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Metformin as an Antidepressant in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Depression and diabetes are diseases that share similar mechanisms with the aging process, specifically inflammation and oxidative stress. Metformin is an approved drug to treat diabetes but appears to several aging-related mechanisms. It currently targets multiple pathways of aging that involves the AMPK pathway, mTOR pathway, and IGF-1 signaling pathway. Thus, for its aging-related mechanism, glucose metabolism may not be the most important one. This study reviews 12 types of research related to the use of metformin to treat depression. This study used online research engines such as PubMed and Google Scholar to review the current finding of metformin and depression-related issues. We found that metformin targets age-related diseases, such as neurocognitive functions other than to regulate blood glucose levels through multiple biological pathways. And the final result of how metformin can be deployed against the aging process might help other researchers and clinicians to determine how to best use this drug.

Keywords: Aging-related mechanisms, AMPK, Depression, Diabetes, IGF-1 signaling

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INTRODUCTION

Depression is classified as a psychiatric disorder, with 17% of sufferers experiencing a lifetime onset; but this disease can also cause physical changes and it may indirectly influence metabolic syndrome and also be a cause of diabetes.[1,2,3,4] The symptoms of depression are a depressed mood, loss of interest in normal activities, and intrusive or suicidal thoughts.[5,6] Several brain regions and circuits regulate emotion, reward, and executive function; but people with depression may exhibit dysfunctional changes in these regions and circuits which manifest as cognitive dysfunction.[7] A frequently replicated finding in depression is the alteration of brain metabolism in the prefrontal cortex, especially in the dorsolateral and dorsoventral brain regions.[7,8] Depression and dementia are related to the condition of mild cognitive impairment (MCI) which is also associated with neuropsychiatric symptoms.[9] Later on, MCI will influence the development of neurodegenerative disorders such as Alzheimer's disease (AD).[10,11] Current research has identified similarities in the cognitive alteration that occurs in both typical aging processes and MCI.[10,11,12]

Depression, AD, and MCI are common conditions within aging populations.[13] Another highly prevalent disease related to aging is Type 2 Diabetes mellitus (T2DM), which affects around 9% of the worldwide population.[14,15] Due to a high occurrence of both neuropsychiatric diseases and T2DM in elderly populations, the discovery of effective solutions and preventive treatments—such as the use of repurposing drugs—is critical.[14,16] Inflammatory pathway and oxidative stress modulation are the basic mechanisms underlying the relation between diabetes and neuropsychiatric disease. Additional factors include increased cerebral amyloid-β peptides, hyperinsulinemia (in the tissues, including those of the brain which can cause brain insulin resistance), vascular risk factors, and the formation of advanced glycation end-products.[17] The most influential factor of diabetes progression is increased blood glucose levels, that exist as a direct result of diabetes; this condition negatively affects the alternation of episodic memory *in vivo* studies and even within people who have not been diagnosed with diabetes.[18,19]

Metformin is a biguanide compound and a common generic drug that counters the hyperglycemic effect produced by T2DM. It functions as an insulin sensitizer that reduces blood glucose by modifying the AMP-activated protein kinase (AMPK) pathway and down-regulating the IGF-1 signaling pathway.[20] Metformin treatment during pregnancy was uncommon due to its safety and, its ability to cross the placenta whereas there are no side effects of taking metformin for lactating mothers.[21,22] Metformin's mechanism of action is to elevate the uptake of glucose into muscle cells while also decreasing glucose production, or gluconeogenesis, in the liver by activating the AMPK pathway.[23] Metformin's effect on inflammation works independently from a patient's diabetes status.[24] Because of this independent mode of action, previous researchers hypothesized that metformin could be adopted as an anti-inflammatory drug, particularly for uses targeting neurodegenerative diseases, especially in the involvement of neurodegenerative diseases. Metformin works by activating the AMPK pathway, similarly to processes that result from a caloric restriction diet.[25,26] *In vivo* study of caloric restriction and metformin showed that both treatments can slow the aging process.[27,28] Improved memory is one positive result of caloric restriction within a geriatric population;[29] this indicates that metformin can also work, to prevent or delay the development of

neuropsychiatric conditions such as dementia and depression.[30]

MATERIALS AND METHODS

Study sites

This review was carried out using the online search engines PubMed and Google Scholar.

