

The Metabolic Syndrome and Cardiovascular Disease

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Abstract

The metabolic syndrome, a group of conditions including obesity, hypertension, insulin resistance and dyslipidemia, is an important target in coronary heart disease (CHD) risk reduction. Many questions regarding CHD risk and pathophysiology, and optimal treatment of metabolic syndrome have been debated in recent years. These conditions individually increase CHD risk, and several lines of evidence suggest that the components, acting together synergistically, additionally raise an individual's risk of developing cardiovascular disease. Many think that insulin resistance is the key component linking the syndrome to the development of CHD from a pathophysiologic point of view; however, a chronic inflammatory state has also been implicated. New medications, such as the cannabinoid antagonists, are being tested as potential treatments for metabolic syndrome. How best to treat advanced coronary disease in patients with metabolic syndrome remains a major challenge.

Key Words: Metabolic syndrome X, cardiovascular diseases, pathophysiology, atherosclerosis.

SINCE 2001, RESEARCHERS have focused increasingly on the metabolic syndrome and its relationship to cardiovascular disease. In that year, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III identified the syndrome as a secondary target (after low density lipoprotein cholesterol lowering) of coronary heart disease risk reduction. Many questions regarding cardiovascular risk and pathophysiology, and optimal treatment of metabolic syndrome have been debated in recent years. For example: Should metabolic syndrome be regarded as a coronary risk equivalent, or does the syndrome place an individual in the intermediate risk category? Does having the syndrome impart a risk above and beyond the risks of its components? Is insulin resistance the common pathway linking the components to heightened risk for the development of cardiovascular dis-

ease? And finally, what is the best way to treat advanced ischemic heart disease in these patients?

Historical Perspective

The syndrome was probably first identified in 1923, when Kylin noted that hypertension, hyperglycemia and gout tend to cluster together (1, 2). The more modern definition, one that includes obesity, hypertension, diabetes, and hyperlipidemia, was first suggested in the 1960s. German researchers of the 1970s (e.g., Haller et al.) are credited with the first use of the term "metabolic syndrome"; they also explored the syndrome's association with atherosclerosis (3). In the early 1990s, Ferrannini et al. and Reaven suggested that the underlying cause of this syndrome was insulin resistance. Because of this, Ferrannini et al. favored the term "insulin resistance syndrome," while Reaven called it "Syndrome X" (1, 3, 4) (not to be confused with the Syndrome X exhibited by angina and a normal angiogram). ATP III used the term "metabolic syndrome" to describe the condition.

Metabolic Syndrome and Cardiovascular Risk

Using National Health and Nutrition Examination Survey (NHANES) III data, it has been estimated that 25% of the adult American population meet diagnostic criteria for metabolic syndrome

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Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on November 15, 2004, and updated as of February 2005.

(5–7). This figure is in agreement with other cohorts studied (8). The percentage increases to 44% if only Americans over fifty years old are considered (3).

The two most common methods for diagnosing metabolic syndrome (Table) focus on visceral adiposity, atherogenic dyslipidemia, glucose intolerance, elevated blood pressure, and renal dysfunction (4, 9). One method gives equal importance to fasting glucose levels, waist circumference, high-density lipoprotein (HDL) levels, triglycerides and blood pressure; it was adopted by the NCEP for its ATP III guidelines. The other method, from the World Health Organization (WHO), is favored by some because it requires measurement of insulin resistance for the diagnosis.

A recent analysis of the San Antonio Heart Study (SAHS) by Hunt et al. (8) looked at all-cause and cardiovascular mortality, using either the NCEP or WHO diagnostic criteria. The SAHS followed over 5,000 patients enrolled between 1979 and 1988 in the San Antonio, Texas area over an average period of 12.7 years. Hunt et al. determined that the NCEP diagnostic criteria predicted all-cause and cardiovascular mortality, while the WHO criteria predicted cardiovascular mortality, but not mortality due to all causes. This finding was in contrast to the Finnish Kuopio Ischemic Heart Disease Risk Factor study, which concluded

that of the two diagnostic methods, only the WHO criteria were associated with increased all-cause and cardiovascular mortality (8, 10).

