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ABOUT CADRE

CADRE (the Council for the Advancement of Diabetes Research and Education) is a nonprofit organization committed to reducing the burden of diabetes by providing health care professionals with scientific information and educational initiatives designed to translate research into effective clinical practice.

Diabetes poses a number of unique challenges to women. With that in mind, *CADRE's Current Diabetes Practice* is pleased to offer this issue devoted to topics relevant to women. Included are articles that discuss the importance of screening women with polycystic ovary syndrome for impaired glucose tolerance or type 2 diabetes mellitus (T2DM); diagnosis of diabetes during pregnancy and appropriate treatment strategies; diabetes and coronary heart disease risk in postmenopausal women; and T2DM as a skeletal fracture risk factor in postmenopausal women.

Also, turn to page 8 to read about CADRE's newest educational initiative: "Cases in Success." These case studies provide learning opportunities in a variety of therapeutic areas, and completion of the 3 cases in each therapeutic area will qualify for CME credit.

We hope you find the articles in this issue of *CADRE's Current Diabetes Practice* informative, and that you will participate in "Cases in Success."

▲ Melissa Miles, Executive Director

GUEST EDITORIAL

POLYCYSTIC OVARY SYNDROME: AN OPPORTUNITY FOR PREVENTION OF DIABETES

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adiposity, manifest profound insulin resistance comparable to that of patients with type 2 diabetes mellitus (T2DM).

In part as a consequence of insulin resistance, women with PCOS are one of the groups at highest risk for development of T2DM. The prevalence of T2DM in PCOS is 7% to 10%, which is 10-fold higher than that in comparably young healthy women. The prevalence of impaired glucose tolerance (IGT)

Continued

The best strategy for defeating diabetes is to prevent it in the first place, and a key to prevention is early identification of individuals at high risk. Arguably, to no other group is this maxim more applicable than women with polycystic ovary syndrome (PCOS).

PCOS affects 5% to 10% of women of childbearing age (ie, between 3.5 and 5.5 million young women in the United States) and is characterized not only by ovulatory dysfunction and androgen excess, but also by a form of insulin resistance that appears to be intrinsic to the syndrome. As a result, lean women with PCOS are as insulin resistant as obese normal women. Obese women with PCOS, who have both the inherent insulin resistance of the syndrome and an added burden of insulin resistance due to their excess

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CADRE's
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ranges from 20% to 35% in PCOS. Hence, it is estimated that 30% to 50% of obese women with PCOS will develop glucose intolerance (either IGT or T2DM) before the age of 30 years. Stating this startling statistic in another way, approximately 1 million young women in the United States have diabetes directly attributable to PCOS, and 3 million have IGT. Because of their youth, these women often are not screened, and their glucose intolerance goes undetected until they become symptomatic.

It is precisely to identify women with undiagnosed diabetes or IGT that the position statements of several professional societies, including the American Diabetes Association and the American Association of Clinical Endocrinologists, recommend that women with PCOS be screened for glucose intolerance. The most comprehensive of these position statements was recently issued by the Androgen

Excess and PCOS (AE-PCOS) Society (see Table 1 on page 3). This position statement, which focuses exclusively on PCOS and thoroughly reviews the relevant literature, recommends that women with PCOS be screened with an oral glucose tolerance test (OGTT) at initial diagnosis and every 2 years thereafter (annually, if IGT is discovered at baseline).

It should be noted that an AE-PCOS minority opinion questioned the need to screen lean women with PCOS. As expected, obesity increases the risk of diabetes in PCOS, but evidence suggests that even lean women with PCOS are at increased risk of glucose intolerance compared with matched healthy women. For example, data from the Nurses' Health Study II, which followed 101,073 women for 8 years, indicate that lean women with oligomenorrhea (most of whom likely have PCOS) develop diabetes at twice the rate of lean eumenorrheic women. Therefore, screening lean women with PCOS with an OGTT seems reasonable given the low cost, minimal risk, and opportunity for prevention when glucose intolerance is identified.

Why screen for glucose intolerance with an OGTT rather than with a fasting glucose or A1C level? Multiple studies have shown that adult women and adolescent girls with PCOS can have fasting glucose or A1C levels in the normal range but demonstrate IGT or frank diabetes during an OGTT. The bottom line is the following: glucose intolerance in a number of women with PCOS will be missed if an OGTT is not performed.

While the necessity of performing an OGTT as a screening test for glucose intolerance in PCOS is amply supported by the literature, less clear is the optimal interval for repeating the OGTT. Lacking additional data, the recommendation of the AE-PCOS Society of repeating the test every 2 years is based on expert opinion, and in general I concur. However, studies need to be performed to determine if women with PCOS who have normal glucose tolerance (NGT) at baseline

and lack a family history of diabetes, lose weight, or are treated with metformin require the recommended frequency of testing. Also, while an A1C is an inadequate screening test for glucose intolerance in PCOS, would it have utility as a follow-up tool to detect a deterioration in glucose tolerance? To wit, if the OGTT and A1C are distinctly normal at baseline, would it be reasonable to retest with an OGTT only if the A1C has increased? These questions will need to be addressed by future studies. At present, it remains prudent to follow the recommendations of the AE-PCOS Society for initial and follow-up screenings for glucose intolerance.

