

Overview of Newer Agents: Where Treatment Is Going

Ralph A. DeFronzo, MD

Diabetes Division, University of Texas Health Science Center, San Antonio, Texas, USA

ABSTRACT

Impaired insulin secretion (β -cell), increased hepatic glucose production (liver), and decreased peripheral (muscle) glucose utilization constitute the traditional primary defects responsible for the development and progression of type 2 diabetes mellitus. β -Cell failure, ultimately leading to decreased insulin secretion, is now known to occur much earlier in the natural history of type 2 diabetes than originally believed. Additionally, a better understanding of the pathophysiology of type 2 diabetes reveals other etiologic mechanisms beyond the classic triad, now referred to as the ominous octet. In addition to the β -cell, liver, and muscle, other pathogenic mechanisms include adipocyte insulin resistance (increased lipolysis), reduced incretin secretion/sensitivity (gastrointestinal), increased glucagon secretion (α -cell), enhanced glucose reabsorption (kidney), and central nervous system insulin resistance resulting from neurotransmitter dysfunction (brain). Currently, the management of type 2 diabetes focuses on glucose control via lowering of blood glucose (fasting and postprandial) and hemoglobin A_{1c}. However, the goal of therapy should be to delay disease progression and eventual treatment failure. Treatment should target the known pathogenic disturbances of the disease (i.e., reducing the deterioration of β -cell function and improving insulin sensitivity). In recent years, treatment strategies have focused on the development of novel therapeutic options that affect many of the defects contributing to type 2 diabetes and that provide durable glucose control through a blunting of disease progression. Optimal management of type 2 diabetes should include early initiation of therapy using multiple drugs, with different mechanisms of action, in combination.

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KEYWORDS: β -Cell function; Exenatide; Ominous octet; Pathophysiology; Type 2 diabetes mellitus

Over the past 2 decades our understanding of the pathophysiology of type 2 diabetes mellitus has expanded from the triumvirate of β -cell-, muscle-, and liver-related defects to the ominous octet described in the 2008 Banting Lecture.^{1,2} It is now apparent that β -cell failure occurs much earlier in the natural history of type 2 diabetes than previously thought, and there is growing evidence that therapeutic interventions that slow or delay the progression of β -cell failure can lead to more durable glycemic control. There now are agents available that can target multiple pathophysiologic mechanisms. This article reviews current perspectives on the pathophysiology of type 2 diabetes, including the prediabetic state, and the need for early intervention. We

also will review therapeutic approaches that target the multiple defects involved in type 2 diabetes.

β -CELL FUNCTION IN THE PREDIABETIC STATE

Among the traditional fundamental defects responsible for the development of type 2 diabetes are impaired insulin secretion resulting from declining β -cell function, decreased glucose uptake by the peripheral (muscle) tissues, and increased hepatic glucose production (HGP) secondary to augmented gluconeogenesis.^{1,3} Paradoxically, insulin secretion may be increased early in the course of type 2 diabetes, as the pancreas attempts to compensate for the elevated fasting plasma glucose (FPG) concentration and underlying insulin resistance. However, as the FPG concentration continues to rise, β -cells no longer are able to sustain their increased rate of insulin secretion and, as insulin secretion begins to decline, impaired glucose tolerance (IGT) and eventually overt type 2 diabetes ensue.^{1,4-6} Increased HGP and decreased muscle glucose uptake further contrib-

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Requests for reprints should be addressed to Ralph A. DeFronzo, MD, Diabetes Division, University of Texas Health Science Center, One UTSA Circle, San Antonio, Texas 78249-1644.

E-mail address: albarado@uthscsa.edu.

ute to the state of hyperglycemia,^{1,4,6} which places further stress on the β -cells and establishes a negative backloop in which the metabolic decompensation (glucotoxicity⁷ and lipotoxicity⁸) contributes to the β -cell failure and worsening insulin resistance.

It is important to recognize that the plasma insulin response to ingested glucose or to a mixed meal does not provide information about the health of the β -cell. The β -cell responds to an increment in plasma glucose (PG) concentration with an increment in plasma insulin, and the system is influenced by the severity of insulin resistance. Thus, the "gold standard" for β -cell function is the insulin secretion/insulin resistance or so called disposition index ($\Delta I/\Delta G \div IR$).

The San Antonio Metabolism (SAM) study⁹ and Veterans Administration Genetic Epidemiology Study (VAGES)⁴ clearly have established that β -cell failure occurs early in the natural course of type 2 diabetes and is more severe than originally appreciated. The SAM study demonstrated a marked and progressive decline in β -cell function in individuals with normal glucose tolerance (NGT).⁹ As the 2-hour PG during an oral glucose tolerance test (OGTT) in NGT subjects increased from <100 to 100-119 to 120-139 mg/dL (1 mg/dL = 0.05551 mmol/L), there was an ~60% decline in β -cell function. In the upper tertile of IGT (2-hour PG = 180 to 199 mg/dL), β -cell function had declined by 75% to 80%. Similar results were reported in VAGES.⁴ In VAGES, individuals with IGT exhibited greater reductions in insulin secretion than individuals with impaired fasting glucose (IFG) when both measures were adjusted for severity of insulin resistance.⁴

