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Recent Advances in the Diagnosis, Pathogenesis, and Treatment of Type 2 Diabetes

Authors: **Niyaz R. Gosmanov, MD, Steven D. Wittlin, MD, and John E. Gerich, MD**, University of Rochester School of Medicine, Department of Medicine, Rochester, NY.

Editor's Note—*During the last decade, there has been a remarkable advance in our understanding of the pathogenesis of type 2 diabetes and the relationship between the control of glycemia and the development of the complications of diabetes. In addition, there has been the introduction of many new treatment modalities, which has enabled us to obtain better glycemic control in a larger percentage of our patients with less side effects.*

In contrast to the studies of the 1980s, studies during the 1990s (clearly illustrated by studies of monozygotic twins) indicate that impaired beta cell function (inappropriate insulin release relative to insulin resistance) is the primary genetic factor involved in type 2 diabetes and that the insulin resistance associated with this disorder is largely explained by obesity, decreased physical activity, high fat diets, and secondary effects of high plasma glucose levels (glucose toxicity) and high plasma free fatty acid levels (lipotoxicity).

Nevertheless, although insulin resistance seems to be a largely acquired problem, it is important and its treatment, along with that of impaired insulin secretion, are vital parts of the therapeutic approach to the condition. Indeed, the argument can be made that both should be targeted from the start by use of combination therapy.

Several clinical trials (the Diabetes Control and Complications Trial [DCCT] and the Stockholm Intervention Trial in type 1 diabetes mellitus [T1DM], the Kumomoto Study, and the United Kingdom Prospective Diabetes Study [UKPDS] Trial in type 2 diabetes mellitus [T2DM]) have shown that maintenance of HbA_{1c} levels below 7.0% can prevent development of microvascular complications. Epidemiological studies indicate that reduction of macrovascular complications may require maintenance of even lower HbA_{1c} levels. For both types of complications the risk decreases with progressive lowering of HbA_{1c} and shows no threshold.

The introduction of insulin sensitizers (metformin and thiazolidinediones) along with new insulin secretogogues (the sulfonylurea glimepiride and the meglitinides-repaglinide and nateglinide) along with more rapid, shorter-acting insulin analogs (lispro and aspart insulin) and the peakless long-acting analog (glargine insulin) now permit better glycemic control to be achieved with less risk of hypoglycemia. Various combinations of these agents have been shown capable of reducing HbA_{1c} levels to less than 7.0%.

In summary, less than half of patients with diabetes in the United States have HbA_{1c} levels less than 7.0%. We now have the tools to correct this and prevent development of diabetic complications in a safe, cost-effective manner.

Introduction

During the past 10 years, there have been remarkable advances in our knowledge of the pathogenesis of T2DM as well as the relationship between glycemic control and the

development of the complications of diabetes. In addition, several new treatment modalities have become available, which have improved our ability to obtain satisfactory glycemic control in a greater proportion of patients. This review will summarize these advances.

Glycemic Control and Complications

The relationship between glycemic control and the development of diabetic complications was controversial. This issue was put to rest by the results of several controlled clinical trials during the last decade. The first to be reported was the DCCT[1]—a study of intensive vs. conventional insulin therapy in patients with T1DM. Patients in the intensive group were managed by basal-bolus regimens of 3-4 insulin injections or pumps per day and used self-glucose monitoring to make dose adjustments; their HbA_{1c} levels over the course of the study averaged about 7.0% compared to 9.0% in the conventional group, which took only 2 insulin injections a day and was not instructed how to adjust its doses based on self-glucose monitoring. This 2.0% difference in HbA_{1c} reduced the development of retinopathy, nephropathy, and neuropathy by 63%, 39%, and 60%, respectively. Furthermore, the progression of microvascular complications already present was reduced by nearly 60%. Similar findings in patients with T1DM were reported in the Stockholm Diabetes Intervention Study.[2]

Most diabetologists considered that the results of these studies could be extrapolated to patients with T2DM since the adverse effects of hyperglycemia should be the same in both types of diabetes. However, there were still many skeptics. Their doubts were put to rest by publication of the results of the Kumomoto Study[3] and the UKPDS[4-6] in 1995 and 1998, respectively. The Kumomoto Study[7] was virtually identical in design to the DCCT and the results were similar. Patients with T2DM randomized to intensive insulin treatment averaged a HbA_{1c} of 7.0% during the 6-year study while those on conventional insulin therapy averaged about 9.5%. Intensive insulin therapy reduced the development of retinopathy and nephropathy by 76% and 62%, respectively, and the progression of these complications was reduced by about 60%.

The UKPDS[4-6] was by far the most ambitious trial. It was started in 1978 as a response to the University Group Diabetes Program,[8] which had failed to demonstrate a beneficial effect of glycemic control and had suggested that the sulfonylurea tolbutamide might be cardiotoxic. The UKPDS randomized more than 5000 patients with newly diagnosed T2DM to conventional or intensive therapy. The latter included initial monotherapy with sulfonylureas (glyburide or chlorpropamide) or insulin in nonobese patients and metformin or insulin in obese patients. Therapy was further intensified by either use of combinations of oral agents or conversion to progressively more intensive insulin regimens if goals were not being achieved. The goal of intensive therapy was a HbA_{1c} below 7.0%. The study had an average follow-up of about 15 years. The purposes of the study were to determine whether good glycemic control affected not only microvascular but also macrovascular complications and whether any particular drug was advantageous. Many lessons were learned from this study.

