Long-Term Care Updates

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Does metformin improve aging and longevity in patients without diabetes?

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Introduction

Metformin, approved to treat type 2 diabetes, has shown promise in modulating aging- and longevity-related mechanisms. Its purported anti-aging activity is thought to be due to its effects on cytokine, insulin, IGF-1, and adiponectin receptors. Metformin also stimulates sirtuin-1 (SIRT1), which protects endothelial cells from damage, activates adenosine monophosphate (AMP)-activated protein kinase (AMPK), and increases inhibition of mammalian target of rapamycin (mTOR), which are mechanisms shown to influence aging.[1] It has also been shown to modulate oxidative stress and remove senescent cells, both of which lead to biological outcomes associated with aging and longevity. Moreover, in vivo research has demonstrated that metformin can delay aging in nematodes and rodents.[2]

This article will review clinical research concerning the safety and efficacy of metformin on aging and longevity in patients without diabetes or with prediabetes.

Clinical Evidence

Three randomized controlled trials addressing the impact of metformin on longevity-related pathways or conditions (beyond diabetes) that may impact aging were identified.

In 2015, Vigili de Kreutzenberg et al published results of a randomized, single-blind, placebo-controlled trial in 38 patients with prediabetes to determine the effect of metformin on longevity-related mechanisms. Participants either received placebo or metformin 500 mg three times daily over a two-month period. The primary endpoint was the change in SIRT1 protein content in peripheral blood mononuclear cells compared to baseline. Secondary endpoints included changes in protein and gene expression of longevity pathway effectors and metabolic parameters. An intention-to-treat analysis was used. Both treatments were well tolerated, no adverse events were reported, and no patients dropped out. After two months, SIRT1 gene expression significantly increased in the metformin group but remained unchanged in the placebo group ($p<0.05$ versus baseline). However, AMPK activation did not significantly change in either group. The increase in gene expression of SIRT1 suggests that metformin can modify one pathway related to longevity in humans.[1] However, given the small sample size, short study duration, and lack of patient-oriented outcomes related to aging and longevity, no conclusion about the long-term effects of metformin on aging can be drawn from this study.

Also in 2015, Lexis et al reported results of a four-month, randomized, double-blind, placebo-controlled trial in 379 patients without known diabetes presenting with ST-segment elevation myocardial infarction (STEMI). Patients received placebo or metformin 500 mg twice daily, and the primary outcome was change in cardiovascular risk profile, which encompassed changes in glycated hemoglobin (HbA1C), fasting glucose, post challenge glucose, body mass index (BMI), body weight, and blood pressure compared to baseline. Total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were also analyzed. No safety outcomes were addressed. At four months, average HbA1c levels were significantly lower ($p=0.049$) in the metformin group (5.83%; 95% CI 5.79 to 5.87) when compared with placebo (5.89%; 95% CI 5.85 to 5.92), although no difference was observed between metformin and placebo for fasting glucose levels or 120-minute post challenge glucose levels. Body weight (83.8 vs 85.2 kg; $p = 0.024$) and BMI (26.8 vs 27.2 kg/m^2; $p = 0.014$) were lower in the metformin group compared to placebo. Patients in the metformin group did not gain weight (0.0 kg; 95% CI -0.84 to 0.90), while patients in the placebo group gained 1.4 kg (95% CI 0.56 to 2.3; $p=0.024$). Systolic and diastolic blood pressure at four months were similar in the metformin and placebo groups. Lastly, total cholesterol (3.85 vs 4.02 mmol/L; $p=0.045$) and LDL (2.10 vs 2.30 mmol/L; $p=0.007$) levels were lower with metformin when compared with placebo. Mean reduction in LDL was 1.74 mmol/L in the metformin group and 1.54 mmol/L in the placebo group. Researchers concluded that metformin in patients without diabetes recovering from STEMI can help manage cardiovascular risks, such as body weight, total cholesterol, LDL, and HbA1c.[3] However, given the short study duration, it remains unclear whether the use of metformin in non-diabetic patients recovering from cardiovascular events will improve longevity.

In 2017, Koenig et al published results of a 16-week randomized, double-blind, placebo-controlled, crossover study of metformin's effects in patients with Alzhemier's disease (AD). The primary outcome of the study was metformin's impact on biochemical, neurophysiological, and cognitive biomarkers of AD. Twenty patients were randomized 1:1 to receive metformin 1000 mg twice daily for eight weeks followed by placebo for eight weeks or vice versa. Eligible patients were 55-80 years old with diagnosis of early dementia due to AD but no known history of diabetes or prediabetes. The most common side effect was gastrointestinal-related symptoms with metformin, but no serious adverse events were reported. Cognition was measured using Paired Associates Learning (PAL) to test memory and learning and a Trail Making Test Part B (Trails-B) to test executive function. A statistically significant treatment effect favoring metformin was observed on a measure of executive functioning (Trails-B, $p<0.05$), and statistical trends favoring metformin were observed in learning and memory (PAL Total Errors, $p=0.06$). Overall, the researchers reported preliminary evidence that patients with AD on metformin had improved learning, memory, and attentional abilities.[4] However, the small sample size, short study duration, and lack of washout period limits the validity of these findings. Additionally, it's unclear whether these results can be generalized to patients without AD or if these improvements in cognitive outcomes lead to improved longevity.

Future Research

Nir Barzilai and the American Federation for Aging Research (AFAR) are planning a six-year clinical trial of 3000 patients between the ages of 65-79 to evaluate the use of metformin for aging-related outcomes. The goals of the Targeting Aging with Metformin Trial (TAME) are to establish that aging can be treated like a disease, confirm if metformin can treat age-related chronic diseases (e.g., heart disease, cancer, and dementia), and get aging added as an FDA-approved indication for metformin. The trial was supposed to start in 2018 but has been delayed and is currently in the recruitment stage.[5]

In addition, several smaller clinical trials are ongoing to evaluate the impact of metformin on muscle strength, frailty, immune function, and genes associated with aging.[6]

Conclusion/Recommendations

Preclinical evidence has shown that metformin influences mechanisms associated with aging and longevity, and three randomized controlled trials suggest that there may be some promise in using metformin to combat aging-related outcomes. However, only one of the studies identified focused explicitly on aging/longevity pathways. The others focused on disease conditions that are reasonable to assume impact aging/longevity. Overall, high-quality evidence supporting the effectiveness and safety of using metformin for aging and longevity is limited. Ongoing research (i.e., TAME trial) might give more direct patient-oriented insight into metformin's safety and efficacy for aging and longevity in patients without diabetes in the future. However, as of now, given to the lack of direct clinical research, metformin should not be recommended to treat aging and longevity in patients without diabetes.

References

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