

Treatment of Type 2 Diabetes: An Update

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Type 2 diabetes mellitus (T2DM) is a chronic disorder of glucose metabolism characterized by impaired insulin secretion and impaired insulin action. It is a serious health condition that affects an estimated 24-million people in the US, almost 8% of the US population.¹ Of those in the US with diabetes, more than 9-million are women and nearly one-third of these women are undiagnosed.² The prevalence of diabetes increases with age, and approximately 20% of persons older than 65 have diabetes. With the increasing life span of women and the continued growth of minority populations with a high prevalence of diabetes in the US, the number of US women who either have or are at high risk for developing diabetes will continue to rise.

Patients with diabetes are at risk for developing serious microvascular and macrovascular complications, including cardiovascular disease (CVD), stroke, renal disease, eye disease and peripheral and/or autonomic neuropathy. Intensive treatment aimed at maintaining glucose concentrations as close to normal as possible will prevent the development or delay progression of these complications. Additional intensive treatment of other cardiovascular risk factors further reduces risk for macrovascular events.

Menopausal Women and T2DM

A consequence of the increasing number of women in the US who have or are at risk for developing diabetes is the increase in the prevalence of diabetes in postmenopausal women. There is evidence from both animal and human studies that menopause is associated with decreased pancreatic insulin secretion and increased insulin resistance,³ and these changes may contribute to an increased risk for

developing T2DM after menopause. However, it is not clear whether these changes are due solely to estrogen deficiency or to a combination of estrogen deficiency and aging.

It is intriguing that both the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) suggest that hormone therapy (HT), either estrogen alone or combined estrogen-progesterone therapy, reduces the in-

cidence of new-onset diabetes.^{4,5} Furthermore, a meta-analysis designed to quantify the effects of HT on components of the metabolic syndrome in postmenopausal women found that HT improved several components, including insulin resistance, lipid levels, blood pressure and abdominal obesity in women without diabetes, and reduced insulin resistance and fasting glucose in women with diabetes.⁶ Taken together, these studies suggest that estrogen deficiency and menopause likely influence the development of insulin resistance and T2DM in peri- and postmenopausal women.

Optimal management of the menopausal woman with T2DM is of great clinical significance due to the fact that a major cause of morbidity and mortality among patients with T2DM is coronary heart disease (CHD),⁷ and because menopausal women represent a population that is already at higher risk for CHD.⁸

Metabolic changes thought to be related to the loss of endogenous estrogen are observed in women during the transition from pre- to postmenopause. These changes include:

- Increased central (intra-abdominal) body fat,
- A more atherogenic lipid profile (increased low-density lipoprotein [LDL] levels and triglycerides, decreased high-density lipoprotein [HDL] levels), and

- Increased glucose and insulin levels (insulin resistance).⁹

Notably, these changes are reminiscent of the metabolic syndrome.

The metabolic syndrome is a constellation of closely related risk factors (central obesity, insulin resistance, dyslipidemia, hypertension, hypercoagulable state and proinflammatory state) that, together, substantially increase a person's cardiovascular risk. It is also notable that the metabolic syndrome increases in prevalence after menopause. Thus, the increased incidence and prevalence of CHD in postmenopausal women, compared to premenopausal women, may, in part, be explained by the metabolic changes associated with menopause. The question of whether menopause increases the risk of CHD independent of normal aging does, however, remains controversial.

Given that postmenopausal women with T2DM are at high risk for developing CVD, a primary focus of treatment in this population is to reduce cardiovascular risk, including optimizing glycemic control and treating all cardiovascular risk factors aggressively. Importantly, recent large randomized trials in patients with T2DM suggest that very tight glycemic control ($HbA_{1c} < 6.5\%$) does not reduce CVD risk in those with established CVD or at high risk for CVD.¹⁰⁻¹²

Intense lifestyle modification—including weight reduction, dietary restriction and exercise—has been shown to improve glycemic control by reducing insulin resistance and by reducing the risk for the development of T2DM in those with impaired glucose tolerance by 58%.¹³ However, lifestyle intervention alone has had limited long-term success in maintaining glycemic goals for most patients with established T2DM, and many people will require medications to maintain glycemic control.



Insulin resistance usually begins many years before the onset of diabetes, worsens with time and then stabilizes.

This review discusses characteristics of the various medications that are currently available for use in the management of T2DM.

