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PERSPECTIVE ARTICLE

Metformin and biological aging: are there implications for Alzheimer's disease?

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Abstract

An aging population with exponentially growing cases of Alzheimer's disease represents a public health problem followed by a medico-social challenge with an economic burden, reaffirming the importance of Alzheimer's disease prevention. Accumulating evidence shows that there is a biological basis for metformin's effect on the brain. Metformin's pleiotropic mechanisms are thought to contribute to its efficacy. However, further development is needed to fully realize its preventive potential. Ongoing efforts must address challenges such as the optimal dose of metformin to accelerate a protective effect, tolerance and bioavailability, and the prevention of adverse events. Currently available findings only show associations rather than proven causal effects, and only completed randomized controlled trials can validate the clinical benefit of metformin. Further research is needed to answer the question of metformin's implications for Alzheimer's disease.

Keywords: Biological aging; Alzheimer's disease; Metformin

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1. Introduction

Biological aging is a universal, natural, complex phenomenon, characterized by the changes in the body that commonly occur as people age.[1] Aging affects different systems and organs, including the brain.

2. Pathogenesis of Alzheimer's disease

More than 57 million people suffer from dementia all over the world, with approximately 10 million new cases diagnosed annually, of which 60%–70% are patients with Alzheimer's disease.[2] These exponentially growing cases in an aging population represent medical and social challenges and reaffirm the importance of preventing Alzheimer's disease.[3]

Alzheimer's disease, as a neurocognitive disorder, manifests as progressive cognitive deterioration and is characterized by beta-amyloid deposits and neurofibrillary tangles in the cerebral cortex and subcortical gray matter, leading to loss of synapses and neurons with subsequent localized atrophy of the brain.[4] Even though the clinical entity of Alzheimer's disease has been known for 120 years, its pathogenesis remains incompletely understood. Different hypotheses exist. The amyloid hypothesis proposes that the progressive accumulation of beta-amyloid in the brain initiates a complex cascade of events resulting in loss of neuronal synapses, neuronal cell death, and progressive neurotransmitter deficiency contributing to the development of clinical symptoms of

dementia.[4] Other theories include a sustained immune response with inflammation and glucose metabolism derangement, respectively. Moreover, prion mechanisms have been identified in Alzheimer's disease.[4] In prion diseases, a normal protein on the surface of brain cells, called the prion protein, misfolds into a pathogenic form named a prion. The prion then causes other prion proteins to misfold similarly, leading to a significant increase in the number of abnormal proteins and, consequently, brain damage.[4] In Alzheimer's disease, beta-amyloid in cerebral amyloid deposits and tau protein in neurofibrillary tangles are believed to have prion-like, self-replicating properties.[4]

At present, the challenge is the proper selection of agents with high preventive potential for Alzheimer's disease. Nowadays, great interest lies in repurposing existing, approved drugs, representing a time-saving, cost-effective approach.[5]

3. Pleiotropic mechanisms of metformin

Metformin could be discussed in this light, taking into account its time-tested use in diabetology as an oral antidiabetic drug. The hypoglycemic properties of metformin are well studied and well confirmed and are beyond the scope of this paper, but in recent years more attention has been paid to its pleiotropic effects, such as anti-inflammatory, autophagy-promoting, antioxidative, antiangiogenic, antifibrotic, neuroprotective, and anti-senescent,[6] exploring new therapeutic targets. Metformin also regulates the cellular processes implicated in aging: dysregulated nutrient sensing, mitochondrial dysfunction, loss of proteostasis, telomere attrition, and genomic instability.[6] These mechanisms are related to pathways involved in the pathophysiology of Alzheimer's disease.[6]

Accumulating evidence indicates that metformin exerts a geroprotective effect through multiple interconnected mechanisms.[7] These include the activation of AMP-activated protein kinase (AMPK), inhibition of the mechanistic target of rapamycin (mTOR), reduction of oxidative stress, modulation of mitochondrial biogenesis, and attenuation of low-grade systemic inflammation. These effects target key hallmarks of aging, such as cellular senescence, dysregulated nutrient sensing, and alterations in proteostasis.

