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DIABETES AND HYPERLIPIDEMIA

New drugs for reducing cardiovascular risk in women

CORONARY ARTERY DISEASE remains the leading cause of death in women in the United States. Most of the risk factors for heart disease in men also apply to women; however, there are important gender differences. Unfortunately, most of the trials of risk reduction, particularly the lipid-lowering trials, have focused on middle-aged men, and some primary prevention strategies are unique to women.

Nonetheless, there are a number of strategies physicians can employ to reduce the cardiovascular risk of their female patients. This review focuses on these strategies, with particular emphasis on newer drugs for hyperlipidemia and the role of antioxidants and smoking cessation in risk reduction. Because of the important role of diabetes mellitus in the health of women and the many new drugs that are available for the treatment of this disease, an accompanying article focuses on the use of these new medications.

■ HYPERLIPIDEMIA

Different guidelines exist for cholesterol screening; those from the American College of Physicians focus mainly on middle-aged men and are generally more restrictive than those from the National Cholesterol Educational Panel, which advise obtaining a baseline cholesterol level in all adults. We recommend obtaining baseline values of total cholesterol and HDL-cholesterol in all adult females. Obese women, diabetic women, and women with low HDL-cholesterol values (< 55 mg/dL) need their fasting

■ ABSTRACT

Atherosclerosis is largely preventable in women. Clinicians need to appreciate the gender-associated risks of cardiovascular disease and emphasize to their women patients that life-style changes can reduce cardiovascular risk. However, newer oral agents for diabetes and the statins for hyperlipidemia are important pharmacological adjuncts.

■ KEY POINTS

Approximately 60% of new cases of diabetes mellitus are in women.

Patient education is the most important intervention in women with type II diabetes mellitus, with a focus on life-style modifications such as proper nutrition and increased exercise.

Drug therapies are usually considered only if life-style modifications have failed to achieve therapeutic goals.

The antidiabetic drugs metformin, acarbose, troglitazone, and glimepiride have different mechanisms of action, and therefore can have additive effects.

Nearly all the excess risk of myocardial infarction in women who use oral contraceptives is attributable to the interaction with cigarette smoking.

Smoking status should be assessed like a vital sign at every office visit.

LDL-cholesterol and triglyceride levels measured as well.

Elevated levels of LDL-cholesterol (> 160 mg/dL) are a risk factor for coronary artery disease in women; HDL cholesterol (which is usually higher in women than in men) is a stronger marker of cardiovascular protection in women than in men.

Treating hyperlipidemia

Goals of therapy are an LDL-cholesterol level of 100 mg/dL or less in women with established coronary artery disease, less than 130 mg/dL in women without coronary artery disease but with two or more risk factors for it, and less than 160 mg/dL in women with fewer than two risk factors.

Diet therapy. A nearly vegetarian diet—low in animal fat, saturated fat, and cholesterol and high in fiber—can reduce the LDL-cholesterol level and the risk of vascular disease in women with hypercholesterolemia. Referral to an experienced nutritionist can help in achieving dietary goals. HDL-cholesterol levels can be raised by stopping smoking, losing weight if obese, and engaging in vigorous aerobic activity.

Estrogen replacement therapy. In postmenopausal women, if dietary treatment fails to achieve the lipid goals, hormone replacement therapy should be considered next, because it has significant beneficial effects on lipid levels as well as significant nonlipid cardiovascular effects. (See Thacker HL. Current issues in menopausal hormone replacement therapy. *Cleve Clin J Med* 1996; 63:344–353.)

Estrogen replacement therapy reduces LDL-cholesterol levels and raises HDL-cholesterol levels. Oral estrogen replacement may cause increases in triglyceride levels, but the transdermal estradiol patch does not. Hormone replacement therapy should be considered in all women with heart disease or those who are at increased risk of heart disease due to expected gains in life expectancy.

Drug therapy. If diet and hormone replacement therapy do not achieve the desired LDL-cholesterol goals, then one should consider an HMG-CoA reductase inhibitor (“statin”) such as lovastatin (Mevacor), simvastatin (Zocor) pravastatin

(Pravachol), or fluvastatin (Lescol). The statin drugs have now been shown to reduce the mortality rate in women with coronary artery disease.

