

Appropriate, Timely, and Rational Treatment of Type 2 Diabetes Mellitus: Meeting the Challenges of Primary Care

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ABSTRACT

Diabetes now affects >24 million people in the United States. As the prevalence of diabetes continues to increase, long-term complications of diabetes have emerged as major health care issues. Although much focus has been placed on diabetes, it is important to note that prediabetes, the intermediate state of type 2 diabetes mellitus (DM), is not benign. The progression to type 2 DM for patients with impaired glucose tolerance (IGT) is 6% to 10% per year; for persons with both impaired fasting glucose and IGT, the cumulative incidence of diabetes in 6 years may be as high as 60%. Given the significant clinical and financial impact of both conditions, it is vital that clinicians initiate treatment of diabetes and prediabetes early and aggressively. Despite advances in diabetes treatment, many health care providers do not initiate or intensify therapy appropriately during patient visits, which contributes to poor diabetes control. Although management of blood pressure and lipid levels can be complex, glycemic control is often problematic for patients and their clinicians. Thus, clinicians must learn to use the various pharmacologic and nonpharmacologic strategies effectively to achieve glucose targets in their patients with type 2 DM. Patients with prediabetes should be managed with a combination of lifestyle intervention and appropriately timed pharmacotherapy. Pancreatic β -cell preservation should be a primary metabolic target. (*Insulin*. 2009;4:144–157) © 2009 Excerpta Medica Inc.

Key words: diabetes, prediabetes, pharmacotherapy, impaired glucose tolerance, impaired fasting glucose.

INTRODUCTION

Diabetes now affects >24 million people in the United States, an increase of >3 million cases in 2 years.¹ Another 57 million Americans have prediabetes, a condition that raises the short-term absolute risk of developing type 2 diabetes mellitus (DM) at least 5- to 6-fold.¹ Prediabetes is characterized by either impaired fasting glucose (IFG; fasting glucose level 100–125 mg/dL) or impaired glucose tolerance (IGT; 2-hour post-75-g glucose challenge level 140–199 mg/dL).¹

As the prevalence of diabetes continues to increase, long-term complications of diabetes (coronary heart disease, stroke, peripheral vascular disease, neuropathy, retinopathy, and chronic kidney disease) have emerged as major health care issues. The associated annual health care cost of diabetes in the United States is now \$174 billion, which includes \$116 billion in direct medical costs and \$58 billion in indirect costs (disability, work loss, and premature mortality).²

Despite advances in diabetes treatment, many health care providers do not initiate or intensify therapy appropriately for their patients with diabetes during office visits.³ Failure to intensify therapy through appropriate pharmacologic interventions has been found to contribute to poor glycemic control in patients with type 2 DM managed in primary care

settings.⁴ This article examines several approaches to managing patients with newly diagnosed, treatment-naïve type 2 DM and delaying the progression of prediabetes in patients with IFG or IGT.

RATIONALE FOR EARLY AND AGGRESSIVE TREATMENT Type 2 DM

Large, long-term, randomized controlled trials (RCTs) in both type 1 and type 2 DM have reported that aggressive treatment of overall hyperglycemia significantly reduces the development and/or progression of diabetic complications.^{5–8} Recent RCTs have not shown a benefit of glucose control on macrovascular disease in patients with type 2 DM of long duration and high cardiovascular risk.^{9,10} However, meta-analyses,^{11,12} observational studies,¹³ and further analysis of subgroups from RCTs^{14,15} have revealed a distinct, yet weaker relationship between hyperglycemia and the development or progression of macrovascular disease, particularly when diabetes is of short duration and cardiovascular risk is low.

Moreover, long-term follow-up on subjects from the Diabetes Control and Complications Trial¹⁴ and the United Kingdom Prospective Diabetes Study (UKPDS)¹⁶ has recently

found evidence that the benefits of early and aggressive treatment are realized long after the trial has ended and the levels of glycemic control in the intervention and control arms have converged. In a long-term follow-up study¹⁶ involving >66,000 person-years, patients who were intensively managed in the UKPDS continued to experience risk reductions for any diabetes-related end point (21%; $P = 0.01$), diabetes-related death (30%; $P = 0.01$), myocardial infarction (33%; $P = 0.005$), and death from any cause (27%; $P = 0.002$) for up to 10 years after cessation of the randomized interventions. Benefits persisted despite the early loss of within-trial differences in glycosylated hemoglobin (A1C) levels between the intensive and conventional therapy cohorts, also known as the “legacy effect.” The trial reported the extended effects of improved glycemic control in patients with newly diagnosed type 2 DM, some of whom were followed for up to 30 years.¹⁶

It is important to note that aggressive glycemic targets may not be safe or appropriate for specific populations, including the elderly and those with known (or at high risk for) cardiovascular disease. The Action to Control Cardiovascular Risk in Diabetes trial,⁹ which targeted A1C levels <6.0% in the intensive treatment arm, reported increases in overall and cardiovascular mortality. In a similar study,¹⁰ which used a target A1C level of <6.5%, the mortality rate and incidences of cardiovascular events were not statistically different between the 2 groups. Nevertheless, health care providers should use good clinical judgment in determining appropriate glycemic goals for each patient.