The protective effects of metformin are realized through activation of key protein molecules, such as AMPK, liver kinase B1 (LKB1), mTOR, sirtuin (SIRT) 1 and SIRT3, nuclear factor erythroid 2-related factor 2 (Nrf2), Forkhead box O3 (FOXO3), and growth differentiation factor 15 (GDF15).[6,8-10] These effects have been reported to involve the key genes: *PRKAA1* and *PRKAA2*, encoding the catalytic subunits of the AMPK protein; *STK11*, encoding the LKB1 protein; *MTOR*, encoding the mTOR protein; *SIRT1* and *SIRT3*, encoding sirtuin enzymes; *NFE2L2*, encoding the Nrf2 protein; *FOXO3*, encoding the FOXO3 transcription factor; *GDF15*, encoding the GDF15 stress-response cytokine.[10,11]

Metformin offers numerous benefits in sporadic Alzheimer's disease: it reduces beta-amyloid levels and tau protein hyperphosphorylation, increases neuronal density, and mitigates histopathological changes in the hippocampus.[12] It also enhances neurogenesis in experimental Alzheimer's disease by upregulating *Dcx* and *Ki67* transcription in the hippocampus and increasing levels of neurotrophic factors. Furthermore, metformin elevates AMPK levels and promotes its phosphorylation, enhances synaptic function by increasing synapsin-1 and dopamine, and improves cholinergic function through several mechanisms—increasing acetylcholine levels and choline acetyltransferase activity while simultaneously reducing the activity of acetylcholinesterase and butyrylcholinesterase in various models of sporadic Alzheimer's disease.[12]

The systematic review by Maciejczyk and Blecharz-Klin[13] described the neuroactive properties of metformin, including its effects on neurotransmission, neuroprotection, and neuroinflammatory pathways, and reports that preclinical studies confirm neuroprotective and neuromodulatory effects of metformin in models of Alzheimer's disease.

4. Clinical findings

A pilot, double-blind, placebo-controlled, randomized clinical trial evaluating the safety and efficacy of metformin (1000 mg twice daily over 12 months) in 80 overweight or obese participants free of diabetes with amnestic mild cognitive impairment was conducted by Luchsinger *et al.*[14] The results demonstrated that metformin improves total recall of the selective reminding test; however, 7.5% of participants did not tolerate metformin, experiencing gastrointestinal symptoms. Doses of 500 mg/day, 1,000 mg/day, 1,500 mg/day, and 2,000 mg/day were tolerable for 15%, 35%, 32.5%, and 10% of participants, respectively.

Another randomized placebo-controlled crossover study investigated metformin impact in 20 patients with mild cognitive impairment or mild dementia due to Alzheimer's disease and without diabetes, who received 8 weeks of metformin and eight weeks of placebo.[15] The authors reported that metformin was safe, well-tolerated, measurable in cerebrospinal fluid, and associated with improved executive functioning, with trends suggesting improved learning/memory and attention. A study conducted as part of the Alzheimer's Disease Neuroimaging

Initiative compared the cognitive performance of 810 individuals with mild cognitive impairment, categorized into groups based on the presence of type 2 diabetes and/or metformin use.[16] It has been shown that patients with diabetes receiving metformin during the early stages of Alzheimer's disease exhibited better cognitive performance and cerebrospinal fluid biomarker profiles; the treatment was associated with higher levels of beta-amyloid and lower levels of tau protein and phosphorylated tau protein.

Another study, based on data from a US administrative database (OPTUM HER), compared the risk of developing dementia in 96,140 patients initiating metformin and 16,451 patients initiating sulfonylureas (mean participant age: 66 years).[17] Over a five-year follow-up period, using inverse probability of treatment weighting to adjust for confounding by indication, the risk of dementia was found to be lower in those taking metformin compared to those taking sulfonylureas (HR = 0.80; 95% CI: 0.73–0.88).

A study based on data from Taiwan's National Health Insurance Research Database evaluated the risk of developing dementia in 31,384 pairs of patients with type 2 diabetes who differed in their adherence to metformin therapy and were matched by propensity score over a 5-year follow-up period.[18] Adherence to metformin therapy was associated with a lower risk of developing dementia (HR = 0.72; $p < 0.001$). The beneficial effects of metformin on cognitive function in patients with diabetes, manifested as improvements in short-term memory, enhanced executive function, and a reduced risk of developing dementia, were documented in two studies.[19,20]

Results from a nested case-control study[21] on patients with diabetes revealed no evidence that metformin use, in general, increases the risk of Alzheimer's disease, and that long-term and high-dose metformin use was associated with a lower risk of incident Alzheimer's disease in older people with diabetes.

