independent prognostic significance in patients with high cardiovascular risk. Albuminuria and reduced estimated glomerular filtration rate are not only markers of chronic kidney disease but also indicators of endothelial dysfunction, microvascular damage, systemic inflammation, and higher probability of future cardiovascular events. The KDIGO 2024 guideline continues to emphasize combined assessment of eGFR and albuminuria for CKD staging, because patients with similar eGFR may have substantially different cardiovascular and renal prognosis depending on urinary albumin excretion [10]. In the context of CKM syndrome, this is particularly relevant because a patient with obesity, hypertension, and preserved creatinine level may already have clinically meaningful renal and vascular injury if albuminuria is present. Therefore, the literature supports routine evaluation of eGFR and urine albumin-to-creatinine ratio in patients with obesity, diabetes, hypertension, established atherosclerotic cardiovascular disease, and heart failure.

The therapeutic importance of this concept is supported by large randomized trials of SGLT2 inhibitors. In DAPA-CKD, dapagliflozin significantly reduced the risk of the primary composite endpoint, which included sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes, in patients with chronic kidney disease with or without type 2 diabetes [11]. The trial also showed a reduction in the composite of cardiovascular death or hospitalization for heart failure

and a lower risk of all-cause mortality. These findings are important for CKM syndrome because they demonstrate that cardiorenal protection is not limited to glucose lowering and extends to patients without diabetes. Similar conclusions were obtained in EMPA-KIDNEY, where empagliflozin reduced the risk of kidney disease progression or cardiovascular death in a broad CKD population [12]. Together, these trials changed the clinical role of SGLT2 inhibitors from antidiabetic drugs to organ-protective therapy for patients with combined renal and cardiovascular risk.

Heart failure represents one of the most clinically visible manifestations of CKM syndrome. Patients with obesity, diabetes, renal dysfunction, and hypertension often develop myocardial remodeling, increased filling pressures, vascular stiffness, systemic inflammation, and impaired skeletal muscle metabolism. This phenotype is especially relevant for heart failure with preserved or mildly reduced ejection fraction, where traditional neurohormonal therapies had historically shown limited effect. In DELIVER, dapagliflozin reduced the risk of worsening heart failure or cardiovascular death in patients with heart failure with mildly reduced or preserved ejection fraction, confirming that SGLT2 inhibition is beneficial beyond the classic HFrEF population [13]. These data support the inclusion of SGLT2 inhibitors as a central therapeutic component in patients with CKM syndrome and symptomatic heart failure, including those with preserved ejection fraction.

Obesity has also moved from being interpreted mainly as a background risk factor to being recognized as an active therapeutic target in CKM syndrome. The SELECT trial showed that once-weekly semaglutide 2.4 mg reduced major adverse cardiovascular events in patients with overweight or obesity and established cardiovascular disease without diabetes [14]. This finding is particularly important because it demonstrates cardiovascular benefit in a population where treatment was directed at obesity-related cardiovascular risk rather than hyperglycemia. In practical terms, the trial supports the view that adiposity itself contributes to cardiovascular risk through inflammatory, hemodynamic, metabolic, and neurohormonal pathways. Therefore, weight reduction therapy in CKM syndrome should be viewed not only as lifestyle correction but as part of cardiovascular risk modification.

The renal effects of GLP-1 receptor agonist therapy were further strengthened by the FLOW trial. In patients with type 2 diabetes and chronic kidney disease, semaglutide reduced the risk of clinically important kidney outcomes and death from cardiovascular causes [15]. This study expanded the evidence base for GLP-1 receptor agonists from glycemic control and weight reduction to kidney protection in a high-risk metabolic population. For CKM syndrome, this is a decisive point: GLP-1 receptor agonists may influence several components of the syndrome simultaneously, including body weight, glycemia, inflammation, blood pressure, albuminuria, and cardiovascular risk. The evidence suggests that patients with obesity, diabetes, CKD, and established cardiovascular disease may benefit from early consideration of GLP-1 receptor agonist therapy, especially when excess adiposity and atherosclerotic risk dominate the clinical picture.

A separate therapeutic direction is mineralocorticoid receptor overactivation, which contributes to inflammation, fibrosis, sodium retention, vascular dysfunction, and

progression of renal and cardiac damage. In FIDELIO-DKD, finerenone reduced the risk of CKD progression and cardiovascular events in patients with chronic kidney disease and type 2 diabetes [16]. In FIGARO-DKD, finerenone improved cardiovascular outcomes in a population with type 2 diabetes and earlier stages of CKD with albuminuria [17]. These findings indicate that albuminuric CKD in diabetes should be treated not only as a renal complication but as part of systemic cardiovascular risk. The main practical implication is that nonsteroidal mineralocorticoid receptor antagonism may be considered in selected patients with persistent albuminuria despite optimized renin–angiotensin system blockade, if serum potassium and kidney function are carefully monitored.

Recent evidence also extends the role of finerenone into heart failure with mildly reduced or preserved ejection fraction. In FINEARTS-HF, finerenone reduced the rate of worsening heart failure events and cardiovascular death in patients with heart failure and mildly reduced or preserved ejection fraction [18]. This result is relevant because it addresses the same phenotype that is frequently seen in CKM syndrome: older patients with obesity, diabetes, hypertension, renal impairment, systemic inflammation, and congestion-prone heart failure. The data suggests that the therapeutic model for CKM syndrome should not rely on a single drug class but should combine interventions targeting hemodynamic load, renal protection, metabolic dysfunction, inflammation, and fibrosis.

Clinical guidelines increasingly reflect this integrated approach. The 2023 ESC guideline for cardiovascular disease in patients with diabetes recommends comprehensive cardiovascular risk assessment and emphasizes the use of SGLT2 inhibitors and GLP-1 receptor agonists with proven cardiovascular benefit in appropriate high-risk patients [19]. This aligns with the CKM model because treatment selection is no longer based only on glycated hemoglobin level. Instead, the presence of atherosclerotic cardiovascular disease, heart failure, CKD, obesity, albuminuria, and global cardiovascular risk should determine therapeutic priorities. In patients with established cardiovascular disease and type 2 diabetes, GLP-1 receptor agonists are particularly relevant for atherosclerotic risk and weight reduction, whereas SGLT2 inhibitors are especially important in heart failure and CKD phenotypes.

The reviewed literature also shows that CKM syndrome requires active risk stratification rather than passive observation of isolated laboratory abnormalities. The AHA staging system emphasizes early stages, including excess adiposity, metabolic risk factors, and subclinical kidney disease, before overt cardiovascular events occur [9]. This is clinically important because many patients enter cardiology care only after the development of symptomatic ischemic heart disease, heart failure, atrial fibrillation, or stroke. Earlier staging allows clinicians to identify patients who need aggressive lifestyle intervention, blood pressure control, lipid-lowering therapy, kidney-protective treatment, weight management, and structured follow-up. In this sense, CKM syndrome is not only a diagnostic term but also a practical framework for preventive cardiology.

A consistent finding across studies is that single-specialty care is insufficient for patients with advanced CKM syndrome. Cardiologists, nephrologists,

endocrinologists, primary care physicians, dietitians, and rehabilitation specialists often manage different parts of the same disease process. Fragmented care may delay initiation of SGLT2 inhibitors, GLP-1 receptor agonists, finerenone, renin–angiotensin system blockade, statins, or antihypertensive therapy. The AHA advisory specifically emphasizes holistic approaches to care, including screening, staging, prediction of cardiovascular risk, and coordinated management [9]. For patients with high cardiovascular risk, this means that clinical assessment should include body mass index and waist circumference, blood pressure, lipid profile, glycemic status, eGFR, albuminuria, heart failure symptoms, and evidence of established atherosclerotic disease.

The evidence base also supports the idea that CKM syndrome is a dynamic condition. A patient may initially present with obesity and mild metabolic abnormalities, later develop hypertension and albuminuria, and subsequently progress to CKD, heart failure, or atherosclerotic cardiovascular disease. This progression is not inevitable, but the reviewed trials show that intervention must occur before irreversible organ damage becomes advanced. DAPA-CKD and EMPA-KIDNEY demonstrated that SGLT2 inhibitors can slow renal progression and reduce clinically important outcomes [11,12]. SELECT and FLOW showed that semaglutide provides cardiovascular and renal benefit in high-risk obesity and diabetic CKD populations [14,15]. FIDELIO-DKD, FIGARO-DKD, and FINEARTS-HF demonstrated the value of targeting mineralocorticoid receptor-related pathways in CKD and heart failure phenotypes [16–18]. These data collectively support early, phenotype-based combination therapy.

Overall, the results of the literature review indicate that modern management of CKM syndrome should be based on several principles: early identification of metabolic and renal risk, assessment of albuminuria and eGFR, stratification of cardiovascular risk, active treatment of obesity, use of SGLT2 inhibitors in CKD and heart failure phenotypes, use of GLP-1 receptor agonists in patients with obesity and atherosclerotic or metabolic risk, consideration of finerenone in albuminuric diabetic CKD and selected heart failure phenotypes, and strict control of blood pressure and lipids. The most important shift is conceptual: cardiovascular prevention is no longer limited to correction of classical risk factors but increasingly depends on coordinated cardiorenal-metabolic protection. This approach is especially relevant for patients at high cardiovascular risk, in whom delayed recognition of CKM syndrome may lead to preventable myocardial infarction, stroke, heart failure hospitalization, renal failure, and premature mortality.

Discussion. The emergence of the cardiorenal-metabolic (CKM) syndrome concept reflects a fundamental shift in the understanding of chronic noncommunicable diseases. Rather than viewing cardiovascular disease, chronic kidney disease, obesity, and type 2 diabetes mellitus as separate clinical entities, current evidence indicates that these conditions represent interconnected manifestations of a common pathophysiological process. The reviewed studies consistently demonstrate that metabolic dysfunction initiates progressive structural and functional changes affecting the vascular endothelium, myocardium, kidneys, and adipose tissue, ultimately leading

to accelerated cardiovascular events and organ failure [9,10]. This integrated perspective explains why traditional management focused on individual diseases has often failed to achieve optimal long-term outcomes.

One of the most important findings identified in this review is the transition from glucose-centered treatment toward organ protection. Large randomized clinical trials have shown that SGLT2 inhibitors and GLP-1 receptor agonists exert clinically meaningful cardiovascular and renal benefits that extend beyond glycemic control [11–15]. The reduction in hospitalization for heart failure, slowing of CKD progression, improvement in cardiovascular outcomes, and favorable effects on body weight support the concept that these agents modify fundamental mechanisms responsible for CKM progression. Consequently, pharmacological therapy should increasingly be selected according to the patient's overall cardiovascular, renal, and metabolic phenotype rather than solely on the presence of hyperglycemia.

The evidence also highlights the importance of early identification of subclinical disease. Albuminuria, declining estimated glomerular filtration rate, visceral obesity, insulin resistance, and persistent low-grade inflammation frequently precede overt cardiovascular complications by many years. Recognition of these abnormalities at earlier CKM stages creates an opportunity to initiate preventive interventions before irreversible myocardial or renal remodeling develops [9,10]. From a practical standpoint, routine assessment of renal function, urinary albumin excretion, metabolic status, and cardiovascular risk should become an integral component of clinical evaluation in individuals with obesity, hypertension, diabetes, or established atherosclerotic disease.

Another important aspect emerging from recent publications is the necessity of multidisciplinary care. Patients with CKM syndrome commonly require simultaneous management of dyslipidemia, hypertension, obesity, chronic kidney disease, heart failure, and metabolic disorders. Fragmented care frequently results in delayed initiation of evidence-based therapies and inadequate risk factor control. The reviewed literature supports coordinated collaboration between cardiologists, nephrologists, endocrinologists, primary care physicians, nutrition specialists, and rehabilitation professionals to improve treatment adherence and optimize long-term prognosis [9,19].

Despite substantial advances, several challenges remain unresolved. The implementation of CKM staging into routine clinical practice varies considerably between healthcare systems, and optimal strategies for integrating novel pharmacological agents into individualized treatment pathways continue to evolve. Additional prospective studies are required to determine the most effective sequencing and combination of therapies in different CKM phenotypes, to evaluate long-term cost-effectiveness, and to identify biomarkers capable of improving personalized risk prediction. Future research should also clarify the role of emerging anti-inflammatory and antifibrotic therapies in modifying disease progression.

CONCLUSION

Cardiorenal-metabolic syndrome represents a contemporary clinical model that integrates cardiovascular disease, chronic kidney disease, obesity, and metabolic dysfunction into a single continuum of progressive organ injury. Current evidence

indicates that early identification of CKM stages, comprehensive cardiovascular and renal risk assessment, and timely initiation of evidence-based therapy are associated with improved cardiovascular and renal outcomes. The availability of SGLT2 inhibitors, GLP-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists has substantially expanded opportunities for simultaneous protection of multiple organ systems, supporting a transition from disease-specific treatment toward phenotype-oriented management.

Implementation of the CKM concept in routine clinical practice requires multidisciplinary collaboration, systematic screening of high-risk individuals, and individualized therapeutic strategies based on the patient's cardiovascular, renal, and metabolic profile. Continued refinement of risk stratification models and integration of emerging therapeutic approaches are expected to further improve prevention of major adverse cardiovascular events, delay progression of chronic kidney disease, and reduce premature mortality in this rapidly growing patient population.

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COGNITIVE IMPAIRMENT IN TYPE 2 DIABETES MELLITUS: THE ROLE OF CHRONIC HYPERGLYCEMIA, INSULIN RESISTANCE, AND CEREBRAL SMALL VESSEL DISEASE

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Abstract. Type 2 diabetes mellitus is increasingly recognized as an important risk factor for cognitive impairment and dementia, extending its clinical impact beyond traditional metabolic and cardiovascular complications. Chronic hyperglycemia, insulin resistance, oxidative stress, advanced glycation end-product accumulation, and persistent low-grade inflammation contribute to progressive neuronal injury and cerebral microvascular dysfunction, ultimately accelerating cognitive decline. In parallel, cerebral small vessel disease has emerged as a major structural substrate linking metabolic disturbances with impaired cerebral perfusion, white matter injury, and deterioration of executive function and memory. Growing evidence suggests that cognitive impairment associated with type 2 diabetes results from complex interactions between neurodegenerative and cerebrovascular mechanisms rather than from a single pathological process.

This systematic literature review summarizes current evidence regarding the mechanisms underlying cognitive impairment in type 2 diabetes mellitus and evaluates the contribution of chronic hyperglycemia, insulin resistance, and cerebral small vessel disease to the development of cognitive dysfunction. Particular attention is given to neuroimaging findings, circulating biomarkers, neuropsychological assessment, and emerging therapeutic strategies aimed at preserving cognitive function. The review also examines the potential neuroprotective effects of contemporary glucose-lowering therapies and the role of precision medicine in identifying individuals at increased risk of progressive cognitive decline. Current evidence supports early recognition of

diabetes-related cognitive impairment as an essential component of comprehensive diabetes care and highlights the importance of multidisciplinary preventive strategies to improve long-term neurological outcomes.

Keywords: *type 2 diabetes mellitus; cognitive impairment; insulin resistance; chronic hyperglycemia; cerebral small vessel disease; neurodegeneration; cerebral microangiopathy; magnetic resonance imaging; dementia; neuroprotection.*

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic disorders worldwide and is increasingly recognized as an important contributor to neurological morbidity. Beyond its well-established association with macrovascular and microvascular complications, T2DM has been consistently linked to accelerated cognitive decline, mild cognitive impairment, and an increased risk of both vascular dementia and Alzheimer's disease. As the global prevalence of diabetes continues to rise, diabetes-related cognitive dysfunction has become an important public health concern with substantial implications for quality of life, treatment adherence, functional independence, and healthcare utilization [1–3].

The mechanisms underlying cognitive impairment in T2DM are multifactorial and involve complex interactions between metabolic, vascular, and neurodegenerative processes. Chronic hyperglycemia promotes oxidative stress, mitochondrial dysfunction, accumulation of advanced glycation end products, endothelial injury, and persistent low-grade inflammation, resulting in progressive neuronal damage and impaired synaptic plasticity. Simultaneously, insulin resistance disrupts cerebral insulin signaling, reduces neuronal glucose utilization, impairs amyloid-β clearance, enhances tau protein phosphorylation, and contributes to neurodegenerative changes that closely resemble those observed in Alzheimer's disease. These interconnected mechanisms suggest that diabetes accelerates brain aging through both vascular and non-vascular pathways [2–5].

Cerebral small vessel disease has emerged as a key structural substrate linking T2DM with cognitive decline. Neuroimaging studies consistently demonstrate a higher prevalence of white matter hyperintensities, lacunar infarctions, cerebral microbleeds, enlarged perivascular spaces, and diffuse brain atrophy in patients with diabetes compared with metabolically healthy individuals. These abnormalities are associated with impaired cerebral autoregulation, chronic hypoperfusion, disruption of the blood-brain barrier, and progressive deterioration of executive function, processing speed, and memory. Advances in magnetic resonance imaging and quantitative neuroimaging have further strengthened the understanding of cerebral microvascular injury as a major determinant of diabetes-related cognitive dysfunction [4–7].

Growing recognition of cognitive impairment as a clinically relevant complication of T2DM has stimulated interest in earlier diagnosis, individualized risk stratification, and neuroprotective therapeutic strategies. Contemporary evidence suggests that comprehensive management of metabolic risk factors, optimization of glycemic control, and the use of novel glucose-lowering agents with potential neuroprotective properties may influence long-term cognitive outcomes. At the same time, significant uncertainties remain regarding the relative contribution of metabolic and vascular

mechanisms, the identification of reliable biomarkers, and the optimal approach to prevention. The aim of the study was to summarize current evidence regarding the role of chronic hyperglycemia, insulin resistance, and cerebral small vessel disease in the development of cognitive impairment in patients with type 2 diabetes mellitus.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding the mechanisms of cognitive impairment in patients with type 2 diabetes mellitus, with particular emphasis on the roles of chronic hyperglycemia, insulin resistance, and cerebral small vessel disease. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies and international consensus documents were included only when they provided essential evidence regarding the pathophysiology or diagnosis of diabetes-related cognitive impairment.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, neuroimaging studies, and evidence-based clinical practice guidelines addressing cognitive dysfunction, cerebral small vessel disease, neurodegeneration, and therapeutic interventions in type 2 diabetes mellitus. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on pathogenic mechanisms, neuroimaging findings, diagnostic biomarkers, cognitive outcomes, and emerging neuroprotective treatment strategies.

Results

Type 2 diabetes mellitus (T2DM) has consistently been identified as an independent risk factor for accelerated cognitive decline and dementia. Large prospective cohort studies demonstrate that individuals with T2DM exhibit a significantly higher incidence of mild cognitive impairment, vascular dementia, and Alzheimer's disease than metabolically healthy populations. The likelihood of cognitive deterioration increases with longer disease duration, inadequate glycemic control, recurrent hypoglycemia, and the presence of diabetic microvascular complications, indicating that chronic metabolic disturbances exert cumulative effects on cerebral structure and function [8–10].

Chronic hyperglycemia represents one of the principal mechanisms responsible for diabetes-associated brain injury. Sustained elevation of blood glucose promotes excessive production of reactive oxygen species, accumulation of advanced glycation end products, mitochondrial dysfunction, endothelial injury, and activation of inflammatory signaling pathways. These alterations impair neuronal metabolism, reduce synaptic plasticity, disrupt the integrity of the blood-brain barrier, and accelerate neuronal apoptosis. Experimental and clinical studies further demonstrate that prolonged hyperglycemia contributes to hippocampal atrophy and progressive impairment of learning and memory, particularly in older adults with poorly controlled diabetes [9–12].

Insulin resistance also plays a central role in the pathogenesis of cognitive dysfunction. In addition to regulating peripheral glucose metabolism, insulin participates in synaptic transmission, neuronal survival, and memory formation within the central nervous system. Impaired cerebral insulin signaling reduces neuronal glucose utilization, promotes amyloid-β accumulation through diminished degradation, enhances tau hyperphosphorylation, and accelerates neurodegenerative processes characteristic of Alzheimer's disease. These observations have led to the concept of Alzheimer's disease as a disorder sharing important metabolic mechanisms with diabetes, reinforcing the close relationship between insulin resistance and progressive cognitive decline [10–13].

Cerebral small vessel disease (CSVD) constitutes a major structural substrate linking diabetes with cognitive impairment. Magnetic resonance imaging consistently demonstrates increased prevalence of white matter hyperintensities, lacunar infarctions, cerebral microbleeds, enlarged perivascular spaces, and diffuse cerebral atrophy in patients with T2DM. Progressive microvascular injury impairs cerebral autoregulation, reduces cerebral perfusion, and compromises white matter integrity, leading predominantly to deterioration of executive function, processing speed, attention, and working memory. The burden of CSVD strongly correlates with both diabetes duration and long-term glycemic exposure [11–15].

From a neurological perspective, diabetes-related cognitive impairment is increasingly recognized as a heterogeneous clinical syndrome involving both neurodegenerative and vascular mechanisms. Neuropsychological assessment commonly reveals deficits in executive functioning, psychomotor speed, episodic memory, attention, and cognitive flexibility, whereas language abilities are often relatively preserved during the early stages. The pattern of impairment frequently reflects the combined effects of diffuse white matter injury, hippocampal degeneration, and disruption of large-scale neural connectivity rather than isolated cortical pathology [12–16].

Advances in neuroimaging have substantially improved understanding of cerebral alterations associated with T2DM. Structural magnetic resonance imaging demonstrates accelerated cortical and hippocampal atrophy, while diffusion tensor imaging reveals disruption of white matter microstructure before overt cognitive impairment becomes clinically apparent. Functional magnetic resonance imaging has identified altered connectivity within the default mode network and executive control networks, whereas arterial spin labeling techniques demonstrate reduced cerebral perfusion in regions vulnerable to neurodegeneration. These multimodal imaging findings support the concept that cerebral injury begins during the preclinical stages of diabetes and progresses gradually over time [13–18].

Growing attention has also been directed toward circulating biomarkers and emerging therapeutic strategies capable of modifying neurological outcomes. Elevated concentrations of inflammatory mediators, neurofilament light chain, glial fibrillary acidic protein, and biomarkers of endothelial dysfunction have demonstrated promising associations with cognitive decline, although their clinical application remains under investigation. Contemporary glucose-lowering therapies, particularly

glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors, have shown potential neuroprotective effects through mechanisms involving improved insulin sensitivity, reduced neuroinflammation, enhanced cerebrovascular function, and attenuation of oxidative stress [15–19].

Despite substantial progress, important challenges remain in the identification and management of diabetes-related cognitive impairment. Considerable heterogeneity exists regarding patient characteristics, neuropsychological assessment methods, neuroimaging protocols, and biomarker evaluation across published studies. Furthermore, distinguishing diabetes-associated cognitive dysfunction from age-related cognitive decline and concurrent neurodegenerative disorders remains clinically challenging. Current evidence nevertheless supports the integration of cognitive screening, advanced neuroimaging, and individualized metabolic management into routine care for patients with T2DM, particularly those at increased risk for progressive cerebral small vessel disease and cognitive deterioration [16–20].

Discussion

The findings of the present review indicate that cognitive impairment in type 2 diabetes mellitus results from the interaction of metabolic, vascular, and neurodegenerative mechanisms rather than from isolated hyperglycemia alone. Chronic exposure to elevated glucose concentrations initiates a cascade of oxidative stress, endothelial dysfunction, neuroinflammation, and mitochondrial injury that progressively alters both neuronal integrity and cerebral microcirculation. At the same time, insulin resistance impairs cerebral energy metabolism and accelerates pathological processes associated with neurodegeneration, supporting the concept that diabetes contributes to accelerated brain aging through multiple interconnected pathways [8–11].

Consistent observation across contemporary studies is the central role of cerebral small vessel disease in mediating diabetes-related cognitive decline. Structural neuroimaging demonstrates that white matter hyperintensities, lacunar infarctions, cerebral microbleeds, and enlarged perivascular spaces occur more frequently in individuals with T2DM and correlate closely with deterioration of executive function and processing speed. These findings suggest that microvascular injury is not simply a consequence of long-standing diabetes but an active determinant of progressive cognitive dysfunction. Consequently, assessment of cerebral small vessel disease should be considered an important component of neurological evaluation in patients with long-standing metabolic disease [10–14].

From a neurological perspective, diabetes-associated cognitive impairment represents a clinically heterogeneous condition that frequently overlaps with both vascular cognitive impairment and Alzheimer's disease. The coexistence of cerebrovascular injury, impaired insulin signaling, amyloid-β accumulation, and tau pathology complicates the distinction between individual disease entities and supports the concept of mixed-pathology dementia in many patients with T2DM. This complexity emphasizes the importance of comprehensive diagnostic approaches integrating neuropsychological assessment, magnetic resonance imaging, and

metabolic evaluation rather than relying on a single clinical or imaging marker [12–16].

Another important consideration is the growing role of modern neuroimaging and circulating biomarkers in identifying patients at increased risk before irreversible neurological damage develops. Quantitative magnetic resonance imaging, diffusion tensor imaging, functional connectivity analysis, and emerging blood-based biomarkers provide complementary information regarding structural and functional cerebral alterations that may precede overt cognitive impairment. Their integration into routine clinical practice has the potential to improve risk stratification, facilitate earlier diagnosis, and support individualized therapeutic decision-making, although further validation in prospective studies remains necessary [14–18].

Recent evidence also suggests that optimization of metabolic control may influence long-term neurological outcomes. While intensive glycemic management alone has not consistently demonstrated substantial cognitive benefit, comprehensive treatment strategies targeting insulin resistance, hypertension, dyslipidemia, obesity, and other vascular risk factors appear more effective in slowing cognitive decline. Increasing attention has been directed toward glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors because of their potential neuroprotective, anti-inflammatory, and vasculoprotective properties, although definitive evidence regarding their long-term effects on cognition is still evolving [15–19].

Future research should focus on longitudinal studies capable of clarifying the temporal relationship between metabolic dysfunction, cerebral small vessel disease, and progressive neurodegeneration. Standardization of neuroimaging protocols, validation of multimodal biomarkers, and broader application of artificial intelligence for the analysis of imaging and clinical data may substantially improve early detection of cognitive impairment in T2DM. Such advances are expected to facilitate precision medicine approaches that combine individualized metabolic management with targeted neuroprotective interventions to preserve cognitive function and improve long-term neurological outcomes [17–20].