Ferrannini and colleagues¹⁰ evaluated the progressive decline in β -cell function in 188 patients with varying degrees of glucose tolerance. Patients were grouped into 4 categories, based on the results of an OGTT and body mass index (BMI). Lean and obese individuals with NGT were matched for BMI with subjects with IGT and type 2 diabetes. The results of this study showed that there was an initial increase in plasma insulin response as the PG concentration increased during the early stages of glucose intolerance, followed by a marked decrease in insulin levels as patients became more insulin resistant and hyperglycemic. Within the range of NGT, β -cell sensitivity to glucose decreased by 50% to 70% as insulin sensitivity declined by 20% to 30%. Thus, β -cell dysfunction is seen at the earliest stages of IGT and strongly correlates with the degree of glucose tolerance (2-hour PG during OGTT). On the opposite end of the spectrum, patients with type 2 diabetes were found to have the highest levels of insulin resistance and the greatest reduction in β -cell function.

Butler and associates¹¹ quantitated β -cell volume in a study that analyzed pancreatic tissue from 124 autopsied individuals with varying degrees of glucose intolerance (NGT, IFG, and type 2 diabetes). In patients with IGT and type 2 diabetes, there was a progressive decrease in β -cell volume that was related to an increase in β -cell apoptosis. This suggests that treatment strategies for patients with

type 2 diabetes should include agents that may delay and/or prevent β -cell apoptosis.¹¹

By the time individuals reach the upper tertile of IGT, most are maximally or near maximally insulin resistant and have lost most (75% to 80%) of their β -cell function. Moreover, in a cohort of the Diabetes Prevention Program (DPP), diabetic microvascular complications such as diabetic retinopathy were reported in ~10% of patients with IGT.¹² In another study, polyneuropathy was found in 13% of patients with IGT.¹³

In summary, from a pathophysiologic standpoint (maximal/near maximal insulin resistance and 75% to 80% loss of β -cell function), individuals with IGT should be considered to have type 2 diabetes. Most importantly, those individuals with IGT who have diabetic retinopathy and/or neuropathy, both pathophysiologically and clinically, should be considered to have diabetes.

INSULIN RESISTANCE AND TYPE 2 DIABETES MELLITUS

Insulin resistance is a key pathologic defect that is a characteristic feature of type 2 diabetes.^{1,2,14-16} Both the liver and muscle are severely resistant to the action of insulin. A strong correlation exists between the increase in HGP and the increase in FPG concentration in type 2 diabetes.^{15,16} The increased rate of glucose production by the liver occurs in the presence of fasting plasma insulin concentrations that are elevated 2- to 3-fold, indicating severe resistance to the suppressive effect of insulin on HGP. When insulin is infused to mimic levels seen after ingestion of a standard meal, the suppression of the HGP is markedly impaired in type 2 diabetes.¹⁷ All of the increase in the HGP can be shown to be secondary to an accelerated rate of hepatic gluconeogenesis.³

Using the gold standard euglycemic insulin clamp technique,¹⁸ it has been shown that skeletal muscle is severely resistant to insulin and accounts for 85% to 90% of the impairment in total body glucose disposal in patients with type 2 diabetes.^{2,15,19} Insulin resistance in skeletal muscle is a hallmark feature of type 2 diabetes. Multiple intracellular defects in insulin action, including decreased glucose transport and phosphorylation, reduced glycogen synthesis, and impaired glycolysis and glucose oxidation contribute to the insulin resistance.² More recent studies from our laboratory have demonstrated that more proximal defects in the insulin receptor signal transduction cascade play the major role in the muscle insulin resistance observed in type 2 diabetes.²⁰⁻²³ However, it is important to note that, although insulin resistance is well established in the liver and muscle in the early phase of the disease, type 2 diabetes does not develop without the onset of progressive β -cell failure.²

INSULIN RESISTANCE AND CARDIOVASCULAR DISEASE

Epidemiologic studies have shown that insulin resistance not only predicts the development of type 2 diabetes,²⁴⁻²⁶

