

MINI-REVIEW: EXPERT OPINIONS



Epidemic Obesity and the Metabolic Syndrome

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Clustering of cardiovascular risk factors, specifically, hypertension, diabetes, dyslipidemia and obesity, was described in the 1960s and 1970s.^{1,2} However, these studies did not emphasize possible etiologies for this clustering phenomenon. In the 1987 Banting lecture, Reaven³ described clustering of cardiovascular risk factors as syndrome X and suggested that insulin resistance may be the cause. Specifically, Dr Reaven argued that this syndrome might occur even in individuals who are not obese. Pouliot et al⁴ emphasized visceral obesity as a possible cause of the metabolic syndrome. Using factor analysis (a multivariate statistical technique that reduces a large number of intercorrelated variables to a smaller number of underlying independent variables), Meigs et al⁵ showed in the Framingham Study that hypertension constitutes a separate factor from hyperinsulinemia. Using a direct measure of insulin resistance, the Insulin Resistance Atherosclerosis Study (IRAS) came to a similar conclusion.⁶ These 2 reports^{5,6} suggest that insulin resistance may be the underlying cause of many, but perhaps not all, clusters of cardiovascular risk factors initially described in the 1960s and 1970s. Insulin resistance is a common feature of both type 2 diabetes and obesity. Because the prevalence of diabetes and obesity has risen dramatically between 1990 and 2000,⁷ the incidence of cardiovascular risk factors is likely to increase as well.

The Metabolic Syndrome

Obesity, type 2 diabetes, and the metabolic syndrome are multifactorial diseases of considerable heterogeneity.⁸ However, whereas diagnostic criteria for obesity and for

type 2 diabetes are clear cut, this is not the case for the metabolic syndrome. There have been a number of attempts to develop standardized criteria for the diagnosis of the metabolic syndrome. The World Health Organization (WHO) developed a definition in 1998 that stated that individuals need to show evidence of insulin resistance and at least 2 of 4 other factors (hypertension, hyperlipidemia, obesity, and microalbuminuria).⁹ Isomaa et al¹⁰ suggested that this definition of the metabolic syndrome strongly predicted cardiovascular disease in the Botnia, Finland, population. A more recent version of the WHO definition¹¹ (Table 1) has been described using a lower cutoff for hypertension, 140/90 versus 160/90 mm Hg.⁹ In 2001, the National Cholesterol Education Program (NCEP) suggested another definition for the metabolic syndrome (Table 2),¹² which required at least 3 of 5 factors to be present for definition of the metabolic syndrome. The 5 factors are the following: increased waist circumference, hypertriglyceridemia, low HDL cholesterol, hypertension, and a fasting glucose of 110 mg/dL or higher. This definition is easier to use in clinical practice because glucose tolerance testing, insulin concentration measurements, and microalbuminuria testing are not required. Lemieux et al¹³ have introduced an even simpler definition of the metabolic syndrome in men, “the hypertriglyceridemic waist” (Table 3). Because of its greater clinical applicability, this review will emphasize the NCEP definition of the metabolic syndrome.

Recently, the Third National Health and Nutrition Examination Survey (NHANES) reported on the prevalence of the NCEP-defined metabolic syndrome.¹⁴ The overall prevalence of the metabolic syndrome in adults over the age of 20 years

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TABLE 1. National Cholesterol Education Program (NCEP) Adult Treatment Panel III: The Metabolic Syndrome*¹²

Risk Factor	Defining Level
Abdominal obesity (waist circumference)	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	>150 mg/dL
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	>130/80 mm Hg
Fasting glucose	>110 mg/dL

*Diagnosis is established when >3 of these risk factors are present.

was 24%, but the age-specific rate increased rapidly. The prevalence in 50-year-old subjects was >30%, and the prevalence in subjects age 60 years and over was 40%. In addition, the prevalence was highest in Hispanics and lower in non-Hispanic whites and in African Americans. The lower prevalence among African Americans may be explained by the 2 separate lipid criteria defined by the NCEP (high triglycerides and low HDL cholesterol), which offset the higher rates of hypertension and glucose intolerance observed in this ethnic group.

The prevalence of coronary heart disease (CHD) in the NHANES population over the age of 50 has recently been explored by Alexander et al.¹⁵ In this study, the prevalence of the NCEP-defined metabolic syndrome among diabetic subjects was 86%. A lower (but still higher-than-average) prevalence of the metabolic syndrome was observed in subjects with impaired glucose tolerance (31%) and impaired fasting glucose (71%). The prevalence of the metabolic syndrome in the NHANES study was 60% greater than the prevalence of type 2 diabetes in the same population. In addition, the

TABLE 2. World Health Organization (WHO) 1999 Definition of Metabolic (Insulin Resistance) Syndrome¹¹: Impaired Glucose Tolerance,* Diabetes Mellitus,† or Insulin Resistance,‡ Together With at Least 2 of the Components Listed in the Table

Components	Criteria
Hypertension	Raised arterial pressure (>140/90 mm Hg) or antihypertensive medication
Dyslipidemia	Raised plasma triglycerides (>1.7 mmol/L) or low HDL cholesterol (<0.9 mmol/L in men and <1.0 mmol/L in women)
Central or general obesity	Waist to hip ratio >0.90 in men; >0.85 in women or body mass index >30 kg/m ²
Microalbuminuria	Urinary albumin excretion rate >20 μg/min or albumin:creatinine ratio >30 mg/g

*Two hours post–glucose load plasma venous glucose >7.8 mmol/L.