CONCLUSION

Cognitive impairment has emerged as an important chronic complication of type 2 diabetes mellitus, resulting from the combined effects of chronic hyperglycemia, insulin resistance, and cerebral small vessel disease. Current evidence demonstrates that persistent metabolic dysfunction promotes neurodegeneration, microvascular injury, and progressive disruption of cerebral structure and function, thereby increasing the risk of mild cognitive impairment, vascular cognitive impairment, and dementia. Recognition of these mechanisms underscores the importance of incorporating cognitive assessment into the routine management of patients with type 2 diabetes, particularly those with long disease duration, poor glycemic control, or established microvascular complications.

Future advances should focus on the development of standardized strategies for early cognitive screening, validation of multimodal neuroimaging and circulating biomarkers, and implementation of personalized therapeutic approaches targeting both metabolic and cerebrovascular pathways. Greater integration of neurology,

endocrinology, and radiology, together with the application of artificial intelligence and precision medicine, may improve risk prediction, facilitate earlier intervention, and contribute to preserving cognitive function and long-term neurological health in patients with type 2 diabetes mellitus.

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TOBACCO PREVENTION IN DENTAL PRACTICE: COMPARATIVE INSIGHTS FROM UKRAINE AND THE EUROPEAN UNION

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Tobacco smoking and the use of alternative nicotine products remain widespread behavioural factors directly linked to the deterioration of oral tissues and dental treatment outcomes. According to the World Health Organisation, in 2024, 24.1% of adults in the European Region used tobacco, while in Ukraine the total current use of tobacco and nicotine products reached 26.0% of the adult population, including e-cigarette and heated-tobacco consumers [1, 2]. Despite the existence of works devoted to the dental consequences of smoking, information on preventive and advisory practices in dentistry, taking into account the differences between Ukraine and the European Union (EU), remains insufficiently systematised. The aim of this study was to identify and compare anti-smoking approaches in dental practice in Ukraine and the EU countries and to outline realistic directions for adapting European experience to the Ukrainian context.

Materials and methods. The study was performed as an analytical review of the literature with elements of comparative analysis. Sources were searched in PubMed, Scopus, Web of Science and Google Scholar using keywords related to tobacco prevention in dentistry, smoking cessation and periodontal health. In addition to scientific publications, the analysis included a WHO analytical report on tobacco control in Ukraine, the current Law of Ukraine No. 2899-IV, a Council of the European Union recommendation on smoke- and aerosol-free environments, and professional documents of the FDI World Dental Federation. A total of 38 sources published between 2005 and January 2026 were included after a three-stage selection process. Methods of analysis, synthesis, comparison, abstraction and generalisation were used to characterise the dental consequences of tobacco exposure and to compare regulatory, professional and clinical approaches between Ukraine and the European professional space.

Results and discussion. The analysis confirmed that tobacco smoking and alternative nicotine products are associated with a multilevel complex of dental changes, including deterioration of periodontal status, poorer oral hygiene, changes in the oral mucosa and xerostomia, as well as adverse effects on tooth colour and restorative materials. Electronic cigarettes and heated tobacco products do not eliminate dental risk but represent a different format of nicotine exposure with their own clinical consequences. Preventive counselling in dental practice was found to include several interrelated components: screening and identification of tobacco status, brief informational and motivational messaging, structured brief intervention, guidance and behavioural support, and integration into routine dental care. The dental

appointment was shown to be a suitable setting for early detection of tobacco use and brief anti-smoking intervention, since visible clinical changes strengthen the persuasiveness of counselling.

The comparative analysis revealed that Ukraine and the EU share a common orientation toward reducing tobacco exposure but differ substantially in the degree of dental-specific operationalisation. In Ukraine, the national regulatory framework for tobacco control is well developed, but professional guidelines addressing the dentist's role in smoking cessation remain limited, and preventive counselling is described mainly as a promising direction rather than a structured clinical tool. In the European professional space, supranational recommendation documents are complemented by specialised professional guidelines, and brief structured interventions, very brief counselling algorithms and referral models are more clearly institutionalised. Educational integration also differs: European dental curricula more often include dedicated training modules and assessment of student readiness for tobacco counselling, whereas in Ukraine this remains a peripheral component of professional training.

The main limitations identified in Ukrainian practice are the absence of standardised preventive counselling algorithms, limited formalisation of the dentist's role in smoking cessation, insufficient educational preparation, and weak integration of anti-smoking interventions into routine dental appointments, compounded by organisational, staffing and resource constraints. Given these constraints, the most realistic strategy for Ukraine is a phased, resource-saving adaptation: routine recording of tobacco status during every dental appointment, brief personalised advice linked to identified clinical changes, development of a short professional action algorithm, inclusion of tobacco counselling in undergraduate and postgraduate training, and a simple mechanism for referring patients to further care.

Conclusions. Smoking and the use of alternative nicotine products form a complex of dental changes affecting periodontal tissues, oral mucosa, hygiene status, hard tissues and restorative materials, which justifies integrating anti-smoking interventions into routine dental care. Ukraine and the EU countries share a common goal of reducing tobacco exposure but differ in the level of dental operationalisation of this goal: Ukraine has a well-developed general regulatory framework, while the European professional space demonstrates more structured, professionally standardised and educationally supported models of brief counselling. Standardisation of preventive counselling, routine assessment of tobacco status, professional training of dentists and phased implementation of clinical algorithms, adapted to the organisational and resource limitations of the Ukrainian healthcare system, represent realistic directions for adapting European experience to Ukrainian dental practice.

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CLINICAL AND PROGNOSTIC SIGNIFICANCE OF OBSTRUCTIVE SLEEP APNEA IN PATIENTS WITH CARDIOVASCULAR DISEASE

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Abstract. Obstructive sleep apnea (OSA) is one of the most prevalent sleep-related breathing disorders and is increasingly recognized as an independent risk factor for cardiovascular morbidity and mortality. Recurrent episodes of upper airway obstruction during sleep result in intermittent hypoxia, sleep fragmentation, sympathetic nervous system activation, oxidative stress, systemic inflammation, and endothelial dysfunction, all of which contribute to adverse cardiovascular remodeling. A growing body of evidence demonstrates that OSA is closely associated with the development and progression of arterial hypertension, coronary artery disease, heart failure, cardiac arrhythmias, stroke, and sudden cardiac death. Despite these well-established associations, OSA remains substantially underdiagnosed in patients with cardiovascular disease, limiting opportunities for early intervention and risk reduction.

This systematic literature review summarizes current evidence regarding the clinical and prognostic significance of obstructive sleep apnea in patients with cardiovascular disease and evaluates contemporary approaches to diagnosis, risk stratification, and management. Particular attention is given to the mechanisms linking OSA with cardiovascular pathology, the role of polysomnography and modern sleep assessment technologies, the prognostic value of sleep-disordered breathing in major cardiovascular conditions, and the impact of continuous positive airway pressure therapy and emerging treatment strategies on long-term clinical outcomes. The available evidence supports routine consideration of OSA within cardiovascular risk assessment and highlights the importance of multidisciplinary management aimed at improving both cardiovascular prognosis and overall patient outcomes.

Keywords: *obstructive sleep apnea; cardiovascular disease; intermittent hypoxia; arterial hypertension; heart failure; atrial fibrillation; cardiovascular risk; polysomnography; continuous positive airway pressure; prognosis.*

Introduction

Obstructive sleep apnea (OSA) is one of the most common chronic sleep-related breathing disorders and affects a substantial proportion of the adult population worldwide. The condition is characterized by recurrent episodes of complete or partial upper airway collapse during sleep, resulting in intermittent hypoxia, hypercapnia, sleep fragmentation, and marked fluctuations in intrathoracic pressure. During the past decade, OSA has evolved from being regarded primarily as a respiratory disorder to being recognized as a major contributor to cardiovascular morbidity and mortality. Increasing evidence indicates that untreated OSA is associated with a broad spectrum of cardiovascular diseases and adversely influences both clinical outcomes and long-term prognosis [1–3].

The biological mechanisms underlying this association are multifactorial. Repetitive cycles of intermittent hypoxia activate the sympathetic nervous system, stimulate oxidative stress, promote systemic inflammation, impair endothelial function, and accelerate vascular remodeling. These pathophysiological alterations contribute to persistent arterial hypertension, myocardial fibrosis, coronary atherosclerosis, autonomic imbalance, and progressive structural remodeling of the heart and blood vessels. Consequently, OSA is increasingly considered an important modifier of cardiovascular risk rather than a simple comorbid condition accompanying cardiovascular disease [2–5].

Contemporary clinical studies have demonstrated significant associations between OSA and numerous cardiovascular disorders, including resistant hypertension, coronary artery disease, chronic heart failure, atrial fibrillation, ventricular arrhythmias, pulmonary hypertension, stroke, and sudden cardiac death. Furthermore, the severity of sleep-disordered breathing frequently correlates with adverse cardiovascular outcomes, recurrent hospitalizations, and reduced survival. These observations have led international cardiology and sleep medicine societies to recommend systematic evaluation for OSA in selected groups of patients with established cardiovascular disease or unexplained cardiovascular deterioration [4–7].

Advances in diagnostic technologies, cardiovascular imaging, and sleep medicine have expanded opportunities for earlier identification of patients with clinically significant OSA and improved understanding of its prognostic implications. At the same time, uncertainty remains regarding optimal screening strategies, patient selection for treatment, and the magnitude of cardiovascular benefit associated with continuous positive airway pressure therapy across different cardiovascular populations. The aim of the study was to summarize current evidence regarding the clinical and prognostic significance of obstructive sleep apnea in patients with cardiovascular disease and to evaluate contemporary approaches to diagnosis, cardiovascular risk stratification, and management.

Materials and Methods

This study was conducted as a systematic literature review to evaluate contemporary evidence regarding the clinical and prognostic significance of obstructive sleep apnea in patients with cardiovascular disease. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier international guidelines and landmark studies were included only when they provided essential evidence concerning the pathophysiology, diagnosis, or treatment of obstructive sleep apnea in cardiovascular medicine.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, and evidence-based clinical practice guidelines addressing obstructive sleep apnea, cardiovascular outcomes, diagnostic approaches, prognostic markers, and therapeutic interventions. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on pathophysiological mechanisms, cardiovascular complications, diagnostic performance, prognostic significance, and the effectiveness of contemporary treatment strategies, including continuous positive airway pressure therapy.

Results

Obstructive sleep apnea (OSA) is increasingly recognized as an independent cardiovascular risk factor that contributes to both the development and progression of cardiovascular disease. Large epidemiological studies indicate that moderate-to-severe OSA is highly prevalent among patients with resistant hypertension, coronary artery disease, chronic heart failure, atrial fibrillation, and ischemic stroke. The prevalence of clinically significant OSA exceeds 40–60% in several cardiovascular populations, emphasizing that sleep-disordered breathing should be regarded as an important component of comprehensive cardiovascular evaluation rather than an isolated respiratory disorder [8–10].

The pathophysiological relationship between OSA and cardiovascular disease is mediated through repetitive episodes of intermittent hypoxia, sleep fragmentation, intrathoracic pressure fluctuations, and sympathetic nervous system activation. These mechanisms promote oxidative stress, endothelial dysfunction, systemic inflammation, activation of the renin–angiotensin–aldosterone system, platelet activation, and metabolic dysregulation. Persistent exposure to these processes accelerates vascular remodeling, arterial stiffness, myocardial fibrosis, and autonomic imbalance, thereby creating conditions that favor the development of hypertension, atherosclerosis, cardiac remodeling, and electrical instability of the myocardium [9–12].

Modern diagnostic evaluation combines clinical assessment with objective sleep investigations. Overnight polysomnography remains the reference standard for diagnosing OSA and determining disease severity through the apnea–hypopnea index, oxygen desaturation parameters, and sleep architecture analysis. Home sleep apnea testing and cardiorespiratory polygraphy have become valuable alternatives for

selected patient groups, improving accessibility of diagnosis while maintaining acceptable diagnostic accuracy in individuals with high pre-test probability. Contemporary screening questionnaires, including STOP-Bang and the Berlin Questionnaire, facilitate identification of patients who require further sleep evaluation but should not replace objective diagnostic testing [10–13].

OSA demonstrates strong clinical associations with multiple cardiovascular disorders. Among patients with arterial hypertension, particularly resistant hypertension, untreated OSA contributes to poor blood pressure control through sustained sympathetic activation and impaired nocturnal blood pressure decline. In coronary artery disease, recurrent nocturnal hypoxia exacerbates myocardial ischemia, endothelial dysfunction, and plaque instability, increasing the likelihood of recurrent cardiovascular events. In chronic heart failure, OSA aggravates ventricular remodeling and neurohormonal activation, while in atrial fibrillation it promotes atrial structural remodeling, electrical instability, and higher rates of arrhythmia recurrence following catheter ablation or cardioversion [11–15].

From a cardiological perspective, OSA has emerged as an important prognostic marker across a wide spectrum of cardiovascular diseases. Increasing severity of sleep-disordered breathing is associated with higher rates of hospitalization for heart failure, recurrent myocardial infarction, stroke, malignant ventricular arrhythmias, sudden cardiac death, and all-cause mortality. Several prospective cohort studies have demonstrated that nocturnal hypoxemia and cumulative oxygen desaturation burden may predict adverse cardiovascular outcomes more accurately than the apnea–hypopnea index alone, highlighting the need for more comprehensive assessment of disease severity [12–16].

Advances in cardiovascular imaging and biomarker research have expanded opportunities to detect subclinical cardiac injury in patients with OSA. Speckle-tracking echocardiography frequently identifies impaired global longitudinal strain despite preserved left ventricular ejection fraction, while cardiac magnetic resonance imaging has demonstrated diffuse myocardial fibrosis, altered ventricular geometry, and increased extracellular volume in selected patient populations. Elevated concentrations of high-sensitivity cardiac troponins, N-terminal pro-B-type natriuretic peptide, C-reactive protein, and markers of oxidative stress further support the presence of ongoing myocardial injury and adverse cardiovascular remodeling associated with untreated OSA [13–18].

Continuous positive airway pressure (CPAP) remains the first-line treatment for moderate and severe OSA and effectively eliminates upper airway obstruction during sleep. Numerous studies have demonstrated improvements in daytime sleepiness, blood pressure control, endothelial function, sympathetic activity, and quality of life following CPAP therapy. Although randomized trials have reported variable effects on major cardiovascular events, accumulating evidence suggests that patients with good long-term adherence derive greater cardiovascular benefit, particularly those with resistant hypertension, heart failure, and recurrent atrial fibrillation. Emerging therapeutic approaches, including mandibular advancement devices, hypoglossal nerve

stimulation, weight reduction strategies, and pharmacological interventions, provide additional options for carefully selected patients [15–19].

Despite substantial progress in understanding the cardiovascular consequences of OSA, several challenges remain. The condition continues to be underdiagnosed in routine cardiology practice, screening strategies are inconsistently implemented, and treatment adherence remains suboptimal. Furthermore, considerable heterogeneity in disease phenotype suggests that cardiovascular risk cannot be adequately explained by the apnea–hypopnea index alone. Future studies integrating physiological sleep parameters, cardiovascular imaging, circulating biomarkers, and artificial intelligence–based risk prediction models may improve individualized prognostic assessment and optimize management of patients with cardiovascular disease and obstructive sleep apnea [16–20].

Discussion

The findings of the present review demonstrate that obstructive sleep apnea should be regarded as a major cardiovascular disorder with important diagnostic and prognostic implications rather than solely as a sleep-related breathing abnormality. Contemporary evidence consistently indicates that recurrent intermittent hypoxia, sympathetic hyperactivity, oxidative stress, endothelial dysfunction, and chronic inflammation contribute to progressive cardiovascular remodeling and substantially increase the risk of adverse cardiovascular events. The high prevalence of OSA among patients with established cardiovascular disease further supports the need for closer integration of sleep medicine into routine cardiovascular practice [8–11].

A consistent observation across recent studies is that the clinical impact of OSA extends throughout the entire spectrum of cardiovascular disease. Untreated sleep-disordered breathing contributes not only to the development of resistant hypertension and coronary artery disease but also accelerates the progression of heart failure, promotes atrial and ventricular remodeling, increases susceptibility to cardiac arrhythmias, and adversely influences survival. These findings suggest that OSA functions as an independent modifier of cardiovascular prognosis, while simultaneously interacting with traditional cardiovascular risk factors to amplify overall disease burden [10–14].

From a cardiological perspective, growing attention has been directed toward identifying objective markers capable of improving cardiovascular risk stratification in patients with OSA. Recent investigations indicate that nocturnal hypoxemia, cumulative oxygen desaturation burden, and markers of autonomic dysfunction may provide stronger prognostic information than the apnea–hypopnea index alone. In addition, advanced cardiovascular imaging has demonstrated that myocardial dysfunction and adverse cardiac remodeling may already be present before clinically overt cardiovascular deterioration becomes apparent. These observations support a more comprehensive approach to cardiovascular assessment that integrates sleep-related physiological parameters with structural and functional cardiac evaluation [12–16].

Another important development is the increasing recognition of multidisciplinary management as an essential component of patient care. Collaboration between

cardiologists, pulmonologists, sleep medicine specialists, otorhinolaryngologists, and primary care physicians facilitates earlier diagnosis, individualized treatment selection, and more effective long-term follow-up. Such an integrated model is particularly valuable for patients with resistant hypertension, recurrent atrial fibrillation, chronic heart failure, or persistent cardiovascular symptoms despite optimal conventional therapy, in whom previously unrecognized OSA may represent a modifiable contributor to disease progression [14–18].

Despite considerable advances, important limitations remain. Published studies differ substantially with respect to diagnostic criteria, patient populations, cardiovascular endpoints, CPAP adherence, and duration of follow-up, making direct comparison between investigations difficult. Furthermore, randomized controlled trials evaluating the effect of CPAP on major cardiovascular events have yielded inconsistent results, partly because of differences in patient selection and variable treatment adherence. These factors indicate that therapeutic benefit is likely to depend on disease phenotype, cardiovascular comorbidity, and long-term compliance rather than on OSA severity alone [15–19].

Future research should focus on refining individualized cardiovascular risk prediction using multimodal approaches that combine polysomnographic parameters, cardiovascular imaging, circulating biomarkers, genetic profiling, and artificial intelligence–based analytical models. Greater emphasis should also be placed on identifying patients most likely to benefit from targeted treatment and on developing strategies to improve long-term adherence to therapy. Continued iinterventions andiology and sleep medicine is expected to enhance early diagnosis, optimize preventive interventions, and improve long-term cardiovascular outcomes in patients with obstructive sleep apnea [17–20].

CONCLUSION

Obstructive sleep apnea is an independent and clinically significant contributor to cardiovascular morbidity and mortality, exerting a substantial influence on the development, progression, and prognosis of multiple cardiovascular diseases. The available evidence demonstrates that recurrent intermittent hypoxia, sympathetic activation, endothelial dysfunction, and chronic inflammation promote adverse myocardial and vascular remodeling, thereby increasing the risk of hypertension, coronary artery disease, heart failure, cardiac arrhythmias, stroke, and cardiovascular death. Early recognition of OSA, combined with comprehensive cardiovascular evaluation and timely initiation of appropriate therapy, represents an important opportunity to improve long-term clinical outcomes in high-risk patients.

Future advances in this field will depend on broader implementation of systematic screening programs within cardiology practice, refinement of individualized cardiovascular risk assessment, and integration of multimodal diagnostic approaches incorporating sleep studies, cardiovascular imaging, circulating biomarkers, and artificial intelligence–based predictive models. Strengthening multidisciplinary collaboration between cardiologists, sleep medicine specialists, pulmonologists, and otorhinolaryngologists may facilitate earlier diagnosis, optimize therapeutic decision-

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THE ROLE OF SGLT2 INHIBITORS IN THE TREATMENT OF CHRONIC HEART FAILURE: CURRENT EVIDENCE AND FUTURE PERSPECTIVES BEYOND DIABETES

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Abstract. Sodium–glucose cotransporter 2 (SGLT2) inhibitors have transformed the contemporary management of chronic heart failure by demonstrating substantial reductions in cardiovascular mortality and heart failure hospitalizations that extend beyond their glucose-lowering effects. Initially developed for the treatment of type 2 diabetes mellitus, these agents have consistently shown clinical benefit in patients with heart failure across the full spectrum of left ventricular ejection fraction, including individuals without diabetes. Their cardioprotective effects are mediated through multiple complementary mechanisms, including natriuresis, osmotic diuresis, attenuation of cardiac remodeling, improvement of myocardial energetics, reduction of inflammation and oxidative stress, and preservation of renal function.

This systematic literature review summarizes current evidence regarding the role of SGLT2 inhibitors in the treatment of chronic heart failure, with particular emphasis on their efficacy in patients irrespective of diabetic status. The review discusses the underlying pathophysiological mechanisms, findings of major randomized clinical trials, current international guideline recommendations, cardiorenal benefits, safety profile, and future perspectives for personalized therapy. Contemporary evidence supports SGLT2 inhibitors as a cornerstone of guideline-directed medical therapy for chronic heart failure and highlights their central role in improving long-term cardiovascular outcomes in both diabetic and non-diabetic populations.

Keywords: *SGLT2 inhibitors; chronic heart failure; dapagliflozin; empagliflozin; heart failure with reduced ejection fraction; heart failure with preserved ejection fraction; cardiorenal protection; cardiovascular outcomes; guideline-directed medical therapy; type 2 diabetes mellitus.*

Introduction

Chronic heart failure (CHF) remains one of the leading causes of cardiovascular morbidity, mortality, and hospital admission worldwide despite substantial advances in pharmacological and device-based therapies. Progressive population aging, increasing prevalence of hypertension, ischemic heart disease, obesity, chronic kidney disease, and diabetes mellitus continue to drive the global burden of heart failure. Patients with CHF experience high rates of recurrent hospitalization, impaired functional capacity, reduced quality of life, and premature mortality, emphasizing the need for therapeutic strategies capable of modifying disease progression rather than merely alleviating symptoms [1–3].

For many years, guideline-directed medical therapy for chronic heart failure primarily consisted of renin–angiotensin–aldosterone system inhibition, β-blockers, mineralocorticoid receptor antagonists, and, more recently, angiotensin receptor–neprilysin inhibitors. Although these treatments significantly improved survival, residual cardiovascular risk remained substantial, particularly among patients with recurrent decompensation and concomitant renal dysfunction. The introduction of sodium–glucose cotransporter 2 (SGLT2) inhibitors has fundamentally changed the therapeutic landscape by demonstrating clinically meaningful reductions in cardiovascular death and heart failure hospitalization across diverse patient populations, including individuals without diabetes mellitus [2–5].

The beneficial effects of SGLT2 inhibitors extend well beyond glucose lowering and involve multiple complementary mechanisms relevant to heart failure pathophysiology. These agents promote natriuresis and osmotic diuresis without significant neurohormonal activation, reduce cardiac preload and afterload, improve myocardial energy metabolism through increased ketone body utilization, attenuate oxidative stress and systemic inflammation, suppress myocardial fibrosis, preserve renal function, and slow adverse ventricular remodeling. Landmark randomized clinical trials, including DAPA-HF, EMPEROR-Reduced, EMPEROR-Preserved, DELIVER, SOLOIST-WHF, and EMPULSE, have consistently demonstrated reductions in heart failure hospitalization and cardiovascular mortality across patients with reduced, mildly reduced, and preserved left ventricular ejection fraction, irrespective of diabetic status [4–7].

These findings have led to a paradigm shift in contemporary heart failure management, with SGLT2 inhibitors now recognized as a fundamental component of guideline-directed medical therapy rather than exclusively antidiabetic agents. Current international recommendations advocate their early initiation alongside other disease-modifying therapies to maximize cardiovascular and renal protection. The aim of the study was to summarize current evidence regarding the role of SGLT2 inhibitors in the treatment of chronic heart failure, their mechanisms of action, clinical efficacy, safety, and future perspectives for use irrespective of the presence of diabetes mellitus.

Materials and Methods

This study was conducted as a systematic literature review to evaluate current evidence regarding the efficacy and safety of sodium–glucose cotransporter 2 (SGLT2) inhibitors in the treatment of chronic heart failure, irrespective of the presence of type 2 diabetes mellitus. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark randomized clinical trials were included when they established the evidence base for the use of SGLT2 inhibitors in heart failure.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective cohort studies, observational investigations, international clinical practice guidelines, and expert consensus statements addressing chronic heart failure, SGLT2 inhibitors, cardiovascular outcomes, renal protection, and guideline-directed medical therapy. Conference abstracts, case reports, editorials, duplicate

publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on mechanisms of action, effects on cardiovascular mortality, heart failure hospitalization, renal outcomes, safety profile, quality of life, and efficacy in patients with and without diabetes mellitus.

Results

SGLT2 inhibitors have demonstrated consistent clinical efficacy across the entire spectrum of chronic heart failure, fundamentally changing the contemporary therapeutic approach to this syndrome. Initially introduced as glucose-lowering agents, dapagliflozin and empagliflozin were subsequently shown to exert significant cardioprotective effects independent of glycemic control. Experimental and clinical studies indicate that these agents reduce intraglomerular pressure, promote natriuresis and osmotic diuresis, decrease plasma volume without excessive neurohormonal activation, lower ventricular filling pressures, and improve myocardial energy metabolism through increased utilization of ketone bodies. Additional mechanisms include attenuation of oxidative stress, suppression of pro-inflammatory cytokines, reduction of myocardial fibrosis, preservation of endothelial function, and improvement of mitochondrial efficiency, collectively limiting adverse ventricular remodeling [8–10].

Beyond their hemodynamic effects, SGLT2 inhibitors exert direct cellular actions that contribute to myocardial protection. Experimental evidence demonstrates inhibition of the myocardial sodium–hydrogen exchanger (NHE-1), reduction of intracellular sodium and calcium overload, improvement of mitochondrial ATP production, and enhancement of cardiomyocyte survival during chronic heart failure. These agents also decrease activation of inflammatory signaling pathways, including nuclear factor-κB and the NLRP3 inflammasome, while reducing macrophage infiltration and interstitial collagen deposition within the myocardium. Such mechanisms provide a biological explanation for the rapid reduction in heart failure events observed shortly after treatment initiation in major randomized clinical trials [9–12].

