INTRODUCTION

The biguanide derivative metformin is the most widely prescribed oral antidiabetic drug (OAD) in the world. On account of its wide clinical use over more than five decades, we now have robust clinical data on its efficacy, tolerability, and safety when used in the treatment of type 2 diabetes mellitus (T2DM). While the role of metformin in therapy of T2D remains unchallenged, exciting evidence has recently emerged regarding the possibility of pleiotropic benefits with use of this molecule. These benefits span a wide spectrum of cardiovascular, oncological, and endocrine conditions and have the potential to change the way we look at this agent. The present chapter looks at some of the evidence for the benefits of metformin beyond glycemic control.

THE MOLECULE

Metformin belongs to the chemical class of biguanide drugs, which are derived from the molecule guanidine, a component of French lilac (Galega officinalis), a traditional remedy for diabetes in many parts of the world. While guanidine by itself has antihyperglycemic effects, its widespread use is limited by significant toxicity. Further research into the antidiabetic properties of guanidine led to the development of the biguanide drugs, initially phenformin and then metformin.

Chemically, metformin is dimethylbiguanide. It was first introduced into the market in 1957 and has now become the most commonly used OAD worldwide. It has virtually replaced phenformin on account of its lower propensity to cause the dreaded complication of lactic acidosis.

USE OF METFORMIN IN DIABETES

Most global guidelines recommend the use of metformin as first line therapy for T2DM. The attractive features of this drug in therapy of T2DM include low risk of hypoglycemia, potential for weight loss, and absence of significant side effects. The main adverse effects associated with metformin relate to the gastrointestinal tract and can be minimized by starting with a small dose and up-titrating slowly; rarely do they necessitate stoppage of the drug.

Metformin is also indicated in “prediabetes” (impaired glucose tolerance and impaired fasting glucose) to prevent progression to diabetes, in individuals deemed to be at high risk of such progression. Metformin is also an option in the treatment of gestational diabetes mellitus.

Notwithstanding the widespread use of metformin for more than half a century, its mechanism of action remains an enigma. It has been postulated that metformin alters fuel sensing by the target cells, by activating cyclic adenosine monophosphate (cAMP) kinase. More recently, it has been suggested that metformin inhibits the mitochondrial isofrom of glycerophosphate dehydrogenase, reducing the availability of substrate for hepatic gluconeogenesis. The net effect of all these actions is inhibition of hepatic glucose output and amelioration of hyperglycemia.

Pleotropic Effects of Metformin

Results of observational studies have pointed to several beneficial effects of metformin over and beyond its effects on glycemic control. A few of these have also been
confirmed by randomized trials, but the clinical impact of these findings is as yet unclear.

The effects of metformin beyond diabetes can be discussed under the following heads:
- Metformin in endocrine disease
- Metformin in inflammation and cardiovascular disease (CVD)
- Metformin as an antitumor agent
- Miscellaneous benefits of metformin.

**Metformin in Endocrine Disease**

Metformin is one of the frontline agents used for ovulation induction in women with the polycystic ovary syndrome (PCOS). Metformin exerts its effect by improving insulin sensitivity and ameliorating hyperinsulinemia, which is one of the major pathophysiologies underlying hyperandrogenism and oligoovulation in PCOS. While various studies have thrown up conflicting results on the efficacy of metformin vis-à-vis other ovulation inducers in PCOS, the current consensus appears to be that it is less efficacious compared to other agents such as clomiphene citrate. The Endocrine Society recommend against routine use of metformin in PCOS, and suggest its use only in women with PCOS who also have “prediabetes” or T2DM that has failed lifestyle modification. Metformin may also be used as adjuvant therapy in women with PCOS undergoing in vitro fertilization so as to help prevent ovarian hyperstimulation syndrome.

**Metformin in Inflammation and Cardiovascular Disease**

Type 2 diabetes mellitus is a proinflammatory state. Increased levels of oxidative stress and enhanced platelet aggregation underlie to a significant extent, the increased risk for CVD in T2DM.

**Metformin and inflammation**

Use of metformin in individuals with impaired glucose tolerance has been shown to reduce serum levels of the inflammation marker, C-reactive protein (CRP) as well as of several macrophage-derived markers of inflammation. In patients with T2DM and coronary artery disease, use of metformin was associated with reduction in serum insulin, plasminogen activator inhibitor-1, CRP, and fibrinogen levels.

Activation of cAMP-kinase by metformin has been shown to inhibit nuclear factor kappa B, which in turn leads to reduced production of proinflammatory cytokines such as interleukin-1β and interleukin-6, as well as nitric oxide and prostaglandin E2. In addition, metformin can also suppress inflammation by inhibiting the formation of advanced glycation end products and reactive oxygen species. Of course, the effects of metformin on hyperglycemia, body weight, and dyslipidemia also contribute to its anti-inflammatory effect. It has proven difficult to isolate the intrinsic anti-inflammatory effects of metformin from these indirect effects.

**Effect on cardiovascular risk factors**

Metformin has a salutary effect on many risk factors for CVD. Small but significant reductions have been noted in both systolic and diastolic blood pressure with use of metformin. While these changes could have occurred secondary to the weight loss produced by metformin, such improvements were also noted in studies where participants did not lose weight. However, a later meta-analysis failed to show an intrinsic effect of metformin on blood pressure.

