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Metformin

New Understandings, New Uses

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Abstract

Metformin, a biguanide, has been available in the US for the treatment of type 2 diabetes mellitus for nearly 8 years. Over this period of time, it has become the most widely prescribed antihyperglycaemic agent. Its mechanism of action involves the suppression of endogenous glucose production, primarily by the liver. Whether the drug actually has an insulin sensitising effect in peripheral tissues, such as muscle and fat, remains somewhat controversial. Nonetheless, because insulin levels decline with metformin use, it has been termed an 'insulin sensitiser'. Metformin has also been shown to have several beneficial effects on cardiovascular risk factors and it is the only oral antihyperglycaemic agent thus far associated with decreased macrovascular outcomes in patients with diabetes. Cardiovascular disease, impaired glucose tolerance and the polycystic ovary syndrome are now recognised as complications of the insulin resistance syndrome, and there is growing interest in the management of this extraordinarily common metabolic disorder. While diet and exercise remain the cornerstone of therapy for insulin resistance, pharmacological intervention is becoming an increasingly viable option. We review the role of metformin in the treatment of patients with type 2 diabetes and describe the additional benefits it provides over and above its effect on glucose levels alone. We also discuss its potential role for a variety of insulin resistant and prediabetic states, including impaired glucose tolerance, obesity, polycystic ovary syndrome and the metabolic abnormalities associated with HIV disease.

In medieval times, *Galega officinalis*, also known as Goat's rue, French lilac or Italian fitch, was found to relieve the intense urination that accompanied diabetes.[1] The active ingredient was later found to be guanidine. Biguanides (containing two linked guanidine rings) became available for clinical use in patients with diabetes in the 1950s. The first two biguanides, phenformin and buformin, were removed from the US market in the 1970s because of increased risk of lactic acidosis.[2] Metformin, a less lipophilic and considerably safer biguanide, has been used worldwide for decades but it became available in the US only in 1995.[3] Since then, it has become the most widely prescribed antihyperglycaemic agent in the US.

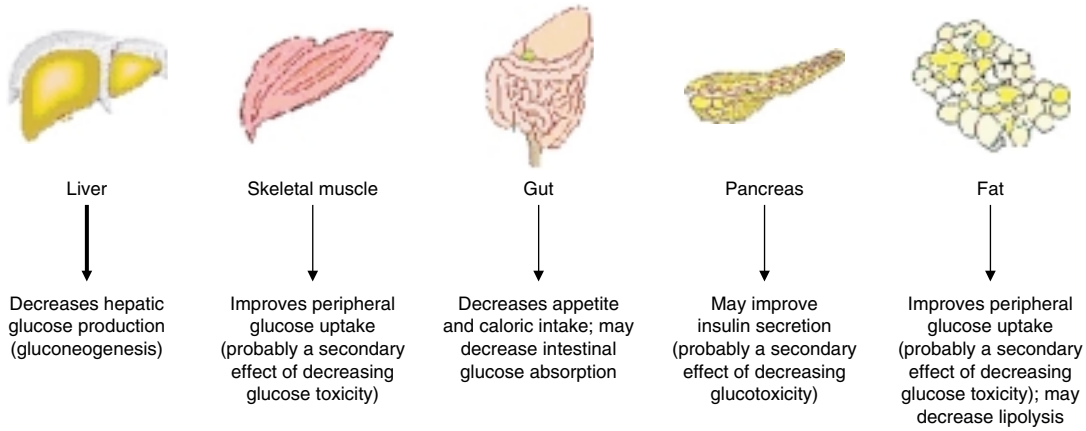

Fig. 1. Metformin: proposed mechanisms of action.

Considered an 'insulin sensitiser', since it lowers glucose levels without increasing insulin secretion, metformin is distinguished from thiazolidinediones by its primary site of action. Metformin lowers endogenous glucose production at the level of the liver, while thiazolidinediones work primarily in peripheral tissues, such as muscle and fat.[4] Despite this distinction, both metformin and the thiazolidinediones improve cardiovascular risk factors, although to date only metformin has been shown to decrease actual cardiovascular outcomes.[5] Metformin has myriad additional beneficial effects in adults with type 2 diabetes, including weight reduction, decreased hyperinsulinaemia, improved lipid profiles, augmented fibrinolysis and enhanced endothelial function.[5] These benefits and its good safety record have led investigators to consider the use of metformin in insulin resistant states even before the development of frank hyperglycaemia.[6-8]

1. Mechanism of Action

The precise mechanism of action of metformin has been a point of controversy for many years, with multiple sites of action being proposed, including decreased hepatic glucose production, increased peripheral glucose disposal and reduced intestinal glucose absorption. The most recent studies strongly support the former as the primary route through which metformin exerts its antihyperglycaemic effect (see figure 1).

