

Metformin: Is it a Truly Magic Drug?

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Editorial

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Editorial

Metformin has been the mainstay of therapy for type 2 diabetes (T2D) for many years; it has been used for its glucose-lowering effect since 1957 in Europe and 1995 in USA. Besides being highly effective in improving glycemic control, metformin has also a low risk of hypoglycemia. Metformin remains at the head of management algorithms for T2D, either as mono therapy or in combination with sulfonylureas, thiazolidinediones and insulin.

Recently, metformin has been investigated as an adjunctive therapy in poorly controlled type 1 diabetes [1]; the addition of metformin to insulin therapy leads to decreased average glucose concentrations and insulin dose requirement, as well as lowered metabolic syndrome prevalence after 1 year of treatment. However, the addition of metformin to insulin therapy is still under debate and not formally recommended in type 1 diabetes [2]. Larger placebo-controlled studies are needed to determine the long-term effects of metformin adjunctive therapy on poorly controlled type 1 diabetes.

The clinical indications of metformin therapy have expanded from T2D to gestational diabetes mellitus, polycystic ovary syndrome (PCOS), metabolic syndrome and diabetes prevention [3]. However, several studies have reported conflicting results regarding the role of metformin in PCOS and the accumulating evidence on the efficacy of metformin has been disappointing. The lack of an emphatic or overwhelming efficacy is largely due to the patients' variability in phenotypes and their metabolic parameters.

Moreover, this drug can positively influence multiple cardiovascular risk markers, including lipid profile

[4], fatty liver [5] and modulate inflammatory markers [6]. Metformin is the first anti-diabetic drug to display cardioprotective properties as shown in long-term randomized clinical trials [7]. However, many promising results are not without dispute. For example, whether metformin treatment can improve cardiovascular morbidity and mortality remains controversial.

Additionally, metformin has been considered to be one of the most promising drugs to target dementia and its related disorders; a growing body of evidence suggests that metformin is associated with a reduction in cognitive impairments in both T2D patients [8] and non-diabetic subjects [9]. However, the efficacy of metformin in improving cognitive function is still controversial; a study done by Moore et al. have shown that administration of metformin rather increased the risk of cognitive impairments [10], whereas Bang et al. have observed neither deleterious effects nor beneficial effects of metformin on cognitive function [11].

Epidemiological studies have also shown that metformin use is associated with a lower incidence and mortality of numerous cancers, particularly in patients with T2D [12,13] putting the drug into the cancer research spotlight. In addition, metformin sensitizes tumor cells to traditional chemo-drugs as well as irradiation therapy [14,15]. With regards to patients without diabetes, one study has demonstrated that metformin is associated with a lower risk of colorectal carcinogenesis [16]. However, metformin therapy did not reduce the risk of breast or prostate cancer [17].

Currently, the detailed mechanisms for the anti-tumor activity of metformin remain elusive. Further studies have

demonstrated that metformin has a direct antitumor effect *in vivo* and *in vitro*, which may repress the proliferation of tumor cells, and induce apoptosis, autophagy and cell cycle arrest [18-20]. An *in vitro* study has demonstrated that metformin may activate AMP-inducible protein kinase (AMPK) and down regulate p70S6K/pS6 protein to inhibit the growth of tumor cells [21]. Metformin also suppresses the secretion of IGF-1, IGF-2, leptin, and the tissue metalloproteinase inhibitor 1 and decreases the lipid accumulation during adipocyte differentiation [22].

The question arises is whether metformin may become an alternative cancer adjuvant therapy, providing a novel approach for cancer prevention and treatment? The potential anti-tumor activity of metformin in numerous cancers remains controversial and needs long-term randomized controlled trials.

Metformin; the most frequently prescribed anti-diabetic treatment worldwide; has gained attention for its pleiotropic effects; however the apparently promising effects in many diseases are challenged by conflicting observations. So, more work is needed to establish its right place with this regards.

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