The AE-PCOS Society guidelines do not address the issue of screening for glucose intolerance if a woman with PCOS is started on an oral contraceptive pill. Several studies indicate that administration of an oral contraceptive pill may aggravate insulin resistance and induce glucose intolerance in women with PCOS. Similarly, as a result of worsened insulin resistance, serum triglycerides may increase as well. For this reason, I recommend repeating an OGTT and serum lipid profile in a woman with PCOS 3 to 4 months after instituting treatment with an oral contraceptive pill.

Approximately 1 million young women in the United States have diabetes directly attributable to PCOS.

Once IGT is diagnosed in a woman with PCOS, is it possible to forestall or prevent diabetes? The only study to directly address this issue specifically in women with PCOS was a small retrospective chart review of women with PCOS and either NGT or IGT who had been treated with metformin and general advice on a portion-controlled diet and regularly scheduled exercise. Notably, none of the women developed diabetes during the nearly 3.5 years of observation; over half the

Continued

women with IGT reverted to NGT; and the annual conversion rate from NGT to IGT was only one-tenth of that reported in the literature for women with PCOS. However, this study suffers from the usual limitations of small retrospective studies, such as lack of a control group, limited statistical power, and possible selection bias.

It is unfortunate that a large, prospective, randomized, controlled trial to address this issue is unlikely to be conducted specifically in women with PCOS. Instead, as clinicians we need to rely on data obtained from existing large trials performed in other patient populations, such as the Diabetes Prevention Program (DPP). This study of individuals with IGT and a positive family history of diabetes or with a history of gestational diabetes demonstrated that both intensive lifestyle modification (ie, diet and exercise) and administration of metformin reduced progression to diabetes, with lifestyle modification providing the more robust protection. The question has been raised whether metformin truly prevented diabetes or simply masked its presence in the DPP. In this regard, it is noteworthy that the number of individuals who developed diabetes when metformin was discontinued was less than would have been expected if masking had been the sole effect.

It is reasonable to extrapolate these findings to women with PCOS. Indeed, given the epidemiology of PCOS and diabetes, it seems likely that a large number of the young women in the DPP had PCOS. The findings of the DPP highlight the importance of early identification of IGT in women with PCOS, since treatment with lifestyle modification, metformin, or both interventions combined would be expected to reduce progression to diabetes. In this regard, the recent demonstrated safety of metformin in women with gestational diabetes is reassuring, since women with PCOS may conceive (intentionally or not) while taking metformin.

Should women with PCOS who have NGT at baseline be treated with life-

style modification or metformin to prevent progression to IGT? As noted earlier, data regarding this issue are scant. Nonetheless, the prescription of diet and exercise is not only reasonable and safe, but may also address several of the other metabolic and reproductive abnormalities of PCOS. For example, weight loss has been shown to improve ovulatory function, enhance fertility, and reduce circulating androgens in women with PCOS. However, while diet-induced weight loss and exercise are effective treatments for PCOS, they may be difficult to achieve in clinical practice. For this reason, treatment with metformin (in addition to lifestyle modification) has become increasingly common in the management of women with PCOS, including women with NGT. In fact, PCOS is now the second most common reason for prescribing metformin in the United States, the first being diabetes.

The above observations become increasingly important given the rising

incidence of obesity among adolescent girls. Just as T2DM is becoming more common in young girls as a result of the obesity epidemic, it appears the incidence of PCOS during the teen years is on the rise as well. It is not surprising that diabetes and PCOS should increase in tandem, but it is a call to arms. The importance of diagnosing PCOS at the earliest possible age, screening for glucose intolerance with an OGTT, and instituting at a minimum preventive treatment in the form of lifestyle modification, cannot be overemphasized. While studies in adolescent girls with PCOS are limited, they suggest that the combination of lifestyle modification and treatment with metformin may be most successful in inducing weight loss and ameliorating the metabolic and reproductive abnormalities of the syndrome.

