Metformin: An Update

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Metformin is an insulin-sensitizing agent with potent antihyperglycemic properties. Its efficacy in reducing hyperglycemia in type 2 diabetes mellitus is similar to that of sulfonylureas, thiazolidinediones, and insulin. Metformin-based combination therapy is often superior to therapy with a single hypoglycemic agent. The antihyperglycemic properties of metformin are mainly attributed to suppressed hepatic glucose production, especially hepatic gluconeogenesis, and increased peripheral tissue insulin sensitivity. Although the precise mechanism of hypoglycemic action of metformin remains unclear, it probably interrupts mitochondrial oxidative processes in the liver and corrects abnormalities of intracellular calcium metabolism in insulin-sensitive tissues (liver, skeletal muscle, and adipocytes) and cardiovascular tissue.

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Insulin resistance contributes greatly to development of cardiovascular disease in patients with the metabolic syndrome and its extreme presentation, type 2 diabetes mellitus. Therefore, treatment with an insulin-sensitizing agent, such as metformin, in patients with type 2 diabetes mellitus may correct several of the primary pathophysiologic abnormalities of the metabolic syndrome. In diabetic patients, metformin appears to provide cardiovascular protection that cannot be attributed only to its antihyperglycemic effects. These additional cardioprotective effects in these patients may be related to the favorable actions of metformin on lipid metabolism, vascular smooth-muscle and cardiomyocyte intracellular calcium handling, endothelial function, hypercoagulation, and platelet hyperactivity. We discuss known mechanisms by which metformin exerts its beneficial glycemic and cardiovascular actions.

Clinical Role of Metformin

Metformin, an insulin-sensitizing biguanide used to treat type 2 diabetes, has been shown to be as effective as insulin or sulfonylureas when used as monotherapy (1–5). In conjunction with diet, metformin reduces fasting glucose concentration by 2.78 to 3.90 mmol/L (50 to 70 mg/dL), which corresponds to a 1.3% to 2.0% reduction in hemoglobin A_{1c} values (1, 2, 4, 6–8). The magnitude of plasma glucose reduction is related to pretreatment glucose levels (7, 9). The efficacy of metformin monotherapy has been shown to be independent of age, body weight, ethnicity, duration of diabetes, and insulin and C-peptide levels (1, 2).

Metformin may have special benefits in overweight patients with type 2 diabetes. Unlike sulfonylureas, insulin, and thiazolidinediones, metformin does not affect body mass index (1) or decreases body weight in obese patients with (4, 10) and without (11, 12) diabetes. Significant reductions in total body fat and visceral fat have been observed in women with preexistent abdominal or visceral obesity who are treated with metformin (11). Excessive fat localized to the paraintestinal region is a major contributor to the pathogenesis of the cardiovascular metabolic syn-

ary to weight loss or fat redistribution) may have additional cardiovascular benefits in insulin-resistant persons treated with metformin (13, 14). Weight loss during metformin treatment has been attributed to decreased net caloric intake (15), probably through appetite suppression, an effect that is largely independent of gastrointestinal side effects of metformin (such as nausea and diarrhea) (10). Reduction in hyperinsulinemia related to reduced insulin resistance may have an additive effect on weight reduction in obese insulin-resistant persons (13, 14).

At doses of 500 to 1500 mg, metformin has an absolute oral bioavailability of 50% to 60% (16). The drug is not protein bound and therefore has a wide volume of distribution (8), with maximal accumulation in the small-intestine wall (17). Metformin undergoes no modifications in the body and is secreted unchanged by rapid kidney excretion (through glomerular filtration and, possibly, tubular secretion) (8). Impaired kidney function slows elimination and may cause metformin accumulation (18). The H_2-blocker cimetidine competitively inhibits renal tubular secretion of metformin, significantly decreasing its clearance and increasing its bioavailability (16, 19).