The rate of endogenous glucose production, which is strongly correlated with increased fasting plasma glucose,[9,10] is increased by approximately 25–100% in patients with type 2 diabetes compared with control subjects as assessed by nuclear magnetic resonance (NMR) spectroscopy.[11,12] This increased glucose production can be entirely attributed to an approximately 3-fold increase in the rate of gluconeogenesis as assessed by the ^{13}C-NMR method and a 2-fold increase in the rate of gluconeogenesis as assessed by the $^{2}H_2O$ method.[11] The glucose lowering effect of metformin results from a 25–30% decrease in the rate of endogenous glucose production,[4,11] which is entirely accounted for by reduction in the rate of gluconeogenesis as determined by both methods.[11] This results in a similar relative reduction in fasting plasma glucose levels.[4,13-15] Others have shown that metformin reduces glucose production either by decreasing gluconeogenesis[16] or by decreasing glycogenolysis,[17,18] although these studies had limitations in the methodologies used to assess the rates of these metabolic processes.[11] To a lesser extent, plasma glucose levels are decreased by the stimulation of

peripheral glucose uptake by skeletal muscles and adipose tissue, which is most likely secondary to the reversal of glucotoxicity and not a direct pharmacological effect.[19] Unlike sulfonylureas, metformin does not stimulate insulin secretion.[11,16]

Similar results are reported from *in vitro* studies, demonstrating inhibition of gluconeogenesis in the perfused liver model by inhibition of hepatic lactate uptake.[20] In isolated rat hepatocytes, metformin has been shown to decrease ATP concentration, an allosteric inhibitor of pyruvate kinase,[21] thus decreasing glucose output by increasing pyruvate kinase flux. However, in a separate study,[22] metformin did not decrease uptake of gluconeogenic precursors nor ATP concentrations. Rather the authors hypothesised that metformin decreased gluconeogenic flux through inhibition of pyruvate carboxylase-phosphoenolpyruvate carboxykinase activity and possibly through increased conversion of pyruvate to alanine. It should be noted that all these studies used very high doses of metformin (250–350 mg/kg) which are 8- to 12-fold higher than those used in the treatment of patients with diabetes.

Metformin also stimulates AMP-activated protein kinase (AMPK) in intact cells and *in vivo*,[23] and possibly inhibits complex 1 of the mitochondrial respiratory chain.[24] AMPK is the downstream component of a protein kinase cascade that acts as a 'sensor' of cellular energy. Once activated by ATP depletion, it turns on ATP-producing catabolic pathways and switches off ATP-consuming anabolic pathways, both directly via phosphorylation of metabolic enzymes and indirectly via effects on gene expression. Metformin stimulates phosphorylation of a key regulatory site on the catabolic subunit of AMPK in intact cells[23] but not in cell-free assays.[25] In the latter study,[25] authors could not establish a definitive mechanism by which metformin activates AMPK, but did show that the mechanism is distinct from that of the existing AMPK-activating agent, 5-aminoimidazole-4-carboxamide riboside (AICAR), which inhibits expression of gluconeogenic enzymes in hepatoma cell lines[26] and endogenous glucose output *in vivo*.[27] Metformin appears to disrupt respiratory chain oxidation of complex 1 substrates (glutamate) in hepatocyte mitochondria, which decreases gluconeogenesis.[28] It remains unclear if metformin acts by slow permeation across the inner mitochondrial membrane[28] or by unidentified cell-signalling pathways.[29] Even at a low concentration of 5–10 μmol/L, biguanides increase the rates of calcium uptake in isolated hepatic mitochondria where calcium ions serve as potent activators of mitochondrial respiration.[30]

In adipose tissue and skeletal muscles, metformin, in the presence of insulin, facilitates the trafficking of the glucose transporters 1 and 4 to the plasma membrane.[31] However, metformin has also been shown to have insulin independent effects, including glucose transport in cultured skeletal muscle,[32] activation of insulin and tyrosine kinase activity in insulin-like growth factor (IGF)-1 receptors of vascular smooth muscle cells,[28] and activation of tyrosine kinase in *Xenopus* oocytes with subsequent stimulation of inositol 1,4,5-triphosphate production and glycogen synthesis.[33]

