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Reviews

Metabolic Syndrome and Cardiovascular Disease: Challenges and Opportunities

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Summary

Metabolic syndrome (MetS) has been defined in different ways. However, key components common to most definitions are a constellation of risk factors including abdominal adiposity, impaired fasting glucose, hypertension, and dyslipidemia. A major mediator of MetS appears to be insulin resistance, which relates to the development of the vascular and metabolic dysfunctions that precede overt cardiovascular disease and type 2 diabetes. Evidence suggests that the mechanisms underlying the elevated cardiovascular risk associated with MetS begin with subclinical organ damage. Therapy for MetS targets individual components of the syndrome and includes lifestyle interventions, lipid-modifying therapy, and antihypertensive agents, particularly those that inhibit the renin-angiotensin system. Results of trials of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have demonstrated reductions in new-onset diabetes and cardiovascular events in a wide range of patients. Clinical trials to investigate further the role of these drugs in the primary prevention of type 2 diabetes in patients with MetS are currently under way. The purpose of this paper is to review the MetS from the perspective of the cardiology workforce with the hope that a better understanding of the links between MetS and cardiovascular disease could lead to improved management of persons at risk.

Key words: renin-angiotensin system, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, cardiovascular disease, insulin resistance, metabolic syndrome, type 2 diabetes mellitus

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Introduction

The clustering within an individual of certain risk factors for cardiovascular disease (CVD), such as abdominal obesity, impaired fasting glucose, dyslipidemia, and hypertension, is termed MetS. This constellation of factors is associated with an increased risk for adverse outcomes that exceed the risk associated with the same conditions considered separately. MetS and its consequences present a challenge to the healthcare system, particularly in view of the increasing prevalence of overweight/obesity and type 2 diabetes mellitus in the United States and worldwide. Ongoing elucidation of the pathophysiologic mechanisms for MetS, however, also provides new targets for management and an opportunity to decrease the disease burden associated with these conditions.

Scope of the Problem

Despite public education programs urging adults and children to modify lifestyles to include healthy food choices and more physical activity, most Americans do not follow recommended dietary or exercise guidelines for maintaining health.[1] A recent analysis of data from more than 153,000 U.S. adults included in the Behavioral Risk Factor Surveillance System found that only 3% of adults followed a healthy lifestyle.[1] Moreover, almost

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1 in 10 followed no weight, dietary, or smoking recommendations at all.[1] These results are not surprising, considering that overweight and obesity have reached epidemic levels in the U.S. and trail only smoking as a preventable cause of death.[2] Excess weight is an important component of MetS as well as a modifiable risk factor for type 2 diabetes and CVD.

Diabetes is a major public health problem in the United States and worldwide. Type 2 diabetes accounts for over 90% of all cases.[2] The estimated prevalence of diabetes in the U.S. was more than 9% in 2002, representing nearly 20 million Americans.[2] The prevalence of diagnosed diabetes rose by 61% between 1990 and 2001, and from 2000 to 2001 alone, the prevalence increased by 8.2%.[2] Globally, diabetes affected an estimated 2.8% of all age groups, or 171 million people in 2000.[2] This number is expected to rise, with a projected increase to 366 million (4.4%) affected with diabetes worldwide by 2030. Developing nations are expected to experience greater increases in diabetes prevalence between 2000 and 2010, with rates in African and Asian countries projected to rise by two to three times their current rates.[3,4]

Undiagnosed diabetes and prediabetes conditions, such as impaired glucose tolerance and impaired fasting glucose, are common. An estimated 29% of all diabetes cases remained undiagnosed among Americans age 20 years or older during 1999–2000.[5] Among U.S. adults aged 40 to 74 years between 1988 and 1994, approximately 15% had impaired glucose tolerance and approximately 34% had impaired fasting glucose.[6] Projecting these rates onto the total U.S. population in 2000, an estimated 41 million adults aged 40 to 74 years would have prediabetes.

