

Oral Combination Therapy With Thiazolidinediones in Type 2 Diabetes

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Abstract

Insulin resistance occurs early in the type 2 diabetes disease process, leading to progressive beta cell failure and overt diabetes. By the time the diagnosis of diabetes is made, advanced macrovascular disease may already be present. Monotherapy with a sulfonylurea or metformin can slow, but does not prevent, the progression of disease. Successful management requires combination therapy that addresses both insulin resistance and beta cell dysfunction. Clinical trials support the use of combinations of agents with complementary mechanisms of action, such as a sulfonylurea or metformin plus a thiazolidinedione. Early aggressive treatment can improve patient outcomes while reducing overall healthcare costs.

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The natural history of type 2 diabetes is summarized in **Figure 1**.¹ Insulin resistance (impaired tissue response to insulin) occurs early in the disease process leading to type 2 diabetes and may be the primary defect²⁻⁴; factors contributing to its development include genetic predisposition and weight gain.² Initially, the pancreatic beta cells respond by secreting more insulin, thus maintaining normal glucose tolerance by means of a compensatory hyperinsulinemia. As insulin resistance increases, however, beta cell function declines, and, eventually, the pancreas cannot produce enough insulin to compensate.⁴ This relative insulin deficiency results in glucose intolerance which, in its early phases (prediabetes), manifests as postprandial and/or fasting glucose levels that are elevated, but still below the threshold for diagnosing diabetes.

- Impaired glucose tolerance (IGT) is defined as a 2-hour plasma glucose level of 140 to 199 mg/dL on an oral glucose toler-

ance test (OGTT). IGT may begin years before elevated fasting glucose levels occur, but is usually not detected¹ because OGTTs are not routinely used for population screening.

- Impaired fasting glucose (IFG) is defined as fasting plasma glucose (FPG) levels of 100 to 125 mg/dL.⁵

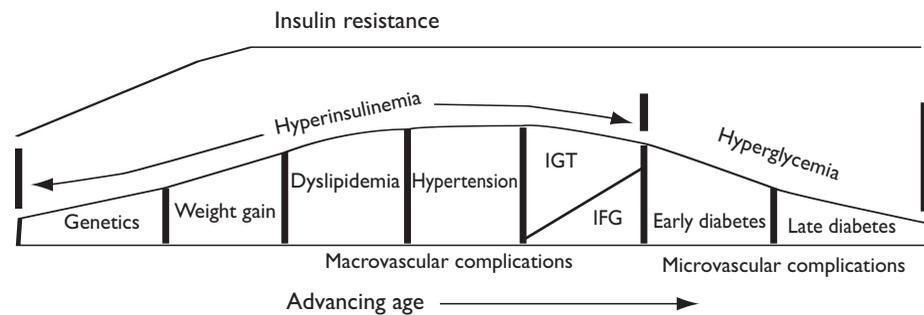
As beta cell function continues to decline, hyperglycemia increases, leading to overt diabetes.

Progressive loss of beta cell function was demonstrated by data from the United Kingdom Prospective Diabetes Study (UKPDS), a long-term trial comparing different treatment approaches in 4209 patients with newly diagnosed type 2 diabetes.⁶ Using homeostasis model assessment (HOMA), the beta cell function of individual patients was estimated from fasting insulin and glucose levels during the first 6 years of treatment. Data from a subset of patients receiving diet therapy alone showed that beta cell function was only 51% at the time of diagnosis, and improved slightly to 53% after 1 year of treatment; however, this was followed by a progressive decline to approximately 28% by year 6.^{6,7} Extrapolation of these data suggests that beta cell loss may begin as long as 12 years before diagnosis; thus, type 2 diabetes is the result of a disease process that often has been going on undetected for more than a decade. Furthermore, by 13 to 14 years after diagnosis, beta cell function and insulin secretion may approach zero.

Diabetes Complications

Type 2 diabetes is associated with both microvascular and macrovascular complications. It has been believed that the risk for microvascular complications (including retinopathy, nephropathy, and neuropathy) begins to increase when glycemia exceeds

Figure 1. Natural History of Type 2 Diabetes: Disease Progression



IGT indicates impaired glucose tolerance; IFG, impaired fasting glucose.