The first lesson was that good glycemic control prevents both micro- and macrovascular complications. The differences in HbA_{1c} between the intensively and conventionally treated groups were modest (ie, 0.9% in the nonobese group and 0.6% in the obese group—roughly 7.0% vs. 7.6-7.9%). Despite this modest difference in glycemic control, the results were dramatic. In the nonobese group, any diabetes-related end point was reduced 12%; microvascular end points were reduced by 25%; myocardial infarction was reduced by 16%; retinopathy was reduced by 21%; and nephropathy was reduced by 33%. In the obese group, any diabetes-related end point was reduced by 32%; myocardial infarction was reduced by 39%; and all-cause mortality was reduced by 36%.

The second lesson was that these regimens were safe: there was no evidence that sulfonylureas or insulin had adverse macrovascular effects (this had been a continuing concern); metformin, when used appropriately, did not cause lactic acidosis (no cases occurred); and severe hypoglycemia with sulfonylureas (~ 0.5%) and insulin treatment (~ 2%) was relatively uncommon.

From an epidemiological point of view, the results of lowering HbA1c in the UKPDS (T2DM) closely coincided with those of the DCCT (T2DM). In fact, data from all of the clinical trials indicate that if the HbA_{1c} could be maintained below 7.0% in patients either T1 or T2DM, then risk of developing microvascular complications would approach that of the general population. The situation, however, appears to be different for prevention of macrovascular complications, which is the major cause of morbidity and mortality in T2DM.[9]

Numerous studies[9-19] have shown that people with impaired glucose tolerance, whose HbA_{1c} would be expected

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to be below 7.0%, have an increased risk for cardiovascular disease. The results of the recent EPIC-NORFOLK study[20] illustrate this. In this prospective study, subjects were categorized by their initial HbA_{1c} level and those with levels 5.0% or below were contrasted with those with higher levels. It was found that people with HbA_{1c} levels between 5.0 and 5.5 had a 40% increase in risk for cardiovascular death in follow-up. These results are consistent with the results of the Honolulu Study[10] and several others.[16] Therefore, it appears that if we wish to prevent *both* macro- and microvascular complications of diabetes, we must try to achieve HbA_{1c} levels lower than those currently recommended by the American Diabetes Association (ADA).

The current ADA recommendations consider a $HbA_{1c} <$ 7.0% as a goal and urge action be taken to improve control if the HbA_{1c} is above 8.0%. These recommendations imply that HbA_{1c} levels between 7.0% and 8.0% constitute adequate control and are not consistent with scientific data regarding the relation between glycemic control and macrovascular complications discussed above. These data suggest, at a minimum, the goal for therapy should be a HbA_{1c} less than 6.0% and that action to improve control must be initiated if the HbA_{1c} is above 7.0%. For several years, The European Diabetes Group consensus panel[21] has recommended as a goal a $HbA_{1c} < 6.5\%$ and intensification of glycemic control if the HbA_{1c} exceeds 7.5%. Similar guidelines have recently been proposed by the American Academy of Clinical Endocrinology (www.aace.com).

It is appreciated that these goals may not be appropriate for all patients (eg, elderly patients or those already having severe complications) and may be difficult to achieve by those involved in primary care and general internal medicine practices who lack time and ancillary resources (ie, dietitians, nurse educators, etc). Therefore, when patients with T2DM cannot achieve an HbA_{1c} of 7.0% or below on maximal doses of 2 different classes of oral agents alone or in combination with a simple insulin regimen, referral to a specialist should be seriously considered.

Pathogenesis of Type 2 Diabetes

The pathogenesis of T2DM is much more complicated than T1DM, which is simply due to autoimmune destruction of pancreatic islet beta cells making insulin. T2DM is a heterogeneous disorder. About 5-10% of patients appearing to have T2DM actually have a late onset variety of T1DM; these patients are generally lean and progress to insulin dependency within a few years.[22] Another 5% have Maturity Onset Diabetes of Youth (MODY),[22] an autosomal dominant disorder of which at least 5 subtypes exist. Patients with this disorder generally only have impaired insulin release and develop their diabetes younger than the age of 25. The remaining 85-90% of patients have classic T2DM in which both insulin resistance and impaired insulin secretion are involved.[22] Each of these factors is affected by genetic and acquired/environmental influences.[22] Furthermore, it is now apparent that T2DM is a polygenic disorder, meaning that it takes the interaction of several diabetogenic genes with acquired/environmental factors to develop/acquire T2DM.[22]

Until a few years ago, it was generally thought that insulin resistance was the primary genetic component. Recent studies, however, have challenged this concept and it now seems most likely that the main genetic component involves pancreatic beta cell dysfunction.