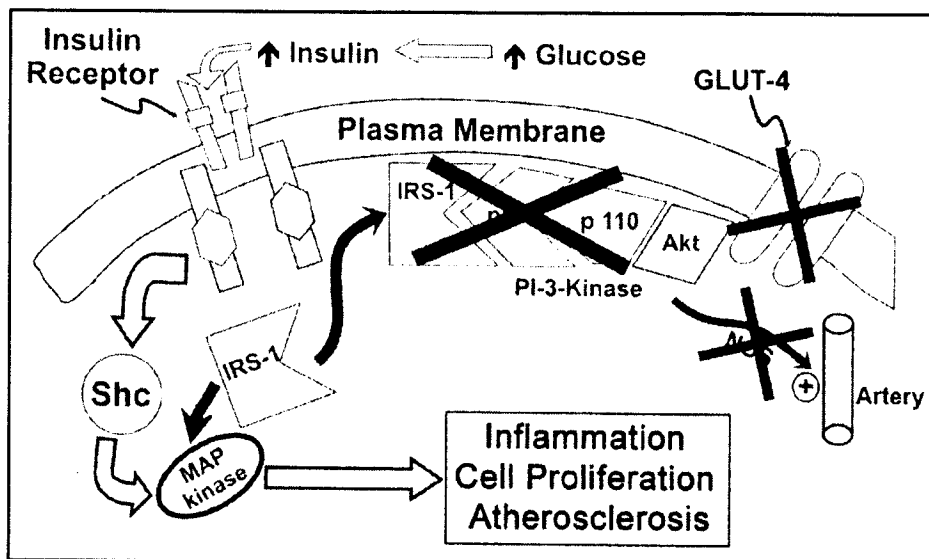


Figure 1 In type 2 diabetes mellitus, insulin signaling through the mitogen-activated protein kinase (MAP kinase) pathway is normally sensitive to insulin and the compensatory hyperinsulinemia (due to insulin resistance in the insulin receptor substrate-1/phosphatidylinositol 3-kinase [IRS-1/PI-3 kinase] pathway) results in excessive stimulation of this pathway that is involved in inflammation, cell proliferation, and atherogenesis (see text for a detailed discussion). Akt = the downstream effector of PI-3 kinase; GLUT-4 = glucose transporter-4; NOS = nitric oxide synthase; p110 = phosphoinositide-3 kinase; Shc = transforming protein which has been implicated in mitogenesis, so named because it contains the Src homology 2 [SH2] domain, as well as being homologous to collagen. (Reprinted with permission from *Diabetes*,² *J Nucl Cardiol*,²⁰ and *J Clin Invest*.²²)

but also is a predictor of cardiovascular (CV) disease.^{27,28} An 8-year follow-up of the San Antonio Heart Study demonstrated a progressive increase in CV events with progressive severity of insulin resistance as measured using the homeostasis model assessment of insulin resistance (HOMA-IR) even after adjustment for age, sex, ethnicity, obesity, blood pressure, and lipids.²⁷ Patients in the highest quintile of HOMA-IR had a >2-fold increase in CV risk compared with patients in the lowest quintile (odds ratio, 2.52; 95% confidence interval, 1.46 to 4.36).²⁷

MOLECULAR ETIOLOGY OF THE INSULIN RESISTANCE: IMPLICATIONS FOR ATHEROSCLEROTIC VASCULAR DISEASE

To initiate its biologic effects, insulin must first bind to the α -subunit of the insulin receptor (Figure 1).^{2,20-22,29,30} This leads to phosphorylation of the β -subunit, with subsequent activation of insulin receptor tyrosine kinase. After activation, insulin receptor tyrosine kinase phosphorylates specific intracellular proteins. In muscle, insulin receptor substrate-1 (IRS-1) serves as the major docking protein that interacts with the insulin receptor tyrosine kinase, undergoes tyrosine phosphorylation, and mediates insulin's effect on glucose metabolism.

In muscle, the phosphorylated tyrosine residues on IRS-1 mediate an association with the p85-kd regulatory subunit of

phosphatidylinositol (PI)-3 kinase, leading to activation of the enzyme. The latter catalyzes the 3' phosphorylation of PI, PI-4 phosphate, and PI-4,5 diphosphate, resulting in the activation of protein kinase B/Akt and stimulation of glucose transport. Activation of PI-3 kinase by phosphorylated IRS-1 also leads to activation of glycogen synthase.

From the physiologic standpoint, it makes sense that activation of glucose transport and glycogen synthase should be linked to the same insulin-signaling mechanism in order to provide a coordinated and efficient stimulation of intracellular glucose metabolism. What is less commonly appreciated is that the insulin signaling pathway plays a critical role in the activation of nitric oxide synthase (NOS), which regulates the generation of nitric oxide (NO).³¹⁻³³ NO is the most potent vasodilator in the human body and exerts potent antiatherogenic effects.^{31,32} Deficient NO production results in the activation of multiple pathways involved in the stimulation of atherogenesis³⁴⁻³⁶ (Figure 1). Thus, a defect in the insulin-signaling cascade not only results in impaired glucose utilization but also leads to the development of hypertension and accelerated atherosclerosis.

Although less commonly recognized, insulin also is a potent growth factor³⁷⁻³⁹ (Figure 1). The growth-promoting effects of insulin are mediated via the mitogen-activated protein (MAP) kinase pathway.⁴⁰ Activation of the MAP kinase pathway leads to the phosphorylation of transcription