Inclusion criteria

The criteria to be included in this review are population, exposure, control, outcomes, and types of studies. *Population:* Human subjects, animal subjects, and cell cultures. *Exposure:* Studies with the treatment of metformin and without the inhibition of dose-dependence and time. *Control:* population without metformin treatment (both positive and negative controls). *Outcomes:* Studies that show risk factors, pathophysiology, and pathogenesis of neuropsychiatric symptoms (including dementia and AD). *Types of studies:* Experimental studies on animals and controlled trials on human subjects, or observational studies such as cohort, case-control, and cross-sectional studies.

RESULTS AND DISCUSSION

Table 1 displays prior studies that found a relationship between diabetes and cognitive impairment diseases such as depression, dementia, and AD.[1,17,31] These study examples indicate that metformin has a significant protective effect on cognitive impairment related diseases when compared with insulin intervention.[31,32,33,34,35] Furthermore, in the Taiwan study, the risk of AD occurrence was not associated with monotherapy or combination either. However, insulin-combined therapy was found to be associated with the risk of AD.[31] This finding might indicate that higher insulin levels in T2DM patients result in a higher incidence of cognitive impairment related diseases. Some of the T2DM patients also demonstrated depressive behavior such as suicidal thoughts; this might indicate that T2DM patients were prone to have a major depressive disorder (MDD).[36] The other interesting finding also correlates depressive people with an increased risk of developing T2DM.[37] The relation between depression and T2DM is influenced by several comorbid factors such as an unhealthy lifestyle, use of antidepressant drugs, alteration of the brain structure and function, sleep disturbance, inflammation, hypothalamic–pituitary–adrenal axis dysfunction, and environmental factors.[38]

In the study of the relationship between T2DM and dementia, AD and vascular dementia (VaD), Ahtiluoto (2010), analyzed the incidence, mortality, and neuropathologic outcomes in a prospective population-based study focused on the elderly. Dementia lasted longer in non-diabetic compared to the diabetic population probably due to the diabetes-related increase in mortality.[17]

Next reviewed the possible pathways targeted by metformin, see Table 2. Metformin works on central metabolic pathways. It influences sugar metabolism and the AMPK signaling pathway, the mTOR mechanism, and the inflammation process.[39] The studies we reviewed indicate that metformin also influences brain metabolism. See Figure 1. The human brain spends 25% of glucose utilization for its energy demands.[40] Neurons have high energy demands that consume almost 70% of brain energy expenditure, while the balance is consumed by glial cells, astrocytes, and microglia.[39] MDD patients exhibit altered glucose metabolism and increased blood flow in the orbital cortex, medial thalamus, and amygdala. Glucose impairment metabolism can cause the dysfunction of mitochondrial ATP production.[41] This underscores the relation between T2DM and MDD, in which both of these diseases include altered glucose metabolism and central metabolism, which is related to the dysfunctional production of mitochondrial ATP's.

In a study of metformin treatment provided to T2DM patients, Guo (2014), found improved cognitive performance with certain criteria (delayed, general, visual and memory index; focus and concentration index). Furthermore, metformin treatment for 24 weeks also prevented the depressive pattern of diabetes patients. This also supports their finding of the depressive phenotype in T2DM related to the controlled effect of metformin towards the hemoglobin A1C levels.[42]

Metformin works by changing the composition of intestinal microbiota and activating mucosal AMPK which maintains the integrity of the intestinal barrier.[43] This effect is combined with AMPK activation in hepatocyte cells where the decreased mechanism of the production of lipopolysaccharides (LPS) circulating in the liver cells happens.[44] Furthermore, when the active compound from metformin reaches the liver, it can prevent the occurrence of gluconeogenesis through four mechanisms of action:

- Metformin activates hepatic AMPK via the liver kinase B1 pathway and a reduction in cell energy consumption.[45]
- Metformin inhibits glucagon-induced cAMP production by inhibiting adenylate cyclase.[46]
- Metformin increases AMPK activity which is associated with the rise in AMP/ATP ratio.[47]
- Metformin inhibits oxidative stress in cells and eliminates senescence cells through enhancement mTOR restoration. [48,49]

