Hypertriglyceridemia, Insulin Resistance, and the Metabolic Syndrome

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The metabolic syndrome consists of a cluster of metabolic disorders, many of which promote the development of atherosclerosis and increase the risk of cardiovascular disease events. Insulin resistance may lie at the heart of the metabolic syndrome. Elevated serum triglycerides commonly associate with insulin resistance and represent a valuable clinical marker of the metabolic syndrome. Abdominal obesity is a clinical marker for insulin resistance. The metabolic syndrome manifests 4 categories of abnormality: atherogenic dyslipidemia (elevated triglycerides, increased small low-density lipoproteins, and decreased high-density lipoproteins), increased blood pressure, elevated plasma glucose, and a prothrombotic state. Various therapeutic approaches for the patient with the metabolic syndrome should be implemented to decrease the risk of cardiovascular disease events. These interventions include decreasing obesity, increasing physical activity, and managing dyslipidemia; the latter may require the use of pharmacotherapy with cholesterol-lowering and triglyceride-lowering drugs. ©1999 by Excerpta Medica, Inc.

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The metabolic syndrome consists of a clustering of several metabolic risk factors in a single patient.[1] The major components of the metabolic syndrome include atherogenic dyslipidemia, increased blood pressure, elevated glucose, and a prothrombotic state. Atherogenic dyslipidemia generally manifests as elevated serum triglycerides, increased small low-density lipoprotein (LDL) particles, and decreased high-density lipoprotein (HDL) cholesterol levels. This combination of abnormal lipoproteins is called the lipid triad. There is growing evidence that each of the components of the metabolic syndrome is independently atherogenic.[1] At the same time, each of these risk factors suggests the presence of the other components of the metabolic syndrome.

The mechanisms underlying the metabolic syndrome are not fully known. Most patients with the syndrome exhibit resistance to the cellular actions of insulin. Insulin resistance at the cellular level appears to modify biochemical responses in a way that predisposes to metabolic risk factors. The presence of insulin resistance appears to be the result of a complex interplay of genetic factors with environmental factors, such as obesity and physical activity level.

Many patients with the metabolic syndrome have an elevation of atherogenic lipoproteins: LDL and very-low-density lipoprotein (VLDL) remnants. The atherogenic lipoproteins initiate and sustain atherosclerosis and predispose individuals to the development of coronary artery disease. In populations with very low levels of atherogenic lipoproteins, coronary artery disease occurs relatively rarely, even when other risk factors are present.[2] High intakes of animal fats and egg yolks increase the levels of atherogenic lipoproteins. In the United States and many Western countries (and increasingly around the world as people consume more animal fats), these lipoproteins are elevated and promote atherogenesis. Thus, consumption of animal fats combined with obesity and a sedentary life-style predispose to both elevated atherogenic lipoproteins and the metabolic syndrome.

IDENTIFYING PATIENTS WITH THE METABOLIC SYNDROME

One method clinicians can use to identify patients who are susceptible to the metabolic syndrome is to measure waist circumference.[3] When waist circumference is >102 cm (40 inches) in men or >88 cm (36 inches) in women, it is called categorical abdominal obesity.[3] When patients have abdominal obesity, they often manifest the multiple risk factors of the metabolic syndrome. The finding of categoric abdominal obesity is one of the most effective ways to detect the presence of the metabolic syndrome; indeed, other atherogenic factors associated with this syndrome often are present even when borderline abdominal obesity is present, e.g., when waist circumference in men is 88–102 cm (36–40 inches).

Hypertriglyceridemia commonly occurs along with other components of the metabolic syndrome.[1] An elevated triglyceride is frequently the most available laboratory marker to uncover the coexistence of multiple risk factors, including nonlipid risk factors, such as hypertension,[4] elevated plasma glucose, and a prothrombotic state.[5] Hypertriglyceridemic patients thus must be carefully evaluated for the other metabolic risk factors that occur with the metabolic syndrome. Any patient whose triglyceride concentrations exceed 150 mg/dL is suspect for the metabolic syndrome. A mild elevation of fasting glucose of 110–125 mg/dL is another clue to the presence of the metabolic syndrome.[6] Impaired fasting glucose often is found together with an increase in triglyceride levels.[7]

