CONTROVERSY IN CLINICAL ENDOCRINOLOGY

Metabolic Syndrome: A Multiplex Cardiovascular Risk Factor

Scott M. Grundy

Center for Human Nutrition, Department of Clinical Nutrition, and Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas 75390-9052

Context: The metabolic syndrome (MetS) is a multiplex risk factor for cardiovascular disease. The syndrome develops through interplay of obesity and metabolic susceptibility.

Objective: This article addresses whether the MetS construct has clinical utility.

Position: The National Cholesterol Education Program and other organizations have proposed that the MetS can be recognized clinically by a clustering of simple clinical measures including waist circumferences, blood pressure, triglycerides, high-density lipoproteins, and glucose. People with this clustering have most or all of the components of the MetS. Identifying the MetS has several advantages. It discovers persons who are at increased risk for cardiovascular disease. A diagnosis focuses more clinical attention on the underlying causes, notably obesity and other lifestyle factors; it thereby reinforces the utility of lifestyle changes in clinical practice. A diagnosis further informs physicians on choice and intensity of drug therapy for elevated cholesterol, aspirin prophylaxis, and blood pressure and glucose control. The introduction of the MetS has led to a large number of epidemiological, metabolic, and genetic studies that have heightened our understanding of the condition’s prevalence and pathogenesis. It has been a stimulus to the development of new drugs or drug combinations that will modify multiple risk factors simultaneously.

Conclusions: This author holds that the MetS counts as a multiplex cardiovascular risk factor that is clinically useful and will lead to advances in diagnosis and treatment of an important cause of cardiovascular disease. (J Clin Endocrinol Metab 92: 399–404, 2007)

RECENTLY, A DEBATE has emerged whether the concept of the metabolic syndrome (MetS) has validity and clinical utility. Some believe it is a useful construct (1–6); others disagree (7, 8). This article reviews some of the key features of the MetS debate and will outline a rationale clinical approach.

MetS as a Multiplex Cardiovascular Risk Factor

The MetS is one of several patterns of risk for atherosclerotic cardiovascular disease (ASCVD). It represents a combination of risk determinants that contrasts it to isolated cigarette smoking, hypertension, hypercholesterolemia, and diabetes. Its components include atherogenic dyslipidemia, elevated blood pressure, elevated glucose, a prothrombotic state, and a proinflammatory state (2, 5, 6). In its advanced form, clinical hyperglycemia (type 2 diabetes) is present. As a multiple-component condition, the MetS can be called a multiplex cardiovascular risk factor. Even without diabetes, the MetS imparts a doubling of relative risk for ASCVD (5). With diabetes, risk is increased even more. It is becoming increasingly common in the United States and worldwide, and is emerging as the dominant risk factor in Asia. The MetS follows in the wake of urbanization, increasing obesity, and sedentary life habits. Moreover, some ethnic groups are particularly susceptible to the MetS (5).

Issue of Pathogenesis

Much of the debate about the MetS centers on its pathogenesis. The metabolic interactions leading to a clustering of metabolic risk factors are not completely understood. Nonetheless, this clustering appears depend on two major factors: excess body fat and metabolic susceptibility. A simplified pathogenic scheme is suggested in Fig. 1. The core abnormality appears to be a metabolic susceptibility to the syndrome. When susceptible individuals acquire excess body fat, the syndrome develops.

Multiple factors appear to predispose to metabolic susceptibility, e.g., genetic defects in insulin signaling pathways, various disorders of adipose tissue (9), physical inactivity, mitochondrial dysfunction, polygenic variability in individuals and certain ethnic groups, advancing age, endocrine dysfunction, and certain drugs (5). Critical mediators of metabolic susceptibility are under intense evaluation; some of the targets of this investigation—so-called master metabolic regulators—include pathways activated by the insulin receptors, inflammatory cascades, AMP kinase, endocannabinoid receptors, nuclear receptors, corticosteroids, and mitochondrial oxidative pathways. Many people with metabolic susceptibility manifest insulin resistance. Because insulin resistance commonly associates with multiple metabolic risk factors (10–12), it is often referred to as the insulin resistance syndrome.
In other words, they accept that this clustering, here called a proinflammatory state—commonly cluster in individuals. Cardiovascular risk—atherogenic dyslipidemia, elevated verses influences contribute to metabolic susceptibility. Multiple adverse influences contribute to metabolic susceptibility.