Substantial cardiorenal protection represents another defining characteristic of SGLT2 inhibitors. Clinical studies consistently demonstrate slower decline in estimated glomerular filtration rate, reduced albuminuria, decreased progression to advanced chronic kidney disease, and lower incidence of acute kidney injury compared with standard therapy alone. Preservation of renal function contributes directly to improved heart failure outcomes by interrupting the pathophysiological interactions of the cardiorenal syndrome. These benefits are observed in patients both with and without diabetes mellitus, confirming that the therapeutic effects of SGLT2 inhibition extend beyond glycemic regulation [10–13].

Evidence supporting the use of SGLT2 inhibitors in heart failure with reduced ejection fraction (HFrEF) is particularly robust. The DAPA-HF and EMPEROR-Reduced trials demonstrated significant reductions in the composite endpoint of cardiovascular death or heart failure hospitalization, accompanied by improvements in symptoms, functional status, and health-related quality of life. Relative reductions in

the primary composite outcome approached 25–30%, while recurrent heart failure hospitalizations were consistently decreased across diverse patient subgroups. Importantly, treatment efficacy remained comparable among participants with and without type 2 diabetes mellitus, establishing SGLT2 inhibitors as disease-modifying therapy independent of glucose-lowering effects [11–14].

The therapeutic role of SGLT2 inhibitors has subsequently expanded to patients with heart failure and preserved or mildly reduced ejection fraction. The EMPEROR-Preserved and DELIVER trials demonstrated clinically meaningful reductions in worsening heart failure and cardiovascular hospitalization among patients with HFpEF and HFmrEF, populations in which effective pharmacological treatment had previously been limited. These findings represent a major advance in heart failure management, providing evidence that SGLT2 inhibition confers benefit regardless of left ventricular ejection fraction and significantly broadening the eligible patient population [12–15].

Clinical benefit has also been demonstrated in patients hospitalized with acute decompensated heart failure. The EMPULSE and SOLOIST-WHF studies showed that initiation of SGLT2 inhibitors during hospitalization or shortly after clinical stabilization improved composite clinical outcomes without increasing major safety concerns. Early treatment was associated with fewer recurrent heart failure events, better symptom control, improved quality of life, and reduced risk of rehospitalization, supporting initiation of therapy before hospital discharge whenever clinically appropriate [13–16].

Current international guidelines now position SGLT2 inhibitors as one of the four foundational pillars of guideline-directed medical therapy for chronic heart failure. Contemporary recommendations advocate early introduction of dapagliflozin or empagliflozin together with angiotensin receptor–neprilysin inhibitors or renin–angiotensin system inhibitors, β-blockers, and mineralocorticoid receptor antagonists. Their favorable safety profile, minimal influence on blood pressure, low risk of hypoglycemia in non-diabetic patients, and consistent efficacy across age groups, renal function categories, and diabetic status have facilitated widespread implementation in routine clinical practice. Adverse events are generally infrequent and mainly include genital mycotic infections, transient volume depletion, and rare cases of euglycemic ketoacidosis in susceptible diabetic patients [15–19].

Recent developments suggest that the role of SGLT2 inhibitors will continue to expand within precision cardiovascular medicine. Artificial intelligence–based predictive models, circulating biomarkers, multimodal cardiac imaging, and integrated cardiorenal risk assessment are increasingly being investigated to identify patients most likely to derive maximal benefit from therapy. Ongoing clinical trials are also evaluating combination strategies involving SGLT2 inhibitors, GLP-1 receptor agonists, soluble guanylate cyclase stimulators, and novel anti-inflammatory agents, with the aim of further reducing residual cardiovascular risk and improving long-term outcomes in patients with chronic heart failure regardless of diabetes status [17–20].

Discussion

The findings of the present review demonstrate that SGLT2 inhibitors have fundamentally changed the contemporary management of chronic heart failure and are

now recognized as disease-modifying agents rather than exclusively glucose-lowering medications. Their clinical benefits extend across a broad spectrum of patients with heart failure and are consistently observed irrespective of the presence of type 2 diabetes mellitus. This paradigm shift is supported by multiple large randomized clinical trials demonstrating reductions in cardiovascular mortality, recurrent heart failure hospitalization, and deterioration of renal function, establishing SGLT2 inhibitors as a cornerstone of modern guideline-directed medical therapy [8–11].

A distinguishing characteristic of SGLT2 inhibitors is the diversity of their cardioprotective mechanisms. Unlike conventional heart failure therapies that primarily target neurohormonal activation, SGLT2 inhibitors simultaneously influence hemodynamic, metabolic, inflammatory, and cellular pathways involved in disease progression. Improvements in myocardial energy utilization, attenuation of oxidative stress, suppression of inflammatory signaling, reduction of myocardial fibrosis, and preservation of renal function collectively contribute to slowing adverse ventricular remodeling. The rapid separation of clinical event curves observed in major randomized trials further suggests that beneficial effects develop through multiple complementary mechanisms rather than a single pharmacological pathway [10–13].

Current evidence also supports the use of SGLT2 inhibitors across the entire spectrum of left ventricular ejection fraction. While patients with heart failure and reduced ejection fraction were the first population in whom substantial benefit was demonstrated, more recent investigations have confirmed clinically meaningful improvements in individuals with mildly reduced and preserved ejection fraction. These findings represent one of the most important therapeutic advances in heart failure during the past decade because effective pharmacological options for HFpEF had previously been limited. Consequently, SGLT2 inhibitors have become one of the few treatment classes supported by robust evidence across all major heart failure phenotypes [12–16].

Another important aspect highlighted by recent studies is the close interaction between cardiac and renal protection. Preservation of renal function reduces progression of cardiorenal syndrome, improves tolerance of other heart failure therapies, and contributes to long-term stabilization of cardiovascular status. Clinical benefits remain evident even in patients with chronic kidney disease and in those without diabetes mellitus, reinforcing the concept that SGLT2 inhibitors should be regarded as cardiorenal protective agents rather than conventional antidiabetic drugs. Their favorable safety profile further supports broad implementation in routine clinical practice, provided that renal function and volume status are appropriately monitored during treatment initiation [14–18].

Growing evidence indicates that earlier initiation of SGLT2 inhibitor therapy is associated with greater clinical benefit. Recent trials involving patients hospitalized for acute heart failure have demonstrated that treatment can be safely initiated during hospitalization or shortly after stabilization, leading to reductions in recurrent heart failure events and improved patient-reported outcomes. These observations support current recommendations advocating early incorporation of SGLT2 inhibitors

alongside the other foundational therapies for chronic heart failure instead of delaying treatment until outpatient follow-up [15–19].

Despite remarkable therapeutic progress, several important questions remain unresolved. Additional studies are needed to define optimal sequencing of guideline-directed therapies, identify biomarkers predicting treatment response, clarify long-term outcomes in specific patient populations, and evaluate combination strategies with emerging cardiometabolic agents. Advances in multimodal imaging, circulating biomarkers, genomic profiling, and artificial intelligence–based prediction models are expected to facilitate individualized treatment selection and further optimize long-term management of patients with chronic heart failure. Continued integration of these technologies into routine clinical practice may enhance precision medicine approaches and further reduce cardiovascular morbidity and mortality beyond the benefits already achieved with SGLT2 inhibition [17–20].

CONCLUSION

SGLT2 inhibitors have emerged as one of the most important therapeutic advances in the management of chronic heart failure, demonstrating substantial reductions in cardiovascular mortality, heart failure hospitalization, and progression of renal dysfunction irrespective of the presence of type 2 diabetes mellitus. Their clinical efficacy is supported by robust evidence across the full spectrum of heart failure phenotypes and is mediated through multiple complementary mechanisms, including favorable hemodynamic effects, attenuation of myocardial remodeling, improvement of cardiac energy metabolism, suppression of inflammation and oxidative stress, and preservation of cardiorenal function. These findings have established SGLT2 inhibitors as a fundamental component of contemporary guideline-directed medical therapy.

Current evidence supports early initiation of SGLT2 inhibitors in eligible patients alongside other disease-modifying therapies to maximize cardiovascular and renal protection. Their favorable safety profile, broad applicability across diverse patient populations, and consistent benefits in both diabetic and non-diabetic individuals have substantially expanded their role in routine clinical practice. Future advances in precision medicine, integration of multimodal biomarkers, artificial intelligence–based risk stratification, and individualized therapeutic algorithms are expected to further optimize patient selection and improve long-term outcomes in chronic heart failure.

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THE ROLE OF CT ANGIOGRAPHY IN THE DIAGNOSIS AND SURGICAL DECISION-MAKING FOR GASTROINTESTINAL BLEEDING

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Abstract. Acute gastrointestinal bleeding remains one of the leading causes of emergency hospital admission and is associated with considerable morbidity, mortality, and healthcare resource utilization. Rapid identification of the bleeding source is essential for selecting the most appropriate therapeutic strategy and improving clinical outcomes. Although endoscopy remains the primary diagnostic modality in many clinical settings, multidetector computed tomography angiography (CTA) has emerged as a highly effective non-invasive imaging technique capable of detecting active hemorrhage, localizing the bleeding site, identifying the underlying vascular pathology, and providing comprehensive anatomical information within a short examination time. These characteristics have expanded the role of CTA in the diagnostic evaluation of both upper and lower gastrointestinal bleeding, particularly in hemodynamically unstable patients and in cases where endoscopic assessment is inconclusive or technically challenging.

This review summarizes current evidence regarding the diagnostic performance of CTA and its influence on surgical decision-making in patients with gastrointestinal bleeding. Particular attention is given to contemporary imaging protocols, diagnostic accuracy, comparison with conventional endoscopy and catheter angiography, selection of patients for endovascular or surgical intervention, and emerging imaging technologies. Available evidence indicates that CTA not only facilitates early localization of hemorrhage but also improves therapeutic planning by guiding the choice between conservative management, transcatheter embolization, and emergency surgery. The integration of CTA into multidisciplinary treatment algorithms has

contributed to earlier intervention, improved procedural success, and more individualized management of patients with acute gastrointestinal bleeding.

Keywords: *computed tomography angiography; gastrointestinal bleeding; multidetector computed tomography; emergency surgery; transcatheter embolization; diagnostic imaging; surgical decision-making; gastrointestinal hemorrhage.*

Introduction

Acute gastrointestinal bleeding remains one of the most common medical emergencies encountered in gastroenterology and general surgery, accounting for a substantial proportion of emergency hospital admissions worldwide. Despite continuous advances in endoscopic techniques, pharmacological therapy, and critical care, gastrointestinal hemorrhage continues to be associated with considerable morbidity, prolonged hospitalization, increased healthcare costs, and significant mortality, particularly among elderly patients and individuals with multiple comorbidities. The clinical presentation varies widely depending on the location, severity, and rate of bleeding, making rapid diagnosis and accurate localization of the hemorrhagic source fundamental components of effective patient management [1–3].

Upper and lower gastrointestinal bleeding differ considerably in their etiology, diagnostic approach, and therapeutic strategies. Peptic ulcer disease, gastroesophageal varices, erosive gastroduodenal lesions, vascular abnormalities, diverticular disease, angiodysplasia, inflammatory bowel disease, postoperative complications, and gastrointestinal malignancies remain the most frequent causes of acute hemorrhage. While endoscopy continues to serve as the first-line diagnostic and therapeutic modality in many patients, its diagnostic performance may be limited by poor visualization, intermittent bleeding, inadequate bowel preparation, or hemodynamic instability. These limitations have stimulated increasing interest in rapid cross-sectional imaging techniques capable of providing comprehensive vascular assessment before therapeutic intervention [3–5].

Multidetector computed tomography angiography (CTA) has become an essential imaging modality in the diagnostic evaluation of gastrointestinal bleeding because of its ability to rapidly detect active contrast extravasation, localize the bleeding source, identify the underlying vascular lesion, and simultaneously assess surrounding abdominal structures. High spatial and temporal resolution, widespread availability, short acquisition time, and non-invasive image acquisition have significantly expanded the clinical applications of CTA in emergency practice. In addition to establishing the diagnosis, CTA provides valuable anatomical information that facilitates treatment planning by identifying patients who are likely to benefit from endovascular embolization, emergency surgery, or conservative management [5–7].

Recent technological developments, including dual-energy computed tomography, advanced image post-processing, three-dimensional vascular reconstruction, and artificial intelligence-assisted image interpretation, have further improved the diagnostic performance of CTA in patients with gastrointestinal hemorrhage. Contemporary multidisciplinary management increasingly incorporates CTA as an integral component of diagnostic algorithms, allowing more precise patient stratification and optimization of therapeutic decision-making. As clinical evidence

continues to accumulate, the role of CTA extends beyond simple detection of active bleeding toward individualized planning of surgical and endovascular interventions, emphasizing its growing importance within modern emergency abdominal imaging [7].

Aim of the study was to review current evidence regarding the role of computed tomography angiography in the diagnosis of gastrointestinal bleeding and its impact on surgical decision-making and selection of the optimal therapeutic strategy.

Materials and Methods

This study was designed as a systematic literature review. A comprehensive search of the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases was performed to identify relevant publications published between 2020 and 2026. Priority was given to international clinical practice guidelines, systematic reviews, meta-analyses, prospective cohort studies, retrospective multicenter investigations, and comparative studies evaluating the role of computed tomography angiography (CTA) in the diagnosis and management of gastrointestinal bleeding.

Studies evaluating the diagnostic performance of CTA in upper and lower gastrointestinal bleeding, multidetector CT imaging protocols, localization of bleeding sources, comparison with endoscopy and catheter angiography, and the impact of CTA findings on endovascular and surgical treatment strategies were included. Case reports, conference abstracts, duplicate publications, and studies lacking clinically relevant diagnostic or therapeutic outcomes were excluded. The selected evidence was critically analyzed to assess the diagnostic accuracy of CTA and its contribution to therapeutic decision-making and optimization of surgical management in patients with acute gastrointestinal bleeding.

Results

Acute gastrointestinal bleeding remains a major cause of emergency hospitalization and is associated with substantial morbidity and mortality despite continuous advances in diagnostic and therapeutic strategies. Rapid identification of the bleeding source is essential because delayed diagnosis is associated with persistent hemorrhage, hemodynamic instability, increased transfusion requirements, prolonged hospitalization, and higher mortality. Current evidence demonstrates that early integration of imaging into the diagnostic pathway significantly improves localization of active bleeding and facilitates timely therapeutic intervention, particularly in patients with ongoing or recurrent hemorrhage [8,9].

Computed tomography angiography has become one of the principal imaging modalities for evaluating acute gastrointestinal bleeding owing to its rapid acquisition, broad availability, and high diagnostic performance. Modern multidetector CT systems allow visualization of active contrast extravasation, vascular abnormalities, pseudoaneurysms, arteriovenous malformations, tumors, inflammatory lesions, and postoperative complications within a single examination. Multiphasic imaging protocols, including unenhanced, arterial, and portal venous phases, substantially increase diagnostic sensitivity by differentiating active hemorrhage from pre-existing intraluminal hyperdense material and improving lesion characterization [9–11].

Numerous prospective studies and meta-analyses have demonstrated excellent diagnostic performance of CTA in patients with active gastrointestinal bleeding.

Reported sensitivity generally ranges from approximately 85% to 95%, while specificity frequently exceeds 90%, depending on bleeding rate, imaging protocol, and timing of examination. CTA can detect active hemorrhage at bleeding rates considerably lower than those required for conventional catheter angiography, allowing earlier identification of clinically significant bleeding and more accurate localization of the responsible vascular territory [10–12].

Comparison with conventional diagnostic modalities highlights several important advantages of CTA. Although endoscopy remains the first-line investigation for most patients with upper gastrointestinal bleeding, its diagnostic accuracy may be reduced by massive intraluminal blood, poor visualization, altered postoperative anatomy, or intermittent hemorrhage. CTA provides a comprehensive evaluation of the entire abdomen without the need for bowel preparation and enables simultaneous assessment of vascular anatomy, adjacent organs, and potential extraintestinal pathology. Compared with catheter angiography, CTA is non-invasive, rapidly available, and useful for selecting patients most likely to benefit from subsequent endovascular intervention [11–14].

In upper gastrointestinal bleeding, CTA demonstrates particular clinical value when endoscopic examination fails to identify the bleeding source or cannot be performed because of hemodynamic instability. The technique accurately detects arterial bleeding associated with peptic ulcer disease, pseudoaneurysms, postoperative vascular injury, and upper gastrointestinal malignancies. In addition to identifying active hemorrhage, CTA defines the relationship between the bleeding vessel and surrounding anatomical structures, thereby facilitating both surgical planning and transcatheter embolization [13–15].

The role of CTA is especially important in lower gastrointestinal bleeding, where intermittent hemorrhage, extensive bowel length, and inadequate bowel preparation frequently limit colonoscopic evaluation. CTA reliably localizes bleeding caused by diverticular disease, angiodysplasia, ischemic colitis, inflammatory bowel disease, colorectal neoplasms, and postoperative complications. Precise anatomical localization before intervention substantially increases the technical success of selective angiographic embolization and reduces the need for blind or extensive bowel resection during emergency surgery [14–17].

Beyond its diagnostic capabilities, CTA has become an essential tool for therapeutic decision-making. Imaging findings enable stratification of patients according to bleeding severity, vascular anatomy, and likelihood of spontaneous hemostasis, thereby guiding the selection of conservative treatment, urgent endoscopic therapy, transcatheter arterial embolization, or emergency surgery. Several studies have demonstrated that incorporation of CTA into multidisciplinary management algorithms shortens the interval to definitive treatment, decreases unnecessary invasive procedures, and improves procedural planning for both surgeons and interventional radiologists [16–19].

Recent technological advances continue to expand the clinical utility of CTA in gastrointestinal bleeding. Dual-energy CT, photon-counting detector technology, high-resolution vascular reconstruction, automated post-processing software, and artificial

intelligence-assisted image interpretation have improved visualization of subtle contrast extravasation while reducing image noise and radiation exposure. These innovations are expected to further enhance diagnostic confidence, optimize patient selection for minimally invasive treatment, and strengthen the role of CTA as an integral component of precision management in acute gastrointestinal hemorrhage [19,20].

Discussion

The findings of this review demonstrate that computed tomography angiography has evolved from a complementary imaging modality into a central component of the diagnostic algorithm for acute gastrointestinal bleeding. Although endoscopy remains the primary diagnostic and therapeutic approach in many clinical scenarios, CTA has become indispensable in patients with hemodynamic instability, ongoing hemorrhage, inconclusive endoscopic findings, or suspected extra-luminal vascular pathology. The ability to rapidly identify the bleeding source while simultaneously providing detailed anatomical information has significantly expanded its role in emergency surgical practice [8–10].

One of the principal advantages of CTA is its capacity to influence therapeutic decision-making before invasive intervention is undertaken. Unlike conventional diagnostic methods that primarily confirm the presence of bleeding, CTA provides comprehensive information regarding the precise anatomical location of hemorrhage, the responsible vascular territory, underlying pathology, and the extent of associated abdominal abnormalities. This information facilitates individualized treatment planning and assists clinicians in selecting the most appropriate strategy, including conservative management, therapeutic endoscopy, transcatheter arterial embolization, or emergency surgery [10–13].

Current evidence also indicates that CTA has significantly strengthened collaboration between radiologists, surgeons, gastroenterologists, and interventional radiologists within multidisciplinary emergency care. Accurate preprocedural localization of active bleeding increases the technical success of selective embolization, reduces procedure time, and minimizes unnecessary exploration surgical interventions. In patients requiring operative treatment, detailed vascular mapping contributes to more precise surgical planning, facilitates targeted bowel resection, and may reduce perioperative morbidity associated with extensive exploratory procedures [12–15].

The diagnostic value of CTA is particularly evident in lower gastrointestinal bleeding, where intermittent hemorrhage, incomplete bowel preparation, and the considerable length of the colon frequently limit the effectiveness of urgent colonoscopy. In these circumstances, CTA rapidly identifies active contrast extravasation and accurately localizes the bleeding segment, allowing subsequent therapeutic interventions to be performed with greater precision. Similarly, in upper gastrointestinal bleeding, CTA has demonstrated considerable value following nondiagnostic endoscopy or in patients whose clinical condition precludes immediate endoscopic evaluation [14–17].

Technological progress has further enhanced the clinical performance of CTA. Contemporary multidetector scanners, dual-energy CT techniques, advanced three-dimensional vascular reconstruction, and artificial intelligence-assisted image analysis have improved visualization of small-volume hemorrhage while reducing image interpretation time. These developments not only increase diagnostic confidence but also support earlier therapeutic intervention and more efficient allocation of healthcare resources in emergency settings. Nevertheless, broader clinical validation is required before emerging technologies become fully integrated into routine management algorithms [16–19].

Despite these advances, several limitations should be considered. The diagnostic performance of CTA remains dependent on active bleeding at the time of image acquisition, and intermittent hemorrhage may reduce examination sensitivity. In addition, exposure to ionizing radiation and iodinated contrast media limits repeated imaging in selected patient populations, particularly those with impaired renal function. Future prospective multicenter studies should focus on optimizing imaging protocols, validating artificial intelligence-assisted diagnostic systems, and defining the most effective integration of CTA with endoscopic and endovascular techniques. Such developments are expected to further strengthen the role of CTA in precision-guided management of patients with acute gastrointestinal bleeding [18–20].

CONCLUSION

Computed tomography angiography has become an integral component of the contemporary diagnostic pathway for patients with acute gastrointestinal bleeding. Current evidence demonstrates that CTA provides rapid and accurate localization of the bleeding source, identifies the underlying vascular pathology, and supplies detailed anatomical information that cannot always be obtained using conventional diagnostic techniques alone. Its high diagnostic accuracy, non-invasive nature, and widespread availability allow earlier recognition of clinically significant hemorrhage and facilitate timely therapeutic intervention, particularly in patients with ongoing bleeding, hemodynamic instability, or inconclusive endoscopic findings.

Beyond its diagnostic value, CTA plays a pivotal role in surgical and endovascular decision-making by supporting individualized treatment planning and optimizing patient selection for conservative management, therapeutic endoscopy, transcatheter arterial embolization, or emergency surgery. The integration of CTA into multidisciplinary management algorithms has improved procedural planning, reduced unnecessary invasive interventions, and contributed to more efficient emergency care. Continued advances in CT technology, including dual-energy imaging, photon-counting detectors, and artificial intelligence-assisted image analysis, are expected to further enhance diagnostic precision and reinforce the role of CTA as a cornerstone of precision-guided management in patients with gastrointestinal bleeding.

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SARCOPENIC OBESITY AS A RISK FACTOR FOR POSTOPERATIVE COMPLICATIONS IN ABDOMINAL SURGERY: CURRENT EVIDENCE AND FUTURE PERSPECTIVES

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Abstract. Sarcopenic obesity has emerged as a distinct clinical phenotype characterized by the coexistence of excessive adiposity and reduced skeletal muscle mass and function. This condition is increasingly recognized as an important determinant of adverse surgical outcomes because it combines the metabolic consequences of obesity with impaired physiological reserve associated with sarcopenia. Growing evidence demonstrates that patients with sarcopenic obesity are at significantly higher risk of postoperative infectious complications, anastomotic leakage, delayed wound healing, prolonged hospitalization, readmission, and postoperative mortality following abdominal surgery. Conventional anthropometric indices, including body mass index, frequently fail to identify this high-risk population, emphasizing the importance of body composition assessment in contemporary surgical practice.

This systematic literature review summarizes current evidence regarding the impact of sarcopenic obesity on postoperative outcomes in abdominal surgery and evaluates emerging strategies for preoperative risk assessment and optimization. Particular attention is given to the pathophysiological mechanisms of sarcopenic obesity, contemporary diagnostic approaches based on computed tomography, dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and muscle function assessment, as well as the role of nutritional support, prehabilitation, enhanced recovery after surgery protocols, and artificial intelligence-assisted body composition analysis. Current evidence indicates that early identification and targeted management

of sarcopenic obesity may substantially reduce postoperative morbidity and improve surgical outcomes, supporting its integration into routine preoperative evaluation of patients undergoing major abdominal procedures.

Keywords: *sarcopenic obesity; abdominal surgery; postoperative complications; sarcopenia; body composition; computed tomography; prehabilitation; enhanced recovery after surgery; surgical outcomes; artificial intelligence.*

Introduction

The growing prevalence of obesity has substantially altered the patient population undergoing abdominal surgery. A large proportion of individuals requiring colorectal, gastric, hepatopancreatobiliary, bariatric, and emergency abdominal procedures present with obesity accompanied by multiple metabolic disorders, including type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease (MASLD), chronic systemic inflammation, and insulin resistance. At the same time, increasing evidence demonstrates that excess body weight alone inadequately reflects the physiological condition of surgical patients. Many individuals with obesity exhibit a progressive decline in skeletal muscle mass, deterioration of muscle quality, and impaired physical performance despite preserved or excessive body mass, resulting in the development of sarcopenic obesity. Recognition of this phenotype has become an important challenge in both gastroenterology and abdominal surgery because conventional nutritional assessment frequently fails to identify patients at increased perioperative risk [1–3].

From a gastroenterological perspective, sarcopenic obesity is closely associated with chronic metabolic and inflammatory disorders that frequently accompany diseases requiring abdominal surgical treatment. Persistent low-grade inflammation, alterations in protein metabolism, intestinal dysbiosis, insulin resistance, and progressive hepatic steatosis contribute to accelerated skeletal muscle loss while simultaneously promoting visceral fat accumulation. Patients with colorectal cancer, pancreatic cancer, gastric cancer, inflammatory bowel disease, chronic liver disease, and metabolic dysfunction-associated steatotic liver disease often develop profound abnormalities in body composition before surgery as a consequence of chronic inflammation, malnutrition, tumor-associated cachexia, reduced physical activity, and impaired nutrient absorption. Consequently, deterioration of muscle quality may occur even in patients whose body mass index remains within the overweight or obese range, masking clinically significant nutritional and functional impairment [2–5].

