

## Cardiovascular Risk in the Spectrum of Type 2 Diabetes Mellitus

INTEKHAB AHMED, M.D., AND BARRY J. GOLDSTEIN, M.D., PH.D.

### Abstract

The clinical importance of the metabolic syndrome is that this group of risk factors greatly increases the likelihood of cardiovascular events, the major source of disease morbidity and mortality in patients with obesity and type 2 diabetes. Recent studies have helped clarify the mechanisms underlying the vascular dysfunction that leads to cardiovascular outcomes in diabetes. This vascular dysfunction is correlated with visceral adiposity, insulin resistance and alterations in the levels of a variety of circulating factors. The vascular effects of overt hyperglycemia also play an important role in diabetes mellitus. Appropriate management of diabetes in the context of the metabolic syndrome requires that we pay close attention to minimizing cardiovascular risk. In this brief review, we will cover several key concepts in the pathophysiology of type 2 diabetes that confer increased cardiovascular risk and influence the choice of oral therapies for this widespread disorder.

**Key Words:** Atherosclerosis, myocardial infarction, insulin resistance, obesity, metabolic syndrome, thiazolidinediones, metformin, sulfonylureas.

THE SIGNIFICANCE of the metabolic syndrome to clinicians is that it confers a dramatically increased risk for cardiovascular events (1). The basis of cardiovascular risk in the setting of the metabolic syndrome is related to visceral adiposity, insulin resistance and alterations in the circulating levels of adipose-tissue-derived circulating factors that lead to a matrix of atherogenic processes. These include glycemic disorders leading to type 2 diabetes, a dyslipidemia characterized by low high-density lipoprotein (HDL) cholesterol and small, dense low-density lipoprotein (LDL) particles, as well as hypertriglyceridemia, hypertension, endothelial dysfunction, vascular inflammation and impaired thrombolysis, among other alterations (Table 1). Given the wide-

spread prevalence of this constellation of disorders in the U.S. and other developed countries of the world, the management of diabetes in the context of the metabolic syndrome requires that we pay close attention to minimizing cardiovascular risks.

In this review, we will cover several key concepts in the pathophysiology and management of type 2 diabetes and the risk factors in the metabolic

TABLE 1

*Visceral Adiposity Leads to a Network of Atherogenic Factors in the Metabolic Syndrome*

Pathogenic Alterations	Disease-State Consequences
Insulin Resistance	Type 2 diabetes and glycemic disorders
↑FFA	Dyslipidemia (low HDL; high triglycerides; small, dense LDL particles)
↑Cytokines (TNF $\alpha$ )	Hypertension
↓Adiponectin	Endothelial dysfunction, vascular inflammation
	Impaired thrombolysis, increased PAI-1 levels

From the Division of Endocrinology, Diabetes and Metabolic Diseases, Department of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA.

Address all correspondence to Barry J. Goldstein, M.D., Ph.D., Director, Division of Endocrinology, Diabetes and Metabolic Diseases, Department of Medicine, Jefferson Medical College, Jefferson Alumni Hall, Suite 349, 1020 Locust Street, Philadelphia, PA 19107-6799; e-mail: Barry.Goldstein@jefferson.edu

Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on February 7, 2005, and updated as of October 2005.

FFA = free fatty acids; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TNF $\alpha$  = tumor necrosis factor  $\alpha$ ; PAI-1 = plasminogen activator inhibitor-1.

syndrome. First, we will consider the growing epidemiologic evidence that abnormalities of glycemia contribute to cardiovascular disease and mortality. Second, we will explore how visceral obesity leads to the metabolic syndrome and diabetes, and how these disease processes contribute to cardiovascular risk. Finally, in the context of the pathophysiology of diabetes and preventing its long-term complications, we will briefly discuss the relative benefits and drawbacks of using currently available oral agents in the clinical management of type 2 diabetes.

### Contribution of Abnormal Glycemia to Cardiovascular Disease and Mortality

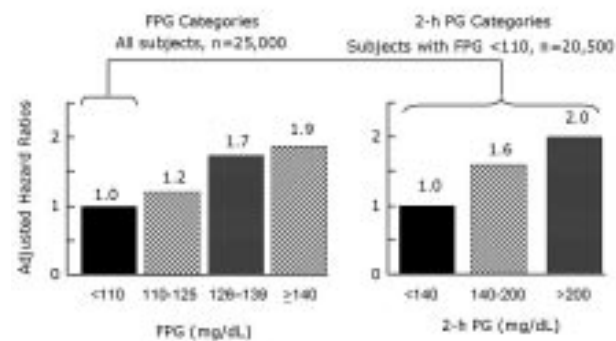
All forms of diabetes, as defined by fasting or post-oral load levels of glucose above a standardized normal range, are well known to be associated with increased risk of microvascular complications such as nephropathy, retinopathy and neuropathy (2). Moreover, major randomized intervention studies in both type 1 diabetes (Diabetes Control and Complications Trial or DCCT) and type 2 diabetes (United Kingdom Prospective Diabetes Study or UKPDS) have clearly shown that lowering the mean glucose level (reducing hemoglobin A1c, or HbA1c) dramatically protects against the microvascular complications of diabetes (3, 4).

