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Perspectives for the use of the antidiabetic drug metformin as a strategy to slow biological aging and age-related diseases

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ABSTRACT

This review focuses on the use of the antidiabetic drug metformin as one of the most studied geroprotective candidates with a well-established safety profile. The primary theories of aging and the development of age-related diseases, such as type 2 diabetes mellitus (T2DM) and Alzheimer disease, as well as the relationship between T2DM and the development of cognitive impairment, are reviewed. Metformin is hypothesized to improve cognitive function, mitigate the severity of anxiety, and reduce the risk of developing Alzheimer disease. In addition, metformin is able to decelerate the aging process and increase longevity in experiments in mice and rats. Despite being among the most frequently prescribed medications globally, with the ability to cross the blood-brain barrier and distribute to all brain regions, the precise mechanisms underlying its effects on the brain remain unclear. Studies show that metformin is able to activate 5'-adenosine monophosphate-activated protein kinase, reduce the levels of advanced glycation endproducts, and restore mitochondrial function. Moreover, metformin enhances autophagy and exerts a neuroprotective effect on neural stem cells. The findings of numerous studies indicate that metformin has antioxidant and anti-inflammatory properties.

Keywords: metformin; aging; type 2 diabetes mellitus; geroprotective agents; Alzheimer disease.

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Перспективы применения противодиабетического средства метформина как способ замедления биологического старения и возраст-ассоциированных заболеваний

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АННОТАЦИЯ

В обзоре рассматриваются вопросы применения противодиабетического средства метформина как одного из наиболее исследованных кандидатов на роль геропротектора с доказанным профилем безопасности. Проанализированы основные теории старения и развития возраст-ассоциированных заболеваний, таких как сахарный диабет и болезнь Альцгеймера, взаимосвязь сахарного диабета 2-го типа с развитием когнитивных нарушений. Предполагается, что метформин улучшает когнитивные функции и уменьшает выраженность тревожного состояния, снижает риск развития болезни Альцгеймера, способен замедлять процессы старения и увеличивать продолжительность жизни в экспериментах у мышей и крыс. Несмотря на то что метформин является одним из наиболее часто назначаемых препаратов в мире, проникает через гематоэнцефалический барьер и распределяется по всем отделам мозга, механизм, лежащий в основе его воздействия на мозг, до конца не изучен. Исследования показывают, что метформин способен активировать 5'АМФ-активируемую протеинкиназу, снижая концентрацию конечных продуктов гликирования и восстанавливая функции митохондрий, усиливает аутофагию, оказывая нейропротекторное действие на нервные стволовые клетки. Результаты многих исследований указывают на то, что спектр полезных эффектов метформина включает антиоксидантные и противовоспалительные свойства.

Ключевые слова: метформин; старение; сахарный диабет 2-го типа; геропротекторы; болезнь Альцгеймера.

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BACKGROUND

According to the United Nations Population Fund, in 2022, the global population aged ≥65 years reached 771 million [1, 2]. A similar trend has been observed in Russia, where one in every four citizens has reached retirement age [3]. Relevant projections indicate that, by 2030, the number of elderly individuals worldwide will increase to 994 million, and that, by 2050, it will reach 1.6 billion, constituting 12% and 16% of the global population, respectively [1, 4]. These reports suggest a global trend toward an aging population.

Aging is a natural physiological process mediated by numerous biological and genetic pathways that influence lifespan and quality of life [4, 5]. However, the concern is not aging, but rather its association with a wide range of age-related diseases, including neurodegenerative disorders (e.g., dementia, Alzheimer's disease [AD]), cardiovascular diseases, immune dysfunction, and metabolic disorders such as diabetes mellitus (DM) [5–7]. These conditions are frequently accompanied by behavioral disturbances, including aggression, heightened anxiety, depression, apathy, and social withdrawal, which trigger even mild cognitive changes into complex, multifaceted challenges that significantly affect various other aspects of human life [7]. For instance, social withdrawal can impair an individual's ability to analyze information, respond appropriately to others' opinions and behaviors, and may result in suspiciousness, anxiety, and complete social isolation. Similarly, cognitive impairments can have profound consequences, particularly, on learning and memory [7]. Usually in the early stages, cognitive decline often spares long-term memories and previously acquired knowledge; however, severely affects short-term memory, making it difficult for individuals to recall recent actions or acquire new information. As this condition progresses, long-term memory also deteriorates. As a result, patients may fail to recognize close relatives, lose access to their vocabulary, and experience impairments in skills such as reading and writing, which further exacerbates behavioral symptoms, such as aggression and apathy [7]. Considering these challenges, substantial efforts are directed toward the development of pharmacological interventions that are aimed at improving both the lifespan and quality of life during natural biological aging [8]. Despite the complex and multifactorial nature of aging, a few key mechanisms have been identified, including genomic instability, increased mutation rates in the population, telomere dysfunction, mitochondrial impairment, reduced neuroplasticity, and stem cell depletion [4].

