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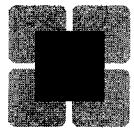

WILLIAM S. WILKE, MD, EDITOR

HIGHLIGHTS FROM MEDICAL GRAND ROUNDS

ROLE OF METFORMIN IN TYPE II DIABETES

THE INSULIN RESISTANCE, obesity, hypertension, and dyslipidemia seen in type II diabetes may conspire with hyperglycemia to accelerate atherogenesis and its vascular sequelae. When diet and exercise fail, metformin, used instead of or in addition to a sulfonylurea, promotes better control of blood sugar levels and, perhaps, ameliorates the risk of vascular complications.

HYPERGLYCEMIA OR INSULIN RESISTANCE?

Evidence that hyperglycemia is the primary etiologic factor in the complications of diabetes comes from epidemiologic data and from the recently completed Diabetes Control and Complications Trial (DCCT). Excess glucose leads to accelerated atherogenesis through glycolsylation of lipoproteins, which accumulate, causing tissue damage and evoking an inflammatory response.

Another hypothesis implicates insulin resistance, which is marked by decreased glucose uptake by muscle and increased hepatic glucose production. The resulting hyperglycemia stimulates more insulin production and downregulation of insulin receptors. Excess insulin could lead to accelerated atherogenesis in a number of ways, including by attaching to the receptor for insulin-like growth factor (IGF-1), causing an increase in cellular activity, anabolism, and endothelial tissue proliferation. Insulin resistance is also associated with other known risk factors such as hypertension, dyslipidemia, and lower-body obesity.

■ Highlights from Medical Grand Rounds present take-home points from selected Cleveland Clinic Division of Medicine Grand Rounds lectures.

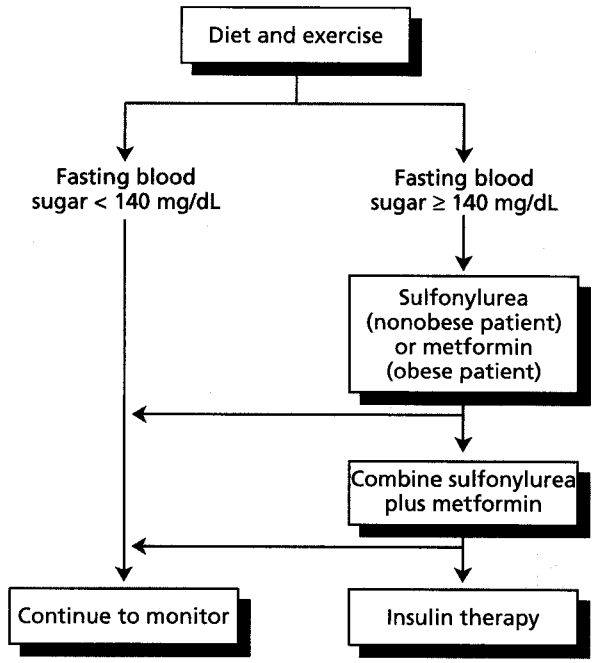

FIGURE. Suggested algorithm for treating type II diabetes.

TREATING TYPE II DIABETES

Patients with plasma glucose levels over 140 mg/dL fasting, 180 mg/dL after a meal, or 160 mg/dL at bedtime, or with hemoglobin A1c levels higher than 8% should undergo an initial trial of a weight-loss diet and exercise, which both improve glucose levels and control. Complex carbohydrates should supply as much as 60% of the total calories; fats should be avoided. Patients should do aerobic exercise for at least 15 minutes three times per week, at 60% to 80% of the maximum heart rate (200 – age, give or take 10 beats per minute).

Unfortunately, nonpharmacologic treatment is effective by itself in only 10% of patients. When blood glucose levels fail to reach target levels after a 4- or 6-month trial of diet and exercise, an oral agent should be given. Obese patients may benefit from metformin, and nonobese patients from a sulfonylurea (*Figure*), but this can be modified according to the individual patient's response.

Sulfonylureas

Sulfonylureas, the mainstays of treatment, stimulate insulin secretion. Approximately 50% of patients will achieve acceptable control with these agents. Once-daily dosage forms probably are associated with better compliance and, perhaps, better control. However, hypoglycemia, the most important complication, is more frequent with the long-acting sulfonylureas, especially chlorpropamide. Merely giving such patients glucose in the emergency department and releasing them does not suffice, as the hypoglycemia can recur repeatedly until the drug is eliminated over the course of days. Such patients need to be hospitalized and monitored closely.

Metformin

In contrast, metformin does not affect insulin secretion. Rather, it increases peripheral glucose uptake and decreases hepatic glucose production.

Metformin is approximately as effective as the sulfonylureas, decreasing plasma glucose concentrations by about 60 mg/dL. In clinical trials, it also lowered hemoglobin A1c, total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels. High-density lipoprotein (HDL) levels rose, but not significantly. Patients lost an average of 2.5 kg. Because it lowers glucose concentrations by a different mechanism, it possesses an additive effect when used with a sulfonylurea. The dosage is 500 mg to 3 g per day, given either as a single dose or twice or thrice daily.

Phenformin, an earlier biguanide agent, was withdrawn in 1976 because of cases of lactic acidosis. Metformin causes less lactic acidosis, but it is contraindicated in states such as renal failure, liver disease, or uncompensated heart failure. The most common side effects are gastrointestinal, and for this reason metformin should be given with meals.

Some authorities advocate beginning therapy with insulin, especially if the fasting glucose level is higher than 400 to 500 mg/dL. Such an approach gives the islet cells a chance to rest, decreases glucose toxicity, and brings the glucose level under control quickly. However, many of such patients might still respond to an oral agent, especially if they are obese or are a transplant recipient taking cyclosporine or steroids.

When to resort to insulin

If the fasting glucose level remains above 140 mg/dL despite combination therapy with a sulfonylurea and metformin, insulin therapy should be instituted. This can occur with advancing age, increasing weight, or decompensating conditions such as infections, trauma, renal disease, or pregnancy.

Our preference is to use insulin alone when it is indicated and not in combination with a sulfonylurea, as the blood sugar control is easier to titrate. Some centers advocate an oral agent with an evening dose of intermediate-acting insulin. However, these regimens are not universally accepted, and the role of metformin in this situation is also not defined.

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SUGGESTED READING

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THE ENDOSCOPE AND INFECTION TRANSMISSION: THE PROBLEMS AND HOW TO AVOID THEM

CONCERN about the transmission of infection is, and always has been, a part of gastrointestinal endoscopy: placing reusable devices into the gastrointestinal tract, with its plethora of potential pathogens, contaminates the equipment and creates the risk of transmitting infection to other patients, the endoscopist, or ancillary personnel.

No well-controlled clinical trials have proven that