Finally, I would note that it is not difficult to diagnose PCOS. The simple question, "How many menses do you have in a year?" is an excellent

Continued

Table 1. Androgen Excess Society screening and treatment recommendations for IGT in PCOS

- All patients with PCOS, regardless of BMI, should be screened for IGT using a 2-hour OGTT (see *Minority Report*, below)
- Patients with NGT should be rescreened at least once every 2 years or earlier if additional risk factors are identified
- Patients with IGT should be screened annually for development of diabetes
- The mainstay of treatment for all patients with PCOS and IGT should be intensive lifestyle modification as well as weight loss in obese patients
- Insulin-sensitizing agents, such as metformin and thiazolidinediones, should be considered in patients with PCOS and IGT
- Adolescents with PCOS should be screened for IGT using a 2-hour OGTT repeated once every 2 years; if IGT develops, they should be treated with intensive lifestyle modification, and treatment with metformin should be considered

Minority Report: A few members of the Androgen Excess Society Board did not agree with this recommendation, as evidence on risk of IGT in lean PCOS patients is limited and still emerging; they recommend OGTT screening for IGT and type 2 diabetes mellitus only in obese PCOS patients (BMI ≥ 30 kg/m²) or screening lean patients only if at least one additional diabetes risk factor (eg, advanced age, family history of diabetes, or previous GDM) is present.

BMI, body mass index; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; PCOS, polycystic ovary syndrome; OGTT, oral glucose tolerance test

Adapted from Salley KES, et al. *J Clin Endocrinol Metab.* 2007;92:4546-4556.

screening tool for identifying women with the syndrome. If a woman has eight or fewer menses a year, the likelihood of PCOS is high. More importantly, we now know that the same question will also identify women at great risk for diabetes.

Therefore, it is incumbent on us as clinicians concerned about diabetes to be on the alert, to make the diagnosis of PCOS, and to then screen women with the syndrome appropriately for glucose intolerance using an OGTT and to institute reasonable treatment interventions to prevent or delay the development of diabetes. Prevention is always the best treatment, and this is especially true in the case of PCOS and diabetes.

Dr. Nestler is a consultant to Bristol-Myers Squibb.

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CONTROVERSIES IN CARE

FROM THE PEDERSEN HYPOTHESIS TO HAPO, NORMOGLYCEMIA IS STILL THE OBJECTIVE FOR DIABETES IN PREGNANCY

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As the prevalence of diabetes rises around the world, more women are diagnosed with diabetes during pregnancy. Several recent articles in the field of pregnancy in diabetes have begun to clarify the relationship between hyperglycemia and neonatal outcomes. The goal of this article is to present an overview of diabetes in pregnancy, treatment goals, and strategies, with an emphasis on recent articles in the literature.

It is estimated that the prevalence of gestational diabetes mellitus (GDM) is between 1% and 14% and mirrors type 2 diabetes mellitus (T2DM) rates in a population. Certainly, specific ethnic groups are more predisposed to developing T2DM. In fact, in some cases, unrecognized T2DM diagnosed during pregnancy could obscure the true GDM prevalence in the population. A recent Australian study examined GDM prevalence between 1995 and 2005 in the province of New South Wales. Over a period of 11 years, the incidence of GDM increased by 45% after adjustment for maternal age and country of birth. This increasingly ethnically diverse region endorsed universal screening for GDM in 1998, which likely contributed to increased reporting. Their data established an association between socioeconomic status and the diagnosis of GDM and confirmed maternal age as a risk factor. Other

previously described risk factors for GDM include smoking, prior history of GDM, family history of T2DM, and high body mass index (BMI).

Despite years of study, there is no international consensus on the best screening test for GDM, and discussion of this is beyond the scope of this article. Universal screening for GDM has not yet been adopted in the US, although it should be noted that the Australasian Diabetes in Pregnancy Society has recommended universal screening. The 2001 American College of Obstetricians and Gynecologists and the 1997 American Diabetes Association practice guidelines state that some women may not derive benefit from GDM screening if certain “low risk” criteria are met. There is agreement that women with a high BMI or prior history of GDM should be screened at the first prenatal visit. However, screening all other women between 24 and 28 to 32 weeks of gestation both covers a broad range of time and excludes the majority of time spent pregnant. If women are screened by 32 weeks at the latest, that leaves approximately 6 weeks to establish good glycemic control. If the Pedersen hypothesis of maternal hyperglycemia driving fetal insulin production and subsequent growth is true, then starting to institute euglycemic measures between 24 and 32 weeks seems a bit delayed. Fetal insulin production is thought to begin between 11 and 15 weeks’ gestation, and macrosomia may begin as early as 20 weeks. Thus, if the mother is diagnosed with T2DM after 24 weeks, the preexisting hyperglycemia has already affected first trimester organogenesis. There are no randomized controlled trials at this time that have specifically studied screening during the early first trimester versus 24 to 32 weeks’ gestation. However, studies of glycemic control in early pregnancy of women already diagnosed with diabetes support the association between earlier good glycemic control and improved birth outcomes.

The recent publication of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study may provide

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further clarity on the impact of even mild hyperglycemia during pregnancy. More than 20,000 pregnant women were recruited over approximately 5 years to participate in this investigator-initiated prospective observational study. Fasting, 1-hour, and 2-hour blood glucose results during a 2-hour 75-g oral glucose tolerance test (OGTT) were divided into ranges for each time point (see Table 1) These ranges were then compared with prespecified birth outcome measures such as birth weight over the 90th percentile for gestational age, primary cesarean delivery, clinical neonatal hypoglycemia, or a cord-blood serum C-peptide level over the 90th percentile.