Prediabetes

Although significant focus has been placed on treatment of diabetes, it is important to understand that the intermediate state of prediabetes is not benign. The progression to diabetes for patients with IGT is 6% to 10% per year, and for persons with both IFG and IGT, the cumulative incidence of diabetes in 6 years may be as high as 60%.^{1,17} Conversion of IFG to diabetes increases cardiovascular mortality 2-fold, whereas IGT increases cardiovascular risk by 50%.¹⁸ Progression rates from IFG or IGT to diabetes vary according to the degree of initial hyperglycemia, racial and ethnic backgrounds, and environmental influences.

Microvascular complications have been reported in patients with IGT. In the Diabetes Prevention Program (DPP),¹⁹ diabetic retinopathy was observed in 8% of patients with IGT compared with 13% of patients who progressed to diabetes. In a study evaluating 77 patients with idiopathic peripheral neuropathy, 56% were found to have abnormal results, including 26 with IGT and 15 with clinical diabetes.²⁰

Fortunately, we now know from large RCTs that lifestyle interventions (with and without pharmacologic therapy) are effective in preventing the progression of prediabetes.^{21,22} The progression from prediabetes to type 2 DM can be delayed or prevented by modest weight loss and regular physical activity.^{21,22} In addition, clinical studies have evaluated several pharmacologic agents that can effectively reduce progression to type 2 DM.^{21,23–25}

UNDERSTANDING THE PATHOGENESIS OF TYPE 2 DM

Type 2 DM is a progressive, complex metabolic disorder that is complicated by coexisting defects of multiple organ sites^{8,26,27} and characterized by hyperglycemia, insulin resistance, and relative impairment of insulin secretion. The development of treatment strategies to effectively manage type 2 DM or to prevent or delay the progression of prediabetes in high-risk patients requires a thorough understanding of the disease pathogenesis. Many of the clinical features of type 2 DM depend on genetic and environmental factors.

Unlike type 1 DM, the progression from prediabetes to type 2 DM occurs over a period of several years. As lean individuals gain weight and become obese over time, insulin sensitivity decreases substantially, but glucose tolerance remains relatively normal due to a compensatory increase in insulin secretion. The higher insulin output is accompanied by reduced insulin activity in the liver, adipose tissue, and skeletal muscles, resulting in diminished intracellular glucose disposal.²⁸ Patients then progress through a spectrum of abnormal glucose states, including IFG and IGT, due to worsening of insulin resistance. However, the increase in plasma glucose concentrations is relatively modest because of a further compensatory increase in insulin secretion. A further decline in β -cell insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting and postprandial hyperglycemia. At this stage of IGT, the tissues in the body are maximally or near-maximally resistant to insulin action, and β -cell function is severely impaired. Eventually, obese glucose-intolerant individuals develop frank diabetes.

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Diminished Insulin Secretion/Altered Insulin Action

The hallmark of the metabolic dysfunction associated with type 2 DM includes a reduction in insulin secretion and altered insulin action, resulting in hyperglycemia. In the prediabetes state of IFG and IGT, pancreatic β -cells excrete increasing amounts of insulin to maintain normal glycemia. However, examinations performed on cadaver pancreases found a 40% decline in pancreatic β -cell mass in obese patients with IFG compared with obese individuals who had normal glucose tolerance.²⁹

Hyperglucagonemia

Hyperglucagonemia is another primary feature of both prediabetes and diabetes. Glucagon is a counterregulatory hormone secreted by pancreatic α -cells found on the periphery of the islet. Under normal conditions, a postprandial

increase in glucose concentration is associated with a corresponding reduction in glucagon. As circulating glucose levels decrease, glucagon levels increase, resulting in a 60% increase in hepatic glucose production and output through gluconeogenesis.³⁰ Glucagon secretion is regulated, in part, by endogenous insulin secretion. Insulin action results in the storage of glycogen within hepatocytes. Insulin resistance, insulinopenia, or an increase in glucagon output signals the liver to depolymerize glycogen, resulting in an increase in ambient glucose levels. As previously stated, glucagon secretion is substantially elevated in the fasting state and is not suppressed during the postabsorptive phase in patients with both prediabetes and clinically apparent diabetes.³¹ This results in a continuous state of hyperglycemia and insulin resistance.

Fatty Acids

Hyperinsulinemia downregulates insulin receptor substrate,² while stimulating the production of sterol response element-binding protein 1c, a transcription factor that stimulates lipogenesis.³² The unfortunate metabolic result leads to increased levels of free fatty acids with impaired insulin-mediated suppression of hepatic glucose production.

Fatty acids are now known to play a major role in the advancement of insulin resistance. Free fatty acids inhibit insulin-mediated glucose uptake by interfering with the translocation of the glucose transport protein, GLUT-4, to the plasma membrane, effectively blocking glucose uptake by muscle cells and increasing peripheral insulin resistance. In hepatocytes, free fatty acids inhibit insulin-mediated suppression of glycogenolysis and gluconeogenesis, resulting in an increase in hepatic glucose production.³³

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In addition, pancreatic β -cell death (apoptosis) is accelerated by the accumulation of free fatty acids within the islets.³⁴ Elevations in free fatty acid levels accelerate insulin resistance and impair insulin secretion by affecting the skeletal muscles' ability to uptake glucose, the hepatocytes' ability to suppress the production of glucose, and the pancreatic β -cells' ability to secrete enough insulin to minimize the resulting hyperglycemia.