Currently, the United States has too few practicing endocrinologists treating adults compared with the millions of people with diagnosed diabetes, undiagnosed diabetes, and impending diabetes in the form of MetS.[7] At the current rate of endocrinologists joining the workforce, it will not be possible to screen, identify, and manage all of the individuals who require metabolic care. Cardiologists and cardiovascular-based physician extenders are in an ideal position not only to identify patients with MetS, but also to provide more aggressive management of risk factors (particularly, dyslipidemia and hypertension) directed at delaying or preventing the development of diabetes.

What is Metabolic Syndrome?

Although the designation of MetS as a unique pathophysiologic condition and as a predictor of disease has recently been questioned,[8] most clinicians and researchers have long maintained that certain metabolic risk factors are prone to cluster, and that this clustering increases the risk of CVD and diabetes.[9] A range of definitions for MetS have been proposed. All include components of obesity, dyslipidemia, hypertension, and elevated fasting glucose, but they differ in how many and which of these components are essential for diagnosis (Table 1).[10–12] Prevalence of MetS in the National Health and Nutrition Examination Survey (1999–2002) ranged from 20% to almost 40%, depending on which MetS definition is used.[13] No matter which definition is used, MetS is associated with significantly increased risk of cardiovascular morbidity and mortality.[14]

Insulin resistance and obesity are generally considered two important underlying risk factors for MetS.[15] Insulin resistance may be caused by excess body fat, particularly abdominal obesity, and by physical inactivity,[16] and it is associated with increased blood pressure through a number of different mechanisms.[9] Chronic insulin resistance leads to glucose intolerance and type 2 diabetes that is an independent risk factor for CVD.[9] Abdominal obesity can be assessed in various ways; several different sets of criteria now specify that waist circumferences be assessed using values specific to different ethnic/racial groups.[12,17]

TABLE 1 Criteria for metabolic syndrome according to NCEP ATP III, WHO, and the IDF

(a) NCEP ATP III, as revised by AHA/NHLBI Three or more of the following:	
Risk factor	Defining level
Abdominal obesity	Waist circumference
Male	>102 cm (>40 in)
Female	>88 cm (>35 in)
Triglycerides	⩾150 mg/dL
HDL-C	
Male	<40 mg/dL
Female	<50 mg/dL
Blood pressure	⩾130 / ⩾85 mm Hg
Fasting glucose	⩾100 mg/dL
(b) WHO	
Risk factor	Defining level
Glucose intolerance (plasma glucose >140 mg/dL), impaired glucose tolerance or diabetes mellitus, and/or insulin resistance plus at least two of the following:	
Blood pressure	⩾ 140/90 mmHg
Triglycerides and/or	⩾ 150 mg/dL
HDL-C	
Men	<35 mg/dL
Women	<39 mg/dL
Abdominal obesity (waist/hip ratio)	
Men	>0.90
Women	>0.85
BMI	>30 kg/m^2
Microalbuminuria	Urinary albumin excretion rate ⩾20 μg/min or albumin : creatinine ratio ⩾30 mg/g

TABLE 1 (*Continued*)

(c) IDF
Central obesity [a]
European men: waist circumference ⩾ 94 cm
European women: waist circumference ⩾ 80 cm
Plus
Any two of the following:
Triglycerides ⩾150 mg/dL
or
Specific treatment for this lipid abnormality
HDL-C
Male: <40 mg/dL
Female: <50 mg/dL
or
Specific treatment for this lipid abnormality
Blood pressure
systolic: ⩾130
or
diastolic: ⩾85 mmHg
or
treatment of previously diagnosed hypertension
Fasting plasma glucose ⩾100 mg/dL
or
previously diagnosed type 2 diabetes

[a] Other ethnicities have different cutpoints for waist circumference.