Of particular interest was the strong association observed in HAPO between higher blood glucose levels at all OGTT time points and C-peptide cord blood values above the 90th percentile. Blood glucose values in the highest range increased the odds ratio of a C-peptide level above the 90th percentile to 7.65. Further, elevated blood glucose at all time points during the OGTT revealed an increasing risk of birth weight above the 90th percentile, with a frequency of 5.3% in the lowest blood glucose group and 26.3% in the highest.

A second HAPO publication reported on neonatal anthropometrics. Skin fold and percent body fat were measured 72 hours after birth in 19,885 babies. There was a significant association between prior 1-hour OGTT blood glucose levels and neonatal skin fold measurements above the 90th percentile, even after adjusting for maternal age. Both of these data sets support an association between mild hyperglycemia and macrosomia with its attendant complications.

The Diabetes in Early Pregnancy trial and a subsequent study by Combs and associates demonstrated the positive impact of glycemic control in the first trimester on fetal macrosomia in women with diabetes prior to conception. However, malformation rates in recent studies of treated diabetic pregnancies have still not approached those of pregnancies not impacted by diabetes.

Table 1. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: blood glucose categories as defined by time points of the 2-hour 75-g OGTT

Blood glucose category	Blood glucose levels (mg/dL)		
	Fasting	1-hour	2-hour
1	<75	≤105	≤90
2	75–79	106–132	91–108
3	80–84	133–155	109–125
4	85–89	156–171	126–139
5	90–94	172–193	140–157
6	95–99	194–211	158–177
7	≥100	≥212	≥178

OGTT, oral glucose tolerance test

Adapted from Metzger BE. *New Engl J Med.* 2008;358:1991-2002.

In these trials, A1C levels <7% were considered good glycemic control. Despite this level of A1C, a study in the Netherlands reported a 6.4% incidence of congenital malformations when the first trimester A1C was between 6.1% and 7%, which is higher than congenital malformation rates in women without diabetes. Likewise, Macintosh and colleagues reported a malformation prevalence of 46 in 1000 births in British women with diabetes compared with 21 in 1000 births in the general European population. In that trial, however, only 37% of women had an A1C <7% by the end of the first trimester.

In response to these data, trials with continuous glucose monitoring (CGM) were conducted to determine the proportion of time spent with blood glucose >140 mg/dL. At 8 weeks' gestation in women with type 1 diabetes mellitus or T2DM, about 10 hours per day were spent with blood glucose levels >140 mg/dL. By the end of pregnancy, despite CGM coupled with intensive monitoring and support, only 16 hours per day were spent with values <140 mg/dL. Another study recently assessed the impact of CGM versus standard prenatal care on A1C in the second and third trimesters. Between 32 and 36 weeks, a significantly lower A1C and lower macrosomia rates were described in the CGM group.

More traditional interventions to reduce blood glucose include carbohydrate restriction to <40% of daily caloric

intake. Major and associates elegantly demonstrated that a diet low in carbohydrate during pregnancy was a safe and effective method to significantly reduce the incidence of large-for-gestational age infants.

A 1-hour postprandial blood glucose >120 mg/dL most closely correlates with macrosomia; we advocate for fasting blood glucose values between 70 and 90 mg/dL and 1-hour postprandial blood glucose values <120 mg/dL. If these goals cannot be achieved by diet alone in GDM, or if T2DM is suspected, insulin should be started. Insulins aspart and lispro have been safely used in pregnancy for many years, along with NPH insulin for basal coverage. Sufficient data are not available to support the use of insulin glargine in pregnancy, especially with regard to stimulation of antibody formation. Studies with insulin detemir are ongoing.

The use of oral agents for blood glucose control has been debated for many years. Sulfonylureas have been proposed by some for control of hyperglycemia in GDM. However, these agents do not sufficiently control 1-hour postprandial blood glucose values because their activity peaks several hours after administration.

Metformin, known to cross the placenta, is another contested oral agent. Rowan and colleagues published a randomized open-label superiority trial of this drug

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in comparison to insulin therapy. Women with GDM, as defined by the Australasian Diabetes in Pregnancy Society criteria, were enrolled in this study. The trial was underpowered in both the metformin and insulin groups. Further, 46.3% of women in the metformin arm required supplemental insulin, started at a median of 20.4 days after randomization to metformin. The composite endpoint of six neonatal outcomes was not statistically different in the 2 groups. A follow-up 75-g OGTT was performed in 552 women 6 to 8 weeks postpartum. The test was diagnostic for impaired glucose tolerance (IGT) or diabetes in 23.0% of the women in the metformin group and 20.6% of the women in the insulin group. Despite the similar primary outcome for the 2 groups, it appears that many women required insulin. Postpartum OGTT results suggested that some women with T2DM were misdiagnosed with GDM. Follow-up to evaluate long-term outcomes of metformin exposure in these infants is planned when they are 2 years old. Therefore, in our opinion, this trial further strengthens the case for insulin use as a first-line therapy during pregnancy.

