



Reduction of Depression in Diabetes: A New Pleiotropic Action of Metformin?

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ABSTRACT

Metformin remains the cornerstone of management for type 2 diabetes mellitus (T2DM). It is also known that it has beneficial pleiotropic actions. In addition, there is emerging evidence that this agent may prove beneficial in ameliorating depression in T2DM. The underlying mechanisms of this new action remain elusive, but experimental studies point to improved synaptic function and increased serotonin activity, along with the known inflammatory and antioxidant properties of metformin. Obviously, we need to further explore the potential utility of such antidepressant effects among T2DM subjects in everyday reality.

Keywords: Antidiabetic treatment; Depression; Metformin; Pleiotropic; Type 2 diabetes

DIGITAL FEATURES

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Metformin remains the cornerstone of type 2 diabetes (T2DM) management [1]. It reduces insulin resistance, thereby decreasing gluconeogenesis and increasing glucose uptake by peripheral tissues [2]. It is also known for its pleiotropic effects such as anti-atherosclerotic effect, weight reduction, diabetes prevention in patients with metabolic syndrome [3], reduced incidence of cancer, and improved response to anticancer therapy [4]. Recently, there has been some evidence that metformin might be beneficial in COVID-19 infection, as well [5]. Impressively, there is emerging evidence that metformin may also prove beneficial in ameliorating depression in T2DM.

A prospective, multi-centre cohort study conducted in four gynaecology clinics showed that women with polycystic ovary syndrome (PCOS) receiving metformin combined with lifestyle modifications improved their mental well-being [6]. Moreover, among elderly subjects with diabetes, depression was not uncommon, while its presence was reduced by metformin therapy [7]. Similarly, Guo et al. have reported that 24-week metformin treatment improved cognitive performance and severity of depressive symptoms as well as improving glucose metabolism in subjects with T2DM and depression [8].

The parallel-group IMPACT trial (Improving Metabolic Parameters in Antipsychotic Child Treatment) [9] included 121 subjects aged 8–19 years with diagnosis of schizophrenia,

bipolar disorder or major depression with psychotic features; overweight or obesity; weight gain of > 10%. These were randomised to add-on metformin, switch of antipsychotic agents or continuation of baseline antipsychotic therapy [9]. Subjects receiving metformin exhibited a significant improvement in the social life subscale [9]. Predictably, this agent also exerted beneficial actions in BMI, prevention of weight increase and fasting glucose [9].

The mechanisms underlying such favourable effects are still unclear. Some relevant evidence comes from experimental studies (Table 1). In male mice, metformin has been shown to ameliorate depression via enhancing the expression of brain-derived neurotrophic factor (BDNF) by activating 5' adenosine monophosphate-activated protein kinase (AMPK)/AMP response element-binding protein (CREB)-mediated histone acetylation when combined with fluoxetine [10]. Ribonucleic acid (RNA) sequencing and Golgi-staining revealed that metformin prevented impaired synaptic functions in the hippocampal circuit [10]. Again in the diabetic depressed rat model, metformin monotherapy or metformin plus ascorbic acid exerted an antidepressant effect, as evidenced by the reduction in immobility time in forced swim test (FST) [11]. The antidepressant effect of metformin could be attributed to the elevation of serotonin and norepinephrine in the brain [11]. In addition, its antidepressant effect appeared to be caused by the reduction of plasma corticosterone levels and adrenocorticotrophic hormone (ACTH) secretion via the

AMPK/liver X receptor α /pro-opiomelanocortin pathway [11]. Metformin has also been shown to act against methamphetamine-induced behavioural changes in rats with experimental diabetes [12]. This protective effect was associated with improved neurotransmission [11, 12]. Further postulated mechanisms include the anti-inflammatory and antioxidant properties of metformin [12].

Finally, peripheral insulin resistance has been associated with anxiogenic-like responses [13]. The latter are associated with increased branched-chain amino acid plasma levels, which in turn reduce tryptophan availability in serotonin receptors [13, 14]. In this context, it is of immense interest that hippocampal serotonin re-uptake was reduced among metformin-treated insulin-resistant mice [14]. These findings pave the way for the consideration of metformin plus serotonin re-uptake inhibitors for the treatment of depression, but it is far too early to draw safe conclusions in humans.

In conclusion, there is accumulating data that the new pleiotropic effect of metformin may be an anti-psychotic, mainly anti-depressive action in the setting of diabetes. The underlying mechanisms of this new postulated action remain elusive, but experimental evidence points to improved synaptic function and increased serotonin activity along with the known anti-inflammatory and antioxidant properties of metformin [10–12]. It is still unclear whether this is of real relevance to humans. However, metformin has already been identified as one of the agents associated with

Table 1 Main mechanisms of action of metformin on mood, according to experimental studies

1. Ameliorate depression via enhancing the expression of BDNF by activating AMPK/AMP response element binding protein (CREB)-mediated histone acetylation [10]
2. Antidepressant effect by elevation of serotonin and norepinephrine in the brain [11]
3. Antidepressant effect due to reduction of plasma corticosterone levels and ACTH secretion via the AMPK/liver X receptor α /pro-opiomelanocortin pathway [11]
4. Protection against methamphetamine-induced behavioural changes through improved neurotransmission as well as through anti-inflammatory and anti-oxidative actions [11, 12]
5. Increase of branched chain amino acid levels in plasma to reduce tryptophan availability in serotonin receptors, which in turn reduce hippocampal serotonin re-uptake [13, 14]

reduced psychiatric hospitalisation and self-harm in subjects with serious mental illness [15]. Accordingly, we are eagerly anticipating what the future has in store for metformin in ameliorating depression among subjects with impaired glucose metabolism.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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