ADVANCES IN THE MANAGEMENT OF DYSLIPIDEMIA IN THE PATIENT WITH DIABETES: CLINICAL CHALLENGES OF SYNDROME X

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SYNDROME X, also known as the metabolic syndrome or the insulin resistance syndrome, is a combination of metabolic abnormalities characterized by the body’s inability to respond normally to endogenous or exogenous insulin. The principal clinical finding in patients with the syndrome is an elevated plasma insulin level. Blood glucose levels can be normal, slightly elevated, or considerably high. In addition, almost all patients with the syndrome have a characteristic dyslipidemia. Most patients also have abnormalities of coagulation and fibrinolysis, and the prevalence of hypertension is high. The approach to therapy begins with diet, exercise, and weight loss. Monotherapy with statins or fibrates is the most common approach used to lower low-density lipoprotein and triglyceride levels and raise high-density lipoprotein levels, although combination therapy with statins plus niacin or a fibrate may be necessary. Aspirin is recommended to reduce hypercoagulability and permit fibrinolysis. Antihypertensive agents are essential to reduce elevated blood pressure. If diabetes is present, aggressive glucose control is required. (Advanced Studies in Medicine 2001;1(9):358-362)
tolerance at the start of the 10-year trial had twice the mortality after 10 years as those with normal glucose metabolism. Subjects known to have diabetes at study entry had to 4 times the mortality as those with normal glucose values.1

THE DYSPLIPIDEMIA OF SYNDROME X

The characteristic dyslipidemia seen in almost all patients with the insulin resistance syndrome includes hypertriglyceridemia, low levels of high-density lipoprotein (HDL) cholesterol, and small, dense low-density lipoprotein (LDL) particles.

Data from the Framingham Offspring Study have shown that HDL levels below 35 mg/dL, triglyceride levels above 250 mg/dL, and the combination of low HDL and high triglycerides are twice as prevalent in men with diabetes than in men who do not have diabetes. In contrast, blood levels of total and LDL cholesterol (without respect to particle size) were found to be similar in both groups of men.2

Findings among the women in the study were similar to those among the men, although the impact of diabetes on low HDL was greater, with a 4-fold increase in the prevalence of HDL levels below 35 mg/dL and a 2-fold increase in the prevalence of elevated total cholesterol levels (240 mg/dL or higher) in women with diabetes compared to women who do not have diabetes. However, a tremendous difference was seen in the prevalence of triglyceride levels above 250 mg/dL, which was higher in nondiabetic (3%) than in diabetic women, as well as a higher prevalence of LDL levels above 160 mg/dL in women with diabetes (35%) than in women who do not have diabetes (22%).3 Both the higher prevalence of elevated LDL levels in diabetic women than in nondiabetic women and the greater impact of elevated LDL levels in women than in men were also seen in the United Kingdom Prospective Diabetes Study (UKPDS).4

Type 2 diabetes has been known for some time to have a greater impact on cardiovascular risk in women—particularly premenopausal women—than in men, probably because of the impact of diabetes on HDL. In both relative and absolute terms, diabetes lowers HDL levels to a greater extent in women than in men. However, the more pronounced effect of diabetes on LDL levels in women also contributes to increased risk.

The link between the characteristic dyslipidemia of insulin resistance syndrome and the pathophysiology of the syndrome is a complex one. First, considerable heterogeneity is seen, with HDL levels ranging from 20 mg/dL in both men and women to 38 or 39 mg/dL in men or the low 40s in women, and LDL levels ranging from low-normal to high. Triglyceride levels can range from 150 to 200 mg/dL to as high as 400 to 600 mg/dL.

Another issue related to the complexity of the processes involved in the development of the basic abnormality in lipid physiology in persons with insulin resistance syndrome and type 2 diabetes—ie, the increased assembly and storage of VLDL.

HOW THE LIPID ABNORMALITY DEVELOPS

Energy is stored in fat cells as triglyceride. When caloric intake exceeds caloric expenditure, more triglyceride is stored in fat cells and an increase in fat mass ensues. When the fat cells are sensitive to insulin, triglyceride is stored efficiently because insulin down-regulates hormone-sensitive lipase, the enzyme that breaks down the triglyceride in the fat cell and allows free fatty acids to be released into the plasma. Insulin also drives glucose into fat cells, where it becomes glyc- erol, the backbone of the triglyceride molecule.

