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 A1c. 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.

© 2010 Published by Elsevier Inc. • The American Journal of Medicine (2010) 123, S38–S48

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 Baniting 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-
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.1,2,4,14-16 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
but also is a predictor of cardiovascular (CV) disease. 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. 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).

**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). 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). NO is the most potent vasodilator in the human body and exerts potent antiatherogenic effects. Deficient NO production results in the activation of multiple pathways involved in the stimulation of atherogenesis. 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 factor (Figure 1). The growth-promoting effects of insulin are mediated via the mitogen-activated protein (MAP) kinase pathway. Activation of the MAP kinase pathway leads to the phosphorylation of transcription factors and the transcription of genes involved in cell growth, proliferation, and survival.
factors that promote cell growth, proliferation, and differentiation. 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.

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. 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. 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. This results in endothelial dysfunction and accelerated atherosclerosis 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 models and in humans.

**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/cerebral 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).
**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.\(^5\)\(^6\) Fat cells are resistant to the antilipolytic effect of insulin in type 2 diabetes, leading to elevated plasma free fatty acid (FFA) concentrations\(^5\) 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 liver\(^5\) and promote β-cell failure.\(^26\) 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.\(^2\)\(^5\)\(^7\)\(^8\) The incretin hormones glucagon-like 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.\(^2\)\(^6\)\(^4\) 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\(^5\)\(^8\)\(^6\)\(^1\) 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 patients 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,\(^7\)\(^6\)\(^3\) 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.\(^2\)\(^6\)\(^4\) 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.\(^65\)\(^6\)\(^7\) In the muscle, TZDs are potent insulin sensitizers\(^3\)\(^6\)\(^6\) whereas metformin is a weak insulin sensitizer.\(^6\)\(^8\)\(^7\) In adipose tissue, the TZDs also are excellent insulin sensitizers, exerting a potent antilipolytic effect.\(^1\) Additionally, the TZDs have been shown to improve and preserve β-cell function.\(^6\)\(^5\)\(^7\)

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.\(^7\) 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  Sulfonlureas (SUs) cause an initial decrease in hemoglobin A1c (HbA1c) over the initial 6 to 12 months of therapy, but thereafter there is a progressive increase in HbA1c 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 = Pioglitaxone 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.)

sion Trial), but this biguanide also was associated with a progressive increase in HbA1c and progressive decline in β-cell function after the first year of treatment.73

In contrast to the sulfonlureas and metformin, 8 studies using TZDs have shown that they maintain long-term durability of glycemic control, following an initial decline in HbA1c, due to their protective effect on β-cell function (Figure 4).74,75 Pioglitazone and rosiglitazone have been shown to augment and maintain the insulin secretion/insulin resistance (disposition) index in both drug-naive and sulfonlurea-treated patients with type 2 diabetes.1,65,71 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.76

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 HbA1c, increases insulin secretion, and preserves β-cell function for ≥3.5 years.78,81 Additionally, it shares many of the glucoregulatory functions of endogenous GLP-1, including suppression of inappropriate glucagon secretion, slowing of postprandial gastric emptying, and appetite suppression and weight reduction.84,85 In a triple-blind controlled study, exenatide 10 μg bid added to metformin significantly (P <0.0005) reduced HbA1c starting at week 4 and continuing throughout the 30-week study period, compared with placebo.86 At 30 weeks, HbA1c was lowered from baseline by ~0.8% with exenatide 10 μg bid compared with an increase of 0.1% with placebo (P <0.002). Among the evaluable patients with baseline HbA1c >7%, 46% treated with exenatide 10 μg bid achieved HbA1c ≤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 HbA1c (~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 HbA1c. 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 HbA1c of 1.3% were sustained at week
Figure 4  Treatment with thiazolidinediones decreases hemoglobin A1c (HbA1c) 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 Glycemia in Diabetes; ROSI = rosiglitazone. (Reprinted with permission from Diabetes.5)

82, with 59% of patients achieving HbA1c ≤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 HbA1c of 1.0% were sustained over 3 years of follow-up, with 46% of patients achieving HbA1c ≤7% and 30% of patients achieving HbA1c ≤6.5%.85

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 HbA1c of 0.6% from baseline compared with placebo.80 Of the patients receiving sitagliptin, 35.8% achieved HbA1c ≤7%, compared with 15.5% of patients receiving placebo.80 Significant (P < 0.001) reductions in HbA1c 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.93,93

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).7 As longer-acting

---

*After submission of manuscripts, liraglutide received US FDA approval on January 25, 2010.
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 \(\beta\)-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%.

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 \(\beta\)-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 \(\beta\)-cell preservation (Table 1). 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 \(\beta\)-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 \(\beta\)-cell function.

Additionally, with newer therapies, achieving an HbA\(_1c\) goal of ≤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 HbA₁c have demonstrated continual disease progression and eventual treatment failure. Therapy therefore should focus on delaying disease progression by restoring 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.

ACKNOWLEDGMENT

I thank Jonathan Wert, MD, of BlueSpark Healthcare Communications, for providing literature research and editorial assistance.

AUTHOR DISCLOSURES

The author of this article has disclosed the following industry relationships:


References

21. Pratipanawatt W, Pratipanawatt T, Ciosi K, et al. Skeletal muscle insulin resistance in normoglycemic subjects with a strong family history of type 2 diabetes is associated with decreased insulin-


63. Morgenst CN. Maximum tubular reabsorption capacity for glucose and renal hemodynamics during rapid hyperemic glucose infusion in