Source: Reference 1.

the diagnostic threshold for diabetes.⁸ However, in a follow-up of the Diabetes Prevention Program (DPP) trial, among a random sample of 302 subjects with IFG who received fundus photography, >7% showed signs of early diabetic retinopathy—suggesting that microvascular risk may be increased even in prediabetes.⁹

In contrast, the risk for macrovascular complications (including coronary, cerebrovascular, and peripheral vascular disease) begins to increase even at normal levels of glycemia (glycated hemoglobin [A1C] <6%). The absence of a glycemic threshold for macrovascular risk was demonstrated by data from the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk).⁸ A1C and cardiovascular risk factors were assessed at baseline in 10 232 study participants. Cardiovascular disease (CVD) events—defined as hospital admission or death due to coronary heart disease (CHD), stroke, or other vascular disease—and all-cause mortality were then recorded during an average follow-up of 6 years. The relationships between A1C and event rates for CHD, CVD, and all-cause mortality were continuous and significant across the entire distribution of A1C (from <5% to ≥7%), independent of other cardiovascular risk factors.⁸

Thus, many patients already have advanced macrovascular disease by the time they are diagnosed with diabetes.¹ This is consistent with the fact that insulin resistance and hyperinsulinemia (which precede hyperglycemia) are linked with a cluster of other cardiovascular risk factors, including:

- Central (visceral) obesity^{10,11}
- Hypertension^{3,11}
- Dyslipidemia, with elevated triglycerides (TGs), reduced high-density lipoprotein (HDL) cholesterol, and small, dense low-density lipoprotein (LDL) cholesterol particles^{3,10,11}

This “insulin resistance syndrome” or “metabolic syndrome” is also associated with endothelial dysfunction,¹¹ vascular inflammation,¹¹ and a prothrombotic state.^{3,11} Together, these factors promote atherosclerosis and increase the risk of macrovascular disease.¹

Pathophysiology of Type 2 Diabetes

The development of type 2 diabetes requires the presence of 2 defects: insulin resistance and beta cell dysfunction.^{2,3}

Insulin Resistance. The major insulin target tissues are liver, skeletal muscle, and adipose tissue.

Liver. After glucose ingestion, insulin enters the portal vein and is carried to the liver, where it suppresses gluconeogenesis. In diabetes (particularly when fasting glucose levels exceed 140 mg/dL), the normal suppression of gluconeogenesis is impaired. This results in excessive hepatic glucose production.²

Muscle. Skeletal muscle is normally a major site of glucose uptake and disposal. Insulin resistance impairs muscle glucose uptake, contributing to hyperglycemia. In

addition, glucose disposal—including both glucose oxidation and glycogen synthesis—is impaired. Thus, a disproportionate amount of the glucose that is taken up is converted to lactate, which serves as additional substrate for hepatic gluconeogenesis.²

Adipose Tissue. Insulin promotes TG storage in adipocytes. Insulin resistance results in excessive lipolysis, leading to elevated free fatty acid (FFA) concentrations,³ which stimulate gluconeogenesis or prevent its normal suppression.^{2,3} Excess FFAs also impair beta cell function, as described below.

Beta Cell Dysfunction. Multiple factors, including lipotoxicity and glucotoxicity, lead to progressive loss of beta cell function.

Lipotoxicity. When adipocytes store excess calories as TGs, they secrete increased amounts of leptin. Evidence suggests that the resulting increased serum leptin levels prevent lipid accumulation in nonadipose tissues. If overnutrition continues, however, leptin resistance may develop. Lipid accumulation can then occur in nonadipose tissues (including pancreatic beta cells), where excess FFAs enter deleterious metabolic pathways, such as ceramide production, resulting in cellular damage.¹²

Mildly elevated FFAs are not toxic to the beta cell, but drive the compensatory increase in insulin secretion that overcomes insulin resistance. Further increases in FFAs, however, lead to beta cell dysfunction and damage, resulting in insulin deficiency, which at first is relative (normal or high levels insufficient to overcome insulin resistance) but eventually becomes absolute.¹³

Glucotoxicity. Once hyperglycemia develops, glucotoxicity contributes to further beta cell loss. In vitro studies suggest several mechanisms—eg, protein glycation^{14,15} and glucokinase downregulation¹⁶—by which long-term exposure to high glucose levels may cause dysregulation of insulin secretion and beta cell apoptosis.

The Role of Incretins. Incretins, such as glucagon-like peptide-1 (GLP-1), are peptide hormones that are secreted by the gut in

response to nutrient ingestion. GLP-1 plays an important role in glucose homeostasis, especially the regulation of postprandial glucose excursions.

GLP-1 stimulates glucose-dependent insulin secretion by activating specific receptors on beta cells. It also inhibits glucagon secretion and suppresses hepatic glucose production; it is unclear, however, whether these effects are due to direct actions on pancreatic alpha cells and hepatocytes, respectively, or are indirect via increased insulin. GLP-1 further moderates postprandial glucose levels by slowing the gastric emptying rate and by promoting satiety.¹⁷⁻¹⁹ In addition, some evidence suggests that GLP-1 may enhance beta cell proliferation and inhibit beta cell apoptosis.^{17,18}

Normally, GLP-1 plasma levels rise within minutes of food ingestion¹⁸; GLP-1 is then rapidly inactivated by the plasma enzyme dipeptidyl peptidase-4 (DPP-4),^{18,19} so that its half-life is <2 minutes.¹⁷ Compared with normal subjects, patients with type 2 diabetes have reduced GLP-1 levels after a meal or an oral glucose load,^{17,19} probably due to decreased GLP-1 secretion.¹⁷ Whether this is a primary or secondary event in diabetes pathogenesis is uncertain.^{17,19} Reduced GLP-1 secretion, however, could help explain the IGT that occurs early in the disease process, as well as the early onset of beta cell loss.