The relationship of metabolic syndrome to cardiovascular risk can be approached in two ways: (a) by considering the individual risks posed by the components, and (b) by considering the components together as a syndrome (7, 11). Insulin resistance is thought by many to be the common pathology linking the components (1, 3, 4, 9), so a lot of attention has focused on glucose homeostasis and its role in the development of cardiovascular disease.

For example, in the mid-1970s, the Helsinki Policeman Study followed nearly 1,000 men without coronary artery disease for a period of 9¹/₂ years and found that plasma insulin levels (as a surrogate of insulin resistance) were associated with coronary heart disease death and non-fatal myocardial infarction (12). Ducimetiere et al. followed more than 7,000 non-diabetic men aged 43–54 and found a similar association between fasting plasma insulin levels and coronary heart disease endpoints (13).

The San Antonio Heart Study was one of the first studies to prospectively test the hypothesis that insulin resistance could lead to metabolic derangements that would favor the development of heart disease (14). In the first phase of the study

TABLE
Definitions of the Metabolic Syndrome

National Cholesterol Education Program Adult Treatment Panel III	World Health Organization
At least 3 of the following:	Hyperinsulinemia (upper quartile of normal) or fasting glucose \geq 110 mg/dL and at least 2 of the following:
Fasting glucose \geq 110 mg/dL	Hyperinsulinemia \geq 75th percentile or insulin resistance (Insulin clamp)
Waist \geq 102 cm for men \geq 88 cm for women	Fasting glucose \geq 110 mg/dL or OGTT-2-hour glucose \geq 140 mg/dL
Triglycerides \geq 150 mg/dL	Waist:Hip \geq 0.90 for men or BMI \geq 30 kg/m ² \geq 0.88 for women
HDL cholesterol \leq 40 mg/dL in men \leq 50 mg/dL in women	Triglycerides \geq 150 mg/dL or HDL-cholesterol $<$ 35 for men $<$ 39 for women
Blood pressure \geq 130/80 mm Hg	Blood pressure \geq 140/90 mm Hg or Urine albumin: Creatinine \geq 30 mg/g
	Microalbuminuria \geq 20 mg/min

OGTT=oral glucose tolerance test, BMI=body mass index, HDL=high density lipoprotein. Reprinted from Natali A, Ferrannini E. Hypertension, insulin resistance, and the metabolic syndrome. *Endocrinol Metab Clin North Am* 2004; 33:417–429 (9) with permission from Elsevier.

(beginning in 1979), approximately 1,100 Mexican and non-Hispanic white Americans were followed for an average of eight years. Individuals with the highest fasting insulin levels at the onset developed diabetes, hypertension, hypertriglyceridemia, and low HDL cholesterol at significantly higher rates (15). The relationship between fasting insulin and these conditions persisted after controlling for age, ethnicity, gender, or body mass index (BMI).

Another well-controlled study looking at insulin levels and cardiovascular disease risk was the Quebec Cardiovascular Study (16). A cohort of more than 2,000 men, recruited from the Quebec City, Canada, area, were followed for 12 years. Higher levels of plasma insulin were associated with increased risk of cardiovascular disease, even after controlling for blood pressure, medication use, family history, age, BMI, tobacco and alcohol use, and plasma lipid and lipoprotein levels.

The ongoing EGIR-RISC (European group for the study of insulin resistance: relationship between insulin sensitivity and cardiovascular disease) is following 1,500 healthy males and females aged 30–60 years over a period of 10 years (14). In this study, insulin sensitivity is being measured by euglycemic insulin clamp, and the primary endpoint is carotid artery intima-medial thickness, determined by ultrasound. Secondary endpoints include other cardiovascular disease markers such as ECG changes, ankle:brachial pressure ratio, symptoms and events, as well as the development of diabetes, dyslipidemia, and hypertension.

