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The Effects of Metformin on Stroke Patients Outcomes: A Literature Review

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Abstract

Diabetes might produce pathological changes to blood vessels in several locations, and if the brain's blood arteries are directly affected, it can lead to strokes. Moreover, stroke survivors having uncontrolled glucose levels had a greater fatality rate and poorer outcomes following the event. Therapeutic interventions for ischemic stroke remain limited; thus, it is vital to create novel therapeutic drugs or combination treatments. Metformin is a widespread biguanide medication owing to its safety and low cost, especially for the treatment of diabetes. Metformin's anti-inflammatory properties protect the brain from ischemia/reperfusion-induced injury. In clinical populations, chronic metformin use is linked to a reduced risk of stroke and cardiovascular mortality.

Keywords: Metformin, Stroke, Diabetes Mellitus

Introduction

Stroke is the third main reason of mortality and disability in the globe. Stroke causes roughly 4.4 million deaths annually worldwide [1]. Diabetes is a prevalent stroke-related risk factor. People with this condition have a significant chance of developing hemorrhagic changes [2]. Diabetes mellitus is predicted to affect about 30% of stroke patients. Metformin is the first therapy of choice for type two diabetes. More than 100 million diabetes people worldwide are administered this medication yearly [3]. Metformin is an anti-diabetic oral medicine that reduces the occurrence of ischemia in diabetic patients. Several molecular mechanisms, such as oxidative stress, activation of endothelial nitric oxide synthase, stimulation of revascularization and neurogenesis, autophagy, and apoptosis, were involved in the neuroprotective function for metformin in the majority of investigations involving animals with middle cerebral artery occlusion (MCAO)-induced cerebral ischemia. However, therapy with metformin in experimental strokes had inconclusive results when compared to the preventive effects of stroke models [5]. Consequently, the purpose of this paper is to explore the use of metformin as an additional treatment for stroke.

Methods

This research is a literature review conducted as secondary research. According to the MeSH term, a literature search was carried out on PubMed utilizing keywords such as stroke, metformin, and diabetes mellitus. The research designs included randomized controlled trials, observational studies, and experimental studies, and the literature was selected according to publication year (2012-2022).

Results

Metformin is an in vivo and in vitro AMPK activator [6]. AMPK is the primary detector and controller of cellular energy homeostasis. AMPK is stimulated once AMP/ATP ratios are sufficient and AMP attaches to AMPK complex components [7]. Metformin functions by inhibiting the respiratory chain in order to raise the AMP:ATP ratio, so activating AMPK. Live kinase B (LKB) influences this activation [8]. It has been shown that activation of AMPK protects against ischemic injury by stimulating nuclear erythroid factor 2-related antioxidant pathways (Nrf2) or blocking NF-B cascades to prevent post-ischemic nerve inflammation [9]. In addition, metformin has a neuroprotective impact by blocking the mitochondrial I respiratory chain complex, which has been discovered to enhance the intracellular calcium absorption as well as inhibit the entrance of the permeability transition pore in mitochondria [10]. In post-stroke patients, metformin is not only useful for preventing immediate infarction, but also for encouraging long-term functional recovery. Its been observed that intraperitoneal therapies of metformin soon after an experimental stroke dramatically decreased acute infarction in rodents and stroke-induced increases in blood glucose [11]. Metformin is claimed to aggravate the severity of a stroke, while having certain properties that promote stroke recovery. Acute activation of AMPK at the neuron level generates negative consequences with an increase in the extent of cerebral infarction compared to chronic therapy for at least 2 to 3 weeks prior to ischemia [12].

The period of metformin administration and the dosage of metformin may account for varying study outcomes [13]. An experimental stroke research demonstrated that acute metformin administration for three days prior to an experimental stroke significantly worsened infarct damage 24 hours after MCAO. In contrast, chronic metformin therapy for three weeks prior to experimental stroke reduces acute infarction 24 hours after MCAO [5]. Patients with type 2 diabetes mellitus who took metformin consistently well before onset of stroke and afterwards hospitalization seemed to have excellent treatment benefit at 90 days, whereas participants who underwent metformin just before the onset of stroke or just after hospitalization did not demonstrate useful outcomes [14]. Metformin administered intravenously to the brain after a stroke worsens acute ischaemia by stimulating cerebral AMPK [11].

In the MCAO model, dosages of metformin varied from 10 mg/kg/day to 500 mg/kg/day of diverse delivery methods (gavage and intraperitoneal) in several investigations [15]. After 24 hours after pMCAO, it has been shown that pretreatment with a single dosage of metformin 10 mg/kg/day dramatically lowers infarct volume and neurological impairments [16]. In contrast, a high dosage of metformin might result in an excessive activation of AMPK, resulting in protracted astrocytic glycolysis and increasing acidosis [5].

Conclusion

Metformin treatment has the potential to promote stroke recovery. It is determined mostly by dose, duration of therapy, and mode of administration. Metformin has a favorable impact on stroke when taken continuously and persistently, however acute metformin treatment, particularly before to stroke, has dose-dependent effects on acute infarction. Regarding the appropriate therapeutic dosage, the use of metformin as an adjuvant treatment for stroke warrants more investigation.

Acknowledgement

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