SUMMARY

The primary aim of type 2 diabetes mellitus treatment is to achieve and maintain good glycemic control, and to minimize the mortality and risk of microvascular and macrovascular complications. Current algorithms for medical management of type 2 diabetes mellitus recommend a combination of lifestyle intervention and metformin as initial therapy and ‘gold standard’ treatment. Numerous studies suggest positive antihyperglycemic and metabolic effects of metformin, with a wide safety profile. There is an increasing evidence for the potential efficacy of this drug in other diseases such as polycystic ovary syndrome, nonalcoholic steatohepatitis, HIV lipodystrophy, and neoplasms.

INTRODUCTION

The prevalence of type 2 diabetes mellitus (DM) is increasing rapidly worldwide, with a prediction of more than 380 million people to be affected by 2025 (1). Insulin resistance in peripheral tissues in combination with relatively impaired insulin secretion is essential in the pathogenesis of the disease, leading to hyperglycemia and compensatory hyperinsulinemia (2). The primary goal of type 2 DM treatment is to achieve and maintain good glycemic control, and to reduce the mortality and risk of microvascular and macrovascular complications (3). The current consensus algorithms for medical management of type 2 DM recommend a combination of lifestyle intervention and metformin as initial therapy for type 2 DM (4), followed by other oral hypoglycemic agents and insulin. Besides biguanides (metformin), other antidiabetic agents include several groups of drugs, i.e. sulfonylureas, glitizides, thiazolidinediones or glitazones, α-glucosidase inhibitors (acarbose), GLP-1 analogues, dipeptidyl peptidase 4 inhibitors, and amylin agonists (pramlintide). Therapeutic profile of metformin has been evaluated for more than five decades. Experimental and clinical studies have shed new light on the multiple beneficial effects of this drug, not only in the treatment of diabetes.
DISCOVERY OF METFORMIN

The work of Dr Jean Sterne, a French clinician and his colleagues led to the discovery of metformin as an oral antidiabetic agent in the 1950s in Paris (5). The first synthesis of metformin (dimethyl biguanide) is attributed to Werner and Bell from Trinity College, Dublin, Ireland, in 1922 (6), and was a basis for further experimental and clinical studies on the potential therapeutic application of biguanides, particularly metformin. The other two biguanide agents, phenformin and buformin, were soon withdrawn from widespread clinical use due to their toxicity, especially lactic acidosis. However, five decades were needed to promote metformin from a minor product to the ‘gold standard’ in the treatment of type 2 DM, with a wide safety profile.

METFORMIN AND ANTIHYPERGLYCEMIC ACTION

Metformin reduces blood glucose levels by inhibiting hepatic glucose production and reducing insulin resistance, particularly in liver and skeletal muscle (7). The plasma insulin levels are unchanged or reduced (8). Metformin decreases intestinal absorption of glucose, and increases insulin sensitivity by enhanced glucose uptake and utilization in peripheral tissues. In vitro and in vivo studies have demonstrated the effects of metformin on membrane-related events, including plasma membrane fluidity, plasticity of receptors and transporters (9); suppression of the mitochondrial respiratory chain (10); increased insulin-stimulated receptor phosphorylation and tyrosine kinase activity (7); stimulation of translocation of GLUT4 transporters to the plasma membrane (11); and enzymatic effects on metabolic pathways, e.g., LKB1 activation of AMP-activated protein kinase – AMPK (12), which inhibits gluconeogenesis and lipogenesis.

Metformin monotherapy will lower HbA1c levels by approximately 1.5% (13), without causing hypoglycemia. In combination with sulfonylureas, HbA1c was decreased by 1.25% with glibenclamide, 0.75% with glipizide and 0.7% with glimepiride in several studies. Glitazones added to metformin decreased HbA1c from 8.1% to 6.8% (13-15). When acarbose was added to metformin, HbA1c was reduced by 0.8%-1.0% (16). A combination of bedtime insulin and metformin was more effective in controlling glycemia, with a significantly less weight gain compared with bedtime insulin plus glibenclamide, bedtime insulin plus metformin plus glibenclamide, or morning and bedtime insulin (17). Metformin and the GLP-agonists exenatide or liraglutide significantly reduced HbA1c compared to placebo (18,19).