Diabetes Screening

For diabetes screening, the American Diabetes Association (ADA) recommends

Table 1. Goals for Diabetes Treatment

Biochemical Index	ADA Goal	ACE/AACE Goal
A1C	<7%	≤6.5%
Preprandial/fasting glucose*	90-130 mg/dL	<110 mg/dL
Peak postprandial glucose*	<180 mg/dL	—
2-hour postprandial glucose*	—	<140 mg/dL

*Based on measurements of plasma (not whole blood) glucose. ADA indicates American Diabetes Association; ACE, American College of Endocrinology; AACE, American Association of Clinical Endocrinologists; A1C, glycated hemoglobin.

Sources: References 5, 20, and 21.

either an FPG, a 2-hour OGTT, or both. FPG is the preferred test in nonpregnant adults. Although OGTT is more sensitive and somewhat more specific than FPG, it is less reproducible, less convenient, and more expensive. It may, however, be the test of choice in patients with IFG to better define their diabetes risk.⁵

The ADA recommends screening at 3-year intervals in all individuals beginning at age

45—especially those who are overweight or obese (body mass index ≥ 25 kg/m²). In people who are overweight or obese and have additional risk factors, earlier and/or more frequent screening should be considered.⁵ The American College of Endocrinology (ACE) and American Association of Clinical Endocrinologists (AACE) specify that for people at high risk, screening should begin at age 30, and they recommend the 2-hour

Table 2. Oral Antidiabetic Agents

Drug Class	Examples	Sites of Action	Antihyperglycemic Actions	Common AEs (Selected)	Comments	Refs
SUs	Chlorpropamide Tolbutamide Glyburide (glibenclamide) Glimepiride Glipizide Gliclazide	Pancreas	Increased insulin release	Hypoglycemia Weight gain	Gliclazide is not available in the United States. See text for more details.	22,23
Biguanides	Metformin	Liver Muscle	Decreased hepatic glucose production (major action) Increased muscle glucose uptake and disposal	GI symptoms	Does not cause weight gain; some patients lose weight. See text for more details.	22,23
TZDs (glitazones)	Rosiglitazone Pioglitazone	Adipose tissue Muscle Liver	Increased insulin sensitivity, especially in peripheral tissues (adipose > muscle); may also decrease hepatic glucose production	Weight gain Fluid retention	See text for more details.	22,23
Meglitinides (glinides)	Nateglinide Repaglinide	Pancreas	Stimulation of glucose-dependent insulin secretion	Hypoglycemia and weight gain (less pronounced than with SUs)	Shorter half-life than SUs; preprandial dosing required	22,23, 25,26
Alpha-glucosidase inhibitors	Acarbose Miglitol	Small intestine	Inhibition of enzymatic carbohydrate breakdown → delayed glucose absorption ^{22,27,28}	GI symptoms	Taken with meals ^{27,28} Weight neutral ²⁴	22-24, 27,28
DPP-4 inhibitors	Sitagliptin	—	Slowing of DPP-4 inactivation → increased and prolonged incretin action	URI Nasopharyngitis Headache	Taken once daily Weight neutral in 24-week placebo-controlled clinical trials	29

AEs indicates adverse effects; SUs, sulfonylureas; GI, gastrointestinal; TZDs, thiazolidinediones; DPP-4, dipeptidyl peptidase-4; URI, upper respiratory infection.

OGTT as the screening test of choice in this population.²⁰

Treatment Goals and A1C

ADA and ACE/AACE treatment goals for pre- and postprandial glucose levels and A1C are summarized in **Table 1**. A1C reflects mean glycemia—the summation of fasting/preprandial and postprandial glucose levels—over the preceding 2 to 3 months,^{5,21} and is considered the “gold standard” for assessing and monitoring glycemic control.^{20,21}

The ACE/AACE treatment goal is an A1C $\leq 6.5\%$.²⁰ The ADA recommendation for patients in general is an A1C $< 7\%$; however, for individual patients the goal is to achieve an A1C as close to normal ($< 6\%$) as possible without causing significant hypoglycemia.⁵ Less stringent treatment goals may be appropriate in some circumstances, for example, in very young children or older adults, in patients with a history of severe hypoglycemia, and in patients with comorbid conditions or a limited life expectancy.⁵

ADA and ACE/AACE recommendations for frequency of A1C testing are similar. In patients with stable glycemic control who are meeting treatment goals, A1C should be tested at least twice a year. In patients whose treatment has changed and/or who are not meeting treatment goals, A1C should be tested at least 4 times a year.^{5,21}

Oral Antidiabetic Agents

Currently, there are 6 classes of US Food and Drug Administration (FDA)-approved oral antidiabetic agents (summarized in **Table 2**).²²⁻²⁹ Of these, the sulfonylureas (SUs), biguanides, and thiazolidinediones (TZDs) are the most widely used and are discussed further below.