Abbreviations: ATP III = designates Adult Treatment Panel III; AHA = American Heart Association; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; IDF = International Diabetes Federation; NCEP = National Cholesterol Education Program; NHLBI = National Heart, Lung, and Blood Institute; WHO = World Health Organization. Adapted from Grundy SM et al.[10] World Health Organization[11] and the International Diabetes Federation.[12]

Insulin Resistance and Vascular Disease

Mechanisms underlying elevated CVD risk associated with MetS appear to involve subclinical target organ damage.[18] Among patients with hypertension but without diabetes, those with MetS seem more likely to have a higher prevalence of microalbuminuria and left ventricular hypertrophy, greater left ventricular mass index, and increased carotid intima thickness than those without MetS.[18] In addition, the greater the number of MetS components present, the greater the microalbuminuria and left ventricular mass index.[18] Furthermore, MetS was associated with a greater risk of target organ damage than any of its individual components.

Many different mechanisms are likely to contribute to the pathophysiology underlying the association between MetS and increased risk of atherosclerotic cardiovascular events. Alterations in metabolic pathways, inflammatory reactions, and other cellular processes may increase the risk of atherosclerosis in the insulin-resistant state. For example, there is growing evidence for cellular interactions between signaling pathways involved in actions of insulin and the renin-angiotensin system (RAS).[19,20] The RAS, through angiotensin II, is involved not only in the pathogenesis of hypertension and atherosclerosis, but also appears to play a role in the development of insulin resistance. Obesity also predisposes to cardiovascular disease: adipose tissue acts as an endocrine organ, secreting hormones and other substances that create a proinflammatory state and promote formation of atherosclerotic plaques.[21]

Nuclear peroxisome proliferator-activated receptors (PPARs) also appear to play a role in the atherogenic mechanisms underlying MetS. The PPARs regulate the expression of a variety of genes, and they modulate lipid metabolism, glycemic control, and vascular inflammation and tone.[22] Modulation of PPAR-related actions by cardiovascular risk factors, such as obesity and overweight, can lead to promotion of atherosclerotic disease.[22]

Therapeutic Approaches

Regardless of the particular definition of MetS used, it is essential to treat each cardiovascular risk factor aggressively. This approach certainly applies to impaired fasting glucose, dyslipidemia, and hypertension. The Diabetes Prevention Program Research Group evaluated the benefits of lifestyle intervention (weight loss and increased physical activity) compared with the antihyperglycemic agent metformin for prevention of diabetes in persons with elevated fasting and postload glucose concentrations.[23] Both treatments decreased new-onset diabetes, but lifestyle intervention led to a 39% (95% confidence interval [CI], 24–51%) lower incidence of diabetes than metformin treatment ($p<0.001$). Another treatment approach has been to use the alpha-glucosidase inhibitor, acarbose, to decrease postmeal blood glucose levels in glucose-intolerant persons and reduce the risk of hypertension and cardiovascular events.[24]

Drugs targeting PPAR-alpha (e.g., fenofibrate and gemfibrozil) and PPAR-gamma (e.g., thiazolidinediones such as rosiglitazone and pioglitazone) are also used in the treatment of MetS. Fibrates decrease triglycerides, increase high-density lipoprotein cholesterol, and may have some anti-inflammatory effects; however, their effect on CVD outcomes continues to be evaluated.[25] Thiazolidinediones increase insulin sensitivity, increase skeletal muscle glucose uptake, and decrease plasma levels of free fatty acids, and have been shown to reduce progression to diabetes in persons with elevated fasting glucose levels.[26] In addition, thiazolidinediones increase high-density lipoprotein cholesterol, generally lower triglycerides, and reduce inflammation, although their effect on low-density lipoprotein cholesterol may vary by drug. While thiazolidinediones are an attractive therapeutic option in patients with MetS, their long-term effects in the prevention of diabetes are yet to be determined and further study is warranted.