Metformin as a Part of Combination Therapy

Metformin has been shown to be effective in combination with insulin, sulfonylureas (2, 10, 20, 21), and thiazolidinediones (22). This finding is important because single-drug therapy often fails to maintain normoglycemia, particularly as diabetes progresses (23, 24). As seen in the United Kingdom Prospective Diabetes Study (UKPDS), 50% of patients treated with diet or a single antidiabetic drug achieved the target hemoglobin A_{1c} value of less than 7% after 3 years of follow-up; after 9 years, only 25% maintained this goal (24). As diabetes progresses and treatment with maximal doses of sulfonylurea fails, addition of metformin significantly improves glycemic control (2). In the UKPDS trial, combination therapy tended to control glycemia more effectively than monotherapy (hemoglobin

PRACTICAL CONSIDERATIONS IN METFORMIN THERAPY

The ideal patient for initiation of metformin treatment would be an obese person with type 2 diabetes mellitus who has normal kidney function (creatinine concentration <133 μm d/L [<1.5 mg/dL] in men and <124 μm d/L in women, or creatinine clearance >1.17 mL/s without coexistent symptomatic congestive heart failure or a hypoxic respiratory condition) (9, 16, 25). Contraindications to metformin therapy are liver failure, alcoholism, and active moderate to severe infection (9, 25); these conditions predispose to development of lactic acidosis, either by increased production or decreased metabolism of lactic acid (9, 16–18, 25). Administration of radiocontrast material to a patient with diabetes may worsen already-compromised kidney function and cause accumulation of metformin, leading to toxic levels of drug. Furthermore, administration of general anesthesia may cause hypotension, which leads to renal hypoperfusion and peripheral tissue hypoxia with subsequent lactate accumulation (25–28). Therefore, if administration of radiocontrast material is required or urgent surgery is needed, metformin should be withheld and hydration maintained until preserved kidney function is documented at 24 and 48 hours after the intervention (9, 26–28). Metformin should be used with caution in elderly patients, whose reduced lean body mass may lead to misleading low creatinine concentrations that fail to reflect decreased glomerular filtration rates (9, 25–28).

Metformin therapy should be initiated with a single dose of medication (usually 500 mg) taken with the patient's largest meal to prevent gastrointestinal symptoms. Gastrointestinal symptoms generally disappear within 2 weeks of treatment (10, 11). Medication doses may be increased by 500-mg increments every 1 to 2 weeks, as indicated by glycemic control, until a desirable blood glucose level or the maximal recommended daily metformin dose of 2550 mg is reached (2, 25). The hypoglycemic effect of metformin is dose related, and a plateau of hypoglycemic action is achieved at a daily dose of 2000 mg (6).

Side effects of metformin are mostly limited to digestive tract symptoms, such as diarrhea, flatulence, and abdominal discomfort (1, 6, 8–10). These symptoms are dose dependent and can usually be avoided by slow titration and, in some cases, reduction of the dose (9). About 5% of patients cannot tolerate treatment because of gastrointestinal side effects (6, 9, 10). The mechanisms of these gastrointestinal side effects remain unclear but probably are related to accumulation of high amounts of metformin in the intestinal tissue (17), with subsequent elevation of local lactate production. Histologic examination has not revealed changes in the intestinal mucosa in metformin-treated animals (29), indicating a functional rather than a structural basis for gastrointestinal symptoms. Ten percent to 30% of patients receiving long-term metformin therapy develop vitamin B_{12} malabsorption, as indicated by decreased concentrations of total vitamin B_{12} and its bioavailferes with mucosal-cell intracellular calcium handling, thus disrupting calcium-dependent absorption of vitamin B_{12} in the ileum (30). Such decreases in vitamin B_{12} levels rarely have clinical significance (2, 9).

Development of hypoglycemia during metformin monotherapy is rare because metformin only partially suppresses gluconeogenesis in the liver and does not stimulate insulin production (9, 31).

Lactic acidosis is a life-threatening complication of biguanide therapy that carries a mortality rate of 30% to 50% (28). Metformin therapy may increase blood lactate levels (1) and is occasionally associated with development of lactic acidosis (2, 28). The estimated incidence of metformin-associated lactic acidosis is 0.03 cases per 1000 patient-years (25), which is 10 to 20 times lower than that seen with phenformin therapy (28). Development of lactic acidosis appears to be unrelated to plasma metformin concentrations (28), and even in persons with chronic renal insufficiency, metformin accumulation does not necessarily lead to lactic acidosis (18). Development of lactic acidosis is almost always related to coexistent hypoxic conditions that are probably responsible for the associated high mortality rate. In one report, 91% of patients who developed lactic acidosis while being treated with metformin had a predisposing condition, such as congestive heart failure, renal insufficiency, chronic lung disease with hypoxia, or age older than 80 years (26). Thus, patients with compromised renal function or coexistent hypoxic conditions should not be given metformin. Chronic or acute intake of large amounts of alcohol may potentiate the effect of metformin on lactate metabolism. A careful history of alcohol use is therefore important before starting metformin therapy (26, 27).