SUs. SUs have long been the mainstay of therapy for type 2 diabetes and are still used as first-line therapy. First-generation SUs (eg, chlorpropamide and tolbutamide) are seldom used today. Later-generation SUs in common use include glyburide (also called glibenclamide), glimepiride, glipizide, and gliclazide (gliclazide is not available in the United States).

SUs directly stimulate insulin release by binding to receptors on the pancreatic beta

cell surface.^{22,23} Common adverse effects (AEs)—similar to those of insulin—are hypoglycemia and weight gain.^{22,23} In some studies, SUs have been associated with increased all-cause and cardiovascular mortality.³⁰ Proposed mechanisms include a direct effect on the heart, a secondary effect of associated weight gain, or toxicity due to elevated insulin levels.³⁰ However, in the UKPDS—the largest and longest-term prospective study of glucose control in type 2 diabetics—SUs neither increased nor decreased the risk for macrovascular disease and all-cause mortality.³¹

Biguanides. Metformin (MET) is the only biguanide in current use. Its exact mechanism of action is unclear; its major effect, however, is to reduce hepatic glucose output, primarily by decreasing gluconeogenesis.^{22,23} To a lesser extent, MET also appears to improve muscle glucose uptake and disposal,²² but this may be a secondary effect of decreased glucotoxicity.²³

In the UKPDS, MET significantly reduced the composite of all macrovascular end points (myocardial infarction [MI], sudden death, angina, stroke, peripheral vascular disease) by 30% compared with diet therapy alone in overweight patients with type 2 diabetes.³² Thus, MET was the first oral antidiabetic agent demonstrated to reduce the risk of macrovascular disease. The most common AEs are gastrointestinal (GI) symptoms.^{22,23} Unlike SUs and insulin, MET does not cause weight gain; in fact, it may result in weight loss and, therefore, has been recommended as first-line therapy for overweight or obese patients.²² Because MET does not increase insulin secretion, hypoglycemia is not a side effect of MET monotherapy.²² Lactic acidosis is a potentially serious AE that occurred frequently with phenformin (another biguanide that is no longer used), but is rarely reported with MET.^{22,23}

TZDs. Currently there are 2 FDA-approved TZDs, rosiglitazone and pioglitazone. TZDs are selective agonists of peroxisome proliferator-activated receptor- γ (PPAR- γ). PPAR- γ activation alters the transcription of numerous genes that regulate carbohydrate and

lipid metabolism,^{22,23,33} vascular function, thrombotic activity, and inflammatory response.³³ Thus, TZDs have multiple, complex actions. Their major effect in patients with type 2 diabetes is to improve insulin sensitivity. Because the negative feedback between glucose and insulin remains intact, this results in a corresponding decrease in insulin secretion.⁴

In adipose tissue, TZDs decrease lipolysis^{22,23} and reduce circulating FFAs²²; in muscle, they increase glucose uptake.²³ TZDs may also decrease hepatic glucose production, although possibly only at high doses.²³ Because PPAR- γ is most highly expressed in adipose tissue, the TZD effect on insulin sensitivity is thought to be mediated primarily via adipocytes.^{22,23}

TZDs appear to preserve beta cell function, as demonstrated in animal models and, indirectly, in humans. The evidence has been extensively reviewed elsewhere.^{13,22,33-36} Proposed mechanisms include “offloading” of beta cells due to improved insulin sensitivity; decreased lipotoxicity due to FFA reduction; and/or a direct effect on beta cells.³⁴

Additionally, TZDs are reported to have beneficial effects on other cardiovascular risk factors, including blood pressure reduction^{33,34,37} and improvement of lipid profiles, with decreased TGs and increased HDL.^{22,23,33,34,38} Although LDL may also increase, TZDs appear to shift it to a less atherogenic subtype.^{23,33,34,38} TZDs may also improve endothelial function,^{23,34,39} decrease thrombogenicity,^{34,39,40} and modulate vascular inflammation.³⁹

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), a randomized placebo-controlled trial in 5238 patients with type 2 diabetes and macrovascular disease, was designed to determine whether TZDs decrease macrovascular risk. After a mean follow-up of 34.5 months, pioglitazone significantly reduced the main secondary end point—a composite of all-cause mortality, nonfatal MI, and stroke.⁴¹ However, reduction of the primary end point—a composite that additionally included acute coronary syndrome, revascularization procedures, and leg amputation—did not reach statistical significance. The

antiatherogenic actions and efficacy of TZDs are discussed further in the accompanying article, Health Outcomes Beyond Glucose Control.

Common AEs of TZDs include fluid retention and weight gain. Fluid retention occurs in 3% to 15% of patients,³³ usually in the form of peripheral edema. Pulmonary edema and congestive heart failure are infrequently reported.²² Weight gain is probably due to a combination of fluid retention and fat accumulation^{42,43}; however, the fat accumulation appears to involve primarily peripheral subcutaneous adipose tissue, whereas visceral adiposity is reduced.^{22,23} The management of TZD-induced weight gain and fluid retention is discussed in the accompanying article.