In contrast to previous studies, in patients with newly diagnosed diabetes, a significantly increased Alzheimer's disease risk (adjusted odds ratio = 1.50) with longer diabetes duration and with higher cumulative daily defined doses per day was evidenced in a retrospective, observational, nested case-control study from a Korean National Health Insurance Service Diabetes Mellitus cohort.[22] Another cohort study also reported an increased risk of Alzheimer's disease (HR: 2.13, 95% CI = 1.20–3.79) and vascular dementia (HR: 2.30, 95% CI = 1.25–4.22).[23]

A cohort study involving 210,237 individuals with type 2 diabetes—using data from the UK Clinical Practice Research Datalink[24]—demonstrated that patients not receiving glucose-lowering medications (n = 95,609) had a lower risk of developing dementia compared to those who initiated metformin therapy (n = 114,628) (adjusted HRs of 0.88 [95% CI: 0.84–0.92] and 0.90 [0.84–0.96], respectively, based on propensity score-adjusted analysis); this was observed despite the fact that individuals not receiving pharmacological treatment had better glycemic parameters (HbA1c levels).

Recently, a few studies comparing the risk of Alzheimer's disease in patients with diabetes treated with metformin or glucagon-like peptide-1 receptor agonists, or sodium-glucose cotransporter-2 inhibitors were conducted.[25-28] The general consensus is that metformin may be associated with a higher relative risk of dementia, particularly Alzheimer's disease and non-vascular types.

Multiple systematic reviews and meta-analyses evaluated metformin's effect on reducing dementia risk.[29-36] The systematic review by Slouha *et al.*[29] presents specific findings concerning metformin, such as a trend that patients using it for more than six years were significantly less likely to develop cognitive impairment, and that longer exposure may reduce the risk and incidence of dementia. The review by Khaliq *et al.*[30] reports that metformin use in diabetic patients was associated with a significantly lower risk of cognitive impairment and dementia, suggesting neuroprotective effects. The umbrella review by Kuate Defo *et al.*,[31] based on 100 systematic reviews and 27 cohort/case-control studies, found that metformin was associated with a significant reduction in dementia risk, reporting a risk ratio of 0.83 (95% CI 0.71–0.96) in the meta-analysis.

Mahoon *et al.*[32] have found that metformin demonstrated improvements in episodic memory and selective executive outcomes, particularly in early-stage disease and metabolically vulnerable groups, suggesting a potential benefit that depends on disease stage and metabolic status. Cimini *et al.*[33] discuss a large pooled analysis of 41 observational studies finding an overall 11% reduction in the risk of all-cause dementia among metformin users, reinforcing the drug's potential protective effects in people with diabetes, and systematic reviews reporting hazard ratios typically ranging from 0.67 to 0.92 for cognitive impairment or dementia in metformin users, noting that some meta-analyses failed to show significant protection specifically against Alzheimer's disease. The latest systematic review and network meta-analysis also evidenced that metformin significantly reduced the overall incidence of dementia with an odds ratio of 0.79.[34] Another systematic review and network meta-analysis by Kato *et al.*[35] stated that no significant association was found between the use of metformin and the risk of dementia. Earlier, Majidazar *et al.*[36] performed an umbrella systematic review of studies published up to

August 25, 2021 and concluded that metformin was not associated with cognitive improvement in patients with Alzheimer's disease.

Results from clinical trials are mixed. While some studies show a benefit, others have not found a significant effect of metformin on cognitive function in patients with Alzheimer's disease. This discrepancy may be due to several factors: the stage of disease at which treatment is initiated; the presence of genetic risk factors; the influence of comorbidities and concomitant medications; the potential for metformin to cause vitamin B12 deficiency, which itself can affect cognitive function. Metformin may modulate biological aging: altering nutrient sensing through AMPK activation and mTOR inhibition; enhancing autophagy; reducing oxidative stress; and suppressing inflammation.

5. Systemic safety concerns

Systemic safety concerns with oral pharmacotherapy with metformin have a strong body of clinical evidence. It is certainly becoming recognized that metformin has the potential to cause systemic adverse events, such as metabolic (vitamin B12 and folate deficiency, lactic acidosis), renal (renal failure), and gastrointestinal (nausea, diarrhea, and loss of appetite).[37]

It is noteworthy that at present, long-term therapy with metformin in the aging population suffering from multimorbidity, especially in persons with diabetes, causes safety concerns. Importantly, one of the most common causes of chronic kidney disease and renal disorders, manifesting as urinary alterations, proteinuria, or kidney failure, is diabetes.[38]

The physiological decline of renal function in older adults requires a pharmacovigilant approach to the risk of lactic acidosis. Clinical guidelines advise extreme caution or stopping metformin in patients aged 80 and older, or when the estimated glomerular filtration rate falls below safe thresholds (usually under 30 to 45 mL/min).[39] Metformin prescription in older adults deserves special attention, given multimorbidity and polypharmacy.