INSULIN RESISTANCE

Authoritative investigators[8,9] contend that a state of insulin resistance plays an essential role in the development of the metabolic syndrome. Insulin resistance

is a complex cellular abnormality that affects multiple organ systems and predisposes to several metabolic defects. The connections between insulin resistance and atherogenic dyslipidemia, hypertension, a prothrombotic state, and glucose intolerance are complex and may be mediated through multiple metabolic pathways. Several organs are affected by insulin resistance; metabolically, the most important appear to be adipose tissue, liver, and skeletal muscle. One of the most important links in insulin resistance is between adipose tissue and the liver; the former provides the latter with excess lipid for the formation of abnormal lipoproteins and several prothrombotic coagulation factors.

Insulin resistance may also exert an action directly on small blood vessels, leading to high blood pressure. In addition, by its stimulatory effect on the β cells in the pancreas, it may accelerate the age-related decrease in insulin secretion and thereby hasten the onset of glucose intolerance. There could even be a direct effect of insulin resistance on cells of the larger arteries that are involved in atherogenesis; in addition, various scenarios have been proposed whereby an elevated serum insulin level, a consequence of insulin resistance, will excite cellular proliferation or other inflammatory responses in the arterial wall, thus promoting atherogenesis.

CAUSES OF INSULIN RESISTANCE

Several factors underlie the development of insulin resistance. Most important are obesity, physical inactivity, and genetic factors. Other factors that may affect the degree of insulin resistance are diet composition, aging, and hormones (particularly glucocorticoids and androgens). High-carbohydrate diets reproduce some of the features of the metabolic syndrome.[10] Insulin resistance worsens with advancing age.[11] High levels of glucocorticoids[12] and androgens[13] promote development of abdominal obesity, the latter being closely linked to insulin resistance. From the public health point of view, obesity and physical inactivity are the primary driving factors for the development of the metabolic syndrome in the US population. Genetic factors, which are important as well, are under intense investigation.

The atherogenic basis of the metabolic syndrome is believed to be the result of multiple risk factors that combine to produce a large increase in risk for coronary artery disease.[1] High triglycerides (including associated atherogenic remnants), increased small LDL, and decreased HDL levels all appear to be independently atherogenic. The prothrombotic state also may promote both atherogenesis and thrombosis, each contributing to clinical coronary disease. Slight elevations of blood pressure can also promote atherosclerosis, although they may be missed in clinical examination. Insulin resistance may further act through yet-to-be identified risk factors in ways that enhance risk for coronary artery disease. The metabolic syndrome does not contain a single overriding atherogenic factor, but instead consists of a myriad of abnormalities that promote the development of atherosclerosis and thus lead to increased risk for coronary disease.

HYPERTRIGLYCERIDEMIA AND INSULIN RESISTANCE

Many investigations reveal that hypertriglyceridemia is closely linked to insulin resistance.[14–16] In unpublished studies from our laboratory, patients with primary hypertriglyceridemia were found to be insulin resistant by the glucose-clamp technique. In another study from our laboratory, Mostaza et al[17] found that patients with primary hypertriglyceridemia have an elevated turnover rate of nonesterified fatty acids; this elevation occurred independently of body fat content and abdominal obesity. This elevation suggests that patients with primary hypertriglyceridemia have insulin resistance at the level of adipose tissue. Presumably, hypertriglyceridemia in patients was secondary to increased secretion of nonesterified fatty acids by adipose tissue, supplying excess fatty acids to the liver for synthesis of triglycerides. In another study, Jensen et al[18] measured the turnover rates of free fatty acids in the plasma of 3 groups of women: controls who were nonobese; women who had lower-body obesity; and those who had abdominal obesity. These workers found that women with abdominal obesity had much higher nonesterified fatty acid concentrations due to higher nonesterified fatty acid output by adipose tissue. Seemingly, persons with abdominal obesity have an increased release of nonesterified fatty acids into the circulation, which exposes the liver to high amounts of nonesterified fatty acids. Flooding the liver with lipid may engender both atherogenic dyslipidemia and a prothrombotic state. Exposure of skeletal muscle to excess nonesterified fatty acids probably increases insulin resistance in this tissue as well.