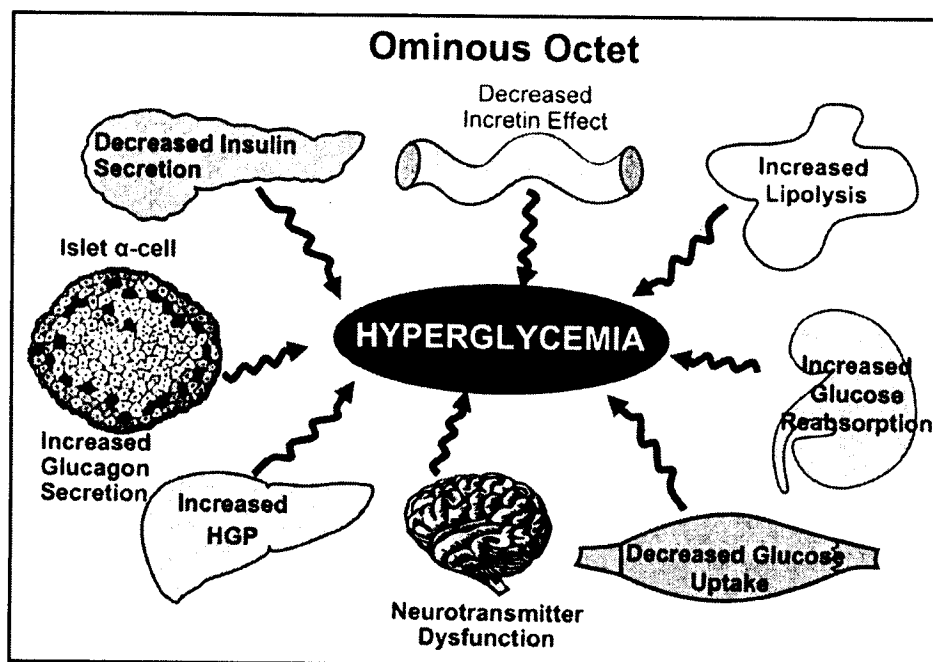


Figure 2 Multiple defects contribute to the progression of type 2 diabetes mellitus. HGP = hepatic glucose production. (Reprinted with permission from *Diabetes*.²)

factors that promote cell growth, proliferation, and differentiation.^{29,31} Thus, this pathway plays an important role in the development of atherosclerosis. Blockade of the MAP kinase pathway prevents the stimulation of cell growth by insulin but has no effect on the metabolic actions of the hormone.⁴¹

We have shown that, in human skeletal muscle of lean healthy subjects with NGT, physiologic hyperinsulinemia increases tyrosine phosphorylation of the insulin receptor and IRS-1 to 150% to 200% of basal values.^{21,22} In contrast, in obese subjects with NGT and in type 2 diabetes, the ability of insulin to activate IRS-1 tyrosine phosphorylation in muscle was severely reduced. The association of p85 protein and PI-3 kinase activity with IRS-1 also was greatly reduced in obese subjects without diabetes and in subjects with type 2 diabetes compared with lean healthy subjects.²² In contrast to the severe deficit in insulin signaling through the metabolic (IRS-1/PI-3 kinase) pathway, the ability of insulin to stimulate MAP kinase pathway activity in individuals with insulin-resistant type 2 diabetes and in obese nondiabetic individuals is completely intact (Figure 1).

Because NOS is activated by the PI-3-kinase/Akt pathway, NO production is markedly impaired in type 2 diabetes.^{42,43} This results in endothelial dysfunction⁴⁴⁻⁴⁶ and accelerated atherosclerosis⁴⁷⁻⁵⁰ that cannot be explained by the classic CV risk factors that typically are measured in the circulation.

Once the insulin-signaling defect becomes established, it initiates a reverberating negative feedback cycle (Figure 1). The defect in glucose utilization causes an increase in the PG concentration, which in turn stimulates insulin secretion.

The increase in plasma insulin concentration leads to an increase in insulin binding to its receptor. However, because the IRS-1/PI-3 kinase pathway is defective, it cannot be activated, and this leads to excessive stimulation of the MAP kinase pathway that is normally sensitive to insulin. In subjects with diabetes and obesity, continued MAP kinase stimulation, in the presence of impaired IRS-1 signaling, leads to inappropriately high MAP kinase pathway activity. This results in the proliferation of vascular smooth muscle cells, increased collagen formation, and excessive production of growth factors and inflammatory cytokines, thereby contributing to the accelerated rate of atherosclerosis in individuals with type 2 diabetes. It should be emphasized that the same insulin-signaling defects that are present in the skeletal muscle of patients with type 2 diabetes have been demonstrated in arterial vascular smooth muscle cells in diabetic animal models⁵¹ and in humans.⁵²

PATHOGENESIS OF TYPE 2 DIABETES FROM TRIUMVIRATE TO OMINOUS OCTET

In addition to the well-recognized triad of β -cell, muscle, and liver, specific organ systems including the adipocyte (accelerated lipolysis), the gastrointestinal tract (incretin deficiency/incretin resistance), the pancreatic α -cell (hyperglucagonemia), the kidneys (increased glucose resorption), and the brain/central nervous system (insulin resistance), play key roles in the pathogenesis of type 2 diabetes. These multiple defects were referred to as the "ominous octet" in the 2008 Banting Lecture (Figure 2).²

Dysharmonious Quartet

Considerable evidence demonstrates that deranged adipocyte metabolism and altered fat topography play an important role in the pathogenesis of glucose intolerance in type 2 diabetes.^{2,53} Fat cells are resistant to the antilipolytic effect of insulin in type 2 diabetes, leading to elevated plasma free fatty acid (FFA) concentrations⁵⁴ and increased levels of toxic lipid metabolites (fatty acyl coenzyme A, diacylglycerol, ceramide), that is, lipotoxicity.⁸ These toxic lipid metabolites cause insulin resistance in muscle and liver⁵⁵ and promote β -cell failure.⁵⁶ Fat cells are in a state of chronic inflammation and secrete excessive amounts of insulin resistance-inducing, inflammatory, and atherosclerosis-provoking cytokines (tumor necrosis factor- α , interleukin-6, resistin, angiotensinogen) and fail to secrete normal amounts of insulin-sensitizing adipocytokines (adiponectin).⁵³

Quintessential Quintet

Patients with type 2 diabetes have diminished incretin effect as a result of incretin hormone deficiency and/or resistance.^{2,57,58} The incretin hormones glucagonlike peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) account for 90% of the incretin effect and are pivotal in maintaining glucose homeostasis. Both GLP-1 and GIP augment insulin secretion; GLP-1 also inhibits glucagon secretion, delays gastric emptying, and suppresses the appetite.⁵⁹

