

Clinical Geriatrics

A CLINICAL JOURNAL OF THE AMERICAN GERIATRICS SOCIETY



Educational Objectives

After reading this article, physicians will:

- Understand the pathophysiology of type 2 diabetes mellitus.
- Be familiar with the various therapies available to treat type 2 diabetes mellitus.
- Be familiar with the proposed algorithm for treating type 2 diabetes mellitus.
- Understand the principles of the primary prevention of type 2 diabetes mellitus.

This activity is valid from August 15, 2004 to August 15, 2005. Time to complete the activity is 1 hour.

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JOHNS HOPKINS UNIVERSITY
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A Supplement to Clinical Geriatrics

August 2004

An Algorithm for Managing Type 2 Diabetes: A Focus on the Disease Process, Not Just the Sugar

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Annals of Long-Term Care

Clinical Care and Aging

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An Algorithm for Managing Type 2 Diabetes: A Focus on the Disease Process, Not Just the Sugar

The introduction in the past decade of several new classes of pharmacologic agents to treat patients with type 2 diabetes now provides the opportunity to focus therapy on treating the underlying disease process instead of just reacting to the blood glucose levels. With the introduction of these new agents and an understanding of the disease process of type 2 diabetes mellitus constantly evolving, it is often difficult to keep up to date with the management of type 2 diabetes. This supplement reviews the pathophysiology of type 2 diabetes, the oral pharmacologic treatment of type 2 diabetes, and proposed treatment algorithms, which are stratified based on fasting plasma glucose levels. The aim of these algorithms is to help guide the practitioner in understanding the use of combination therapy earlier in the course of diabetes. This is important because data from recent studies indicate that sulfonylureas, biguanides, and

insulin do not prevent the decline in beta-cell function and cannot provide sustainable glycemic control. The basis for the use of combination therapy earlier in diabetes is twofold: to preserve beta-cell function while maintaining appropriate glycemic control for a longer duration than is usually attained through monotherapy with a secretagogue or biguanide, and to improve the insulin resistance so that less insulin is required to maintain glycemic control. Insulin resistance is commonly associated with cardiovascular risk factors, and decreasing insulin resistance will improve many of these risk factors, which also may reduce the incidence of cardiac events associated with the metabolic syndrome.

Diabetes mellitus affects approximately 8.7% of American adults, and the majority of these patients develop type 2 diabetes.¹ Between 1990 and 2002, the incidence of type 2 diabetes increased by 61% in the United States.² Population esti-

Table I American Diabetes Association 2004 Diagnostic Criteria for "Pre-Diabetes" and Type 2 Diabetes³

Any one of the following criteria confirms diagnosis of:

Pre-Diabetes:

1. Impaired glucose tolerance
 - 2-hour value on a 75-g glucose tolerance test 140-199 mg/dL (7.8-11.1 mmol/L)
2. Impaired fasting glucose
 - Fasting plasma glucose 100-125 mg/dL (5.6-6.9 mmol/L)

Type 2 Diabetes:

- Fasting plasma glucose \geq 126 mg/dL (7.0 mmol/L) noted on two occasions
- 2-hour post-load 75-g glucose level \geq 200 mg/dL (11.1 mmol/L) noted on two occasions
- Random plasma glucose level \geq 200 mg/dL (11.1 mmol/L) associated with symptoms (polyuria, polydipsia, weight loss) noted on two occasions

mates from the Centers for Disease Control and Prevention (CDC)—utilizing data from the National Health Interview Survey (NHIS) and the National Health and Nutrition Examination Surveys (NHANES), including both NHANES III and NHANES 1999-2000—indicate that approximately 19 million persons have diabetes mellitus. In addition, using estimates of the prevalence

bolic syndrome.⁴ The most dramatic increases in the prevalence of diabetes during the past decade (from 1990-2000) have been in the population younger than age 50 years, with a 76% increase in the 30- to 39-year-old age group.^{2,5}

The increasing prevalence of diabetes is concerning because there is significant morbidity and mortality associated with the disease. Microvascular diseases of the eye and kidney and neuropathy can develop during the period of impaired glucose tolerance, prior to the patient's diagnosis of diabetes.⁶ In addition, patients with type 2 diabetes have an increased incidence of cardiovascular complications. Macrovascular disease is the leading cause of death in patients with type 2 diabetes, and this type of diabetes is considered an independent risk equivalent for developing another vascular event.⁷ Death rates related to diabetes also have risen at an unabated rate since 1992 (Figure 1).⁸

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Data from the United Kingdom Prospective Diabetes Study (UKPDS)

recently confirmed that improved glycemic control, as measured by reductions in hemoglobin A_{1c} (HbA_{1c}), reduces the incidence of microvascular complications.^{9,10} However, the UKPDS also demonstrated that most patients with diabetes receiving pharmacologic therapy with sulfonylureas, biguanides, and insulin do not achieve long-lasting glycemic control. During this time the average HbA_{1c} level has not changed in the U.S., while glycemic control, defined as a HbA_{1c} level of < 7%, has deteriorated.¹¹⁻¹³ These alarming statistics raise the questions of how to

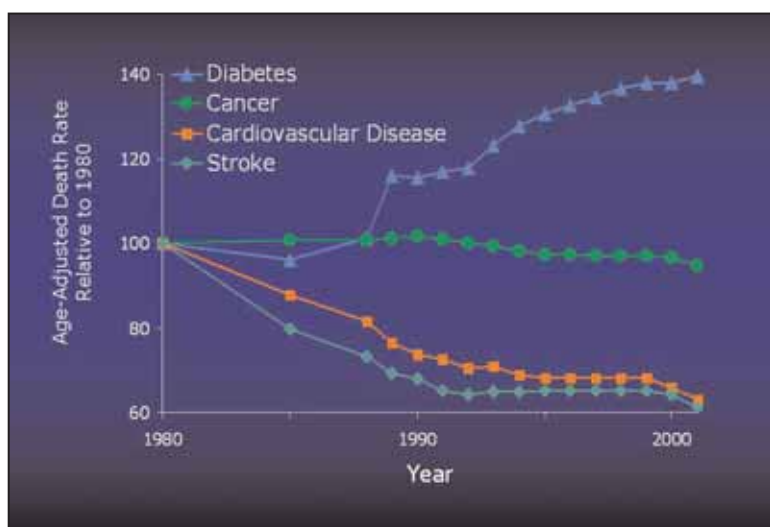


Figure 1. Increasing deaths due to diabetes.⁸

of “pre-diabetes” (impaired glucose tolerance [IGT] or impaired fasting glucose [IFG]), utilizing the prevalence data from the NHANES III, which is certainly an underestimation, and applying those prevalence rates to the 2000 U.S. population, indicates that about 35 million adults aged 40-74 would have IFG and 16 million would have IGT, totaling 41 million adults with pre-diabetes using the new American Diabetes Association (ADA) diagnostic criteria (Table I).³ The NHANES III data show that at least 47 million individuals in the United States have meta-

improve the rate of glycemic control and how to lower HbA_{1c} into the normal range in patients with type 2 diabetes to maximally prevent the complications. Current treatment strategies for managing type 2 diabetes will be reviewed here so that patients may achieve prolonged glycemic control. Currently available oral pharmacologic therapies will be discussed, as well as proposed algorithms for treating patients stratified by fasting blood glucose levels, which can serve as an initial guide for treating nonacutely ill patients with type 2 diabetes.