Summary

Our understanding of the impact of even seemingly minor elevations of blood glucose in pregnancy has expanded in the past year. Insulin continues to be the best medication to treat hyperglycemia during pregnancy, especially 1-hour postprandial blood glucose levels. Future studies using CGM could further elucidate methods to limit hyperglycemic excursions and improve neonatal outcomes. Perhaps these innovative data will lead to further research on earlier diabetes screening in gestation, consensus on a more distinct definition of GDM, and agreement on lower thresholds for diagnosis of diabetes in pregnancy.

Neither Dr. Semrad nor Dr. Jovanović have any commercial relationships to disclose related to the content of this article.

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DIABETES AND MENOPAUSE

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Introduction: Diabetes and Coronary Heart Disease Risk in Women

The prevalence of type 2 diabetes mellitus (T2DM) among US adults is estimated at approximately 8% of the population, or 23.6 million persons. Although T2DM prevalence is similar among men and women, women with diabetes are at substantially greater risk for coronary heart disease (CHD) and CHD-related mortality than are men with diabetes. Table 1 outlines relative risk (RR) data from more than 20 years

of follow-up among women in the Nurses' Health Study (mean age range, 60 to 66 years) and a parallel 10-year follow-up of men in the Health Professionals Follow-up Study (HPFS; mean age range, 54 to 64 years). Both studies found that RR increased with diabetes duration, but the increase was steeper for women than for men. Furthermore, a meta-analysis of 37 studies examining T2DM and fatal CHD conducted by Huxley and colleagues indicated that T2DM not only eliminates the gender gap in CHD that traditionally favors women, but is associated with a 50% increased RR of CHD death in women compared with men. It appears likely the increased risk experienced by women with T2DM is due to a greater prevalence of cardiovascular (CV) risk factors such as hypertension, dyslipidemia (high low-density lipoprotein cholesterol and/or low high-density lipoprotein cholesterol), obesity, and high levels of inflammatory markers.

These data demonstrate why CHD is a primary concern for postmenopausal women with diabetes. Given this

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Table 1. Age-adjusted relative risk for fatal coronary heart disease

Persons with a history of:	Relative risk	
	Women	Men
T2DM, no CHD	8.7	3.8
CHD, no T2DM	10.6	7.9
T2DM and CHD	25.8	13.4

Data from a 20-year follow-up study of women in the Nurses' Health Study (mean age range 60 to 66 years) and a parallel 10-year follow-up study of men in the Health Professionals Follow-up Study (mean age range 54 to 64 years).

CHD, coronary heart disease;
T2DM, type 2 diabetes mellitus

Adapted from Hu FB, et al. *Arch Intern Med*. 2001; 161(14):1717-1723.

increased risk, it is important for women of all ages with T2DM, and particularly those who have reached the age of menopause, to work on reducing and/or modifying CHD risk. This article will discuss the effects of menopause on women with diabetes, as well as options for lifestyle management, nutrient supplementation, and medical therapy.

Menopause and Hormones

Increased androgen levels in women are associated with a greater risk of T2DM, as well as with elevated CHD risk factors (eg, obesity, hypertension, and dyslipidemia), CHD, and CHD events. The specific mechanisms for these associations have not been determined; however, androgens may affect insulin resistance both independently of and via their impact on adiposity. As women approach menopause, estrogen levels decline to a greater degree than androgen levels, leading, in some cases, to an elevated androgen/estrogen ratio and an increase in CHD-related risks. In particular, women with diabetes and an unfavorable premenopausal ratio may see the impact of this risk factor increase at menopause.

Research now suggests that hormone replacement therapy (HRT) for menopause is not cardioprotective among women at elevated risk of CHD. The Women's Health Initiative (WHI), which included a randomized trial of the morbidity and mortality associated with estrogen plus progestin in 16,608 women, enrolled healthy postmenopausal women aged 50 to 79 years. This trial found that HRT was associated with an increased risk of CHD events (overall hazard ratio [HR] 1.24 [nominal 95% confidence interval (CI)], 1.00-1.54). Risk was greatest in the first year of HRT (1-year HR 1.81 [95% CI, 1.09-3.01]). The risks were greatest among women more distant from the onset of menopause and those at increased risk of CHD due to high low-density lipoprotein cholesterol levels.