Several lines of evidence suggest that the components of metabolic syndrome, acting together synergistically, raise an individual's risk of developing cardiovascular disease. Data from the Framingham Heart Study have suggested that metabolic syndrome confers a 10-year risk of 10–20% for developing cardiovascular disease (4). However, as noted by the report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to the definition of metabolic syndrome (4), statistical analysis using several models have determined that adding metabolic syndrome risk factors not already accounted for by the traditional Framingham cardiovascular risk assessment did not add to its predictive value.

The Botnia Study from Finland and Sweden studied approximately 4,500 individuals, starting in 1990, in an attempt to identify “early metabolic defects in families with type 2 diabetes” (1). Patients were divided into groups with normal glucose tolerance, abnormal glucose tolerance, and frank diabetes. The Botnia researchers found that in all groups combined, a history of coronary heart disease (angina, nitroglycerin use, or previous myocardial infarction) and

stroke were more common in individuals with metabolic syndrome (defined by WHO criteria) than in those without metabolic syndrome (RR 2.96 and 2.27, respectively). Additionally, coronary heart disease risk was elevated in individuals with metabolic syndrome and normal glucose tolerance (RR 1.73). Both total mortality and cardiovascular mortality were higher in subjects with metabolic syndrome.

Alexander et al. set out to examine the increased prevalence of coronary heart disease in individuals with metabolic syndrome, by using NHANES III data for people over 50 years old. In their analysis they found that, when using univariate regression, metabolic syndrome predicted coronary heart disease prevalence with an odds ratio of 2.07. If multivariate regression was applied, metabolic syndrome was no longer a significant predictor of coronary heart disease, but blood pressure, HDL cholesterol, and diabetes were (3). A similar analysis of NHANES III data by Ninomiya et al., using multivariate statistical techniques, revealed that metabolic syndrome was associated with an increased risk of myocardial infarction and stroke (17).

Pathophysiology of Metabolic Syndrome

Understanding the pathophysiology responsible for the metabolic syndrome aids in determining the best treatment options. While the exact mechanism responsible for increased cardiovascular risk has not been elucidated, the possibilities were reviewed by Deedwania (18). He noted that insulin's action could lead to hypertension by “stimulating sympatho-adrenal axes” or by stimulating vascular smooth muscle cell hypertrophy. Insulin could also cause hypertriglyceridemia and low HDL-cholesterol through increased catecholamines. Insulin, he also pointed out, can lead to the secretion of the prothrombotic plasminogen activator inhibitor-1. Other prothrombotic conditions in metabolic syndrome include increased serum fibrinogen, von Willebrand factor, factor VII, and thrombin, as well as increased platelet aggregation (19).

Vascular endothelial dysfunction is thought to play a key role in atherogenesis. While type II diabetes is known to be associated with endothelial dysfunction, only recently has there been evidence that endothelial dysfunction also takes place in insulin resistance states without diabetes (20, 21). The reasons for this have not been worked out yet, but one possibility could be related to angiotensin II, which shares a common signaling pathway with insulin (20). It is thought that a hyperinsulinemic state may lead to increased sensitivity to angiotensin II, which in turn could cause increases in cell growth, plasminogen activator inhibitor-1, in-

tracellular adhesion molecule-1 and monocyte chemoattractant protein-1. Defects in insulin sensitivity may interfere with insulin-stimulated endothelial vasodilation. This may occur through defects in the phosphatidylinositol 3-kinase pathway, which normally stimulates endothelial nitric-oxide synthase to produce the vasodilator nitric oxide.

The excess adiposity associated with metabolic syndrome may also play an important pathophysiologic role in the development of cardiovascular disease. The impact of obesity's role in metabolic syndrome was recently reviewed by Grundy (11), who noted that "obesity is associated with all the risk factors of the metabolic syndrome." Adiposity, especially visceral, can lead to increased free fatty acid formation from lipolysis, which has been shown to decrease insulin sensitivity by interfering with the mobilization of the glucose transporter, GLUT4 (22, 23). Other candidates for linking adiposity to insulin resistance are tumor necrosis factor- α (TNF- α), adiponectin, resistin (4, 22, 24), and leptin (25, 26).