A more difficult task has been to decipher from the available clinical data whether interventions that reduce glucose *per se* will have a positive impact on cardiovascular events. The Framingham Heart Study showed that diabetic patients had markedly increased age-adjusted risks for cardiac failure, coronary heart disease, intermittent claudication and total cardiovascular disease and that these risks were much higher than those of the nondiabetic cohort (5). Importantly, this study also pointed out that the increase in risk was significantly greater for diabetic women. Other studies in type 2 diabetes have demonstrated that the incidence of heart attacks in type 2 diabetics is 2–4 times greater than in nondiabetics, and that the risk of myocardial infarction for a diabetic patient may be comparable to the risk for someone without diabetes who has already had a myocardial infarction (6, 7).

From a pathogenic standpoint, what the significance of elevated glucose itself might be in type 2 diabetes mellitus is still not entirely clear, given the multiple factors of the metabolic syndrome that typically accompany the hyperglycemia in patients with type 2 diabetes. Recent work in type 1 diabetes mellitus has suggested that high glucose may contribute directly to atherosclerosis, since a follow-up report to the landmark DCCT trial showed

that the intensively treated group had reduced intima-media thickness on carotid ultrasonography compared to the conventionally treated group, suggesting less progression of vascular disease (8). Other epidemiologic data support a link between hyperglycemia and an increased risk of cardiovascular disease. This includes hyperglycemia in the range of “pre-diabetes” in patients with impaired fasting glucose (100–125 mg/dL) or impaired glucose tolerance (140–200 mg/dL at 2 hours following a 75 gm oral glucose tolerance test) (7, 9). An epidemiologic analysis of cross-sectional data from the UKPDS trial showed a strong association for each 1% reduction in glycosylated hemoglobin (HbA1c) with reductions in risk of myocardial infarction in the range of A1c from <6 to 10% (10). A striking relationship between mean glycemia and cardiovascular mortality was shown in the EPIC-Norfolk Study of men not previously known to have diabetes; the relationship extended even into the normal range for A1c, in comparing a group with a mean <5 with a group in the range of 5.1–5.4% (11). Another widely cited example is the Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe (DECODE) Study, which showed that for diabetic and non-diabetic individuals a direct link exists between different categories of fasting or post-prandial glucose levels and increased risk of cardiovascular mortality (12). For example, this study showed that patients with impaired fasting glucose had an adjusted hazard ratio of 1.6 compared to normal individuals (Fig. 1).

These considerations have led to the development of clinical guidelines for glycemic control



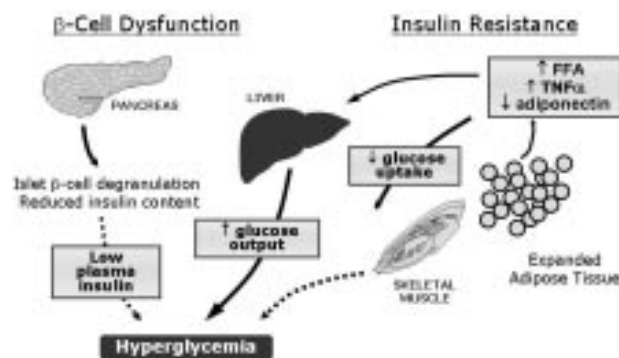
**Fig. 1.** Fasting plasma glucose and 2-hour plasma glucose post-oral glucose loading predict mortality in persons not known to have type 2 diabetes. Data from the DECODE cohort of 14 European studies with the numbers of patients included (n) shown for each graph. The adjusted hazard ratio for cardiovascular mortality is clearly influenced by either the fasting or post-glucose load category. Adapted with permission from data presented by the DECODE Study Group (12). FPG = fasting plasma glucose; PG = plasma glucose.

based on the prevention of the long-term complications of diabetes (Table 2). The epidemiologic data showing an association of cardiovascular outcomes with the entire range of A1c, even into what is considered “normal,” will be further evaluated in several ongoing trials. For example, Action to Control Cardiovascular Risk in Diabetes or ACCORD ([www.accordtrial.org](http://www.accordtrial.org)) is a large randomized prospective trial to determine whether aggressive glucose control in type 2 diabetes can improve cardiovascular outcomes, supporting the predictions made in the previously cited epidemiologic data.

### Pathophysiology of Insulin Resistance and Hyperglycemia in Type 2 Diabetes

Historically, the components of the metabolic syndrome have been linked to an underlying state of insulin resistance, i.e., a reduced biological effect of insulin in the body (13). This underlying insulin resistance leads to compensatory hyperinsulinemia, and at least some of the complex responses that lead to the metabolic syndrome and increase the risk of cardiovascular events. Other pathogenic factors that occur in the syndrome may not be due to effects of hyperinsulinemia or tissue responses that are resistant to insulin itself, but rather to an imbalance in insulin-signaling pathways, some of which remain sensitive to insulin (14). Insulin resistance affects all of the tissues responsive to insulin including the liver, skeletal muscle and adipose tissue (15). In the liver, this leads to ineffective insulin suppression of glucose output, contributing to fasting and steady-state hyperglycemia. In skeletal muscle, inadequate insulin-stimulated glucose disposal also contributes to increased glycemia (Fig. 2).