In summary, when patients have elevated secretion of nonesterified fatty acids, whether due to excess adipose tissue (obesity), abnormal fat distribution (abdominal obesity), or a primary insulin resistance in adipose tissue, they will have an elevated level of nonesterified fatty acids in the plasma. Excess nonesterified fatty acids overload a variety of different tissues in the body with lipid and apparently alter cellular processes, predisposing patients to the metabolic syndrome.

OVERPRODUCTION OF APOLIPOPROTEIN C-III WITH INSULIN RESISTANCE

High serum triglyceride levels in patients with insulin resistance are due in part to overproduction of VLDL triglyceride, secondary to increased triglyceride synthesis in the liver. Another cause of elevated serum triglycerides may be an enhanced synthesis of apolipoprotein C-III. This apolipoprotein is carried on VLDL particles and has 2 properties that cause retention of triglycerides in the circulation. First, apolipoprotein C-III interferes with the action of lipoprotein lipase,[19] the enzyme responsible for hydrolysis of VLDL triglyceride. Second, apolipoprotein C-III interferes with the uptake of VLDL remnants by LDL receptors on liver cells.[20]

SMALL LDL PARTICLES, DECREASED HDL, AND INSULIN RESISTANCE

High triglyceride levels, secondary to insulin resistance, are accompanied by small LDL particles; the latter are probably atherogenic in their own right. Independent studies have shown an association between small dense LDL and insulin resistance.[21,22] Most patients with isolated low HDL-cholesterol levels also exhibit insulin resistance.[23] Thus, all components of atherogenic dyslipidemia—elevated triglycerides, increased small LDL, and decreased HDL cholesterol—have been shown to be linked with insulin resistance. Growing evidence suggests that each of these lipoproteins independently promotes the development of atherosclerosis; when the abnormalities are combined, they rival LDL in atherogenic potential.

HYPERTRIGLYCERIDEMIA AND HYPERTENSION

All patients found to have elevated serum triglycerides should be checked carefully for an abnormal blood pressure. A large body of research suggests that insulin resistance predisposes to hypertension.[24–27] The mechanisms underlying this relation have not been fully defined, but probably are multiple; examples include stimulation of the sympathetic nervous system, retention of sodium by the kidneys, and defective calcium transport in arterioles. Plasma triglyceride levels have been positively correlated with blood pressure levels.[28,29] In a patient with hypertriglyceridemia, the blood pressure may be only slightly increased; but even this slight elevation can increase the risk for coronary artery disease.[30] Blood pressure levels, therefore, should be thoroughly evaluated, either by 24-hour blood pressure readings or by home blood pressure monitoring.

HYPERTRIGLYCERIDEMIA AND A PROCOAGULANT STATE

Another finding in many patients with hypertriglyceridemia is the presence of abnormalities in the coagulation system.[31–37] According to Miller,[31] these abnormalities include: (1) activation of endothelial cells, promoting thrombin generation and fibrin production; (2) promotion of LDL oxidation, which activates macrophages; (3) enhanced platelet aggregation, which predisposes to microthrombi; (4) activation of factor VII, a potent procoagulant; (5) increased levels of factor X, factor IX, and prothrombin; and (6) increased concentrations of plasminogen activation inhibitor-1, causing a decreased plasma fibrinolytic activity. Miller[31] speculates that these changes play a role in the formation of atherosclerotic plaques as well as increasing the size of thrombi that occur when plaques rupture. Similar changes in the coagulation system have been reported to occur in patients with insulin resistance.[38–41]

MANAGING THE PATIENT WITH INSULIN RESISTANCE

The most effective approach to treating insulin resistance and to decreasing the components of the metabolic syndrome are through weight control (weight reduction in overweight patients) and increased physical activity. Many studies have demonstrated that when weight loss occurs,[42–47] or when there is increased physical activity,[48–55] the plasma levels of insulin go down, insulin resistance is decreased, and all of the components of the metabolic syndrome are improved. When a clinician encounters a patient with hypertriglyceridemia, abdominal obesity, and other features of the metabolic syndrome, he or she should consider that the patient may have insulin resistance. Such a patient should be referred to a dietitian for weight reduction and to an exercise trainer. In addition, the various components of the metabolic syndrome, e.g., hypertriglyceridemia, may require independent therapy.