In addition, metformin decreases plasma free fatty acid concentrations by 10–30% in individuals with diabetes.[11,34,35] Elevated levels of free fatty acid may contribute to increased hepatic glucose production and peripheral insulin resistance.[36-38] Therefore, it is possible that a reduction in the circulating plasma free fatty acid levels by metformin contributes to reduced rates of gluconeogenesis. By ameliorating the effects of high free fatty acid and glucose levels on pancreatic β cells, metformin may also partially correct the impaired insulin secretion that characterises the type 2 diabetic state.[39]

Metformin is found in high concentrations in the small intestine[31,40] and may also decrease intestinal glucose absorption;[41] thereby, affecting postprandial hyperglycaemia. Postprandial glucose is also

reduced by the normal suppression of hepatic glucose production after meal ingestion, which is recognised to be impaired in patients with type 2 diabetes.

In summary, metformin exerts its antihyperglycaemic effect primarily through inhibition of increased rates of hepatic gluconeogenesis in patients with diabetes, thereby decreasing endogenous glucose production and lowering of both fasting and postprandial plasma glucose. It may also have some effect on improving peripheral insulin sensitivity, decreasing intestinal glucose absorption, and possibly ameliorating the effect of glucotoxicity and/or lipotoxicity on insulin action and insulin secretion by pancreatic β cells.

2. Pharmacokinetics, Tolerability and Adverse Effects

2.1 Pharmacokinetics and Dosage Adjustments

As a pharmacological agent, metformin has an oral bioavailability of 50–60%,[42] is not highly protein bound, and has a wide volume of distribution with maximal accumulation in the small intestine.[40] It is excreted unchanged in the urine, and impaired renal function will lead to metformin accumulation and increases the risk of potentially life-threatening lactic acidosis (see section 2.2). Therefore, its use should be restricted only to those patients with normal renal function (serum creatinine <133 μmol/L [<1.5 mg/dL] in males and <124 μmol/L [<1.4 mg/dL] in females). In the elderly with decreased muscle mass, creatinine clearance should be calculated and metformin should be avoided when this is <1–1.17 mL/s (60–70 mL/min). Other contraindications include hepatic dysfunction, congestive heart failure, acute or chronic metabolic acidosis, alcoholism and dehydration. It should be withdrawn temporarily in any patient with the potential for impending haemodynamic collapse, or in anyone undergoing surgical procedures or receiving radiocontrast agents. In such situations, metformin may be restarted 48 hours after the procedure, when normal renal function is ensured.

2.2 Tolerability and Adverse Effects

Adverse effects include gastrointestinal complaints, such as nausea, diarrhoea and/or abdominal cramping, occurring in up to 50% of treated patients, usually improving or completely subsiding as treatment is continued. These effects can be minimised by beginning therapy at 500mg once or twice daily with meals, with gradual upward titration over the following several weeks.[3,42,43] If adverse effects occur, the dose should be decreased to the previously tolerated level and 1–2 weeks should pass before any further increases are attempted. A minority of patients cannot tolerate treatment because of adverse effects. Of those patients receiving long-term metformin therapy, up to 10–30% may develop mild vitamin B12 malabsorption which is rarely clinically relevant.[15,43]

The adverse effect of greatest concern is certainly lactic acidosis, which has been reported to occur only in 1 per 30 000 patient-years of use.[44] In a large series of metformin treated patients with lactic acidosis, neither lactate nor plasma metformin levels were of prognostic significance in relation to mortality. Death in these patients appeared to be associated with the underlying severity of illness.[45] Unlike phenformin, which had a lipophilic side chain, metformin is poorly bound to mitochondrial membranes, and therefore does not substantively inhibit oxidative phosphorylation nor influence lactate turnover or oxidation in either the basal or the insulin-stimulated state. Metformin-related increases in lactate levels may actually arise from extrahepatic splanchnic bed sources and not from skeletal muscles.[46] Metformin-associated lactic acidosis is therefore classified as a 'type B lactic acidosis' (i.e., with increased lactate production).

Most cases of lactic acidosis with metformin occur exclusively in patients with contraindication(s) to its use (see table I) and, therefore, following the strict prescription guidelines is imperative. Several studies have recently demonstrated that a large percentage of patients currently receiving metformin have actual current contraindications for its use,[44,45] although admittedly no significant increases in the number of patients developing lactic acidosis were reported in these series.

In patients with type 2 diabetes, the optimally efficacious dose of metformin appears to be 2000 mg/day,[14] although doses up to 2550mg are approved. A long-acting preparation is now available, which can be given once daily and may be associated with fewer gastrointestinal adverse effects.