Setaceous Sextet

Glucagon and enhanced hepatic sensitivity to glucagon also play a key role in the pathophysiology of type 2 diabetes.^{2,60,61} Glucagon plays a pivotal role in the maintenance of the majority of basal HGP in patients with type 2 diabetes. Plasma glucagon concentrations are increased in patients with IGT and type 2 diabetes compared with individuals with NGT^{58,61} despite hyperglycemia and hyperinsulinemia, which should suppress glucagon secretion. Elevated concentrations of glucagon, resulting from increased pancreatic α -cell secretion, enhance HGP and aggravate the hepatic insulin resistance. In type 2 diabetes, when glucagon secretion is inhibited by somatostatin, fasting plasma glucagon levels decline in association with a marked reduction in basal HGP and FPG concentrations.⁶⁰

Septicidal Septet

Animal models of diabetes have shown an increase in the maximal renal tubular reabsorptive capacity for glucose.² In the normal state, 90% of the filtered glucose is reabsorbed by the sodium glucose cotransporter (SGLT)-2 in the convoluted segment of the proximal renal tubule, with the remaining 10% reabsorbed by the SGLT1 transporter in the straight segment of the descending proximal tubule.² Cultured human proximal renal tubular cells from patients with type 2 diabetes demonstrate increased SGLT2 concentrations, with a 4-fold increase in the uptake of the nonmetabolizable glucose analogue α -methyl-D-glucopyranoside.⁶² In pa-

tients with diabetes, it would be desirable for the kidney to excrete the excessive filtered load of glucose in an attempt to restore normoglycemia. In contrast, the diabetic kidney responds to the ambient hyperglycemia by enhancing glucose reabsorption,^{2,63} thereby contributing to the pathogenesis of glucose intolerance.

Ominous Octet

Neurotransmitter dysfunction in the central nervous system plays a key role in etiology of type 2 diabetes.^{2,64} Under normal circumstances, insulin signals the brain to stop eating and decrease energy intake. Obese patients with and without type 2 diabetes are markedly insulin resistant, and the β -cell responds to the insulin resistance with a compensatory increase in insulin secretion. Despite hyperinsulinemia, which should suppress the appetite, obese people continue to overeat, indicating that the appetite centers must be resistant to insulin; indeed, this has been demonstrated using functional magnetic resonance imaging.⁶⁴

When viewed collectively, the components of the ominous octet involved in the pathophysiology of type 2 diabetes have important clinical implications: (1) the treatment of patients with type 2 diabetes requires administration of a combination of agents to improve the underlying defects and to prevent disease progression; (2) management of type 2 diabetes should be based on the known pathogenic abnormalities of the disease rather than on just reducing hemoglobin A_{1c} (HbA_{1c}); and (3) because many of the defects begin early in the natural course of the disease, therapy should be initiated as soon as possible to protect the remaining β -cell function.

TREATMENT OF TYPE 2 DIABETES MELLITUS: RELATION TO DISEASE MECHANISMS

Based on the known pathophysiologic mechanisms responsible for the evolution of type 2 diabetes, a review of current therapeutic options is in order. At the level of the liver, metformin and the thiazolidinediones (TZDs) are potent insulin sensitizers that inhibit the increased rate of hepatic gluconeogenesis responsible for the elevated rate of basal HGP in patients with type 2 diabetes.⁶⁵⁻⁶⁷ In the muscle, TZDs are potent insulin sensitizers^{23,68} whereas metformin is a weak insulin sensitizer.^{69,70} In adipose tissue, the TZDs also are excellent insulin sensitizers, exerting a potent antilipolytic effect.³ Additionally, the TZDs have been shown to improve and preserve β -cell function.^{3,65,71}

The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that, over the 15-year course of the study, neither the sulfonylureas nor metformin provided any β -cell protective effect in newly diagnosed patients with type 2 diabetes.⁷² Many other studies have shown that, following an initial decline in HbA_{1c}, sulfonylureas were associated with a progressive decline in β -cell function with an accompanying loss of glycemic control (Figure 3).² Metformin produced a more sustained reduction of HbA_{1c} than the sulfonylureas in ADOPT (A Diabetes Outcome Progres-