MECHANISMS OF ANTIHYPERGLYCEMIC ACTION OF METFORMIN

The glucose-lowering effects of metformin are mainly a consequence of reduced hepatic glucose output (primarily through inhibition of gluconeogenesis and, to a lesser extent, glycogenolysis) and increased insulin-stimulated glucose uptake in skeletal muscle and adipocytes (25, 27, 31–35) (**Figure 1**). Its major mode of action is to reduce hepatic glucose production, which is increased at least twofold in patients with type 2 diabetes (32, 36). In a recent study of the mechanism by which metformin decreases endogenous glucose production in patients with type 2 diabetes, the increased plasma glucose level was attributed to a threefold increase in the rate of gluconeogenesis, as assessed by nuclear magnetic resonance spectroscopy (32). Metformin treatment decreased fasting plasma glucose concentrations by 25% to 30% and reduced glucose production (32), findings that are consistent with those of other investigators (27, 35). The decrease in glucose production was attributable to a reduction in the rate of gluconeogenesis (32).

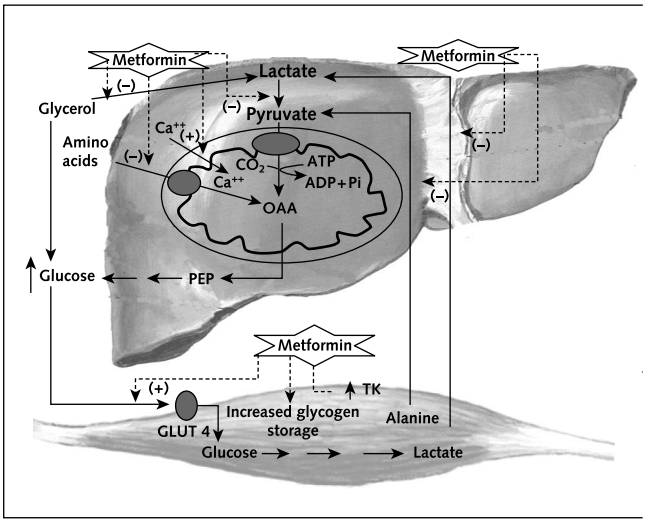
Data from in vivo studies (27, 32, 36) are consistent with those of in vitro studies demonstrating an inhibitory effect of

ple, metformin was observed to decrease gluconeogenesis in perfused liver, primarily through inhibition of hepatic lactate uptake (37). Others reported that metformin therapy decreased concentrations of adenosine triphosphate in isolated rat hepatocytes (38). Because adenosine triphosphate is an allosteric inhibitor of pyruvate kinase, the investigators suggested that the metformin-mediated reduction in hepatic glucose production resulted from increased pyruvate kinase flux. Metformin also decreases gluconeogenic flux through inhibition of pyruvate carboxylase–phosphoenolpyruvate carboxykinase activity and possibly through increased conversion of pyruvate to alanine (34). Metformin also facilitates insulin-induced suppression of gluconeogenesis from several substances, including lactate, pyruvate, glycerol, and amino acids (31), and opposes the gluconeogenic actions of glucagon (39) (**Figure 1**).

The exact mechanism through which metformin reduces hepatic glucose production remains unclear, but its primary site of action appears to be hepatocyte mitochondria, where it disrupts respiratory chain oxidation of complex I substrates (for example, glutamate) (15, 39). Inhibition of cellular respiration decreases gluconeogenesis (39) and may induce expression of glucose transporters and, therefore, glucose utilization (40). It is not clear whether metformin acts on mitochondrial respiration directly by slow permeation across the inner mitochondrial membrane (39) or by unidentified cell-signaling pathways (15). It has been suggested that biguanides bind specifically and competitively to divalent cation sites on proteins, thus interfering with intracellular handling of calcium ($[Ca^{2+}]i$) (41, 42) especially in the mitochondria (41). Davidoff and colleagues (41) showed that even small doses of biguanides increase the rates of $[Ca^{2+}]i$ uptake in isolated hepatic mitochondria, where $[Ca^{2+}]i$ serves as a potent activator of mitochondrial respiration (**Figure 1**). This effect was shown at biguanide concentrations as low as 5 to 10 μm (41), levels that are expected in the liver with antihyperglycemic doses of the drug and are 20- to 50-fold lower than those that inhibit mitochondrial respiration. In several tissues, including skeletal muscle and adipocytes, metformin facilitates trafficking of glucose transporters 4 and 1 to the plasma membrane (25, 31, 43). Moreover, metformin may increase the glucose transport capacity of glucose transporter 4, and to some extent, glucose transporters 1 (31).