Atorvastatin (Lipitor)

Atorvastatin (Lipitor), a new HMG-CoA reductase inhibitor, not only lowers LDL-cholesterol levels but also lowers triglyceride levels by 20% to 35%, an effect that may be important in diabetic women, who generally have high triglyceride levels.

Cautions. Erythromycin and cyclosporine may increase the hepatotoxic effects of the statin drugs.

Dosage. 10 to 20 mg by mouth every evening. (All of the statin medications should be given in the evening, when most cholesterol is synthesized in the liver.)

■ TOBACCO USE

Cigarette smoking is a significant coronary risk factor, yet women are smoking in record numbers. Women who smoke—who may now outnumber men who smoke—have a fourfold higher risk of coronary artery disease than do nonsmoking women. The risk increases with the number of cigarettes smoked: even women who smoke as few as one to four cigarettes per day have twice the cardiovascular risk.

Stopping smoking is effective as both primary and secondary coronary prevention. With smoking cessation, the cardiac risk drops very rapidly within the first year.

At least 5% of smokers would stop if a physician told them to. Smoking status should be assessed like a vital sign at every office visit. Nicotine chewing gum and transdermal patches are now available over-the-counter and may be a helpful adjunct for some women who are nicotine-dependent.

Unfortunately, many women continue to smoke because they think it helps them stay slim. As a weight-control strategy, smoking falls short for several reasons. The increased risks of vascular disease and cancer far outweigh any health benefit from weight reduction. At the very least, it should be noted that for appearance-conscious women, smoking accelerates facial aging.

A nearly
vegetarian
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■ HYPERTENSION

Hypertension is a well-proven risk factor for stroke and coronary artery disease. Treating hypertension reduces the risk of stroke more markedly than it reduces coronary artery disease, perhaps because a longer duration of blood pressure control is necessary to demonstrate any effect on coronary artery disease than on stroke. Even modest weight loss can often reduce the blood pressure.

Excess alcohol intake is a common cause of high blood pressure; other causes are obesity, excess sodium intake, and, perhaps, deficient calcium intake. American women tend to consume less than the recommended daily allowance of calcium.

■ PHYSICAL ACTIVITY

Several studies have convincingly shown that regular aerobic activity can reduce several of the risk factors for coronary artery disease, notably obesity, the total-to-HDL cholesterol ratio, and the incidence of type II diabetes. Even moderate levels of physical activity, such as walking three times weekly, are of apparent benefit.

■ ALCOHOL USE

Moderate alcohol consumption can reduce the risk of coronary artery disease. However, women are much more sensitive to the effects of alcohol than men. Moreover, moderate alcohol consumption is associated with an increased risk of breast cancer. Further, alcohol is calorie-dense and may contribute to obesity and hypertension in women, and the problem of alcoholism is widespread. Therefore, we do not promote regular alcohol intake as a means of preventing heart disease in women.

■ VITAMIN AND ANTIOXIDANT USE

Elevated homocysteine levels lead to an increased risk of coronary artery disease, and observational studies suggest that the link is stronger in women than in men. In most instances, hyperhomocystinemia is due to inadequate intake of vitamins B₆ (pyridoxine),

B₁₂, and, especially, folate. Only a minority of women consume the recommended intake of 400 µg/day of folate. Subclinical deficiencies of vitamin B₆ may occur in women who take oral contraceptives, which enhance the metabolism of pyridoxine. Vitamin B₁₂ deficiency from anemic and nonanemic pernicious anemia is more of a problem in older women than in younger women.

Adequate intake of the above vitamins usually reduces homocysteine levels to normal and therefore may reduce the risk of coronary artery disease; however, no randomized trials have been conducted to test whether lowering homocysteine levels reduces cardiovascular risk.

In the Boston Nurses' Health Study, women who took vitamin E supplements had about a 40% lower cardiovascular risk than did nonusers, suggesting that vitamin E supplements may reduce the risk of coronary artery disease. The most plausible mechanism of this reduced risk is via reduction of LDL-cholesterol oxidation.