However, if the fat cells are resistant to insulin for any reason, an already exceedingly complex array of investigation, they will then turn over their triglyceride stores, break them down, and release fatty acids. When these fatty acids enter muscle tissue, they cause insulin resistance. So, muscle cells can produce more triglyceride in the liver, which can be reconverted to triglyceride, which drives the assembly and secretion of VLDL, the lipoprotein particle that carries triglyc- erides in the typical fasting individual.

In persons with insulin resistance or type 2 dia- betes, therefore, the assembly of VLDL particles and their secretion into the plasma are increased, thereby elevating triglyceride levels. After plasma VLDL and triglycerides are elevated, the other lipid abnormalities seen in the insulin resistance syndrome—ie, increases in HDL levels and small, dense LDL particles—follow.

The low HDL levels and changes in LDL particle size result largely from the actions of cholesterol ester transfer protein (CETP) in the plasma. When a VLDL particle literally collides with an HDL particle in the circulation, CETP mediates the movement of a cho- lesterol ester—ie, cholesterol plus a fatty acid from the core of the HDL particle—into the VLDL particle. It also mediates the movement of triglyceride from the VLDL particle into the HDL particle. Thus, HDL cholesterol levels are lowered because the HDL particle is not holding on to its core cholesterol esters, while proatherogenic VLDL particles are further enriched with cholesterol esters.

Triglyceride-enriched HDL is a good substrate for hepatic lipase, an enzyme that breaks down triglycer- ide, shrinks the HDL particle, and leads to the dis- sociation of apolipoprotein A-1 (Apo A-1) from the HDL particle. When Apo A-1, the protein that gives the HDL particle its structural integrity, is dissociated from the HDL particle, it is cleared from the circulation 3 or 4 times more quickly than when it is not dis- sociated from HDL.5 Thus, lower Apo A-1 levels and fewer HDL particles are present to exert antioxidant effects, inhibit smooth muscle cell proliferation, or initiate the reverse cholesterol transport process.

In a similar way, VLDL particles can collide with LDL particles in the circulation. In the presence of CETP, cholesterol ester from LDL particles moves into VLDL particles, and triglycerides from VLDL particles move into LDL particles. Triglyceride-rich LDL particles are then subject to the hydrolytic actions of either hepatic lipase (as is the case with HDL) or lipoprotein lipase, a lipase made in adipose and muscle tissue. When the triglyceride is hydrolyzed from the LDL particle, the LDL particle shrinks.

The smaller, denser LDL particle that remains, how- ever, does not lose its apolipoprotein B (Apo B). The net result is that a greater number of smaller LDL particles relative to larger ones are present. Because strong evi- dence indicates that small LDL is more atherogenic than large LDL—eg, it penetrates the artery wall more easily and is more easily oxidized—the population of small dense LDL particles in the total LDL fraction is an important marker. It indicates that patients with LDL particles that have predominantly small dense particles have more total LDL particles than patients with identi- cal LDL cholesterol levels that have predominantly large LDL particles. These individuals should therefore be treated to lower LDL goal levels.

Another mechanism that leads to the development of the characteristic dyslipidemia of the insulin resist- ance syndrome involves the presence of higher insulin levels in persons with type 2 diabetes. High insulin levels in insulin-resistant individuals drive the syn- thesis of fatty acids from glucose molecules into the liver. Because lipogenesis-derived fatty acids can also lead to increased VLDL secretions, the remaining com- ponents of the characteristic dyslipidemic pattern follow.

TREATMENT OF DYSPLIPEMIA

The approach to therapy begins with nonpharma- cologic measures such as a low-caloric, low-cholesterol diet that includes increased amounts of fruits, vegeta- bles, and fiber; increased physical activity; and weight loss. Implementing these measures could significantly reduce, perhaps by one third to one half, the number of persons who would otherwise require treatment with pharmacologic agents.

Clearly, environmental and lifestyle factors play an important role in the penetrance of the genetic predis- position for insulin resistance and the conversion of insulin resistance to type 2 diabetes. However, large numbers of people adopt lifestyle changes to control dyslipidemia and prevent insulin resistance and its conversion to type 2 diabetes, pharmacologic agents that normalize the lipid profile are the mainstay of treatment.

The primary focus of treating dyslipidemia is reaching LDL goals that are based on an individual patient’s overall risk for a coronary event, as defined by the latest report from the National Cholesterol Education Program (NCEP).6 Followed, by lowering triglyceride levels and raising HDL levels.

Monotherapy with statins or fibrates is the most com- mon approach, but combination therapy with statins plus niacin or a fibrate may be necessary.