Incretin Effect

Approximately two thirds of the insulin response to an oral glucose load is due to the potentiating effect of gut-derived incretin hormones.³⁵ The incretin effect has been mostly attributed to peptide hormones that are released into the bloodstream from the intestinal K- and L-cells in response to a meal. Glucagon-like peptide-1 (GLP-1), which is secreted

by L-cells,³⁵ appears to play a significant role in the incretin effect. GLP-1 secretion in response to meals declines progressively from normal glucose tolerance to overt diabetes.³⁶ This is significant because GLP-1 facilitates the regulation of postprandial glucose levels by stimulating insulin secretion in a glucose-dependent manner^{37,38} and helps to regulate the rate of glucose appearance by inhibiting glucagon secretion,³⁹ inhibiting hepatic glucose production,³⁹ regulating gastric emptying,^{40,41} and reducing food intake by postulated centrally mediated mechanisms.^{39,42}

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GLP-1, an incretin hormone, is rapidly released by L-cells in the distal ileum and colon as food is being digested by neurohormonal mechanisms. This hormone works by glucose-dependent action. As long as glucose levels remain elevated, GLP-1 suppresses glucagon secretion from pancreatic α -cells while enhancing the secretion of insulin from pancreatic β -cells. As glucose levels normalize, glucagon and endogenous insulin levels normalize, and the patient does not experience hypoglycemia.

Enzymatic inactivation by dipeptidyl peptidase-4 (DPP-4) shortens the biologic activity of GLP-1 to <2 minutes,³¹ making certain that the effects of this hormone are not prolonged and will not induce hypoglycemia. GLP-1 controls both fasting and postprandial blood glucose concentrations by multiple actions, primarily by stimulating insulin secretion from pancreatic β -cells while inhibiting glucagon secretion. GLP-1 also slows gastric emptying and enhances satiety, thereby reducing food intake. Whereas short-term administration of a GLP-1 agonist limits food intake, long-term subcutaneous injection of GLP-1 results in weight loss.^{43,44} In animal models, GLP-1 promotes expansion of β -cell mass while inhibiting β -cell death (apoptosis).⁴⁵

TREATMENT STRATEGIES

Large studies have found that intensive management of all risk factors, including lipids, blood pressure, and glycemia, have significant beneficial effects on cardiovascular-related deaths and that these interventions can be cost-effective.^{8,46-52} Although management of blood pressure and lipid levels can be complex, glycemic control is often problematic for patients and their clinicians. In this section, we describe various pharmacologic and nonpharmacologic strategies for achieving glucose targets.

Although A1C is still considered the "gold standard" for assessing glycemic status, postprandial hyperglycemia is now recognized as a significant risk factor for macrovascular disease independent of A1C.⁵³ Epidemiologic studies have

found a strong link between postprandial/postchallenge glycemia and cardiovascular risk and outcomes.⁵⁴⁻⁵⁶ A growing body of evidence also suggests a causal relationship between postprandial hyperglycemia and oxidative stress,⁵⁷ carotid intima-media thickness,⁵⁸ and endothelial dysfunction,^{59,60} all of which are known markers of cardiovascular disease.

Because of this association, the International Diabetes Federation⁵³ now recommends aggressive management of postprandial glycemia. However, treatment regimens that target both fasting and postmeal glycemia are needed to achieve optimal glucose control. Therefore, it is important to understand and address the impact of both components on the current glycemic status of each patient.

Lifestyle Interventions

Although patients tend to “tune out” when physicians provide them with the typical “5-minute lifestyle lecture,” exercise and dietary intervention have been found to be highly effective strategies in the war against diabetes. Moderate physical activity has also been reported to be effective in reducing both premeal glucose and postprandial glucose excursions.^{61,62} Furthermore, although it is well accepted that reducing total calories clearly impacts postprandial glucose levels, emerging evidence suggests that daily incorporation of low-glycemic index carbohydrates in meal planning can also be an effective diabetes self-management strategy for glycemic control and weight management.^{63,64} Moderate physical activity has also been found to be effective in reducing both premeal glucose and postprandial glucose excursions.^{61,62}

Regular exercise together with dietary modification has long been considered the cornerstone of diabetes management. However, these interventions have also been shown to play a key role in preventing or delaying the progression from prediabetes to diabetes.^{21,22}

In the DPP study,²¹ 3234 subjects with IGT were randomly assigned to 1 of 3 groups: (1) lifestyle intervention (intensive nutritional and exercise counseling); (2) metformin treatment (medication, standard diet, and exercise); or (3) control (placebo, standard diet, and exercise). The study reported a 58% relative reduction in the progression to diabetes in the lifestyle group and a 31% relative reduction in the metformin treatment group compared with the control group after an average follow-up of 2.8 years. The key to these results was weight reduction; ~50% of subjects in the lifestyle intervention group achieved a weight reduction of ≥7% in the first year and sustained a 5% total weight loss for the duration of the study.

The Finnish Diabetes Prevention Study²² reported similar results in 522 middle-aged obese subjects with IGT who were randomly assigned to receive either brief diet and exercise counseling (control group) or intensive personalized instruction on weight reduction and food intake, as well as guidance on increasing physical activity (intervention group). The study reported a 58% relative reduction in the incidence of DM in the intervention group compared with the control

group after a mean follow-up of 3.2 years. Halting the progression to diabetes was strongly correlated with the degree to which subjects were able to achieve ≥1 of the following goals: (1) weight loss >5% of total body weight; (2) <30% of energy intake from fat; (3) <10% of energy intake from saturated fat; (4) fiber intake ≥15 g/1000 kcal; and (5) >150 minutes of exercise per week.