The evidence for this view can be summarized as follows:

1. Most of the insulin resistance found in T2DM can be attributed to nondiabetes-specific factors such as obesity (especially visceral obesity),[22] physical inactivity,[23] high-fat diets,[24] glucose,[25] and lipotoxicity.[26] To some extent, obesity and fat distribution are genetically determined,[22] but such genes are not diabetes specific.
2. Although most (> 90%) patients with classic T2DM are obese (and therefore insulin resistant), most insulin resistant obese individuals are not diabetic. What distinguishes obese individuals with and without diabetes is the ability to compensate for insulin resistance with increased insulin secretion.[27]

A clear example of this is gestational diabetes.[28] All women become insulin resistant during the third trimester of pregnancy. Some women develop diabetes during this period. What distinguishes women who do and do not develop diabetes are their plasma insulin levels, which are higher in women who do not develop gestational diabetes. After pregnancy, women who have gestational diabetes return to normal glucose tolerance. Nevertheless, gestational diabetes is a strong risk factor for subsequent development of T2DM, which approaches 50%.[28]

When women who had developed gestational diabetes have been studied after return to normal glucose tolerance, an impairment in beta cell function has been detected while insulin sensitivity has been found to be normal.[29] This not only illustrates that, as discussed below, impaired beta cell function precedes insulin resistance, but also the importance of insulin resistance, even if not genetic, in the pathogenesis of T2DM since with resolution of pregnancy-associated insulin resistance, glucose tolerance returns to normal.

3. A third line of evidence is that impaired beta cell function can be detected earlier in people with normal glucose tolerance who are genetically predisposed to develop T2DM (eg, first-degree relatives of individuals with T2DM).[30] The strongest evidence for this comes from studies of monozygotic twins, in which one twin has T2DM while the other still has normal glucose tolerance.[31] The twin with normal glucose tolerance has about an 80% chance of developing T2DM and thus can be considered to be a true prediabetic individual. All 4 studies of such twin pairs have found that the twin with normal glucose tolerance had impaired beta cell function[22] and the only study that simultaneously assessed insulin sensitivity found it to be normal.[31]
4. Another line of evidence comes from examining the reversibility of insulin resistance and impaired beta cell function in obese individuals with T2DM. Several studies[22] have demonstrated complete normalization of insulin sensitivity after weight loss but persistence of impaired beta cell function. The marked improvement in glycemic control after weight loss and normalization of insulin sensitivity illustrates again the importance of insulin resistance, but the fact that patients remained diabetic also points out the essentiality of impaired beta function.

Mechanisms for Impaired Beta Cell Function and Insulin Resistance

The mechanisms responsible for impaired beta cell function are not known. Some studies have suggested that a reduced beta cell mass may be involved. The UKPDS[32] demonstrated that beta cell function was already reduced by 50% in patients with newly diagnosed T2DM and that there was subsequent progressive deterioration. Other factors may involve amyloid deposition, alterations in growth factors necessary for establishment maintenance of normal beta cell function/mass, and toxic effects of increased exposure to glucose and free fatty acids (FFA).[27]

Obesity and Type 2 Diabetes

The insulin resistance of obesity has been shown to be associated with reduced numbers of insulin receptors, reduced insulin receptor kinase activity, reduced activation of insulin signaling proteins, and glucose transport.[33] Quantitatively similar defects have been found in obese individuals with T2DM.[33] Several factors may be involved in the insulin resistance associated with obesity: higher circulating levels of 1) free fatty acids; 2) tumor necrosis factor alpha;[34] and 3) the newly discovered hormone resistin,[35] all of which are released from adipose tissue. Reduced physical activity, high-fat diets, increased plasma glucose levels, and certain drugs (eg, nicotinic acid, glucocorticoids, diuretics) may also contribute to the insulin resistance found in patients with T2DM.

Metabolic Consequences of Insulin Resistance and Impaired Beta Cell Function

As a consequence of insulin resistance and impaired beta cell function, there is overproduction of glucose by liver and kidney in the fasting state and impaired suppression of hepatic glucose release after meal ingestion.[36,37] Although glucose uptake by peripheral tissues is normal in an absolute sense, it is not appropriate for the prevailing hyperglycemia and plasma insulin concentrations[37] (ie, glucose uptake is less efficient). Circulating FFA levels are generally increased in both the fasting and postprandial states; these promote greater release of glucose[26] and impede tissue glucose uptake.[26] The failure to "turn off" release of glucose after meal ingestion has been specifically linked to impaired early insulin release.[38] This exacerbates postprandial hyperglycemia, which can result in late hyperinsulinemia. These insulin levels, however, are still not appropriate for the prevailing hyperglycemia.

Revised Diagnostic Criteria for Diabetes

In 1997, a consensus panel of the ADA recommended changes in the Diagnostic Criteria for Diabetes.[39] The old criteria were a fasting plasma glucose above 140 mg/dL or a value above 200 mg/dL at 2 hours of a 75 g oral glucose tolerance test (OGTT). Two-hour values above 140 mg/dL but below 200 mg/dL categorized a person as having impaired glucose tolerance. The new criteria were established mainly because review of epidemiologic data indicated that a fasting criterion value of 140 mg/dL was too high. Many people with a 2-hour value greater than 200 mg/dL during the OGTT had a fasting plasma glucose level considerably below 140 mg/dL. Examination of the data indicated that a fasting value above 126 mg/dL was more appropriate because most people with values above 126 mg/dL would also have 2-hour values greater than 200 mg/dL. A fasting value of 110 mg/dL or below was deemed normal since most of these individuals had normal values during OGTTs, whereas values between 110 and 126 mg/dL categorized a person as having impaired fasting glucose tolerance, presumably carrying the same implications of the category of impaired glucose tolerance (ie, increased risks to develop diabetes and coronary heart disease).

This change in diagnostic criteria also came with the recommendation to rely more on fasting plasma glucose levels while discouraging use of the OGTT. It was argued that fasting plasma glucose levels were more reproducible than 2-hour values of the OGTT and that because fasting values would be more convenient, this would encourage more testing.