If the symptoms of menopause (eg, hot flashes, night sweats, disrupted sleep) are severe, lifestyle modifications should be implemented first. These

include portable fans, wearing layered clothing, increased dietary soy intake, and decreased exposure to triggers such as alcohol, tobacco, spicy foods, and coffee. For symptoms not responsive to lifestyle modification, antidepressant medications are also potentially useful and can be discussed with a physician. If estrogen is considered, the risks and benefits must be weighed carefully and the lowest effective dose used. A transdermal route of administration may be preferable to oral, due to this method's decreased potential for adverse effects on hemostatic and inflammatory pathways.

Menopause and Bone Health

Compared with women without T2DM, women with T2DM have an increased risk of osteoporosis and fracture. Moreover, following menopause, a woman's risk of osteoporosis and fracture increases. Therefore, postmenopausal women with diabetes need to ensure they are receiving 1200 mg of calcium daily. Adequate vitamin D intake is also essential (see the section on supplements below). Current issues surrounding bone density, women, and T2DM are discussed in greater depth by Dr. Andrew Grey in this issue of *CADRE's Current Diabetes Practice*.

Lifestyle: Diet, Exercise, Alcohol, and Smoking

The general principles of a healthy diet are especially important for menopausal and postmenopausal women with diabetes (Table 2).

Regular exercise, another component of a generally healthy lifestyle, is critically important and is associated with a reduced risk of CHD in women with T2DM. Over 14 years of follow-up in the Nurses' Health Study, 5,125 women with diabetes were assessed for the relationship between exercise and CHD events. The study found that risk reduction was significant and showed a dose-response pattern according to the number of hours of moderate or vigorous exercise per week (<1 hour, 1 to 1.9 hours, 2 to 3.9 hours, 4 to 6.9 hours, and ≥7 hours), with RRs of 1.0, 0.93, 0.82, 0.54, and 0.52, respectively

Table 2. Dietary guidelines for menopausal and postmenopausal women with diabetes

- Eat 5 to 9 servings per day of fruits and vegetables
- Consume fish and fiber
- Select whole grains instead of refined carbohydrates
- Use poly- and monounsaturated fats (eg, found in nuts) and omega-3 fatty acids (eg, fish/fish oil/flax seed)
- Limit saturated fats to <7% of daily calories
- Avoid trans fats
- Monitor carbohydrates, with attention to the glycemic index/glycemic load of foods

($P=0.001$ for trend). After adjustment for body mass index, smoking, and other CV risk factors, these figures did not change substantially.

Alcohol consumption is somewhat controversial in diabetes management, and some physicians are concerned that even moderate intake may have deleterious effects on glucose tolerance and liver function. However, research suggests moderate alcohol intake (≤ 1 drink/day for women; ≤ 2 drinks/day for men) may reduce the risk for CHD events among individuals with diabetes. An analysis of participants in the Nurses' Health Study found that moderate consumption was associated with a lower risk of CHD events compared with no alcohol use (<0.5 drinks/day, RR 0.74 [95% CI, 0.56-0.98]; ≥ 0.5 drinks/day, RR 0.48 [95% CI, 0.32 -0.72]). Additionally, moderate consumption of alcohol does not appear to have adverse effects on glucose control; however, the number of available studies is insufficient to draw definitive conclusions. The effects of alcohol consumption on microvascular and/or noncardiac complications of diabetes (eg, retinopathy, nephropathy, neuropathy) are also not known. Therefore, no patient should be encouraged to imbibe alcohol, but for those patients who choose to use alcohol, it is important that intake be limited to moderate amounts.

Continued

Smoking poses a particularly great risk for women with T2DM. Multi-variate analysis of data from the Nurses' Health Study shows that smoking among women with T2DM significantly increases CHD risk in a dose-dependent manner. Further, smoking may synergistically increase risk among those with diabetes: the increased risk for women with diabetes is substantially greater than for women without diabetes. A secondary analysis in the Nurses' Health Study found a CHD RR of 7.67 (95% CI, 5.88-10.01) for women with diabetes who smoked ≥ 15 cigarettes/day compared with nonsmokers; for women without diabetes, those who smoked ≥ 15 cigarettes/day had a RR of 2.65 (95% CI, 2.06-3.40).

Supplements

The importance of adequate calcium intake is discussed above. In addition, vitamin D is known to improve calcium absorption and thus protect against osteoporosis and fracture. However, growing evidence indicates that, at higher doses, vitamin D may help protect against a number of diseases, including diabetes and cardiovascular disease (CVD). An analysis of 83,779 Nurses' Health Study participants over 20 years of follow-up found that vitamin D intake was inversely associated with T2DM incidence; in particular, intake of >800 IU/day of vitamin D combined with >1200 mg/day of calcium was associated with a 33% risk reduction for T2DM development (compared with intake of 400 IU/day of vitamin D plus <600 mg/day of calcium). In addition, data from a number of long-term epidemiologic studies, including the Framingham Offspring Study, the HPFS, and the Third National Health and Nutrition Examination Survey (NHANES III), show significant relationships between vitamin D insufficiency and incident CVD (Framingham: RR 1.62 [95% CI, 1.11-2.36]), CHD (HPFS: RR 2.09 [95% CI, 1.24-3.54]), and total mortality (NHANES III: 26% increase for lowest quartile). Given this evidence, and data suggesting that $>50\%$ of women over 40 years of age have sub-optimal concentrations of vitamin D, many experts now recommend vitamin D intake of 800 to 1000 IU/day.