■ OBESITY

More than one fourth of American women are obese; the prevalence increases with age and is much higher among African-Americans and women of lower socioeconomic status.

Obesity causes a number of conditions that predispose to atherosclerosis: type II diabetes mellitus, hypertriglyceridemia, decreased HDL-cholesterol and increased LDL-cholesterol levels, and hypertension. It also contributes to gallbladder disease, some forms of cancer, obstructive sleep apnea, chronic hypoxemia and hypercapnia, and degenerative joint disease. As a preventable cause of death, obesity-related complications are second only to smoking-related complications—and smoking and obesity are both increasing in prevalence among women.

Measuring obesity—and risk

Among middle-aged women, body weight and mortality from all causes are directly related. Lean women do not have an excess mortality rate, after excessive tobacco use and underlying systemic illness are accounted for. In fact,

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the lowest mortality rate is among women who weigh at least 15% less than the US desirable weight.

The **body mass index** (BMI—the weight in kilograms divided by the square of the height in meters) is gaining favor as a measure of obesity and of risk. Normal is < 25. Even women with a moderately increased BMI of 25 to 29 have a 60% to 80% higher risk of cardiovascular disease than do lean women. The risk of death is 60% to 70% higher among women with a BMI between 29 and 32 compared with women who have a BMI between 25 and 27.

The **pattern of adiposity** may also be important: apple-shaped abdominal adiposity (ie, “android” obesity), may be of greater risk than pear-shaped “gynecoid” adiposity.

Treating obesity

Even small degrees of weight loss consistently lead to lower blood pressure and lipid levels and better glucose tolerance. Unfortunately, traditional weight-loss programs have been mostly ineffective, particularly in the long term. Therefore, primary prevention is key: we must help more women avoid becoming obese in the first place. For women who are already obese, the best results occur in programs that use diet therapy combined with behavior modification, exercise, and, in selected patients, new anti-obesity drugs.

The controversy over antiobesity drugs

As this article was going to press, the Food and Drug Administration and the manufacturers of dexfenfluramine (Redux) and fenfluramine (Pondimin) announced that these two anti-obesity drugs were being withdrawn from the market and patients were being instructed to stop taking these medications.

Over the last year there has been growing concern about these drugs and the complication of primary pulmonary hypertension. However, the issue that forced the removal of these drugs from the market was recent reports of a possible link with valvular heart disease.

It is too soon for the authors of this article to assess the implications of this decision. Nonetheless, we feel a sense of disappointment. There had been great hope that these new medications would be effective for the treatment of obesity, which in most cases is resistant to standard treatment.

PRIMARY PREVENTION STRATEGIES UNIQUE TO WOMEN

The potential impact of postmenopausal hormone replacement therapy on reducing cardiovascular risk is impressive, and is explained in depth elsewhere (see Thacker HL. Current issues in menopausal hormone replacement therapy. *Cleve Clin J Med* 1996; 63:344–353). However, even though the benefits of hormone replacement therapy outweigh the risks for most menopausal women, the nuisance of withdrawal bleeding and the misinformation about the risk of breast cancer prevent many women from using it.

Oral contraceptives may increase the risk of myocardial infarction in older women who smoke, but by a thrombotic mechanism, not by atherosclerosis. Nearly all the excess risk of myocardial infarction in women who use oral contraceptives is attributable to the interaction with cigarette smoking.

Women who take oral contraceptives and smoke have a risk of myocardial infarction 30 times higher than that of nonsmoking women who do not use oral contraceptives. However, there is no convincing evidence that there is a higher risk of coronary artery disease among nonsmokers who use oral contraceptives. Indeed, there is modest evidence in animals that modern, low-dose oral contraceptives may actually decrease the risk of cardiovascular disease, due to a reduction in atherosclerosis.

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Low-dose oral
contraceptives
may actually
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cardiovascular
risk

Many more treatment options available

MORE THAN 13 MILLION PERSONS in the United States have diabetes mellitus, and approximately 60% of new cases are in women. The toll is higher in Native American, African-American, and Hispanic women, who have a higher prevalence of diabetes and its complications than do non-Hispanic white women.