Furthermore, we know that the combination of exercise and dietary modification is also effective in controlling glycemia. In the UKPDS,⁶⁵ patients in both the intensive and conventional treatment arms had a baseline A1C of 9.1%. For a period of 1 to 2 years, all patients underwent intensive lifestyle intervention and were able to lower their A1C to ~7.0%. However, because subjects in this study had already progressed to overt diabetes and had already lost ~50% of β-cell function, deterioration of β-cell function continued despite improvements in glycemic control. Patients with newly diagnosed type 2 DM were successful in lowering their A1C levels by almost 2% with lifestyle intervention. However, even as they exercised, ate healthier meals, and worked at weight management, their β-cell mass further deteriorated. Over time, the A1C levels in both the intensive and the conventional cohorts deteriorated.

The message is clear: early lifestyle interventions in prediabetes can prevent or significantly delay the progression to type 2 DM. However, although lifestyle interventions can improve glycemic control, they cannot halt β-cell deterioration once patients have progressed to overt type 2 DM.

The message is clear: early lifestyle interventions in prediabetes can prevent or significantly delay the progression to type 2 DM.

Although lifestyle interventions are difficult for patients to adopt, they remain fundamental to the successful management of prediabetes. Persons with prediabetes should reduce their weight by 5% to 10%, with long-term maintenance at this level. Even modest weight loss (7–10 lb) results in decreased fat mass and improvements in systolic blood pressure, fasting blood glucose, low-density lipoprotein cholesterol (LDL-C), and triglycerides.²⁸

Although lifestyle management is difficult to maintain, patient self-monitoring, group interventional strategies, and positive reinforcement are all likely to increase the chances of success. A program of moderately intense physical activity for 30 to 60 minutes, 5 days each week, is recommended. The diet should be low in total saturated fat and trans-fatty acids, and should include adequate dietary fiber. Patients may also want to consider incorporating low-glycemic index carbohydrates into their meal planning for improved postprandial glucose control and weight management.^{63,64}

Pharmacologic Strategies for Type 2 DM

Effective management of type 2 DM often requires early and aggressive use of multiple pharmacologic therapies in combination with lifestyle interventions. In addition to our expanded understanding of the pathogenesis of type 2 DM, clinicians now have several new pharmacologic treatments to address the specific metabolic abnormalities associated with this disease. These include medications to supplement or replace insulin production/secretion (insulin, secretagogues), reduce hepatic glucose production/secretion (metformin), improve insulin sensitivity (thiazolidinediones, metformin), and improve postprandial glucose control (α -glucosidase inhibitors). These drugs have been well studied and widely used in clinical practice. However, in recent years, new drugs have been developed to address defects in incretin hormone availability and action. A list of common treatments, along with their associated target metabolic abnormality, is presented in **Table I**.^{53,66-71}

GLP-1 Replacement

Exenatide

Exenatide is a novel GLP-1 incretin mimetic hormone that has been approved by the US Food and Drug Administration

(FDA) for use in patients with poorly controlled type 2 DM who are taking metformin, a sulfonylurea, a thiazolidinedione, a combination of metformin plus sulfonylurea, or a combination of metformin and a thiazolidinedione. Gila monsters, which are native to the Sonora Desert, harbor a naturally occurring GLP-1 agonist (exendin-4) in their salivary glands. Although the Gila monster's exendin-4 is only 53% homologous with human GLP-1, the analogue is not rapidly degraded by DPP-4 and has equal affinity to GLP-1 receptor sites.⁷²

Exenatide is a synthetic form of exendin-4. Because exenatide is not rapidly degraded by DPP-4, the drug has a half-life of 2.4 hours and is present in the plasma for up to 10 hours, allowing twice-daily administration.⁷² Mean weight loss in an open-label extension trial of 393 patients using exenatide, 10 mg twice daily for 82 weeks, was 8 to 10 lb.⁷³ Weight loss was steady and continuous as long as the patients remained on the drug. Klonoff et al⁷⁴ recently reported findings from a 3-year follow-up study of 217 subjects from 3 placebo-controlled trials and their open-label extensions to evaluate the long-term (≥ 3 years) effects of exenatide on glycemic control, body weight, cardiometabolic markers, and tolerability. They reported that adjunctive

Table I. Common treatments for type 2 diabetes mellitus.

Intervention	Target Metabolic Abnormality	Glucose Focus
Lifestyle changes		
Weight-reduction strategies ⁶⁶	Improve insulin sensitivity	Fasting
Reduce/modify carbohydrate intake ^{53,67}	Improve first-phase insulin release	Postprandial
Regular physical activity ⁶⁸	Improve insulin sensitivity	Fasting
Postmeal physical activity ^{68,69}	Improve insulin sensitivity	Postprandial
Pharmacologic treatment		
Thiazolidinediones ⁷⁰	Improve insulin sensitivity	Fasting
Biguanides ⁷⁰	Decrease hepatic glucose production/output Improve insulin sensitivity	Fasting
α -Glucosidase inhibitors ⁷⁰	Improve first-phase insulin release	Postprandial
Sulfonylureas ⁷⁰	Stimulate insulin production/output	Fasting
Glinides ⁷⁰	Stimulate insulin production/output (at meals)	Postprandial
Basal insulins ⁷⁰	Supplement basal insulin output	Fasting
Rapid-acting bolus insulins ^{70,71}	Reduce postprandial glucose excursion Reduce oxidative stress	Postprandial
Incretin mimetics ⁷⁰	Stimulate insulin release Decrease hepatic glucose production/output Increase satiety Promote weight loss Reduce glucagon secretion Improve gastric emptying	Postprandial
Pramlintide ⁷⁰	Reduce postprandial glucose excursion Reduce oxidative stress Promote weight loss	Postprandial