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There is controversy as to whether taking the mineral/trace element supplement chromium is of benefit to patients with diabetes. At this time, the evidence is inconclusive, and chromium supplementation is not recommended. The evidence for benefits from other supplements, including multivitamins, B vitamins, and antioxidants, has been less than compelling, and although appropriate for some patients, these supplements are not routinely recommended.

Other Medications

Many postmenopausal women with diabetes will be candidates for CV risk-lowering with aspirin (75 to 162 mg/day); physicians should discuss this option with their patients. Statin therapy, if not contraindicated, may be appropriate for treating dyslipidemia and attenuating CHD risk. Even women with normal cholesterol levels, but elevated C-reactive protein concentrations, may be appropriate candidates for statin therapy. In addition, angiotensin II inhibition via an angiotensin-converting enzyme (ACE) inhibitor or the use of an angiotensin receptor blocker may help protect kidney function. If such a medication has not already been prescribed for hypertension, this is an option for women with microalbuminuria.

Screening

Screening schedules for postmenopausal women with diabetes should follow general adult recommendations, including assessment and monitoring

of CVD risk factors such as hypertension and dyslipidemia. In addition, regular A1C measurements and annual screenings for microvascular complications, including retinal eye exam, neuropathy screening, and albumin screening to assess kidney function, should be performed. Bone health, skin/foot care, and dental/periodontal hygiene should also receive emphasis.

Conclusion

All individuals with diabetes are at increased risk for CHD; this is especially true for women with diabetes. As for all patients with T2DM, glucose control, screening for diabetes-related microvascular and CV complications, and careful attention to CV risk factors, diet, and exercise are all critical for women. However, given the increased risk profile for postmenopausal women with diabetes, CV and bone health deserve added attention.

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PRACTICE POINTERS

THIAZOLIDINEDIONES AND SKELETAL HEALTH IN POSTMENOPAUSAL WOMEN

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Type 2 Diabetes and Bone

Fragility fractures are a major cause of morbidity and public health expenditure. The most devastating fracture, of the hip, is associated with a 20% risk of dying within 6 months of the event and a substantial risk of loss of independence. Other fractures are associated with considerable periods of disability and loss of productivity. Important risk factors for fragility fracture include low bone mineral density (BMD), older age, female gender, light body weight, previous fracture, cigarette smoking, and glucocorticoid use. Thus, fracture risk is highest in postmenopausal women. Recently, absolute fracture risk algorithms have been developed, using these risk factors, to provide 5- to 10-year estimates of the risk of any osteoporotic fracture or hip fracture (see the World Health Organization's Fracture Risk Assessment Tool [FRAX[®]] in "Suggested Reading," below). Table 1 highlights the 10-year probability of hip fracture for some United States women 65 years of age according to FRAX[®].

Several recent epidemiologic studies have suggested that skeletal fragility

is increased in type 2 diabetes mellitus (T2DM), despite increased body weight and normal or higher than normal BMD. Meta-analysis of this body of observational evidence has confirmed an increase in risk of all fractures, and those of the hip, proximal humerus and foot, in T2DM. In the Study of Osteoporotic Fractures, a prospective cohort study of fracture epidemiology in older American women, participants with T2DM had a statistically significant, 22% higher risk of nonspine fractures than non-T2DM participants. Similar findings were reported from the Women's Health Initiative Observational Study, in which a significantly increased risk of fractures was reported at various skeletal sites, including the spine, in women with T2DM, with relative risk estimates of 1.2 to 1.6.

The mechanism(s) by which T2DM increases skeletal fragility is uncertain. It is clear that low bone mass is not responsible, since BMD is higher in T2DM than in nondiabetic subjects. However, BMD remains an important risk factor for fracture in T2DM, since fractures occur more frequently in T2DM subjects with decreased BMD. It is possible that complications of T2DM that increase the risk of falling, such as neuropathy, vascular disease, and impaired vision, contribute to the increased risk of fracture. In the Health, Aging and Body Composition (Health ABC) study, a prospective study of older American men and women, including African-American participants, there were strikingly higher prevalences of neuropathy, cerebrovascular disease, and falls in T2DM patients who

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Table 1. 10-year probability of hip fracture for 65-year-old women from the US according to BMI and the number of clinical risk factors