The effects of metformin on peripheral insulin-sensitive tissues require the presence of insulin for its full action. Metformin enhances most of the biological actions of insulin, including glucose transport and glycogen and lipid synthesis, in persons with preexisting insulin resistance (31). It facilitates glucose transport in cultured skeletal muscle in the absence of insulin (44, 45). Metformin activates insulin and tyrosine kinase activity in insulin-like growth factor-1 receptor of vascular smooth-muscle cells independently of insulin action (46). The drug activates tyrosine kinase in *Xenopus* oocytes, with subsequent stim-

Figure 1. **Mechanisms of metformin action on hepatic glucose production and muscle glucose consumption.**



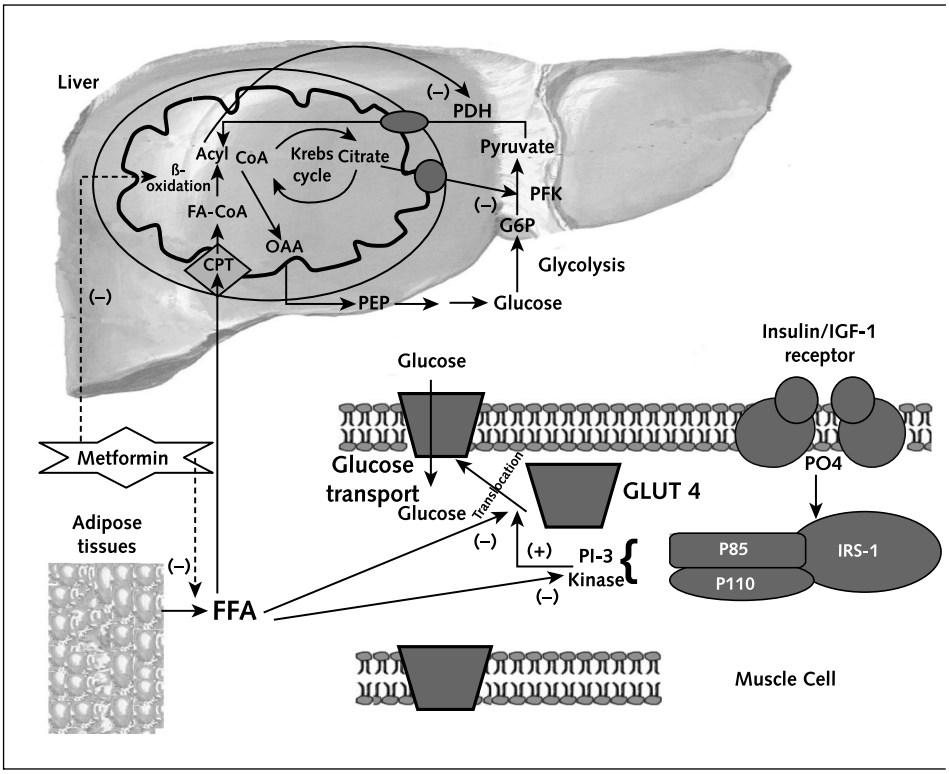
Metformin decreases hepatic gluconeogenesis by interfering with respiratory oxidation in mitochondria. It suppresses gluconeogenesis from several substrates, including lactate, pyruvate, glycerol, and amino acids. In addition, metformin increases intramitochondrial levels of calcium (Ca^{++}), a modulator of mitochondrial respiration. In insulin-sensitive tissues (such as skeletal muscle), metformin facilitates glucose transport by increasing tyrosine kinase activity in insulin receptors and enhancing glucose transporter (*GLUT*) trafficking to the cell membrane. ADP = ●●●; ATP = ●●●; Ca^{++} = intracellular calcium levels; OAA = ●●●; PEP = phosphoenolpyruvate; Pi = ●●●; TK = ●●●.

cogen synthesis (47) (**Figure 1**). Thus, metformin has metabolic effects on insulin-sensitive tissues that may contribute to its glucose-lowering effect.