†Fasting plasma venous glucose >6.1 mmol/L or 2-hour post–glucose load plasma venous glucose >11.1 mmol/L.

‡Highest quartile fasting insulin or Homeostasis Model Assessment score for population under investigation.

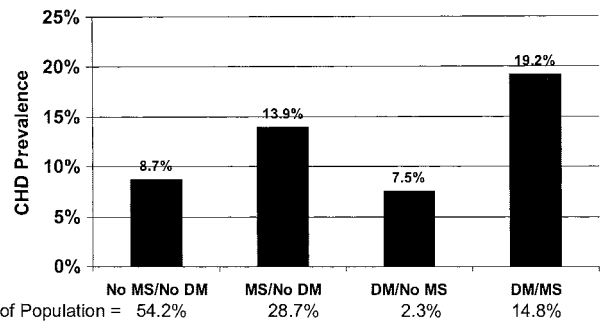
TABLE 3. Criteria for Hypertriglyceridemic Waist in Men¹³

Characteristics	Criteria
Triglyceride	>2.0 mmol/L
Waist	>90 cm

prevalence of CHD in nondiabetic subjects who also had the metabolic syndrome was intermediate, falling between the prevalence among nondiabetic subjects without the metabolic syndrome and diabetic subjects with the metabolic syndrome (Figure). Interestingly, the relatively rare diabetic subjects without the metabolic syndrome (≈15%) had a prevalence of CHD similar to that of nondiabetic subjects without the metabolic syndrome. Although these results need to be replicated in other populations, and particularly in prospective studies, these observations suggest that subjects with the NCEP-defined metabolic syndrome have an intermediate risk of CHD and are not equivalent in risk to subjects with only CHD or type 2 diabetes.

Insulin Resistance, Sympathetic Tone, and Hypertension

Abnormalities of glucose, insulin, and lipoprotein metabolism are common in patients with hypertension,^{16,17} and hyperinsulinemia has been proposed as the link between hypertension, obesity, and impaired glucose tolerance.¹⁸ The mechanism behind this association is unclear, as short-term insulin infusion induces skeletal muscle vasodilation¹⁹ that is mediated by NO²⁰ and results in a decrease in systemic vascular resistance.²¹ Because insulin is a direct vasodilator, other physiological mechanisms will have to come into play if insulin is to have a causal role in the pathogenesis of hypertension.¹⁷ In normal individuals, acute increases in plasma insulin within a physiological range increase sympathetic neural outflow without elevating arterial pressure.²² It is reasonable to postulate that the sympathetic nervous system overrides the normal vasodilatory effects of insulin under more extreme conditions such as sucrose feeding,²³ in obesity,



Age-adjusted prevalence of coronary heart disease in the US population >50 years of age categorized by presence of metabolic syndrome (MS) and diabetes mellitus (DM). Combinations of metabolic syndrome and diabetes mellitus status are shown.¹⁵

and with hypertension.²⁴ Even lean individuals with essential hypertension have insulin resistance and hyperinsulinemia.^{16,25} In short, the link between insulin resistance and hypertension is given through the sympathetic nervous system.

Insulin Resistance and Heart Failure

Obesity, type 2 diabetes, and insulin resistance are also important risk factors for the development of heart failure.^{26,27} Conversely, heart failure causes insulin resistance and is associated with increased risk for the development of type 2 diabetes.²⁸ Like the development of cardiovascular disease due to impaired intracellular insulin signaling,²⁹ the development of insulin resistance with heart failure is likely to be multifactorial.²⁷ Heart failure may cause insulin resistance by sympathetic overactivity, impaired endothelial function, loss of skeletal muscle mass, or increased circulating cytokines such as tumor necrosis factor α . We have argued that a vicious cycle is set into motion in which heart failure and insulin resistance worsen each other.²⁷

Subclinical Inflammation and the Metabolic Syndrome

Recently, much attention has been given to the metabolic syndrome. Ridker et al³⁰ have shown that C-reactive protein (CRP), a marker of subclinical inflammation, strongly predicts the risk of coronary events. In addition, CRP predicts the development of coronary events even after Framingham global risk is considered.³¹ One link between subclinical inflammation and CHD may be the metabolic syndrome and insulin resistance. In nondiabetic IRAS subjects, CRP levels were significantly correlated with cardiovascular risk factors (correlation of CRP with body mass index, 0.40; with waist, 0.43; with systolic blood pressure, 0.20; with fasting glucose, 0.18; with fasting insulin, 0.33; and with insulin sensitivity, -0.37 ; all probability values, <0.001).³¹ In addition, the level of CRP was strongly correlated with the number of metabolic disorders (dyslipidemia, upper body adiposity, insulin resistance, and hypertension).³¹ Consistent with the observational studies discussed above, insulin-sensitizing pharmacological agents such as rosiglitazone reduced CRP levels by $\approx 25\%$ in diabetic subjects.³² This result is similar to the effect of various statins in reducing CRP in other studies.³³