Number of CRFs	BMI = 25 kg/m ²				BMI = 35 kg/m ²			
	Asian	Black	Caucasian	Hispanic	Asian	Black	Caucasian	Hispanic
0	0.7%	0.5%	1.2%	0.7%	0.4%	0.3%	0.7%	0.4%
1	1.2%	1.0%	2.1%	1.2%	0.7%	0.6%	1.3%	0.7%
2	2.1%	1.7%	3.7%	2.1%	1.3%	1.0%	2.3%	1.3%
3	3.6%	2.9%	6.4%	3.6%	2.2%	1.7%	3.9%	2.2%
4	6.2%	5.0%	11.0%	6.2%	3.8%	3.0%	6.7%	3.8%
5	10.0%	8.3%	18.0%	10.0%	6.4%	5.1%	11.0%	6.4%
6	17.0%	14.0%	28.0%	17.0%	11.0%	8.4%	18.0%	11.0%

BMI, body mass index; CRF, clinical risk factor

Adapted from the FRAX[®] Fracture Risk Assessment Tool; © World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK; available at www.shef.ac.uk/FRAX/index.htm. Additional data for men, for other age/BMI/bone mineral density/geographic regions, and for major osteoporotic fracture (clinical spine, forearm, hip, or shoulder) are also available at this URL. Image used with permission of the WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield. FRAX[®] is registered to Professor JA Kanis, University of Sheffield.

suffered a fracture, compared with those with T2DM who did not fracture.

It is also possible that disease complications affect regional bone mass and therefore fragility. Animal studies suggest that the interruption of nerve supply to bone decreases regional bone mass independent of changes in mechanical loading. The limited available evidence suggests that T2DM patients with neuropathy and nephropathy have lower BMD than those without these complications. In addition, there is a growing body of evidence that advanced glycation end products, products of nonenzymatic glycation that are produced in higher quantities in diabetic than nondiabetic patients, may exert detrimental effects on bone remodeling and/or strength.

TZDs and Bone

Thiazolidinediones (TZDs) are insulin-sensitizing drugs that activate the gamma isoform of the peroxisome proliferator-activated receptor (PPAR γ) family of nuclear transcription factors. PPAR γ is expressed in bone, and preclinical studies over the past decade have clearly demonstrated that it acts as a molecular switch in promoting the differentiation of pluripotent mesenchymal stem cells into adipocytes at the expense of osteoblasts, and as a positive regulator of osteoclastogenesis. Correspondingly, in animals, TZDs have been shown to decrease bone formation and either increase bone resorption or maintain it at an inappropriately normal level.

Recent clinical studies in humans have provided evidence that treatment with either of the currently available TZDs, rosiglitazone and pioglitazone, decreases bone density by inhibiting bone formation without altering bone resorption. Importantly, data collected as adverse events during the conduct of randomized controlled trials of each TZD in T2DM demonstrated a twofold increase in the risk of distal limb fractures in women. These studies were conducted in middle-aged subjects, in whom limb fractures are the most common type of fracture. Observational data from an older

cohort of individuals with T2DM suggest that fracture risk is also increased in men exposed to TZDs and that the incidence of classical osteoporotic fractures (hip, forearm, humerus) is higher in TZD users.

The mechanisms underlying the adverse skeletal effects of TZDs may involve both direct actions (discussed above) and indirect pathways. Indirect actions of TZDs that potentially contribute to their detrimental skeletal effects include decreasing systemic and skeletal production of insulin-like growth factor 1, modulating production of skeletally active adipokines, and decreasing levels of pancreatic β -cell hormones with known skeletal activity.

The skeletal toxicity of TZDs has prompted interest in the effects of other oral hypoglycemic agents on bone health. Currently available data suggest that metformin and sulfonylureas are neutral in regard to the skeleton. It is noteworthy that some of the randomized studies that identified an increased risk of fracture in TZD users had sulfonylureas as active comparators.

Investigation and Management of Osteoporosis in Diabetes

T2DM should be regarded as a risk factor for fragility fracture and included in clinical fracture risk assessment, along with recognized risk factors such as age, gender, body weight, previous fracture, cigarette smoking, glucocorticoid use, and BMD. This is particularly relevant to postmenopausal women, in whom fracture risk is greatest. Recently developed fracture risk algorithms may be useful in determining an individual patient's absolute fracture risk. Though BMD is on average increased in T2DM, measurement of BMD in patients with T2DM is still helpful in defining that person's fracture risk. Patients with T2DM who are found to be at high risk of fracture should not be prescribed TZDs unless there are compelling reasons to do so. Minimizing the risk of falls is another important component of skeletal management in diabetes; this can be achieved by interventions aimed at reducing both macrovascular and

microvascular disease complications, minimizing the risk of hypoglycemia, optimizing visual acuity, and minimizing the use of other medications known to increase the risk of falls. Although there are no data from intervention studies on the effects of pharmacologic treatments of osteoporosis in T2DM, it is reasonable to assume that agents known to prevent fractures in nondiabetic osteoporotic populations, such as bisphosphonates, will also be effective in diabetic patients.

Dr. Grey has served on an advisory board for GlaxoSmithKline.

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