The consensus panel concluded that these changes would not increase the actual number of people with diabetes, but rather would diminish the number of people with undiagnosed diabetes. In other words, more people will be diagnosed earlier and receive appropriate treatment earlier, which should reduce the incidence of diabetic complications. In the UKPDS, more than 25% of patients with newly diagnosed diabetes already had diabetes-related complications.[40]

Another implication of the new criteria is that a greater proportion of the HbA_{1c} level of the patients diagnosed earlier would be determined by postprandial hyperglycemia. Treatment of patients with fasting plasma glucose levels between 126 mg/dL and 140 mg/dL with potent long-acting sulfonylureas may increase the risk for hypoglycemia. In such patients, use of the short-acting meglitinide insulin secretogogues, which primarily target postprandial hyperglycemia, may have advantages.

New Treatment Modalities

Until 1992, the only pharmacologic treatments available in the United States for T2DM were sulfonylureas and insulin. Since that time, a new so-called third-generation sulfonylurea (glimepiride); nonsulfonylurea secretogogues (the so-called meglitinides, repaglinide, and nateglinide); metformin—a biguanide on the market in Europe for 40 years; alpha glucosidase inhibitors (acarbose and miglitol); and insulin analogs either with a more rapid onset and shorter duration of action (lispro and aspart insulin) or with a longer duration than neutral protamine Hagedorn (NPH) and lack of a peak (insulin glargine) have become available. Some of the basic clinical pharmacology of the new oral agents are summarized in Table 1.

Insulin Secretogogues

Sulfonylureas and meglitinides (nateglinide and repaglinide) act by promoting insulin secretion.[41] With improvement in glycemic control, there will also be a modest improvement in insulin sensitivity due to alleviation of glucose toxicity.[25,42] Both groups (sulfonylureas and meglitinides) bind to receptors on pancreatic beta cells. This leads to closure of ATP-sensitive potassium channels, which causes depolarization of the cell membrane and an influx of calcium through voltage-sensitive channels. The resultant increase in intracellular calcium stimulates the release of insulin. Meglitinides and sulfonylureas differ in their binding sites and binding kinetics. This leads to dif-

ferences in their onset and duration of action as well as the different characteristics of the response in plasma insulin levels. Sulfonylureas are slower in onset, have a longer duration of action (up to 24 hours), and primarily affect second-phase insulin release whereas meglitinides have a rapid onset (< 15 minutes), relatively short duration (~ 3-4 hours), and primarily affect first phase insulin release.[41,43]

Glimepiride has a similar efficacy to the other commonly used sulfonylureas (glyburide and glipizide), lowering HbA_{1c} on average 1.5-2.0%.[44] It has a duration of action comparable to glipizide XL (ie, ~ 24 hours and thus is administered once a day in doses ranging from 2-8 mg/d).[44] Compared to glyburide, it has been reported to cause less hypoglycemia and less weight gain and not to impair cardiac preconditioning; compared to glyburide, it is more selective in its binding to islet receptors and those in cardiac muscle.[45-47] The clinical significance of the latter finding is unclear.

Nateglinide (120 mg) and repaglinide (1-4 mg) are given just prior to meal ingestion (ie, 3-4 times/d).[41,48,49] With nateglinide, in contrast to repaglinide, no dose titration is needed; the starting dose of 120 mg per dose is also the maintenance dose. These agents have only a modest effect on fasting plasma glucose levels but are particularly effective in reducing postprandial hyperglycemia[43,50] and have the same side effects as sulfonylureas. However, their short duration of action has been reported to lead to less hypoglycemia and weight gain than sulfonylureas.[51,52] There have been no head-to-head comparisons of nateglinide and repaglinide in clinical trials in T2DM. Repaglinide has been reported to lower HbA_{1c} to a comparable extent to glyburide[50,53] and glipizide.[54] In short-term studies (8 weeks), nateglinide (120 mg/d) was reported to reduce overall glycemia less than glyburide (5 mg b.i.d.).[43] Nateglinide has also been reported to lower HbA_{1c} and fasting plasma glucose less than metformin, but to reduce postprandial plasma glucose excursions more.[48,55] No long-term comparison of monotherapy with repaglinide and metformin is available; however, repaglinide has been reported to be more effective in lowering HbA_{1c} than the thiazolidinedione troglitazone.[56] Meglitinides are ineffective in patients already on maximal doses of sulfonylureas and in patients who have failed sulfonylurea therapy.[50,53] As monotherapy, meglitinides may be advantageous in patients whose hyperglycemia is mainly postprandial and in elderly patients prone to develop hypoglycemia.[51,55] No adjustments in doses are needed in patients with renal insufficiency.[49,53,57]

Insulin Sensitizers

Metformin[58] and thiazolidinediones[59] (rosiglitazone and pioglitazone) fall into this category. These agents improve all of the actions of insulin in insulin-resistant patients with T2DM and have been shown to reduce insulin resistance in nondiabetic individuals with polycystic ovary syndrome.[58,60]