The first TZD available in the United States, troglitazone, was removed from the market due to hepatotoxicity. Cases of hepatotoxicity associated with rosiglitazone and pioglitazone have been reported, but less frequently, and rarely involving hepatic failure. It is recommended that liver enzymes be checked before and periodically during TZD treatment.^{30,43,44} TZDs should not be started in patients with evidence of active liver disease,^{30,43} and patients who develop hepatic dysfunction during TZD therapy should not be rechallenged with another TZD.⁴⁴

ADA/EASD Management Guidelines

Although it is well established that tight glycemic control is desirable, there is a scarcity of high-quality studies comparing the efficacy of different drugs or drug combinations in achieving and maintaining glycemic goals. Therefore, the 2006 consensus guidelines of the ADA and the European Association for the Study of Diabetes (EASD) are based largely on noncomparative data about individual interventions. The guidelines incorporate an algorithm for use of MET, SUs, TZDs, and insulin. Other oral agents and injectable agents other than insulin (incretin mimetics and amylin agonists) may be used in selected patients, but are not included in the guidelines because of limited data, lower efficacy, and/or high cost.²⁴

The ADA/EASD algorithm includes the following steps²⁴:

- **Step 1:** Initiate MET at the time of diagnosis; most patients cannot maintain glycemic goals with lifestyle intervention alone.
- **Step 2:** If A1C remains or becomes $\geq 7\%$ with lifestyle intervention plus maximal MET doses, add a second medication. Basal insulin is the most effective and is the recommended choice for patients with A1C $> 8.5\%$ or symptomatic hyperglycemia. For asymptomatic patients with A1C $\leq 8.5\%$, either an SU or a TZD may be added to MET as an alternative to insulin.
- **Step 3:** If A1C remains or becomes $\geq 7\%$ —particularly if A1C is $\geq 8\%$ —add basal insulin (for patients receiving MET plus either an SU or TZD) or intensify insulin therapy (for patients already receiving basal insulin). If A1C is $\geq 7\%$ but $< 8\%$, addition of a third oral agent—a TZD (added to MET plus an SU) or an SU (added to MET plus a TZD) can be considered instead of insulin.²⁴

The Case for Early Use of TZDs

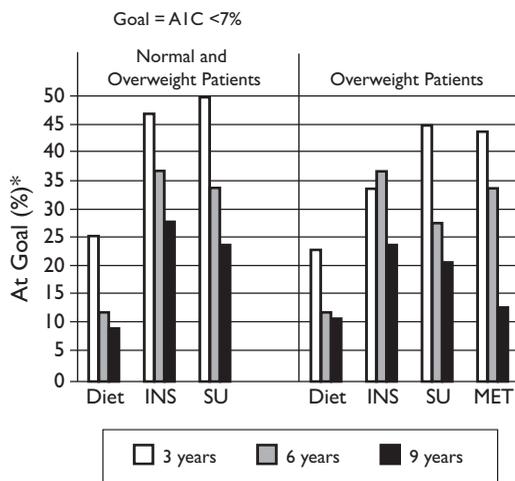
Although the ADA/EASD guidelines recommend MET as first-line therapy, a case can be made for early use of TZDs (eg, in combination with MET or an SU)—addressing the primary defect of insulin resistance and preserving beta cell function before too many beta cells have been lost.^{1,13,36,39,45,46}

Long-term data from the UKPDS demonstrate that monotherapy with MET or an SU does not prevent beta cell decline. The UKPDS was designed to assess 2 pharmacological approaches⁶:

- Enhancing insulin supply (in both obese and nonobese patients): either an SU or insulin plus diet therapy versus diet alone
- Enhancing insulin sensitivity (in obese patients only): MET plus diet versus diet alone

Figure 2 shows the percentages of patients (among those remaining on their allocated therapy) who were at the ADA goal of A1C $< 7\%$ after 3, 6, and 9 years.⁴⁷ These data demonstrate increasing failure of SU or MET monotherapy to maintain tight glucose control over the first 9 years after diagnosis. By year 3, $> 50\%$ of patients had failed monotherapy; by year 9, $> 75\%$ had failed monotherapy.