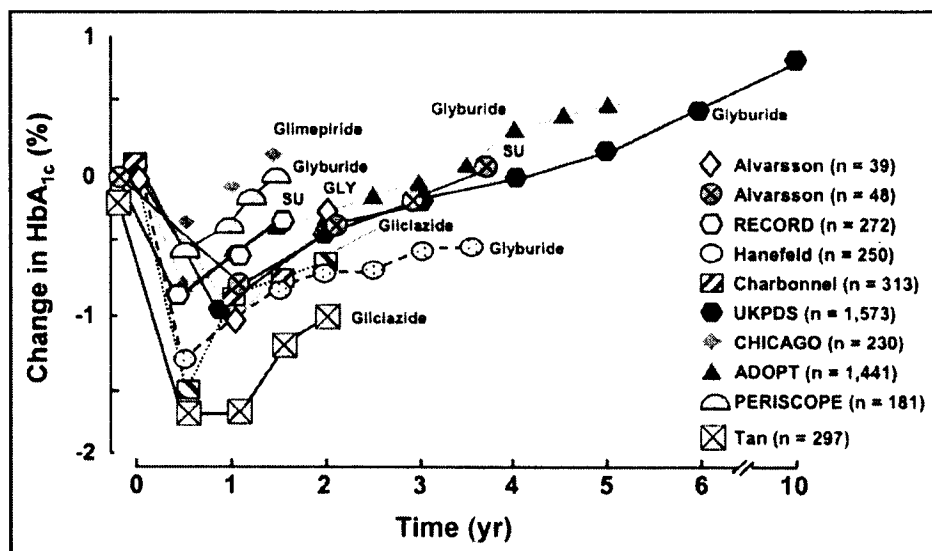


Figure 3 Sulfonylureas (SUs) cause an initial decrease in hemoglobin A_{1c} (HbA_{1c}) over the initial 6 to 12 months of therapy, but thereafter there is a progressive increase in HbA_{1c} due to the progressive loss of β -cell function. ADOPT = A Diabetes Outcome Progression Trial; CHICAGO = Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone; GLY = glyburide; PERISCOPE = Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; RECORD = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; UKPDS = United Kingdom Prospective Diabetes Study. (Reprinted with permission from *Diabetes*.²)

sion Trial), but this biguanide also was associated with a progressive increase in HbA_{1c} and progressive decline in β -cell function after the first year of treatment.⁷³

In contrast to the sulfonylureas and metformin, 8 studies using TZDs have shown that they maintain long-term durability of glycemic control, following an initial decline in HbA_{1c}, due to their protective effect on β -cell function (Figure 4).^{2,71,74,75} Pioglitazone and rosiglitazone have been shown to augment and maintain the insulin secretion/insulin resistance (disposition) index in both drug-naïve and sulfonylurea-treated patients with type 2 diabetes.^{3,65,71} The insulin secretion/insulin resistance index is the gold standard for quantitating β -cell function. Five studies have shown that progression of IGT to type 2 diabetes is lowered by 50% to 80% in patients treated with TZDs.⁷⁶⁻⁸⁰ The Actos Now for Prevention of Diabetes (ACT NOW) study showed a 78% reduction in the conversion of IGT to type 2 diabetes with pioglitazone, primarily due to a protective effect on the β -cell and, to a lesser extent, enhanced tissue sensitivity to insulin.^{2,79}

The incretins also have been shown to improve β -cell function and maintain durability of glycemic control.^{2,81} Within the past 5 years, the GLP-1 receptor agonist exenatide has become available in the United States.⁸² Exenatide is a synthetic version of exendin-4, with ~53% homology with native GLP-1.⁸³ Administered parenterally, exenatide reduces HbA_{1c}, increases insulin secretion, and preserves β -cell function for ≥ 3.5 years.^{2,81,84} Additionally, it shares many of the glucoregulatory functions of endoge-

nous GLP-1, including suppression of inappropriate glucagon secretion, slowing of postprandial gastric emptying, and appetite suppression and weight reduction.^{59,85} In a triple-blind controlled study, exenatide 10 μ g bid added to metformin significantly ($P < 0.0005$) reduced HbA_{1c} starting at week 4 and continuing throughout the 30-week study period, compared with placebo.⁸⁶ At 30 weeks, HbA_{1c} was lowered from baseline by -0.8% with exenatide 10 μ g bid compared with an increase of 0.1% with placebo ($P < 0.002$). Among the evaluable patients with baseline HbA_{1c} $> 7\%$, 46% treated with exenatide 10 μ g bid achieved HbA_{1c} $\leq 7\%$ by week 30.

Bunck and associates⁸¹ compared the effects of exenatide and insulin glargine on β -cell function in 69 metformin-treated patients with type 2 diabetes who were randomized to receive exenatide or insulin glargine and were monitored for glucose parameters as well as stimulated C-peptide secretion. After 1 year of treatment, the 2 groups of patients achieved similar reductions in HbA_{1c} (-0.8% with exenatide vs. -0.7% with insulin glargine). However, first- and second-phase glucose-induced C-peptide secretion increased by 1.53- and 2.85-fold, respectively ($P < 0.0001$ for both comparisons), in patients receiving exenatide compared with patients receiving insulin glargine.⁸¹

Two open-label extension studies reported the long-term effects of exenatide on HbA_{1c}. Ratner and colleagues⁸⁷ followed 150 patients who completed 30 weeks of metformin/exenatide therapy and who subsequently were monitored for an additional 52 weeks in an open-label extension trial. Reductions in HbA_{1c} of 1.3% were sustained at week