3. Antihyperglycaemic Effects in Type 2 Diabetes

In clinical trials, metformin decreases fasting plasma glucose by 3.3–3.9 mmol/L (60–70 mg/dL) with a 1–2% decline in haemoglobin A_{1c} (HbA_{1c}).[14,15,34,43,47-52] This is equivalent to the glucose lowering effect of sulfonylureas or thiazolidinediones when used as monotherapy. The decreases in the plasma glucose levels by metformin are independent of age, ethnicity, duration of diabetes, body mass index (BMI), or either fasting and glucose-stimulated insulin or C-peptide levels.[15,47]

Table I. Contraindications for metformin therapy

Known hypersensitivity to metformin
Renal insufficiency - serum creatinine ≥1.5 mg/dL (men) or ≥1.4 mg/dL (women) or abnormal creatinine clearance[a]
Abnormal hepatic function
Congestive heart failure requiring pharmacological therapy
Acute haemodynamic compromise or hypoxic states
Dehydration
Acute or chronic metabolic acidosis, including diabetic ketoacidosis
Use of iodinated contrast for radiological examinations (withdraw on the day of and for 48h after the procedure; restart once normal renal function is documented)

a Documentation of normal creatinine clearance is recommended when using metformin in the elderly, since serum creatinine may be a poor indicator of actual renal function in this age group.

Metformin is a unique drug, which, unlike sulfonylureas, thiazolidinediones and exogenous insulin, does not cause weight gain. Indeed, metformin often leads to modest weight reduction in obese patients with[3,11,14,16,34,47,49,53] or without diabetes.[54,55] Weight loss has been attributed to a decreased net caloric intake through appetite suppression,[29] an effect which appears to be independent of the mild nausea that is frequently encountered in the initial phases of therapy. Because glucose is decreased through nonpancreatic mechanisms, metformin therapy is also associated with a small decline in circulating insulin levels and no increased risk of hypoglycaemia is observed when the drug is used as monotherapy.[4,11,49,51] Metformin also reduces both visceral and total body fat in patients with central adiposity.[56]

Notably, type 2 diabetes is a progressive disease that frequently requires additional therapy with combinations of drugs that have distinct mechanisms of action. For example, in the UK Prospective Diabetes Study (UKPDS), less than 25% of patients with newly diagnosed type 2 diabetes were able to maintain an HbA_{1c} of <7% after 9 years of monotherapy.[57] In this light, metformin has been shown to be efficacious in combination therapy with sulfonylureas,[15,58-60] insulin,[61-63] α-glucosidase inhibitors,[64,65] thiazolidinediones[4,66,67] and non-sulfonylurea insulin secretagogues.[68-72] Metformin has also been shown to decrease insulin requirements in patients with type 1 diabetes, resulting in improvement in glycaemic control, although it is not approved nor recommended for use in this setting.[73]

4. Nonhypoglycaemic Effects in Patients with Type 2 Diabetes

The beneficial cardiovascular effects of metformin in patients with type 2 diabetes are summarised in table II.

In a substudy of the UKPDS,[50] metformin therapy was compared with conventional diet therapy and with treatment with a sulfonylurea or insulin. Over 1700 overweight subjects (>120% of ideal bodyweight) with newly diagnosed type 2 diabetes, (mean age 53 years) were randomised to either diet ('conventional', n = 411) or intensive treatment with metformin (n = 342), with an aim of reducing fasting plasma glucose to <6 mmol/L (108 mg/dL). In a secondary analysis, the patients administered metformin were compared with 951 overweight patients allocated to intensive blood glucose control with either chlorpropamide (n = 265), glibenclamide (n = 277) or insulin (n = 409). During 10.7 years of follow up, the metformin group achieved a HbA_{1c} of 7.4% vs 8% in the conventional group. Metformin therapy was associated with a 32% risk reduction for any diabetes related endpoint (p = 0.0023), a 42% reduction in diabetes related death (p = 0.017), 39% fewer myocardial infarctions (p = 0.01) and a 36% reduction in all cause mortality (p = 0.011) compared with the conventionally treated group. Despite the similar levels of HbA_{1c} achieved in metformin and other intensively treated groups (sulfonylureas, insulin), an additional benefit of metformin was observed in a reduced risk for any diabetes related endpoint, all mortality and stroke. There were no significant differences between metformin recipients and sulfonylurea/insulin recipients with regards to microvascular endpoints, such as retinopathy and albuminuria, which were reduced compared with the control (diet-treated) group.[74] The benefit in macrovascular outcomes may be explained by the effects of metformin on bodyweight, plasma lipids or fibrinolysis (see later this section).[75]

Table II. Beneficial cardiovascular effects of metformin in patients with type 2 diabetes

Variable	Metformin effect
Glucose concentrations	↓
Insulin	↓
Bodyweight	↓ to ↔
Blood pressure	↔
Triglycerides	↓ to ↔
Total cholesterol	↓ to ↔
LDL cholesterol	↓ to ↔
HDL cholesterol	↑ to ↔
Lipoprotein(a)	↓
Hypercoagulability	↓
C-reactive protein	↓ to ↔
Endothelial function	↑
Cardiovascular events	↓

HDL = high-density lipoprotein; **LDL** = low-density lipoprotein; ↑ indicates increases; ↓ indicates decreases; ↔ indicates neutral effect.