Metformin reduces the excessive glucose release found in

Table 1. Efficacy and Side Effects of Commonly Used Oral Antidiabetic Drugs

Class	Dose	Efficacy (Reduction in HbA1c)	Common Side Effects of Class
Secretogogues			
1. Sulfonylureas			Hypoglycemia
a. Glyburide (Diabeta®, Glynase®)	1.25-10 mg	1.5-2.0%	Weight gain
b. Glipizide (Glucotrol®)	5-20 mg	1.5-2.0%	
c. Glimepiride (Amaryl®)	2-8 mg/d	1.5-2.0%	
2. Meglitinides			Hypoglycemia
a. Repaglinide (Prandin®)	1-4 mg premeal	1.0-1.5%	Weight gain
b. Nateglinide (Starlix®)	120 mg premeal	0.5-1.0%	
Sensitizers			
1. Metformin (Glucophage®)	500-2500 mg/d	1.5-2.0%	Anorexia; diarrhea; dyspepsia; lactic acidosis
2. Thiazolidinediones			Fluid retention; weight gain; possible precipitant of CHF
a. Rosiglitazone (Avandia®)	2-8 mg/d	1.0-1.5%	
b. Pioglitazone (Actos®)	15-45 mg/d	1.0-1.5%	
Alpha Glucosidase Inhibitors			Flatulence; diarrhea
1. Acarbose (Precose®)	25-100 mg t.i.d.	0.5-1.0%	
2. Miglitol (Glyset®)	25-100 mg t.i.d.	0.5-1.0%	

people with T2DM, primarily by reducing gluconeogenesis.[61-63] To a lesser extent, it improves the efficiency of glucose disposal. Although in animals it reduces intestinal glucose absorption, this does not apparently occur at doses used in humans.[63] Metformin is available as 500-mg and 850-mg tablets taken 1-3 times daily and a sustained release preparation taken once a day (Glucophage XR®); its maximally effective dose is 2000-2550 mg/d. As monotherapy, it is generally as effective as sulfonylureas, lowering HbA_{1c} levels 1.5-2.0%[4,58] in obese as well as nonobese patients.[58] About a third of patients transiently develop gastrointestinal side effects (loose stools/epigastric discomfort), which can be minimized by starting with a low dose (500 mg) once or twice daily taken with meals.[58] When used as monotherapy, hypoglycemia is not observed. Patients generally do not gain weight and actually may lose weight because it reduces appetite.[4] Whereas sulfonylureas and meglitinides are generally neutral with respect to lipids, metformin may lower plasma triglycerides, especially if patients are hypertriglyceridemic,[58] and has been reported to decrease plasma plasminogen activator inhibitor-1 (PAI-1) and fibrinogen levels.[58] These and other actions may explain why in the UKPDS Trial, metformin had more beneficial effect on macrovascular end points than sulfonylureas.[4]

The most serious adverse event associated with metformin therapy is lactic acidosis, which has been reported to occur with an incidence of 0.03/1000 patient years—about the same as death from prolonged sulfonylurea hypoglycemia—and generally in patients who should not have been on metformin in the first place.[58] In the UKPDS, there was not a single case.[4] The contraindications for metformin use are basically those conditions associated with overproduction or underuse of lactate. These conditions include: pregnancy, heart failure, and hypoxic disorders because of overproduction due to increased anaerobic glycolysis; hepatic disease, renal insufficiency, and alcoholism because of decreased lactate use. In addition, because metformin is not metabolized and its sole route of excretion is via the kidney, it will accumulate in renal insufficiency. Diabetic patients undergoing contrast media studies can develop acute renal failure, and it is therefore recommended that metformin be withheld 24 hours before the procedure and not reinstituted until renal function is known to be intact. It is also recommended that metformin not be used in patients with heart disease requiring medication because an acute deterioration in cardiac output could precipitate lactic acidosis.

Thiazolidinediones are useful alternatives to metformin when the latter is contraindicated or not tolerated. These agents lower HbA_{1c} levels on average 1.0-1.5% as monotherapy.[59] They are thought to act primarily by binding to intracellular PPAR-γ receptors and this complex then binds to DNA and alters regulation of synthesis of various factors involved in lipid and glucose metabolism.[59] Some of their actions may be indirect, mediated through reductions in FFA, tumor necrosis factor alpha and resistin and through reductions in intracellular lipid in liver, muscle, and pancreatic islets.[35,64] As insulin sensitizers, like metformin, they improve all actions of insulin in insulin-resistant patients. It is presently controversial whether they exert a selective effect on glucose disposal in contrast to metformin's apparent selective effect on glucose production.[61,62] Rosiglitazone (2-8 mg) and pioglitazone (15-45 mg) are both effective at once-daily dosing. Their onset of action is slower than those of secretogogues and metformin and it may take up to 4 months to observe their maximum effect. Like secretogogues and insulin, their use is associated with weight gain, part of which is due to fluid retention (which can cause a dilutional reduction in hemoglobin values) and a redistribution of fat from visceral to subcutaneous sites.[59] Because of the fluid retention that has been reported to exacerbate heart failure, use of these agents is contraindicated in patients with heart failure Class III and IV and other disorders in which fluid retention would be a problem.[59]

As a class, these agents increase HDL and LDL cholesterol levels and are either neutral or lower plasma triglycerides.[59] The increase in plasma LDL is in the buoyant fraction rather than the small dense particles so that the net effect on plasma lipids is probably beneficial.[65] Like metformin, hypoglycemia is not observed when these agents are used as monotherapy and several nonglucose-related effects have been reported, eg, decreases plasma PAI-1,[66] improvement of endothelial function,[66] and, in animal experiments, preservation of beta cell function.[67] The latter have been confirmed in short-term (2-year) human studies.[68] If confirmed in longer-term studies, use of these agents to prevent T2DM and as early first-line therapy alone or in combination with other agents may be warranted. Currently, since these agents are relatively expensive compared to sulfonylureas and metformin, slow to reach maximum effect, and are not more effective than sulfonylureas or metformin, they are generally not used as initial monotherapy. In Europe, they are approved only as combination therapy (*see below*).