Premenopausal nondiabetic women have a lower rate of cardiovascular disease than do men, but diabetes appears to abolish that difference. In addition, diabetes mellitus is a stronger risk factor for coronary artery disease in women than in men, imparting a relative risk of between 3 and 7 in women, compared with 2 to 4 in men.

There are no conclusive data that glycemic control per se reduces cardiovascular risk in persons with diabetes, although aggressive therapy has been shown to decrease the incidence of microvascular complications such as retinopathy, kidney failure, and neuropathy. Further, persons with diabetes are prone to a number of other conditions that also increase cardiovascular risk, some of them treatable.

■ Type I or type II?

Diabetes mellitus is categorized as either type I or type II.

Type I diabetes, an insulin-deficient state, usually develops in childhood. When late-onset type I diabetes mellitus is suspected (eg, in a nonobese woman with no family history of type II diabetes), the serum C-peptide level should be measured. C-peptide levels are normal in type II diabetes mellitus, but low or absent in type I. If this test indicates that a patient truly has late-onset type I diabetes, secondary causes should be sought, such as hemochromatosis or pancreatic cancer.

Type II diabetes, an insulin-resistant state, is more common than type I and usually develops in adulthood. Insulin resistance and compensatory hyperinsulinemia often occur in

conjunction with a variety of other abnormalities, including:

- Varying degrees of glucose intolerance.
- High plasma triglyceride concentrations.
- Low high-density lipoprotein cholesterol (HDL-cholesterol) concentrations.
- Smaller and denser low-density lipoprotein (LDL) particles.
- Increased plasminogen activator inhibitor-1 levels.
- High blood pressure.

All of these abnormalities have been shown to increase the risk of coronary heart disease and collectively have been named "Syndrome X."

■ Preventing and treating type II diabetes mellitus

Obesity is the main etiologic culprit in type II (non-insulin-dependent) diabetes mellitus; therefore, the main strategy for preventing type II diabetes is to encourage people not to gain too much weight, or to lose weight if they are obese.

The Diabetes Control and Complications Trial (DCCT), published in 1993, showed that rigorous control of blood sugar delays the onset and slows the progression of microvascular complications in type I diabetes. Strong circumstantial evidence indicates that the same applies to type II. The goals of intensive diabetic therapy are to achieve near-normal fasting blood sugar levels and to reduce the glycosylated hemoglobin (HbA_{1c}) level to less than 7%.

Patient education is the most important intervention in women with type II diabetes mellitus, with a focus on life-style modifications such as proper nutrition and increased exercise. However, fewer than 20% of patients with newly diagnosed type II diabetes achieve good glycemic control with these measures. Drug therapy is indicated if fasting blood sugar and HbA_{1c} levels remain above 140 mg/dL and 7.6%, respectively.

TABLE 1

COMPARISON OF ORAL AGENTS FOR TYPE II DIABETES MELLITUS

Consideration	Acarbose (Precose)	Troglitazone (Rezulin)	Metformin (Glucophage)	Glimepiride (Amaryl)
Hypoglycemia*	No	No	No	Yes
Hyperinsulinemia	No	No	No	Yes
Weight gain	No	No	No	Yes
Lactic acidosis	No	No	Yes	No
GI symptoms	Common	No	Common	Rare
Liver enzyme elevations	Rare	Rare	No	Rare
Use in patients with liver disease	No	No	No	No
Use in patients with renal disease	Yes, if creatinine < 2.0 mg/dL	Yes	Yes, if creatinine < 1.3 mg/dL (women) (monitor renal function carefully) < 1.4 mg/dL (men)	Yes, if creatinine < 2.0 mg/dL
Advantageous in insulin-resistant state	Yes	Yes	Yes	Maybe
Cost per month in dollars†	41	104	47	20

*When used as monotherapy; data not from comparative studies

†Cost to the pharmacist for 30 days' treatment with the lowest daily dosage based on wholesale price

For many years, the sulfonylureas were the only oral agents available for managing type II diabetes; however, four new oral drugs have been introduced in the past 2 years: metformin, acarbose, troglitazone, and glimepiride (TABLE 1). Each of these agents has a different mechanism of action and affects the disease process in a different way (FIGURE 1).