TYPE 2 DIABETES MELLITUS: PATHOGENESIS AND DIAGNOSIS

Pathogenesis

Normal glucose tolerance is maintained by stimulation of insulin secretion from the pancreas, suppression of endogenous hepatic glucose production, and stimulation of glucose uptake by peripheral insulin-responsive tissues (ie, muscle and fat). The latter two processes are mediated by insulin and are dependent on the first process—the release of insulin. Patients with type 2 diabetes become hyperglycemic because of a resistance to insulin-stimulated glucose uptake and concomitant deterioration of beta-cell function (Figure 2).¹⁴ Insulin resistance is defined as the inefficient use of insulin and is a fundamental abnormality underlying the onset of type 2 diabetes.^{15,16} Insulin resistance is often observed years prior to the clinical diagnosis of diabetes and a proportion of patients with insulin resistance progress to diabetes.^{15,17} Insulin resistance has also been associated with increased incidence of cardiovascular disease.^{18,19} Consequently, treat-

ment strategies must address insulin resistance, and, if insulin resistance does not sufficiently decrease the workload of the beta-cell, the lacking beta-cell function must be replaced.

Diagnosis

The ADA created an international expert committee to develop clinical practice guidelines for the diagnosis and classification of diabetes.⁶ The ADA criteria for diagnosis of type 2 diabetes are shown in Table I.³ In the ADA report, the HbA_{1c} was not included as part of the diagnostic criteria. The ADA recently reviewed the possibility of including the HbA_{1c} in the diagnostic crite-

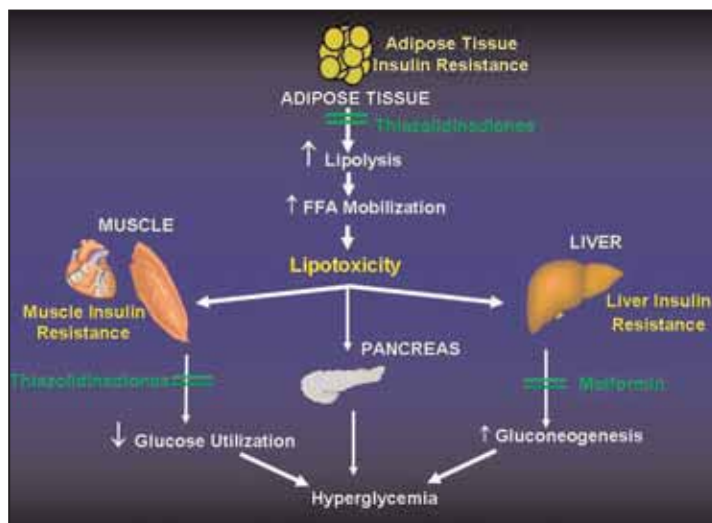


Figure 2. Pathogenesis of type 2 diabetes and targets of action for oral antidiabetic agents.¹⁴

ria but concluded that the test does not have adequate sensitivity, specificity, or accuracy to be utilized as a screening test.²⁰ The ADA no longer recommends “action points” above which therapy should be initiated or changed. Instead, they recommend glycemic goals of therapy that in-

clude a preprandial plasma glucose of 90-130 mg/dL and a postprandial glucose of < 180 mg/dL. Although they recommend a goal of HbA_{1c} less than 7%, the committee does recognize that “more stringent goals (ie, a normal A_{1c} of < 6%) can be considered in individual patients based on epidemiologic analyses that suggest that there is no lower limit of A_{1c}, at which further lowering does not reduce risk of complications, at the risk of increased hypoglycemia....”²¹ Recent guidelines were published by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology.²² The AACE guidelines are more stringent than the ADA guidelines, recommending patients be treated to HbA_{1c} of less than 6.5%. The Canadian Diabetes Association now has the most stringent guidelines, whereby they recommend that a normal HbA_{1c} can be considered for patients in whom it can be achieved safely.²³

PRIMARY PREVENTION OF TYPE 2 DIABETES

Recent studies, including the Diabetes Control and Complications Trial (DCCT) and the UKPDS, have demonstrated that intensive glucose control prevents microvascular disease in both type 1 and type 2 diabetes.^{9,10,24} Lowering HbA_{1c} to the normal range decreases the incidence of microvascular disease in patients with type 2 diabetes.²⁵ The drawback of these studies is that they are secondary prevention trials, in which subjects were already diagnosed with the disease process at enrollment, and the intervention (glycemic control) was initiated to prevent complications of the disease process.

Currently, several primary prevention trials are

in progress to evaluate both type 1 and type 2 diabetes. Two recently stopped studies, the Diabetes Prevention Trial Type 1 (DPT-1) and the European Nicotinamide Diabetes Intervention Trial (ENDIT), showed no benefit of insulin (oral or low-dose injected) or nicotinamide, respectively.^{26,27} Trials that have been traditionally thought of as primary prevention trials of type 2 diabetes include the Da Qing IGT and Diabetes Study, the Finnish Diabetes Prevention Study (DPS), the American Diabetes Prevention Program (DPP), the Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), TRogliptazone In the Prevention Of Diabetes (TRIPOD) study, and the XENical in the prevention of Diabetes in Obese Subjects (XENDOS) study.²⁸⁻³³

One of the first studies to evaluate the impact of changes in diet and/or exercise (both of which improve insulin sensitivity) on the progression of IGT to type 2 diabetes mellitus was the Da Qing IGT and Diabetes Study.²⁸ Subjects with IGT were randomized to either no intervention or to one of three active treatment groups: diet only, exercise only, or diet plus exercise. At the end of 6 years, the diet, exercise, and diet-plus-exercise interventions were associated with 31%, 46%, and 42% reductions in risk of developing diabetes, respectively.²⁸ Subsequently, the Finnish DPS and the American DPP showed a 58% decrease in the progression from IGT to type 2 diabetes (Table I).