Targets for Glycemic Control

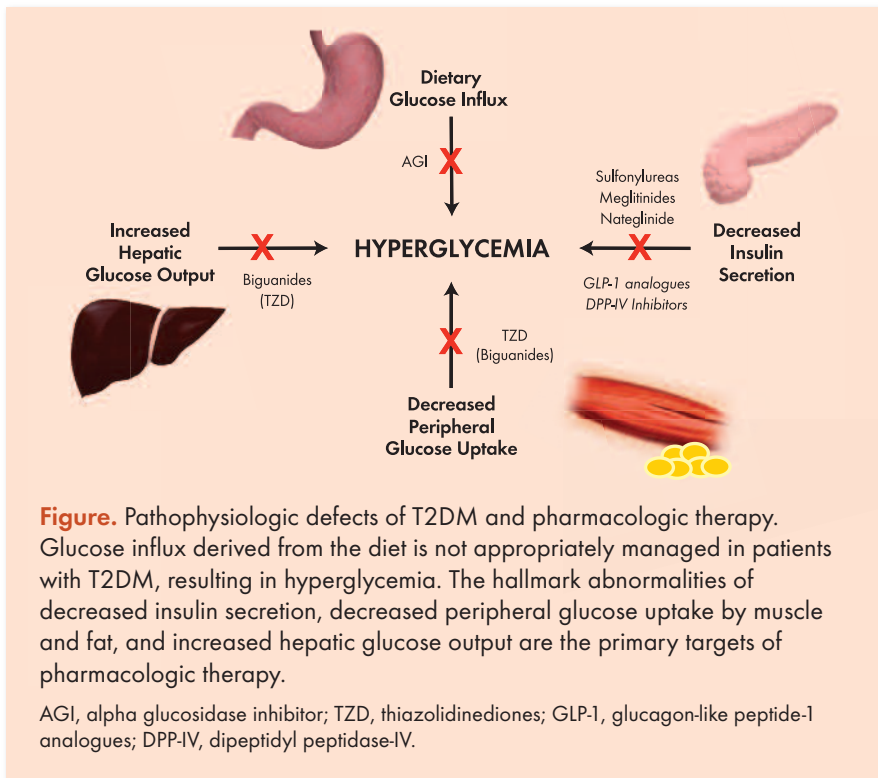
The normal hemoglobin A_{1c} (HbA_{1c}) is 4%–6%. The American Diabetes Association (ADA) recommends a HbA_{1c} target of $< 7\%$, while the American Association of Clinical Endocrinologists recommends a more stringent target of $< 6.5\%$.^{14,15} All organizations agree that glucose levels should be as close to normal as possible, provided that this can be achieved safely (ie, with minimal risk of hypoglycemia) and that targets for glycemic control need to be individualized. Thus, targets are less strict for elderly or frail patients, patients with co-morbidities, those with a history of severe hypoglycemia or hypoglycemic unawareness, and for those whose life expectancy is limited.^{14,15}

Pharmacologic Therapy

Before reviewing the pharmacologic

agents currently available for treatment of T2DM, it is appropriate to briefly review the pathophysiology of the disorder, as the abnormalities exhibited in T2DM are the primary targets of pharmacologic therapy (Figure, page 22).

T2DM is a complex metabolic disorder characterized by two major pathophysiologic abnormalities: 1) insulin resistance, which results in excessive hepatic glucose production and decreased glucose uptake in skeletal muscle and adipose tissue, and 2) impaired insulin secretion by the pancreatic beta cell.¹⁶ Insulin resistance usually begins many years before the onset of diabetes, worsens with time and then stabilizes. Initially, the beta cell is able to compensate for the increasing insulin resistance by increasing its insulin secretion to maintain glucose levels in the normal range. However, insulin secretion ultimately declines and, consequently, glucose levels rise. By the time diabetes is diagnosed, almost 50% of beta cell function has been lost.



Current antihyperglycemic medications are classified by their mechanisms of action, and include the following: 1) insulin sensitizers (biguanides and thiazolidinediones [TZDs]), which reduce insulin resistance at target tissues, 2) insulin secretagogues (sulfonylureas [SUs], metglitinides, glucagon-like peptide-1 [GLP-1] analogues and dipeptidyl peptidase-IV [DPP-IV] inhibitors), 3) alpha glucosidase inhibitors (AGIs), agents that delay gastrointestinal absorption of carbohydrates, and 4) insulin.