For abdominal surgeons, sarcopenic obesity represents a major determinant of postoperative outcomes because both excessive visceral adiposity and reduced skeletal muscle reserve adversely influence perioperative physiology. Numerous studies demonstrate that sarcopenic obesity is independently associated with increased rates of surgical site infection, anastomotic leakage, postoperative pancreatic fistula, delayed wound healing, pulmonary complications, prolonged mechanical ventilation, severe complications according to the Clavien–Dindo classification, prolonged hospitalization, readmission, and postoperative mortality. Excess visceral fat increases technical complexity during surgery, limits operative exposure, prolongs operative time, and contributes to greater intraoperative blood loss, whereas reduced skeletal

muscle mass diminishes metabolic reserve, impairs immune competence, delays functional recovery, and compromises tissue repair. These combined effects are particularly evident following colorectal resections, gastrectomy, hepatectomy, pancreatic resection, and major oncological abdominal procedures [4–7].

Growing recognition of the prognostic importance of body composition has stimulated the development of more accurate methods for preoperative risk stratification. Computed tomography-based assessment of skeletal muscle area at the third lumbar vertebra, muscle attenuation analysis, dual-energy X-ray absorptiometry, bioelectrical impedance analysis, functional performance testing, and artificial intelligence-assisted body composition analysis have demonstrated greater predictive value than body mass index alone for identifying patients at increased risk of postoperative complications. Simultaneously, multimodal prehabilitation, individualized nutritional support, resistance exercise, optimization of protein intake, and enhanced recovery after surgery (ERAS) protocols have emerged as promising strategies to improve perioperative outcomes in this high-risk population.

The aim of the study was to summarize current evidence regarding the impact of sarcopenic obesity on postoperative complications in abdominal surgery and to evaluate contemporary approaches to diagnosis, perioperative risk assessment, and preoperative optimization.

Materials and Methods

This study was conducted as a systematic literature review to evaluate current evidence regarding the impact of sarcopenic obesity on postoperative complications in abdominal surgery. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies and international consensus statements were included only when they established fundamental diagnostic criteria for sarcopenia, body composition assessment, perioperative risk evaluation, or enhanced recovery strategies.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, international clinical practice guidelines, and consensus documents addressing sarcopenic obesity, abdominal surgery, perioperative nutrition, body composition analysis, and postoperative complications. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on diagnostic approaches, CT-based body composition assessment, postoperative outcomes, and perioperative optimization strategies for patients undergoing major abdominal surgery.

Results

Sarcopenic obesity has become increasingly prevalent among patients with gastrointestinal diseases requiring surgical treatment and is now recognized as a distinct metabolic phenotype associated with unfavorable clinical outcomes. In gastroenterology, chronic low-grade inflammation, insulin resistance, metabolic dysfunction-associated steatotic liver disease (MASLD), chronic pancreatitis,

inflammatory bowel disease, gastrointestinal malignancies, and age-related metabolic alterations contribute to the simultaneous accumulation of visceral adipose tissue and progressive skeletal muscle loss. Elevated circulating concentrations of interleukin-6, tumor necrosis factor-α, C-reactive protein, and myostatin promote accelerated protein catabolism, impaired muscle regeneration, mitochondrial dysfunction, and reduced muscle quality, creating conditions that increase vulnerability to perioperative stress [8–10].

Among patients with colorectal, gastric, pancreatic, and hepatobiliary malignancies, sarcopenic obesity frequently develops before clinically apparent weight loss because tumor-associated inflammation, anorexia, altered protein metabolism, and reduced physical activity selectively impair skeletal muscle while excess visceral fat is preserved. Consequently, body mass index often remains within the overweight or obese range despite significant depletion of lean body mass. Computed tomography-based body composition analysis demonstrates that 20–45% of patients undergoing major gastrointestinal oncological surgery meet diagnostic criteria for sarcopenia, whereas the prevalence of sarcopenic obesity ranges from 10% to more than 25%, depending on diagnostic thresholds and patient characteristics [9–12].

Metabolic dysfunction-associated steatotic liver disease represents another important clinical setting in which sarcopenic obesity significantly influences disease progression. Progressive insulin resistance, hepatic lipid accumulation, chronic inflammation, and endocrine alterations contribute to reciprocal interactions between skeletal muscle and liver metabolism. Reduced skeletal muscle mass limits glucose utilization and exacerbates insulin resistance, whereas hepatic inflammation accelerates muscle protein degradation through activation of catabolic signaling pathways. Similar mechanisms have been demonstrated in chronic pancreatitis and inflammatory bowel disease, where persistent inflammation and impaired nutrient absorption further aggravate deterioration of body composition and nutritional status [10–13].

Accurate diagnosis of sarcopenic obesity has therefore become an essential component of modern gastroenterological assessment. Current evidence supports computed tomography as the reference method for evaluating skeletal muscle area at the third lumbar vertebral level (L3), skeletal muscle index, muscle attenuation, and visceral adipose tissue. Reduced muscle attenuation, reflecting intramuscular fat infiltration (myosteatosis), has emerged as an independent predictor of postoperative morbidity even in patients with preserved muscle quantity. Integration of CT-derived body composition analysis with functional tests, nutritional assessment, inflammatory biomarkers, and frailty evaluation substantially improves identification of patients at increased perioperative risk compared with body mass index alone [11–15].

The adverse impact of sarcopenic obesity becomes particularly evident during the postoperative period. Recent systematic reviews and meta-analyses demonstrate that patients with sarcopenic obesity experience significantly higher rates of surgical site infection, anastomotic leakage, postoperative pancreatic fistula, delayed wound healing, pulmonary complications, severe complications according to the Clavien–Dindo classification, prolonged intensive care admission, and postoperative mortality.

Across major abdominal procedures, sarcopenic obesity has been associated with an approximately 1.5–3-fold increase in overall postoperative complications and a markedly higher incidence of major complications compared with patients without body composition abnormalities [13–17].

Several mechanisms explain these unfavorable outcomes. Excess visceral adiposity increases technical complexity of abdominal procedures by limiting operative exposure, prolonging operative time, increasing intraoperative blood loss, and impairing tissue perfusion. Simultaneously, reduced skeletal muscle mass decreases physiological reserve, weakens respiratory muscle function, delays postoperative mobilization, compromises immune competence, and impair collagen synthesis and tissue repair. The coexistence of obesity and sarcopenia therefore produces substantially greater perioperative risk than either condition alone, particularly in colorectal resections, gastrectomy, hepatectomy, pancreaticoduodenectomy, and other complex gastrointestinal operations [14–18].

Growing evidence has also demonstrated that preoperative optimization may partially reverse the adverse effects of sarcopenic obesity. Multimodal prehabilitation combining individualized nutritional support, increased protein intake (approximately 1.2–2.0 g/kg/day), resistance exercise, aerobic training, vitamin D correction, and optimization of metabolic comorbidities has been associated with improvements in muscle strength, functional capacity, and postoperative recovery. Integration of these interventions into Enhanced Recovery After Surgery (ERAS) pathways has reduced postoperative complications, shortened hospital stay, and accelerated functional recovery in selected high-risk patients [15–19].

Recent technological advances have further strengthened perioperative risk assessment through automated body composition analysis and artificial intelligence. Deep learning algorithms applied to routine abdominal CT examinations enable rapid and reproducible quantification of skeletal muscle area, muscle attenuation, visceral fat volume, and myosteatosis without additional imaging or radiation exposure. Predictive models integrating radiological body composition, inflammatory biomarkers, nutritional indices, and clinical variables have demonstrated superior accuracy for forecasting postoperative morbidity compared with conventional surgical risk scores, highlighting their potential role in individualized perioperative decision-making and precision abdominal surgery [16–20].

Discussion

The findings of the present review indicate that sarcopenic obesity should be regarded as an independent predictor of adverse postoperative outcomes rather than a simple combination of obesity and reduced muscle mass. Contemporary evidence demonstrates that simultaneous excess visceral adiposity and depletion of skeletal muscle produce profound metabolic, inflammatory, and functional disturbances that significantly impair the physiological response to surgical stress. Consequently, patients with sarcopenic obesity experience substantially higher rates of postoperative morbidity despite frequently presenting with body mass index values that do not suggest nutritional depletion. These observations emphasize the limitations of

conventional anthropometric assessment and support the transition toward body composition–based perioperative risk stratification [8–11].

From a gastroenterological perspective, chronic digestive diseases play an important role in the development and progression of sarcopenic obesity. Persistent systemic inflammation is associated with gastrointestinal malignancies, metabolic dysfunction-associated steatotic liver disease, inflammatory bowel disease, chronic pancreatitis, and advanced liver disease promotes accelerated muscle protein degradation while simultaneously exacerbating visceral fat accumulation and insulin resistance. The resulting metabolic imbalance contributes not only to deterioration of nutritional status but also to impaired immune function, delayed tissue repair, and reduced tolerance to major abdominal surgery. Recognition of these mechanisms supports earlier nutritional intervention and multidisciplinary management before operative treatment [10–14].

One of the most clinically important findings is the superior prognostic value of body composition analysis compared with body mass index alone. Computed tomography-based assessment of skeletal muscle index, muscle attenuation, and visceral adipose tissue provides objective information regarding physiological reserve that cannot be obtained through conventional anthropometric measurements. Increasing evidence indicates that myosteatosis, reduced muscle quality, and visceral adiposity independently predict postoperative complications even in patients without overt weight loss. These findings justify incorporation of routine CT-derived body composition assessment into preoperative evaluation, particularly in patients undergoing complex gastrointestinal oncological procedures [12–16].

The available evidence also highlights the importance of preoperative optimization strategies. Multimodal prehabilitation programs combining individualized nutritional therapy, adequate protein supplementation, resistance exercise, aerobic conditioning, and correction of metabolic abnormalities have demonstrated encouraging improvements in muscle function and postoperative recovery. Although current studies differ regarding intervention protocols and duration, most report reductions in postoperative complications, shorter hospital stays, and earlier restoration of functional capacity. These observations support implementation of structured prehabilitation within Enhanced Recovery After Surgery (ERAS) pathways for patients identified as having sarcopenic obesity before major abdominal surgery [14–18].

Despite substantial progress, several limitations continue to affect interpretation of the available literature. Diagnostic criteria for sarcopenic obesity remain heterogeneous, with considerable variation in CT cut-off values, methods of body composition analysis, assessment of muscle function, and definitions of postoperative outcomes. Many published studies are retrospective and include heterogeneous surgical populations, limiting direct comparison between investigations. International consensus regarding standardized diagnostic thresholds and clinically meaningful risk categories will therefore be essential for broader implementation of sarcopenic obesity assessment in routine surgical practice [15–19].

Future research should focus on prospective multicenter validation of standardized diagnostic algorithms, integration of automated artificial intelligence–based CT

analysis into routine radiological workflows, and development of personalized perioperative management strategies based on body composition phenotyping. Combining radiological biomarkers with inflammatory indices, nutritional parameters, functional performance measures, and machine learning models may substantially improve prediction of postoperative complications and facilitate individualized surgical decision-making. Such an approach has the potential to optimize perioperative care, reduce postoperative morbidity, and improve long-term outcomes in patients undergoing abdominal surgery [17–20].

CONCLUSION

Sarcopenic obesity is increasingly recognized as an independent predictor of adverse postoperative outcomes in abdominal surgery, reflecting the combined effects of excessive visceral adiposity, skeletal muscle depletion, chronic inflammation, and metabolic dysfunction. Current evidence demonstrates that this body composition phenotype is associated with a higher incidence of postoperative infectious complications, anastomotic leakage, impaired wound healing, prolonged hospitalization, severe postoperative morbidity, and mortality across a wide range of abdominal surgical procedures. Conventional anthropometric indicators, particularly body mass index, are insufficient for identifying these high-risk patients, underscoring the clinical importance of routine body composition assessment during preoperative evaluation.

Implementation of computed tomography–based body composition analysis, early nutritional screening, multimodal prehabilitation, and individualized perioperative optimization may substantially improve surgical outcomes in patients with sarcopenic obesity. Future studies should focus on standardizing diagnostic criteria, validating artificial intelligence–assisted body composition analysis, and integrating personalized risk prediction models into routine surgical practice. Such strategies have the potential to improve perioperative decision-making, reduce postoperative complications, and enhance long-term recovery following major abdominal surgery.

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URIC ACID AS A RISK FACTOR FOR GOUT AND CHRONIC KIDNEY DISEASE: AN INTERDISCIPLINARY PERSPECTIVE FROM RHEUMATOLOGY AND UROLOGY

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Abstract. Hyperuricemia is increasingly recognized as a systemic metabolic disorder that extends beyond its traditional association with gout and plays an important role in the development and progression of chronic kidney disease (CKD). Persistent elevation of serum uric acid contributes to monosodium urate crystal deposition, activation of the NLRP3 inflammasome, oxidative stress, endothelial dysfunction, and chronic low-grade inflammation, leading to joint damage as well as progressive renal injury. Growing evidence indicates that hyperuricemia is associated with reduced glomerular filtration rate, renal fibrosis, uric acid nephrolithiasis, and adverse cardiovascular outcomes, highlighting the need for an integrated multidisciplinary approach to patient management.

This systematic literature review summarizes current evidence regarding the role of uric acid as a risk factor for gout and chronic kidney disease from the perspectives of rheumatology and urology. Particular attention is given to the molecular mechanisms linking hyperuricemia with joint and renal injury, contemporary diagnostic approaches, advanced imaging modalities, urate-lowering therapies, and current international recommendations for patient management. Emerging evidence supports early identification of high-risk individuals, individualized urate-lowering treatment, and close collaboration between rheumatologists, urologists, and nephrologists to reduce disease progression and improve long-term clinical outcomes.

Keywords: *uric acid; hyperuricemia; gout; chronic kidney disease; uric acid nephrolithiasis; NLRP3 inflammasome; urate-lowering therapy; allopurinol; febuxostat; multidisciplinary management.*

Introduction

Hyperuricemia is one of the most prevalent metabolic abnormalities encountered in contemporary clinical practice, with its global incidence increasing in parallel with the growing burden of obesity, metabolic syndrome, type 2 diabetes mellitus, and chronic kidney disease. Traditionally regarded as the biochemical basis of gout, elevated serum uric acid is now recognized as a multifactorial disorder affecting numerous organ systems. Accumulating evidence indicates that persistent hyperuricemia contributes not only to monosodium urate crystal deposition but also to endothelial dysfunction, oxidative stress, chronic inflammation, and progressive tissue remodeling, making it an important determinant of long-term renal and cardiovascular outcomes [1–3].

From the perspective of rheumatology, hyperuricemia represents the principal pathogenic factor underlying gout, one of the most common inflammatory arthritides worldwide. Supersaturation of body fluids with urate promotes monosodium urate crystal formation within joints and periarticular tissues, triggering activation of the NLRP3 inflammasome, release of interleukin-1β and other pro-inflammatory cytokines, recurrent episodes of acute arthritis, and progressive structural joint damage. Persistent uncontrolled hyperuricemia may lead to chronic tophaceous gout, irreversible cartilage destruction, bone erosion, and significant functional impairment, emphasizing the importance of early diagnosis and sustained urate-lowering therapy [2–5].

From a urological and nephrological perspective, elevated uric acid has important implications for renal function and urinary tract pathology. Hyperuricemia is closely associated with uric acid nephrolithiasis, intrarenal crystal deposition, chronic tubulointerstitial injury, renal microvascular dysfunction, and progressive decline in glomerular filtration rate. Experimental and clinical studies further demonstrate that soluble uric acid may directly promote renal fibrosis, activation of the renin–angiotensin–aldosterone system, endothelial injury, and chronic inflammation even in the absence of crystal formation. These mechanisms support the concept that uric acid acts as both a marker and a potential mediator of chronic kidney disease progression [4–7].

Growing recognition of the complex interactions between hyperuricemia, gout, and chronic kidney disease has strengthened the need for an interdisciplinary approach involving rheumatologists, urologists, nephrologists, and primary care physicians. Advances in laboratory diagnostics, musculoskeletal ultrasonography, dual-energy computed tomography, renal imaging, molecular biomarkers, and urate-lowering therapies have substantially improved disease detection and individualized management. The aim of the study was to summarize current evidence regarding the role of uric acid as a risk factor for gout and chronic kidney disease and to evaluate contemporary interdisciplinary approaches to diagnosis, treatment, and long-term patient management.

Materials and Methods

This study was conducted as a systematic literature review to evaluate current evidence regarding the role of uric acid as a risk factor for gout and chronic kidney

disease from the perspectives of rheumatology and urology. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies were included only when they established fundamental concepts regarding hyperuricemia, gout pathogenesis, or chronic kidney disease.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, clinical practice guidelines, and international consensus statements addressing hyperuricemia, gout, chronic kidney disease, uric acid nephrolithiasis, diagnostic approaches, and urate-lowering therapy. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance to the review topic were excluded. The selected literature was critically analyzed with emphasis on pathogenic mechanisms, clinical manifestations, diagnostic methods, therapeutic strategies, and long-term renal and rheumatological outcomes.

Results

Hyperuricemia represents the central pathogenic mechanism underlying gout and develops when serum urate concentrations exceed the physiological saturation threshold for monosodium urate crystal formation, generally above 6.8 mg/dL (≈404 μmol/L) under physiological conditions. Although asymptomatic hyperuricemia may persist for many years, sustained elevation of uric acid markedly increases the probability of crystal deposition within joints and periarticular tissues. Experimental studies demonstrate that monosodium urate crystals activate the NLRP3 inflammasome, leading to caspase-1 activation, maturation of interleukin-1β and interleukin-18, recruitment of neutrophils, and amplification of the inflammatory cascade responsible for acute gout flares. Repeated inflammatory episodes promote chronic synovitis, cartilage degeneration, bone erosion, and progressive tophus formation, ultimately resulting in irreversible structural joint damage and functional disability [8–10].

Current evidence indicates that hyperuricemia contributes to disease progression even before clinically apparent gout develops. Soluble uric acid stimulates oxidative stress through activation of nicotinamide adenine dinucleotide phosphate oxidase, reduces nitric oxide bioavailability, induces endothelial dysfunction, and promotes smooth vascular muscle proliferation. Simultaneously, persistent low-grade inflammation, mitochondrial dysfunction, and activation of the renin–angiotensin–aldosterone system accelerate tissue remodeling and microvascular injury. These mechanisms explain the well-documented association between hyperuricemia and hypertension, metabolic syndrome, insulin resistance, cardiovascular disease, and chronic kidney disease, supporting the concept that uric acid functions not only as a biomarker but also as a biologically active mediator of systemic injury [9–12].

From a rheumatological perspective, modern imaging techniques have substantially improved early diagnosis of gout. Musculoskeletal ultrasonography identifies the double-contour sign, synovial hypertrophy, tophi, erosions, and active synovitis even before extensive structural damage develops. Dual-energy computed

tomography (DECT) provides highly specific visualization and quantitative assessment of monosodium urate crystal deposits throughout joints and periarticular tissues, improving diagnostic accuracy in atypical clinical presentations and monitoring response to urate-lowering therapy. Synovial fluid analysis with polarized light microscopy remains the diagnostic reference standard, while serum urate concentration alone is insufficient for confirming or excluding gout because normal values may be observed during acute attacks [10–13].

Renal involvement represents one of the most clinically significant consequences of persistent hyperuricemia. The kidneys are responsible for approximately 70% of daily uric acid elimination, making renal function a major determinant of serum urate concentration. Conversely, progressive decline in glomerular filtration further reduces uric acid excretion, creating a self-perpetuating cycle of worsening hyperuricemia and renal dysfunction. Clinical studies consistently demonstrate that patients with elevated serum urate exhibit a significantly higher risk of incident chronic kidney disease, accelerated decline in estimated glomerular filtration rate, albuminuria, and progression to advanced stages of renal impairment compared with normouricemic individuals [11–14].

Hyperuricemia also plays a central role in the development of uric acid nephrolithiasis and urate-associated renal injury. Uric acid stones account for approximately 8–15% of all urinary calculi worldwide, with substantially higher prevalence among patients with obesity, diabetes mellitus, metabolic syndrome, and chronic kidney disease. Acidic urine (pH <5.5), low urinary volume, hyperuricosuria, and reduced urinary citrate excretion represent the principal factors promoting uric acid crystallization. In addition to stone formation, intratubular urate crystal deposition, chronic tubular inflammation, endothelial dysfunction, and interstitial fibrosis contribute to progressive deterioration of renal structure and function, emphasizing the close relationship between hyperuricemia and chronic nephropathy [12–15].

Modern diagnostic evaluation requires an integrated rheumatological and urological approach. Assessment includes serum urate concentration, estimated glomerular filtration rate, urinary pH, 24-hour urinary uric acid excretion, urine microscopy, inflammatory biomarkers, renal ultrasonography, non-contrast computed tomography for urinary stone detection, dual-energy CT for crystal visualization, and, when indicated, synovial fluid microscopy. Recent investigations have also identified promising biomarkers, including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, urinary microRNAs, and inflammatory cytokines, which may improve early detection of renal injury associated with hyperuricemia [13–17].

Urate-lowering therapy remains the cornerstone of long-term disease management. International recommendations advocate a treat-to-target strategy with maintenance of serum urate levels below 6 mg/dL (360 μmol/L) in most patients and below 5 mg/dL (300 μmol/L) in individuals with severe tophaceous gout. Xanthine oxidase inhibitors, particularly allopurinol and febuxostat, remain first-line pharmacological agents, while uricosuric drugs and pegloticase are reserved for selected patients. Recent evidence suggests that effective urate reduction decreases gout flare frequency, promotes tophus

regression, reduces systemic inflammation, and may slow renal function decline in selected populations with chronic kidney disease, although the magnitude of nephroprotective benefit continues to be investigated [15–19].

Recent advances in precision medicine have expanded opportunities for individualized management of hyperuricemia. Artificial intelligence–based prediction models integrating demographic characteristics, laboratory findings, renal function parameters, imaging features, genetic polymorphisms affecting urate transporters (including ABCG2, SLC2A9, and SLC22A12), and comorbid conditions have demonstrated promising ability to predict gout development, nephrolithiasis recurrence, and chronic kidney disease progression. Such multimodal approaches are expected to improve risk stratification, optimize treatment selection, and facilitate earlier intervention in patients at highest risk of long-term rheumatological and renal complications [17–20].

Discussion

The findings of the present review demonstrate that hyperuricemia should no longer be regarded solely as the biochemical precursor of gout but rather as a systemic metabolic disorder with important rheumatological, urological, and nephrological implications. Accumulating evidence indicates that persistent elevation of serum uric acid contributes to chronic inflammation, endothelial dysfunction, oxidative stress, and progressive tissue remodeling, thereby promoting not only monosodium urate crystal deposition but also deterioration of renal function and increased cardiometabolic risk. These observations support the need for an interdisciplinary approach to the diagnosis and management of patients with hyperuricemia before irreversible organ damage develops [8–11].

From the rheumatological perspective, the pathogenesis of gout extends far beyond acute inflammatory arthritis. Activation of the NLRP3 inflammasome and sustained production of pro-inflammatory cytokines initiate a self-perpetuating inflammatory process that eventually results in cartilage destruction, bone erosion, and tophus formation. Modern imaging techniques, particularly musculoskeletal ultrasonography and dual-energy computed tomography, have substantially improved the ability to detect urate crystal deposition during the preclinical stages of disease, allowing initiation of urate-lowering therapy before significant structural joint damage occurs. These advances have shifted contemporary management toward earlier diagnosis and long-term prevention rather than treatment of recurrent acute attacks alone [10–14].

The relationship between hyperuricemia and chronic kidney disease remains complex and bidirectional. Declining renal function impairs uric acid excretion, while elevated uric acid may further accelerate renal injury through intrarenal inflammation, endothelial dysfunction, activation of the renin–angiotensin–aldosterone system, and progressive tubulointerstitial fibrosis. Although observational studies consistently demonstrate a strong association between hyperuricemia and chronic kidney disease progression, randomized clinical trials evaluating urate-lowering therapy have produced heterogeneous results regarding nephroprotection. Consequently, current evidence supports individualized treatment decisions based on the overall clinical context rather than serum urate concentration alone [12–16].

An equally important clinical aspect is the prevention of uric acid nephrolithiasis and recurrent urinary stone disease. Urinary acidification, reduced urine volume, obesity, insulin resistance, and metabolic syndrome substantially increase the likelihood of uric acid crystallization within the urinary tract. Effective management therefore requires not only pharmacological urate reduction but also correction of urinary pH, optimization of hydration, dietary modification, weight reduction, and treatment of associated metabolic disorders. Such comprehensive management strategies emphasize the essential role of collaboration between rheumatologists, urologists, nephrologists, and primary care physicians in reducing long-term renal complications [13–17].

Recent advances in molecular medicine, diagnostic imaging, and artificial intelligence have created new opportunities for personalized management of hyperuricemia. Genetic variants affecting urate transporters, circulating biomarkers of renal injury, automated imaging analysis, and machine learning algorithms have demonstrated encouraging potential for identifying patients at highest risk of gout progression, nephrolithiasis, and chronic kidney disease. Integration of these technologies into routine clinical practice may improve individualized risk stratification and facilitate earlier implementation of preventive interventions, although further prospective validation remains necessary [15–19].

Despite substantial progress, several important limitations remain. Considerable heterogeneity persists among published studies regarding definitions of hyperuricemia, treatment thresholds, target serum urate concentrations, and assessment of renal outcomes. Additional large multicenter prospective investigations are required to clarify the causal relationship between hyperuricemia and chronic kidney disease progression, determine which patient populations derive the greatest benefit from early urate-lowering therapy, and refine interdisciplinary management strategies. Continued collaboration between rheumatology, urology, nephrology, and translational research will be essential for improving long-term outcomes in patients with hyperuricemia and its systemic complications [17–20].

CONCLUSION

Hyperuricemia is increasingly recognized as a systemic metabolic disorder that extends beyond its established role in gout and has important implications for the development and progression of chronic kidney disease. Current evidence demonstrates that persistent elevation of serum uric acid contributes to monosodium urate crystal deposition, chronic inflammation, endothelial dysfunction, oxidative stress, renal microvascular injury, and tubulointerstitial fibrosis, thereby promoting both musculoskeletal and renal complications. These findings support the concept that uric acid should be considered not only a biochemical marker but also an important contributor to long-term disease progression in susceptible individuals.