The proposed mechanism of metformin on the mTOR pathway is related to both complexes of mTOR (mTORC1 and mTORC2). Both mTOR complexes are important for cellular growth and as a receiver stimulus for energy metabolism and signaling of hormones. The complex of mTORC1 influenced by signals from insulin, IGF1, IGF2, and AMPK. Metformin inhibits mTORC1 via IGF-1 and insulin signaling pathways which lead to the inhibition of cellular growth. This mechanism also influences TSC1 and TSC2 which are normally blocked by IGF-1 and insulin. Conversely, metformin induction of TSC1 and can exert their inhibitory effect on mTORC1. [49,50]

Metformin can also induce p53, a protein that inhibits the mTORc1 signaling pathway.[51] P53 can stop cellular growth and proliferation by sensing genotoxic stress, for example, DNA damage clearance. When p53 is activated, it in turn activates AMPK, TSC1, and TSC2 which leads to the inhibition of mTORC1. [50,51] See Figure 2.

The condition of insulin-like growth factor-1 receptor (IGF-1R) deficiency and downstream kinase disorders of the biomarker, such as inhibition of the insulin/phosphoinositide 3-kinase (PI3K) signaling, act in the brain of patients with type T2DM and AD will affect the activity levels of Tau protein phosphorylation. Metformin functions in the downregulation system of IGF-1R which is useful in regulating autophagy and protein synthesis in brain cells.[52]

IGF-1 is actively transported through the plasma and is produced in the brain by both neuron and glial cells. Microglial cells produce more IGF-1 than astrocyte and neuron cells. In general, IGF-1R is expressed more in

neurons and astrocytes which is the target site for IGF-1 lesions. IGF-1 promotes neuronal survival and M2 microglial repair/regenerative phenotype and inhibits astrocytes from responding to inflammation in other astrocytes due to the stimulation of M1 microglial phenotype. Thus, IGF-1 induces the repression of the M1 microglial neurotoxic phenotype and increases the transition from M2. The decreased levels of IGF-1 in the aging process can cause a reduction in the capacity of microglia in M2 activation, which in turn causes the neuroinflammation process to occur. The interaction of IGF-1, estrogen, and angiotensin in the brain modulates the neuroinflammation response. Metformin, which specifically lowers blood glucose can also work as a sensitizer agent to insulin and IGF-1 and result in a protective mechanism against neurodegenerative. [50,51,53,54,55,56]

CONCLUSION

In conclusion, metformin might act as a potential agent to counteract the aging process, particularly concerning neurodegenerative diseases such as MDD and AD that are correlated with depression in both T2DM patients or populations at risk of diabetes. A superior understanding of the mechanism of metformin action towards aging and neurodegenerative disease will close the knowledge gap. Therefore, it can be summarized that the effect of metformin on multistage energy processing and the sensitization of insulin receptors might explain how metformin can minimize the reactive oxygen species (ROS) production while slowing the processing of aging-related diseases. Besides, the energy production in mitochondria that can trigger signaling pathways in the production of glucose can be optimized by the work of metformin which results in a lower production of glucose and insulin. The more efficient the energy production, the less damage can occur. More research both *in vitro* and *in vivo* to understand this underlying mechanism is needed due to the complicated interactions of metformin within multiple metabolic and biologic pathways. Finally, the research supporting metformin as harboring a mode of action against the aging process might help researchers and clinicians in deciding how to use this drug.

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Table 1. Relevant studies of metformin and neuropsychiatric diseases

Author of the study	Design	Comparator	Study Population	Total Participant /time of the study	Result(s)
Huang [31]	Metformin or metformin and combination	Other diabetes management	Cohort study. New diabetes patients with no development of AD	7 years Overall:71,433/346 5.5 years	Diabetes subjects were more prone to have AD than healthy subjects. Besides, both monotherapy and combination therapy with oral antidiabetic medications were associated with the risk of AD. Combination therapy with insulin was found to be associated with greater risk of AD (HR, 2.17; 95% CI, 1.04–4.52, p = 0.039
Cheng [32]	New-onset T2DM who used metformin only (did not have drug combination or never given insulin)	New-onset T2DM (with a sulphonylurea or TZD drug only)	Taiwan. Cohort. 65 years old and above, dementia-free and T2DM free	Metformin: 1,033/39 TZD: 28/4 Sulph: 796/40 6 years	The risk of dementia is higher in T2DM group compared to metformin group and sulphonylurea group The comparison of hazard ratios for dementia between the diabetes group and the non-diabetes group was 1.56 (95%CI: 1.39–2.18). Meanwhile RR of dementia for group that used TZD