The extent to which insulin resistance is a cause of the metabolic risk factors or is secondary to their multiple causes is uncertain. Finally, the severity of different metabolic risk factors varies among individuals and ethnic groups. This extends the pathogenesis to a susceptibility to particular risk factors. Some affected persons are more prone to dyslipidemia, others to hypertension, and still others to diabetes. Undoubtedly, influences on development of individual risk factors also vary, and these must be factored into the pathogenic sequence of the syndrome.

Although multiple influences contribute to the MetS, the syndrome appears to be relatively uncommon in the absence of some excess body fat. As obesity increases so does the prevalence of the MetS. Obesity thus can be said to be the predominant driving force behind the MetS. It is particularly detrimental in persons who have concomitant metabolic susceptibility from other causes. In obese persons, excess adipose tissue releases a variety of factors that likely contribute to metabolic risk factors. Excess release of non-esterified fatty acids predisposes to ectopic fat accumulation in liver, muscle, and visceral adipose tissue stores. Ectopic fat links particularly closely to risk factors. Other adipose tissue products are reported to affect systemic metabolism, among these are adiponectin, leptin, inflammatory cytokines, plasminogen activator inhibitor-1, resistin, and angiotensinogen. With obesity, the outputs of all of these products are higher except for adiponectin, which is abnormally low. Many studies implicate all of these changes to systemic insulin resistance and relate them to risk factor development.

**Issue of Definition and Overlapping Interests**

Most investigators agree that a set of factors that increase cardiovascular risk—atherogenic dyslipidemia, elevated blood pressure, elevated glucose, a prothrombotic state, and a proinflammatory state—commonly cluster in individuals. In other words, they accept that this clustering, here called MetS, exists and is common. All of these components can be detected through laboratory testing of varying degree of sophistication. Disagreement, however, exists on how best to identify this clustering phenomenon through a small set of simple clinical measures. The latter is what some investigators call a definition of the syndrome, analogous to defining hypertension on the basis of blood pressure levels and diabetes on the basis of fasting glucose levels. They criticize the MetS concept because of imperfection in identifying a complex disorder through a set of simple clinical measures. The National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines, recently updated, proposed that the finding of any three of five components (abdominal obesity, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, elevated blood pressure, and elevated glucose), which can be easily recognized, are sufficient for a diagnosis of MetS in clinical practice. Commonly accepted definitions were used for each component. Other clinical formulations of the syndrome have been proposed; but ATP III criteria are widely accepted in the literature. Other criteria in fact are quite similar to those of ATP III. This simple, practical approach in lieu of more complex measurements has been accepted by most, but not all, investigators.

Many different fields of medicine have an interest in the metabolic complications arising out of obesity and metabolic susceptibility. The MetS, which is one of these, is typically viewed as a cardiovascular risk factor. Nonetheless, it commonly occurs along with other medical problems—prediabetes and type 2 diabetes, fatty liver disease, cholesterol gallstones, polycystic ovary syndrome, obstructive sleep apnea, gout, and possibly even some forms of cancer. Many viewpoints and even vested interests yield different constructions of the consequences of metabolic dysregulation. At the same time, the overlapping of metabolic conditions provides an opportunity for multiple fields to interact more efficiently with one another.

**MetS Is a Progressive Disorder**

Achieving a consensus definition of the MetS is further complicated by the fact that it is progressive, i.e. its several components tend to worsen over time. Early in life, moderate obesity generally is well tolerated. But with advancing years, there commonly is progressive weight gain, a gradual loss of muscle mass, stiffening of the arterial tree, decline in secretory capacity of pancreatic β-cells, mitochondrial dysfunction, and increased inflammatory changes in adipose tissue as well as other age-related alterations. All of these changes accentuate the syndromes various components and raise the risk ASCVD. The syndrome often culminates in type 2 diabetes in which risk for vascular disease is markedly raised.