Among the various adipose tissue depots, expanded visceral fat is especially resistant to insulin, leading to the increased release of free fatty acids. While obesity itself is associated with insulin resistance, it is the central abdominal fat that demonstrates the closest correlation with insulin resistance (16). This study showed that 79% of the



**Fig. 2.** Insulin resistance and  $\beta$ -cell dysfunction produce hyperglycemia in type 2 diabetes. The pathogenesis of type 2 diabetes is rooted in insulin resistance, with a failure of  $\beta$ -cell insulin secretion to compensate for the increased insulin demands of the body. Recent studies have highlighted the role of an expanded adipose tissue mass, which leads to several pathogenic alterations. Increases are seen in the release of free fatty acids (FFA) and several “adipokines,” including tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), which adversely affects insulin action in skeletal muscle and liver. In addition, levels of the insulin-sensitizing protein adiponectin are increased, which tends to enhance insulin suppression of hepatic glucose production. (See text for further discussion.)

variance in insulin sensitivity is associated with central fat regardless of the overall body mass index (BMI). Much recent research has highlighted the role of excess adiposity in causing insulin resistance and type 2 diabetes mellitus, and a better understanding of the underlying mechanisms has begun to emerge (17). By directly interfering with cellular signaling mechanisms, increased levels of fatty acids in the circulation aggravate insulin resistance in skeletal muscle and the liver (18, 19). Increased levels of inflammatory cytokines such as tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and interleukin-6 (IL-6) are released by expanded visceral adipose tissue (called “adipokines”) and can also adversely influence the insulin signaling cascade (20, 21). These signaling mediators have a detrimental effect on insulin action in liver and skeletal muscle tissue and are believed to contribute to systemic insulin resistance. Interesting

**TABLE 2**  
*Current Targets Recommended for Glycemic Control in Clinical Practice*

Glycemic Parameter	American Diabetes Association	International Diabetes Federation	American College of Endocrinology
HbA1c (%)	<7.0	≤6.5	≤6.5
Fasting glucose	80–120	<100	<110
2-hour post-meal glucose	–	<135	<140

HbA1c = glycosylated hemoglobin.

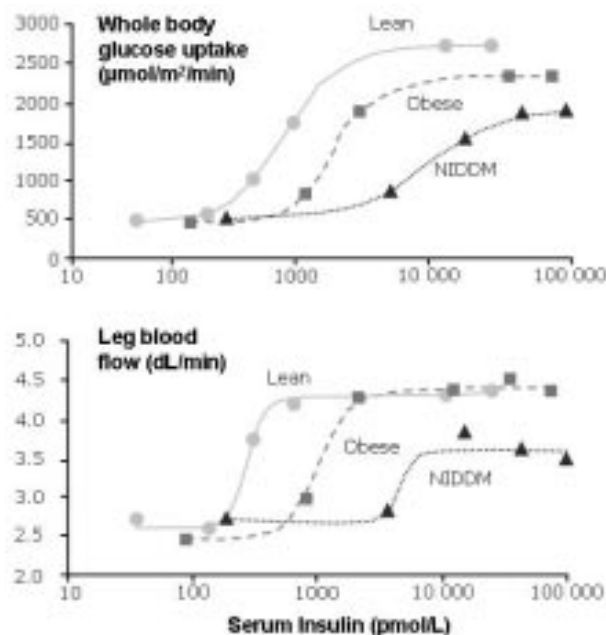
recent work has highlighted the close connection between the cellular signaling pathways conferring insulin resistance and classical inflammatory signaling pathways involving the nuclear transcription factor NF- $\kappa$ B (22). High doses of salicylates, which block activation of the NF- $\kappa$ B cascade, can ameliorate insulin resistance and hyperglycemia in diabetes (23). As a common denominator in the cellular action of free fatty acids and various adipokines, the NF- $\kappa$ B pathway appears to be an important target for the development of new therapeutics in insulin resistance, especially in the setting of visceral adiposity.

Increased visceral fat is also associated with accumulation of triglyceride and fatty acid molecules within liver and skeletal muscle cells, which also adversely affects insulin signaling. In susceptible people, the latter may be due to inadequate mitochondrial fat metabolism, which is emerging as a key mechanism leading to intracellular fat accumulation in overfed and sedentary individuals (24).

The adipose-specific secretory protein adiponectin has received much attention recently, since this abundant protein in the bloodstream has insulin-sensitizing effects on liver, muscle and fat tissue as well as anti-inflammatory protective effects on the vasculature (25, 26). Levels of adiponectin are reduced in obese patients with diabetes, and epidemiologic data suggests that it may play a protective role against heart disease in patients with diabetes (27). Interestingly, adiponectin signals via adenosine monophosphate (AMP) kinase, a stress-activated signaling enzyme implicated in a variety of metabolic responses that help to maintain normal glucose metabolism and endothelial function (28). AMP kinase has also been implicated in the mechanism of action of metformin and the thiazolidinediones (TZDs), suggesting that it has a role in clinical anti-diabetic responses (29).