Figure 2. UKPDS 49: Patients (N = 4075) at Goal on Monotherapy



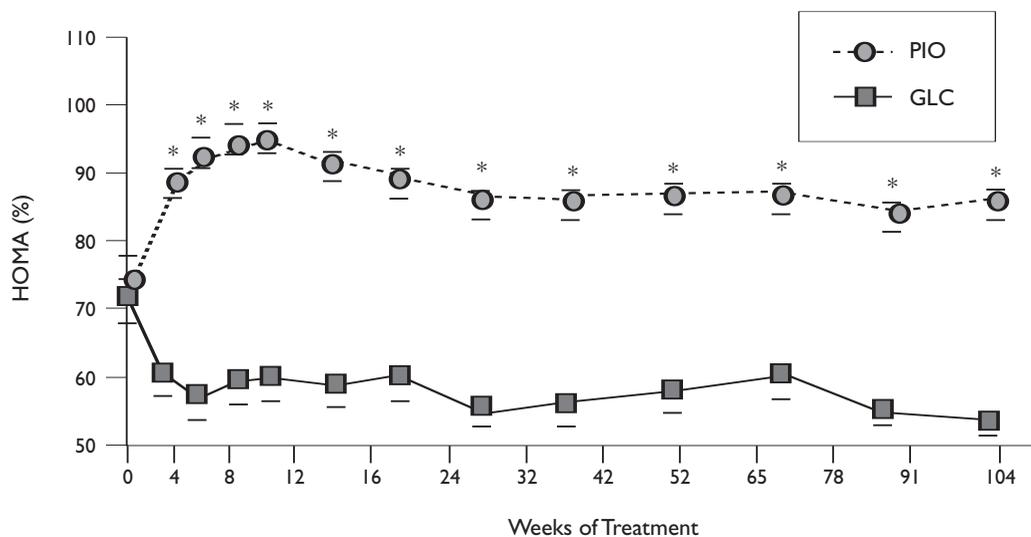
*% of patients allocated and remaining on allocated monotherapy. UKPDS indicates United Kingdom Prospective Diabetes Study; INS, insulin; SU, sulfonylurea; MET, metformin. Source: Reference 47.

(Not even insulin maintained A1C goals—possibly because UKPDS patients received mainly basal insulin, which does not reduce postprandial glucose excursions.)⁴⁷

As discussed previously, HOMA data from the UKPDS revealed that diet therapy alone produced a slight initial increase in beta cell function during the first year, followed by a progressive long-term decline. The same pattern occurred in patients receiving SU or MET monotherapy—except that, with monotherapy, the initial increase in beta cell function was larger (more so with SU than with MET).⁶ Thus, SU or MET monotherapy can delay, but does not prevent, disease progression.

TZDs were not included in the UKPDS, but results of subsequent studies suggest that they have more sustained efficacy than SUs. In a 2-year randomized, double-blind trial (N = 567) comparing pioglitazone versus gliclazide as first-line therapy,⁴⁸ A1C improvement was initially greater with gliclazide; however, during the second year of therapy, it was significantly greater with pioglitazone. Pioglitazone also improved insulin sensitivity and decreased fasting insulin levels; these effects were sustained over the 2-year study period. In contrast, gliclazide increased insulin levels and

Figure 3. Improved Insulin Sensitivity Over 2 Years: TZD vs SU



*P < .0001.

TZD indicates thiazolidinedione; SU, sulfonylurea; HOMA, homeostatic model assessment; PIO, pioglitazone; GLC, gliclazide.

Source: Reference 48.

decreased insulin sensitivity. The HOMA insulin sensitivity results are shown in **Figure 3**. A similar pattern was found in a 2-year randomized, double-blind trial of pioglitazone versus gliclazide as second-line therapy (added to failing MET).^{49,50} Thus, TZDs can achieve stable glycemic control for at least 2 years, probably as a result of improved beta cell function.³³

TZDs are reported to increase insulin sensitivity more effectively than MET, despite similar glycemic efficacy.^{51,52} However, one small (N = 78) study suggests that the rela-

tive efficacy of TZDs versus MET may depend in part on the patient's baseline beta cell status. In this randomized trial, either pioglitazone or MET was added to failing SUs. Although both groups overall had similar A1C improvement at 4 months, the subset of patients with relatively preserved beta cell function (by HOMA estimates) did better with pioglitazone, whereas those with reduced beta cell function did better with MET.⁵³ Although this evidence is preliminary, it supports the hypothesis that TZDs are most effective when used early in the disease process.

Table 3. Fixed-dose Combinations

SU + MET
• Glyburide/metformin (Glucovance)
• Glipizide/metformin (Metaglip)
TZD + MET
• Rosiglitazone/metformin (Avandamet)
TZD + SU
• Rosiglitazone/glimepiride (Avandaryl)
• Pioglitazone/glimepiride (Duetact)

SU indicates sulfonylurea; MET, metformin; TZD, thiazolidinedione.

Combination Therapy

TZDs as monotherapy can lower A1C by up to 1.4 percentage points,²⁴ a result no better than that of other oral agents. Thus, patients with moderate-to-severe hyperglycemia are likely to require combination therapy to achieve A1C goals without using insulin.

Oral agents with complementary mechanisms may have additive or synergistic effects. For example, TZDs can be combined with SUs. The TZD reduces insulin resistance and preserves beta cell function, whereas the SU increases insulin secretion.