The trials involving pharmacologic therapy have typically shown about a 30% decrease in progression with the exception of the TRIPOD study, which found a 56% decrease in progression in women who had a history of gestational

diabetes. Data from the Swedish Obese Subjects (SOS) study suggests that a longer period of study, if associated with significant weight loss, may result in a decrease in the diagnosis of diabetes based on the response of obese subjects treated with bariatric surgery, regardless of underlying glycemic status.³⁴ Although these studies showed similar rates in the decrease of progression from IGT to type 2 diabetes mellitus, it can be argued that these are not true primary prevention trials because the development of IGT indicates that a mismatch had already developed between the insulin resistance and ability of the beta cell to secrete insulin. The DPP and the STOP-NIDDM have both evaluated the subjects in the active treatment group after stopping the trial and found an increase in the diagnosis of diabetes^{31,35} (Table I). In contrast, no increase in diabetes was observed 8 months after stopping the thiazolidinedione troglitazone in the TRIPOD study, and that protection appears to continue after reinitiating pharmacologic therapy with pioglitazone.³⁶ These data suggest that decreasing the sugar (as is done by metformin, a sulfonyleurea, and acarbose) is not sufficient enough to halt the underlying disease process.

The TRIPOD study could be considered as both a primary and secondary prevention study, as it enrolled women who had a history of gestational diabetes regardless of their current glucose tolerance status, for treatment with troglitazone, an insulin sensitizer. Interestingly, this study showed the largest pharmacologic decrease (> 50%) in the progression to diabetes of any of the trials to date. Further analysis of this population has shown that if the thiazolidinedione is initiated at the diagnosis of diabetes, then glu-

cose tolerance and beta-cell function, which had deteriorated significantly during development of diabetes on placebo, did not change significantly during treatment with troglitazone and post-treatment washout (median of 7.9 months after study medications were stopped). The average duration of treatment with troglitazone plus post-trial washout was 2.3 ± 1.0 years. Strikingly, the group that was treated with troglitazone from the onset of the trial did not have the deterioration of glucose tolerance and beta-cell function that was observed in the placebo group, unless insulin resistance did not improve with troglitazone therapy. If insulin resistance did not improve in response to troglitazone, progression to hyperglycemia was inevitable.³⁷ Once diabetes was diagnosed, therapy was changed to open-label troglitazone. A recent analysis of 2.3 years follow-up after the diagnosis of diabetes, including almost 8 months of no therapy after troglitazone was removed from the market in the U.S., shows that the loss of beta-cell function stopped completely once troglitazone was added.³⁷

There is one additional small study that has looked prospectively at beta-cell function and found that therapy with the thiazolidinedione rosiglitazone induced recovery of beta-cell function, as evidenced by the restoration of the first-phase insulin response to glucose in subjects with type 2 diabetes who were failing oral hypoglycemic therapy, independently of the correction of glucose toxicity.³⁸ There are now additional data indicating that thiazolidinediones improve insulin sensitivity in patients with impaired glucose tolerance, hypertension, and polycystic ovarian syndrome.³⁹⁻⁴⁶ Together, the studies of lifestyle changes (namely, exercise and

Table II Post Hoc Analysis of the Likelihood of Being Diagnosed With Diabetes During Hypertension or Lipid Therapy Trials⁴⁷⁻⁵⁰

Study	Follow-up (yrs)	Incidence of New T2DM in Treated (%)	Incidence of New T2DM in Controls (%)	P Value	Decrease
ALLHAT	4.9	2.0	3.1	< 0.001	35%
ALPINE	1.0	0.5	4.1	0.03	88%
CAPP	6.1	6.5	7.3	0.03	11%
CHARM	3.1	6.0	7.4	NS	-
HOPE	4.5	3.6	5.4	< 0.0001	33%
LIFE	4.8	6.0	8.0	< 0.0001	25%
SCOPE	3.7	4.3	5.3	0.09	19%
SOLVD	2.9	5.9	22.4	< 0.0001	74%
STOP-2	6.0	4.7	4.9	NS	-
WOSCOPS	4.9	1.9	2.7	0.042	30%
HPS	5.0	4.6	4.0	0.10	-
BIP	6.2	42.3	54.4	0.04	22%

T2DM = type 2 diabetes mellitus; NS = not significant.

weight loss) and the TRIPOD study suggest that therapies that improve insulin sensitivity may delay or possibly prevent the onset of type 2 diabetes in high-risk individuals. This highlights the importance of modifying the disease process (the loss of beta-cell function and insulin resistance) by improving insulin resistance, which effectively “afterload reduces” the beta cell, which then does not have to work as hard and may last longer.

There are now a number of analyses from trials that utilized traditional therapies for lowering blood pressure or lipids, which found in post hoc analysis that active treatment with an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), a peroxisome proliferator-activated receptor (PPAR) ligand, or some, but not all, statin agents was associated with a decreased likelihood of being diagnosed with diabetes while participating in the respective trial (Table II).⁴⁷⁻⁵⁰ The decrease in being diagnosed

with diabetes in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) is likely due to the benefit from the ACE inhibitor therapy and is probably an underestimation, as some were offset by the increased likelihood of diabetes in the presence of thiazide therapy. There are two large ongoing international trials that will test this observation as compared to either a thiazolidinedione (Diabetes REduction Assessment with ramipril and rosiglitazone Medication [DREAM]) or a rapid-acting secretagogue (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research [NAVIGATOR]).^{51,52}

These trials will test whether inhibition of the renin angiotensin system by either an ACE inhibitor (DREAM) or an ARB (NAVIGATOR) will impact the progression from IGT to type 2 diabetes; however, their comparators treat either the insulin resistance or the beta-cell defect, respectively.

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Although patients who are at high risk for developing diabetes can be identified, it remains difficult to predict the time course of progression to hyperglycemia. Studies involving first-degree relatives of patients with type 2 diabetes have shown that the ability of the beta cell to increase insulin secretion in response to decreasing insulin sensitivity is one of the major determinants as to whether a patient develops hyperglycemia. The heritability of the acute insulin response to glucose (AIR_{glucose}) has been independently studied in four populations and was shown to be approximately 70%.^{32,53-55}

The longevity of the beta cell appears to be a function of how much stress is placed on it and what kind of genetic programming it possesses to enable it to respond to that stress. This is exemplified by the recent epidemic of type 2 diabetes in children and adolescents.⁵⁶ These children typically have a family history of type 2 diabetes, whereby their parents develop diabetes as adults in their fourth decade while their grandparents are still being diagnosed in their sixth and seventh decades of life. These data suggest that therapies need to be developed to effectively decrease the workload and stabilize the function of the beta cell.