tive treatment with exenatide over the 3-year period resulted in progressive mean (SD) weight reduction (-5.3 [0.4] kg from baseline at 3 years; $P < 0.001$) and reductions in A1C from baseline to week 12 (-1.1% [0.1%]) sustained for up to 3 years (-1.0% [0.1%]; $P < 0.001$), with 46% of patients achieving A1C levels $\leq 7.0\%$. Patients also experienced improvement in hepatic biomarkers. Patients with elevated serum alanine aminotransferase (ALT) at baseline ($n = 116$) had reduced ALT (-10.4 [1.5] IU/L; $P < 0.001$), and 41% achieved normal ALT. Cardiovascular biomarkers also improved. Triglycerides decreased 12%, total cholesterol decreased 5%, LDL-C decreased 6%, and high-density lipoprotein cholesterol (HDL-C) increased 24% (all, $P < 0.001$).

Liraglutide

Liraglutide is an analogue of human GLP-1 with 97% homology to this endogenous protein and a half-life of 13 hours, making the drug suitable as a once-daily injection.⁷⁵ Although not currently approved by the FDA for clinical use, liraglutide has been studied in a head-to-head, 26-week, RCT evaluating 464 subjects with type 2 DM.⁷⁶ Patients were randomized to receive treatment with either liraglutide 1.8 mg once daily or exenatide 10 μ g twice daily, both as an add-on to their existing treatment, consisting of metformin and/or a sulfonyleurea. Patients in the liraglutide group experienced significantly less minor hypoglycemia than did those in the exenatide group (2 vs 2.5 per patient-year; $P = 0.013$), with no episodes of major hypoglycemia reported for the liraglutide group. Although nausea was the most common adverse event in both treatment arms, the percentage of patients who reported nausea with liraglutide decreased to 8% after 5 weeks and to 4% after 10 weeks. The exenatide group reported nausea in $>10\%$ of patients for >20 weeks. Weight loss was the same for the 2 incretins (~ 2 – 3 kg). However, β -cell function (measured using the homeostasis model assessment [% from baseline]) was significantly greater with liraglutide than with exenatide (32.1% vs 2.7%; $P < 0.001$). Finally, the percentage of patients achieving A1C levels $< 7.0\%$ was 54% with liraglutide and 43% with exenatide.

DPP-4 Inhibitors

Endogenous levels of GLP-1 can be increased pharmacologically with the use of DPP-4 inhibitors such as sitagliptin. The DPP-4 inhibitors do not bind directly to GLP-1 receptors and have less potent pharmacologic action than GLP-1 agonists. The DPP-4 inhibitors inhibit the proteolytic cleavage of GLP-1 in the circulation by binding to the DPP-4 enzyme, thereby increasing the concentration of endogenous GLP-1 by ~ 2 -fold.⁷⁷ Sitagliptin has been found to reduce plasma glucagon, increase C-peptide and insulin concentrations, and preserve β -cell mass in rodent models of type 2 DM.⁷⁸ A recent meta-analysis, including data from 8 placebo-controlled Phase III studies with durations of up to 1 year, reported that sitagliptin reduced A1C levels by 0.74% (mean baseline A1C, 7.9%) and was associated with neutral effects on body weight.⁷⁹

A head-to-head, double-blind, randomized crossover study comparing sitagliptin and exenatide reported pharmacologic superiority of the GLP-1 analogues over the DPP-4 inhibitors.⁸⁰ Patients taking a stable dose of metformin were randomized to receive treatment with exenatide 5 μ g for 1 week and then 10 μ g for 1 week before crossing over to sitagliptin 100 mg for 2 weeks. The cohort randomized to initiate with sitagliptin crossed over to the exenatide protocol after 2 weeks. Patients underwent a standardized meal tolerance test at baseline and at the end of each 2-week treatment period. Primary end points included postprandial and fasting glucose levels, gastric emptying rates, caloric intake, insulin secretion rates, and adverse event rates. Both treatments reduced the postprandial plasma glucose concentrations relative to baseline. The change in the 2-hour postprandial glucose concentration from baseline was -112 mg/dL for exenatide and -37 mg/dL for sitagliptin ($P < 0.001$). The decrement in fasting plasma glucose was similar between the 2 cohorts. Acute β -cell function, as assessed with insulinogenic index and insulin secretion rate, was significantly improved with exenatide compared with sitagliptin ($P < 0.024$). Exenatide reduced the rate of gastric emptying relative to baseline and sitagliptin. Finally, exenatide reduced the mean caloric intake in patients during a standard test meal (-134 kcal vs 63 kcal for sitagliptin; $P < 0.023$).

Diabetes Prevention

The rapid and often relentless progression of type 2 DM suggests that patients at high risk for developing diabetes should be provided with an equally aggressive strategy to protect their remaining β -cell function and endogenous insulin secretion. Management of patients with prediabetes should incorporate both lifestyle and pharmacologic interventions.

The rapid and often relentless progression of type 2 DM suggests that patients at high risk for developing diabetes should be provided with an equally aggressive strategy to protect their remaining β -cell function and endogenous insulin secretion.