METFORMIN AND SAFETY PROFILE

Gastrointestinal side effects, i.e. diarrhea, nausea, bloating and metallic taste in the palate are not uncommon when treatment with metformin is started, affecting 1%-30% of patients. Increasing the dose gradually, most side effects may be diminished. There is clear relationship between the dosage and effect of metformin, so the most effective dosage of metformin observed in studies (20) was 2000 mg/day. Increasing the metformin dosage from 2000 to 3000 mg/day only reduced fasting blood glucose levels by further 5%, raising the incidence of gastrointestinal side effects. The risk of hypoglycemia was low, almost the same as in the placebo group (8). Lactic acidosis is the most dangerous side effect, fortunately rare, with an incidence of 0-0.084 cases/1000 patient years (21). To minimize the risk of lactic acidosis, contraindications should be observed, i.e. impaired renal function (limit value of creatinine clearance 60 mL/min), severe liver disease, pancreatitis, alcoholism, hypoxic states, respiratory insufficiency, severe cardiac insufficiency (NYHA III/IV), cardiovascular shock, metabolic acidosis, diabetic ketoacidosis, consumptive diseases, low serum level of vitamin B12, preoperative, perioperative and postoperative states, radiological procedures using contrast, advanced age, and calorie restrictions (<1000 cal per day) (22).
METFORMIN AND BODY WEIGHT

While insulin secretagogues, thiazolidinediones and insulin itself promote increased body weight in many patients, treatment with metformin usually results in no change in body weight or in modest weight loss, and in combination with other agents it may mitigate weight gain (8). A meta-analysis of nine trials of at least 6-week duration found an average difference in body weight of -4 kg for metformin versus a sulfonylurea, unaffected by patient age (23). The ADOPT (A Diabetes Progression Outcomes Trial) study showed the mean increase in body weight at study end in the rosiglitazone group relative to metformin of 6.9 kg (95% CI 6.3 to 7.4%; \(P<0.001\)) (24). A 26-week study in a comparable patient population showed a reduction in body weight of 2.0 kg with metformin (\(P<0.05\) versus baseline) compared with an increase of 0.6 kg with rosiglitazone (not significant versus baseline) (25). A 12-month study reported a decrease in body weight of 2.5 kg with metformin compared with an increase of 1.9 kg with pioglitazone (26). The anorectic effect of metformin may be at least partly attributable to the inhibiting effect of DPP-4 (27). Adding metformin in patients suboptimally controlled on insulin therapy compared with intensification of the insulin dose by 20% resulted in lower body weight, lower body mass index, insulin dose and HbA\(_1c\) at the end of the study in the metformin arm (28). Modest weight loss with metformin has also been observed in subjects with impaired glucose tolerance enrolled in the Diabetes Prevention Program (29) and in the Indian Diabetes Prevention Program (30). Although a meta-analysis of studies in patients with polycystic ovary syndrome (PCOS) treated with metformin suggests no significant effect of metformin on body weight compared to placebo, some studies have reported a mean weight loss (1.5-3.6 kg) during 8 months of treatment with metformin in obese women with PCOS (31).

METFORMIN AND LIPID PROFILE

A meta-analysis of 41 randomized, controlled evaluations of metformin of at least 6-week duration showed significant reductions in total cholesterol, LDL cholesterol and triglycerides in patients randomized to metformin relative to comparator treatments (32); HDL-cholesterol was rarely improved by metformin treatment. Some non-randomized studies have demonstrated significant reductions in free fatty acids following treatment with metformin (33), while others did not (34). In nondiabetic persons and those with impaired glucose tolerance randomized in the Diabetes Prevention Program (35), the metformin effect on lipid profile was modest and generally smaller than the effect of the intensive lifestyle intervention included in this trial. It suggests that reductions in the risk of macrovascular endpoints with metformin, showed in the UK Prospective Diabetes Study (UKPDS) (8), is associated with other mechanisms, not only the effects on lipids.