**MetS as a Marker for Long-Term Risk**

Some researchers have envisioned the MetS as a risk assessment tool to predict absolute, short-term risk for ASCVD. But because it is only one of several risk factors and does not incorporate all other risk factors, it is not an adequate global risk assessment tool. Persons with MetS nonetheless can be considered to be at a higher lifetime risk for ASCVD. Figure 2 shows how two position papers have placed the MetS relative to other risk factors. Persons with
MetS are candidates for more advanced short-term (10-yr) risk assessment for ASCVD, such as Framingham scoring (2), or when diabetes is present, with the UKPDS risk engine (18). But the major utility of detecting individuals with the MetS is to find those who are at high lifetime risk for both ASCVD and who desire more intensive intervention on lifestyle risk factors—obesity and physical activity—to slow progression to a higher absolute-risk category, which may eventually require drug treatment of individual risk factors.

**Lifestyle Interventions: Health Care Failure**

The emerging epidemics of obesity and its clinical complications threaten to reverse many of the advances in reducing the burden of cardiovascular disease and other chronic diseases. Beyond the public health sphere, available health care systems are ill-suited to cope with these epidemics. For example, in the United States, approximately three-fourths of all adults are overweight and obese (19), and at least one-third of these have advanced to the stage of MetS (20). The latter in particular are candidates for long-term medical intervention even if not yet drug therapy. Unfortunately, clinical therapies to treat underlying obesity often are unsuccessful (21). Modifying the health care system to more effectively cope with the MetS through lifestyle therapy will be necessary to reduce the burden of chronic disease associated with advancing age.

**Therapeutic Strategies**

All patients with MetS are at high enough relative risk for ASCVD to justify long-term intervention and monitoring in the clinical setting. But the MetS is not a risk-assessment tool for determining absolute risk for ASCVD; it is a target of therapy. The goals of therapy are to reduce both lifetime risk and short-term risk. The presence of the MetS per se indicates a higher lifetime risk. Estimation of absolute, short-term risk (e.g. 10-yr risk for coronary heart disease) also should be performed in all patients with the MetS. The latter commonly is divided into three categories: lower-to-moderate, moderately high (intermediate) (10–20%), and high (>20%). In the absence of clinically manifest ASCVD or diabetes, any person with MetS but without ASCVD or diabetes should undergo Framingham risk scoring (2) to determine 10-yr risk as one guide to clinical intervention. Affected patients with ASCVD or diabetes already are in a high-risk category without the need for Framingham risk scoring.

In Table 1, the primary goals of therapy for the MetS as a whole, for its underlying causes, and for metabolic risk factors are listed; also given are secondary goals that can be pursued based on clinical judgment. Factors that inform clinical judgment are those that can modify the risk category plus considerations of efficacies of available therapies and their costs and safety. The presence of emerging risk factors can be used to adjust the absolute risk status, but only after 10-yr risk-scoring has been carried out. Intervenational strategies are directed toward the causes of MetS or toward its consequences, which are direct causes of ASCVD.

**Goals for the MetS as a whole**

For persons found to be at lower-to-moderate risk, the primary goal is to reduce lifetime risk for ASCVD. The earlier the MetS can be detected and treated, the better for long-term prevention. Once a person has progressed to a moderately high global risk, efforts to reduce short-term (10 yr) risk should blend with reduction in lifetime risk. At this stage, consideration must be given to using drug therapies such as lipid-lowering drugs and aspirin. But lifestyle therapies remain paramount in intervention. For those who have progressed to the high-risk category, intensive intervention to reduce a high absolute risk must be instituted, usually with drug therapy directed at each of the metabolic risk factors.