The guidelines published by the American Diabetes Association (ADA)⁸¹ suggest that metformin therapy and lifestyle intervention be initiated once the patient's A1C is $\geq 7.0\%$. Unfortunately, this benchmark to initiate drug therapy is unrealistic if one hopes to preserve, restore, and prolong any remaining pancreatic β -cell function. Furthermore, the medications currently used to treat type 2 DM have not been approved by the FDA for prediabetes. Thus, clinicians must use their own clinical judgment in utilizing these medications.

It is important to note that use of the insulin sensitizers, thiazolidinediones, and metformin has been found to be beneficial in delaying the progression from prediabetes to

diabetes.^{21,23} For example, the Actos Now for Prevention of Diabetes study,⁸² a recently completed RCT in 602 subjects with IGT, compared pioglitazone 45 mg/d with placebo. Patients were observed for an average of 3.75 years to determine whether they progressed from IGT to clinical diabetes. Patients who received pioglitazone showed an 82% reduction in progression versus 28% for those who received placebo. Results of this study clearly suggest that patients with prediabetes who are aggressively managed with pioglitazone can improve their insulin sensitivity and restore their pancreatic β -cell function.

In addition, the DPP study²¹ reported that metformin 850 mg twice daily reduced the relative risk of progression to type 2 DM by 31%. Metformin was found to be most effective in reducing progression toward diabetes in subjects <45 years of age and in individuals with a body mass index >35 kg/m².¹⁸ Metformin may also improve outcomes by inducing weight loss. Thus, patients with prediabetes who are unable or unwilling to participate in lifestyle-intervention programs might benefit from pharmacologic therapy using metformin.

Metformin has also been shown to improve the inflammatory markers that are linked to cardiovascular risk. The drug reduces triglyceride levels by 10% to 30%⁸³ and LDL-C and total cholesterol by 5% to 10%,⁸⁴ while having no significant influence on HDL-C levels.⁸⁴ Levels of fibrinogen⁸⁵ and C-reactive protein⁸⁶ were also lower in metformin-treated patients. The UKPDS reported that obese patients who received metformin as monotherapy had a lower risk of myocardial infarction and stroke than subjects taking metformin with a sulfonylurea.⁸⁷ It should be noted that metformin has no effect on blood pressure.⁸³

Although incretin hormones have been shown to preserve β -cell function in animal models, their role in human β -cell preservation remains to be established. Nevertheless, incretins play an important role in lowering postprandial secretion of glucagon, thereby lowering postabsorptive glucose levels, reducing oxidative stress, and preventing weight gain.³¹

PRACTICAL APPLICATIONS

Primary care physicians are in a unique position to screen patients at risk for glucose intolerance and manage most of the patients with type 2 DM. Primary care physicians are trained in incorporating behavioral and lifestyle interventions that can augment pharmacotherapy. More emphasis is being placed on chronic disease–state management models than on assessing each patient with diabetes acutely.⁸⁸ In addition, one of the most requested topics for continuing medical education each year at the American Academy of Family Physicians Annual Scientific Assembly continues to be diabetes management. Therefore, primary care physicians are demonstrating a stronger desire to become actively involved in helping their patients navigate the often controversial pathways leading to progressive β -cell dysfunction.

The ADA⁸⁹ has recommended the following metabolic parameters for patients with diabetes:

1. Glycemic goals
 - a. A1C <7.0% in most patients, assuming no cardiovascular risk, normal life expectancy, and low risk of hypoglycemia
 - b. Fasting glucose level 90 to 130 mg/dL
 - c. 2-Hour postprandial glucose level <180 mg/dL
2. Blood pressure <130/80 mm Hg
3. Lipids
 - a. LDL-C <100 mg/dL
 - b. Triglycerides <150 mg/dL

When planning a treatment strategy, one must evaluate and treat every patient as an individual, taking into account their coexisting medical disorders, cardiovascular risk factors, and age, as well as their lifestyle, education, and cultural and financial issues. The “lead” member of the diabetes team is always the patient, who, by default, assumes responsibility for self-management. The primary care physician should assist the patient in acquiring the skills needed to treat to success rather than manage toward failure.

Management of diabetes becomes more challenging as patients develop additional complications and comorbidities over time. *Malglycemia* (defined as hyperglycemia, hypoglycemia, and increased glycemic variability) has been associated with increased mortality.⁹⁰ A retrospective cohort study⁹⁰ evaluated 66,062 blood glucose measurements obtained from 1175 patients who underwent allogeneic hematopoietic stem cell transplantation between 2000 and 2005. Patients with the greatest daily glycemic variability (malglycemia) had a 15-fold increased risk of nonrelapse mortality ≤ 200 days after receiving their transplant compared with patients with the least variability ($P < 0.001$).⁹⁰ Thus, health care providers must be cautious about the effects of hyperglycemia, hypoglycemia, and glycemic variability on increased risk of morbidity and mortality.

Type 2 DM Treatment

Identifying significant metabolic abnormalities requires access to information about both long-term and intraday glucose status. Although A1C is generally considered to be the “gold standard” for assessing glycemic control and often serves as a surrogate for complications of diabetes, it does not provide information about intraday blood glucose profiles. Thus, self-monitoring of blood glucose levels (SMBG) is required, in addition to A1C testing, to assess intraday variations in fasting, premeal, and postmeal plasma glucose levels; identify specific metabolic abnormalities; and guide effective therapeutic decision-making.