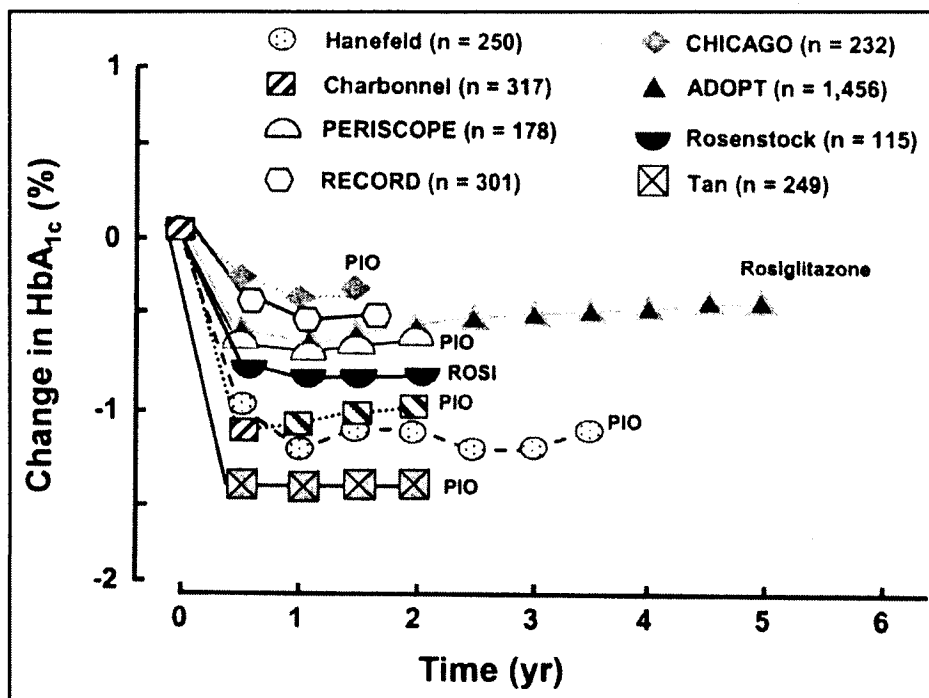


Figure 4 Treatment with thiazolidinediones decreases hemoglobin A_{1c} (HbA_{1c}) over 6 to 12 months and sustains these lower levels over several years. ADOPT = A Diabetes Outcome Progression Trial; CHICAGO = Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone; PERISCOPE = Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; PIO = pioglitazone; RECORD = Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; ROSI = rosiglitazone. (Reprinted with permission from *Diabetes*.²)

82, with 59% of patients achieving HbA_{1c} ≤7%.⁸⁷ Klonoff and associates⁸⁴ reported similar results after ≥3 years of open-label follow-up of 217 patients enrolled in 3 placebo-controlled trials. Reductions in HbA_{1c} of 1.0% were sustained over 3 years of follow-up, with 46% of patients achieving HbA_{1c} ≤7% and 30% of patients achieving HbA_{1c} ≤6.5%.⁸⁴

A number of GLP-1 receptor agonists are currently in clinical development. One of these agents, liraglutide,* a once-daily human GLP-1 analogue, has been submitted to the US Food and Drug Administration (FDA) for approval. In a 14-week study in 39 patients with type 2 diabetes, liraglutide (0.65, 1.25, or 1.9 mg/day) produced improvements in first- and second-phase insulin secretion and in arginine-stimulated insulin secretion during hyperglycemia.⁸⁸ The data from exenatide and liraglutide studies suggest that GLP-1 receptor agonists slow the progression of β-cell failure, which should lead to long-term sustained glucose control.

The other incretin-based agents are the dipeptidyl peptidase-4 (DPP-4) inhibitors. They are orally administered and increase endogenous levels of GLP-1 by inhibiting the

catalytic enzyme DPP-4.^{82,89} Sitagliptin, the first agent in this class for the treatment of type 2 diabetes, became available in the United States in 2006. Saxagliptin, another DPP-4 inhibitor, was approved for use in type 2 diabetes in August 2009.

Monotherapy with sitagliptin over 18 weeks resulted in a reduction in HbA_{1c} of 0.6% from baseline compared with placebo.⁹⁰ Of the patients receiving sitagliptin, 35.8% achieved HbA_{1c} <7%, compared with 15.5% of patients receiving placebo.⁹⁰ Significant ($P < 0.001$) reductions in HbA_{1c} of 0.67% and 0.85% from baseline were observed when sitagliptin was added to metformin or pioglitazone, respectively, after 24 weeks of treatment.^{91,92} Additionally, sitagliptin therapy resulted in improvements in HOMA-β (homeostasis model assessment of β-cell function), the fasting proinsulin to insulin ratio, and the 3-hour postprandial insulin to glucose area under the curve ratio, suggesting an effect on β-cell function. However, it remains to be determined whether these effects will provide long-term β-cell function preservation and durability of glucose control.^{90,93}

With the development of newer antihyperglycemic agents, it is clear that combination therapy targeting the fundamental defects that underlie type 2 diabetes is both a viable and rational approach for managing patients early in the course of their disease (Figure 5).² As longer-acting

*After submission of manuscripts, liraglutide received US FDA approval on January 25, 2010.