However, interestingly, in a subset of patients in which metformin was added to otherwise failing sulfonylurea treatment in another substudy of the UKPDS, a significant increase in diabetes related death and all cause mortality was observed.[50,76] It should be noted that these patients were, on average, 5 years older, more hyperglycaemic at baseline and more overweight than the comparator group. Therefore, selection bias may have influenced these results. In addition, a *post hoc* epidemiological analysis of all UKPDS patients who received the combination of sulfonylurea and metformin was performed, and no increased mortality risk could be detected overall. It is also noteworthy that metformin monotherapy was the only pharmacological UKPDS treatment option that was not associated with weight gain[50]

As previously noted, metformin also has additional beneficial effects on cardiovascular disease risk factors. Hyperinsulinaemia, an important component of metabolic syndrome, may be an independent risk factor of coronary heart disease[77,78] and metformin has been consistently shown to lower fasting insulin levels in type 2 diabetes[4,11,17,54] as well in other insulin resistant states.[55,56,79] Type 2

diabetes is also characterised by elevated free fatty acid and triglyceride levels, low high-density lipoprotein (HDL)-cholesterol levels, and increased numbers of small dense low-density lipoprotein (LDL) particles, which are highly atherogenic. Increased free fatty acids may contribute to increased hepatic glucose production and peripheral insulin resistance.[36-38] Metformin mildly decreases total cholesterol and LDL cholesterol,[11,15,80] decreases plasma free fatty acids[11,59,81] and triglycerides,[13,15,59,82] and may even slightly increase HDL cholesterol.[15,59,79,82] Metformin also lowers lipoprotein(a) levels.[83,84] Taken together, metformin appears to have modest beneficial effects on lipid profiles, which may at least partially contribute to the benefit imparted upon macrovascular disease seen in the UKPDS.[50]

Insulin resistance is associated with decreased fibrinolysis resulting in an increased propensity towards intravascular thrombosis. Metformin decreases concentrations and activity of plasminogen activator inhibitor-1 (PAI-1),[75,85,86] tissue plasminogen activator (tPA) antigen,[87] von Willebrand factor,[87] platelet aggregation and adhesion,[88] and increases tPA activity,[89] each of which improves hypercoagulability. However, metformin may also mildly increase total serum homocysteine levels, a potential risk factor for cardiovascular disease, possibly through decreasing vitamin B12 levels.[90,91] The clinical implication of this is not clear at the present time.

Hypertension and endothelial dysfunction also commonly characterise insulin resistant states.[92,93] Metformin therapy minimally reduces[89,94] or exerts no effect[15,42] on blood pressure in patients with type 2 diabetes. Any potential antihypertensive effect may involve both insulin-dependent and insulin-independent vasodilatory actions.[1] Recently, metformin has been shown to improve endothelial dysfunction, as measured by acetylcholine-stimulated vasodilation in patients with type 2 diabetes,[95] as well as in other insulin resistant states.[96] Endothelin-1, an important marker of endothelial dysfunction and a potent vasoconstrictor, is significantly reduced by metformin in both obese and nonobese patients with polycystic ovary syndrome (PCOS).[96] C-reactive protein, one of the important inflammatory markers and an emerging nontraditional risk factor for cardiovascular disease,[97] was also significantly decreased after four months of therapy with metformin.[98]

A newer class of antihyperglycaemic agents, the thiazolidinediones, are more aptly referred to as 'insulin sensitisers', since they clearly improve insulin sensitivity in peripheral tissues (muscle, fat), and to a lesser extent in liver. Cardiovascular risk reduction has also been attributed to the thiazolidinediones, probably to a greater extent than metformin.[5,98] However, unlike metformin, the thiazolidinediones have not yet been associated with an actual reduction in cardiovascular endpoints, although studies are currently underway to test this very hypothesis.