Insulin resistance at the level of the adipocyte causes increased release of fatty acids due to a lack of glucose uptake for its use in triglyceride formation and a decreased inhibition of hormone-sensitive lipase (24). In addition to causing muscle insulin resistance and hyperinsulinemia, increased fatty acids will stimulate the liver to produce and secrete triglyceride and very-low density lipoprotein (VLDL) particles. Increased serum VLDL is "nearly always" associated with low HDL (24).

Fatty acids also serve as ligands for peroxisome proliferator-activated receptors (PPARs), which are nuclear receptors that affect gene expression. One type, PPAR α , which is activated by fibrates, increases fatty acid oxidation and attenuates triglyceride synthesis and VLDL secretion. Stimulation of PPAR α also leads to increased production of apolipoprotein (apo) A-I, which enhances HDL levels. PPAR γ is bound by thiazolidinediones (TZDs), which stimulate the receptors and improve insulin sensitivity (24).

The role of PPARs in the development of cardiovascular disease is being investigated, but is so far unclear. For example, some data have suggested that, when activated by modified fatty acids, PPAR γ may stimulate lipid accumulation in macrophages. However, activation of PPAR γ has also been shown to stimulate cholesterol efflux, and TZD treatment has been shown to inhibit atheroma formation in mouse atherosclerosis models (27).

A chronic inflammatory state has been implicated in the development of atherosclerosis. Several studies have shown a link between metabolic syndrome and systemic inflammation (28, 29). For example, Festa et al., analyzed the relationship between

metabolic syndrome and markers of inflammation, including C-reactive protein (CRP), in the Insulin Resistance Atherosclerosis Study (IRAS) (30). Using data from approximately 1,000 nondiabetic individuals, they showed that BMI, waist circumference, and insulin sensitivity (by glucose tolerance test and fasting insulin) were associated with levels of CRP, fibrinogen and white cell count. Furthermore, the number of metabolic conditions (dyslipidemia, visceral adiposity, insulin resistance, hypertension) that subjects had was directly proportional to CRP levels.

Ridker et al. also found this to be the case in an evaluation of the Women's Health Study (WHS) (31). In an analysis of 14,719 women (those who participated in the WHS but had diabetes or a history of hormone-replacement therapy were excluded), they determined that participants with metabolic syndrome and elevated CRP levels (≥ 3 mg/L) had a greater age-adjusted relative risk for future cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization procedures, cardiovascular death) than those with metabolic syndrome and low CRP levels. Participants with metabolic syndrome had age-adjusted incident rates for future cardiovascular events of 5.9 per 1,000 person-years if the CRP level was ≥ 3 mg/L and 3.4 per 1,000 person-years if it was lower.

Matrix metalloproteinases (MMPs) are higher in people with diabetes and coronary disease, and are thought to have a role in atherosclerotic plaque instability (32). Treatment of diabetes with TZDs leads to a reduction in serum levels of MMP-9 (33). The same study that showed this effect on MMP-9 also demonstrated a significant decline in serum CRP with TZD treatment.

Treatment Issues

The pharmacologic treatment of metabolic syndrome and its attendant cardiovascular risk has been reviewed extensively elsewhere (18, 22, 24, 34) and will not be repeated here. One pharmacologic intervention worth mentioning for its novelty is the use of rimonabant, a selective cannabinoid type 1 blocker, for obesity and metabolic syndrome. As presented at the European Society of Cardiology 2004 meeting, the results of the RIO-Europe trial, a Phase III study comparing rimonabant to placebo in the treatment of obesity over a period of two years, showed that half of those individuals diagnosed with metabolic syndrome at the beginning of treatment no longer had the diagnosis at one year. This reversal was characterized by a decrease in waist circumference, a 27% increase in HDL-cholesterol, an 11% decrease in triglycerides, and an improvement in insulin sensitivity (35).

More recently, the results of the RIO-NA (North American) trial were presented at the American Heart Association 2004 Scientific Session. This randomized, double-blind trial showed that after two years, the percentage of those randomized to rimonabant who met diagnostic criteria for metabolic syndrome was 22.4%, down from 34.8% at the study's enrollment. As with RIO-Europe, there were statistically significant reductions (compared with placebo) in waist circumference and triglycerides, and an increase in HDL cholesterol (36).