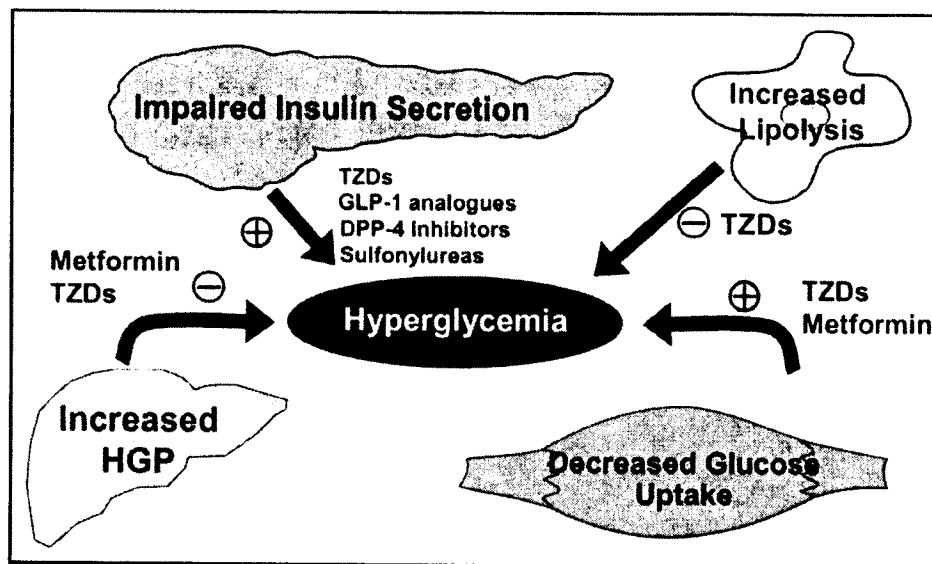


Figure 5 Because type 2 diabetes mellitus is characterized by multiple pathophysiologic defects, combination therapy targeting these multiple abnormalities at the time of diagnosis of diabetes represents a rational approach to therapy. DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagonlike peptide-1; HGP = hepatic glucose production; TZDs = thiazolidinediones. (Reprinted with permission from *Diabetes*.²)

Table 1 Comparison of treatment algorithms

	ADA	Pathophysiologic Based
Durability	No	Yes
β -Cell preservation	No	Yes
Hypoglycemia	Yes	No
Weight gain	Yes	No

ADA = American Diabetes Association.

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derivatives are developed, many of the challenges of patient adherence may be addressed. Additionally, weight gain with TZDs can be prevented by combining therapy with exenatide. This combination is likely to be highly effective in producing a durable reduction in HbA_{1c}, because both exenatide and the TZDs preserve β -cell function, while the TZDs also are potent insulin sensitizers. The generic availability of pioglitazone over the next several years may help address the cost of combination therapy. Future therapeutic regimens must involve drugs with different mechanisms of action to target the multiple contributors of disease progression.

NEW PARADIGM FOR THE TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

A writing group of the American Diabetes Association (ADA), in tandem with the European Association for the Study of Diabetes (EASD), has published a treatment algorithm for the management of patients with type 2 diabetes, with a primary goal of reducing HbA_{1c} to <7%.⁹⁴ Upon

diagnosis, they recommend that the patient be started on a regimen of lifestyle modification and metformin therapy. If the HbA_{1c} goal (<7%) is not met, they recommend treating the patient with a sulfonylurea or basal insulin (tier 1 therapy) with the subsequent addition of pioglitazone or a GLP-1 receptor agonist (tier 2 therapy), if necessary. In clinical practice, physicians are more likely to prescribe metformin plus a sulfonylurea, rather than insulin, for glucose control as a second-line therapy. Insulin is not widely used as a second-line agent because of weight gain, hypoglycemia, and the need for frequent home glucose monitoring with strips, and physicians are hesitant to initiate TZD therapy because of its side effects. However, it is clear that neither metformin nor the sulfonylureas preserve β -cell function; therefore, they allow disease progression, which ultimately leads to the need for insulin therapy.

Although current guidelines and algorithms focus on achieving HbA_{1c} goals and glucose control, the recommendations do not offer proven durable efficacy in reducing the rate of disease progression or β -cell preservation (Table 1).² Additionally, many of the agents (especially the sulfonylureas and insulin) currently used are associated with hypoglycemia and weight gain. Given our increased knowledge regarding the pathophysiology of type 2 diabetes and the role of β -cell dysfunction, a more targeted approach is warranted. A pathophysiology-based algorithm with early triple-combination therapy consisting of a TZD, metformin, and exenatide, can provide durable results with agents (TZDs and exenatide) proved to preserve β -cell function.

Additionally, with newer therapies, achieving an HbA_{1c} goal of $\leq 7\%$ is possible without the hypoglycemic effects

of insulin and the sulfonylureas. Metformin and the TZDs increase insulin sensitivity in muscle and liver and reduce hepatic gluconeogenesis. The TZDs also inhibit lipolysis and lower plasma FFA levels. The TZDs and GLP-1 receptor agonists preserve β -cell function, which is essential to halt the progression from NGT to IGT to type 2 diabetes. Importantly, neither the insulin sensitizers nor the GLP-1 analogues cause hypoglycemia. Much evidence demonstrates that neither metformin nor the sulfonylureas can stop the progressive decline in β -cell function in patients with type 2 diabetes. Whether the DPP-4 inhibitors can preserve β -cell function on a long-term basis remains to be proved. Importantly, neither the insulin sensitizers nor the GLP-1 analogues cause hypoglycemia.

SUMMARY

Ongoing research has provided more in-depth knowledge about the pathophysiology of type 2 diabetes, leading to a better understanding of the multiple defects involved in disease progression. Clinical trials, which focus only on reducing HbA_{1c}, have demonstrated continual disease progression and eventual treatment failure. Therapy therefore should focus on delaying disease progression by targeting the pathogenic disturbances underlying type 2 diabetes (i.e., increasing insulin sensitivity and maintaining β -cell function). To achieve these goals, aggressive combination therapy should be initiated early in the natural course of the disease. Newer therapeutic options and agents in development make this therapeutic approach increasingly feasible.

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