Taken together, for older adults with multiple comorbidities, metformin carries known risks, including lactic acidosis, gastrointestinal intolerance, dose constraints related to renal function, and drug-drug interactions.

6. Ongoing clinical trials

A protective effect of metformin in delaying the onset and slowing the progression of Alzheimer's disease is under evaluation in the ongoing clinical trials: MetMemory (Preventing Cognitive Decline with Metformin)[40] and MAP (Metformin in Alzheimer's Dementia Prevention).[41]

MetMemory clinical trial[40] was initiated in 2022 and designed to evaluate the impact of Metformin XR, 500–2,000 mg, on cognitive decline, neuroimaging, and biomarkers in 242 persons with mild cognitive impairment and without diabetes mellitus over three years. The study will be completed by the end of 2027.

Another multi-center placebo-controlled, randomized clinical trial MAP[41] recruited 326 overweight or obese patients with early and late mild cognitive impairment, who have no history of diabetes and metformin use, aged 55–90 years. Patients are randomized 1:1 to long-acting metformin (reduced-mass Glucophage XR) or identical placebo. All patients will be followed up at 6-month intervals: baseline, 6 months, 12 months, and the final 18 months. MAP trial will start with a screening phase, followed by randomization, and a titration period during which metformin/placebo dose will be titrated from one tablet (500 mg per day) to four tablets (2,000 mg per day), increasing by 500 mg (one tablet) every 10 days. Participants will remain in the randomized controlled trial, taking the tolerated dose, and will be included in the analysis based on the intention-to-treat principle. Neuropsychological examination, clinical interviews, physical examination, and blood sampling will be performed at baseline and every 6 months. Brain magnetic resonance imaging, brain amyloid positron emission tomography, and tau positron emission tomography will be conducted in approximately half of the participants (186) twice, at baseline and after the final study visit at month 18. The rates of change in the Free and Cued Selective Reminding Test as a primary outcome measure, and as a secondary outcome measure, the rates of change in global cognitive performance, measured with the Alzheimer's Disease Cooperative Study Preclinical Alzheimer's Cognitive Composite; in neurodegeneration, ascertained as cortical thickness in areas affected by Alzheimer's disease on brain magnetic resonance imaging; in whole-brain beta-amyloid standardized uptake value ratio; in tau standardized uptake value ratio in a composite brain region comprising medial and inferolateral temporal cortex; in serum biomarkers of Alzheimer's disease will be compared between treatment groups. The study will be completed by the end of April of 2027.

7. Limitations and future outlook

Accumulating evidence has shown that there is a biological basis for the effect of metformin on the brain. The pleiotropic mechanism of metformin is thought to contribute to its efficacy. However, continued development is necessary to fully utilize its preventive potential. Ongoing efforts must address challenges such as the optimal dose and route of delivery to accelerate protective effects, improve tolerance and bioavailability, and prevent undesirable adverse

events, especially in elderly patients with multimorbidity. Pharmacokinetics of oral metformin have shown that the drug, hydrophilic by nature, has poor blood–brain barrier penetration and only 10%–20% of the drug reaches the central nervous system.

Intranasal delivery, utilizing signaling pathways from the olfactory and trigeminal nerves to the brain, is a non-invasive method that enables the direct entry of substances into the brain without crossing the blood-brain barrier.[42] This allows for the direct and efficient transport of drugs from the nasal cavity to the brain, ensuring targeted action with minimal entry into the systemic circulation, while also reducing the risk of systemic side effects and toxicity.[43]

Future research, taking into account the challenges of bioavailability, should be aimed at the development of lipid-based or polymer-based nanocarriers, or an intranasal delivery route[44] of metformin in order to improve efficiency. With ongoing advancements, metformin as an affordable drug deserves attention.

8. Conclusion

The relationship between metformin and biological aging is an area of active research. Metformin influences multiple hallmarks of aging, including mitochondrial dysfunction, cellular senescence, epigenetic alterations, telomere attrition, and genomic instability. The primary molecular target of metformin is AMPK. Activation of AMPK leads to downstream effects such as enhanced mitochondrial biogenesis, stimulation of autophagy, and inhibition of mTOR signaling. At present, available findings show associations rather than proven causal effects, and only completed randomized controlled trials can validate metformin's clinical benefit. It is noteworthy that the effects of metformin in healthy individuals without diabetes are not yet fully established; individual genetic differences may influence how a person responds to metformin. The long-term safety of metformin as an anti-aging intervention requires additional investigation. Further research is needed to answer the question of metformin's implications for Alzheimer's disease.

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