In conclusion, many have proposed that given its unsurpassed antihyperglycaemic effect, positive influence on a variety of cardiovascular risk intermediaries, especially bodyweight, and its demonstrated positive effect on macrovascular outcomes, metformin should be considered the optimal first-line therapy for patients with type 2 diabetes – barring any contraindications to its use.

5. Potential Clinical Uses of Metformin

5.1 Paediatric Use

By recent estimates, type 2 diabetes may now account for nearly half of all new cases of diabetes in certain paediatric centres.[99] The actual prevalence has been estimated at between 2 and 50 per 1000 in various paediatric populations, and rates have increased as much as 10-fold over the past two decades. This is most probably a reflection of the

modern trends of obesity and inactivity in Western societies.[100] In almost all published series, the mean BMI of children with type 2 diabetes exceeds the 95th reference percentile for age. Unfortunately, in children, weight loss, being the cornerstone of therapy for this disease, is as difficult to achieve as it is in adults. As a result, pharmacological therapy is often required to control hyperglycaemia.

Metformin has been used safely and effectively in children with type 2 diabetes and insulin resistance, and appears to prevent further weight gain.[101] In a recent study involving obese adolescents with fasting hyperinsulinaemia and a family history of type 2 diabetes, treatment with metformin for 6 months resulted in 1.3% decline in BMI from baseline, a 40% decrease in fasting plasma insulin, and a progressive decline in fasting plasma glucose (from a mean of 4.71 mmol/L [85 mg/dL] to 4.16 mmol/L [75 mg/dL])[101] Metformin was well tolerated by the majority of patients, with transient gastrointestinal complaints in 40% of treated subjects. Metformin also causes weight loss in obese adolescent girls, who failed to lose weight with diet intervention alone.[102]

In a randomised, double-blind, placebo-controlled study,[103] metformin 1000mg twice daily was administered to 82 patients with type 2 diabetes aged 10-16 years for up to 16 weeks. Metformin significantly decreased fasting plasma glucose (−2.38 mmol/L [−43 mg/dL], $p < 0.001$) and significantly lowered HbA_{1c} (7.5% vs 8.6% in placebo recipients, $p < 0.001$). More impressively, 84% of metformin treated patients achieved an HbA_{1c} of <7% vs 22% in the placebo group. While there was no significant decrease in bodyweight, total cholesterol levels improved ($p = 0.04$ vs placebo). Transient diarrhoea and/or abdominal pain were reported in 25% of participants. Regarding the use of metformin in adolescent girls, it should be noted that there are also no reports of teratogenicity and metformin is currently classified as a Class B drug during pregnancy (see section 5.3).

Metformin also appears to be effective in preventing weight gain commonly associated with use of psychotropic drugs like olanzapine, risperidone, quetiapine and valproic acid in children. As many as 50% of patients will experience weight gain when taking these drugs.[104] In 19 patients receiving one of these drugs, 15 lost weight and, in one patient, weight remained stable with metformin treatment.

In summary, metformin appears to be an effective and well tolerated antihyperglycaemic agent in the paediatric patient with type 2 diabetes, when diet and exercise have failed to normalise blood glucose levels. Metformin may have an advantage over insulin or sulfonylureas *vis-à-vis* weight gain. It is not yet formally approved by the US FDA for the paediatric use indication. Larger clinical trials in the paediatric population are currently underway.

5.2 Role in Diabetes Prevention

BMI is a major risk factor for type 2 diabetes.[105] For every 1kg weight gain, for instance, there is nearly a 5% increase in the risk of diabetes.[106] Weight reduction through diet and exercise improves insulin sensitivity and could prevent the progression to hyperglycaemia. In a recent clinical trial from Finland[107] involving 522 subjects, lifestyle changes significantly reduced the risk of diabetes in middle-aged, overweight individuals with impaired glucose tolerance. Those in the intervention group enjoyed a 58% reduction in the incidence of diabetes over 4 years. Moreover, blood pressure, triglyceride levels and HDL-cholesterol levels also improved significantly with intervention. In a similar prevention study conducted in US, the Diabetes Prevention Program (DPP),[108] 3234 individuals with impaired glucose tolerance were randomised to placebo, metformin 850mg twice daily or a life style modification programme with goals that included a 7%

weight loss and at least 150 minutes of physical activity per week. The mean age of the participants was 51 years and the mean BMI was 34 kg/m^2, with an average follow up of nearly 3 years. By the study's conclusion, the incidence of diabetes was 11, 7.8 and 4.8 cases per 100 person years in the placebo, metformin and lifestyle modification groups, respectively. This calculated to a risk reduction of 58% with lifestyle changes (interestingly the precise same result as in the Finnish study) and 31% with metformin, as compared with placebo. Metformin was more effective in those with a higher body mass index and those with higher fasting plasma glucose levels, and less effective in the elderly. Cost-effectiveness analyses are pending at this time. However, based on these results, metformin therapy may be a reasonable option to prevent diabetes in those individuals who are overweight with mild hyperglycaemia, particularly in younger groups who have failed initial attempts at lifestyle modification.