Insulin Sensitizers

Biguanides. Metformin is the only biguanide currently available in the US, and was made available in 1995. It is widely used as monotherapy, as well as in combination with SUs and/or TZDs. As monotherapy, metformin typically reduces HbA_{1c} by 1%–2%.^{17–19} Use of metformin as monotherapy does not cause hypoglycemia and is sometimes associated with a small amount of weight

loss.^{17,20,21} It also has been shown to decrease the progression from impaired glucose tolerance to T2DM.¹³

Metformin is effective in improving glycemia and reducing the risk of long-term complications of T2DM. In the United Kingdom Prospective Diabetes Study (UKPDS), treatment with metformin in overweight individuals with T2DM was associated with fewer diabetes-related complications (micro- and macrovascular) and lower mortality rates.²² This drug is a reasonable first-choice medication for the treatment of T2DM, and has been recommended as such by the ADA.

The precise mode of action of metformin is somewhat controversial, but its major effect is in suppressing hepatic glucose production (in the presence of insulin). Metformin does not stimulate insulin secretion, but does increase glucose utilization by peripheral tissues (skeletal muscle, adipose tissue and liver), particularly after meals. These effects of metformin result in decreased fasting and post-

prandial serum glucose concentrations.²³ Fasting blood glucose is typically reduced by approximately 20% (similar effect of sulfonylurea therapy).^{17,20,23} Furthermore, metformin is associated with decreased plasma triglyceride and free fatty acid concentrations, increased plasma HDL cholesterol concentrations and a small decrease in plasma LDL cholesterol concentrations.^{17,20,23}

Metformin is generally well-tolerated, but is associated most commonly with gastrointestinal side effects, including abdominal pain, nausea and diarrhea in up to 50% of patients.¹⁷ These adverse effects may be avoided by titrating the dose slowly and by dosing the medication with food.

Metformin may cause lactic acidosis, but this complication is rare (occurs in fewer than 1 case per 100,000 treated patients) and usually occurs in situations in which the drug is contraindicated.²⁴ In one study, the incidence of lactic acidosis in patients taking metformin was 9 per 100,000 person-years.²⁵ However, in a systematic review of 176 studies (including 17,156 patients taking metformin and 8,943 other patients) there were no cases of lactic acidosis.²⁴ Metformin should be avoided in patients with renal impairment (serum creatinine level ≥ 1.5 mg/dL for men, ≥ 1.4 mg/dL for women) as there is an increased risk for developing lactic acidosis due to diminished clearance of the drug. Similarly, metformin should be temporarily withheld in patients who will receive intravenous iodinated contrast for radiographic studies due to the potential risk of developing contrast-induced nephropathy. Other contraindications include hepatic dysfunction, congestive heart failure, metabolic acidosis, dehydration and alcoholism.

Thiazolidinediones. The TZDs represent a novel class of drugs, which, unlike metformin and SUs, decrease

hepatic fat content and increase insulin sensitivity in muscle. They are highly selective and potent agonists of peroxisome proliferator-activated receptor-gamma (PPAR-gamma), the nuclear receptor that is essential for normal adipocyte differentiation and proliferation, as well as fatty acid uptake and storage.^{26,27} It is through PPAR-gamma that TZDs mediate increased glucose-stimulated uptake in peripheral tissues and increased insulin sensitivity in hepatic and adipose tissue, resulting in insulin-dependent suppression of endogenous glucose production in the liver and insulin-dependent suppression of free fatty acid concentrations (as reviewed by Bailey).²⁰

In January 1997 the first TZD, troglitazone, was approved as a glucose-lowering therapy for patients with T2DM. This medication was, however, subsequently withdrawn from the market in March 2000 due to its association with hepatotoxicity. The two currently available TZDs, rosiglitazone and pioglitazone, were approved in the US in 1999. They are approved for use in the treatment of hyperglycemia, either as monotherapy or in combination with SUs or metformin. Both drugs also have been approved for use in combination with insulin, provided certain precautions are followed. However, due to a higher risk of myocardial ischemia and congestive heart failure observed in several controlled, double-blind clinical trials in which rosiglitazone was added on to established insulin therapy, co-administration of rosiglitazone with insulin is not recommended (Avandia product label revision, 10/20/2008; <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>; search Avandia label information).