### Vascular Endothelial Dysfunction in Type 2 Diabetes and Links to Inflammation

A better understanding of the actions of adiponectin has helped to highlight the pathogenic interconnections between obesity and insulin resistance in metabolic processes as well as on vascular function (25). Early studies showed that patients with type 2 diabetes and insulin resistance had a significantly impaired increase in leg blood flow in response to insulin, suggesting that these patients had defects in endothelial function (Fig. 3; 30). Normal endothelial cells synthesize and release biologically active substances to maintain vascular homeostasis, ensuring adequate blood flow and nu-



**Fig. 3.** Insulin resistance and diabetes mellitus impair endothelial function. In lean subjects, obese subjects, and obese subjects with type 2 diabetes (NIDDM), whole body insulin-mediated glucose uptake and leg blood flow in response to insulin were measured. In subjects with diabetes, the response of both measures at maximal insulin infusion was significantly reduced and the sensitivity of these responses to insulin was shifted to a higher dose level. These data show that reduced skeletal muscle blood flow is found in diabetic subjects, and impaired insulin-mediated augmentation of skeletal muscle blood flow is due to the diabetic state *per se* and not to the obesity status. Reproduced with permission from the American Diabetes Association from Laakso et al. (30).

trient delivery while preventing thrombosis and leukocyte diapedesis (31). In insulin-resistant subjects, endothelium-dependent vasodilation is reduced. There appears to be an imbalance between the normal effects of insulin to stimulate nitric oxide (NO) production and vascular dilation, and the growth-promoting effects of insulin that may increase smooth muscle cell proliferation. The insulin resistance in the vasculature arises from the effects of circulating mediators in the endothelium and smooth muscle cells, including free fatty acids, cytokines and adiponectin (25). In overt diabetes, hyperglycemia contributes to endothelial dysfunction and increases vascular oxidative stress (32). Platelet function and plasma coagulation factors are also altered in diabetes, favoring platelet aggregation and a propensity for thrombosis (Fig. 4; 33).

### Hyperglycemia in Type 2 Diabetes

Although insulin resistance is typically the first noted defect and is fundamental to the devel-



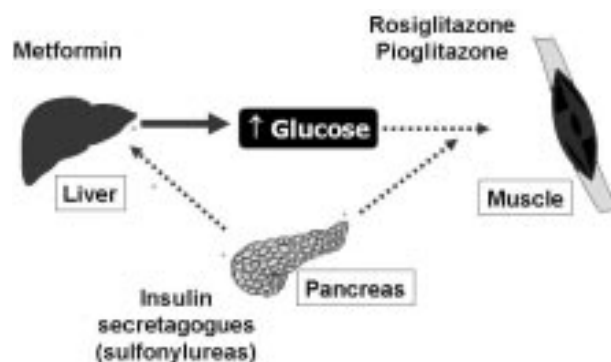
**Fig. 4.** Mechanisms of vascular injury in insulin resistance and type 2 diabetes mellitus. Many of the same pathogenic factors that cause tissue insulin resistance in glucose and lipid metabolic regulation also lead directly to endothelial dysfunction and increase the risk of atherosclerosis. The array of changes that contribute to type 2 diabetes as well as cardiovascular risk include increases in free fatty acids, tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), interleukin-6 (IL-6), angiotensin II (Ang II) and glucose, and reduced levels of adiponectin. These factors impact on oxidative stress in vascular tissues and lead to a matrix of alterations that are detrimental to the normal functions of the vascular endothelial and supporting structures. (See text for further discussion.)

BP = blood pressure; PAI-1 = plasminogen activator inhibitor-1; NO = nitrous oxide; ACE = angiotensin-converting enzyme.

opment of type 2 diabetes, if compensatory increases in circulating insulin occur, blood glucose levels can be held in check (Fig. 2). Only with an accompanying failure of  $\beta$ -cell insulin secretion will glucose levels climb, leading to overt diabetes (17). It has been estimated that by the time diabetes is manifest; approximately 50% of  $\beta$ -cell function has been lost (34). Many of the mechanisms in obesity that contribute to tissue defects in insulin action also play a role in the decline in  $\beta$ -cell function in diabetes, including excess circulating free fatty acids, accumulation of triglycerides in the islets and mitochondrial abnormalities (24).

### Choosing among Oral Therapies for Type 2 Diabetes

Consideration of the pathogenesis of type 2 diabetes and the role of inflammation and vascular dysfunction as risk factors for the long-term cardiovascular consequences of the disease helps the physician select from among the many available options for oral treatment of this disorder (Fig. 5), once lifestyle modifications have been implemented and found to be insufficient. Our general approach involves the early use of metformin and TZDs, which use the insulin already available in the patient's circulation, and can lower blood glucose without causing hypoglycemia, even when

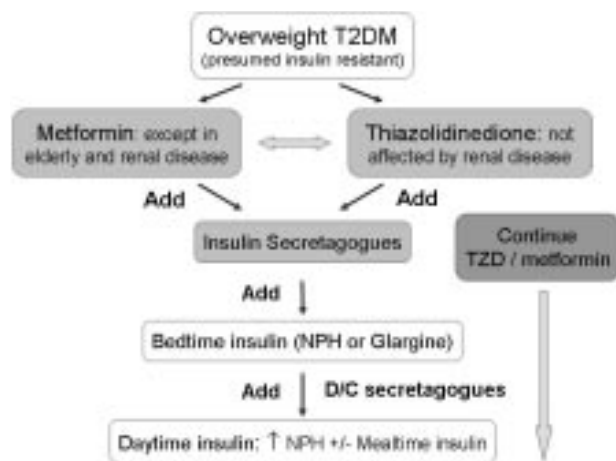


**Fig. 5.** Sites of action of major oral therapies for type 2 diabetes mellitus. Metformin is thought to act primarily in the liver to suppress hepatic glucose production. The thiazolidinediones (rosiglitazone and pioglitazone) act via an entirely different mechanism that involves an initial interaction with the peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) nuclear receptor in adipose tissue. This causes a redistribution of adipose stores and alterations in the secretion of free fatty acids and several “adipokines,” which helps to ameliorate the insulin resistance, primarily in skeletal muscle. Thus, the major effect of the thiazolidinediones is to enhance insulin-stimulated glucose disposal in skeletal muscle. The insulin secretagogues, including the long-acting sulfonylureas and the shorter-acting meglitinide and phenylalanine derivatives (repaglinide and nateglinide), increase insulin secretion from the pancreatic  $\beta$ -cells. (See text for further discussion.)