5.3 Use in Polycystic Ovary Syndrome

PCOS affects 6–10% of women of child-bearing age and is the most common cause of female infertility in the US.[109] Both lean and obese women with PCOS are frequently insulin resistant,[110-112] and hyperinsulinaemia is thought to be a major contributing factor to its pathogenesis, by increasing ovarian androgen secretion[113,114] and decreasing the synthesis of sex hormone binding globulin by the liver[115] (which, in turn, increases the amount of biologically active free testosterone).

In women with PCOS, metformin at dosages up to 1500 mg/day,[116] decreases: (i) bodyweight;[50,117] (ii) insulin, total and free testosterone,[55,56,118] and luteinizing hormone (LH) levels;[119] and (iii) the 17-hydroxy progesterone response to human chorionic gonadotropin.[120] In some studies, the degree of hirsutism is also attenuated.[51,121] Importantly, metformin therapy also improves menstrual cyclicity and ovulatory function in most,[55,56,118,122-125] but not all,[126,127] studies. In women with PCOS, metformin may actually be more effective than clomiphene in inducing ovulation, as demonstrated by the percentage of women who ovulated while receiving metformin (34%) versus those who took or clomiphene (8%).[124] Moreover, the combination of metformin and clomiphene further improved ovulatory success (19 of 21 women [90%]).[124] Lastly, use of metformin in women with PCOS not responding to clomiphene, improves their chances of ovulation and subsequent pregnancy. In the metformin-treated group in one study, 75% of women ovulated compared with only 27% in the placebo group.[125] Fifty-eight percent of women on metformin became pregnant versus 13% with placebo.

Metformin 1500 mg/day for 1 month prior to ovulation induction with follicle stimulating hormone (FSH) also results in fewer follicles larger than 15mm in diameter on the day of human chorionic gonadotropin administration compared with women who did not receive metformin (mean of 2.5 vs 4.5 follicles, respectively).[128] The mean estradiol concentration was 45 ng/dL in women treated with FSH and metformin versus 72 ng/dL in women treated with FSH alone, suggesting that metformin prevents hyperstimulation with FSH and may potentially reduce the risk of multiple pregnancies during fertility treatments. Metformin significantly increases the number of mature oocytes, fertilisation rates, and the number of embryos produced in women with PCOS who undergo gonadotropin-stimulated *in vitro* fertilisation-embryo transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI).[129]

Finally, with rates of early pregnancy loss as high as 30–50% in women with PCOS, the continuation of metformin therapy throughout gestation has been associated recently with a dramatic decline in the miscarriage rate.[130,131] These data have led obstetricians to consider the continuation of this drug during early pregnancy in women with PCOS who con-

ceive while taking metformin. Metformin is classified as a Category B drug during pregnancy and has been used in women with gestational diabetes with no apparent teratogenic effects.[132,133] While neither are currently approved for use during pregnancy, metformin would appear to be safer in women contemplating pregnancy than thiazolidinediones, which also improve fertility in insulin resistant women with PCOS[134,135] but which exert their effects through the modulation of gene transcription and which are classified as Category C drugs.

In summary, metformin has been shown to improve the metabolic and reproductive abnormalities in patients with PCOS, increasing their chances of conception and possibly even preventing early trimester pregnancy loss. Given its beneficial metabolic effects as described earlier, metformin may also decrease the risk of developing type 2 diabetes[136] and cardiovascular disease. Whether the benefit of metformin in this group of patients is mediated through the reduction in insulin levels, bodyweight or through a direct beneficial effect on the ovaries remains unclear.

5.4 Use in HIV-Associated Metabolic Abnormalities

The use of highly active antiretroviral therapy (HAART) in HIV-infected patients is associated with abnormalities of glucose homeostasis, including insulin resistance and hyperinsulinaemia, impaired glucose tolerance and, at times, frank type 2 diabetes. Hypertriglyceridaemia, low HDL cholesterol and an increased risk of cardiovascular events are also reported in this population. These metabolic alterations frequently occur in association with changes in body composition (increased visceral fat and loss of subcutaneous fat).[137,138] Protease inhibitors (PI), one of the specific antiretroviral therapies in HAART, reduce insulin sensitivity *in vivo*[139] and inhibit glucose transporter (GLUT)-4 mediated glucose transport *in vitro*.[140] They are likely to be, at least, partly responsible for the insulin resistance and body composition changes in HIV-infected patients (although these have also been described in the absence of PI therapy).