METFORMIN AND CARDIOVASCULAR EFFECTS

Patients with type 2 DM have a two- to fourfold risk of heart disease and stroke found in the general population, with a reduction in life expectancy of five to ten years (36). UKPDS (8) was the first randomized trial demonstrating that metformin treatment was associated with significant reductions compared with diet in the risk of any endpoint related to diabetes (risk reduction 32%; \(P=0.0023\)), myocardial infarction (risk reduction 39%; \(P=0.01\)), all-cause mortality (risk reduction 35%; \(P=0.011\)), and diabetes-related death (risk reduction 42%; \(P=0.017\)). Reductions in the risk of stroke, peripheral vascular disease and microvascular endpoints did not achieve statistical significance for metformin compared with diet. Randomization to sulfonylurea/insulin was not associated with significant reductions in any of the clinical outcomes mentioned above (although significant microvascular benefits were observed with this treatment in a larger analysis of UKPDS 33) (8).
Retrospective and prospective observational studies showed a strong cardioprotective effect of metformin in patients with a high prevalence of cardiovascular disease, including patients with prior coronary heart disease events, heart failure, or symptomatic angina pectoris (37,38).

Besides the effects on the classic cardiometabolic risk factors (dysglycemia, insulin resistance, obesity, dyslipidemia and high blood pressure) observed in type 2 DM patients and demonstrated in several studies, metformin has other potential anti-atherothrombotic actions. Treatment with metformin improves endothelial function by decreasing circulating levels of sVCAM-1 and E-selectin, which are markers of endothelial activation (39); reduces circulating levels of plasminogen activator inhibitor-1 (40); improves other hemostatic parameters, decreasing Factor XIII activity and reducing the levels of Factor VII, a powerful endogenous promoter of coagulation (41). Metformin reduces circulating C-reactive protein level (42); inhibits activation of the pro-inflammatory nuclear transcription factor, NF-kappaB, secondary to an increase in the activity of the enzyme AMP-kinase (AMPK), which has been proposed as a cellular mechanism for the anti-inflammatory effects of metformin (43). Metformin also decreases oxidative stress, inhibits lipid peroxidation of LDL and HDL, and the production of the superoxide free radical (O2-) in platelets (44). Metformin may reduce the production of advanced glycation endproducts (AGE) indirectly, by reduction of hyperglycemia, and directly by an insulin-independent mechanism (45). Experimental studies suggest that metformin may inhibit the binding of monocytes to cultured vascular cells, and differentiation of monocytes into macrophages and their transformation into foam cells (46).

**METFORMIN AND POLYCYSTIC OVARY SYNDROME**

Polycystic ovary syndrome (PCOS) is the most common endocrine disease in women, affecting 5%-10% of those in reproductive age (47). PCOS includes several cardiometabolic risk factors associated with insulin resistance, such as abdominal obesity, hypertension, hyperinsulinemia, low HDL cholesterol, hypertriglyceridemia and impaired fibrinolysis, resembling the metabolic syndrome (48-50). A meta-analysis of studies comparing metformin with placebo or no treatment in women with PCOS showed that metformin significantly reduced fasting plasma glucose, systolic and diastolic blood pressure, LDL cholesterol and fasting insulin, although total cholesterol, HDL cholesterol or triglycerides did not change significantly (51). A Cochrane meta-analysis of trials that compared metformin with the oral contraceptive pill showed significant improvement in fasting insulin and triglycerides with metformin, but no overall improvement in fasting glucose (52). Besides, both meta-analyses revealed that metformin significantly reduced serum testosterone, androstenedione and dehydroepiandrostenedione sulfate. Many guidelines suggest the use of metformin as initial pharmacological therapy for most women with PCOS, particularly when overweight or obese (53), or in addition to clomifene in clomifene-resistant anovulatory women (54). Although metformin crosses the placenta, observational studies to date suggest that metformin does not adversely affect fetal or neonatal development (55-57). Metformin used during pregnancy decreased the risk of gestational diabetes in women with PCOS (58,59).