A major concern with this class has been hepatoxicity. The first thiazolidinedione on the market in the United States, troglitazone, was withdrawn because about 2-4% of patients developed an idiosyncratic reaction similar to that observed with isoniazid. This resulted in numerous deaths or liver transplantation when the drug was not stopped in time. So far, rosiglitazone and pioglitazone have not shown this hepatoxicity and it is generally not considered to be a class effect, but rather one that was unique for troglitazone. Differences in the metabolism of troglitazone offer an explanation of why this may not be a class effect.[59] Nevertheless, it is currently recommended that liver function tests be monitored before therapy and every other month thereafter for a year, in patients treated with these agents, and that they not be used in patients with plasma hepatic enzyme levels more than 2 times the upper limit of normal.

α Glucosidase Inhibitors

These agents (acarbose and miglitol) are competitive inhibitors of intestinal a glucosidase and consequently slow the breakdown of dietary starches and thus the intestinal absorption of glucose derived from ingested complex carbohydrates.[69,70] The primary effect of these agents, therefore, is on postprandial hypoglycemia with little or no effect on fasting hyperglycemia. In general, they lower HbA_{1c} levels by 0.5-1.0% and, like the meglitinides, must be given just prior to each meal. To reduce side effects, initial doses are generally 25 mg with subsequent increments of 25 mg per dose every 2 or 3 weeks up to a maximal dose of 100 mg before each meal. Although extremely

safe, these agents have a common side effect (flatus, which often makes them unacceptable to patients) due to undigested carbohydrate reaching the large intestine, being metabolized by gas-producing bacteria. This side effect can be reduced by starting at low doses, which allow induction of the enzyme in the distal part of the small intestine.

New Insulins

Insulin Glargine. As indicated earlier, T2DM is a disorder of progressive deterioration in beta cell function and therefore, eventually, many patients will require some form of insulin therapy. It has been common practice that when patients on 2 or more oral agents fail to achieve adequate glycemic control (HbA_{1c} < 7.0%), to add bedtime NPH to the regimen while keeping the patient on one oral agent.[71] Such a regimen has been reported to be capable of reducing HbA_{1c} levels from 9.8% to 7.0%.[71] Recently, an alternative to NPH, insulin glargine, has become available.[72] This insulin analog is the result of an exchange of glycine for asparagine at the end of the A chain of insulin and the addition of 2 arginine residues on the B chain. These modifications cause an altered isoelectric point[72,73] that results in a clear soluble insulin that precipitates in subcutaneous tissue. As a consequence, its absorption into the circulation is peakless and prolonged.[74] Its duration of action, for example, averages about 24 hours compared to about 14 hours with NPH.[74] Clinical trials comparing glargine with NPH in patients with T1 or T2DM have demonstrated that glargine is at least as efficacious as NPH while significantly reducing the frequency of nocturnal hypoglycemia.[73,75,76] From a practical point of view, an additional advantage of the long duration of this insulin is that at steady state, missing a bedtime injection of glargine would be expected to have a minimal effect on the next day's fasting plasma glucose level and the patient could inject the glargine in the morning with minimal effect on daytime glycemia. In contrast, with NPH in this scenario, fasting plasma glucose levels would be increased and taking NPH in the morning would significantly alter daytime values. When a patient is already taking a single dose of NPH, glargine can be substituted unit for unit. When a patient is taking 2 injections of NPH, it is recommended that glargine be started at 80% of the sum of the NPH dosage.[72] Glargine is also used as a part of the basal component of a basal-bolus insulin regimen (*see below*).

Insulin Lispro (Humalog R) and Aspart (Novolog R). With the progressive deterioration in beta cell function as part of the natural history of T2DM, many patients will ultimately require more sophisticated insulin regimens. Indeed, the Veteran's Administration Study showed that about a third of obese T2DM patients ultimately need a basal-bolus regimen (ie, preprandial short-acting insulin plus a long-acting insulin) to maintain HbA_{1c} levels below 7.0%.[77]

Insulin lispro results from inverting the 28th and 29th B-chain aminoacids from proline-lysine to lysine-proline. Insulin aspart is the result of a substitution of aspartic acid for proline at position 28 on the B-chain.[78] As a consequence, both these insulin analogs are less prone to self-aggregation and exist as monomers after subcutaneous injection, leading to more rapid absorption into the circulation than regular insulin, which exists as hexomers after injection. This rapid absorption also results in a shorter duration of action of these analogs than regular insulin (2-4 h vs 4-6 h). To achieve maximal effectiveness, regular insulin must be injected 30-45 minutes prior to meals.[79] Most patients do not do this. These new insulin analogs can be injected ~ 5 minutes prior to meal ingestion with maximal effectiveness. Thus, use of these analogs has been shown to improve glycemic control compared to the way people customarily use regular insulin.[80] Furthermore, because of the short duration of these analogs, there is less hypoglycemia,[80] but in patients with T1DM this often requires 2 injections of NPH and occasionally of glargine. Overall, these insulins represent a substantial improvement in terms of convenience and safety for patients. There have been no head-to-head comparisons of lispro and insulin aspart in terms of clinical efficacy so that at this time no recommendation between them can be made. There are subtle differences in their pharmacokinetics[81] but the clinical importance of these differences is unclear. Lispro (75/25) and aspart (70/30) insulins are also available as mixtures of free and protamine conjugated analog at least comparable to 70/30 mixtures of regular and NPH insulin.[72,82]