TZDs can also be combined with MET. Although both drugs reduce insulin resistance, they have different target tissues, with TZDs acting predominantly in peripheral tissues and MET predominantly in the liver.²²

Another potential advantage of combination therapy is better tolerability. For example, addition of a TZD to submaximal MET has been associated with reduced GI AEs compared with maximal-dose MET monotherapy.^{54,55} Conversely, MET may moderate TZD-induced weight gain.⁵⁵

On the other hand, combination therapy can also result in increased AEs. For example, a TZD plus an SU may cause more weight gain than SU alone.⁵⁶ However, this may be mitigated by the fact that TZD-induced fat accumulation is primarily subcutaneous rather than visceral.

Another potential disadvantage of combination therapy is the inconvenience of taking 2 drugs, which may impact adherence. This can often be avoided, however, by the use of fixed-dose combinations (FDCs). In at least 2 retrospective studies, patients with diabetes who were previously receiving monotherapy and required a second agent demonstrated significantly better adherence when switched to an FDC versus addition of a second pill. Furthermore, patients already receiving combination therapy who switched to an FDC had significantly better adherence after the switch.^{57,58} FDCs available in the United States are listed in **Table 3**.

A comprehensive review of TZD combination therapy is beyond the scope of this article, but results from several illustrative trials are discussed below.

TZD Plus MET as First-line Therapy. In a single-arm, open-label study,⁵⁹ 190 patients with severe hyperglycemia (A1C >11% or FPG >270 mg/dL) were treated with a rosiglitazone/MET FDC (4 mg/1 g) titrated to a maximum dose of 8 mg/2 g per day. Despite their poor glycemic control at baseline, 50% and 38% of the patients achieved the ADA and ACE/AACE goals, respectively, by the end of the 24-week study period.

TZD Plus MET Versus MET Monotherapy. In a double-blind trial,⁶⁰ 348 patients whose diabetes was inadequately controlled on

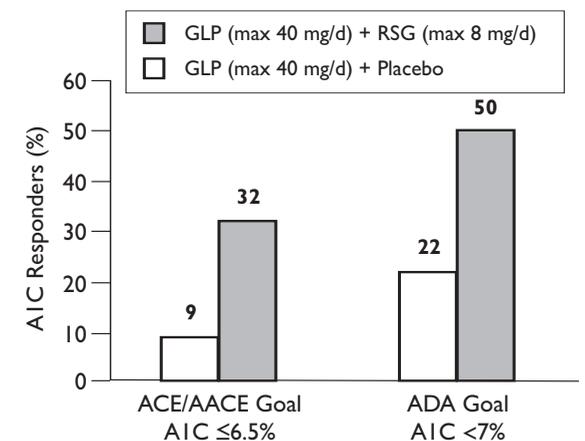
MET (2.5 g/day) were randomly assigned to addition of either rosiglitazone (4 or 8 mg/day) or placebo. The main outcomes were A1C, FPG, insulin sensitivity, and beta cell function. Compared with MET alone, addition of rosiglitazone significantly improved all of these outcomes in a dose-dependent manner. In both rosiglitazone dose groups, FPG decreases began within the first 4 weeks, reached a plateau by 8 to 12 weeks, and were maintained to the end of the 26-week study period.

In another double-blind trial,⁵⁴ 766 patients with inadequate control on submaximal MET (1 g/day) were randomized to either uptitrated MET (2 g/day) or add-on rosiglitazone (8 mg/day). The primary outcome was A1C at week 24. Rosiglitazone plus submaximal MET was at least as effective as uptitrated MET in improving A1C, and was significantly more effective in lowering FPG. The percentages of patients reaching ADA and ACE/AACE A1C goals were, respectively, 58.1% and 40.9% in the combination therapy group compared with 48.4% and 28.2% in the uptitrated MET group. Similar results were seen in a third randomized, double-blind trial (N = 569) using higher MET doses, in which MET (2 g/day) plus rosiglitazone (8 mg/day) was significantly superior to uptitrated MET (3 g/day).⁵⁵

TZD Plus MET Versus SU Plus MET. An established long-term economic model, the Diabetes Decision Analysis of Cost—Type 2 (DiDACT), was used to determine the cost-effectiveness of adding rosiglitazone versus an SU to failing MET in a cohort of 1000 overweight and obese patients with diabetes. Rosiglitazone plus MET was more cost-effective than an SU plus MET, and was predicted to extend the viability of oral therapy by up to 8 years.⁶¹

In a 2-year double-blind trial,^{49,50} 630 patients whose diabetes was poorly controlled on MET monotherapy were randomly assigned to add either pioglitazone (up to 45 mg/day) or gliclazide (up to 320 mg/day). The primary outcome was A1C change. Although maximum A1C improvement occurred earlier with gliclazide, by the end of the first year there was no significant between-group difference in A1C. At the

Figure 4. TZD + SU Versus SU Monotherapy: Percent of Patients at A1C Goal After 2 Years



TZD indicates thiazolidinedione; SU, sulfonylurea; A1C, glycosylated hemoglobin; GLP, glipizide; RSG, rosiglitazone; ACE, American College of Endocrinology; AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association.
 Source: Reference 56.

end of the second year, A1C improvement was relatively sustained in the pioglitazone group, but appeared to be declining in the gliclazide group (although the between-group difference was still nonsignificant).