aggressively used in combination to drive the A1c into the normal range (Fig. 6). Since both metformin and TZDs require endogenous insulin to be effective, if these medications do not enable a patient to reach glucose goals, an insulin secretion enhancer should be added. Of course, the secretion enhancers rely on a responsive mass of  $\beta$ -cells, so when this becomes inadequate, insulin itself must be added to the oral agents. The best ways to achieve and maintain glucose goals over the long term include individualization of the therapy and regular review and modifications.

### Metformin and the TZD Class

Metformin and TZDs work independently of the pancreas and help to lower insulin levels by unique mechanisms (35, 36). Metformin is an “insulin-sparing” drug that suppresses hepatic glucose production, while the TZDs affect adipose tissue metabolism in a manner that alters the secretion of free fatty acids and adipokines, and helps to suppress the “inflammatory” milieu that contributes not only to insulin resistance in metabolic tissues but also to vascular dysfunction (14). While metformin has been shown in some studies to produce increases in insulin sensitivity, the TZDs are true insulin-sensitizers that exhibit more potent effects on a number of metabolic syndrome param-



**Fig. 6.** General scheme for initiating and intensifying oral therapy in type 2 diabetes. Overweight patients with type 2 diabetes mellitus (T2DM) can be presumed to be insulin resistant, and therapy should be initiated with metformin, with the early addition of a thiazolidinedione (TZD) when necessary. Metformin is strictly contraindicated in renal insufficiency and in many elderly patients with reduced renal function or congestive heart failure, as discussed in the text. One of the benefits of the metformin-thiazolidinedione combination is the lack of hypoglycemia, even with aggressive treatment, since both of these drugs work independently of the pancreas and lower circulating insulin levels. If additional insulin is needed to support the action of metformin and/or thiazolidinediones, a secretion enhancer should be added for “triple” oral therapy. With a failing  $\beta$ -cell mass, as in long-standing diabetes, the secretagogues may not provide an adequate glucose lowering effect, and exogenous insulin is required. Once exogenous insulin therapy is intensified, the oral secretion enhancers should be discontinued (D/C), but since these patients typically remain insulin resistant, thiazolidinediones and/or metformin should be continued in combination with insulin. NPH = isophane insulin.

ters that are associated with insulin resistance (see below).

### Role of Metformin in Cardiovascular Protection

Most of the data supporting a role for metformin in cardiovascular protection arises from a small sub-study in which compared to conventional treatment, the intensive use of metformin in obese patients showed a reduction of 36% in all-cause mortality and 39% in myocardial infarction ( $p=0.01$ ) (37). However, the mechanism of metformin action in regard to reduction of cardiovascular events is not well understood. In a meta-analysis of 32 studies involving more than 2,400 patients, metformin was effective in lowering A1c, but had no significant effect on blood pressure or HDL. Also, the effects on LDL and triglycerides were statistically significant, but small, and felt unlikely to be of major clinical bene-

fit (38). A recent study reported a 16-week interim analysis of metformin vs. placebo as an adjunct to insulin in patients with type 2 diabetes (39). In this study, metformin did not lower albumin excretion or reduce C-reactive protein (CRP) levels, which is unlike the response to TZDs. Metformin did have significant effects on several markers of endothelial and thrombolytic function, including reductions in vascular cell adhesion molecule-1 (VCAM-1), plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA). Additional data from this ongoing trial should help to show potential long-term effects of metformin in these patients.

Metformin has a long record of safety and has been used extensively in Europe for decades. A unique benefit of metformin among oral treatments for diabetes is that it does not cause weight gain, and in combination therapy it helps to limit the weight gain associated with the use of TZDs or sulfonylureas (Table 3). The most common limitations to the use of metformin include intolerance to the drug secondary to its gastrointestinal side effects and the contraindication against using metformin in renal or hepatic insufficiency. Metformin cannot be used by patients with elevated serum creatinine and abnormal creatinine clearance ( $<60-70$  mL/min), or by patients with congestive heart failure requiring pharmacological management, because of the risk of lactic acidosis if the drug is allowed to accumulate. For patients admitted to the hospital for radiological or surgical procedures, metformin should be stopped until the patient fully recovers and then restarted only after the serum creatinine level is checked and demonstrated to be normal (40).