					was 5.31 (95% CI: 1.89–14.96) (n = 28) and 1.22 (95% CI: 0.78–1.91) for those taking sulfonylureas (n = 796) In comparison with metformin group (n = 1,033).
Heneka [33]	In the use of metformin	Diabetes with or without metformin or no-diabetes	Germany. Cohort. Aged 60 and older, dementia-free, not receiving insulin	Metformin: 67,822(person-years)/1,478; No-metformin: 122,036(person-years)/3,854; healthy non-diabetes: 443,559 (person-years)/7,845 Being followed 5 years	The comparison of dementia incidence rate per 1,000 person-years between diabetes with metformin group is lower than the diabetes group without metformin intervention T2DM MET: 20.71–22.93 T2DM NO-MET: 30.60–32.59 Meanwhile, the diabetes group with insulin intervention has a higher incidence rate of dementia compared to with non-insulin intervention especially with metformin group T2DM insulin: 39.82–47.77 T2DM NO-INSULIN: 26.41–27.94
Herath[34]	In the use of metformin	Other diabetes medication	Australia. Cohort. Aged 65–69, with no history of stroke, epilepsy, or dementia. Any treatment for treating diabetes	4years metformin:49/Na; Other: NR	Diabetes drug group vs diet only has shown no significant difference in their cognitive function. Indeed, both diet and Metformin had a protective effect on dementia, stroke, and epilepsy
Hsu [35]	Monotherapy of metformin	T2DM but not given any diabetes drug, or healthy (non-diabetic)	Cohort Study. Aged 50 or older (Place: Taiwan, does not have dementia	Metformin: 1,864/66. No drug: 10,519/434; No-diabetes:101,816/3376	Diabetes patients have a higher incidence of AD after 11 years followed up compare to non-diabetes patients (0.48% vs. 0.37%, p<0.001) The comparison between HR of metformin monotherapy vs insulin was higher on the insulin group MET: 0.69 (0.28–1.71 Insulin: 2.17 (1.04–4.52) p<0.01
Guo [42]	Metformin	Placebo	Shanghai, China. A randomized placebo-controlled trial. T2DM patient, age 40-65 with depression status.	58 patients with depression and T2DM treated with metformin for 24 weeks	Chronic metformin treatment produces antidepressant effects and improves cognitive function in T2DM patients with depression assessed by verbal memory index, visual memory index, general memory index, attention and concentration, delay memory index.

Table 2. Studies identifying metformin's possible pathway targets

Substance	Pathway	Source
Metformin	AMPK	[39,43,44,45,46,47,49,56]
Metformin	IGF1 signaling	[50,51,52,53,54,55,56]
Metformin	Mammalian target of rapamycin (mTOR)	[39,48,49,50,51]