To initiate a downward trend in HbA_{1c}, attention needs to be directed toward treating the underlying disease process. Type 2 diabetes is a multi-organ disease resulting from insulin resistance at the level of the liver, skeletal muscle, and heart, combined with a beta-cell secretory defect.^{57,58} Traditionally, it was believed that at least 10-20 years elapsed from the onset of metabolic disturbances to the development

of clinical diabetes. However, the recent escalation of type 2 diabetes in children and adolescents has challenged that dogma. Epidemiologic studies have shown that obesity, sedentary lifestyle, and high-calorie, high-fat diets play a direct role in the diabetes epidemic.^{59,60} To understand how this process can be accelerated so dramatically, the etiology of type 2 diabetes needs to be investigated. The picture that has begun to emerge is that the underlying disease process is well established by the time type 2 diabetes is diagnosed, based on the current criteria of hyperglycemia. Although the ADA recently lowered the criteria for impaired fasting glucose to a fasting glucose of 100-125 mg/dL, the concern remains that the identification of “at risk” individuals is based on elevation of sugar that occurs after the mismatch in beta-cell function and insulin resistance has developed.⁶¹ Although the ability of the beta cell to compensate for insulin resistance appears to be the major determinant of the development of hyperglycemia, the impact of insulin resistance and hyperinsulinemia on insulin-sensitive organs also needs to be assessed.

Insulin resistance has been difficult to measure in subjects at risk for type 2 diabetes mellitus because there is not a single parameter that is highly specific and sensitive for the presence of insulin resistance. In a study headed by Reaven, McLaughlin and colleagues⁶² evaluated the Adult Treatment Panel (ATP) III criteria as a predictor of insulin resistance in a group of 258 overweight/obese individuals who did not have diabetes. In this study, insulin resistance was calculated from the insulin-mediated glucose uptake measured by the euglycemic-hyperinsu-

linemic clamp technique, and the values obtained were used to calculate the sensitivity and specificity of the ATP III criteria to identify insulin-resistant individuals.⁶² They found that the ATP III criteria for the metabolic syndrome had a sensitivity of 52% and a specificity of 85% for predicting insulin resistance. These data are consistent with other data looking at utilization of two or more criteria from ATP III to identify metabolic syndrome.⁶³ Interestingly, Reaven's study group found that more insulin-resistant individuals (n = 87) were identified by simply using a fasting triglyceride concentration of > 130 mg/dL and/or a triglyceride/high-density lipoprotein of > 3.0 than by using the ATP III criteria.⁶² While these data do need to be validated in non-Caucasian populations, this is a parameter that can be easily calculated from studies that are typically obtained in our patients. Importantly, this ratio provides a potential marker for the dysregulation of fat metabolism that underlies the process of insulin resistance.

Insulin resistance at the level of the muscle has been demonstrated in humans with type 2 diabetes; however, the cellular mechanism associated with this process has been elusive.^{64,65} In a study headed by Shulman, Dresner and colleagues⁶⁶ demonstrated in subjects without diabetes that acute elevation of free fatty acids (FFAs) results in decreased glucose utilization by muscle. These results support the epidemiologic studies that show a relationship between plasma FFA levels and insulin resistance, and between plasma FFA and hepatic glucose production.⁶⁷⁻⁶⁹ Interestingly, FFAs are elevated in subjects with IGT, suggesting that the component of insulin resistance induced by FFAs (or lipotoxicity) be-

gins before the onset of hyperglycemia.⁷⁰ This relationship has been demonstrated in greater detail in rodent models, such as the Zucker diabetic fatty (ZDF) rat, which develops obesity and insulin resistance followed by type 2 diabetes.⁷¹ In the ZDF rat, elevations in circulating FFAs are first seen 2-3 weeks prior to the onset of hyperglycemia, which correlates with approximately 2-3 years of a human life. These excess circulating FFAs have been linked with lipid deposition in nonadipocyte tissues, which then become resistant to insulin.

Elevated circulating FFAs have also been associated with lipid accumulation in the beta cell leading to apoptosis in rat models.⁷² This beta-cell toxicity represents failure of the adipocytokines to confine the storage of FFAs to the adipocyte. Rodent studies have demonstrated that thiazolidinediones are associated with a sustained decrease in circulating free fatty acids and prevent lipid deposition in the beta cell, skeletal muscle, cardiac muscle, and liver.⁷³⁻⁷⁵ Human studies, thus far, have shown that thiazolidinediones enhance insulin sensitivity by promoting increased insulin sensitivity in peripheral adipocytes in patients with type 2 diabetes, resulting in lower FFA concentrations and a redistribution of intracellular lipid from insulin-responsive organs into peripheral adipocytes.⁷⁶⁻⁸⁴

The elevated glucose production by the liver that is characteristic of type 2 diabetes can be accounted for primarily by increased gluconeogenesis and glycogenolysis.⁸⁵ However, by the time a subject develops hyperglycemia, hepatic glucose production is no longer regulated by circulating insulin. Elevated hepatic glucose output has been shown to correlate with plasma FFAs and with

fasting hyperglycemia in patients with type 2 diabetes.⁶⁷ Metformin and thiazolidinediones have been demonstrated to decrease hepatic glucose output; thus, pharmacologic therapy is now available to treat this aspect of type 2 diabetes.^{86,87} However, data from the UKPDS showed that the use of metformin alone in patients newly diagnosed with type 2 diabetes did not maintain HbA_{1c} in the normal range for a sustained period of time.⁸⁸ The lack of sustained glycemic control with metformin may be associated with the fact that the primary action of this agent is in decreasing unregulated hepatic gluconeogenesis with inadequate effect on decreasing FFAs and insulin resistance. Thus, sustained glycemic control will require managing all aspects of the disease process, particularly insulin resistance.