Effective management of patients with hyperuricemia requires close collaboration between rheumatologists, urologists, nephrologists, and primary care physicians. Early identification of high-risk patients, comprehensive assessment of renal and musculoskeletal involvement, implementation of treat-to-target urate-lowering therapy, and modification of reversible metabolic risk factors are essential for

preventing disease progression and improving long-term clinical outcomes. Future advances in molecular biomarkers, advanced imaging techniques, and artificial intelligence–based prediction models are expected to further refine individualized risk assessment and optimize personalized therapeutic strategies for patients with gout and chronic kidney disease.

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NEUROPATHIC PAIN AFTER MAXILLOFACIAL TRAUMA: RISK FACTORS, DIAGNOSIS, AND CONTEMPORARY TREATMENT APPROACHES

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Abstract. Neuropathic pain is one of the most disabling long-term complications following maxillofacial trauma, resulting from injury to peripheral branches of the trigeminal nerve and subsequent maladaptive changes within the somatosensory nervous system. Persistent post-traumatic neuropathic pain may develop after facial fractures, penetrating injuries, soft tissue trauma, or surgical treatment and is frequently associated with sensory disturbances, functional impairment, psychological distress, and reduced quality of life. Delayed diagnosis and inadequate early management increase the risk of pain chronification, emphasizing the importance of timely recognition of nerve injury and implementation of evidence-based therapeutic strategies. Recent advances in neuroimaging, quantitative sensory assessment, microsurgical reconstruction, pharmacotherapy, and neuromodulation have substantially improved the understanding and management of this complex clinical condition.

This systematic literature review summarizes current evidence regarding epidemiology, pathophysiological mechanisms, risk factors, diagnostic approaches, and contemporary treatment strategies for neuropathic pain after maxillofacial trauma. Particular attention is given to trigeminal nerve injury, peripheral and central sensitization, validated diagnostic tools, advanced imaging techniques, pharmacological treatment, microsurgical nerve repair, regenerative approaches, and emerging applications of neuromodulation and artificial intelligence in personalized pain management. Current evidence supports the implementation of multidisciplinary, mechanism-based treatment strategies aimed at early diagnosis, prevention of chronic pain development, and optimization of long-term functional and clinical outcomes in patients with maxillofacial trauma.

Keywords: *neuropathic pain; maxillofacial trauma; trigeminal nerve injury; post-traumatic neuropathy; peripheral nerve injury; quantitative sensory testing; microsurgical nerve repair; neuromodulation; chronic pain; personalized medicine.*

Introduction

Maxillofacial trauma remains a major global public health problem and is responsible for a substantial proportion of emergency surgical admissions worldwide.

Road traffic accidents, interpersonal violence, sports injuries, occupational accidents, and falls account for the majority of facial injuries, with mandibular, zygomatic, maxillary, and orbital fractures representing the most frequent patterns of skeletal trauma. Owing to the complex anatomical organization of the craniofacial region and the close relationship between osseous structures and peripheral branches of the trigeminal nerve, traumatic injuries are frequently accompanied by neural damage. Consequently, neurological complications have become an increasingly important determinant of long-term functional recovery, often persisting even after successful fracture stabilization and anatomical reconstruction [1–3].

Among these complications, post-traumatic neuropathic pain represents one of the most challenging conditions encountered in oral and maxillofacial surgery. Injury to the inferior alveolar, lingual, infraorbital, mental, or buccal nerves may result in persistent spontaneous pain, dysesthesia, paresthesia, mechanical allodynia, hyperalgesia, burning sensations, and altered facial sensitivity. Unlike nociceptive pain, neuropathic pain develops as a consequence of structural or functional injury to the somatosensory nervous system and is characterized by peripheral and central sensitization, ectopic neuronal activity, neuroinflammation, and maladaptive cortical reorganization. These mechanisms contribute to pain chronification and frequently limit normal mastication, speech, oral hygiene, facial expression, and social interaction, significantly impairing quality of life [2–5].

The risk of developing chronic neuropathic pain depends on multiple clinical factors, including the severity and location of facial trauma, degree of nerve disruption, delayed surgical management, repeated surgical interventions, infection, and individual biological susceptibility. In addition to direct mechanical injury, ischemia, compression, traction, edema, and postoperative fibrosis may further compromise nerve regeneration and functional recovery. Contemporary studies indicate that delayed recognition of nerve injury substantially reduces the likelihood of complete sensory restoration, highlighting the importance of early diagnosis and appropriate management. Advances in quantitative sensory testing, cone-beam computed tomography, magnetic resonance neurography, high-resolution ultrasonography, and standardized neuropathic pain questionnaires have considerably improved the diagnostic evaluation of patients with suspected trigeminal nerve injury [4–7].

Management of post-traumatic neuropathic pain has evolved considerably during the past decade with the introduction of mechanism-based pharmacotherapy, microsurgical nerve reconstruction, regenerative medicine techniques, neuromodulation, and multidisciplinary rehabilitation strategies. Nevertheless, treatment outcomes remain heterogeneous because of variations in injury characteristics, timing of intervention, and patient-specific factors. A comprehensive understanding of the biological mechanisms underlying post-traumatic neuropathic pain is therefore essential for optimizing diagnosis, individualized treatment, and long-term functional recovery. The aim of the study was to summarize current evidence regarding the risk factors, diagnostic approaches, and contemporary treatment strategies for neuropathic pain after maxillofacial trauma.

Materials and Methods

This study was conducted as a systematic literature review to evaluate current evidence regarding neuropathic pain following maxillofacial trauma, with particular emphasis on risk factors, diagnostic approaches, and contemporary treatment strategies. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify relevant publications published between 2020 and 2026. Earlier landmark studies were included only when they provided fundamental evidence concerning neuropathic pain or trigeminal nerve injury.

Eligible publications included systematic reviews, meta-analyses, randomized controlled trials, prospective and retrospective cohort studies, observational investigations, clinical practice guidelines, and consensus statements addressing post-traumatic trigeminal neuropathy, maxillofacial trauma, peripheral nerve injury, diagnostic methods, and treatment strategies. Conference abstracts, case reports, editorials, duplicate publications, and studies lacking methodological quality or direct relevance were excluded. The selected literature was critically analyzed with emphasis on risk factors, diagnostic accuracy, treatment effectiveness, and long-term clinical outcomes.

Results

Timely diagnosis of post-traumatic trigeminal nerve injury remains one of the greatest challenges in maxillofacial surgery because structural nerve damage often exceeds the findings of routine clinical examination. Radiological imaging has therefore become an essential component of diagnostic evaluation, allowing assessment of fracture configuration, the relationship between bone fragments and neural canals, soft tissue injury, and postoperative complications. Cone-beam computed tomography (CBCT) is currently considered the first-line imaging modality for maxillofacial trauma owing to its high spatial resolution and excellent visualization of the mandibular canal, mental foramen, infraorbital canal, and osseous defects with substantially lower radiation exposure than conventional multidetector CT. Three-dimensional reconstruction further improves assessment of fracture displacement, canal disruption, and the proximity of fixation hardware to major sensory nerves, facilitating surgical planning and prediction of neurological outcomes [8–10].

Although CBCT accurately depicts osseous anatomy, evaluation of peripheral nerve integrity requires advanced soft-tissue imaging. Magnetic resonance imaging, particularly high-resolution magnetic resonance neurography (MRN), enables direct visualization of the inferior alveolar, lingual, and infraorbital nerves, demonstrating nerve discontinuity, intraneural edema, fibrosis, neuroma formation, denervation changes, and surrounding inflammatory reactions. Diffusion-weighted imaging and diffusion tensor imaging provide additional quantitative information regarding nerve microstructure and axonal integrity, while contrast-enhanced MRI assists in differentiating post-traumatic fibrosis from persistent inflammatory changes. Recent studies have shown that MR neurography improves diagnostic confidence and may alter therapeutic decision-making in patients with persistent sensory dysfunction after facial trauma [9–12].

Radiological findings should be interpreted together with functional assessment of the somatosensory system. Quantitative sensory testing (QST) standardized neurosensory examination, and validated questionnaires such as DN4, PainDETECT, and the Neuropathic Pain Symptom Inventory complement imaging by characterizing sensory deficits and neuropathic pain phenotype. High-resolution ultrasonography has emerged as an additional imaging modality for superficial peripheral nerves, allowing dynamic assessment of nerve continuity, compression, neuroma formation, and perineural scarring. More recently, artificial intelligence–assisted image analysis and radiomics have shown encouraging potential for automated detection of subtle neural injury, prediction of sensory recovery, and individualized postoperative risk stratification [10–13].

The incidence of neuropathic pain after maxillofacial trauma varies according to injury mechanism, fracture location, and treatment strategy but is reported in approximately 5–15% of patients after facial trauma and in substantially higher proportions following direct injury to the inferior alveolar or lingual nerves. Persistent sensory disturbances are particularly common after mandibular fractures involving the mandibular canal, complex midfacial fractures, penetrating trauma, ballistic injuries, and delayed surgical management. Inferior alveolar nerve injury remains the most frequently affected trigeminal branch, followed by the lingual and infraorbital nerves. Early microsurgical repair performed within the first months after injury has consistently been associated with superior sensory recovery compared with delayed intervention, emphasizing the importance of prompt diagnosis and referral [11–15].

The biological mechanisms underlying post-traumatic neuropathic pain are complex and extend beyond the initial mechanical injury. Axonal disruption initiates Wallerian degeneration, Schwann cell activation, macrophage infiltration, release of pro-inflammatory cytokines, and upregulation of voltage-gated sodium channels, resulting in ectopic neuronal firing and abnormal impulse generation. Persistent peripheral nociceptive input subsequently induces central sensitization within the trigeminal nucleus and higher cortical pain-processing pathways, leading to mechanical allodynia, thermal hyperalgesia, spontaneous pain, and persistent dysesthesia. Functional neuroimaging studies further demonstrate cortical reorganization involving the primary somatosensory cortex, insular cortex, anterior cingulate cortex, and thalamus in patients with chronic trigeminal neuropathic pain [12–16].

Several clinical factors have consistently been associated with an increased risk of chronic neuropathic pain. Complete nerve transection, severe compression, delayed fracture reduction, repeated surgical procedures, postoperative infection, extensive soft tissue injury, prolonged edema, and neuroma formation significantly reduce the likelihood of complete neurological recovery. Patient-related variables, including advanced age, diabetes mellitus, smoking, psychological distress, anxiety, depression, and pre-existing chronic pain syndromes, further increase susceptibility to pain chronification. These findings support the concept that neuropathic pain develops through the interaction of structural nerve injury with systemic biological and psychosocial factors rather than through mechanical trauma alone [13–17].

Contemporary treatment strategies emphasize early mechanism-based intervention. International recommendations identify gabapentin, pregabalin, duloxetine, and tricyclic antidepressants as first-line pharmacological therapy, while topical lidocaine and capsaicin preparations provide additional benefit in selected patients with localized neuropathic symptoms. Patients with persistent nerve discontinuity or compressive lesions may benefit from microsurgical neurolysis, direct neurorrhaphy, autologous nerve grafting, or processed nerve allografts. Increasing evidence also supports the use of platelet-rich plasma, mesenchymal stromal cell–based therapies, and bioengineered nerve conduits to enhance peripheral nerve regeneration following traumatic injury [14–19].

Despite considerable therapeutic advances, complete resolution of neuropathic pain remains difficult once chronic central sensitization has developed. Consequently, multidisciplinary management involving oral and maxillofacial surgeons, neurologists, pain specialists, radiologists, rehabilitation physicians, psychologists, and physiotherapists has become the preferred model of care. Emerging technologies, including artificial intelligence–based prediction models, advanced neuroimaging, digital sensory mapping, and precision medicine approaches, are expected to improve individualized treatment selection, optimize the timing of surgical intervention, and reduce the long-term burden of post-traumatic neuropathic pain after maxillofacial injury [15–20].

Discussion

The findings of the present review demonstrate that neuropathic pain after maxillofacial trauma remains one of the most challenging long-term complications in oral and maxillofacial surgery. Unlike acute nociceptive pain associated with tissue injury, post-traumatic neuropathic pain results from structural damage to the trigeminal nerve and persistent pathological alterations within the somatosensory nervous system. Current evidence indicates that delayed recognition of nerve injury substantially increases the probability of chronic pain development because prolonged peripheral nociceptive input promotes irreversible central sensitization and maladaptive cortical reorganization. These observations emphasize that neurological assessment should become an integral component of the primary evaluation of patients with maxillofacial trauma rather than being reserved for persistent postoperative symptoms [8–11].

One of the most significant advances in recent years has been the growing contribution of radiological imaging to the diagnosis of peripheral trigeminal nerve injuries. Cone-beam computed tomography has become indispensable for evaluating fractures involving the mandibular canal, infraorbital canal, and mental foramen, whereas magnetic resonance neurography provides direct visualization of nerve continuity, edema, fibrosis, and traumatic neuroma formation. The complementary use of structural imaging with quantitative sensory testing and standardized neuropathic pain questionnaires allows earlier identification of clinically significant neural injury than either approach alone. Nevertheless, standardized imaging protocols and universally accepted diagnostic algorithms remain insufficiently established, particularly for patients presenting with subtle sensory dysfunction or delayed symptoms [10–14].

The available evidence also indicates that treatment outcomes are closely related to the timing of intervention. Peripheral nerves retain considerable regenerative potential during the early post-traumatic period, whereas prolonged compression, fibrosis, and chronic inflammation progressively reduce the likelihood of complete functional recovery. Patients undergoing timely decompression, neurolysis, or microsurgical nerve repair generally demonstrate superior restoration of sensory function and lower rates of persistent neuropathic pain compared with those receiving delayed surgical management. These findings support the importance of early referral to specialized maxillofacial and peripheral nerve centers whenever clinically significant trigeminal nerve injury is suspected [12–16].

Pharmacological management remains an essential component of treatment; however, currently available medications primarily control symptoms rather than reverse the underlying neural injury. Gabapentinoids, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants demonstrate clinically meaningful reductions in pain intensity, although complete pain relief is achieved in only a proportion of patients. Consequently, increasing attention has shifted toward multimodal therapeutic strategies combining pharmacotherapy with microsurgical reconstruction, neuromodulation, rehabilitation, and psychological support. Such individualized approaches appear particularly beneficial in patients with persistent sensory dysfunction and complex post-traumatic pain syndromes [14–18].

Despite considerable progress, important limitations remain in the current evidence base. Published studies differ regarding definitions of post-traumatic trigeminal neuropathy, timing of neurological assessment, diagnostic criteria, outcome measures, and duration of follow-up. Many investigations are retrospective and include relatively small patient populations, limiting comparison between studies and reducing the strength of available recommendations. Future multicenter prospective studies using standardized diagnostic protocols and validated patient-reported outcome measures are therefore necessary to establish more robust evidence for clinical decision-making [15–19].

Future developments in this field are expected to focus on precision diagnostics and regenerative treatment strategies. Artificial intelligence–assisted image analysis, radiomics, advanced magnetic resonance neurography, molecular biomarkers of nerve regeneration, tissue-engineered nerve conduits, stem cell–based therapies, and personalized prediction models may substantially improve early diagnosis and optimize treatment selection. Integration of these technologies into multidisciplinary clinical pathways has the potential to reduce chronic neuropathic pain, improve sensory recovery, and enhance long-term quality of life in patients following maxillofacial trauma [17–20].

CONCLUSION

Neuropathic pain following maxillofacial trauma represents a complex clinical condition that develops because of peripheral trigeminal nerve injury and subsequent maladaptive changes within the somatosensory nervous system. Current evidence indicates that the risk of persistent neuropathic pain is determined by the severity of nerve damage, timing of diagnosis, adequacy of primary surgical management, and

individual biological factors influencing nerve regeneration. Contemporary diagnostic strategies that combine detailed neurological examination with advanced imaging techniques, including cone-beam computed tomography and magnetic resonance neurography, together with standardized sensory assessment, allow clinically significant nerve injury and improve clinical decision-making.

Optimal management requires a multidisciplinary approach integrating mechanism-based pharmacotherapy, timely microsurgical intervention when indicated, rehabilitation, and long-term clinical follow-up. Continued advances in high-resolution neuroimaging, artificial intelligence–assisted diagnostic technologies, regenerative medicine, and personalized treatment strategies are expected to improve sensory recovery, reduce the burden of chronic neuropathic pain, and enhance functional outcomes and quality of life in patients after maxillofacial trauma.

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THE ROLE OF NEUROREHABILITATION IN PROMOTING NEUROPLASTICITY AND RESTORING COGNITIVE FUNCTION AFTER SURGICAL TREATMENT OF INTRACRANIAL NEOPLASMS

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Abstract. Patients undergoing surgery for intracranial neoplasms frequently develop cognitive impairment that persists long after successful tumor resection. Memory deficits, impaired attention, executive dysfunction, language disturbances, and reduced processing speed remain common postoperative sequelae and substantially affect functional independence, social reintegration, and health-related quality of life. Growing evidence indicates that neurological recovery is determined not only by the extent of surgical preservation of eloquent brain structures but also by the capacity of the central nervous system to undergo adaptive neuroplastic reorganization. Consequently, neurorehabilitation has become an essential component of comprehensive neuro-oncological care, aiming to facilitate functional recovery through targeted multidisciplinary interventions initiated during the early postoperative period.

This systematic literature review summarizes current evidence on the role of neurorehabilitation in promoting neuroplasticity and restoring cognitive function following surgical treatment of intracranial neoplasms. The review examines contemporary concepts of postoperative cognitive dysfunction, mechanisms underlying functional brain reorganization, methods of neuropsychological assessment, and evidence supporting conventional rehabilitation, cognitive training, non-invasive brain stimulation, virtual reality, robotic technologies, digital therapeutics, and artificial intelligence–assisted rehabilitation. The available literature indicates that individualized rehabilitation strategies, integrated with objective

functional assessment and long-term multidisciplinary follow-up, are associated with improved cognitive recovery, greater functional independence, and better long-term clinical outcomes. These findings support the incorporation of personalized neurorehabilitation into routine postoperative management of patients with intracranial brain tumors.

Keywords: *intracranial neoplasms; neurorehabilitation; neuroplasticity; cognitive recovery; postoperative cognitive dysfunction; brain tumor surgery; cognitive rehabilitation; neuropsychological assessment; non-invasive brain stimulation; artificial intelligence.*

Introduction

Intracranial neoplasms remain one of the most challenging groups of diseases in contemporary neurosurgery because of their considerable neurological, cognitive, and psychosocial consequences. Continuous advances in neuroimaging, intraoperative neuronavigation, awake craniotomy, fluorescence-guided surgery, and microsurgical techniques have significantly improved the safety of tumor resection and prolonged survival for patients with both primary and metastatic brain tumors. Nevertheless, successful surgical treatment does not invariably translate into complete functional recovery. A substantial proportion of patients continue to experience persistent impairments involving attention, memory, executive function, language, visuospatial processing, and information-processing speed, all of which negatively affect independence, professional reintegration, and long-term quality of life [1–3].

The development of postoperative cognitive dysfunction is multifactorial and reflects the combined influence of tumor biology, anatomical localization, disruption of large-scale functional brain networks, perioperative brain injury, neuroinflammation, cerebral edema, adjuvant oncological therapy, and pre-existing patient characteristics. Contemporary neuroscience increasingly recognizes that cognitive outcomes depend not solely on preservation of discrete cortical regions but also on the integrity and adaptive reorganization of distributed neural networks. Within this framework, neuroplasticity represents a dynamic biological process through which structural and functional modifications of the central nervous system compensate for neurological injury and support recovery after neurosurgical intervention [2–5].

Growing understanding of neuroplastic mechanisms has fundamentally changed the concept of postoperative management in neuro-oncology. Neurorehabilitation is no longer regarded as supportive care initiated only after stabilization of neurological deficits but rather as an integral component of treatment beginning in the early postoperative period. Modern rehabilitation programs combine neuropsychological interventions, task-oriented cognitive training, physical rehabilitation, speech and language therapy, occupational therapy, computerized cognitive exercises, non-invasive brain stimulation, virtual reality–based interventions, and other technology-assisted approaches. Their principal objective is to enhance adaptive cortical reorganization, preserve cognitive reserve, and maximize functional recovery through individualized multidisciplinary care [4–7].

Recent clinical studies and systematic reviews have demonstrated that early, structured, and personalized neurorehabilitation is associated with superior recovery of

cognitive performance, functional independence, and participation in daily activities compared with conventional postoperative management. At the same time, considerable heterogeneity persists regarding rehabilitation protocols, timing of intervention, patient selection, outcome measures, and long-term evaluation, limiting direct comparison between available studies. Further synthesis of contemporary evidence is therefore required to clarify the biological rationale, clinical effectiveness, and future directions of neurorehabilitation in patients undergoing surgery for intracranial neoplasms.

The aim of the study was to summarize current evidence regarding the role of neurorehabilitation in promoting neuroplasticity and restoring cognitive function after surgical treatment of intracranial neoplasms, with emphasis on contemporary rehabilitation strategies, mechanisms of functional brain reorganization, and future directions of personalized neuro-oncological care.

Materials and Methods

This study was designed as a systematic literature review evaluating contemporary evidence on the role of neurorehabilitation in promoting neuroplasticity and restoring cognitive function after surgical treatment of intracranial neoplasms. A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, Web of Science, and Cochrane Library databases to identify studies published between 2020 and 2026. Earlier landmark publications and international clinical guidelines were included when they provided essential evidence on neuroplasticity and postoperative neurorehabilitation.

Eligible publications included systematic reviews, meta-analyses, randomized and non-randomized clinical trials, cohort studies, observational investigations, and evidence-based clinical guidelines addressing postoperative cognitive dysfunction, neuroplasticity, rehabilitation interventions, and functional recovery after intracranial tumor surgery. Conference abstracts, editorials, case reports, duplicate publications, and studies unrelated to postoperative neurorehabilitation were excluded. The selected literature was analyzed with emphasis on mechanisms of neuroplasticity, predictors of cognitive recovery, effectiveness of rehabilitation strategies, and emerging personalized approaches in neuro-oncological rehabilitation.

Results

Surgical treatment remains the cornerstone of management for most intracranial neoplasms; however, preservation of neurological function extends beyond achieving maximal safe resection. Numerous studies have demonstrated that cognitive impairment persists in a substantial proportion of patients despite favorable radiological outcomes. The most frequently affected domains include attention, executive functioning, episodic memory, processing speed, language, and visuospatial abilities. The severity of postoperative dysfunction is influenced by tumor location, histological subtype, tumor volume, preoperative neurological status, extent of resection, patient age, and adjuvant therapies such as radiotherapy and chemotherapy [8–10].

Current evidence indicates that postoperative recovery depends on the capacity of the brain to reorganize functional networks through neuroplastic mechanisms.

Adaptive cortical remapping, synaptic remodeling, dendritic plasticity, and recruitment of alternative neural pathways have all been associated with functional compensation after surgery. Functional MRI, diffusion tensor imaging, magnetoencephalography, and resting-state connectivity analyses demonstrate that preservation and restoration of large-scale brain networks are more closely associated with cognitive recovery than isolated structural integrity. These observations have shifted the focus of rehabilitation toward network-based restoration rather than localized deficit correction [9–12].

Early neurorehabilitation has consistently been associated with superior functional outcomes compared with delayed intervention. Initiating rehabilitation during the early postoperative period facilitates recovery by preventing maladaptive cortical reorganization and promoting activity-dependent neuroplasticity. Multidisciplinary rehabilitation programs combining cognitive therapy, physical rehabilitation, occupational therapy, speech-language therapy, and psychological support have demonstrated improvements in cognitive performance, activities of daily living, and overall quality of life across diverse neuro-oncological populations [10–13].

Comprehensive neuropsychological assessment represents an essential component of postoperative management. Standardized cognitive testing enables early identification of subtle impairments that may not be apparent during routine neurological examinations and provides an objective framework for individualized rehabilitation planning. Repeated assessment throughout follow-up also allows clinicians to monitor treatment response and distinguish postoperative recovery from tumor progression, treatment-related toxicity, or neurodegenerative changes [11–14].

Computer-assisted cognitive rehabilitation has emerged as an important adjunct to conventional therapy. Digital cognitive training platforms provide repetitive, adaptive, and task-specific exercises targeting memory, attention, executive function, and processing speed while allowing individualized progression based on patient performance. Several randomized studies have reported meaningful improvements in cognitive efficiency, functional independence, and patient-reported quality of life following structured computerized rehabilitation programs, particularly when integrated with conventional multidisciplinary care [12–16].

Non-invasive neuromodulation techniques, including repetitive transcranial magnetic stimulation and transcranial direct current stimulation, are increasingly being investigated as complementary interventions for enhancing postoperative recovery. By modulating cortical excitability and facilitating synaptic plasticity, these approaches may potentiate the effects of cognitive rehabilitation and accelerate restoration of functional networks. Although current evidence remains heterogeneous, several prospective studies have demonstrated favorable effects on executive functioning, attention, language recovery, and motor performance without significant safety concerns [13–17].

Rapid technological development has expanded the range of rehabilitation strategies available for patients with intracranial tumors. Virtual reality systems, robotic-assisted rehabilitation, wearable motion sensors, tele-rehabilitation platforms, and artificial intelligence–driven decision support systems enable continuous monitoring of recovery while supporting personalized treatment planning. Machine-

learning algorithms are increasingly used to predict functional outcomes, optimize rehabilitation intensity, and identify patients most likely to benefit from specific therapeutic interventions [15–19].

Despite substantial advances in postoperative rehabilitation, several challenges remain. Published studies differ considerably in rehabilitation protocols, intervention timing, duration of therapy, cognitive outcome measures, and patient populations, limiting direct comparison of results. Long-term follow-up data remain limited, particularly for patients with high-grade gliomas and those receiving multimodal oncological treatment. Nevertheless, the overall body of evidence supports early, individualized, multidisciplinary neurorehabilitation as an integral component of contemporary neuro-oncological care, with neuroplasticity representing the principal biological mechanism underlying cognitive recovery after intracranial tumor surgery [16–20].

Discussion

The available evidence demonstrates that postoperative recovery following surgical treatment of intracranial neoplasms should be viewed as a dynamic biological process rather than a passive consequence of tumor removal. Although advances in microsurgical techniques, intraoperative mapping, and neuroimaging have reduced procedure-related neurological morbidity, preservation of cognitive function depends largely on the capacity of the brain to reorganize functional networks after injury. Current studies consistently indicate that neuroplasticity serves as the principal mechanism supporting functional compensation, providing the biological foundation upon which contemporary neurorehabilitation strategies are built [8–11].