Metformin has been shown to reduce free fatty acid oxidation by 10% to 30% (25, 31–33). Elevated levels of free fatty acid are commonly seen in diabetes and obesity (48), and they contribute to increased hepatic glucose production and development of insulin resistance (49, 54) (**Figure 2**). Increased fatty acid oxidation inhibits key enzymes of the glycolytic pathway by accumulation of acetyl coenzyme A and citrate, by-products of free fatty acid oxidation (51). Increased glucose 6-phosphate concentrations, in turn, inhibit the hexokinase enzyme, resulting in reduced glucose uptake and oxidation (51). In addition, free fatty acid independently inhibits insulin receptor substrate-1–associated PI3-kinase activity (52) and subsequently attenuates transmembrane glucose transport (48) (**Figure 2**). By decreasing free fatty acid levels, metformin not only improves insulin sensitivity but may also help correct impaired insulin secretion by β-cells (53). Metformin has no direct effect on β-cell function (9), but it can improve insulin secretion that has been altered by long-term exposure to free fatty acid or hyperglycemia (glucose toxicity) (53).

Metformin may also improve hyperglycemia by attaining high concentrations in the small intestine (17, 31) and decreasing intestinal absorption of glucose (29, 54), an ac-

Figure 2. **Metformin and fatty acids.**



Metformin inhibits fatty acid (*FA*) production and oxidation, thereby reducing fatty acid–induced insulin resistance and hepatic glucose production. CoA = coenzyme A; CPT = ●●●; FFA = free fatty acid; GLUT = glucose transporter; IGF-1 = ●●●; IRS-1 = ●●●; OAA = ●●●; PDH = ●●●; PFK = ●●●; PI-3 = ●●●.

glucose levels (55). It has been speculated that increased glucose consumption in the small intestine of metformin-treated patients may prevent further glucose transport to the hepatic circulation (29).

In summary, metformin decreases hepatic glucose production through inhibition of gluconeogenesis and possibly glycogenolysis and improves peripheral insulin sensitivity. In addition, metformin decreases gastrointestinal glucose absorption and indirectly improves pancreatic β-cell response to glucose by reducing glucose toxicity and free fatty acid levels.

Effect of Metformin in the Polycystic Ovary Syndrome

Hyperinsulinemia reflecting insulin resistance is a common feature in lean and obese patients with the polycystic ovary syndrome (11, 56, 57). Hyperinsulinemia contributes directly to excessive testosterone production by the ovaries (56) and decreased synthesis of sex hormone–binding globulin in the liver (11, 58), thereby increasing levels of total and free testosterone. Metformin therapy increases insulin sensitivity and decreases insulin levels in patients with the polycystic ovary syndrome (56, 57, 59). Improvement of hyperinsulinemia is associated with decreased levels of total and free tes-

Clinically, administration of metformin improves hirsutism (11), normalizes menstrual cycles (11, 12, 57, 59), and induces ovulation (57, 59) in a substantial number of patients with the polycystic ovary syndrome.

Effect of Metformin Treatment on Cardiovascular Morbidity and Mortality

In the UKPDS 34, metformin therapy was compared with conventional treatment or treatment with sulfonylurea or insulin (5). In this trial, which was designed to achieve fasting plasma glucose levels less than 6 mmol/L (<108 mg/dL), 342 patients with newly diagnosed type 2 diabetes were allocated to receive metformin treatment and 951 patients were allocated to receive either chlorpropamide, glibenclamide, or insulin. The control group included 411 overweight diabetic patients who were randomly assigned to conventional therapy, primarily with diet alone, which resulted in suboptimal glycemic control. During 10 years of follow-up, both drug-treated groups achieved equal degrees of glycemic control (median hemoglobin A_{1c} value of 0.074 [7.4%]), whereas the conventionally treated group had a median hemoglobin A_{1c} value of 0.08 (8.0%) (5). Compared with the conventionally treated group, metformin-treated patients had a risk reduction of 32%

tion, 42% for diabetes-related death, and 36% for all-cause mortality (5). These differences may be partially explained by differences in the degree of glycemic control between the metformin and diet groups. In the UKPDS 35 (60), the risk for cardiovascular events, stroke, and all-cause death was closely related to the degree of glycemia in diabetic patients. In that study, each 1% reduction in the hemoglobin A_{1c} value during treatment of type 2 diabetes was associated with a reduction of 21% in diabetes-related deaths, 14% in the incidence of myocardial infarction, 12% in fatal and nonfatal strokes, and 16% in heart failure (60). Nevertheless, metformin was more effective than sulfonylureas or insulin in reducing rates of any diabetes-related end point, all-cause mortality, and stroke, even though both agents decreased hemoglobin A_{1c} values equally (5). These observations suggest that metformin might have additional cardiovascular protective actions beyond its antihyperglycemic properties. However, data indicate that metformin in combination with sulfonylurea might increase cardiovascular mortality in patients with type 2 diabetes (5, 61). In those studies, metformin was not used as an initial therapy but rather was added to treatment when sulfonylurea therapy failed. Patients taking combination therapy with metformin and sulfonylurea tended to have long-standing poorly controlled diabetes before addition of the biguanide (62). Moreover, they had greater obesity (61), which could independently increase mortality. Therefore, the reported increase in risk for cardiovascular disease in patients treated with combination therapy might reflect selection bias attributable to the natural history of long-standing diabetes rather than to adverse effects of this combination.