Treatment of the Metabolic Syndrome

The NCEP¹² suggests that behavioral interventions promoting weight loss and increasing physical activity are the basis of therapy for the metabolic syndrome (Table 4). Indeed, weight loss and increased physical activity have been shown by the Diabetes Prevention Program to reduce the risk of type 2 diabetes by 58%.³⁴ This reduction was greater than that seen with metformin in subjects with impaired glucose tolerance (25%). Additionally, the NCEP

TABLE 4. Approaches to the Treatment of the Metabolic Syndrome

Behavioral
Weight loss
Increased physical activity
Pharmacological (treat underlying conditions)
Lipid disorders
Hypertension
Diabetes
Should treatment of these underlying disorders be intensified because the subject has the metabolic syndrome?
Should underlying insulin resistance be treated in nondiabetic subjects?
No clinical trial data to date support the use of pharmacological agents to improve insulin sensitivity in nondiabetic subjects, although this is an area of active interest

suggests that subjects with the metabolic syndrome be treated for underlying conditions such as hypertension, diabetes, and lipid disorders. Currently, it is controversial whether nondiabetic subjects with the metabolic syndrome should be treated with insulin-sensitizing therapies. A case could be made for such intervention given that thiazolidinediones can reduce CRP to the degree that has been observed with statin therapy.^{32,33} However, insulin-sensitizing therapies have not yet been shown to reduce cardiovascular disease in randomized clinical trials.

The NCEP does not specify whether subjects with the metabolic syndrome should receive more intense therapy for underlying conditions (ie, hypertension, lipid disorders) than that called for by their estimated global risk based on the Framingham Study. A possible approach to this issue is given in Table 5. Global risk should be calculated for all subjects with the metabolic syndrome, even if they have <2 major risk factors. For example, if a subject has a global risk of 5% to 10% (corresponding to a LDL cholesterol goal of <160 mg/dL) and also has the metabolic syndrome, one might consider treating this subject as if he/she had a global risk of 10% to 20% (using an LDL cholesterol goal of <130 mg/dL).

If diabetes is considered a model for the metabolic syndrome and 85% of diabetic subjects have the metabolic syndrome, then a strong case can be made for drug treatment

TABLE 5. Clinical Approach to the Treatment of Dyslipidemia in the Metabolic Syndrome: Calculate Global Risk Even if Fewer Than 2 or More Major Risk Factors

Target therapy on the basis of global risk
If global risk is 15–20% and +metabolic syndrome, consider treating as if global risk is $>20\%$ *
If global risk is 5–10% and +metabolic syndrome, consider treating as if is high-risk primary prevention†

*CHD risk equivalent with LDL cholesterol goal <100 mg/dL.

†Global risk of 10–20% LDL cholesterol goal <130 mg/dL.

of the underlying conditions. Antihypertensive therapy using various initial treatments has been shown to be at least as effective in reducing cardiovascular morbidity and mortality in diabetic subjects as in nondiabetic subjects in the Hypertension Optimal Treatment (HOT) trial.³⁵ In addition, statin therapy was shown to reduce coronary events in diabetic subjects in the Scandinavian Simvastatin Survival Study (4S).³⁶ However, most subjects with the metabolic syndrome do not have diabetes.¹⁵ Unfortunately, few data exist on the treatment of nondiabetic subjects with the metabolic syndrome. In the 4S study, statin therapy reduced the prevalence of CHD in subjects with diabetes and in subjects with impaired fasting glucose.³⁶ Additionally, statin therapy was more effective in the 4S subjects with the lipid triad (high LDL cholesterol, high triglycerides, and low HDL cholesterol) than in subjects with isolated high LDL cholesterol.³⁷ Although the latter 2 reports from the 4S study did not test a specific definition of the metabolic syndrome, they imply that subjects with characteristics of the metabolic syndrome are likely to benefit from statin therapy.

Summary

An increasingly recognized risk factor for cardiovascular disease is the metabolic syndrome. Although many investigators believe that insulin resistance is the underlying cause of it, some features, such as hypertension, are more weakly correlated with insulin resistance. The NCEP definition of the metabolic syndrome is relatively simple and is related to risk of cardiovascular disease. Primary treatment should be behavioral intervention, but treatment of existing comorbid conditions such as hypertension and dyslipidemia needs to be considered. It is likely that subjects with the metabolic syndrome will receive more aggressive therapy than those with similar global risk without the metabolic syndrome. However, no guidelines address this issue at present.

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