Monnier et al⁹¹ reported a strong relationship between A1C, fasting glucose, and postprandial glucose levels. They claimed that the relative contribution of fasting glucose levels to overall glycemia is ~70% in patients with A1C levels >10.0% but ~30% in those with A1C levels <7.3%. Understanding this relationship allows clinicians to use A1C testing and SMBG in combination to quickly identify glucose abnormalities and initiate or adjust therapy to achieve glycemic goals.

Although frequent SMBG may not be necessary for many patients, it is valuable for all patients to perform intensive SMBG periodically to generate data sets that allow clinicians to identify glucose patterns.^{70,92} For example, patients may use 7-point profiles (testing before and after each meal and at bedtime) or a staggered regimen (testing before and after alternating meals).^{93,94} By staggering SMBG measurements at different times on different days, patients can generate an accurate portrait of day-to-day glycemic excursions while avoiding the need to test many times in a single day. An example of a staggered SMBG regimen is presented in **Table II**.⁹³ Based on SMBG data, the clinician can make informed decisions about interventions that will address the specific glucose abnormality. Reasonable approaches to using SMBG and A1C data to guide therapy are listed in **Table III**.^{70,95} These recommendations are adapted from the American Association of Clinical Endocrinologists (AACE) medical guidelines for clinical practice for the management of DM⁷⁰ and the AACE Diabetes Road Map,⁹⁵ and they are based on clinical judgment and experience.

A promising adjunct to SMBG is continuous glucose monitoring (CGM), which uses a sensor that measures an interstitial glucose reading every 1 to 10 minutes and then transmits the data to a receiver for review and storage. Although reimbursement for CGM in type 1 DM is gaining momentum, payers are slow to provide coverage for this technology in type 2 DM. However, recent studies have begun reporting the value and feasibility of CGM in the type 2 DM population in terms of improved clinical outcomes⁹⁶ and in enhancing patient understanding of their disease.⁹⁷

Prediabetes Care

As previously stated, no diabetes medications are currently approved by the FDA for prediabetes. Furthermore, despite strong evidence that these medications may be effective in preventing or delaying progression to overt diabetes, reimbursement for these treatments is limited. Therefore, clinicians must use their clinical judgment when prescribing pharmacologic therapy for their patients with prediabetes.

This places even greater importance on lifestyle interventions for these individuals.

Use of SMBG, particularly before and after meals, can be very effective in promoting disease knowledge and self-management skills by enabling people with prediabetes to see how meal composition and size affect blood glucose levels. This, in turn, empowers them to change eating behaviors or activity levels to ultimately improve glycemic control.^{98,99} As with pharmacologic interventions, obtaining reimbursement for SMBG in patients with prediabetes will be challenging. However, given the significant and growing increase in the prevalence of diabetes and its associated costs, both clinical and financial, all clinicians should be aggressive in preventing diabetes.

To assist clinicians in these efforts, the National Diabetes Education Program (NDEP), a joint program of the National Institute of Diabetes and Digestive and Kidney Diseases and the Centers for Disease Control and Prevention, recently released a toolkit for health care providers as part of its "Small Steps. Big Rewards. YOUR GAME PLAN to Prevent Type 2 Diabetes" campaign. The GAME PLAN toolkit arms health care providers with information on identifying and treating patients with prediabetes. It also includes patient materials designed to help patients reduce their risk of developing type 2 DM.

The toolkit includes a "how to" guide for providers with suggestions for helping patients begin and maintain healthier habits, a question-and-answer section about diabetes prevention strategies, and a GAME PLAN office poster. Patient materials include an information brochure about diabetes and prediabetes, a GAME PLAN booklet to help patients set goals and track progress, a Food and Activity Tracker, a Fat and Calorie Counter, and a brochure on starting a walking program. The toolkit can be downloaded free of charge from the NDEP Web site (http://www.ndep.nih.gov/media/GP_Toolkit.pdf).

CONCLUSIONS

Diabetes is a chronic disease with an ill-defined onset, a variable transition phase, and a devastating final chapter. Health

Table II. An example of a staggered self-monitored blood glucose regimen.⁹³

	Before Breakfast	After Breakfast	Before Lunch	After Lunch	Before Dinner	After Dinner	Bedtime
Monday	X	X					X
Tuesday	X		X	X			
Wednesday	X				X	X	
Thursday	X	X					X
Friday	X		X	X			
Saturday	X				X	X	
Sunday	X	X					X

This type of regimen can be used to create a profile (fasting/premeal/postmeal) periodically and before office visits to assess glycemic control.

Table III. Reasonable use of glycosylated hemoglobin (A1C) and self-monitored blood glucose (SMBG) data to manage hyperglycemia in noninsulin-treated type 2 diabetes mellitus.^{70,95}