ORAL TREATMENT OF TYPE 2 DIABETES

The currently available classes of oral antidiabetic agents (Table III)⁸⁹⁻¹⁰⁵ reduce plasma glucose levels by targeting four processes: (1) stimulation of pancreatic beta cells to produce more insulin (sulfonylureas, non-sulfonylurea secretagogues); (2) stimulation of glucose uptake by muscle and adipose tissues (thiazolidinediones); (3) reduction of glucose output by the liver (thiazolidinediones, biguanides); and (4) reduction of glucose absorption by the gut (alpha-glucosidase inhibitors).¹⁰⁶ As seen in Figure 2, these agents target the various pathophysiologic mechanisms of type 2 diabetes.¹⁴ However, diet and exercise remain the cornerstone for management of type 2 diabetes. Caloric restriction, weight loss, and exercise can enhance insulin sensitivity and glycemic control even when pharmacologic

Table III Oral Antidiabetic Agents and Their FDA-Approved Indications and Uses⁸⁹⁻¹⁰⁵

Class	Agent	FDA-Approved Indications and Uses
Thiazolidinediones	Rosiglitazone	Monotherapy or in combination with sulfonylurea, biguanide, or insulin
	Pioglitazone	Monotherapy or in combination with sulfonylurea, biguanide, or insulin
Biguanides	Metformin	Monotherapy or in combination with sulfonylurea or insulin
Alpha-glucosidase inhibitors	Acarbose	Monotherapy or in combination with sulfonylurea, biguanide, or insulin
	Miglitol	Monotherapy or in combination with sulfonylurea
Sulfonylureas (selected)	Chlorpropamide	Monotherapy
	Glipizide	Monotherapy
	Glyburide	Monotherapy or in combination with insulin or biguanide
	Glimepiride	Monotherapy or in combination with biguanide or insulin
Non-sulfonylurea secretagogues	Nateglinide	Monotherapy or in combination with biguanide or thiazolidinedione
	Repaglinide	Monotherapy or in combination with biguanide or thiazolidinedione
Fixed-dose combinations	Metformin/glyburide	Monotherapy or in combination with thiazolidinedione
	Metformin/glipizide	Monotherapy
	Metformin/rosiglitazone	Monotherapy

Table IV Oral Antidiabetic Agents and Their FDA-Approved Doses⁸⁹⁻¹⁰⁵

Class	Agent	FDA-Approved Dosage Range (Daily)
Thiazolidinediones	Rosiglitazone	4-8 mg
	Pioglitazone	15-45 mg
Biguanides	Metformin	500-2550 mg
Alpha-glucosidase inhibitors	Acarbose	25-300 mg
	Miglitol	25-300 mg
Sulfonylureas (selected)	Chlorpropamide	100-500 mg
	Glipizide	5-40 mg
		5-20 mg
	Glyburide	1.25-20 mg
		1.5-12 mg
Glimepiride	1.25-20 mg	
Non-sulfonylurea secretagogues	Nateglinide	180-360 mg
	Repaglinide	0.5-16 mg
Fixed-dose combinations	Metformin/glyburide	1.25 mg/250 mg once daily to 10 mg/2000 mg in divided doses
	Metformin/glipizide	2.5 mg/250 mg once daily to 10 mg/2000 mg in divided doses
	Metformin/rosiglitazone	4 mg/1000 mg to 8 mg/2000 mg in two divided doses

therapy is being utilized. The following section will provide a brief overview of the available classes of the oral antidiabetic agents.

Thiazolidinediones

Rosiglitazone and pioglitazone are the only two currently available thiazolidinediones in the United States.^{89,90} Both of these agents are indicated as monotherapy in patients with type 2 diabetes or as combination therapy with a sulfonylurea, a biguanide, or insulin (Table III).⁸⁹⁻¹⁰⁵ For patients who do not achieve optimal glycemic control at maximum effective (or indicated) doses of thiazolidinediones, a sulfonylurea, a biguanide, or insulin may be added to

the regimen. The opposite is also true: for patients who do not receive adequate glycemic control at maximum effective doses of a sulfonylurea, a biguanide, or insulin, thiazolidinediones should be initiated as add-on therapy. Dosage ranges of oral therapies are described in Table IV.⁸⁹⁻¹⁰⁵

Therapeutic benefits of using thiazolidinediones early in the treatment of type 2 diabetes include the preservation of beta-cell function, augmentation of insulin sensitivity, and minimization of hypoglycemic adverse events.¹⁰⁷ Studies suggest that the thiazolidinediones increase the responsiveness of beta cells by reducing external factors (ie, glucose and free fatty

acids) that impair insulin secretion.^{74,108} Studies have also shown that treatment with thiazolidinediones significantly reduces the proinsulin-to-insulin levels, indicating improved beta-cell function.¹⁰⁹ Thiazolidinediones also may exert direct effects on beta-cell recovery.^{38,110,111}

Preservation of beta-cell function and improvement of insulin sensitivity are the major efficacy rationales for the use of thiazolidinediones as first-line therapy, especially because current evidence suggests that deterioration of beta-cell function and resistance to insulin begin long before the diagnosis of diabetes.^{37,112-117} These data suggest that because thiazolidinediones preserve beta-cell function and improve insulin sensitivity, their use from the time of diagnosis of diabetes, or even before diagnosis, may improve glycemic control and prevent diabetic complications.

Rosiglitazone and pioglitazone have been proven safe and effective for long-term therapy in a number of clinical trials. The thiazolidinediones are rarely associated with hypoglycemia, and severe hypoglycemia, as can occur with sulfonylureas or insulin, is no longer a barrier to achieving glycemic targets.⁸⁷ Using an agent that would minimize the occurrence of this adverse event is a good way to ensure compliance from the initiation of therapy, particularly in patients who have experienced hypoglycemic events on other therapies.

As for adverse events, thiazolidinediones may cause weight gain and edema when initiated at high doses.⁸⁷ The thiazolidinediones have been associated with fluid retention and dilutional anemia, which is due to an increase in plasma volume, and are not recommended for use in pa-

tients with New York Heart Association Class 3 or 4 cardiac status; combination use with insulin may increase the incidence of cardiac failure.^{89,90} Troglitazone, an older thiazolidinedione, was removed from the market because of hepatotoxicity. Studies show that hepatic failure is not a class effect with these agents; rosiglitazone and pioglitazone have a more favorable hepatic safety profile than troglitazone or placebo.¹¹⁸ Monitoring of liver function tests is no longer required by the Food and Drug Administration (FDA).