### Thiazolidinediones

Just as insulin resistance plays an important role in the development and progression of type 2 diabetes mellitus, the TZD insulin sensitizers ex-

**TABLE 3**  
*Metformin in the Management of Type 2 Diabetes Mellitus*

Advantages	Disadvantages
Suppresses hepatic glucose production	Gastrointestinal side effects in up to 50%
High initial response rate	Not tolerated in up to 4%
“Insulin-sparing” with rare hypoglycemia	Risk of lactic acidosis in renal insufficiency
Long record of safety	Contraindicated in patients with CHF
Limits weight gain	Twice-daily dosing
Decreased CVD in UKPDS substudy	

CHF = congestive heart failure; CVD = cardiovascular disease.

hibit a variety of biological actions that ameliorate many of the abnormalities and cardiovascular risk factors that accompany type 2 diabetes and the metabolic syndrome (Table 4). At present two TZDs, pioglitazone and rosiglitazone are Food and Drug Administration (FDA) approved for the treatment of type 2 diabetes mellitus. The TZDs act by binding to the nuclear transcription factor peroxisome proliferator-activated receptor (PPAR)- $\gamma$ , which is found primarily in adipose tissue. The precise mechanism of action of TZDs is still under investigation, but the initial action of these drugs is mediated by effects in adipose tissue, where they modify the fat distribution in the body, reduce tissue accumulation of triglycerides and alter the secretion of adipokines in a manner that ameliorates the latter's influence on insulin resistance and vascular endothelial function. Levels of adiponectin increase and levels of pro-inflammatory cytokines decrease (36, 41). The TZDs also have direct anti-atherosclerotic effects on the vascular wall and anti-inflammatory effects on circulating leukocytes.

The TZDs exert beneficial effects on the dyslipidemia of type 2 diabetes, increasing HDL cholesterol and reducing LDL particle density, and tend to reduce triglycerides (42). Although the mechanisms of these effects are not entirely understood, they may arise from an improvement in the underlying insulin resistance and changes in lipid transfer proteins and hepatic lipase. Microalbuminuria is a cardiovascular risk marker that is believed to represent not only glomerular leakage, but also systemic endothelial dysfunction and permeability (43). TZDs as a class are associated with a reduction in microalbuminuria in type 2 diabetics

independent of reductions in glycemia or blood pressure. Most likely, this effect of TZDs is a reflection of their vascular protective properties, which may also translate to a decrease in the cardiovascular risk (44). Acting via the PPAR- $\gamma$  mechanism, the TZDs also ameliorate several "non-traditional" cardiovascular risk factors and inflammatory mediators, including CRP, IL-6, matrix metalloproteinase-9 (MMP-9), and the leukocyte count (45, 46). As a summation of the many and varied effects of TZDs in the vasculature, endothelial functions are improved by treatment with TZDs, as assessed by brachial artery reactivity (47, 48). And by enhancing endothelial function and NO availability, the TZDs have also been shown to have a favorable effect on blood pressure in diabetic individuals. In one study, addition of rosiglitazone in patients taking sulfonylureas who had equivalent glycemic control after 1 year was associated with significant reduction of both systolic and diastolic blood pressures in the rosiglitazone group (49).

### Insulin Secretagogues

Before the re-introduction of metformin in the U.S. and the availability of TZDs, insulin secretagogues were the mainstay of oral treatment for the management of type 2 diabetes (Table 5). The long-acting sulfonylureas and the shorter-acting prandial secretion enhancers (meglitinides) are still in use, although most of the treatment guidelines for type 2 diabetes place them at least second to metformin, and some guidelines suggest using the secretagogues third in line after TZDs. This suggested ordering of the introduction of oral therapies for type 2 diabetes mellitus takes into account our current understanding of the pathophysiology of insulin resistance in diabetes and its intimate relation to the risk of cardiovascular disease. Perhaps the most important consid-

**TABLE 4**

*Thiazolidinediones in the Management of Type 2 Diabetes Mellitus*

Advantages	Disadvantages
Acts <i>via</i> PPAR- $\gamma$ in adipose tissue with secondary effects in skeletal muscle and vascular cells	Delayed onset of action
Insulin sensitizer—no hypoglycemia	Weight gain common
Safe in renal insufficiency	Fluid retention possible with rare episodes of CHF
Evidence for preserved $\beta$ -cell function	
Various protective vascular effects	
Positive lipid effects	

PPAR- $\gamma$  = peroxisome proliferator-activated receptor- $\gamma$ ; CHF = congestive heart failure.

**TABLE 5**

*Insulin Secretion Enhancers in the Management of Type 2 Diabetes Mellitus*

Advantages	Disadvantages
Increases $\beta$ -cell insulin secretion	No insulin sensitization or vascular effects
High initial response rate	Hypoglycemia common with aggressive dosing
No lag time	May exacerbate visceral fat accumulation
Once-a-day or multiple dosing schemes possible	May worsen progressive loss of $\beta$ -cell function
Least expensive	

eration is that, unlike metformin and the TZDs, the sulfonylureas have not shown any significant protective role against the development of cardiovascular disease.

When additional insulin is needed to control blood glucose, insulin secretion enhancers are effective in triggering insulin release from the pancreas, as long as the  $\beta$ -cell mass in the pancreas remains responsive. In patients with long-standing diabetes, loss of  $\beta$ -cell responsiveness may preclude a clinical benefit from sulfonylureas and necessitate insulin injections (50).