■ Metformin

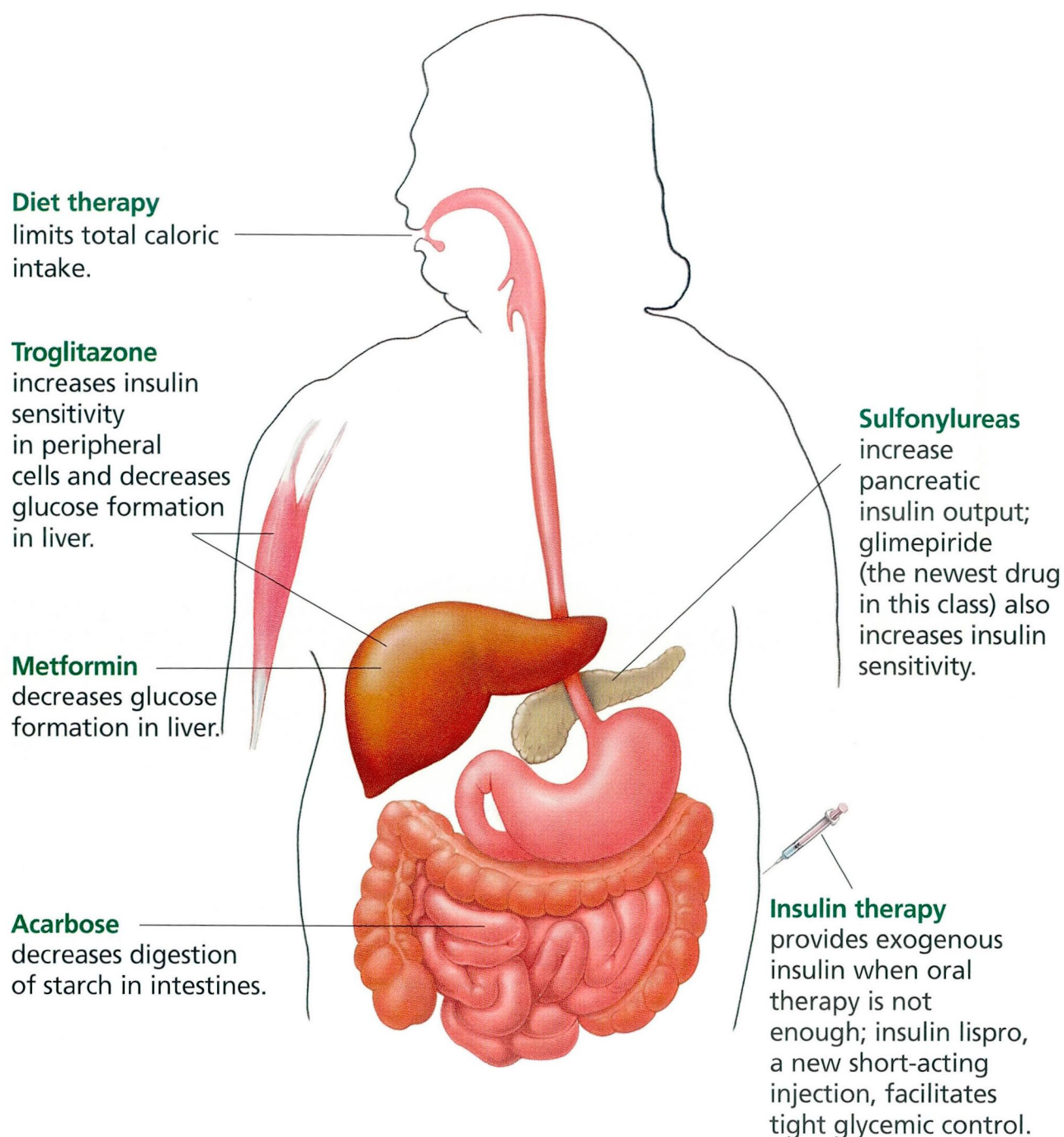
Metformin (Glucophage) has been used in Europe for several years and recently became available in the United States. Metformin is a biguanide that works mainly by decreasing glucose formation in the liver; it also may increase glucose use by muscle cells, perhaps by improving glucose transport.