Antihypertensive agents have differing effects on components of the MetS. Diuretics and beta-blockers are

known to have metabolic effects that promote conditions favorable to the development of diabetes.[27] In contrast, patients without diabetes treated with (antihypertensive) regimens containing angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) show improved glucose metabolism and increased insulin sensitivity compared with regimens containing beta-blockers and diuretics.[28]

Furthermore, in large-scale trials, ACE inhibitors and ARBs have demonstrated efficacy in delaying development of new-onset diabetes.[28–31] The Heart Outcomes Prevention Evaluation (HOPE)[29] reported that 5 years of ramipril treatment in patients with vascular disease significantly reduced the incidence of new-onset diabetes (3.6% versus 5.4% with placebo; $p<0.001$). In a population of hypertensive patients with coronary artery disease, the International Verapamil SR Trandolapril Study (INVEST) showed lower rates of newly diagnosed diabetes in subjects randomized to the verapamil SR strategy, who were exposed to the ACE-inhibitor trandolapril, compared with those in the atenolol strategy (7.0 and 8.2%, respectively) during 2.7 years of follow-up.[31] Trials with ARBs have shown similar results. The Losartan Intervention For Endpoint reduction in hypertension study (LIFE) found that, among patients with hypertension and left ventricular hypertrophy, losartan-based treatment significantly reduced the risk of new-onset diabetes compared with beta-blocker–based therapy (6% versus 8%, respectively) after a mean of approximately 5 years.[32] After 4 years of follow-up in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) in high-risk hypertensive patients, the risk of new-onset diabetes was significantly decreased with valsartan compared with amlodipine, which is considered a metabolically neutral agent (hazard ratio, 0.77; 95% CI, 0.69–0.86; $p<0.0001$).[33]

The potential use of ACE-inhibitor and ARB therapy in primary treatment of MetS requires further investigation. Clinical trials that may provide further evidence for the metabolic benefits of these drugs are under way. The Metabolic Assessment of Diovan's Efficacy Incomparison to Thiazide Therapy (MADE-ITT) trial is a 16-week, randomized trial that will assess the effect of valsartan compared with hydrochlorothiazide on the metabolic profile of approximately 500 obese patients with National Cholesterol Education Program (NCEP) Adult Treatment Panel III-defined MetS. In particular, effects on insulin sensitivity, inflammatory markers, and plasma lipid levels will be assessed. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial will evaluate whether valsartan or the antidiabetic agent nateglinide will prevent new-onset diabetes or cardiovascular events in patients with impaired glucose tolerance at high cardiovascular risk. A total of 9,518 patients have been randomized, and results are expected in 2008.[34]

Conclusion

The rising prevalence of type 2 diabetes and the continued high rate of cardiovascular morbidity and mortality underscore the importance of recognition and diagnosis of associated metabolic risk factors. The vascular and target organ damage associated with insulin resistance and other components of what has been termed the MetS begin long before cardiovascular disease or type 2 diabetes becomes clinically evident. Cardiologists are positioned to play an important role not only in identifying patients at high risk for MetS but also in aggressively managing hypertension and dyslipidemia in order to stave off further metabolic insult.

Note Added in Proof

Since this review on MetS was written and accepted for publication, the results of the Diabetes Reduction Assessment with Ramipril and Rosiglitazine Medication trial (DREAM) have been published.[35,36] The DREAM study was a two-by-two factorial, double blind, randomized controlled trial of rosiglatozine and ramipril in 5269 patients with MetS, but without a history of heart disease, who were followed for a median of 3 years. The primary composite outcome was incident diabetes or death. Compared with placebo, rosiglitazone significantly reduced the occurrence of the primary outcome (HR 0.40, 95% CI 0.35–0.46), and approximately 50% of rosiglitazone treated patients became normoglycemic compared to 30% of placebo treated patients (HR 1.71, 95% CI 1.57–1.87). Ramipril did not significantly reduce occurrence of the primary outcome compared with placebo (HR 0.91, 95% CI 0.81–1.03), however there was a significant increase in the outcome of regression to normoglycemia in ramipril treated patients compared with placebo treated patients (HR 1.16, 95% CI 1.07–1.27). These data suggest that in patients with MetS, without a history of heart disease, inhibition of the RAS resulted in a trend towards suppression of death or incident diabetes. Furthermore, regression to normoglycemia in MetS patients treated with ramipril suggests inhibition of the RAS to be an important component in the armamentarium of agents available to manage risk factors in these patients.

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