Biguanides

The primary action of biguanides is to reduce the production of glucose by the liver.^{87,91} Metformin is the only biguanide available in the United States. Because the mode of action does not increase pancreatic insulin secretion, hypoglycemia is generally not associated with biguanides. However, lactic acidosis, a serious metabolic complication, has very rarely been reported with the use of metformin, particularly in individuals with renal dysfunction or advancing age.¹¹⁹ There may be some vitamin B₁₂ and folate malabsorption with metformin use, so it may be prudent to measure a hemoglobin, hematocrit with red blood cell indices, and vitamin B₁₂ and folate levels at initiation and at least annually. Certain drugs such as cimetidine and ranitidine may increase metformin blood levels by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy individuals, but the clinical implications remain to be determined.

Metformin is excreted unchanged in the urine (primarily through tubular secretion) and

Table V Contraindications and Precautions to Be Aware of When Prescribing Metformin⁹¹

CONTRAINDICATIONS

1. Renal disease or renal dysfunction (eg, as suggested by serum creatinine levels of > 1.5 mg/dL [males], > 1.4 mg/dL [females], or abnormal creatinine clearance), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia.
2. Congestive heart failure requiring pharmacologic treatment.
3. Known hypersensitivity to metformin hydrochloride.
4. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.
5. Metformin or metformin XR should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function.

PRECAUTIONS

Monitoring of Renal Function:

1. Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive metformin or metformin XR.
2. In patients with advanced age, metformin or metformin XR should be carefully titrated to establish the minimum dose for adequate glycemic effect because aging is associated with reduced renal function.
3. In elderly patients, particularly those > 80 years of age, renal function should be monitored regularly and, generally, metformin or metformin XR should not be titrated to the maximum dose.
4. Before initiation of metformin or metformin XR therapy, and at least annually thereafter, renal function should be assessed and verified as normal.
5. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and metformin or metformin XR should be discontinued if evidence of renal impairment is present.

Use of Concomitant Medications That May Affect Renal Function or Metformin Disposition:

1. Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution.

Radiologic Studies Involving the Use of Intravascular Iodinated Contrast Materials (eg, intravenous urogram, intravenous cholangiography, angiography, and computed tomography scans with intravascular contrast materials):

1. Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin.
2. Therefore, in patients in whom any such study is planned, metformin or metformin XR should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure, and reinstated only after renal function has been re-evaluated and found to be normal.

Hypoxic States:

1. Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia.
2. When such events occur in patients on metformin or metformin XR therapy, the drug should be promptly discontinued.

Surgical Procedures:

1. Metformin or metformin XR therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids), and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake:

1. Alcohol is known to potentiate the effect of metformin on lactate metabolism.
2. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving metformin or metformin XR.

does not undergo hepatic metabolism. In patients with decreased renal function (ie, < 50-70 mL/min, based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the risk for lactic acidosis, which is fatal in 50% of cases, increases significantly. For this reason, the precautions outlined in Table V, as recommended by the FDA, should be carefully followed in all patients.⁹¹ Importantly, serum creatinine should be monitored routinely in all patients receiving a biguanide. The FDA recommends that a creatinine clearance be measured prior to initiating therapy in patients 80 years of age or older. A more conservative approach would be to measure the creatinine clearance in any patient who is 70 years of age or older at the time of initiating therapy. Ideally, all patients with type 2 diabetes, regardless of age, should have a creatinine clearance measured annually or semi-annually if they have excellent glucose and blood pressure control. Biguanides are indicated for monotherapy or combination therapy (Table III).⁸⁹⁻¹⁰⁵ They have similar efficacy to sulfonylureas and thiazolidinediones, and the most common adverse events include abdominal pain, nausea, and diarrhea, which can be minimized by dosing after meals and by initiating therapy at low doses and increasing slowly.

Alpha-Glucosidase Inhibitors

Acarbose and miglitol are alpha-glucosidase inhibitors that act by delaying carbohydrate absorption in the small intestine.⁸⁷ These agents are approved for use as monotherapy or combination therapy and are taken by patients at the beginning of each main meal.^{92,93} The main advantage of these agents is that essentially they

are only minimally absorbed and are rarely associated with hypoglycemia and weight gain. However, they are less efficacious than biguanides and sulfonylureas, and frequently cause loose stools and flatulence when used at the recommended doses (ie, 100 mg acarbose three times daily). When used in low doses (ie, 12.5-25 mg acarbose once or twice daily) the side effect of loose stools may be useful in a patient who is preoccupied with constipation. Post hoc analysis of the STOP-NIDDM trial database suggests that treatment of patients who have IGT with acarbose is associated with a reduction in the risk of cardiovascular disease and hypertension.¹²⁰ These data will need to be confirmed in a prospective, randomized, controlled clinical trial. Because of their mechanism of action, these drugs are contraindicated in patients with diseases of the gastrointestinal tract (eg, inflammatory bowel disease). These agents are poorly absorbed with less than 2% of an oral dose recovered in the urine as active (ie, parent compound and active metabolite) drug. Pharmacokinetic studies showed that patients with renal impairment (creatinine clearance < 25 mL/min/1.73m²) attained about five times higher peak plasma concentrations of acarbose than volunteers with normal renal function. Consequently, alpha-glucosidase inhibitors are not recommended for use in patients with severe renal impairment (serum creatinine > 2 mg/dL) because this population has not yet been studied. The concern is that the risk of drug accumulation in renal impairment through the increased plasma levels may have the potential for hepatotoxicity. However, when used in very low doses (ie, 12.5-25 mg acarbose once or twice dai-

ly), it is possible that this will be less of a risk, but studies are needed in the population with stage 4 or 5 chronic kidney disease.

Secretagogues

Antidiabetic drugs that act by increasing insulin secretion are called secretagogues, and they can be separated into two groups: sulfonylureas and non-sulfonylurea secretagogues. A number of sulfonylureas are available, since this is one of the oldest classes of antidiabetic agents. These agents are approved for use as either monotherapy or combination therapy. The two adverse events most commonly associated with sulfonylureas are hypoglycemia and weight gain. The newer or second-generation sulfonylureas (ie, glyburide, glipizide, glimepiride) are more effective and are associated with lower incidences of adverse events than the older agents.⁸⁷ The non-sulfonylurea secretagogues are a newer class and include two currently available products: nateglinide, a phenylalanine derivative, and repaglinide, a benzoic acid derivative. Both products are approved for use as monotherapy or in combination with a biguanide (Table III).⁸⁹⁻¹⁰⁵ They have shorter half-lives than sulfonylureas and a reduced risk of hypoglycemia.⁸⁷ Because of their short half-lives, resulting in shorter duration action, the non-sulfonylurea secretagogues are administered at meals to improve postprandial glycemic control. The short half-life and short duration of action may be particularly useful in patients who do not eat three meals daily or eat at irregular times including geriatric patients, those with renal disease, and high school or college students with type 2 diabetes.