Findings from placebo-controlled trials suggest that both pioglitazone and rosiglitazone are moderately ef-

fective in achieving glycemic control; they lower fasting and postprandial glucose concentrations as well as free fatty acid concentrations.²⁸⁻³¹ At maximum doses, TZD therapy lowers HbA_{1c} by 1.0%–1.5%.^{29,30} However,

Both weight gain and edema are more common in patients who take TZDs in combination with insulin, and these patients also have an increased incidence of heart failure.^{32,33}

the onset of action of these drugs is slower than that of other oral medications, and may take up to 3 months to achieve full effect.

The use of TZDs as monotherapy or in combination with metformin, SU or insulin is associated with a weight gain of 2–4 kg.^{27,32} A subgroup of patients also develop fluid retention and plasma volume expansion, which leads to peripheral edema.³² Peripheral edema has been reported in 4%–6% of patients taking TZDs, compared to 1%–2% of patients receiving placebo or other hypoglycemic therapies.³² Both weight gain and edema are more common in patients who take TZDs in combination with insulin, and these patients also have an increased incidence of heart failure.^{32,33} Thus, patients with advanced congestive heart failure (CHF) should not be treated with TZDs.

In a recent meta-analysis, rosiglitazone use was found to be associated with an increased risk of myocardial infarction.³⁴ However, a study designed to evaluate the effect of rosiglitazone on cardiovascular outcomes (RECORD study) showed no significant increase in cardiovascular events other than CHF with the use of the drug. These results were published in an interim report of the study³⁵ and were also reported at the 69th Scientific Sessions of the ADA (New Orleans, June 5–9, 2009). Two additional

studies evaluating the impact of intensive glucose lowering on cardiovascular outcome also did not show that rosiglitazone use was associated with increased cardiovascular risk (ADVANCE and VA Diabetes trial).^{11,12}

Despite the above findings, the drug carries a warning that states, “A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 patients), comparing Avandia to some other approved oral anti-diabetic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.”

Pioglitazone has not been associated with increased cardiovascular events other than CHF (related to edema/fluid retention, which is known to occur with TZDs). Liver toxicity observed with troglitazone does not seem to be a class effect. In 13 double-blind studies, 1.91% of 2,510 patients, 0.26% of 1,526 patients and 0.17% of 3,503 patients receiving troglitazone, pioglitazone and rosiglitazone, respectively, had alanine aminotransferase (ALT) values that were more than 3 times the upper limit of the reference range.³⁶ Furthermore, 0.68% of patients taking troglitazone had ALT levels more than 10 times the upper limit of normal, compared to none of the patients who were taking rosiglitazone and pioglitazone.³⁴

Insulin Secretagogues

Insulin secretagogues consist of SUs and the non-SU insulin secretagogues (metglitinides, GLP-1 analogues and DPP-IV inhibitors).

Sulfonylureas. Available since 1955, SUs are the oldest class of oral hypoglycemic agents. This class of medications promotes insulin secretion by binding adenosine triphosphate (ATP)-sensitive potassium channels localized on the cell membranes of pancreatic beta cells. SU binding leads to inhibition of these potassium channels, which alters the resting potential of the cell, causing calcium influx and stimulation of insulin secretion. The net effect is insulin release at lower-than-normal glucose thresholds and increased responsiveness of beta cells.

SUs are approved for use and are effective both as monotherapy and in combination with all other oral agent classes (except the non-SU secretagogues) and insulin. When compared to placebo, SU therapy reduces blood glucose concentrations by approximately 20% and lowers HbA_{1c} by 1%–2%; however, their efficacy has been observed to decrease over time.^{13,22,37} Second-generation SUs (glipizide, glyburide) are more potent and safer than first-generation SUs (chlorpropamide, tolbutamide, acetohexamide and tolazamide) and, thus, are most commonly used. The newest member of this class is the third-generation SU glimepiride, which varies slightly in its binding specificity.

SUs are generally well tolerated, but are associated with two clinically significant adverse effects. First, these medications are associated with weight gain of approximately 5–10 pounds (2–5 kg),^{22,38} which is problematic for many patients with T2DM who are already overweight and struggling to lose weight. Second, SUs are associated with hypoglycemia, which is

more likely to occur in the elderly, in patients with worsening renal function and in those with irregular meal schedules. Hypoglycemia also may be potentiated when SUs are taken in combination with insulin sensitizers (ie, metformin, TZDs), insulin or ACE inhibitors. Furthermore, SUs are metabolized by the liver and cleared by the kidneys, and should thus be used cautiously in patients with significant impairment of renal and/or hepatic function.