Metformin is a promising pharmacological candidate in this domain. It is also the most widely used oral antidiabetic drug and is considered an essential medicine. Beyond its well-established hypoglycemic effects, metformin exhibits anti-inflammatory and antioxidant properties as well as reduces the production of β-amyloid, the key component of amyloid plaques in AD [8, 9].

According to the World Health Organization (WHO), DM is among the top ten leading causes of mortality across the world. By 2030, the global prevalence of type 2 DM is projected to rise to 7,079 cases per 100,000 people [10, 11]. Currently, approximately 120 million individuals worldwide use metformin, accounting for approximately 40% of all antidiabetic prescriptions [12].

Owing to its multi-targeted action mechanism, favorable safety profile, and efficacy, metformin is emerging as a promising geroprotective candidate for slowing the process of biological aging and neurodegeneration [12].

AGING AND AGE-RELATED DISEASES

Aging is a key stage of ontogenesis, leading to irreversible qualitative changes in an organism's functional activity at all levels—cellular, tissue, and organ [5, 13]. Aging shares certain pathological mechanisms with various diseases, and can be classified as a complex biological process rather than a disease [4]. The etiology, pathogenesis, and potential interventions for aging remain open to scientific enquiry. Meanwhile, aging triggers the onset of age-related diseases, affecting key physiological systems, including the nervous, endocrine, cardiovascular, and immune systems. This aspect underscores the interconnection between aging and disease, considering that the prevalence of chronic conditions is significantly higher among the elderly. In addition, conditions such as hypertension, atherosclerosis, and DM can accelerate pathological premature aging [4, 5, 14]. Aging includes two primary outcomes: normal aging—physiological age-related changes that occur even in the absence of any disease and represent a natural ontogenetic development; pathological aging—characterized by a reduction in the number of healthy life years, showing the association between the overall process of aging and age-related disease [14, 15].

Currently, no single dominant cause of pathological aging has been identified, albeit several theoretical models have been proposed [16]. One of the most widely accepted notions is the metabolic waste accumulation theory, which suggests that metabolic reactions within cells generate a significant number of byproducts, which disrupt homeostasis both within individual cells and across the entire organ systems. These accumulations occur intracellularly (e.g., hyperphosphorylated tau protein) and extracellularly (e.g., β-amyloid) [16].

Considering the marked role of the mitochondria in metabolic processes—and, consequently, in aging—several researchers identify mitochondrial dysfunction, which may result from an increase in highly reactive oxygen species (ROS), as one of the key causes of aging [16]. Elevated ROS levels contribute to damage in mitochondrial DNA (mtDNA) and other cellular components, thereby considerably increasing the risk of premature aging. This hypothesis was originally proposed by Denham Harman in 1954 and is now known as the free radical theory of aging [14, 17].

Closely related to this theory is the concept based on the hyperactivation of inflammatory processes in the body. According to this hypothesis, the occurrence of age-related

changes in immune cell populations stimulates innate immunity and suppresses adaptive immunity, resulting in decreased production of T and B lymphocytes alongside an increase in the immunoglobulin levels, which are characterized by the high autoantigenic reactivity and polyspecificity. The functional activity of these immunoglobulins is weakly regulated by lymphocytes and depends primarily on the relative levels of proinflammatory cytokines—interleukin (IL)-1, IL-6, IL-18, tumor necrosis factor-alpha (TNF-α), and C-reactive protein. Similar to free radicals, these inflammatory markers tend to increase with age [17–19]. The combination of these factors can trigger a systemic chronic inflammatory process known as inflammaging (a blend of "inflammation" and "aging"). Inflammaging is recognized as an indicator of age-related changes and a major risk factor for age-associated diseases, including AD, Parkinson's disease, atherosclerosis, hypertension, type 2 DM (T2DM), and even cancer [16]. The development of these pathologies may, to an extent, be driven by inflammatory responses and accompanying factors, including hormonal imbalances, oxidative and genotoxic stress, and alterations in the gut microbiota composition [13, 18–21].