Fixed-Dose Combinations

Fixed-dose combination pills for the management of type 2 diabetes have recently been introduced in the U.S. The advantages include better efficacy with lower doses of each component, improved compliance and adherence, fewer complications (ie, less hypoglycemia) due to lower dosing, and the financial advantage of the tablets usually priced at the same cost as the more expensive component alone. The currently available combinations include metformin/glyburide, metformin/glipizide, and metformin/rosiglitazone.⁹⁴⁻⁹⁶ There is also a rosiglitazone/glimepiride combination pill that is undergoing regulatory evaluation by the FDA. One strategy for utilizing these fixed-dose combination pills is to combine the different combination pills such that the patient receives a low dose of a secretagogue, a low dose of a thiazolidinedione, and the highest tolerable dose of metformin. This can be done by giving one combination tablet in the morning and a different one at night.

Future Therapies

There are several new pharmacologic classes in development that may facilitate the management of type 2 diabetes. The identification of the incretins, or gut hormones, as modulators of insulin sensitivity and of the insulin response to an oral glucose load was an unexpected but intriguing addition to our potential armamentarium. Currently, glucagon-like peptide (GLP-1) is receiving a lot of attention. GLP-1 is a 31 amino acid peptide that was first identified as a gastrointestinal hormone and shown to be a cleavage product of the proglucagon precursor.

sor.^{121,122} These studies are being done with either derivatives of GLP-1 or exendin-4, the GLP-1 analogue derived from a hormone found in the saliva of the Gila monster. Patients with type 2 diabetes who are given GLP-1 analogues increase insulin secretion in response to glucose in conjunction with a modest reduction in weight. Interesting data are also emerging that suggest that GLP-1 analogues may induce beta-cell regeneration and help preserve beta-cell function in type 2 diabetes.¹²² It is very possible that combining these agents with a thiazolidinedione will optimally decrease insulin resistance, and will stabilize and perhaps rejuvenate beta-cell function. The other very interesting compound is a highly selective dipeptidyl-peptidase (DPP)-IV inhibitor, which enhances the levels of the endogenous incretins, leading to a decrease in glucose excursion, increase in insulin and C-peptide responses, and a decrease in glucagon secretion following a glucose challenge.¹²³ So far, the most progress has been made with inhibitors of DPP-IV (which have the advantage of being orally bioavailable) and with the peptide exendin-4, which, although needs to be given by injection, may be amenable to formulation to provide a long-lasting depot preparation.

PROPOSED TREATMENT ALGORITHMS FOR MANAGEMENT OF TYPE 2 DIABETES

Utilizing all of the available tools to manage type 2 diabetes will require a deliberate approach to combination therapy rather than just reacting to the glucose changes. Treatment algorithms can be useful as an initial guide for management. The following proposed treatment algorithm (Figure 3) is designed to aid the practitioner in the treat-

ment of patients with type 2 diabetes. However, if the patient has recently lost significant amounts of weight, is dehydrated, ketotic, or acutely ill, then they should be treated with basal-bolus insulin. When their condition has stabilized, consideration may be given to adding oral agents such as metformin or thiazolidinediones to the insulin. If patients do not respond to treatment or remain acutely hyperglycemic during therapy, referral to a diabetes specialist may be appropriate.

Type 2 Diabetes

Patients should have an HbA_{1c} test performed as a baseline and every 3 months during therapy. The goal of treatment is to reduce HbA_{1c} levels to at least 6.5-7% or lower (ie, normal, referenced to a nondiabetic range of 4.0-6.0% using a DCCT-based assay) if it can be achieved safely (< 6%).^{21,22}

First-line oral therapy may include double or triple therapy with any combination of a thiazolidinedione, a biguanide, or a secretagogue, as depicted in Figure 3. Including a thiazolidinedione as part of first-line therapy would be more likely to preserve the beta-cell function and improve insulin sensitivity than a secretagogue. Combination therapy with a thiazolidinedione and a biguanide offers the additional benefit of complementary mechanisms of actions without increasing the risk for hypoglycemia. Ideally, secretagogues will be reserved for second- or third-line therapy, unless the plasma glucose is very high, because these agents do not treat the underlying insulin resistance. Indeed, the secretagogues, by the nature of their action, force additional insulin to be secreted by beta cells, which

are already unable to produce sufficient insulin and are to some extent functionally compromised. It is unlikely that beta-cell function would be prolonged with such an approach. If a secretagogue is utilized, it should be at one-quarter to one-half the maximum recommended dose to minimize hypoglycemia and because of the lack

of further insulin increase at the higher doses. If hypoglycemia occurs, back titrate or consider changing the sulfonylurea to a short-acting secretagogue. After adequate time, if the patient does not respond to oral triple therapy, an insulin regimen may replace the secretagogue and the thiazolidinedione/biguanide should be continued.