During metformin therapy, HbA_{1c} levels decreased by 1.9 percentage points in some studies, a difference comparable with that seen with intensive vs conventional therapy for diabetes. Further, the ratio of total-to-HDL cholesterol decreased. Of particular importance, patients do not tend to gain weight during metformin therapy, as they do with sulfonylureas or insulin. When used alone, metformin does not cause hypoglycemia, as it does not stimulate insulin secretion (which is the mechanism of action of the sulfonylureas).

Indications. Metformin can be used as monotherapy or combined with a sulfonylurea. It is currently not approved by the Food and Drug Administration (FDA) for use in conjunction with insulin, but many physicians are using

FIGURE 1

ATTACKING TYPE II DIABETES MELLITUS FROM DIFFERENT DIRECTIONS



it in patients with type II diabetes who wish to wean themselves from insulin.

Cautions. Metformin is excreted by the kidneys and should not be used in patients with renal insufficiency; ie, in women with serum creatinine concentrations of 1.3 mg/dL or higher. It should be stopped 72 hours before any surgery, radiographic contrast procedures, or other event that may predispose a patient to hypoperfusion of the kidney.

Metformin can impair the absorption of vitamin B₁₂ and folic acid. It should be used with caution in patients who are also receiving cimetidine, which can increase plasma metformin levels considerably.

Side effects. Common side effects of metformin are nausea, vomiting, metallic taste, and gastrointestinal (GI) intolerance; these can be lessened by starting with a low dosage and increasing it slowly.

The major concern about this drug (and the reason that the FDA delayed its approval) is the possibility of lactic acidosis, which occurs in one case per 30,000 patient years. This complication usually occurs in patients with established renal insufficiency, those at risk for metabolic acidosis, patients with a history of alcohol abuse, or with hepatic insufficiency.

Dosage. The initial dosage is 500 mg twice a day with meals, to be increased to three times a day with meals. The dosage can be titrated upward to a maximum of 2,550 mg/day; ie, 850 mg three times a day.

■ Acarbose

Acarbose (Precose) is a competitive inhibitor of intestinal glucosidase, the enzyme that digests starch and sugars in the intestine. Acarbose is not absorbed—it works by reducing alimentary hyperglycemia.

Side effects. Acarbose often causes flatulence and GI discomfort due to undigested carbohydrates in the intestine. Women may not tolerate this side effect as well as men do.

Cautions. If hypoglycemia develops in a person taking acarbose, the patient should take dextrose (glucose), not sucrose, because dextrose is a simple sugar that does not require

digestion. Acarbose may increase the bioavailability of metformin and decrease iron absorption.

Dosage. 25 to 50 mg three times a day. Acarbose can be added as a “booster therapy” to either oral hypoglycemic agents or insulin therapy.

■ Troglitazone

Troglitazone (Rezulin), approved by the FDA in January 1997, belongs to a new class of antidiabetic agents known as thiazolidinediones. These agents increase the sensitivity of peripheral tissues to the action of insulin without directly stimulating insulin secretion from the islet cells; they also suppress hepatic gluconeogenesis. In addition, they reduce hepatic production of very low-density lipoproteins (VLDLs) and increase VLDL clearance, resulting in lower triglyceride concentrations.

In multicenter studies, plasma glucose levels decreased by 40 to 80 mg/dL in patients receiving troglitazone, and insulin requirements decreased by 5% to 30%. Body weight did not change significantly, and there was a trend toward lower blood pressure in hypertensive patients.

In studies in nonpregnant women with impaired glucose tolerance and a history of gestational diabetes mellitus, who as a group have an 80% risk of developing overt diabetes mellitus within 5 years, short-term troglitazone treatment increased insulin sensitivity in a dose-dependent manner. Long-term studies are in progress to determine whether troglitazone can delay or prevent the onset of diabetes mellitus in this population.