**Goals for obesity management**

Weight reduction strikes at the heart of the MetS and will reduce all metabolic risk factors (22). Importantly, it delays progression of hyperglycemia (23). The primary goal of weight reduction at all levels of risk is to achieve a 10% reduction in total body weight in overweight/obese persons with the MetS (22). Secondarily, reduction of body mass index into the normal range of less than 25 kg/m² is desirable. Four therapies can be used for weight reduction: caloric restriction (e.g. 500 kcal/d deficit), increased physical activity, behavioral medication, and, in appropriate patients, FDA-approved weight-reduction drugs (22). Weight-loss drugs may be particularly appropriate in patients at higher risk. In addition to weight loss, all persons with the MetS should be instructed to consume a diet designed to maximally retard atherogenesis. At a minimum this diet should contain less than 7% saturated fatty acids, less than 1% trans fatty acids, and less than 200 mg/d cholesterol. The diet further should be designed to reduce blood pressure.

**Goals for systemic metabolic susceptibility**

Beyond weight reduction, increased physical activity is the most available way at present to reduce a generalized met-
TABLE 1. Therapeutic strategy for metabolic syndrome: primary goals of therapy (recommended) → secondary goals (informed by clinical judgment)

<table>
<thead>
<tr>
<th>Risk factor 10-yr risk for coronary heart disease</th>
<th>Lower-to-moderate risk (&lt;10%)</th>
<th>Moderately high risk (10–20%)</th>
<th>High risk (&gt;20%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>MetS as a whole</td>
<td>Reduce lifetime risk for ASCVD and diabetes</td>
<td>Reduce both lifetime and short-term risk</td>
<td>Reduce short-term risk</td>
</tr>
<tr>
<td>Obesity</td>
<td>10% reduction in body weight (preference to lifestyle therapy) → BMI &lt; 25%</td>
<td>10% reduction in body weight (consider weight loss drugs) → BMI &lt; 25%</td>
<td>10% reduction in body weight (consider weight loss drug) → BMI &lt; 25%</td>
</tr>
<tr>
<td>Atherogenic diet</td>
<td>Maximal antiatherogenic diet</td>
<td>Maximal antiatherogenic diet</td>
<td>Maximal antiatherogenic diet</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Exercise 30 min/d → 60 min/d</td>
<td>Exercise 30 min/d → 60 min/d</td>
<td>Exercise 30 min/d → 60 min/d</td>
</tr>
<tr>
<td>Atherogenic dyslipidemia:</td>
<td>LDL cholesterol (non-HDL cholesterol) &lt; 130 (160) mg/dl → &lt;100 (130) mg/dl (with lifestyle)</td>
<td>LDL cholesterol (non-HDL cholesterol) &lt; 130 (160) mg/dl (with drugs if necessary) → &lt;100 (130) mg/dl</td>
<td>LDL cholesterol (non-HDL cholesterol) &lt; 130 (160) mg/dl (with drugs if necessary) → &lt;70 (100) mg/dl (in CHD patients)</td>
</tr>
<tr>
<td>Atherogenic dyslipidemia:</td>
<td>Raise HDL (lifestyle therapy)</td>
<td>Raise HDL (lifestyle therapy)</td>
<td>Raise HDL (consider drug therapy)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>BP &lt; 140/90 mm Hg (with drugs if necessary) → 130/80 (with lifestyle therapies)</td>
<td>BP &lt; 140/90 mm Hg (with drugs if necessary) → 130/80 (with lifestyle therapies)</td>
<td>BP &lt; 140/90 mm Hg (with drugs if necessary) → 130/80 (with drugs in diabetes and chronic renal failure)</td>
</tr>
<tr>
<td>Elevated FBG (prediabetes)</td>
<td>FBG &lt; 100 mg/dl (with lifestyle therapy)</td>
<td>FBG &lt; 100 mg/dl (with lifestyle therapy)</td>
<td>FBG &lt; 100 mg/dl (consider insulin sensitizer)</td>
</tr>
<tr>
<td>Elevated FBG (diabetes)</td>
<td>HbA1c 6–7%</td>
<td>HbA1c 6–7%</td>
<td>HbA1c 6–7%</td>
</tr>
<tr>
<td>Prothrombotic state</td>
<td>No drug</td>
<td>Consider antiplatelet drugb</td>
<td>Antiplatelet drugb</td>
</tr>
<tr>
<td>Proinflammatory state</td>
<td>Complete smoking cessation</td>
<td>Complete smoking cessation</td>
<td>Complete smoking cessation</td>
</tr>
</tbody>
</table>