### Combination Therapies

One of the most important lessons of the UKPDS is the realization that patients with type 2 diabetes endure a progressive loss of  $\beta$ -cell secretory capacity, which necessitates the use of combination therapy, often within a few years of diabetes diagnosis. The general acceptance of tight glucose goals has also led to the need for earlier adoption of combination oral therapies. The combination of a TZD with metformin in the early stages of diabetes appears to be among the best approaches available. These two agents can help ameliorate both insulin resistance and hyperinsulinemia, along with many of the disease manifestations that accompany this pathogenic condition. Importantly, the use of combination TZD and metformin can help to achieve glucose goals without causing hypoglycemia, which is a frequent side effect of an insulin secretion enhancer.

When additional insulin secretion is needed, sulfonylureas can be efficacious in combination with TZDs or metformin. In one recent 2-year study of an elderly cohort of patients with type 2 diabetes with mildly elevated A1c (~7.5%), the addition of rosiglitazone to half-maximal sulfonylurea therapy was well tolerated and resulted in about half of the patients achieving A1c below the American Diabetes Association target of 7%. Interestingly, although fluid retention with the TZD class has been observed to be potentially increased in combination with sulfonylureas, in this study patients had a 9–10% incidence of edema at baseline, and while there were more patients with edema in the rosiglitazone-treated group than expected, only 2 patients withdrew from the study due to edema, and there were no cases of congestive heart failure (51).

In keeping with an attempt to achieve aggressive glucose goals, many patients require treatment with each of the three major modalities of oral therapy, i.e., triple oral therapy. Studies have typically shown that patients adding a TZD to their regimen of metformin and a sulfonylurea can expect to have

an additional 0.7–1.0% drop in their hemoglobin A1c (52). The use of triple oral therapy should therefore be considered prior to adding insulin, in order to achieve glucose goals in type 2 diabetes.

### Conclusions

Diabetes and obesity are widespread conditions with major implications in the modern world and an increasing burden for developing societies. Controlling the long-term complications of diabetes will go a long way toward ameliorating patient morbidity, and mortality, as well as helping to defray costs of medical care and lost time from employment. As a core defect in type 2 diabetes mellitus and a source of cardiovascular risk in the metabolic syndrome, insulin resistance must be addressed in any initial treatment strategy and attention should be paid to it throughout the course of type 2 diabetes. One of the best ways to improve insulin resistance is through lifestyle changes, reduction of body weight and exercise, although this approach frequently fails over the long term. Since most patients need medications in the course of managing their diabetes, this review has outlined a rationale for initiating therapy aimed at cardiovascular risk and insulin resistance by using metformin with the early addition of a TZD. Since the secretion enhancers do not offer any specific protection from cardiovascular risk, their use should be delayed until the patient requires supplemental insulin for the best therapeutic benefit from metformin and the TZDs, even in combination as “triple therapy.” Although beyond the scope of this review, when insulin is required to achieve glucose goals, the clinician should bear in mind that, even when insulin deficient, most patients with type 2 diabetes remain insulin resistant, and the insulin should be added to ongoing therapy with either metformin or in combination with TZDs as well. Patients should be helped to achieve glucose goals, including HbA1c of less than 6.5–7.0%, and to gain control of other major cardiovascular risk factors, including lipids and blood pressure. The clear demonstration of improved patient outcomes by paying attention to various cardiovascular risk factors and glucose control, as shown in the Steno 2 study (53) and others, firmly supports this approach to protecting patients from the devastating consequences of this all-too-common disorder.

### Acknowledgement

This work was supported by grants to Dr. Goldstein from the American Diabetes Association and R01-DK63018 and R01-DK71360 from the NIH.

