Brief Communication

Metformin: Midlife maturity, maiden charm

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ABSTRACT

Metformin is one of the most commonly prescribed drugs for management of Type 2 diabetes mellitus. It has been in use for almost five decades. Now, pharmacological properties of this agent are being exapted for use in a number of other indications. New facets of its personality are coming up, generating more interest of the scientific community in this "middle-aged" molecule. This article explores the role of metformin in cardioprotection and its hepatoprotective properties. Nephroprotective, protection against excess body fat and gonadoprotective actions, properties have also been discussed. Additionally, this manuscript briefly reviews the thyroid stimulating hormone (TSH)-lowering properties in diabetic and non-diabetic patients, besides reviewing its actions on different types of cancers. Some of these actions may become approved indications for use of metformin following generation of new evidence. Metformin still has many unexplored dimensions that deserve further exploration.

Key words: Biguanides, cancer, cardioprotection, diabetes, gonad, hepatoprotection, oral hypoglycemic drugs, renoprotection, thyroid

Introduction

Although metformin is perhaps the most widely prescribed oral antidiabetic drug worldwide, and was synthesized a century ago, newer aspects of its personality are still being discovered.

Apart from its glycemic effects in type 2 diabetes, for which it is approved, it is used in other forms of diabetes such as pre-diabetes,[1] type 1 diabetes[2] and gestational diabetes mellitus.[3] Its properties have also been put to use in other facets of metabolic syndrome, such as obesity,[4] non-alcoholic fatty liver disease (NAFLD)[5] and hyperlipidemia.[6] Also, it is used in other endocrine diseases like polycystic ovary syndrome (PCOS)[7] and hypothyroidism.[8] Non-endocrine indications, including anti-ageing, potential role in primary prevention of colonic cancer[9] and treatment of cancer,[10] complete the list.

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No wonder then, that although metformin has achieved midlife maturity as a molecule, it cont\inues to exude maiden charm. The use of metformin in type 2 diabetes, both as monotherapy and in combination, is well researched and well documented. This review, therefore, will focus on the potential uses of metformin other than the prevention and management of diabetes.

Cardioprotection

Various animal studies have demonstrated that metformin reduces infarct size in myocardial infarction.[11] This has been shown in both diabetic and non-diabetic rodents. This effect is partly mediated by AMP kinase (AMPK) activation, which increases phosphorylation of endothelial nitric oxide synthase (eNOS). It also prevents apoptosis of ventricular cardiomyocytes, activates AKT, one of the kinases of the reperfusion injuring salvage kinase (RISK) pathway, and stimulates the adenosine receptor.[11] Metformin also modulates post-infarct remodeling and prevents heart failure in the post-myocardial infarction setting.[11] Multiple mechanisms contribute to this beneficial effect, including a reduction in mitochondrial dysfunction in the failing

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myocardium,[12] reduction in collagen expression[13] and inhibition of transforming growth factor (TGF)-β1.[14] The drug has been shown to reduce apoptosis in cardiac allografts in animal models, both in the acute and in the chronic phases. Thus, it has potential for use as therapy to minimize acute and chronic rejection after cardiac transplantation.[15]

Nephroprotection

Metformin has unfairly been targeted in the past as a renotoxic agent. In fact, it may have beneficial effects on the kidney. The risk of lactic acidosis associated with metformin use seems to have been exaggerated. It is suggested that metformin should be contraindicated in patients on dialysis[16] and with a glomerular filtration rate <30 mL/min.[17] In other patients with chronic kidney disease, metformin may have beneficial effects in glycemic control as well as long-term survival.[16] The drug may also be used in new-onset diabetes after renal transplantation.[16]

Hepatoprotection

Metformin has important effects in the liver, where it reduces hepatic gluconeogenesis and benefits lipid metabolism. It improves insulin sensitivity and liver morphology, as assessed by ultrasonography and histology. These findings have been replicated in many, but not all, studies in adults.[5] In children, beneficial biochemical and metabolic effects have also been reported.[5]

Adipoprotection

Metformin helps reduce body weight in both diabetic and non-diabetic patients, with beneficial effects on total body fat and visceral fat.[5] This is due to a reduced caloric intake because of suppression of appetite[18] and due to correction of hyperinsulinemia.[19] Metformin, therefore, can be used as an adjuvant to weight loss therapy.