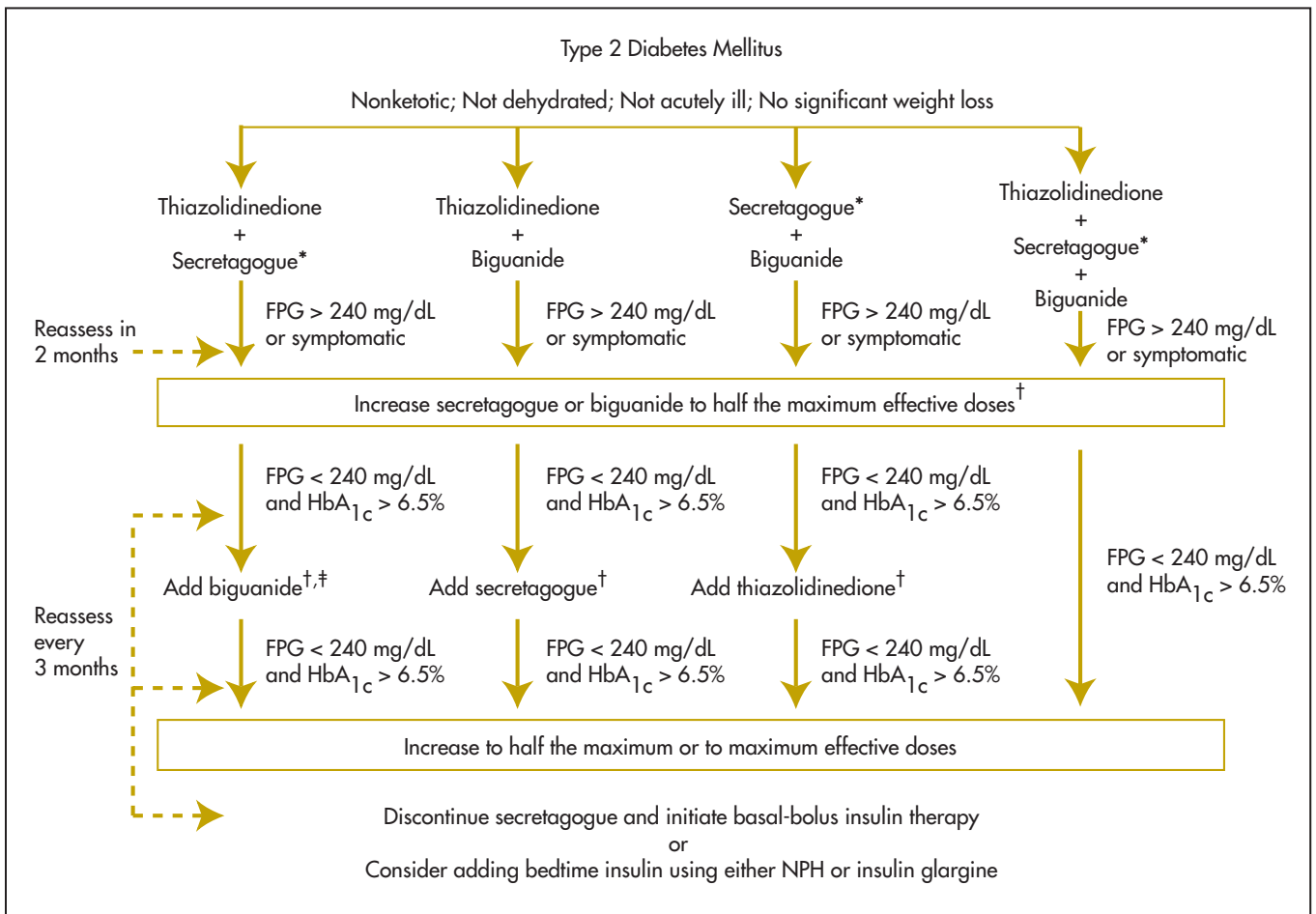


Figure 3. Proposed algorithm for the treatment of type 2 diabetes. At any point, consider referral to endocrinologist for more intensive treatment.

* Sulfonylureas may potentiate or cause hypoglycemia and their use should therefore be reserved for patients with higher blood glucoses.

† Although unlikely, if hypoglycemia occurs, back titrate or discontinue the non-thiazolidinedione agent.

‡ If biguanide is contraindicated, change secretagogue to basal insulin.

FPG = fasting plasma glucose; HbA_{1c} = hemoglobin A_{1c}.

Notably, thiazolidinediones may not exert an effect on HbA_{1c} immediately, so failure to see a response within the first few weeks should not result in their discontinuation. With very high plasma glucoses, consideration should be given to initiating insulin, which may be useful in lessening not only symptoms but also the effects of glucotoxicity on insulin resistance and insulin release from the beta cells.

At maximum effective doses of triple therapy with a thiazolidinedione, a secretagogue, a biguanide, or basal-bolus insulin or, perhaps, a long-acting insulin may be substituted for the secretagogue if the fasting plasma glucose level remains elevated or if the patient is symptomatic. If the patient has had known diabetes for more than about 5 years, then the secretagogue should probably be changed to basal-bolus insulin rather than just a long-acting insulin because they are unlikely to have adequate beta-cell reserve to attain and maintain an HbA_{1c} of < 6.5-7% with only basal insulin and no supplemental prandial insulin (ie, short-acting insulin or secretagogue). Because of the urgency to reduce such high glucose levels that could lead to the dangerous consequences from continued hyperglycemia, it may be recommended that further management be conducted by a specialist.

CONCLUSIONS

A treatment regimen for type 2 diabetes that does not include an agent to improve insulin resistance and preserve beta-cell function is incomplete. The proposed algorithm described here recommends the early use of combination therapy to improve beta-cell function and insulin sensitivity from the onset of therapy. Insulin may be needed if the pa-

tient does not attain glycemic goals on triple oral therapy. In conclusion, the early use of thiazolidinediones may preserve the integrity of the beta cell and does improve insulin sensitivity, the underlying pathologic defect associated with type 2 diabetes. Appropriate management of patients with type 2 diabetes mellitus will slow the progression of disease, reduce the development of diabetic complications, and improve clinical outcomes.

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CME Examination & Evaluation

An Algorithm for Managing Type 2 Diabetes: A Focus on the Disease Process, Not Just the Sugar

Please answer the following questions in the CME Examination Answer Key:

- All of the following can be used to diagnose type 2 diabetes mellitus EXCEPT:
 - Fasting plasma glucose
 - High random glucose with symptoms
 - 2-hour glucose on OGTT
 - Hemoglobin A_{1c}
- Which of the following have NOT proven to be of value in preventing type 2 diabetes mellitus?
 - Diet and/or exercise
 - Weight loss
 - Sulfonylureas
 - Thiazolidinediones
- All of the following are associated with type 2 diabetes mellitus EXCEPT:
 - An increase in hepatic glucose production
 - Insulin resistance at the level of the muscle and fat
 - A relative lack of insulin
 - A complete lack of insulin
- The major site of action of metformin is the:
 - Myocyte
 - Adipocyte
 - Liver
 - Pancreas
- Combination therapy with small doses of 2 or more drugs rather than a large dose of a single drug is associated with:
 - More efficacy
 - Less side effects
 - A cost savings if combined in a single pill
 - Better compliance if combined in a single pill
 - All of the above

CME Examination Answer Key

A score of 70% or higher on the post-test is required to receive CME credit. For each question, please fill in the circle that corresponds to the correct answer for each of the five questions. When you have completed this test sheet, please mail it with a check for \$10 (please reference course number 55-0642 on your check payable to Johns Hopkins-Office of Funded Programs). Valid through August 15, 2005. No credit will be given after this date. You will receive your certificate of completion by return mail in approximately 6-8 weeks.

- | | | |
|------------|------------|--------------|
| 1. A B C D | 3. A B C D | 5. A B C D E |
| 2. A B C D | 4. A B C D | |

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1 2 3 4 5 6 7
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GSK-04103