Similar glycemic outcomes have been

demonstrated in 2 other randomized double-blind trials. In a comparison of pioglitazone plus MET versus glimepiride plus MET (N = 210), A1C improvement was initially greater with glimepiride, but the difference was nonsignificant by the end of the 26-week study period.⁶² In a comparison of rosiglitazone plus MET versus glimepiride plus MET (N = 99), A1C improvement was initially greater with rosiglitazone, but the difference was nonsignificant at the end of the 12-month study period.⁶³

These results suggest that a TZD plus MET is a reasonable alternative to an SU plus MET. However, at least 1 randomized, double-blind trial (N = 318; duration, 24 weeks) has given conflicting results, with significantly better glycemic control in patients receiving a MET/glyburide FDC compared with MET plus rosiglitazone. In this trial, MET/glyburide also resulted in significantly lower fasting insulin levels.⁶⁴

TZD Plus SU Versus SU Monotherapy. In two 26-week double-blind trials, patients (N = 340 and N = 473) who were inadequately controlled on SU monotherapy were randomized to either add-on rosiglitazone or uptitrated SU. Both trials significantly favored add-on rosiglitazone.^{65,66}

Further support for TZD plus SU use is provided by a 2-year double-blind trial, the Rosiglitazone Early vs Sulfonylurea Titration (RESULT) study.⁵⁶ In this trial, 227 patients previously receiving submaximal SU therapy were randomized to receive glipizide (titrated as needed to a maximum of 40 mg/day) plus either rosiglitazone (up to 8 mg/day) or placebo. The primary end point was disease progression, defined as FPG ≥10 mmol/L (≥180 mg/dL). Compared with glipizide monotherapy, glipizide plus rosiglitazone reduced the risk of progression by approximately 95% (hazard ratio, 0.048), despite the fact that a significantly higher percentage of the monotherapy group required glipizide titration to the maximal dose. Furthermore, a higher percentage of the glipizide plus rosiglitazone group achieved A1C goals, as shown in **Figure 4**.

These data suggest that early addition of a TZD to submaximal SU is more effective than SU dose escalation alone. Furthermore,

Table 4. TZD + SU Versus SU Monotherapy: Healthcare Costs

Event	Cost Per Patient Per Month (\$)		
	GLP	RSG + GLP	Difference
Hospitalization	360.70	126.10	234.60
Emergency department visits	7.80	3.50	4.30
Physician visit	40.80	37.60	3.20
Prescription, study medication	11.00	98.60	-87.60
Prescription, nonstudy medication	195.00	182.10	12.90
Laboratory tests	6.70	9.70	-3.00
Supplies/self-monitoring	22.50	22.50	0
Total	644.50	480.10	164.40

TZD indicates thiazolidinedione; SU, sulfonylurea; GLP, glipizide; RSG, rosiglitazone.
 Source: Reference 67.

an analysis of resource utilization and cost of care in the RESULT study concluded that TZD plus SU combination therapy is cost-effective. Although the calculated costs of the study medication were higher for combination therapy, this was more than offset by lower costs of healthcare utilization, particularly hospitalization and emergency department visits.⁶⁷ **Table 4** summarizes calculated healthcare costs based on the RESULT study.

TZD Plus an SU Versus MET Plus an SU. In a double-blind trial,^{50,68} 639 patients poorly controlled with SU monotherapy were randomly assigned to addition of either pioglitazone (up to 45 mg/day) or MET (up to 2.55 g/day). The primary outcome was A1C change. Maximal A1C response occurred at 24 weeks in both groups, followed by a slow decline of this improvement in both groups, with no significant between-group difference at 2 years. Thus, TZD plus SU therapy is a reasonable alternative to MET plus an SU.

Summary

- In type 2 diabetes, insulin resistance is the primary abnormality and leads to progressive beta cell dysfunction and apoptosis.
- Screening for type 2 diabetes should be done with FPG and/or 2-hour OGTT every 3 years beginning at age 45 (earlier and/or more frequently in people at high risk).
- A1C is the gold standard for monitoring treatment response. Lowering A1C reduces the risk for both microvascular and macrovascular complications.
- Monotherapy with maximal doses can delay, but does not prevent, disease progression. Successful management requires aggressive combination therapy that addresses both insulin resistance and beta cell dysfunction.
- Clinical trials support the use of various combinations of agents with complementary mechanisms of action (eg, a TZD plus MET or a TZD plus an SU). Submaximal doses of each drug may result in fewer AEs.
- When combination therapy is used, FDCs can improve adherence.
- Aggressive treatment enhances patient outcomes while alleviating the cost burden to the healthcare system.

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