Gonadoprotection

Metformin is frequently used in the management of PCOS in women. This use is based on its anti-androgenic as well as insulin-sensitizing effects. The drug decreases production of testosterone from the ovaries and improves follicular growth within the ovaries. This occurs indirectly through reduction of hyperinsulinemia and directly through an increase in AMPK, coupled with a reduction in CMP 17 activity. These effects translate into clinical benefits in hirsutism, menstrual regularity and ovulation.[7,20]

Thyroprotection

Metformin has recently been shown to decrease TSH levels in subjects with hypothyroidism.[21,22] It started as an incidental retrospective finding from cases of hypothyroidism that were prescribed metformin for diabetes and NAFLD. The finding was confirmed in retrospective and prospective[23] studies involving patients of diabetes with or without hypothyroidism. Now, it is a well-established fact that treatment with metformin reduces serum TSH levels. Although the mechanisms responsible for this finding still remain an enigma, a number of hypotheses have been proposed. One possible explanation is the sensitization of the cells in the anterior pituitary to the effects of thyroxine, augmenting the negative feedback effect.[23] The same mechanism can also lead to sensitization of peripheral tissues to the actions of thyroxine. The effect is proposed to be mediated through the actions of co-regulators, regulating the transcription of genes in response to binding of thyroid receptor complex to the nuclear DNA.[24] Interestingly, this effect is not seen in euthyroid patients but it is well developed in patients with abnormal pituitary–thyroid axis. Treatment with thyroxine replacement does not alter the response, while loss of this effect is seen when metformin is discontinued.[23,25] This effect can be labeled as thyroprotective effect.

Antitumor effect

The association between reduced caloric intake and reduction in incidence of cancer is well established.[26] The generation of lactate in the absence of oxygen is seen in normal cells, while the same phenomenon is seen in cancer cells in the presence of oxygen also. This effect of aerobic glycolysis is called "Warburg Effect."[27] Metformin is known to act on some of the pathways of energy metabolism affected by caloric restriction and interfere with these processes in cancer cells with potentially beneficial outcomes.

Signals about reduction in incidence of cancer with use of metformin were generated in epidemiological studies in diabetic patients initially.[28-30] Later on, the role of metformin for primary prevention and treatment of tumors was explored in the general population also. Interestingly, the findings were not replicated in all patient groups. Specific sub-groups of patients could be identified who are not likely to respond to metformin therapy.[31]

A number of *in vitro* studies using cancer cell lines and a number of other models have tried to explore the underlying mechanisms. Although the exact mechanism of action in cancer cells still remains an enigma, a number of hypotheses have been proposed. Activation of AMPK

and increased sensitivity to insulin[32] are proposed to be the important mechanisms responsible for these findings.

The carcinomas that are being proposed as potential targets of metformin therapy are breast,[31,33,34] colon,[35,36] thyroid,[37,38] pancreatic,[39,40] prostate,[41] head and neck tumors,[42] lymphomas[43] and leukemias.[44] A number of studies using human breast cancer cell lines and implanted tumor cells in rodents have explored metformin alone or as add-on therapy[45] with existing anticancer agents. The results from these studies have shown that metformin is able to decrease the proliferation of tumor stem cells,[33] induce apoptosis in tumor cells[34] and increase the sensitivity of tumors to existing chemotherapeutic agents.[46] These findings were replicated in other tumor cell lines also. Clinical studies have been conducted to find the sub-group of patients who are likely to respond to the metformin, e.g. in patients with breast carcinoma, presence of estrogen receptor predicts responsiveness to metformin,[47] while one clinical study has found no effects of metformin therapy in triple receptor-negative breast carcinoma patients.[31] More scientific information will accumulate in the future about the potential role of metformin in many other cancers and sub-types of patients.

In a nut shell, metformin is a promising candidate for prevention and treatment of a variety of cancers because of its unique mechanism of action, because of which it can specifically target cancer cells.

Conclusion

Even 50+ years after its initial use, metformin continues to be the first-line choice for management of type 2 diabetes mellitus. This testifies to its maturity as a "mid-life" molecule. Newer indications are also being discovered for this drug, ranging from glycemic and metabolic disorders to varied endocrine and non-endocrine conditions. This underscores the maiden charm that metformin continues to exert on students of medicine. The future will unfold many more mysterious actions of this unique molecule.

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