Considering that aging is a natural stage of ontogenesis, genomic instability contributes to the development of pathological aging and/or age-associated diseases. Past studies have identified numerous genes that directly or indirectly influence aging, namely, *GSTM1, GSTT1, NAT2, CYP2D6,* and *CYP17* of the detoxification systems; *APOE* in the lipid metabolism; *IGF* and *rIGF* in the carbohydrate metabolism; *IFNγ* and *IL10* in immune responses; *TNF-α* and *TGF-β* related to growth factors [15, 21, 22] Polymorphisms in these genes can alter xenobiotic metabolism, initiate inflammatory responses, promote apoptosis, and disrupt vascular integrity and tissue nutrition. In combination with environmental factors, such genetic variations often induce the onset of age-related diseases [22]. For example, *APOE* polymorphism (E2 allele) regulates the balance of very low-density lipoproteins and is predominant in long-lived individuals, whereas *APOE* (E4 allele) polymorphism increases the risk of atherosclerosis, T2DM, and AD [15, 21].

Equally important are genes involved in DNA replication and repair. In 1961, University of California professor Hayflick discovered that normal human cells have a limited capacity for division, a phenomenon now known as the Hayflick limit, which forms the basis of the telomere theory of aging [21]. Telomeres are nucleotide sequences located at the distal ends of chromosomes that progressively shorten with each cell division. When telomeres reach a critical length, any further division becomes impossible [21–23]. The enzyme telomerase plays a key role in maintaining the telomere length. This ribonucleoprotein complex can add new nucleotide sequences to a DNA strand at the telomeres, thereby preserving the cell's replicative capacity [22, 23]. The appeal of the telomere theory of aging lies in its strong experimental evidence from both *in vitro* and *in vivo* studies, suggesting that increased telomerase expression can extend the replicative potential of stem cells and prolong the lifespan in mice [21].

A comprehensive perspective on aging synthesizes the most relevant theories, considering aging as both an intrinsic part of ontogenetic programming and a consequence of cumulative cellular and systemic damage. Although aging itself is not classified as a disease, it inevitably results in age-associated disorders such as T2DM and AD, which, in turn, accelerate the aging process.

ASSOCIATION OF TYPE 2 DM WITH COGNITIVE IMPAIRMENT AND AD

According to the WHO, DM affects 422 million people worldwide and is responsible for more than 1 million deaths annually [24]. This increasing prevalence of T2DM is particularly alarming, and more than 90% of all diabetes cases are classified as T2DM. As such, the global prevalence of T2DM is expected to rise further by 2030 [11].

T2DM is a chronic progressive disease characterized by relative insulin deficiency and insulin resistance, which result in enhanced gluconeogenesis and impaired glycogen synthesis [25]. Owing to its metabolic nature and the complex pathophysiological mechanisms—including altered insulin sensitivity, dysregulated insulin synthesis, lipid and carbohydrate metabolism disorders, vascular damage, chronic inflammation, and gut microbiota imbalance—T2DM can be classified as an age-associated disease [11, 24, 25]. This heterogeneous pathogenic process inevitably involves comorbid conditions. Even mild episodes of hypo- or hyperglycemia contribute to early-onset dementia or exacerbate cognitive decline. Notably, AD is often referred to in the scientific literature as "type 3 diabetes" [25].

For instance, insufficient insulin production by the pancreatic islets of Langerhans in DM leads to chronic hyperglycemia. Prolonged hyperglycemic episodes can induce protein and lipid glycation, increased generation of free radicals, and the onset of inflammaging [25]. Insulin crosses the blood—brain barrier and is distributed throughout different brain regions, particularly the hypothalamus and cerebral cortex. In addition, small amounts of insulin are synthesized within the brain. Many individuals with T2DM exhibit insulin resistance, which is often accompanied by chronic hyperinsulinemia and subsequent episodes of hypoglycemia [26, 32]. Hypoglycemia shifts the brain's energy metabolism toward ketone body utilization, potentially resulting in neurotoxicity, memory impairment, and cognitive dysfunction [27–31].

The development of insulin resistance in T2DM is linked to an increased activity of glycogen synthase kinase 3β (GSK-3β)—an enzyme responsible for glycogen synthesis. Elevated GSK-3β activity stimulates β-amyloid production and promotes tau protein hyperphosphorylation, both of which play a significant role in AD pathogenesis [33, 34].