Several studies have shown that metformin has beneficial effects on the lipid profile. Reductions in total cholesterol and low-density lipoprotein (LDL) cholesterol as well as increases in high-density lipoprotein cholesterol have been reported in association with metformin use. However, these changes have been modest in magnitude and have not been consistent. While a meta-analysis published in 2004 showed that metformin reduces total and LDL-cholesterol significantly in patients with T2DM, another meta-analysis published in the same year concluded that the drug reduces total cholesterol alone and that too only at higher doses.

With respect to beneficial effects on CVD, the actions of metformin on intracellular lipid dynamics are perhaps more important than its effect on the lipid profile. Metformin has been shown to prevent lipid accumulation in macrophages as well as adipocytes. Depletion of lipid content of macrophages renders them less prone to develop into foam cells and reduces the likelihood of atheroma formation.

The antiobesity effect of metformin also contributes to its beneficial effects on CVD risk profile. Its favorable effects on body weight help to blunt the weight gain caused by other antidiabetic agents such as insulin, sulfonylureas, and thiazolidinediones. While metformin does have an anorectic effect, it cannot be recommended as therapy for weight loss in the absence of T2DM or impaired glucose tolerance.
CHAPTER 24: Metformin Beyond Diabetes

Effect on atherosclerosis and coronary events

In view of the above effects of metformin, it is perhaps not surprising that use of this agent has been associated with a reduced incidence of atherosclerotic CVD. In the United Kingdom Prospective Diabetes Study, use of metformin was associated with reduced incidence of acute myocardial infarction among obese individuals with T2DM, compared to sulfonylurea or insulin use. The antiatherosclerotic effect of metformin appears to be independent of its antihyperglycemic effects and is more likely related to its pleiotropic effects mentioned above. Recently, it has been shown that metformin attenuates atherosclerosis in euglycemic mice fed on a high-fat diet. It has been suggested that this effect is mediated by downregulation of angiotensin II receptor type 1 expression and by increase in the levels of the antioxidant, superoxide dismutase.

Metformin as an Antitumor Agent

Perhaps the most exciting "nonconventional" indication for metformin is its potential role in the management and prevention of various forms of malignancy. Several preclinical, epidemiological and observational studies have shown that use of metformin is associated with lower cancer risk in patients with T2DM compared to other antidiabetic agents. Metformin has also been found to inhibit cancer cell proliferation and reduce all cancer events.

The exact mechanism of action of the antitumor effect of metformin is not clear, but has been postulated to involve inhibition of the mammalian target of rapamycin complex 1 (mTORC1). Activation of mTORC1 is essential for metabolism, growth, and proliferation of malignant cells. Metformin has been shown to inhibit mTORC1 by both cAMP kinase-dependent and independent mechanisms.

Numerous meta-analyses have shown a 30-50% reduction in incidence of malignancy among patients with T2DM on metformin compared to other antidiabetic medications. Studies on diabetes databases in Canada and Scotland showed lower cancer incidence and mortality in patients on metformin compared to those on insulin or sulfonylureas. The incidence rates of colorectal cancer and breast cancer have been reported to be lower in patients with T2DM on metformin compared with other agents. However, in another meta-analysis in patients with diabetes, the inverse relation between metformin and cancer risk was found to be significant only for pancreatic and hepatocellular cancer and not for breast, colon, or prostate cancer.

In a study of more than 2,500 women with breast cancer, it was found that use of metformin significantly improved response rates to treatment without effect on overall survival. In patients with T2DM and prostate cancer, longer duration of metformin therapy post-diagnosis was found to be associated with reduced all-cause and cancer-specific mortality.

It is not clear from the available evidence whether the apparent protective effect of metformin on development of malignancy stems from an inherent benefit of metformin or a potential negative effect of the comparator therapies (such as insulin or sulfonylureas). Similarly, reductions in cancer-related mortality could be due either to inhibition of cancer cell growth or better response to anticancer medications. Finally, in all these nonrandomized trials, one has to consider the possibility that the baseline characteristics of the patients prescribed metformin might have also contributed to the favorable outcome. It has also been recently suggested that the antitumor effects of metformin may be due to time-related biases and may not stand-up to the rigors of a prospective randomized controlled clinical trial.

Miscellaneous Benefits of Metformin

Metformin has been shown to improve liver function in patients with nonalcoholic fatty liver disease, but has no effect on liver histology. On account of its antioxidant effects, metformin has also been suggested as therapy for neurodegenerative disorders associated with diabetes.

CONCLUSION

The list of pleiotropic actions of metformin is large and continues to expand rapidly. However, the evidence base underlying most of these effects is weak and do not support the use of this agent over and above its currently approved indications. Large well-designed randomized controlled trials, are therefore, needed in order to confirm or refute these potential benefits of metformin and to better delineate its role in the diabetologist’s therapeutic armamentarium. In the meantime, the purported benefits of metformin should serve to strengthen the confidence of clinicians in continuing its use as the first line therapeutic agent for T2DM.
REFERENCES