Combination Therapy. The UKPDS showed that less than 50% of patients who initially achieved a HbA_{1c} < 7.0% on sulfonylurea or metformin monotherapy still had an HbA_{1c} < 7.0% at 3 years.[83] The results of the Belfast Study[84] indicate that this is due to progressive deterioration in beta cell function rather than changes in insulin sensitivity. It can therefore be inferred that even if patients achieve initial adequate glycemic control with monotherapy, most will ultimately require additional medication. It is of no benefit to change medication class in patients who have failed to achieve adequate glycemic control on maximal dose of either a secretogogue or a sensitizer.[85] Rather, addition of a second agent, which works via a different mechanism, is used in combination when a single agent has failed to provide adequate glycemic control. The results of several clinical trials indicating the reductions to be expected from different combinations are presented in Table 2.[55,68,77,85-89]

A combination pill of glyburide and metformin (Glucovance®) is already on the market (1.25/250, 2.5/500, 5/500 mg glyburide/metformin). This combination has been shown to lower HbA_{1c} more than monotherapy with larger doses of the individual drugs, with less overall side effects (less hypoglycemia than glyburide; less gastrointestinal side effects than metformin).[90] Since T2DM is accompanied by both beta cell dysfunction and insulin resistance, an argument can be made for using combination therapy (a secretogogue and a sensitizer) as initial management to treat both of these defects.

The question arises as to how to proceed when a patient fails to achieve adequate glycemic control on a combination of 2 oral agents. Should a third oral agent be added, or should bedtime insulin be used? Aside from cost factors (3 pills are more expensive than 1 pill + insulin), it has been shown that addition of a third pill can further lower HbA_{1c}.[86,91] Thus, if a patient on 2 pills has an HbA_{1c} > 8.5%, they will usually not achieve adequate glycemic control (HbA_{1c} < 7.0%) on 3 pills and instead, insulin should be started. For patients with lower

Table 2. Effect of Different Combination Therapies

Combination of Drugs				HbA_{1c}	
Initial Drug	**Add-on Drug**	**Reference**	**Duration**	**Initial**	**Decrement**
Glyburide	Metformin	85	29 wks	8.7	1.6
Metformin	Rosiglitazone	68	26 wks	8.8	1.2
Metformin	Pioglitazone	88	72 wks	9.86	1.36
Nateglinide	Metformin	55	24 wks	8.4	0.9
Metformin	Repaglinide	87	3 mos	8.3	1.1
Metformin	Acarbose	89	12 mos	7.8	0.8
Glyburide	Acarbose	89	12 mos	8.0	0.9

HbA_{1c} levels, a third oral agent may be tried on the basis of convenience. All classes of oral agents may be used in combination with insulin.[71,91] It has been demonstrated that metformin plus bedtime NPH was superior to glyburide plus bedtime NPH in terms of greater HbA_{1c} lowering and less hypoglycemia.[71] There are no comparisons of metformin with thiazolidinediones or with insulin secretogogues other than glyburide used with bedtime insulin. Conceivably, different results may be achieved when using glargine rather than NPH as bedtime insulin.

When a patient fails to achieve adequate glycemic control using a combination of an oral agent plus bedtime insulin, several progressively more complex insulin regimens may be used: 1) twice daily NPH; 2) morning 70/30 or 75/25 insulin mixtures plus bedtime NPH or glargine; 3) prebreakfast and predinner 70/30 or 75/25 insulin mixtures and finally; 4) a basal bolus regimen consisting of preprandial short-acting insulin (regular, lispro or aspart) plus NPH or glargine. Researchers tend to reserve premixed insulins for those who have difficulty mixing insulins or the elderly. A drawback is that one may not change the dose of one insulin species without changing the other. In general, when a patient is on 2 or more injections of insulin, concomitant use of an oral agent provides little benefit vs. using more insulin and is less cost-effective. The Veterans Administration Study[77] showed that a third of obese T2DM subjects required a basal-bolus regimen. In this study, overall daily insulin doses averaging about 1.3 U/kg (130 U/d) and achieved an average HbA_{1c} of 6.9% with little or no weight gain or serious hypoglycemia.

Summary and Conclusions

During the last decade, great strides have been made in our knowledge of the pathogenesis of T2DM, the relationship between glycemic control and complications, and in our ability to achieve adequate glycemic control due to the introduction of new therapeutic modalities. Both acquired insulin resistance and genetically determined deterioration in insulin secretion are key elements in the pathogenesis of this condition and both, therefore, are logical targets for therapeutic intervention. Clinical trials have clearly demonstrated that to prevent the development and slow the progression of micro- and macrovascular complications, it is desirable to maintain HbA_{1c} below 6.5%. Values above 7.5% are no longer considered acceptable. Use of new oral agents that work by different mechanisms alone or in combination with each other or insulin, and use of various insulin regimens as needed can reduce HbA_{1c} with greater safety and efficacy than was previously possible.