Troglitazone has also been studied in women with hyperandrogenism, hyperinsulinemia, and anovulation—the so-called polycystic ovary syndrome. In this group, troglitazone decreased insulin resistance significantly, lowered androgen and insulin levels, and, in some, restored ovulation.

Indications. Troglitazone is approved for use in patients with type II diabetes mellitus that is not well controlled (ie, with an HbA_{1c} level > 8.5%) despite more than 30 units of insulin per day given as multiple injections.



Side effects. In clinical trials, troglitazone was well tolerated and had a favorable side effect profile. A mild decrease in hemoglobin, which in most cases did not lead to stopping the drug, has been observed in 1% to 2% of patients treated with troglitazone, and approximately 1% have experienced reversible elevations in bilirubin and transaminase levels.

Cautions. As a category B drug, troglitazone should not be used during pregnancy unless the potential benefit justifies the risk to the fetus.

Troglitazone is metabolized in the liver; thus, it should be used with caution in patients with liver disease. No dosage adjustment is necessary in patients with renal dysfunction.

Of particular importance to women of reproductive age, troglitazone reduces plasma concentrations of oral contraceptives by approximately 30%. Physicians should warn women who take oral contraceptives about this drug interaction, which can make the contraceptive less effective.

Dosage. The initial dosage is 200 mg with food once daily. The insulin dosage should initially be maintained. If, after 2 to 4 weeks, the fasting blood sugar level is still high, the troglitazone dosage should be increased. The usual dosage is 400 mg daily, and the maximum recommended daily dose is 600 mg. Insulin doses should be decreased by 10% to 20% when the fasting plasma glucose concentration decreases by 20 mg/dL.

■ Glimepiride

Glimepiride (Amaryl), a new second-generation oral sulfonylurea, is an adjunct to dietary therapy in type II diabetes and the first sulfonylurea to be approved for concomitant use with insulin. In addition to increasing insulin output by the pancreas, it also improves insulin sensitivity in peripheral tissues.

Cautions. Because glimepiride is metabolized in the liver, it has a number of drug interactions. Cimetidine may increase the hypoglycemic effect of glimepiride.

Dosage. 1 to 8 mg/day.

■ Combination oral drug therapy in type II diabetes

Unfortunately, in many cases, using one oral agent does not suffice to achieve adequate glycemic control in type II diabetes. Most patients need a second agent starting approximately 5 to 7 years after starting therapy with a sulfonylurea. The most common combinations consist of a sulfonylurea plus either metformin or acarbose. The combination of acarbose plus metformin is less favorable, because of gastrointestinal reactions. We believe that these combinations will allow at least some women to avoid taking insulin for 15 to 20 years. Eventually, however, many patients will require insulin, owing to islet beta cell exhaustion.


Insulin can be used alone or in combination with oral agents in type II diabetes. For some patients, insulin therapy, started early, allows the beta cells to recover enough that the patient can go back to taking oral agents alone.

In type I diabetes, insulin is the only approved medication, although the addition of acarbose has been shown to be of some benefit as "booster" therapy.

■ Insulin lispro

Insulin lispro (Humalog), a new short-acting insulin injection, is absorbed faster than regular insulin, as it is a monomer instead of a polymer. Insulin lispro can be taken at mealtimes, a strategy that may be particularly good for adolescent women, who may not always eat at regular times. Conversely, its rapid absorption may be a problem for patients with gastroparesis. Unlike regular insulin, insulin lispro does not form complexes with zinc-based insulin suspensions such as lente and ultralente, and thus can be mixed with these preparations.

■ Tight glycemic control

Patients attempting tight glycemic control will need education and support beyond that provided most patients with diabetes. Details of instituting and monitoring such a regimen are beyond the scope of this article. Nonetheless, because of the increased risk of hypoglycemia in patients attempting intensive glycemic control, these patients who are taking insulin should be provided with a glycogen injection kit. 

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SUGGESTED READING

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