Aging is an inevitable stage of ontogenesis, although it is not the primary reason for seeking medical attention or premature mortality. Pathologically accelerated aging, is often driven by age-associated diseases that result in significant

deterioration of both the quality-of-life and the lifespan [35, 36]. Slowing the biological aging process involves identifying strategies to preserve individuals' health and functional capacity, aiming to ultimately extend the quality-adjusted life years.

METFORMIN AS A CANDIDATE FOR GEROPROTECTION

The concept of combating aging is a priority in both Russian and global medicine practices, which has prompted numerous scientific institutes to focus on researching and developing drugs that can prevent physiological aging or slow down the progression of age-associated diseases through the use of geroprotectors [37–39]. To date, numerous compounds have been identified that target diverse mechanisms of cellular aging, including growth factor-signaling pathways, carbohydrate and lipid metabolism, insulin-dependent processes, epigenetic factors, and others [35–37, 40].

One of the most well-studied geroprotector candidates with a proven safety profile is metformin, which is widely used for T2DM treatment. Metformin is included in the list of essential medicines and is prescribed in more than half the T2DM cases worldwide [8, 9, 12].

The antidiabetic effects of metformin are primarily owing to its ability to reduce hepatic glucose production, inhibit glucose absorption from the gastrointestinal tract, and increase insulin-stimulated glucose uptake in skeletal muscles and adipocytes by activating GLUT-4 phosphorylation [41].

According to reports, metformin's primary glucose-lowering effect and its low incidence of hypoglycemic episodes can be achieved through the activation of adenosine monophosphate-activated protein kinase (AMPK) in the intestine, as well as the stimulation of glucagon-like peptide synthesis in enteroendocrine K-cells, which indirectly regulates hepatic glucose production [41].

The mechanisms underlying metformin's potential as a geroprotector and a therapeutic agent for age-related neurodegenerative diseases remain unclear. Most studies in this area focus on patients with T2DM and diabetic animal models. This is because diabetes induces neurodegeneration through the overproduction of advanced glycation end products (AGEs). AGEs are proteins or lipids that undergo glycation by carbohydrates. They may contribute to aging as well as to the development and progression of degenerative diseases, atherosclerosis, cancer, and other age-related disorders [42]. AGE accumulation accelerates neuronal stem cell death and disrupts mitochondrial function by suppressing the AMPK activity and its downstream signaling pathways. AMPK plays a critical role in regulating the intracellular systems, including lipid metabolism, glucose uptake, and mitochondrial biogenesis [42, 43]. Metformin mitigates AGE-induced effects, restores mitochondrial function, and exerts neuroprotective effects on neural stem cells by activating AMPK, which is metformin's primary therapeutic target [43]. Moreover, the baseline AMPK activity is essential for normal autophagy function [44]. Autophagy is the lysosomal-degradation process responsible for recycling damaged cellular components and eliminating damaged organelles and protein aggregates. Defective autophagy leads to the accumulation of pathological protein aggregates, ultimately inducing neuronal degeneration [45]. Metformin enhances autophagy via AMPK activation, thereby regulating the expression of abnormal proteins. This effect may play a crucial role in neurodegenerative processes [45].

Metformin alleviates oxidative stress by lowering the malondialdehyde levels and enhancing the superoxide dismutase activity [46]. Oxidative stress, along with the subsequent increase in its markers, such as oxidized lipids and proteins, plays a key role in neurodegeneration and aging. Relevant findings suggest that the beneficial effects of metformin include anti-inflammatory properties [46].

Metformin has been shown to reduce the TNF-α, IL-1, and IL-6 levels. Considering that these cytokines can cross the blood—brain barrier, metformin may help prevent neuroinflammation [25, 47]. Both inflammation and oxidative stress are the key contributors to T2DM pathogenesis, neurodegenerative diseases, and cellular-aging processes [47].

As metformin can rapidly cross the blood–brain barrier and is distributed across various brain regions [12, 47], particularly the hippocampus and prefrontal cortex, it can slow the progression of neurodegenerative processes and cognitive dysfunction, which are closely associated with oxidative stress and inflammation [25]. In addition, one of metformin's key action mechanisms is its ability to inhibit acetylcholinesterase (AChE)—the enzyme responsible for acetylcholine degradation. Acetylcholine is a neurotransmitter essential for learning and memory processes [48, 49]. Several *in vivo* studies have examined metformin's effects on the AChE activity [49, 50]. For instance, chronic metformin administration (30 days) at a dose of 500 mg/kg has been shown to improve cognitive function and reduce AChE activity in a T2DM rat model [51].