## References

1. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005; 28:2289–2304.
2. Harris MI. Diabetes in America: epidemiology and scope of the problem. *Diabetes Care* 1998; 21 Suppl 3:C11–C14.
3. DCCT Study Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329(14):977–986.
4. Turner RC, Holman RR, Cull CA, et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837–853.
5. Brand FN, Kannel WB, Evans J, et al. Glucose intolerance, physical signs of peripheral artery disease, and risk of cardiovascular events: the Framingham Study. *Am Heart J* 1998; 136(5):919–927.
6. Eckel RH. Perspectives on vascular biology and diabetes. *J Invest Med* 2001; 49:100–103.
7. Haffner SJ, Cassells H. Hyperglycemia as a cardiovascular risk factor. *Am J Med* 2003; 115 Suppl 8A:6S–11S.
8. Nathan DM, Lachin J, Cleary P, et al. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 2003; 348:2294–2303.
9. Gerstein HC. Glycosylated hemoglobin: finally ready for prime time as a cardiovascular risk factor. *Ann Intern Med* 2004; 141:475–476.
10. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321:405–412.
11. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk). *BMJ* 2001; 322:15–18.
12. Balkau B, Hu G, Qiao Q, et al. Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor. The DECODE Study. *Diabetologia* 2004; 47:2118–2128.
13. Reaven GM. Why Syndrome X? From Harold Himsworth to the insulin resistance syndrome. *Cell Metab* 2005; 1(1):9–14.
14. Goldstein BJ. Insulin resistance as the core defect in type 2 diabetes mellitus. *Am J Cardiol* 2002; 90:3–10.
15. DeFronzo RA, Bonadonna RC, Ferrannini E. Pathogenesis of NIDDM. A balanced overview. *Diabetes Care* 1992; 15(3):318–368.
16. Carey DG, Jenkins AB, Campbell LV, et al. Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes* 1996; 45:633–638.
17. Stumvoll M, Goldstein BJ, van Haefen TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet* 2005; 365:1333–1346.
18. Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest* 2000; 106:171–176.
19. Boden G. Effects of free fatty acids (FFA) on glucose metabolism: significance for insulin resistance and type 2 diabetes. *Exp Clin Endocrinol Diabetes* 2003; 111:121–124.
20. Rajala MW, Scherer PE. Minireview: the adipocyte—at the crossroads of energy homeostasis, inflammation, and atherosclerosis. *Clin Exp Pharmacol Physiol* 2003; 144:3765–3773.
21. Lazar MA. How obesity causes diabetes: not a tall tale. *Science* 2005; 307:373–375.
22. Savage DB, Petersen KF, Shulman GI. Mechanisms of insulin resistance in humans and possible links with inflammation. *Hypertension* 2005; 45:828–833.
23. Shoelson SE, Lee J, Yuan M. Inflammation and the IKK beta/I kappa B/NF-kappa B axis in obesity- and diet-induced insulin resistance. *Int J Obes Relat Metab Disord* 2003; 27 Suppl 3:S49–S52.
24. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science* 2005; 307:384–387.
25. Goldstein BJ, Scalia R. Adiponectin: a novel adipokine linking adipocytes and vascular function. *J Clin Endocrinol Metab* 2004; 89:2563–2568.
26. Trujillo ME, Scherer PE. Adiponectin—journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *J Intern Med* 2005; 257:167–175.
27. Schulze MB, Shai I, Rimm EB, et al. Adiponectin and future coronary heart disease events among men with type 2 diabetes. *Diabetes* 2005; 54:534–539.
28. Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab* 2005; 1(1):15–25.
29. Fryer LG, Carling D. AMP-activated protein kinase and the metabolic syndrome. *Biochem Soc Trans* 2005; 33(Pt 2):362–366.
30. Laakso M, Edelman SV, Brechtel G, Baron AD. Impaired insulin-mediated skeletal muscle blood flow in patients with NIDDM. *Diabetes* 1992; 41:1076–1083.
31. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. *Clin Exp Pharmacol Physiol* 2003; 144:2195–2200.
32. Kuroki T, Isshiki K, King GL. Oxidative stress: the lead or supporting actor in the pathogenesis of diabetic complications. *J Am Soc Nephrol* 2003; 14:S216–S220.
33. Creager MA, Luscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. *Circulation* 2003; 108:1527–1532.
34. Lebovitz HE. Insulin secretagogues: old and new. *Diabetes Reviews* 1999; 7:139–153.
35. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann Intern Med* 2002; 137:25–33.
36. Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. *Diabetes* 2005; 54:2460–2470.
37. Turner RC, Holman RR, Stratton IM, et al. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352:854–865.
38. Wulfele MG, Kooy A, Zeeuw D, et al. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. *J Intern Med* 2004; 256:1–14.
39. De Jager J, Kooy A, Leher PH, et al. Effects of short-term treatment with metformin on markers of endothelial function and inflammatory activity in type 2 diabetes mellitus: a randomized, placebo-controlled trial. *J Intern Med* 2005; 257(1):100–109.
40. Millican S, Cottrell N, Green B. Do risk factors for lactic acidosis influence dosing of metformin? *J Clin Pharm Ther* 2004; 29:449–454.
41. Lebovitz HE. Rationale for and role of thiazolidinediones in type 2 diabetes mellitus. *Am J Cardiol* 2002; 90:34G–41G.
42. Chiquette E, Ramirez G, DeFronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. *Arch Intern Med* 2004; 164:2097–2104.

43. Bakris G. Proteinuria: a link to understanding changes in vascular compliance? *Hypertension* 2005; 46:473–474.
44. Bakris G, Viberti G, Weston WM, et al. Rosiglitazone reduces urinary albumin excretion in type II diabetes. *J Hum Hypertens* 2003; 17(1):5–6.
45. Haffner SM, Greenberg AS, Weston WM et al. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. *Circulation* 2002; 106:679–684.
46. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk hispanic women. *Diabetes* 2002; 51(9):2796–2803.
47. Natali A, Baldeweg S, Toschi E, et al. Vascular effects of improving metabolic control with metformin or rosiglitazone in type 2 diabetes. *Diabetes Care* 2004; 27:1349–1357.
48. Dandona P, Aljada A. Endothelial dysfunction in patients with type 2 diabetes and the effects of thiazolidinedione antidiabetic agents. *J Diabetes Complications* 2004; 18(2):91–102.
49. St. John Sutton M, Rendell M, Dandona P, et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. *Diabetes Care* 2002; 25(11):2058–2064.
50. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). *JAMA* 1999; 281:2005–2012.
51. Rosenstock J, Goldstein BJ, Vinik AI, et al.; RESULT Study Group. Effect of early addition of rosiglitazone to sulfonylurea therapy in older type 2 diabetes patients (>60 years): the Rosiglitazone Early vs. SULfonylurea Titration (RESULT) study. *Diabetes Obes Metab* 2006; 8(1):49–50.
52. Bell DS, Ovalle F. Long-term efficacy of triple oral therapy for type 2 diabetes mellitus. *Endocr Pract* 2002; 8(4):271–275.
53. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348(5):383–393.