BP, Blood pressure; FBG, fasting blood glucose.

a High-risk patients include those ASCVD, diabetes, and those multiple risk factors and 10-yr risk for coronary heart disease greater than 20%.
b Antiplatelet drug: typically aspirin (81 mg).

<table>
<thead>
<tr>
<th>Therapeutic goals for each MetS component</th>
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</table>
| If treatment of the underlying causes is insufficient, attention can turn to the individual risk components. For atherogenic dyslipidemia, although low-density lipoprotein (LDL) cholesterol is the accepted first target of lipid-lowering therapy, non-HDL cholesterol, which is closely correlated with total apo B, and should be attacked as well in patients with the MetS (5). In subjects at lower-to-moderate risk, LDL cholesterol and non-HDL cholesterol should be reduced to less than 130 and less than 160 mg/dl, respectively. Lifestyle therapies are preferred to achieve these goals; whether to use adjunctive lipid-lowering drugs for higher cholesterol levels after lifestyle therapies is a matter of clinical judgment. For patients at moderately high risk, the primary goal for LDL cholesterol is less than 130 mg/dl (and non-HDL cholesterol < 160 mg/dl); if necessary, cholesterol-lowering drugs can be used to achieve this goal. A secondary goal of LDL cholesterol less than 100 mg/dl (non-HDL cholesterol < 130 mg/dl) may be prudent based on clinical judgment. In high-risk patients with the MetS, the primary goal is an LDL cholesterol less than 100 mg/dl (non-HDL cholesterol < 130 mg/dl) (5). For patients with established coronary heart disease, a secondary goal of LDL cholesterol less than 70 mg/dl (non-HDL cholesterol < 100 mg/dl) appears to give incremental benefit (24). It is recommended that an attempt be made to raise HDL cholesterol after the goals for LDL cholesterol and non-HDL cholesterol are achieved (5). However, no specific target of therapy is given because current therapies are inadequate to tailor responses.

The goal for blood pressure is a pressure less than 140/90 mm Hg; blood pressure-lowering goals may be required to achieve this goal. Further reduction to less than 130/80 is prudent if it can be achieved through lifestyle change (5, 25). Furthermore, the latter is a specific goal in high patients with diabetes and/or chronic renal failure (25).

The primary goal for prediabetes is to reduce fasting glucose levels to less than 100 mg/dl. This goal should be achieved if possible through lifestyle therapies. Clinical trials show that lifestyle therapies can retard the worsening of hyperglycemia in many patients (23). For higher-risk patients, consideration might be given to using insulin-sensitizing drugs in the attempt to slow progression of hyperglycemia (23). Once diabetes ensues, the primary goal is to reduce HbA1c to a range of 6–7% at all levels of coronary heart disease risk (26).

For MetS patients at high or moderately high risk, low-dose aspirin is considered advisable to diminish a prothrombotic state (5). If 10-yr risk is less than 10%, then the benefits of aspirin may be outweighed by the danger of bleeding. In addition, complete smoking cessation is mandatory in patients with the MetS to curtail a proinflammatory state.
MetS and the Crisis in Polypharmacy