COAGULATION ABNORMALITIES

Several abnormalities of coagulation and fibrinoly- sis are seen in most patients with insulin resistance. These include elevated levels of fibrinogen and factor VII, both of which are prothrombotic, and increased levels of plasminogen activator inhibitor-1 (PAI-1), which is antifibrinolytic.

PAI-1 is a protein that inhibits fibrinolysis, the process that breaks down fibrin in clots. PAI-1 is manu- factured in endothelial cells, fat cells, and platelets. Its gene is regulated by a number of molecules that play important roles, at least in isolated experimental systems, in the dyslipidemia seen in the insulin resis- tance syndrome. These molecules include VLDL, fatty acids (which are elevated in patients with the syn- drome), and insulin. If the PAI-1 gene is also turned
on by these molecules in vivo, it would explain the very close relationship between insulin resistance and high levels of PAI-1 in the circulation. It could also explain the relationship between the hypercoagulability resulting from high levels of factor VII, a coagulation factor found in patients with hypertriglyceridemia, and the fibrinolytic abnormalities seen in insulin-resistant type 2 diabetes.

Aspirin is the basic therapeutic regimen for correcting the abnormalities of coagulation and fibrinolysis. However, data from several trials evaluating aspirin therapy demonstrate that aspirin is beneficial in secondary prevention of coronary disease and suggest that it is as beneficial in primary prevention as well. Some experts, in fact, believe that all patients with diabetes should be receiving aspirin therapy.

HYPERTENSION

Hypertension is present in at least half of all patients with the insulin resistance syndrome and is most probably exacerbated by the onset of hyperglycemia and the presence of diabetes. However, as several large studies have shown, blood pressure reduction in patients with diabetes confers considerable clinical benefit.

The UKPDS 36 report, which examined the association of systolic blood pressure with the macrovascular and microvascular complications of type 2 diabetes, found that lowering blood pressure from 154/87 mm Hg to 144/82 mm Hg with either a beta-blocker or an angiotensin-converting enzyme (ACE) inhibitor reduced heart failure by 56%, diabetes-related death by 32%, and any diabetes-related endpoint by 24%.4

In the subgroup of patients with diabetes in the Hypertension Optimal Treatment study, which looked at the effects of lowering diastolic pressure to below 90 mm Hg, the beneficial reduction in all-cause mortality compared with placebo was greater than 24%.6 As demonstrated in these and other studies, aggressive lowering of elevated blood pressure in patients with diabetes is beneficial, with most experts recommending 130/85 mm Hg as the treatment goal.

SECONDARY PREVENTION AND LIPID-LOWERING THERAPY

Although many physicians who treat patients with diabetes avoid using beta-blockers because they can cause hypoglycemia (with the patient being unaware of it), can lower HDL levels, and may worsen insulin resistance, the use of these agents in secondary prevention should be reevaluated because of their beneficial effects on survival in men with diabetes who have had a nonfatal myocardial infarction.

The beneficial effects of lipid-lowering therapy in secondary prevention of cardiovascular events have been well documented in both diabetic and nondiabetic subjects. In both the Scandinavian Simvastatin Survival Study7 and the Cholesterol and Recurrent Events study evaluating pravastatin,8 lowering LDL levels with a statin reduced cardiovascular events significantly in both diabetic and nondiabetic patients, with diabetics having similar relative reductions in events.

Because diabetics in most trials account for more events than nondiabetics, regardless of treatment or lack thereof, some researchers suggest that diabetics be treated to lower LDL goal levels. However, in the most recent recommendation of the NCEP, a 40 mg/dL or less with a statin alone or with a statin plus niacin or a fibrate. Many physicians are wary of combination therapy because they think it may increase the risk for side effects.

The available literature allows a whole indicates that such risk is quite low, and that it is a small risk compared with the potential for significant improve-

Normalizing the lipid profile can be accomplished by nonpharmacologic means alone, such as dietary changes, exercise, and weight loss, or in conjunction with monotherapy with statins or fibrates or combination therapy with statins plus niacin or a fibrate. Many physicians are wary of combination therapy because they think it may increase the risk for side effects.

The overall strategy is to treat patients aggressively and to treat them sooner, before they have a cardiovascular event.

CONCLUSION

The key message is that people with insulin resistance syndrome, as well as those with both the syndrome and type 2 diabetes, need aggressive treatment to lower LDL and triglyceride levels, raise HDL levels, correct abnormalities of coagulation and fibrinolysis, and reduce elevated blood pressure. Aggressive glucose control is required in those with diabetes.

REFERENCES