Metglitinides. Metglitinides (repaglinide and nateglinide) are short-acting, glucose-lowering non-SU insulin secretagogues approved for use as monotherapy or in combination with metformin. These medications typically lower HbA_{1c} by 0.5%–1.0%^{39,40} and cause less weight gain than SUs.⁴¹

The meglitinides are structurally different from the SUs, but their mechanism of action is similar to that of SUs in that they also stimulate insulin secretion by regulating ATP-dependent potassium channels in pancreatic beta cells.⁴² Meglitinides are distinguished from SUs by their rapid onset of action and short metabolic half-life; for this reason they must be administered more frequently (usually 3 times daily with meals).

The benefit of using this class of medications is that post-prandial glycemic excursions are attenuated since the drug is taken at meal time and leads to increased insulin secretion immediately after meal ingestion; accordingly, these medications should be skipped if a meal is missed. Another benefit associated with the use of these medications is that late post-prandial hypoglycemic episodes are decreased due to decreased insulin secretion several hours after the meal.^{40,43} Thus, this class of medication may be most useful in patients with irregular eating patterns or with post-prandial hyperglycemia.

Of note, repaglinide and nateglinide are hepatically metabolized and renally cleared and should therefore be used cautiously, particularly in the setting of impaired liver function. Repaglinide and nateglinide appear to have similar clearance in patients with mild-to-moderate renal dysfunction (creatinine clearance [CrCl], 40–80 mL/min), but caution may be indicated in patients with severe renal function impairment (CrCl, 20–40 mL/min). Of note is that studies were not conducted in patients with CrCls below 20 mL/min, or in those with renal failure requiring hemodialysis.^{44,45} As with SUs, hypoglycemia may occur with these medications and is dose-related.⁴⁶ The risk of hypoglycemia also is increased if these drugs are used with insulin.

GLP-1 analogues and DPP-IV inhibitors. The newest class of medications for T2DM augments incretin action either by acting as an incretin mimetic (GLP-1 receptor agonist) or as an incretin enhancer (inhibitor of DPP-IV activity). Incretins are gastrointestinal peptides that are secreted in response to enteral nutrient ingestion and affect glucose homeostasis via several mechanisms (discussed below).

GLP-1 is a member of the incretin family of peptides and is secreted from cells in the small intestine when food enters the stomach. It has been shown to stimulate glucose-dependent insulin secretion, to inhibit glucagon secretion, to delay gastric emptying, to increase satiety and, possibly, increase pancreatic islet cell mass.⁴⁷ Of note, levels of GLP-1 have been shown to be reduced in individuals with T2DM. Thus, treatment of T2DM with GLP-1 would seem to be a reasonable strategy. However, GLP-1 has a half-life of only a few minutes since it is quickly degraded by the enzyme dipeptidyl-peptidase type IV. Therefore, GLP-1 itself cannot be used therapeutically.

Exenatide. Exenatide is the first GLP-1-based therapy to be FDA approved for the treatment of T2DM. It was approved in April 2005 as an adjunctive medication for patients with T2DM that is poorly controlled on other oral medications. It is not currently approved for use with insulin therapy. Exenatide is a synthetic form of Exendin-4, which is a naturally occurring GLP-1 receptor agonist that was originally isolated from the venom of the Gila monster (*Heterodermasuspectum*).⁴⁸ Exenatide mimics all of the glucose-lowering actions of GLP-1 following parenteral administration and exhibits a long half-life due to its resistance to DPP-IV degradation.^{49,50}

When added to SUs, thiazolidinediones and/or metformin, treatment with exenatide results in additional lowering of HbA_{1c} by 0.5%–1%.^{51–53} Exenatide is available in prefilled syringes that contain 1 month's supply of either 5-mcg or 10-mcg doses and is administered subcutaneously twice daily immediately before or within 1 hour prior to the morning and evening meals. Patients are usually started on the 5-mcg dose, which is then increased to 10-mcg after 1 month, if tolerated.