DRUG TREATMENT OF INSULIN RESISTANCE

The ideal drug to treat insulin resistance would accomplish the same changes as exercise and weight reduction. Unfortunately, ideal drugs are not currently available. One drug that does decrease insulin resistance is metformin. However, it is not recommended that this drug be used in patients without diabetes. The National Institutes of Health (NIH) has sponsored a clinical trial to determine whether metformin therapy in patients with impaired glucose tolerance, who are basically insulin resistance patients without diabetes, will result in a delayed onset of type 2 diabetes.

Other drugs that have potential to decrease insulin resistance are the thiazolidinediones, such as troglitazone. These agents activate the peroxisome proliferator-activated receptor gamma, which in some way causes a generalized reduction in insulin resistance.[56] Unfortunately, rare cases of liver failure have been associated with troglitazone therapy.[57–59] The NIH study originally included troglitazone as one of the components of its trial with metformin. Troglitazone was dropped from the study because there was concern about the ethics of treating patients who did not yet have diabetes.

THE METABOLIC SYNDROME

The first priority in treating the dyslipidemia of the metabolic syndrome should be to lower atherogenic lipoproteins, such as LDL and VLDL remnants. This approach should help to forestall the adverse effects of the other atherogenic components of the disorder. Statins are the most effective drug to decrease atherogenic components, particularly LDL, but also VLDL remnants. Other risk factors, such as hypertriglyceridemia, can then be addressed.

There is some uncertainty about whether there is any benefit to treating dyslipidemia other than decreasing elevated LDL levels. Several studies nonetheless strongly suggest that treatment of hypertriglyceridemia with fibric acids, independently of LDL lowering, will decrease risk for coronary artery disease.[60–62] Thus, consideration must be given to using fibric acids, with or without statins, depending on LDL-cholesterol levels in

patients with hypertriglyceridemia and the metabolic syndrome.

Many patients with the metabolic syndrome have combined hyperlipidemia (an increase in both cholesterol and triglycerides in serum). The first step in treating patients with combined hyperlipidemia is to lower the atherogenic lipoproteins. In studies from our laboratory,[63] treatment of patients having combined hyperlipidemia with a statin alone decreased LDL cholesterol levels by 35% and VLDL plus intermediate-density lipoprotein (IDL) cholesterol by 39%. The VLDL–IDL cholesterol factor can be taken as a good indicator of atherogenic remnant lipoproteins. In our study, when gemfibrozil was added as a second drug, there was a further reduction in the atherogenic lipoproteins.[63] A greater lowering in triglyceride levels occurred; this would have decreased the number of small, dense LDL particles as well as remnants. With the combined therapy, HDL levels rose markedly; the combined result was an overall improvement in the lipoprotein profile. Considerable potential benefit thus may be forthcoming from adding fibric acids to statin therapy in patients with combined hyperlipidemia.

Most patients tolerate the combination of a statin plus a fibric acid drug without side effects. However, about 1 in 50 patients will develop myopathy, which, if left untreated, can produce acute tubular necrosis. Patients taking this drug combination should be informed to alert their physician immediately if they develop flu-like myalgias or brown urine (myoglobinuria). A serum creatine kinase should be measured, and if found to be elevated, the medications should be discontinued immediately.

SUMMARY

Clinicians who treat patients to decrease the risk of cardiovascular disease should be aware of markers for the metabolic syndrome. This syndrome is a condition that consists of a cluster of metabolic disorders, including insulin resistance, elevated blood pressure, elevated plasma glucose, a prothrombic state, and atherogenic dyslipidemia. The mechanisms underlying the metabolic syndrome are not fully known, although most patients with the syndrome exhibit a resistance to the actions of insulin. The metabolic syndrome is closely associated with elevation of atherogenic lipoproteins. Patients with the metabolic syndrome can be identified by an increase in atherogenic lipoproteins and by the appearance of abdominal obesity. Hypertriglyceridemia is a particularly good clinical clue in the presence of abdominal obesity. Patients with the metabolic syndrome should lose weight and increase their level of physical activity. In addition, dyslipidemia should be treated with drugs, if necessary. Statins should be used in most patients to achieve the recommended targets for LDL cholesterol. Consideration should then be given to employing a fibric acid in patients with hypertriglyceridemia and atherogenic dyslipidemia. If LDL cholesterol levels are low, fibric acids can be used as monotherapy.

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