Metformin has garnered attention as a cognitive function modulator in T2DM patients not solely based on its AChE-inhibitory properties. The brain tissues are highly sensitive to glucose deficiency, which is compensated by ketone body metabolism activation [51, 52]. Metformin can enhance glucose uptake by the brain tissues and thereby reduce insulin resistance; this property may further contribute to its neuroprotective effects [50–52].

Metformin is classified as a geroprotector primarily owing to its potential to delay the onset of age-associated diseases. As previously discussed, T2DM is a significant risk factor for dementia, including AD. Most studies have indicated that metformin may lower the risk of developing dementia or AD in T2DM patients [53, 54].

However, some studies have shown that metformin may increase the risk of AD [55]. Preclinical studies have also demonstrated the positive effects of metformin on the cognitive function of AD animal models [56, 57]. One proposed

mechanism is its ability to reduce the β-amyloid levels, amyloid precursor protein, and tau protein [25, 56].

Owing to its broad spectrum of beneficial effects, metformin is a promising candidate for the treatment of neurodegenerative diseases and associated dementias.

In recent years, data on the effects of metformin on a healthy organism during physiological aging, particularly when administered in low (subtherapeutic) doses have been obtained. Aging inevitably leads to cognitive decline and age-related memory deficits [25], which may also be accompanied by behavioral changes, such as increased levels of anxiety [58].

Past studies have demonstrated that, in mice receiving metformin at relatively low doses, age-related changes were delayed, and the lifespan was extended [58]. Furthermore, metformin at low doses has been shown to improve cognitive functions in experimental models [25].

The beneficial effects of metformin in subtherapeutic doses have been confirmed in aged animals. In a 36-day study on elderly rats, metformin administration led to improved spatial memory performance in the Morris water-maze test [49]. As age-related declines in spatial learning ability are largely attributable to functional and morphological changes in the hippocampus [59], metformin can enhance hippocampal neurogenesis [50, 59, 60] and inhibit AChE (thereby potentiating acetylcholine effects in hippocampal cholinergic synapses) [25]. Finally, neurotrophic effects of metformin cannot be overlooked—the drug enhances brain-derived neurotrophic factor expression via the AMPK/CREB pathway activation, which may play a key role in its memory-enhancing properties [60].

Metformin's ability to reduce anxiety-like behavior in patients with T2DM has led researchers to explore its potential anxiolytic effects. Past studies have demonstrated the high efficacy of the drug, even at subtherapeutic doses [61]. Specifically, metformin reduces anxiety-like behavior in rodents. Unlike classical benzodiazepine tranquilizers, anxiolytic effects of metformin develop rapidly without inducing tolerance. This effect is primarily attributable to its ability to enhance the GABA A receptor expression and membrane transport in the hippocampus, partially via AMPK activation [61]. Considering these properties of metformin and it's well-established safety profile, some researchers suggest that metformin may serve as a safer alternative to diazepam—one of the most commonly prescribed anxiolytics [62].

These findings are particularly significant for anxiety management in older adults, as benzodiazepine anxiolytics in this population are often associated with serious side-effects [61].

Despite metformin's potential benefits in age-related disease management, its use is not without risks. The possible side-effects include lactic acidosis, gastrointestinal disturbances (e.g., abdominal discomfort and diarrhea, reported in 20%–30% of patients), and vitamin B12 deficiency [62–64].

The Targeting Aging with Metformin (TAME) trial is a multicenter, randomized, double-blinded, placebo-controlled six-year study involving adults aged between 65–79 without diabetes. The TAME trail aims to provide insights into metformin's potential for reducing the risk of age-related diseases and evaluating its efficacy in slowing the aging process [65].

Metformin's favorable safety profile positions it as a promising geroprotective candidate, with the potential to slow down pathological aging, improve the quality-of-life, and delay the onset of age-related diseases, including T2DM, neurodegenerative disorders, dementia, and other age-associated conditions.

ADDITIONAL INFORMATION

Authors' contribution. A.Z.H. — collection and processing of materials, writing the review; I.I.S. — writing the review, analyzing and editing the review; D.O.N. — writing the review, R.I.M. — consultation in writing the review. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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