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CME Questions

41. Which of the following statements is *false*?
    a. Several controlled clinical trials have proven that diabetic complications can be prevented by maintaining good glycemic control in patients with either type 1 or type 2 diabetes.
    b. Generally, a lower HbA1c is needed to prevent macrovascular disease than microvascular disease.
    c. In the UKPDS trial, insulin was shown to be superior to other treatment modalities.
    d. No clinical trial has ever shown that insulin treatment accelerates macrovascular disease.
    e. The goal for treatment of type 1 and type 2 diabetes is an HbA_{1c} less than 6.5%, and levels above 7.5% are clearly unacceptable.

42. Which of the following statements is *false*?
    a. Macrovascular disease is more important than microvascular disease as a cause of morbidity and mortality in type 2 diabetes.
    b. At diagnosis, people with type 2 diabetes already have complications.
    c. People with impaired glucose tolerance are at increased risk for macrovascular disease.
    d. Hyperinsulinemia causes macrovascular disease.
    e. In type 2 diabetes, the diagnosis is often delayed.

43. Which of the following statements is *false*?
    a. Diabetes can be diagnosed by a fasting plasma glucose level greater than 126 mg/dL.
    b. An oral glucose tolerance test is needed to diagnose diabetes.
    c. The normal fasting plasma glucose concentration is one below 110 mg/dL.
    d. Fasting plasma glucose concentration above 110 mg/dL is associated with an increased risk to develop diabetes.
    e. The new ADA recommendations permit an oral glucose tolerance test be performed.

44. Which of the following statements is *false*?
    a. Type 1 diabetes is simply due to autoimmune destruction of islet beta cells.
    b. Type 2 diabetes results from a combination of insulin resistance and impaired insulin secretion.
    c. In type 2 diabetes, insulin resistance is the primary genetic factor.
    d. Insulin resistance in type 2 diabetes is related to obesity, physical inactivity, high-fat diets, and adverse effects of hyperglycemia and high plasma free fatty acid levels.
    e. Weight loss can completely reverse insulin resistance in type 2 diabetes.

45. Which of the following statements is *false*?
    a. Fasting hyperglycemia in type 2 diabetes is primarily the result of impaired tissue glucose uptake.
    b. Increased glucose release in type 2 diabetes is the result of increased gluconeogenesis by the liver and kidney.
    c. Increased circulating free fatty acids increase glucose release and impair glucose uptake.
    d. Obesity may cause insulin resistance by decreasing the binding of insulin to its receptors and impairing postreceptor intracellular signaling.
    e. Increased release of TNFa and resistin from adipocytes as well as FFA may contribute to the insulin resistance of obesity and type 2 diabetes.

46. Which of the following statements is *false*?
    a. In type 2 diabetes, there is a progressive deterioration of insulin secretion.
    b. For treatment of type 2 diabetes, agents that increase insulin secretion are clearly superior to agents that decrease insulin resistance.
    c. Metformin is as efficacious as sulfonylureas and meglitinides in the treatment of type 2 diabetes.
    d. Thiazolidinediones, insulin sensitizers, are not first-line treatment for type 2 diabetes.
    e. Of all treatments available, metformin is the only one that reduces appetite and generally leads to no weight gain.

47. Which of the following statements is *false*?
    a. Insulin treatment directly stimulates appetite and, therefore, causes weight gain.
    b. The weight gain associated with improvement of glycemic control can largely be explained by failure to reduce caloric intake for reduced glucosuria and overtreatment of hypoglycemia.
    c. Insulin treatment is always associated with weight gain.
    d. Metformin prevents weight gain by reducing appetite.
    e. Meglitinides in general are associated with less hypoglycemia and improved postprandial glucose excursions.

48. Which of the following statements is *false*?
    a. When patients fail to respond to maximal doses of 2 oral agents and have an $HbA_{1c} > 8.5$, it is appropriate to add a third oral agent.
    b. In patients who fail to achieve adequate glycemic control on maximal doses of 2 oral agents and have an $HbA_{1c} > 8.5$, insulin is indicated.
    c. Bedtime insulin added to an oral agent can reduce HbA_{1c} levels from 9.0% to 7.0% if enough insulin is given.
    d. The above can be achieved with little or no weight gain and minimal hypoglycemia.
    e. Most patients with type 2 diabetes will require insulin treatment because of the natural history of the disease.

49. Which of the following statements is *false*?
    a. When a patient fails to respond to a maximal dose of one oral agent, it is logical to switch categories (ie, from a secreto-

gogue to a sensitizer).

b. Adding a second drug that acts via a different mechanism will improve glycemic control in patients with type 2 diabetes.

c. When a patient is on maximal dose of 2 oral agents that act via different mechanisms and has an HbA_{1c} level > 8.5, the next step is insulin.

d. New insulin analogs lispro and aspart are an improvement over regular insulin.

e. Insulin glargine is superior to NPH in causing less hypoglycemia and being peakless.

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3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

Publisher *(Name and Complete Mailing Address)*
Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and Complete Mailing Address)*
Robin Mason, same as above

Managing Editor *(Name and Complete Mailing Address)*
Valerie Loner, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400
	Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Medical Economics Data, Inc.	Five Paragon Drive
	Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

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13. Publication Name: Primary Care Reports
14. Issue Date for Circulation Data Below: November 2001

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1423	1523
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	1115	1223
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			1115	1223
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			5	5
f. Total Free Distribution *(Sum of 15d and 15e)*			5	5
g. Total Distribution *(Sum of 15c and 15f)*			1120	1228
h. Copies Not Distributed			303	295
i. Total *(Sum of 15g, and h.*			1423	1523
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership
Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/27/01

Brenda L. Mooney

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

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