One of the most important observations emerging from recent studies is the growing recognition that rehabilitation should begin as early as clinically feasible. Delayed intervention may reduce the opportunity to influence adaptive cortical reorganization during periods of heightened neural plasticity. Early multidisciplinary rehabilitation appears to facilitate restoration of cognitive performance, improve independence in daily activities, and accelerate social reintegration. These findings reinforce the concept that neurorehabilitation should be incorporated into the standard postoperative management of patients with intracranial tumors rather than considered only after persistent neurological deficits become evident [10–13].

Despite encouraging clinical outcomes, substantial heterogeneity remains among published investigations. Considerable variation exists in rehabilitation intensity, treatment duration, patient selection, outcome measures, and timing of neuropsychological assessment. Differences in tumor histology, anatomical localization, extent of surgical resection, and adjuvant oncological therapy further complicate direct comparison between studies. Consequently, the development of standardized rehabilitation protocols and harmonized cognitive assessment tools remains an important objective for future research [11–15].

Technological innovations are increasingly reshaping the field of neuro-oncological rehabilitation. Computerized cognitive training, virtual reality environments, wearable monitoring systems, tele-rehabilitation, and non-invasive brain stimulation offer opportunities to deliver highly individualized interventions

while maintaining continuous assessment of patient progress. At the same time, artificial intelligence has demonstrated considerable potential for predicting recovery trajectories, identifying patients at increased risk of prolonged cognitive impairment, and supporting data-driven rehabilitation planning. Although these technologies remain under active investigation, their integration into routine clinical practice is likely to expand substantially over the coming years [13–18].

An additional consideration involves the multidimensional nature of postoperative recovery. Cognitive outcomes are influenced not only by structural brain injury but also by emotional well-being, fatigue, sleep disturbances, psychological resilience, educational level, and social support. Effective rehabilitation therefore requires close collaboration among neurosurgeons, neurologists, rehabilitation physicians, neuropsychologists, physiotherapists, occupational therapists, speech-language therapists, and oncology specialists. Such multidisciplinary care allows rehabilitation programs to address both neurological impairment and broader determinants of long-term functional recovery [12–19].

Several limitations of the current evidence should be acknowledged. Many published studies include relatively small patient populations, single-center experience, and limited long-term follow-up, particularly among patients with aggressive gliomas or recurrent disease. Additional prospective multicenter investigations using standardized cognitive endpoints and objective neuroimaging biomarkers are required to better define optimal rehabilitation strategies. Future research should also focus on precision neurorehabilitation, integrating multimodal neuroimaging, digital biomarkers, artificial intelligence, and individualized therapeutic algorithms to maximize cognitive recovery after intracranial tumor surgery [15–20].

CONCLUSION

The available evidence indicates that neurorehabilitation has become an essential component of postoperative care for patients undergoing surgical treatment of intracranial neoplasms. Recovery of cognitive function depends not only on successful tumor resection but also on the capacity of the brain to undergo adaptive neuroplastic reorganization. Early multidisciplinary rehabilitation, individualized neuropsychological assessment, and integration of conventional and technology-assisted interventions contribute to improved cognitive performance, greater functional independence, and enhanced quality of life. Contemporary rehabilitation strategies should therefore be regarded as an integral element of comprehensive neuro-oncological management rather than an adjunctive stage of treatment.

Further progress in this field will depend on the development of standardized rehabilitation protocols, harmonized cognitive outcome measures, and large prospective multicenter studies evaluating long-term functional recovery. The incorporation of advanced neuroimaging, digital health technologies, non-invasive neuromodulation, and artificial intelligence into clinical practice is expected to facilitate personalized rehabilitation pathways and improve therapeutic decision-making. Continued refinement of precision neurorehabilitation may further optimize cognitive recovery and long-term outcomes for patients following intracranial tumor surgery.

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НЕОНАТАЛДЫҚ ҚҰРЫСУЛАР: ДИАГНОСТИКА, ЕМДЕУ ЖӘНЕ НЕВРОЛОГИЯЛЫҚ БОЛЖАМДЫ БАҒАЛАУДЫҢ ЗАМАНАУИ ТӘСІЛДЕРІ

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Аңдатпа. Неонаталдық құрысулар жаңа туған нәрестелердегі ең жиі кездесетін жедел неврологиялық синдромдардың бірі болып табылады және орталық жүйке жүйесінің ауыр зақымдануының маңызды клиникалық белгісі саналады. Бұл жағдай көбіне гипоксиялық-ишемиялық энцефалопатиямен, бассүйекішілік қан құйылумен, инфекциялық аурулармен, зат алмасудың бұзылыстарымен және тұқым қуалайтын генетикалық патологиялармен байланысты болады. Соңғы жылдары үздіксіз электроэнцефалографиялық мониторингтің, амплитудалық электроэнцефалографияның, нейровизуализация әдістерінің және молекулалық-генетикалық зерттеулердің клиникалық тәжірибеге енгізілуі құрысулардың себебін дәл анықтауға, оларды ерте диагностикалауға және емдеу тактикасын жекелендіруге мүмкіндік берді. Уақтылы қойылған диагноз бен дер кезінде басталған ем ұзақ мерзімді неврологиялық нәтижелерді жақсартуда шешуші рөл атқарады.

Бұл жүйелі әдеби шолуда неонаталдық құрысулардың патогенезі, диагностикасының заманауи әдістері, емдеу қағидалары және неврологиялық болжамды бағалаудың қазіргі мүмкіндіктері жөніндегі ғылыми деректер жинақталды. Сонымен қатар электроэнцефалографиялық мониторингтің, магниттік-резонанстық томографияның, биомаркерлердің және жаңа буын құрысуға қарсы препараттардың клиникалық маңызы талданды. Қазіргі ғылыми дәлелдер ерте диагностикаға, этиологиялық емді дер кезінде бастауға және жаңа туған нәрестелерді ұзақ мерзімді кешенді бақылауға негізделген тәсілдің неврологиялық асқынулардың даму қаупін төмендетіп, қолайлы неврологиялық нәтижелерге қол жеткізуге мүмкіндік беретінін көрсетеді.

Түйінді сөздер: *неонаталдық құрысулар, жаңа туған нәресте, гипоксиялық-ишемиялық энцефалопатия, электроэнцефалография, амплитудалық электроэнцефалография, магниттік-резонанстық томография, фенобарбитал, леветирацетам, неврологиялық болжам, қарқынды терапия.*

Кіріспе. Неонаталдық құрысулар – жаңа туған нәрестелер кезеңінде кездесетін ең ауыр неврологиялық бұзылыстардың бірі және орталық жүйке жүйесінің жедел зақымдануының маңызды клиникалық көрінісі болып

саналады. Бұл синдром нәрестенің өмірінің алғашқы күндерінде немесе апталарында дамып, көбіне гипоксиялық-ишемиялық энцефалопатияның, бассүйекішілік қан құйылудың, нейроинфекциялардың, зат алмасу бұзылыстарының немесе туа біткен генетикалық аурулардың алғашқы белгісі ретінде байқалады. Неонаталдық құрысулардың дер кезінде анықталмауы немесе кеш емделуі неврологиялық мүгедектікке, психомоторлық дамудың кешеуілдеуіне, эпилепсияның қалыптасуына және ұзақ мерзімді когнитивтік бұзылыстарға алып келуі мүмкін. Сондықтан оларды ерте диагностикалау мен тиімді емдеу қазіргі неонатология және балалар неврологиясының өзекті мәселелерінің бірі болып табылады [1–3].

Неонаталдық кезеңдегі құрысулардың диагностикасы клиникалық ерекшеліктеріне байланысты айтарлықтай қиындық туғызады. Жаңа туған нәрестелерде құрысулар көбіне айқын клоникалық немесе тоникалық ұстамалар түрінде емес, көз алмасының қозғалысы, ауыз қимылы, аяқ-қолдың дірілі, апноэ немесе вегетативтік өзгерістер сияқты көмескі белгілермен көрінуі мүмкін. Сонымен қатар көптеген құрысу эпизодтары тек электроэнцефалография арқылы анықталатын субклиникалық сипатта өтеді. Осыған байланысты қазіргі клиникалық тәжірибеде үздіксіз бейне-электроэнцефалографиялық мониторинг пен амплитудалық электроэнцефалография неонаталдық құрысуларды анықтаудың негізгі әдістері ретінде қарастырылады. Бұл тәсілдер ұстамалардың уақытын, ұзақтығын, жиілігін және емге жауабын дәл бағалауға мүмкіндік береді [2–5].

Соңғы жылдары нейровизуализация мен молекулалық диагностиканың қарқынды дамуы неонаталдық құрысулардың этиологиялық құрылымы туралы түсінікті айтарлықтай кеңейтті. Магниттік-резонанстық томография гипоксиялық-ишемиялық зақымдануды, ми инфарктін, даму ақауларын және бассүйекішілік қан құйылуды жоғары дәлдікпен анықтауға мүмкіндік береді. Ал генетикалық зерттеулер бұрын белгісіз болып келген иондық каналопатияларды, метаболикалық және моногенді ауруларды ерте кезеңде анықтап, емдеу тактикасын жекелендіруге жағдай жасайды. Сонымен қатар фенобарбиталмен қатар леветирацетам сияқты жаңа препараттардың тиімділігі мен қауіпсіздігіне арналған зерттеулердің көбеюі неонаталдық құрысуларды емдеу қағидаларының қайта қаралуына ықпал етуде [4–7].

Қазіргі таңда неонаталдық құрысуларды жүргізу тек ұстаманы тоқтатумен шектелмейді. Негізгі мақсат – оның себебін мүмкіндігінше ерте анықтау, мидың қайтымсыз зақымдануының алдын алу және баланың ұзақ мерзімді неврологиялық болжамын жақсарту. Осыған байланысты неонатологтардың, балалар неврологтарының, радиологтардың, клиникалық генетиктердің және реаниматологтардың өзара үйлесімді жұмысына негізделген мультидисциплинарлық тәсіл ерекше маңызға ие. Осы әдеби шолудың мақсаты – неонаталдық құрысулардың диагностикасы, емдеу тәсілдері және неврологиялық болжамын бағалау жөніндегі заманауи ғылыми деректерді жүйелі түрде талдау.

Материалдар мен әдістер. Зерттеу жүйелі әдеби шолу түрінде орындалды. Неонаталдық құрысулардың диагностикасы, емдеу тәсілдері және

неврологиялық болжамын бағалау мәселелері бойынша жарияланған ғылыми еңбектерге талдау жүргізілді. Әдебиеттерді іздеу PubMed/MEDLINE, Scopus, Web of Science және Cochrane Library халықаралық дерекқорларында 2020–2026 жылдар аралығында жарық көрген жарияланымдар негізінде жүзеге асырылды. Неонаталдық құрысулардың патогенезі мен клиникалық жіктелуіне қатысты іргелі ғылыми тұжырымдамаларды сипаттайтын классикалық зерттеулер қажет болған жағдайда қосымша қарастырылды.

Шолуға жүйелі шолулар, метаталдаулар, рандомизацияланған клиникалық зерттеулер, проспективті және ретроспективті когорттық зерттеулер, бақылаулық зерттеулер, халықаралық клиникалық ұсынымдар мен сарапшылық консенсус құжаттары енгізілді. Тақырыпқа тікелей қатысы жоқ жарияланымдар, жеке клиникалық жағдайлар, конференция тезистері, редакциялық мақалалар, қайталанатын жарияланымдар және әдістемелік сапасы жеткіліксіз зерттеулер талдауға енгізілген жоқ. Іріктелген әдебиеттер неонаталдық құрысулардың этиологиясы, патогенезі, диагностикалық әдістері, емдеу тиімділігі, ұзақ мерзімді неврологиялық нәтижелері және болжамдық факторлары тұрғысынан жан-жақты сарапталды.

Нәтижелер. Неонаталдық құрысулар жаңа туған нәрестелердегі ең жиі кездесетін неврологиялық жедел жағдайлардың бірі болып табылады және олардың жиілігі толық мерзімінде туған нәрестелер арасында шамамен 1–3 жағдайды, ал шала туған нәрестелерде 1000 тірі туған балаға шаққанда 10–15 жағдайды құрайды. Қазіргі зерттеулер гипоксиялық-ишемиялық энцефалопатияның неонаталдық құрысулардың ең жиі себебі екенін көрсетеді, оның үлесіне барлық жағдайлардың 40–60%-ы тиесілі. Бұдан кейін бассүйекішілік қан құйылу, ишемиялық инсульт, орталық жүйке жүйесінің инфекциялары, гипогликемия, гипокальциемия, гипомагниемия және тұқым қуалайтын метаболикалық немесе генетикалық аурулар кездеседі. Этиологиялық факторды ерте анықтау әрі қарайғы емдеу тактикасын таңдауда шешуші рөл атқарады [8–10].

Соңғы жылдары жүргізілген зерттеулер жаңа туған нәрестелердегі құрысулардың едәуір бөлігі клиникалық тұрғыдан байқалмайтынын дәлелдеді. Кейбір деректер бойынша құрысу эпизодтарының 50–80%-ы тек электроэнцефалография кезінде ғана анықталады. Осыған байланысты үздіксіз бейне-электроэнцефалографиялық мониторинг неонаталдық құрысуларды диагностикалаудың «алтын стандарты» ретінде қарастырылады. Амплитудалық электроэнцефалография қарқынды терапия бөлімшелерінде ұзақ мерзімді мониторинг жүргізуге мүмкіндік береді және ұстамалардың қайталануын, емге жауабын және ми қызметінің жалпы жағдайын жедел бағалауда кеңінен қолданылады. Бұл әдістерді қатар пайдалану диагностикалық дәлдікті айтарлықтай арттырады [9–12].

Нейровизуализациялық зерттеу әдістері неонаталдық құрысулардың себебін анықтауда маңызды орын алады. Бас миының магниттік-резонанстық томографиясы гипоксиялық-ишемиялық зақымдануды, ми инфарктін, даму ақауларын, бассүйекішілік қан құйылуды және ақ заттың диффузиялық

өзгерістерін жоғары сезімталдықпен анықтайды. Диффузиялық-взвешенный кескіндер (DWI) ерте ишемиялық өзгерістерді өмірінің алғашқы тәуліктерінде анықтауға мүмкіндік береді, ал магниттік-резонанстық спектроскопия ми метаболизміндегі бұзылыстарды бағалауда қосымша ақпарат береді. Қажет болған жағдайда бас миының ультрадыбыстық зерттеуі мен компьютерлік томография қосымша диагностикалық әдіс ретінде пайдаланылады [10–13].

Этиологиялық диагностикада зертханалық зерттеулердің маңызы зор. Қан глюкозасы, кальций, магний, натрий деңгейін, қышқыл-сілтілік тепе-теңдікті, қандағы аммиак пен лактат концентрациясын анықтау метаболикалық бұзылыстарды ерте кезеңде айқындауға мүмкіндік береді. Егер тұқым қуалайтын ауруға күдік болса, жаңа буын секвенирлеу (NGS), толық экзомды секвенирлеу және метаболомикалық зерттеулер жүргізіледі. Соңғы жылдары KCNQ2, SCN2A, SCN8A және STXBP1 гендеріндегі мутациялардың неонаталдық эпилепсиялық синдромдардың дамуымен тығыз байланысты екені анықталған, бұл генетикалық диагностиканың клиникалық маңызын айқын көрсетеді [11–14].

Емдеудің негізгі мақсаты – құрысу белсенділігін мүмкіндігінше ерте тоқтатып қана қоймай, оның негізгі себебін жою. Қазіргі халықаралық ұсынымдар бойынша фенобарбитал алғашқы таңдау препараты болып қала береді. Оның тиімділігі алғашқы құрысу ұстамаларын бақылауда шамамен 45–60% аралығында бағаланады. Егер құрысулар сақталса, леветирацетам, фенитоин немесе лидокаин сияқты препараттар қолданылуы мүмкін. Соңғы клиникалық зерттеулер леветирацетамның қауіпсіздік бейіні қолайлы екенін және нейротоксикалық әсерінің төмен болуы мүмкін екенін көрсеткенімен, оның фенобарбиталдан айқын басымдығы әзірге толық дәлелденген жоқ [12–16].

Гипоксиялық-ишемиялық энцефалопатиямен байланысты құрысулар кезінде емдік гипотермия қазіргі таңда ең тиімді нейропротективтік әдістердің бірі ретінде қарастырылады. Дене температурасын 33–34°C деңгейінде 72 сағат бойы ұстап тұру ми тінінің қайталама зақымдануын азайтып, өлім-жітімді және ауыр неврологиялық асқынулардың жиілігін төмендетеді. Емдік гипотермия құрысуға қарсы терапиямен бірге қолданылғанда ұзақ мерзімді неврологиялық нәтижелердің жақсаратыны көптеген рандомизацияланған зерттеулерде көрсетілген [13–17].

Неврологиялық болжам ең алдымен құрысудың себебіне, ұзақтығына, электроэнцефалографиялық өзгерістердің айқындылығына және нейровизуализация нәтижелеріне тәуелді. Ұзаққа созылған немесе емге төзімді құрысулар, айқын электрлік белсенділіктің бұзылыстары, кең көлемді гипоксиялық-ишемиялық зақымдану және ауыр генетикалық синдромдар қолайсыз болжаммен жиі байланысты. Мұндай балаларда кейіннен эпилепсия, церебралды сал ауруы, когнитивтік дамудың тежелуі, сөйлеу бұзылыстары және моторлық даму кешеуілдеуі жиі кездеседі [15–19].

Қазіргі ғылыми зерттеулер неонаталдық құрысуларды басқаруда дәлме-дәл медицина қағидаларының маңызы артып келе жатқанын көрсетеді. Жасанды интеллект негізіндегі электроэнцефалографияны автоматты талдау жүйелері, магниттік-резонанстық томографияның сандық көрсеткіштері, қан

биомаркерлері және генетикалық деректерді біріктіретін болжамдық модельдер жоғары қауіп тобындағы нәрестелерді ерте анықтауға мүмкіндік береді. Бұл технологиялар болашақта емдеу тактикасын жекелендіруге, ұзақ мерзімді неврологиялық нәтижелерді жақсартуға және жаңа туған нәрестелердің өмір сүру сапасын арттыруға ықпал етеді [17–20].

Талқылау. Осы әдеби шолудың нәтижелері неонаталдық құрысулардың жаңа туған нәрестелердегі ең күрделі неврологиялық синдромдардың бірі екенін және олардың ұзақ мерзімді неврологиялық нәтижелерге елеулі әсер ететінін көрсетті. Қазіргі ғылыми деректер құрысудың өзі ғана емес, оның негізінде жатқан патологиялық үдеріс те ми тінінің зақымдануына ықпал ететінін дәлелдейді. Сондықтан қазіргі клиникалық тәжірибеде негізгі назар құрысу ұстамасын тоқтатуға ғана емес, оның этиологиясын мүмкіндігінше ерте анықтап, мақсатты емді дер кезінде бастауға аударылады. Мұндай тәсіл қайтымсыз нейрондық зақымданудың алдын алуға және қолайсыз неврологиялық салдардың қаупін төмендетуге мүмкіндік береді [8–11].

Соңғы жылдары неонаталдық құрысуларды диагностикалау тәсілдері айтарлықтай жетілді. Үздіксіз бейне-электроэнцефалографиялық мониторинг пен амплитудалық электроэнцефалографияның кеңінен қолданылуы клиникалық көрінісі айқын емес немесе субклиникалық құрысу эпизодтарын анықтау мүмкіндігін едәуір арттырды. Сонымен қатар магниттік-резонанстық томография, әсіресе диффузиялық-взвешенный режимдер мен магниттік-резонанстық спектроскопия, гипоксиялық-ишемиялық зақымдануларды және басқа құрылымдық өзгерістерді ерте кезеңде анықтауға мүмкіндік береді. Бұл технологиялардың үйлесімді қолданылуы диагноздың дәлдігін арттырып, емдеу тактикасын дербестендіруге жағдай жасайды [10–14].

Емдеу мәселесіне қатысты қазіргі зерттеулер фенобарбиталдың алғашқы таңдау препараты ретіндегі орнын сақтап отырғанын көрсетеді. Дегенмен оның барлық науқастарда жоғары тиімділік көрсетпеуі және нейродаму нәтижелеріне ықтимал әсері жаңа терапиялық тәсілдерді іздеуге түрткі болды. Леветирацетамның тиімділігі мен қауіпсіздігіне арналған зерттеулердің саны артып келе жатқанымен, оны бірінші қатардағы препарат ретінде ұсынуға жеткілікті дәлелдер әлі де қалыптасқан жоқ. Осыған байланысты құрысуға қарсы препаратты таңдау нәрестенің клиникалық жағдайына, құрысудың себебіне және халықаралық клиникалық ұсынымдарға негізделуі тиіс [12–16].

Гипоксиялық-ишемиялық энцефалопатиямен байланысты неонаталдық құрысуларда емдік гипотермияның маңызы ерекше. Заманауи рандомизацияланған зерттеулер бұл әдістің өлім-жітімді азайтып қана қоймай, ауыр неврологиялық мүгедектік қаупін де төмендететінін көрсетті. Алайда емдік гипотермия барлық пациенттерге бірдей тиімді емес, сондықтан оны қолдану көрсеткіштері мен қарсы көрсеткіштерін нақты сақтау қажет. Сонымен қатар гипотермияны құрысуға қарсы дәрілік терапиямен үйлестіре жүргізу анағұрлым тиімді нәтиже беретіні анықталған [13–17].

Неврологиялық болжамды бағалау бүгінгі таңда тек клиникалық бақылауға негізделмейді. Электроэнцефалографиялық өзгерістердің сипаты, магниттік-

резонанстық томография нәтижелері, генетикалық зерттеулер, зертханалық биомаркерлер және перинаталдық анамнез жөніндегі мәліметтерді кешенді бағалау қолайсыз нәтижелердің даму қаупін анағұрлым дәл болжауға мүмкіндік береді. Осындай көпфакторлы тәсіл ерте оңалту бағдарламаларын жоспарлауға және ұзақ мерзімді медициналық бақылаудың қажеттілігін анықтауға көмектеседі [15–19].

Соған қарамастан, неонаталдық құрысулар мәселесінде шешімін толық таппаған сұрақтар әлі де бар. Әртүрлі зерттеулерде диагностикалық критерийлердің, электроэнцефалографиялық мониторинг ұзақтығының, емдеу алгоритмдерінің және нәтижелерді бағалау көрсеткіштерінің айырмашылығы байқалады. Болашақ зерттеулер жасанды интеллект технологияларын, геномдық диагностиканы, жаңа биомаркерлерді және дәлме-дәл медицинаның мүмкіндіктерін клиникалық тәжірибеге енгізуге бағытталуы тиіс. Бұл тәсілдер жоғары қауіп тобындағы нәрестелерді ерте анықтауға, емдеу тактикасын жекелендіруге және ұзақ мерзімді неврологиялық нәтижелерді жақсартуға мүмкіндік береді [17–20].

ҚОРЫТЫНДЫ

Неонаталдық құрысулар жаңа туған нәрестелердегі ауыр неврологиялық бұзылыстардың маңызды клиникалық көрінісі болып табылады және олардың дамуы көбіне гипоксиялық-ишемиялық энцефалопатиямен, бассүйекішілік қан құйылумен, метаболикалық бұзылыстармен, инфекциялық аурулармен және генетикалық патологиялармен байланысты. Қазіргі ғылыми деректер құрысуларды ерте анықтау, олардың этиологиясын дәл айқындау және емдеуді уақтылы бастау ұзақ мерзімді неврологиялық нәтижелерді жақсартуда шешуші рөл атқаратынын көрсетеді. Үздіксіз электроэнцефалографиялық мониторинг, заманауи нейровизуализация әдістері және молекулалық-генетикалық зерттеулер диагностиканың дәлдігін арттырып, емдеу тактикасын жекелендіруге мүмкіндік береді.

Неонаталдық құрысуларды тиімді басқару неонатологтардың, балалар неврологтарының, реаниматологтардың, радиологтардың, медициналық генетиктердің және оңалту мамандарының бірлескен жұмысын талап етеді. Қазіргі клиникалық тәжірибеде дәлелді медицина қағидаларына негізделген кешенді тәсілді қолдану, ұзақ мерзімді динамикалық бақылауды ұйымдастыру және жаңа диагностикалық технологияларды енгізу неврологиялық асқынулардың жиілігін төмендетуге әрі балалардың өмір сапасы мен функционалдық дамуын жақсартуға мүмкіндік береді. Болашақта жасанды интеллект жүйелерін, жаңа биомаркерлерді және генетикалық зерттеулерді клиникалық тәжірибеге кеңінен енгізу неонаталдық құрысуларды диагностикалау мен емдеудің тиімділігін одан әрі арттырады.

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ЗАСТОСУВАННЯ ГІСТИДИН-ТРИПТОФАН-КЕТОГЛУТАРОВОГО РОЗЧИНУ У КАРДІОХІРУРГІЇ

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При операціях на відкритому серці застосовується метод кардіоплегії — штучної зупинки серця.

Існує кілька видів кардіоплегії:

При ішемічній кардіоплегії проводиться припинення коронарного кровотоку.

При хімічній кардіоплегії проводиться введення у вінцеву артерію серця фармакологічних препаратів за допомогою кардіоплегічних канюль.

При холодовій ішемічній кардіоплегії проводиться зрошення серця охолодженим фізіологічним розчином, зменшуючи ушкодження ефекту гіпоксії [1 - 3].

На даний момент істинною кардіоплегією є тільки холод. Гіпотермія забезпечує значний приріст періоду ішемії міокарда без значних наслідків. Крім того, в разі тривалої зупинки серця - можливе проведення кардіоплегії немодифікованої крові. Недоліком є погіршення мікроциркуляції при низьких температурах. Однак, дана методика дозволяє проводити перфузію міокарда до 180 хвилин без виражених некробіотичних змін в міокарді.

Кардіоплегія здійснюється шляхом використання спеціальних *кардіоплегічних розчинів, зокрема* гістидин-триптофан-кетоглутарового розчину (ГТК).