How best to treat advanced coronary disease (CAD) in patients with metabolic syndrome and diabetes remains a major challenge. Primary and secondary prevention of myocardial infarction is especially important in the diabetic patient, because diabetics have higher mortality rates than nondiabetics following myocardial infarction (37, 38).

There is a need for clinical trials focusing on the treatment of coronary artery disease in the metabolic syndrome patient, but many insights can be gained by a survey of the trials of revascularization in the diabetic patient. The well-known *post hoc* analysis of the Bypass Angioplasty Revascularization Investigation (BARI), a trial that predated the use of intracoronary stents and glycoprotein IIb/IIIa inhibitors, showed that outcomes were improved for bypass surgery as compared to angioplasty. A seven-year follow-up of the BARI study focusing on diabetic patients (39) revealed a statistically better survival rate and a decreased incidence of non-Q wave myocardial infarction for diabetics undergoing coronary artery bypass grafting (CABG). Patients randomized to angioplasty also had a much greater revascularization rate (59.7%) compared with those randomized to CABG (13.1%).

Since then, the optimal treatment of multivessel CAD in diabetics has been the subject of some controversy. The Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) suggested a greater survival rate at two years for those diabetic patients treated with CABG, and an eight-year follow-up of the Emory Angioplasty versus Surgery Trial (EAST) also supported the BARI findings (40, 41). However, the Randomized Intervention Treatment of Angina (RITA) study, and the Medicine, Angioplasty, or Surgery Study (MASS-II), which included some diabetic patients, had similar prognoses for angioplasty and CABG (42–44). Analyses of other randomized and nonrandomized trials have provided conflicting results (42).

The Northern New England Cardiovascular Disease Study Group observed 2,700 diabetic patients over five years, who were similar to the population studied in BARI but were non-randomized. Roughly 45% had three-vessel CAD, and these patients had a

significantly higher mortality rate (hazard ratio = 2.02) if treated initially with angioplasty as compared with CABG. Those with two-vessel CAD also had a trend towards a mortality benefit with CABG, but it was not statistically significant (42).

A subanalysis of the Arterial Revascularization Therapy Study (ARTS) trial by Abizaid et al. (45) focused on the one-year outcomes for diabetics enrolled in this study, which randomized 1,200 patients with multivessel CAD to CABG or intracoronary stenting. Of the total number of enrollees, 200 were diabetic. Diabetic patients treated with stenting had a lower event free survival rate (63%) at one year than those treated with CABG (84%), owing to a higher rate of repeat revascularization. However, rates of all-cause mortality, cerebrovascular events, and myocardial infarction were similar, although the incidences were generally small. It should also be pointed out that only 3.5% of the diabetic patients received a glycoprotein IIb/IIIa inhibitor as adjunctive therapy to stent placement (40).

The idea that advances in percutaneous intervention such as adjunctive medical therapy would lead to better outcomes for diabetics treated with stents has been challenged by the results of a subanalysis of the Prevention of Restenosis with Tranilast and its Outcomes (PRESTO) by Mathew et al. (46). Roughly 2,600 diabetics were enrolled in this trial designed to test the efficacy of tranilast in preventing stent restenosis. Mathew et al. concluded that diabetics had a higher incidence of death, myocardial infarction and target vessel revascularization, even after controlling for a number of factors including age, smoking status, history of congestive heart failure, number of diseased vessels, and lesion type. However, the use of glycoprotein IIb/IIIa inhibitors in PRESTO was still relatively low (43%) compared to current practice.

An attempt to determine the best revascularization method for diabetics with multivessel CAD will be made by the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial (47). FREEDOM is a multicenter, prospective trial that will randomize individuals with diabetes and multivessel CAD to either CABG or percutaneous coronary intervention with sirolimus-eluting stent. Follow-up of the primary endpoint of mortality will continue for five years.

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