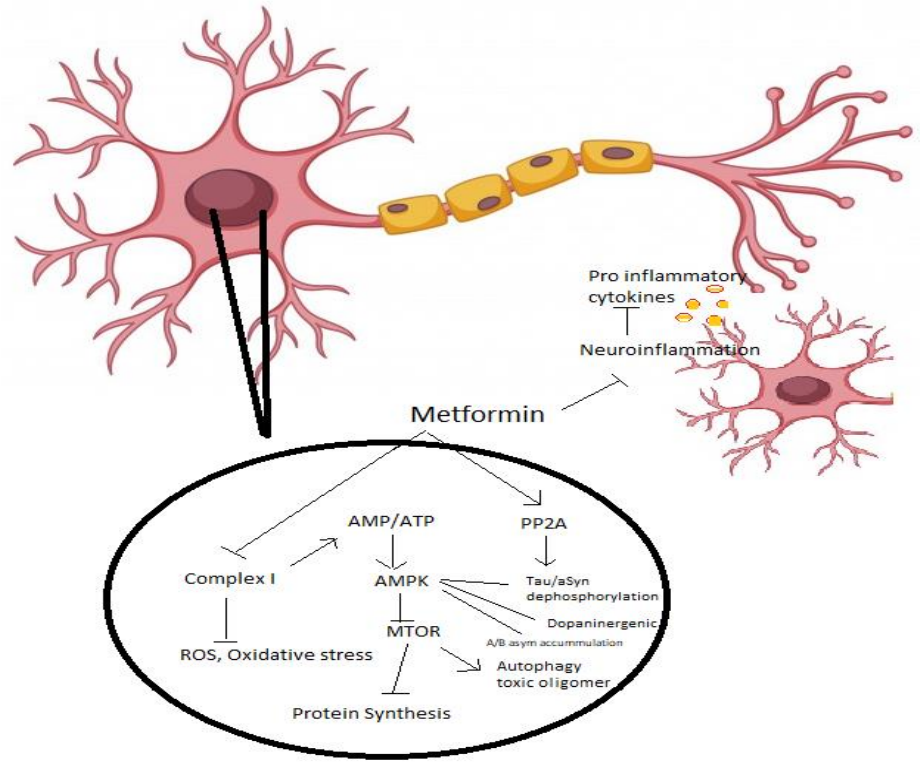

Figure 1. The effect of metformin on neuronal metabolism
Metformin works on major metabolism and cell signaling pathways. For example, the formation of energy glucose metabolism and AMPK signals), mTOR signaling, and inflammatory signals.[39]

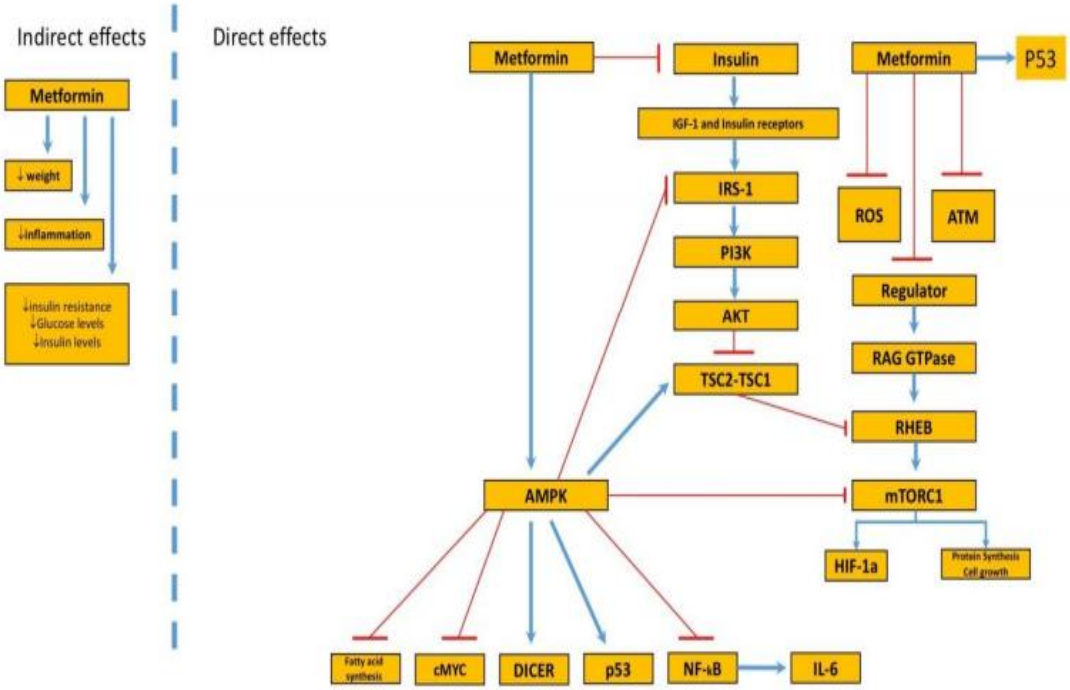

Figure 2. The multiple pathways that Metformin effects: AMPK, mTOR, and insulin-related pathways (recreated from Amin, 2019).[50]