Mechanism of the Cardioprotective Action of Metformin

Insulin resistance, a cornerstone of type 2 diabetes and the metabolic cardiovascular syndrome, is commonly associated with hypertension, abdominal obesity, atherogenic dyslipidemia, and vascular dysfunction, all of which contribute greatly to the development of accelerated atherosclerosis (63). Hyperinsulinemia reflects insulin resistance and may be an independent risk factor for coronary artery disease (64–66). Metformin, an insulin-sensitizing agent, decreases insulin resistance in patients with (20, 31, 55) and without (11, 12, 57, 67) diabetes, thus effectively reducing baseline and glucose-stimulated insulin levels (12, 20, 55, 57, 67).

Several studies have shown that metformin improves lipoprotein profiles in diabetic patients (2, 10, 20, 55, 68). Dyslipidemia in diabetes is characterized by hypertriglyceridemia (increased levels of very low-density lipoprotein cholesterol); decreased levels of high-density lipoprotein cholesterol; and elevated levels of small, dense atherogenic low-density lipoprotein cholesterol (LDL) particles. The poorly controlled diabetes (48) contribute not only to development of insulin insensitivity but also to increased synthesis and secretion of very low-density lipoprotein (69). Elevated triglyceride levels inhibit degradation of apoprotein B in the liver and lead to increased assembly of very low-density lipoprotein and smaller, denser LDL particles (69). Excessive generation of reactive oxygen species and free radicals (such as peroxynitrates) by cardiovascular tissue, in combination with increased nonenzymatic glycation of lipoproteins (glycooxidation), leads to formation of atypical glycooxidized LDL particles. These particles bind poorly to classic LDL receptors but have high affinity for "scavenger" receptors, which are located predominantly on macrophages (63). Accumulation of glycooxidized small, dense LDL particles converts macrophages into foam cells, which are essential participants in the early steps of atherosclerotic plaque formation (63). Compared with the general population, diabetic persons have a twofold to fourfold increased risk for cardiovascular disease at any cholesterol level (70), which indicates a more aggressive type of dyslipidemia. Furthermore, decreasing cholesterol and triglyceride levels has been shown to be particularly beneficial in patients with diabetes (70, 71). In addition, hypertriglyceridemia may be an independent risk factor for cardiovascular disease in patients with type 2 diabetes (72). Metformin has major effects on lipid metabolism in patients with insulin resistance. It decreases plasma levels of free fatty acid (20, 73) and oxidation of these acids by tissue (25, 28, 32); it decreases levels of triglycerides (2, 10, 20, 55, 74) and, therefore, very low-density lipoprotein (20). Metformin therapy decreases levels of total cholesterol (2, 68, 74) and LDL cholesterol (2, 68, 74) while maintaining (68, 74) or increasing (2, 20, 55, 57, 67) levels of high-density lipoprotein cholesterol. Metformin decreases oxidative stress and reduces lipid oxidation (75) by lowering plasma glucose levels (2). Taken together, these observations suggest that the beneficial effects of metformin on lipoprotein metabolism may contribute to its protective effects against cardiovascular disease.

Metformin has also been shown to lessen hypercoagulation and increase fibrinolysis in insulin-resistant states by decreasing levels of plasminogen activator inhibitor-1 (76, 77) and increasing tissue plasminogen activator activity (74). Therapy with metformin also reduces thrombogenic propensity by decreasing levels of tissue plasminogen activator antigen (78) and von Willebrand factor (78). In the Biguanides and the Prevention of the Risk of Obesity study, 457 nondiabetic patients with visceral obesity (body mass index of 32.5 kg/m^2) were randomly assigned to treatment with diet or metformin (850 mg twice daily) (78). Weight loss was associated with a 30% to 40% decrease in plasminogen activator inhibitor-1 activity, regardless of the method used, whereas metformin produced significantly larger decreases in von Willebrand factor levels than did diet therapy (78). Furthermore, metformin therapy decreased platelet aggregation in diabetic

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