The mechanisms of metformin effects in PCOS pertain to its central and peripheral action. At the central level, the possible effect is reduction in serum LH level. At the peripheral level, metformin decreases hepatic gluconeogenesis, increases the synthesis of sex hormone-binding globulin (SHBG), consecutively decreasing free androgen levels. Metformin also increases insulin sensitivity in peripheral tissues, reduces free fatty acid oxidation, and reduces ovarian and adrenal secretion of androgens. Pleiotropic actions of metformin are mediated by the AMPK pathway. Experimental data show the effect of metformin on the expression of some genes involved in glucose metabolism (60).
METFORMIN AND OTHER POTENTIAL FUTURE USES

Nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH) and lipodystrophy syndrome associated with highly-active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV) are associated with insulin resistance and cardiovascular and metabolic risk factors.

The management of NASH includes lifestyle intervention with gradual weight loss, fibrates to control hypertriglyceridemia, gastrointestinal lipase inhibitor, orlistat, and agents that improve insulin sensitivity (metformin and thiazolidinedione) (61). In randomized studies comparing metformin plus diet versus diet, plasma glucose, body mass index, plasma insulin and plasma cholesterol improved significantly in both groups, while plasma C-peptide and insulin resistance index improved significantly only on metformin plus diet treatment (62). Another study compared metformin with vitamin E in patients with NAFLD and found significant improvement in metabolic parameters in the metformin group (63).

In patients with HIV-associated lipodystrophy, metformin significantly reduces hyperinsulinemia, body weight and diastolic blood pressure (64), and has superior effects on lipids and endothelial function compared to diet, placebo and rosiglitazone, although a combination of treatments is more effective than metformin alone (65).

METFORMIN AND ITS POTENTIAL FOR THE TREATMENT OF NEOPLASTIC DISEASE

Experimental studies suggest a role for the enzyme AMPK among the important molecular mechanisms responsible for the beneficial metabolic actions of metformin. Metformin induces tumor suppressor LKB1, which is an upstream regulator of AMPK, supporting the hypothesis on the potential anti-neoplastic effect of metformin. Activating AMPK, metformin negatively regulates mTORC1 (mammalian target of rapamycin), which is associated with a number of human pathologies (66). In vitro studies in human breast cancer cells showed that metformin inhibited cell proliferation, reduced colony formation, and caused partial cell cycle arrest (67). Metformin was also a potent inhibitor of cell proliferation in endometrial cancer lines (68). A combination of metformin and 2-deoxyglucose induced p53-dependent apoptosis in prostate cancer cells (69). Two large observational studies report on a decreased incidence of neoplastic disease in type 2 DM patients treated with metformin, compared with sulfonylurea and insulin (70,71). UKPDS revealed that metformin treatment reduced the risk of death from cancer by 29% relative to diet. Other studies also observed significantly lower cancer mortality rate in patients treated with metformin versus patients not receiving metformin (72).

CONCLUSION

Distinctive positive antihyperglycemic and metabolic effects of metformin have been observed and demonstrated in numerous trials and meta-analyses. The potential metformin action in other diseases such as PCOS, NASH, HIV lipodystrophy and neoplasms has been suggested in several studies. Metformin is not currently indicated for the management of these conditions. Thus, additional prospective randomized studies are needed for approval of indications for the treatment and prevention of the mentioned diseases.
REFERENCES