A1C, %	Fasting/ Premeal	Postmeal	Reasonable Intervention	Reasonable SMBG Regimen
<6.5	Near target	Near target	Continue lifestyle interventions Continue current medications Continue to monitor glycemia	SMBG 1–3x/wk Fasting Before and after meals Intensive, episodic SMBG profile before office visits Fasting SMBG 3–5x/wk until fasting glucose goal is achieved
	Well above target	Near target	Weight reduction Regular exercise/physical activity Consider adding/increasing medication (MET, TZD) Reduce/modify CHO consumption Exercise after meals	Intensive, episodic SMBG profile before office visits SMBG before and after meals 2–4x/wk (focusing on problem meals) until postmeal glucose goal is achieved
	Near target	Well above target	Consider adding/increasing medication (AGI, GL) Check patient understanding of/adherence to treatment regimen; address as needed Weight reduction Regular exercise/physical activity Consider adding/increasing medication (SU, MET, TZD, basal insulin)	Intensive, episodic SMBG profile before office visits Fasting SMBG 3–5x/wk until fasting glucose goal is achieved Intensive, episodic SMBG profile every 1–2 mo and before office visits
6.5–8.5	Well above target	Near target	Check patient understanding of/adherence to treatment regimen; address as needed Weight reduction Regular exercise/physical activity Consider adding/increasing medication (AGI, GL)	SMBG before and after meals 2–4x/wk (focusing on problem meals) until postmeal glucose goal is achieved Intensive, episodic SMBG profile every 1–2 mo and before office visits
	Near target	Well above target	Consider IM or DPP-4 in combination with MET Check patient understanding of/adherence to treatment regimen; address as needed Reduce/modify CHO consumption Exercise after meals Consider adding/increasing medication (AGI, GL, rapid-acting insulin)	SMBG before and after meals 2–4x/wk (focusing on problem meals) until postmeal glucose goal is achieved Intensive, episodic SMBG profile every 1–2 mo and before office visits
	Well above target	Well above target	Check patient understanding of/adherence to treatment regimen; address as needed First address fasting/premeal glucose Weight reduction Regular exercise/physical activity Consider adding/increasing medication (SU, MET, TZD, basal insulin, IM) Then address postmeal glucose Reduce/modify CHO consumption Exercise after meals Consider adding/increasing medication (AGI, GL, rapid-acting insulin)	Fasting SMBG 3–5x/wk until fasting glucose goal is achieved SMBG before and after meals 2–4x/wk (focusing on problem meals) until postmeal glucose goal is achieved Intensive, episodic SMBG profile monthly and before office visits

(continued)

Table III (continued).

A1C, %	Fasting/ Premeal	Postmeal	Reasonable Intervention	Reasonable SMBG Regimen
>8.5	Well above target	Near target	Check patient understanding of/adherence to treatment regimen; address as needed Weight reduction Regular exercise/physical activity Consider adding/increasing medication (SU, MET, TZD, basal insulin)	Fasting SMBG 3–5x/wk until fasting glucose goal is achieved Intensive, episodic SMBG profile every 1–2 mo and before office visits
	Near target	Well above target	Check patient understanding of/adherence to treatment regimen; address as needed Reduce/modify CHO consumption Exercise after meals Consider adding/increasing medication (AGI, GL, rapid-acting insulin)	SMBG before and after meals 4–6x/wk (focusing on problem meals) until postmeal glucose goal is achieved Intensive, episodic SMBG profile monthly and before office visits
	Well above target	Well above target	Check patient understanding of/adherence to treatment regimen; address as needed First address fasting/premeal glucose Weight reduction Regular exercise/physical activity Consider adding/increasing medication (SU, MET, TZD, basal insulin) Then address postmeal glucose Reduce/modify CHO consumption Exercise after meals Consider adding/increasing medication (AGI, GL, rapid-acting insulin) Screen patient for mental illness (depression, bipolar disorder, eating disorders)	Fasting SMBG 3–5x/wk until fasting glucose goal is achieved SMBG before and after meals 4–6x/wk (focusing on problem meals) until postmeal glucose goal is achieved Intensive, episodic SMBG profile monthly and before office visits

MET = biguanides; TZD = thiazolidinediones; CHO = carbohydrate; AGI = α -glucosidase inhibitor; GL = glinides; SU = secretagogues; IM = incretin mimetics; DPP = dipeptidyl peptidase-4.

care systems that emphasize acute care to the exclusion of disease prevention or chronic disease management will fail patients with diabetes and those with prediabetes. Physicians and health care providers must begin to understand this disease continuum and intervene at the earliest possible stage using appropriate interventions guided by A1C and SMBG data.

The primary focus of managing prediabetes is β -cell preservation. Lifestyle modification, including exercise and weight loss, can have beneficial effects on metabolic parameters such as fasting glucose, lipids, and blood pressure. However, once β -cell function and mass begin to decline, the body is exposed to the ravages of chronic hyperglycemia, insulin resistance, and oxidative stress. Even if patients remain asymptomatic, they develop microvascular and macrovascular complications of diabetes, which may be difficult to reverse.

From a clinical standpoint, we can ask ourselves which type of patient we would rather manage in our own busy practices. Would we prefer consulting on and managing an asymptomatic patient with newly diagnosed prediabetes, or a patient with a 30-year history of poorly controlled type 2 DM, an A1C of 10.0%, severe peripheral diabetic neuropathic pain, and a recent acute myocardial infarction? With aggressive and timely management of the former patient, there is a strong likelihood of minimizing his/her risk of developing chronic, long-term complications. Unfortunately,

for the latter patient, the clinician is spending time attempting to manage poorly controlled diabetes and the secondary complications; the patient's disease has now become more expensive and more time consuming for the practitioner to manage.

Patients with prediabetes should be managed with a combination of lifestyle intervention and appropriately timed pharmacotherapy. Pancreatic β -cell preservation should be a primary metabolic target. Because primary care physicians will be the flashpoint for screening patients with prediabetes, educational programs that explain β -cell preservation to primary care physicians should be advocated.

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