Metformin therapy has been investigated recently in this setting. HIV-related fat distribution is associated with significantly increased levels of PAI-1 compared with controls and metformin 500mg twice daily for 12 weeks has been shown to significant decrease circulating levels of this prothrombotic factor.[141] In another study,[142] 26 HIV-infected patients without diabetes who had fat redistribution and abnormal glucose or insulin responses to oral glucose tolerance testing (OGTT) were randomised to receive metformin 500mg twice daily or placebo for 3 months. There were significant decreases in insulin levels during the OGTT ($p = 0.01$), bodyweight ($p = 0.005$), diastolic blood pressure ($p = 0.009$) and visceral abdominal fat ($p = 0.08$) with metformin versus placebo recipients. Metformin was well tolerated with no significant adverse effects, including no increase in plasma lactate levels. Other investigators have reported similar reductions in measures of insulin resistance and visceral adiposity after 8 weeks of therapy of metformin at the higher dose of 850mg 3 times daily.[143] Larger studies of metformin and other insulin sensitisers are currently underway in HIV-infected patients with HAART-associated insulin resistance and abnormal glucose metabolism.

5.5 Use for Weight Reduction

As noted previously, metformin has been associated with some weight loss in most short-term studies conducted in patients with type 2 diabetes. With this in mind, metformin has been tried in obese individuals without diabetes as a tool for inducing weight loss. In several studies, metformin decreased BMI,[144-146] fasting insulin levels,[144,147,148] fasting and postprandial plasma glucose,[149] waist-to-hip ratio,[146] total cholesterol,[144,148,149] and increased

insulin sensitivity[145,147] and HDL cholesterol[149] in obese but nondiabetic adults. There is either no effect[150] or a decrease[144,145] in plasma leptin levels.

In one study, the effect of metformin was compared with other weight loss agents, sibutramine and orlistat.[146] One hundred and fifty females with BMI >30 kg/m^2 were randomised to one of these three drugs for 6 months. All three groups showed significantly reduced BMI, fasting and postprandial blood glucose levels, and a measure of insulin resistance, as well as in total cholesterol, LDL cholesterol, triglycerides, lipoprotein(a) and apolipoprotein B levels, and blood pressure. However, there was a significantly greater decrease in BMI in the sibutramine group than in either of the other two groups ($p \leq 0.0001$). Metformin was well tolerated in these studies with minimal transient gastrointestinal side effects.

However, in the UKPDS and the DPP, while metformin therapy was associated with initial modest weight reduction, this effect was lost over time. Thus, metformin is best considered a weight-neutral drug with long-term therapy, at least in patients with type 2 diabetes or impaired glucose tolerance.

5.6 Use in Nonalcoholic Steatohepatitis

Fatty liver disease is extremely common in patients with type 2 diabetes mellitus and the insulin resistance syndrome. When severe, it may lead to nonalcoholic steatohepatitis (NASH) which, over time, may result in cirrhosis.[151] Insulin sensitisers have been proposed by some as a logical therapeutic avenue. Since the use of both metformin and the thiazolidinediones is problematic in those with underlying liver disease, there are few studies in this patient population. In the insulin resistant ob/ob mouse, metformin therapy reversed hepatomegaly, steatosis and aminotransferase abnormalities.[152] There is only one published clinical study to date, an uncontrolled, nonrandomised investigation of 20 patients with NASH.[153] Metformin therapy normalised transaminases in 50% of patients and liver volume decreased by 20%. Further investigation in this important area appears warranted.

6. Conclusion

Metformin is a popular, generally well tolerated, effective antihyperglycaemic agent with demonstrated benefit on vascular risk and outcomes in patients with diabetes. As a result, many consider it the optimal treatment of choice in a patient with type 2 diabetes which remains suboptimally controlled despite diet and exercise. Given its demonstrated effects and safety, an expanded role for metformin in insulin resistant, prediabetic states is under intense investigation. Metformin is already being used in an 'off-label' fashion for glucose control in children and teenagers with type 2 diabetes, in nondiabetic women with PCOS to improve ovulatory function, and in patients with insulin resistance and/or impaired glucose tolerance to prevent the progression to diabetes. Data are also emerging as to the safety and efficacy of metformin in these new therapeutic arenas. Further study is necessary before more widespread use is encouraged.

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