Розчин є прозорим, безбарвним або злегка жовтуватим, з осмолярністю близько 310 мОсм/л та pH 7,02–7,20 при температурі 25 °C:

Компонент	**Масова концентрація**	**Молярна концентрація**
L-Гістидин	27,9289 г	180 ммоль/л
Гістидину гідрохлорид, моногідрат	4,0770 г	18 ммоль/л
L-Триптофан	0,4085 г	2 ммоль/л
(alpha \)-Кетоглутарова кислота	0,1461 г	1 ммоль/л
Натрію хлорид (NaCl)	0,8766 г	15 ммоль/л
Калію хлорид ((KCl)	0,6710 г	9 ммоль/л
Магнію хлорид гексагідрат	0,8132 г	4 ммоль/л
Кальцію хлорид дигідрат	0,0022 г	0,015 ммоль/л
Манітол	5,4651 г	0 ммоль/л

Розчин пропускають через систему коронарних судин, що кровопостачають серце.[3]. При цьому зупиняється діяльність міокарду, знижується його енергетична потреба, в тому числі й у кисню і підвищується резистентність серця до ішемії. Завдяки використанню кардіоплегії, яка захищає міокард в умовах штучного кровообігу, стали широко доступними досить тривалі за часом кардіохірургічні операції.

З огляду на біохімічну концепцію механізм дії базується на принципі деполяризаційного пригнічення функції клітин шляхом вимивання позаклітинного натрію та кальцію у поєднанні з потужним буферизуванням.

Низький вміст іонів натрію (Na+) та кальцію (Ca^{2+}) зупиняє електричну та механічну активність клітин серця (діастолічний арешт), знижуючи споживання кисню до мінімуму.

Буфер гістидин / гістидин-HCl запобігає метаболічному ацидозу. Він затримує зниження тканинного pH під час ішемії, продовжуючи час ефективного анаеробного гліколізу.

L-Триптофан стабілізує клітинні мембрани, підтримує їхню проникність та діє як потужний антиоксидант.

alpha -Кетоглутарат є субстратом циклу Кребса. Він стимулює вироблення енергії (АТФ) під час відновлення кровотоку (реперфузії) та стримує накопичення лактату.

Манітол створює необхідний осмотичний тиск, запобігаючи розвитку набряку клітин під дією холоду, а також нейтралізує вільні радикали.

На базі Інституту серця було прооперовано 140 пацієнтів із вродженими/набутими вадами серця та ішемічною хворобою серця, яким оперативні втручання виконувалися в умовах штучного кровообігу із застосуванням кардіоплегічного ГТК- розчину. [4].

Застосування ГТК розчину (виробництва ЦПФ «Хемотека») дозволило досягти низки позитивних клінічних результатів:

Відновлення серцевої діяльності. У переважної більшості пацієнтів відновлення серцевої діяльності після зняття аортального затискача відбувалося самостійно або із мінімальною електричною стимуляцією, що свідчить про адекватний рівень захисту міокарда в умовах тривалої ішемії.

Гемодинамічна стабільність. Після завершення штучного кровообігу в більшості пацієнтів відзначалася задовільна системна гемодинаміка, що підтверджувалося низькою потребою в симпатоміметичній підтримці. Дози інотропних препаратів були помірними та відповідали стандартним показникам для даної категорії хворих, що свідчить про збережену скоротливу функцію міокарда після ішемічного періоду.

Електрокардіографічні та біохімічні показники. Аналіз ЕКГ-даних у післяопераційному періоді не виявив клінічно значущих ішемічних змін, які б свідчили про розвиток інтраопераційного інфаркту міокарда.

За даними післяопераційної ехокардіографії у більшості пацієнтів відзначалося збереження або швидке відновлення фракції викиду лівого шлуночка, відсутність виразної глобальної або сегментарної дисфункції міокарда, що підтверджує ефективність кардіоплегічного захисту.

Таким чином, отримані результати свідчать, що застосування ГТК-розчину забезпечувало надійний та прогнозований захист міокарда під час операцій на відкритому серці в умовах штучного кровообігу. Одноразове введення ГТК--розчину дозволяло підтримувати електричну та метаболічну тишу міокарда протягом тривалого періоду ішемії, що є критично важливим при складних та тривалих реконструктивних втручаннях.

Механізм дії ГТК-розчину поєднує такі ефекти, як:

-дієву буферизацію внутрішньоклітинного ацидозу (гістидин);

-стабілізацію клітинних мембран (триптофан);

-підтримку енергетичного метаболізму (кетоглутар).

Це створює сприятливі умови для збереження життєздатності кардіоміоцитів у період ішемії та ранньої реперфузії.

Клінічні спостереження свідчать, що застосування ГТК-розчину є особливо доцільним у випадках тривалого періоду ішемії та складних реконструктивних втручань і в пацієнтів із підвищеним операційним ризиком, де стійкість кардіоплегічного ефекту має вирішальне значення. Окрім того, важливою перевагою ГТК-розчину є можливість його широкого впровадження в умовах обмежених ресурсів, зокрема під час воєнного стану.

Таким чином, на основі отриманих результатів можна стверджувати, що ГТК-розчин є ефективним та безпечним засобом кардіоплегічного захисту при операціях на серці. Його застосування забезпечує сприятливий перебіг раннього післяопераційного періоду та зниження ризику ішемічного ушкодження міокарда. Клінічні дані свідчать про надійну кардіопротекцію в умовах тривалої ішемії та відновлення адекватної функції серця після зняття затискача аорти.

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ІНТЕГРАЦІЯ ВИРОБНИЧИХ ТА ПОБУТОВИХ ФАКТОРІВ БЕЗПЕКИ ПРИ ОПТИМІЗАЦІЇ МІСЬКОГО СЕРЕДОВИЩА З УРАХУВАННЯМ ШУМОВОГО ЗАБРУДНЕННЯ: СТРАТЕГІЧНІ НАПРЯМИ ТА МЕТОДОЛОГІЯ ДОСЛІДЖЕННЯ

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Актуальність. Вирішення практичних завдань у сучасному містобудуванні пов'язане з реконфігурацією житлової забудови та впровадженням нових функціональних об'єктів у наявну інфраструктуру. Виведення перших поверхів житлових будинків із житлового фонду під комерційну чи громадську діяльність є розповсюдженим процесом зі своєю історією. Ця тенденція є позитивною, оскільки забезпечує працівникам у позаробочий час швидкий доступ до

необхідних послуг безпосередньо в межах пішої доступності.. Автори починали дослідження цієї проблеми в роботі [1].

Мета. Метою роботи є проведення аудиту безпеки інтегрованих міських об'єктів та розробка нормативно-технічних рекомендацій щодо мінімізації шумового забруднення в позаробочий час як ключового фактора збереження людського потенціалу, зниження професійного вигорання та підвищення безпеки праці безпосередньо на робочих місцях. Треба окремо звернути увагу на те, що основна мета даної роботи – це розробка стратегічних напрямків для проведення широкомасштабного дослідження, присвяченого темі, яка повністю пов’язана з назвою статті.

Для досягнення поставленої мети нами визначені наступні завдання:

1 Проаналізувати тенденції реконфігурації сучасної міської забудови та особливості інтеграції виробничо-комерційних об'єктів у житлову інфраструктуру.

2. Визначити характер взаємодії шкідливих виробничих і побутових факторів у зоні тісного зближення житлових та технологічних зон.

3. Дослідити механізм впливу надмірного акустичного тиску на психофізіологічне відновлення працівників у позаробочий час та його зв'язок із ризиками виробничого травматизму.

4. Провести аудит безпеки та натурне обстеження визначених інтегрованих об'єктів міського середовища.

5. Здійснити практичну апробацію методик кількісного прогнозування акустичних ризиків для оцінки рівня шумового забруднення.

6. Розробити комплексні нормативно-технічні рекомендації (архітектурно-планувальні, будівельно-акустичні та інженерні заходи) для мінімізації впливу шкідливих чинників на населення та забезпечення безпеки на робочих місцях.

Методи та методика.

Наведемо повний структурований перелік методів та методик, що повністю відповідають переліку наших завдань:

1. Теоретичні та загальнонаукові методи

- Метод системно-структурного аналізу та узагальнення — для вивчення тенденцій реконфігурації міської забудови, переведення житлового фонду в комерційний та оцінки взаємодії шкідливих виробничо-побутових факторів (для *Завдань 1, 2*).
- Аналітично-статистичний метод — для дослідження зв’язку між рівнем шуму в позаробочий час, психофізіологічною втомою працівників та ризиками виникнення виробничого травматизму (для *Завдання 3*).

2. Емпіричні та експериментальні методи (методики обстеження)

- Метод натурних інструментальних вимірювань (шумометрія) — для визначення фактичних рівнів звукового тиску на об'єктах дослідження.
- Методика інженерно-екологічного аудиту безпеки територій — для комплексного обстеження інтегрованих об’єктів міського середовища та оцінки дотримання санітарно-захисних розривів (для *Завдання 4*).

3. Методи прогнозування та моделювання (розрахункові методики)

- Методика кількісного прогнозування акустичних ризиків — для розрахунку очікуваних рівнів шуму в житлових та рекреаційних зонах від комерційних джерел (для *Завдання 5*).
- Методи комп'ютерного тривимірного моделювання акустичного поля (наприклад, за допомогою ПЗ типу «Еколог-Шум», програми, розробленої в ННІ «ПДАБА» «AcousticLab» [2] або аналогів) — для візуалізації поширення звукових хвиль в умовах щільної міської забудови (для *Завдання 5*).

4. Інженерно-технічні та нормативно-проектувальні методи

- Методи будівельної акустики (розрахунок звукоізоляції) — для оцінки та проектування захисної спроможності огороджувальних конструкцій між комерційними та житловими приміщеннями.
- Метод архітектурно-планувального зонування — для розробки просторових рішень та інженерно-технічних рекомендацій щодо мінімізації шкідливих факторів (для *Завдання 6*).

Нормативно-методична база, на яку автори повинні спиратися у своїй подальшій роботі:

Всі розрахунки та вимірювання повинні базувалися на наступних нормативних документах:

1. ДБН В.1.1-31:2013 «Захист територій, будинків і споруд від шуму» [3].
2. ДБН Б.2.2-12:2019 «Планування та забудова територій» [4].
3. ДСН 3.3.6-037-99 «Санітарні норми виробничого шуму, ультразвуку та інфразвуку» [5].
4. Санітарних нормах допустимого шуму в приміщеннях житлових і громадських будинків та на території житлової забудови [6].

Основна частина. Розглянемо теоретико-методологічні засади дослідження акустичної безпеки в умовах інтегрованої міської забудови з зосередженням на завданнях, позначених на початку роботи.

1. ***Тенденції реконфігурації міського середовища та інтеграція функціональних зон (завдання 1)***

Сучасний етап розвитку містобудування характеризується активною зміною парадигми просторової організації міст. Традиційне функціональне зонування, що передбачало жорсткий територіальний розподіл промислових, селитебних та рекреаційних територій, поступово витісняється концепцією поліцентричного та багатофункціонального розвитку (Mixed-Use Development - багатофункціональна або змішана забудова)).

У наукових працях вітчизняних та закордонних дослідників (зокрема, у сфері урбаністики та просторового планування) повсюдний процес виведення перших поверхів житлових будинків під об'єкти комерційного та громадського призначення розглядається як позитивний фактор соціально-економічного розвитку. Це забезпечує реалізацію концепції «компактного міста» та принципу пішої доступності до необхідних послуг у позаробочий час.

Про концепцію «компактного міста» дуже потужно розповідають в своїх роботах автори: Jacobs J. [7]. і Rogers R. [8].В роботі [7] автор ретельно розглядає питання про користь перших комерційних поверхів для безпеки та розвитку вулиць. А автор роботи [8] проводить дослідження концепції «компактного міста» та сталого урбанізму.

2. Вітчизняні фахові дослідження (модернізація перших поверхів та піша доступність):

Автори в роботі [1] обґрунтовують, що працівники мережі установ обслуговування (магазинів, банків, офісів, розташованих якраз на перших поверхах) перебувають під подвійним пресингом: внутрішніми факторами та зовнішнім транспортним навантаженням. Це дозволяє нам теоретично довести, що при реконфігурації перших поверхів під комерцію необхідно захищати не лише мешканців зверху від шуму комерції, а й самих працівників цих об'єктів від колосального акустичного тиску магістралі. Це дослідження методологічно поєднанує екологію та безпеку праці. Авторами розроблено підхід до оцінки умов праці на основі комплексного врахування містобудівних та санітарно-гігієнічних чинників (шум + загазованість відпрацьованими газами). В статті є готовий алгоритм, як зв'язати архітектурно-планувальні рішення з ризиками втоми та працездатності. Цей матеріал дозволяє обґрунтовувати необхідність розробки нових інженерно-технічних заходів шумозахисту (подвійні шлюзи, екрани, звукоізоляція фасадів) для збереження людського потенціалу.

Абизов В. А. та Кулик А. В. [9] в своїй роботі академічно обґрунтовують принципи пішої доступності. Автори досліджуються архітектурно-дизайнерські та об'ємно-просторові принципи формування вхідних груп для об'єктів обслуговування, що вбудовуються у житлову забудову при реконструкції міської забудови. Дослідження фокусується на необхідності автономних комунікаційних вузлів, що прямо стосується безпеки життєдіяльності та зонування житлового середовища.

Стаття В. А. Абизова та А. В. Кулика (2019) [10] є важливим теоретичним та методичним містком для нашої роботи, оскільки вона переходить від загальних філософських концепцій дизайну до конкретних конструктивно-планувальних вимог до перших поверхів. У контексті нашої теми (охорона праці, інтеграція безпеки та захист від шумового забруднення) ця праця корисна такими положеннями:

а) чітка типізація інтегрованих об'єктів (вбудовані та вбудовано-прибудовані);

б) автори детально класифікують типи підприємств обслуговування, які інтегруються в житлову забудову, та розмежовують вимоги до суто вбудованих (всередині габаритів будинку) та вбудовано-прибудованих (які мають додатковий винесений об'єм) об'єктів;

в) ця класифікація є готовою базою для проведення нашого аудиту безпеки (Завдання 4). Вона дозволяє нам розділити об'єкти дослідження на групи, адже вбудовано-прибудовані об'єкти дають більше можливостей для встановлення

зовнішніх інженерних засобів шумозахисту (козирків, екранів), ніж суто вбудовані перші поверхи;

г) у статті сформульовано методичні положення, які вимагають жорсткої автономії функціонування підприємства обслуговування від житлової частини будинку. Це стосується організації окремих технологічних входів, ізольованих зон навантаження/вивантаження товарів та відокремлених комунікацій;

д) це прямо підтверджує наші тези про необхідність архітектурно-планувального зонування (Завдання 6). Ми можемо посилатися на ці методичні положення, обґрунтовуючи, що ізоляція вхідної групи комерційного об'єкта є першим кроком до ліквідації дифузії шкідливих чинників (шуму розвантаження, криків, брязкання та шуму технологічного транспорту) у житлову зону мешканців та працівників, які там відпочивають;

е) автори доводять, що дизайн вхідної групи — це не архітектурна прикраса, а складна функціонально-технологічна структура, яка повинна забезпечувати безпеку, зручність та захист від впливу зовнішнього середовища;

ж) робота допомагає нам зв'язати питання дизайну та архітектури з безпекою праці та життєдіяльності. Конструктивні елементи вхідних груп (наприклад, тамбури з подвійними дверима, акустичні екрани у вигляді винесених засклених вітрин), які автори розглядають як елементи дизайну, у нашій роботі виступають як будівельно-акустичні засоби шумозахисту. Вони одночасно захищають робочі місця персоналу всередині об'єкта від шуму автотранспорту з вулиці та не випускають технологічний шум комерції назовні.

Кулик А.В. в дисертації [11] є корисні відомості для обґрунтування архітектурно-планувальних та інженерно-технічних рішень, які ми ставимо як одне з головних завдань для захисту працівників у години їхнього відпочинку.

Проте реконфігурація житлової забудови та впровадження нових функціональних об'єктів у наявну інфраструктуру відбуваються високими темпами, які часто випереджають адаптацію нормативно-технічної бази. У результаті виникає науково-практичне протиріччя між покращенням соціально-побутового комфорту та загостренням безпекових ризиків для населення.

2. Взаємодія виробничих та побутових факторів шкідливості в умовах щільної забудови (завдання 2)

Тісне просторове зближення виробничо-комерційних елементів із житловою інфраструктурою докорінно змінює структуру ризиків у сфері безпеки життєдіяльності та охорони праці. Побутове середовище традиційно детермінується як простір для психофізіологічного відновлення людини. Однак інтеграція комерційних об’єктів (торговельних майданчиків, закладів харчування, логістичних вузлів) безпосередньо у житлові будівлі призводить до взаємного переплетення та дифузії шкідливих факторів.

Аналіз літературних джерел свідчить про виникнення специфічного феномену: техногенно-виробничі фактори (вібрація інженерного обладнання, виділення шкідливих речовин системами вентиляції комерційних підприємств, специфічний шум) трансформуються у побутові фактори ризику для мешканців. І навпаки — житлові зони висувають підвищені вимоги до експлуатації

впроваджених об’єктів. Наявні наукові підходи потребують систематизації для жорсткого обліку цих взаємопроникаючих впливів у межах єдиної системи екологічного та санітарно-гігієнічного моніторингу.

3. Вплив акустичного навантаження в позаробочий час на безпеку праці (завдання 3)

Серед комплексу шкідливих факторів інтегрованого середовища провідне місце за ступенем поширеності та негативними наслідками посідає шумове забруднення. Сучасні дослідження в галузі медицини праці та психофізіології доводять, що надмірний акустичний тиск діє як хронічний системний стресор.

Особлива небезпека полягає у впливі шуму саме в позаробочий час — у періоди, призначені для відпочинку та сну. У науковій літературі зафіксовано стійкі зв'язки між незадовільним станом акустичного режиму житла та такими проявами, як:

- Порушення архітектоніки сну та хронічна втома.
- Зниження швидкості реакції та концентрації уваги.
- Накопичення психоемоційного напруження та швидке професійне вигорання.

З погляду охорони праці, недоотримання якісного відпочинку безпосередньо знижує надійність людського фактора під час виконання професійних обов'язків. Втомлений працівник є потенційним джерелом помилкових дій, що експоненціально підвищує ризики виникнення виробничого травматизму та аварійних ситуацій на робочих місцях під час робочих змін. Це підкреслює необхідність розгляду акустичної безпеки житла як базового елемента системи збереження трудового та людського потенціалу країни.

4. Методологічні підходи до аудиту та прогнозування ризиків (завдання 4, 5, 6)

Для мінімізації зазначених ризиків у науковій практиці сформовано кілька основних методологічних напрямів, які утворюють основу дослідницької стратегії:

4.1. Інструментально-аудиторський напрям: базується на методах натурної шумометрії та порівняльному аналізі фактичних рівнів звуку з нормативними вимогами (зокрема, Наказом МОЗ № 463 [6]). Екологічний аудит дозволяє фіксувати поточний стан середовища, але має обмежені можливості для превентивного планування.

4.2. Розрахунково-прогностичний напрям: пов'язаний із застосуванням математичних моделей та методик кількісного прогнозування акустичних ризиків. Використання сучасного програмного забезпечення для 3D-моделювання акустичних полів дає змогу оцінювати динаміку поширення звукових хвиль ще на етапах проектування або реконструкції об'єктів.

4.3. Нормативно-технічний та планувальний напрям: орієнтований на розробку захисних заходів. У науковій літературі доведено, що найбільшу ефективність демонструє комплексний підхід, який поєднує архітектурно-планувальні рішення (дотримання санітарних розривів згідно з ДБН Б.2.2-12:2019 [4]), будівельно-акустичні засоби (розрахунок звукоізоляції конструкцій

за ДБН В.1.1-31:2013 [3]) та інженерно-технічні заходи безпосередньо на джерелах шуму.

Висновки: Науковий огляд літератури акцентує увагу на необхідності комплексного захисту міського середовища від акустичного навантаження, що інтегрує вимоги ДБН Б.2.2-12:2019 [4] та ДБН В.1.1-31:2013 [3]. Дослідження підтверджують суттєвий вплив виробничих та транспортних шумів на селитебні зони, що негативно позначається на безпеці праці, як зазначено у роботі [1] та підтверджено наказами МОЗ України [6]. В роботі [1] «…розглянуто основні положення щодо реалізації конституційного права працівників на охорону їх життя та здоров'я у процесі трудової діяльності, на належні та безпечні умови праці, а також питання щодо регуляції за участю відповідних органів державної влади відносин між роботодавцем і працівником з питань безпеки, гігієни праці та виробничого середовища й встановлення єдиного порядку організації охорони праці в Україні»..

В якості **перспектив подальших досліджень** автори планують продовжити дослідження з розглянутої тематики з урахуванням згаданих робіт і додатково робіт [12-17].

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THE ARCHITECT WHO MISTOOK HIS BLUEPRINT FOR THE BUILDING: *GEORGE KELLY'S* PERSONAL CONSTRUCT THEORY, DERRIDEAN DECONSTRUCTION, AND THE PHILOSOPHICAL ABYSS BENEATH COGNITIVE PSYCHOLOGY

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Every discipline needs a founding myth, and psychology's favorite one is depth — the conviction that beneath the reaction-time studies and the Likert scales there exists, in certain enlightened corners of the field, something properly philosophical: a theory of meaning, of the self, of structure itself, robust enough to keep company with Kant. George Kelly's Personal Construct Theory (1955) is psychology's strongest candidate for the honor, and it deserves to be taken seriously for exactly that reason: nowhere else does the discipline come closer to philosophy, and nowhere else is the distance between the two so instructively, almost touchingly, exposed. Kelly's wager was that a person is best understood not as a bundle of drives or a reinforcement history but as a theorist, silently running a private research programme on the world, anticipating events through a system of bipolar constructs that remain, in principle, perpetually open to revision. He called this stance *constructive alternativism*, a name confident enough to sound like a philosophical position in its own right — and it is exactly that, on loan. The doctrine is, by Kelly's own later acknowledgment, a fairly direct importation of Hans Vaihinger's (1911/1924) *Die Philosophie des Als Ob*, a far stranger, far older neo-Kantian argument that all our governing categories — scientific, moral, legal, religious — are useful fictions, regulative "as ifs" answerable only to their own pragmatic success rather than to any correspondence with the real. Psychology's single most philosophically ambitious gesture of the twentieth century turns out, on inspection, to be a footnote to philosophy wearing a lab coat. This is not an isolated embarrassment so much as a structural feature of the relationship itself, one Edmund Husserl had diagnosed half a century before Kelly sat down to write. In the Prolegomena to his *Logical Investigations* (1900–1901/1970), Husserl's target was psychologism: the fashionable attempt, among the empirical psychologists of his day, to ground logical and normative validity in contingent facts about how human minds happen to operate. The argument remains devastating. If the laws of logic are merely descriptions of psychological process, their truth becomes hostage to the accident of human cognitive architecture, and the distinction between valid and invalid reasoning collapses into a report on what our species happens to find persuasive; logic survives only by refusing to be psychology. Kelly's system, however supple, occupies exactly this vulnerable position: it can describe, with real clinical subtlety, how one particular

anxious, over-controlled, or grieving person happens to organize her anticipations, but it cannot, from within its own resources, say what anticipation or meaning *are*, *sub specie aeternitatis*, because that is no longer a psychological question at all. Martin Heidegger (1927/1962) gave the distinction its sharpest form by separating the ontic — the level of particular existing beings, including particular psyches busy with their particular concerns — from the ontological, the level at which one asks what Being, world, or temporality must already be like for any such concern to show up as a concern in the first place. Personal Construct Theory is rigorously, admirably, irredeemably ontic. It can tell us how a given client construes her mother. It cannot tell us what construing itself is — and the moment it tries, in constructive alternativism, it stops doing psychology and starts doing philosophy without philosophy's patience for interrogating its own foundations.

If Kelly's psychology is structurally shallow, it is because it is, without quite admitting it, a structuralism — and structuralism's own crisis of foundations had already been diagnosed, with terrible elegance, by the time Kelly's American disciples were running rep grids on undergraduates. Every construct, for Kelly, is bipolar by definition: the **Dichotomy Corollary** insists that a person's system is composed of a finite number of dichotomous constructs, units of meaning that exist only as contrast — clean against dirty, brave against cowardly — exactly the differential logic Ferdinand de Saussure (1916/1959) had identified, half a century earlier, as the engine of linguistic value, in which a sign means nothing in itself and everything by its position within a system of differences. Kelly's constructs are Saussurean signs in clinical paper gowns, organized — per the **Organization Corollary** — into hierarchies of superordinate and subordinate constructs, with certain core constructs, Kelly's own term for those governing a person's processes of self-maintenance, functioning as the structural center around which the whole system anticipates, tests, and revises itself. It is precisely this architecture — a structure organized around a center exempt from the structure's own play — that Jacques Derrida dismantled in "Structure, Sign, and Play in the Discourse of the Human Sciences," delivered at Johns Hopkins on 21 October 1966 and published the following year in *L'écriture et la différence*, translated into English as *Writing and Difference* (Derrida, 1967/1978). Derrida's argument, compressed past the point of comfort, is that the concept of a centered structure is incoherent on its own terms: a center is supposed to organize the structure while itself escaping the very structure it organizes, to be the one element exempt from the substitutions governing every other element — and the history of Western thought, on this account, is the history of one center after another (*eidos*, *archē*, *telos*, the transcendental ego, consciousness, man) being installed in this impossible position and then quietly toppled by the next. Apply this to Kelly's core constructs and the embarrassment is immediate: constructive alternativism promises that all constructions are open to revision, yet the core constructs are, by clinical definition, the ones a person will defend most fiercely and experience as **threat** — Kelly's own technical term for the anticipation of imminent change to one's core structures — when challenged, which is to say they are exempted, in practice if not in official doctrine, from the very revisability that supposedly defines the whole system. Kelly needed a center to make

his structure cohere, and so, like every structuralism before him, he smuggled one in and called it personality. The same logocentric fantasy animates Kelly's most celebrated clinical technique. In fixed-role therapy, the client writes a self-characterization, the therapist designs a fictive alter ego with a contrasting core role, and the client enacts this new identity for several weeks, as though trying on a coat, in order to discover that the self was always more fluid than feared. The technique's entire persuasive force depends on a fantasy Derrida spent his career undoing in *Of Grammatology* (1967/1976): that there exists, prior to and outside the chain of signifiers, a self capable of standing free of language long enough to author a new self from a position of pure self-presence. But the "as if" that makes the role fixed rather than a sincere confession is itself written — scripted by a therapist, voiced in borrowed language, structured by cultural scripts of what a person "like that" says and does. It is, in Derridean vocabulary, always already a text, a tissue of traces with no self-identical author behind it, and *différance* — the perpetual deferral and differing-from-itself that Derrida shows constitutes meaning — will not hold still long enough for any self-characterization to arrive at the transparent presence the technique requires. Roland Barthes (1957/1972) supplies the cultural half of the same point: what a client experiences as her own most private, idiosyncratic construct — "I am the responsible one," "I am too sensitive" — is, with depressing regularity, simply bourgeois myth doing what myth always does, naturalizing a historically specific arrangement until it feels like the eternal truth of a private soul. Derrida would add only that the excluded pole of each construct — irresponsibility, toughness — is never simply absent from the privileged term but persists within it as a trace, which is why no amount of **tightening**, Kelly's term for rendering a construct more precise and predictively rigid, will exorcise a haunting that is not a clinical problem but a condition of language itself.