Nausea is a common adverse effect, but is generally mild to moderate and usually wanes with duration of therapy. Nausea also can be reduced with dose titration. Mild-to-moderate hypoglycemic events may occur when exenatide is given with an SU;⁵² thus, in a patient already taking an SU, it is recommended that the SU dose be decreased when exenatide is added. The drug is not recommended in patients with CrCl < 30 mL/min.

Sitagliptin. Sitagliptin is a DPP-IV inhibitor approved in October 2006 for the treatment of T2DM; it can be prescribed as monotherapy; in combination with metformin, a TZD

or SUs; or as a third agent in an SU+metformin regimen.^{54–56} DPP-IV is a ubiquitous enzyme that deactivates a variety of peptides, including GLP-1. An inhibitor of the DPP-IV enzyme would thus increase the half-life of innate GLP-1 in patients with T2DM. (Refer to Januvia product labeling, available at www.januvia.com).

The efficacy of glucose lowering is dependent on the degree of hyperglycemia; after 24 weeks of treatment, the average HbA_{1c} reduction is 0.7% in patients with a baseline A_{1c} < 8.0, and the reduction is 1.4% in patients with a baseline A_{1c} > 9.0. Similar HbA_{1c} reductions were observed after 24 weeks of treatment with sitagliptin as monotherapy or in combination with metformin or pioglitazone.^{54,55,57}

The usual dose is 100 mg once daily administered orally. Dose reduction is recommended in patients with moderate-to-severe renal insufficiency (glomerular filtration rate [GFR] < 30–50 mL/min) and 25 mg for those with severe renal insufficiency (GFR < 30 mL/min) because the drug is excreted mainly in the urine. Sitagliptin is generally well tolerated and not associated with hypoglycemia or weight gain when used as monotherapy or in combination with insulin sensitizers; it may, however, be associated with hypoglycemia if used in combination with SUs, and an initial reduction in SU dose is, therefore, recommended in such instances.^{58,59}

Alpha Glucosidase Inhibitors

The AGIs (acarbose, miglitol) were introduced in 1996 and are approved for use as monotherapy and in combination with SUs for the treatment of hyperglycemia. Unlike the other classes of drugs described earlier, AGIs do not target a pathophysiologic defect of T2DM. Instead, these drugs competitively inhibit an enzyme called alpha glucosidase, which acts

to break down disaccharides and complex carbohydrates in the brush border of the proximal small intestinal epithelium, thereby delaying intestinal carbohydrate absorption and decreasing postprandial glucose excursions.⁴⁷

As a class, these medications are attractive in that they are not associated with hypoglycemia or weight gain. Small reductions in triglyceride and postprandial insulin levels have also been observed.⁴⁷ AGIs are, however, less effective than metformin or SUs in lowering HbA_{1c}, with an average lowering effect of 0.5%–1%, compared to placebo-treated subjects.^{39,47,48} Given their mechanism of action, it is not surprising that the greatest blood-glucose-lowering effect of AGIs is on postprandial levels, and that there is little effect on fasting levels.

AGIs are given orally three times a day at the start of each meal. Adverse effects of AGIs are dose-dependent and include flatulence, abdominal discomfort and diarrhea, which often results in discontinuation of the drug.⁴⁸

Insulin

Due to the progressive nature of diabetes and the gradual loss of beta cell function, many patients will eventually require insulin therapy to achieve glycemic targets. Insulin therapy should be considered in patients with suboptimal glycemic control on oral agents and can be used alone or in combination with oral medications. (An overview of insulin therapy is beyond the scope of this review.)

Conclusions

T2DM is increasingly common and is associated with the development of both microvascular and macrovascular complications. Intensive treatment to achieve improved glycemic control will prevent the development or delay progression of these complications. The initial approach in the management

of T2DM should involve lifestyle modification, including weight reduction, dietary restriction and exercise. Further management with medications will likely be necessary. Several classes of drugs, all with advantages and disadvantages, are currently available; choice of medication should be individualized.

In the postmenopausal woman with diabetes, CHD is a major concern as both menopause and diabetes are associated with increased cardiovascular risk. Thus, optimizing diabetes management and glycemic control should be a primary focus of treatment in this population in order to reduce cardiovascular risk.

An important consideration in the management of diabetes in perimenopausal women is the possibility of glycemic swings, which may occur in the setting of fluctuating insulin sensitivity associated with changing hormone levels during the transition to menopause. Thus, more frequent blood glucose monitoring and careful medication adjustments may be required during the perimenopausal period. ■

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