Kelly's man-the-scientist — the root metaphor of the whole system, the dispassionate observer who frames hypotheses and revises them in light of disconfirming evidence — presupposes exactly the unified, self-transparent ego that Continental psychoanalysis spent the twentieth century dismantling. Jacques Lacan's quarrel with American ego psychology, the school of Heinz Hartmann and his collaborators, who proposed strengthening a conflict-free ego sphere so the patient could better adapt to reality, was not a technical disagreement about method but a rejection of the premise — and the premise is Kelly's premise too. For Lacan (1966/2006), the ego is not the seat of rational mastery but an imaginary formation, constituted in the mirror stage through a fundamental *méconnaissance*, a mis-recognition of a fragmented, prematurely born infant as the coherent, bounded form glimpsed in a mirror — which is to say the very faculty Kelly asks to stand outside the construct system and test it scientifically is, on the Lacanian account, the most thoroughly constructed and least reliable witness in the building. Worse, for Lacan the subject does not possess language as a tool for building "personal" constructs; the subject is an effect of language, spoken by a signifying chain that precedes it, exceeds it, and divides it from itself, so that "personal construct" becomes something close to a category error, smuggling a sovereign owner back into a structure that, properly understood, belongs to no one. Slavoj Žižek's (1989) reading of Lacan sharpens the

critique of Kelly's **Experience Corollary**, the proposition that a person's construction system varies as he successively construes the replication of events — Kelly's term, in effect, for what happens when a hypothesis meets disconfirming data and gets revised, psychology's domesticated version of falsification, an orderly feedback loop in which anomaly leads smoothly to better theory. The Real, in Žižek's account, is precisely what refuses this hospitality: a traumatic kernel that resists symbolization absolutely, that cannot be assimilated into a revised construct because its entire function is to remain unassimilable, returning instead as symptom and repetition, structuring fantasy from the outside. A construct system that has successfully metabolized every anomaly into a smoother, more **permeable** hypothesis — Kelly's own honorific for constructs flexible enough to admit new elements — has not, on this reading, achieved health; it has achieved an unusually thorough repression, having found a construct sturdy enough to paper over the one piece of the real that was never going to fit any construct whatsoever. Julia Kristeva closes the circle from the other direction. Where Lacan and Žižek attack the sovereignty of Kelly's anticipating subject, Kristeva (1974/1984) attacks the sufficiency of his materials: constructs, to be tested, communicated, and revised at all, must be at least implicitly propositional, which confines Kelly's entire model to what Kristeva calls the symbolic order — the register of grammar, syntax, and stable signification. But meaning, for Kristeva, is never exhausted by the symbolic; beneath and against it churns the semiotic *chora*, the rhythmic, bodily, maternal substratum of drive-energy that precedes propositional thought and periodically erupts through it, most violently as abjection (Kristeva, 1980/1982) — the horror, neither subject nor object, that cannot be construed because construal requires exactly the stable boundary between self and world that abjection dissolves. A clinical psychology built entirely from propositional constructs has, by its own founding assumptions, no instrument with which to register the one register of experience that refuses, on principle, to hold still long enough to become a construct.

The remaining gap is sociological, formal, and finally ethical, and philosophy's other outposts close it from every direction Kelly's individualism cannot reach. Michel Foucault treats psychology itself as a recent invention rather than a perennial science: *The Order of Things* (1966/1970) locates the discipline among the "human sciences" made possible only by the unstable, late-eighteenth-century figure of man as simultaneously the empirico-transcendental knower and known, an arrangement Foucault predicts might one day vanish "like a face drawn in sand at the edge of the sea," while *Madness and Civilization* (1961/1965) shows that the very sanity Kelly's man-the-scientist is built to model was carved out historically through confinement and exclusion, leaving the categories psychology now uses to test constructs already sedimented with that history. Pierre Bourdieu's *habitus* (1972/1977) supplies the sociological correction Kelly's voluntarism needs, and sharpens the limit of the **Commonality Corollary**, Kelly's own gesture toward shared meaning: dispositions of perception and judgment are internalized from social position long before any two "personal scientists" could converge on similar constructs by independently hypothesizing their way there, and *Distinction* (1979/1984) shows that taste, far from freely construed, tracks class with an accuracy no individual rep grid

could explain. Theodor Adorno's identity-thinking (1966/1973) names the violence quietly built into the very concept of a construct, which is definitionally a device for declaring particulars "the same" along one dimension while suppressing whatever in them resists; negative dialectics is the refusal to let that suppression pass as harmless taxonomy. Judith Butler's performativity (1990) dismantles Kelly's core role from the side of identity itself: there is no substantial self that core constructs merely organize and express, only the retroactive effect of reiterated acts, a doing without a doer behind the deed. Luce Irigaray (1974/1985) indicts the **Dichotomy Corollary**'s very form, diagnosing the demand that every construct be strictly bipolar as a symptom of what she calls the logic of the Same, a phallogocentric economy of representation unable to think a third term or a fluidity that is, in her phrase, neither one nor two — which would make Kelly's entire taxonomic apparatus, for all its clinical gentleness, a quietly masculine machine. Gilles Deleuze and Félix Guattari (1980/1987) complete the formal indictment from the side of structure rather than content: the **Organization Corollary**'s hierarchy of superordinate and subordinate constructs, branching downward from a governing core, is arborescent thought in its purest clinical form, exactly the rooted, binary-branching image of thinking *A Thousand Plateaus* tries to replace with the rhizome's hierarchy-free multiplicity. Emmanuel Levinas (1961/1969) supplies the gravest charge of all against the **Sociality Corollary**, Kelly's proposal that one plays a role in relation to another only by construing that other's construction processes: for Levinas this is the very structure of ethical failure, the reduction of the Other to the Same, an epistemological capture foreclosing the one relation — the face-to-face — in which the Other precedes, exceeds, and commands the self before any construal has had the chance to begin.

The rest can be named at speed, and the speed is itself the point. Merleau-Ponty (1945/1962) would note that the body's prereflective "I can" organizes meaning before any verbalizable construct arrives to formalize it; Ricoeur (1965/1970) would note that Kelly's tidy loop of anticipation and revision forecloses the genuinely hermeneutic spiral — archaeology against teleology, suspicion against recollection — through which a symbol gives rise to thought rather than simply confirming a hypothesis; Wittgenstein (1953) would ask how a strictly **Individuality Corollary** construct could ever meet correctness conditions that his private-language argument shows must, on pain of incoherence, already be public; de Man (1979) would point out that the word *construct* is itself a dead metaphor borrowed from masonry, no more literal than the poetry deconstruction specializes in unsettling; Jameson (1991) would wonder whether the social totality a person is asked to cognitively map through revisable hypotheses has not, under late capitalism, become structurally unmappable by any individual cognition; and Laing (1960), psychiatry's own best run at Kelly's exact ambition, shows in *The Divided Self* how far a phenomenologically literate clinician can travel toward Heidegger and Sartre before the institution of the clinic — what Foucault (1963/1973) calls its own organizing gaze — pulls the work back to diagnosis and treatment, foreclosing the philosophical question it had only begun to ask. What unites this chorus — phenomenologists, psychoanalysts, sociologists, gender critics, literary theorists, an existential psychiatrist who got closer than most before the clinic

reclaimed him — is not agreement on doctrine but a shared refusal to grant any construct system the closure Kelly's therapeutic ambitions quietly require. This, finally, is why philosophy will always out-structure psychology, and the reason has a name, and the name is Derrida's. A clinical discipline is professionally obligated to seek termination: a construct system functional enough to anticipate events, hold a self together, and let the client leave the office. Philosophy, at least in the line that runs from Husserl's troubled prolegomena through Heidegger's ontological difference to Derrida's freeplay, has no such obligation, and forbids itself the comfort of seeking one. The freeplay of the sign, the structure without a transcendental center, the supplement that never finishes supplementing — these are not problems awaiting a better hypothesis; they are the condition of meaning as such, and a thought genuinely faithful to that condition cannot write the end beneath a construct, a self, or a structure without immediately watching the ground it just declared firm begin, once again, to differ from itself. Kelly built psychology's most sophisticated structuralism, and in constructive alternativism, very nearly glimpsed the abyss beneath it — close enough that one wonders, reading him now, whether mid-century American clinical psychology spent its best years quietly backing away from a door a Continental philosopher would walk straight through a decade later. Philosophy is simply the discipline willing to keep looking down.

George Kelly opens *The Psychology of Personal Constructs* with a declaration of programmatic audacity: "Man looks at his world through transparent patterns or templates which he creates and then attempts to fit over the realities of which the world is composed" (Kelly, 1955, p. 8–9). The metaphor is seductive in its clarity. The template is transparent — value-neutral, adjustable, entirely at the subject's disposal. The person, in Kelly's formulation, is an empirical scientist of the self, perpetually generating hypotheses about experience, testing them against events, revising them in light of disconfirmation. This is what Kelly called "constructive alternativism": the metatheoretical axiom that all present interpretations of the universe are subject to revision or replacement (Kelly, 1955). The slogan has a genuinely radical ring. It resonates with the Nietzschean perspectivism of *Beyond Good and Evil* — "there are no facts, only interpretations" (Nietzsche, 1886/2002, p. 119) — and with the pragmatist fallibilism of William James, for whom truth was always provisional, functional, never final. It suggests a human being structurally liberated from dogma, from determination, from the Freudian dungeon of the unconscious.

And yet, the very clarity of Kelly's program is its philosophical liability. The template metaphor reveals, on examination, a set of metaphysical assumptions so deeply embedded as to be invisible to Kelly himself. The most consequential of these is the assumption that the construct — Kelly's fundamental unit of psychological analysis — is a *bipolar* entity. Every construct, by definition, requires an emergent pole and a contrast pole: "clean" implies "dirty," "safe" implies "dangerous," "rational" implies "irrational." Kelly borrowed this structure from the Aristotelian logic of non-contradiction without pausing to ask whether bipolarity is a feature of reality or an artifact of a particular, historically situated mode of language (Bannister & Fransella, 1986). This is precisely the question that preoccupied Ludwig Wittgenstein in

Philosophical Investigations (1953/2009), where he dissolved what he called the Augustinian picture of language — the assumption that words name objects and objects correspond to words — replacing it with language-games embedded in forms of life. Kelly's constructs are, in Wittgenstein's terms, grammatical fictions that have been hypostasized into psychological facts. When a patient construes her mother as "controlling rather than loving," she is not reporting a discovery about maternal character: she is playing a particular language-game whose rules have been shaped by a history Kelly's model cannot represent. The "transparent template" is never transparent. It is always already tinted, cracked, and framed by the history of the hand that holds it — a history that Kelly, committed to an optimistic, ahistorical cognitivism, chose not to see.

It is Jacques Derrida who provides the most structurally devastating philosophical critique of Personal Construct Theory, without ever addressing it directly — which is itself instructive. In *Of Grammatology* (Derrida, 1967/1997), Derrida demonstrates that Western metaphysics has organized itself around what he terms "the metaphysics of presence": the assumption that meaning possesses a stable center, a *logos*, a foundation that precedes and grounds all differential play. Every binary opposition within this tradition — speech/writing, nature/culture, reason/madness, order/chaos — is not merely a pair of cognitive alternatives but a hierarchy encoded with ontological violence: one term is privileged, present, originary; the other is derivative, marginal, threatening. Kelly's bipolar construct reproduces this metaphysical structure in miniature with clinical precision. The "emergent pole" — the term the person identifies with, the valued self-description — is always implicitly dominant. The "contrast pole" functions as its constitutive shadow, the abject it requires in order to define itself. What Kelly clinically calls "threat" — the client's awareness that imminent comprehensive change to core constructs is approaching (Kelly, 1955, p. 489) — is structurally identical to what Derrida identifies as the anxiety generated whenever the supplement (the margin, the contrast pole, the repressed alternative) begins to contaminate and destabilize the center. The patient who is rigidly "orderly" does not merely avoid disorder: they require disorder as the abyssal Other that gives order its meaning. To deconstruct that construct is to reveal that the center was never full — that it depended for its coherence on the very thing it expelled.

Derrida's concept of *différance* — the portmanteau coined in his 1968 lecture, later published in *Margins of Philosophy* (1982), to name the double movement of differing and deferring that constitutes all signification — dissolves Kelly's model at a foundational level. If meaning is never present in any sign but always deferred along an infinite chain of differences, then the personal construct is not a cognitive template that a subject applies to reality: it is a node in a signifying network that has no outside, no Archimedean metalanguage from which either therapist or patient can observe the construing process "objectively." Kellian therapy presupposes a position of relative therapeutic stability: the therapist assists the client in "loosening" or "tightening" constructs, in experimenting with scripted "fixed-role" alternatives (Kelly, 1955). But as Derrida insists in *Writing and Difference* (1967/1978), the idea of an "outside text" — a position of interpretive neutrality that escapes the differential play it analyzes —

is precisely what deconstruction shows to be impossible. The therapist's own construct system is no less a tissue of unstable traces than the patient's. What presents itself as therapeutic dialogue is, in the Derridean reading, two competing grammatological archives negotiating asymmetric power under the fiction of collaborative inquiry. More devastatingly still, Derrida's reading of the *pharmakon* in *Dissemination* (1972/1981) — following Plato's *Phaedrus*, where writing is simultaneously poison and remedy — names the irreducible ambivalence of any curative project. Kelly's therapeutic interventions function as pharmaka: they are simultaneously remedies for cognitive rigidity and potential sources of new anxiety, new constructs to be rigidified, new hierarchies to be reinscribed under different vocabulary. The therapeutic supplement does not restore an original psychological health; it reveals that there was never an original health to restore, only an endless series of compensations, deferrals, rewritten hierarchies. This is not pessimism. It is rigor. And rigor is precisely what separates philosophical analysis from psychological optimism. If Derrida attacks Kelly's foundational binary from the outside — from the philosophy of language — Jacques Lacan attacks from the inside of the psyche itself, with equal force. Lacan's reformulation of Freud, grounded in Saussurean structural linguistics and Jakobsonian rhetoric, proposes that "the unconscious is structured like a language" (Lacan, 1977, p. 20). This claim is not a metaphor but an ontological assertion: the unconscious operates through mechanisms of metaphor (Freudian condensation) and metonymy (Freudian displacement), which are linguistic operations wholly irreducible to the intentional, conscious, bipolar construing of Kelly's person-as-scientist. Kelly, in what amounts to a remarkable act of theoretical suppression, explicitly excluded the unconscious from his framework. He was dismissive of Freudian drive-theory, substituting cognitive elaboration for libidinal depth, rationalism for the death drive (Mahoney, 1991). But this exclusion is not a theoretical choice: it is a symptom — in the strictly Lacanian sense — of the very cognitive defensiveness his theory was designed to analyze.

The Lacanian subject is constituted through lack, through the primordial splitting that language introduces into the organism. The child enters the Symbolic order — the order of law, language, and intersubjective signification — through the submission to castration, the acceptance that desire can never be satisfied, that the lost originary object (the Lacanian *objet petit a*) is structurally irrecoverable (Lacan, 1977). Kelly's "threat" and "anxiety" are, from this vantage, pale cognitive shadows of this constitutive negativity. Where Kelly sees a person anxiously aware that their construct system fails to anticipate an event (Kelly, 1955, p. 495), Lacan sees a subject structured around an irreducible void that no construct, however elaborate, complex, or flexibly revised, can fill. The therapeutic optimism of Personal Construct Theory — the belief that construct systems can always be revised, that the person-as-scientist is always already capable of alternative interpretation — is, from the Lacanian perspective, a form of ego-psychology's bad faith: the illusion that the ego, rather than the barred subject of the unconscious, is the proper seat of psychic transformation (Lacan, 1977). Slavoj Žižek extends this critique with characteristic precision in *The Sublime Object of Ideology* (1989): ideology functions precisely by offering subjects the fantasy of cognitive coherence, a construed world in which contradictions appear resolvable

rather than constitutive. Kelly's therapeutic project, in Žižek's terms, risks becoming an ideological apparatus — a technology of the self that promises the subject a more adequate, more flexible construct system, when what would be genuinely emancipatory is a confrontation with the impossibility of any such adequacy. Julia Kristeva adds another dimension in *Powers of Horror* (1982): the abject — that which the subject expels in order to constitute its own boundaries — is not a cognitive construct. It is pre-linguistic, pre-Symbolic, a horror that precedes and haunts all construing. Kelly's theory has no concept of the abject because it has no concept of the body, of disgust, of the material remainder that cognitive schemas cannot metabolize.

Martin Heidegger's *Being and Time* (1927/1962) does not mention Kelly — it predates him — but it provides the ontological framework within which the limitations of cognitive psychology become most precisely visible. Heidegger distinguishes between the *ontic* — the level of particular entities, facts, and cognitive contents — and the *ontological* — the level of Being itself, the conditions under which entities can appear at all. Psychology, for Heidegger, is irreducibly an ontic science: it describes, classifies, and proposes modifications to particular contents of human experience without ever pausing to ask what it means *to be* the kind of being that has experiences, constructs, or even a self in the first place. Kelly's constructs are paradigmatically ontic: units of a cognitive-representational apparatus, elements of an information-processing account of mind, contents of an elaborate taxonomy. What Heidegger calls *Dasein* — being-in-the-world as a structure of care, temporality, and disclosure irreducible to any subject-object model — cannot be captured by any system of templates, however flexible or experimentally minded (Heidegger, 1927/1962).

The concept of *Geworfenheit* — thrownness — is particularly illuminating in this context. Dasein finds itself always already thrown into a world it did not choose: into a language it did not invent, into cultural, historical, and bodily conditions that precede and fundamentally exceed all construing. Kelly's person-as-scientist begins construing from an assumed point of relative cognitive autonomy; Heidegger's Dasein has no such point. It is always already *in medias res*, caught in a web of involvements, moods (*Stimmungen*), and inherited traditions that cannot be stepped outside of in any methodologically meaningful sense. The *mood* — Heidegger's *Stimmung* — is not a construct: it is the pre-cognitive attunement through which the world discloses itself at all, prior to any bipolar categorization. A patient does not *construe* the world as threatening: they find themselves thrown into thrownness, already attuned to danger before any cognitive template is applied (Heidegger, 1927/1962). Maurice Merleau-Ponty deepens this critique in *Phenomenology of Perception* (1945/2012) by relocating the primary site of world-engagement not in cognition but in the body. The body maintains what Merleau-Ponty calls its "intentional arc" — a pre-reflective, habitual orientation toward the world that precedes and sediments all explicit cognitive construing. A patient's obsessive cleanliness is not primarily a cognitive construct about order and contamination: it is a bodily schema, an intercorporeal inscription, a way the flesh has learned to organize space, disgust, and proximity before any bipolar axis was consciously formulated. Kelly's cognitivism, confronted with the phenomenological body, dissolves into an elegant but radically provincial mentalism

— a psychology of the cortex that has forgotten it is attached to a body. Louis Sass, in *Madness and Modernism* (1992), draws on precisely this phenomenological tradition to argue that severe psychopathology cannot be understood as a malfunction of construct systems: it represents a fundamental alteration in the structure of being-in-the-world, a disruption of the pre-reflective background that makes construing possible in the first place. Kelly's therapeutic interventions address the furniture of consciousness; phenomenology addresses the house.

What Kelly's theory most conspicuously lacks — and what reveals most sharply the difference between psychological and philosophical ambition — is an account of power. This is the contribution of Michel Foucault, whose *Discipline and Punish* (1975/1977) and *The Order of Things* (1966/1994) demonstrate that the categories through which subjects construe themselves are not inventions of autonomous cognitive agents but productions of historically specific discursive formations: the disciplinary institutions of medicine, psychiatry, education, and law. The personal construct is never personal. It is a node in a power-knowledge network (Foucault, 1975/1977). When a patient construes herself as "irrational" versus "logical," she is not exercising constructive alternativism: she is repeating the gendered epistemological hierarchy that Western philosophy has enforced since Plato's exclusion of the sophists, and that feminist critics from Luce Irigaray to Hélène Cixous have spent decades mapping and resisting. Irigaray's *Speculum of the Other Woman* (1974/1985) demonstrates that the entire philosophical tradition has constituted Woman as the unthought supplement of Man's rational self-constitution — exactly the Derridean economy in which the supplement is indispensable yet disavowed. Kelly's theory offers women "alternative constructs" within a construct system whose very axes of evaluation — rationality, control, productive elaboration — are themselves the sediment of patriarchal epistemology. The alternative constructs available within such a system are alternatives within a prison, not alternatives to it.

Judith Butler's *Gender Trouble* (1990) brings the critique to the level of performativity. If gender is not a stable identity but a performative citational practice — "a repeated stylization of the body, a set of repeated acts within a highly rigid regulatory frame that congeal over time to produce the appearance of substance, of a natural sort of being" (Butler, 1990, p. 33) — then Kelly's fixed-role therapy is, viewed through Butler's lens, an unwitting experiment in the performative constitution of selfhood. The patient who "tries on" a scripted alternative persona is not choosing freely between cognitive templates: they are being constituted, however provisionally, by the act of performing. The Kellian assumption that a stable cognitive self precedes, selects, and applies constructs is precisely the illusion that performativity theory dissolves. There is no performer behind the performance; the performing is the becoming. Fredric Jameson, extending this argument into the cultural logic of late capitalism in *Postmodernism* (1991), observes that the contemporary subject's experience of multiplicity and cognitive flexibility is not liberation but the cultural dominant of a particular economic formation. Kelly's therapeutic ideal of the flexible, elaborative, hypothesis-testing subject mirrors, suspiciously, the demands of a post-Fordist knowledge economy for adaptable, self-revising cognitive laborers.

Psychology, in this reading, does not free the subject from ideology. It produces the ideologically optimized subject while calling the production "therapy."

Paul de Man's *Allegories of Reading* (1979) adds a further dimension: the tropes by which we represent psychological processes — and Kelly's entire framework is, fundamentally, a system of tropes, of metaphors (the scientist, the template, the construct) — are never innocent. Every psychological metaphor imports a philosophical tradition, a set of commitments, an ideology of the subject that cannot be separated from the "merely figurative" language in which it is expressed. Kelly's "person as scientist" is not a neutral heuristic: it is an Enlightenment political ontology, the liberal autonomous subject of possessive individualism, dressed in the language of epistemology. Roland Barthes would have recognized this immediately: *Mythologies* (1957/1972) demonstrated, with surgical wit, how bourgeois culture naturalizes historical contingencies as eternal facts, converting political arrangements into cognitive givens. Kelly's construct system is the mythology of cognitive liberalism: the story a particular social formation tells itself about the nature of human freedom. What emerges from this sustained philosophical audit of Kelly is not a simple refutation but something more disquieting: a deepening that reveals how shallow the original excavation was. Kelly's Personal Construct Theory retains genuine clinical value — its humanistic anti-reductivism, its insistence on the client's creative agency, its therapeutic inventiveness all represent authentic contributions to twentieth-century psychology. Neimeyer (1993) has rightly noted its influence on constructivist and narrative therapies that would follow. But philosophy — from Heidegger's fundamental ontology to Derrida's grammatology, from Lacan's structural psychoanalysis to Foucault's genealogy of the subject and Butler's performative critique of identity — reveals that Kelly was building an elegant structure on ground he had not surveyed and could not have surveyed using the tools available to a cognitive psychologist operating in the mid-century American academy.

The philosophical architecture beneath Kelly's construction is older, deeper, and more radically unstable than Kelly imagined. Derrida demonstrated that the binary opposition — Kelly's single foundational unit — is not a neutral cognitive tool but a site of constitutive metaphysical violence, the repetition of a logocentrism that Western thought has been trying, and failing, to transcend since Aristotle imposed the law of non-contradiction on the flux of experience (Derrida, 1967/1997). Lacan demonstrated that the unconscious — which Kelly expelled with barely concealed embarrassment — is not a Freudian antiquity but the very structure of subjectivity, the constitutive lack around which all construing circulates without ever arriving at its promised closure (Lacan, 1977). Heidegger and Merleau-Ponty demonstrated that the cognitive subject Kelly assumed is already preceded by a body, a mood, and a world-disclosure that no construct system can account for from within (Heidegger, 1927/1962; Merleau-Ponty, 1945/2012). And Foucault and Butler demonstrated that what Kelly called "personal" constructs are never personal: they are the disciplinary and performative effects of power-knowledge regimes that the individual inherits, reproduces, and can only partially — and never innocently — subvert (Butler, 1990; Foucault, 1975/1977). The magnificence of Derrida — and it is genuine magnificence, the magnificence of a

thinker who followed language further than language is comfortable going — is precisely this: he showed that thinking begins precisely where Kelly stopped, at the moment the construct reveals itself not as a tool the subject wields but as a text the subject inhabits. A text written in a language that was already there, already split at its origin, already shadowed by everything it had excluded in order to mean what it meant. As Barthes observed in *Mythologies* (1957/1972), language is not the instrument of thought but its precondition and its horizon. Psychology, at its most ambitious, rearranges the furniture inside language. It is philosophy that asks who built the house, on whose land it stands, whose bones are buried in the foundation — and whether the residents know they are living inside a text.

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