Lifestyle therapies (weight reduction, increased physical activity, and an anti-atherogenic diet) offer the greatest promise for controlling the emerging epidemic of the MetS. However, many patients with advanced stages of MetS will require risk-reducing drugs; and, if so, current treatment guidelines should be followed for each risk factor. Promising new drugs to treat obesity and metabolic susceptibility are on the horizon (27). But drug treatment of metabolic risk factors presents a special challenge. Those with the MetS and/or diabetes are particularly likely to require polypharmacy, which increases costs and decreases compliance. Possible solutions to the growing problem of polypharmacy include combining multiple drugs into single pills or to create drugs with multiple metabolic actions (27). The ideal drug for metabolic risk factors would be one that simultaneously lowers apo B-containing lipoproteins, raises HDL cholesterol, and reduces blood pressure and glucose levels. Such a drug has yet to be developed; it presumably will be necessary to target a master regulatory pathway.

Medical Utility of MetS

The MetS was introduced into ATP III clinical guidelines to highlight the ASVCD risk accompanying obesity (5). Although some have questioned whether the MetS has any clinical utility (7, 8), there are several reasons why many believe that it is useful. It is a simple means of calling attention to patients who are at approximately twice the risk for ASCVD and five times the risk for type 2 diabetes (5), and who deserve increased attention in clinical management and monitoring. Affected persons are at high lifetime risk for both ASCVD and diabetes. Such persons deserve more intensive lifestyle therapies at an early stage to delay progression to still higher risk. Presence of the MetS further calls for a more thorough short-term (10 yr) risk assessment (e.g. Framingham risk scoring) as a guide to drug therapy of risk factors. An understanding of the MetS concept by health care professionals will heighten awareness that multiple risk factors likely are present when a single risk factor is identified. It will further focus clinical attention on the underlying causes of these risk factors, i.e. obesity and physical inactivity. This should reinforce the need for lifestyle therapies. Beyond ASCVD risk factors, the presence of the MetS will alert clinicians to the likelihood of related conditions, e.g. obstructive sleep apnea, fatty liver, cholesterol gallstones, and polycystic ovarian disease. The occurrence of the MetS can also serve as a guide to drug therapies for treatment of metabolic risk factors. For example, its identification calls for consideration for a lower LDL cholesterol goal in patients at moderately high risk for ASCVD (28), in patients with diabetes (28), and in patients with established coronary heart disease (24). In hypertensive patients with the MetS, renin-angiotensin blockade and calcium blockers may have priority over diuretics and β-blockers (29). Because of higher risk, the presence of the MetS calls for consideration of aspirin prophylaxis for prevention of ASCVD events.

Identification of a clinical condition is a stimulus to other areas of medicine beyond clinical practice. Epidemiologists have shown great interest in the MetS; they have determined its prevalence in different populations and estimated the proportion of risk attributable to the syndrome (5). Their studies have documented that risk factor clustering exists beyond chance occurrence of risk factors; they have also shown different patterns of clustering in different ethnic groups. The introduction of the MetS into clinical practice has been a stimulus to metabolic and genetic research on the underlying causes of the syndrome; this has been shown by an increasing number of publications. It has further encouraged more attention to research on lifestyle approaches to reduce risk for its complications. Finally, its introduction has been a boon to pharmacological research to discover new drugs for treatment of the syndrome (27). The goal for drug therapies is to discover agents that will simultaneously reduce multiple risk factors (e.g. reduced LDL cholesterol, raise HDL cholesterol, lower blood pressure, and to mitigate dysglycemia). This may be achieved either by developing drugs that will strike at core metabolic susceptibility or by combining medications into single preparations to reduce the need for polypharmacy (27).

Conclusions

Global urbanization and sedentary life habits are producing a sharp increase in obesity and its concomitant metabolic risk; the latter combined into a multiplex risk factor for ASCVD goes by the name of MetS. A high prevalence of MetS is particularly common in some ethnic groups, especially in the Asian world. However, in no country is the health care system geared to cope with this medical crisis. Public health efforts to promote weight control and physical activity should be given a high priority in all nations. Health care systems need to be reconfigured to focus on preventive medicine, and especially for obesity and the MetS. Unless this is done, humanity will pay a terrible price—economically, socially, and individually—in the 21st century.

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Address all correspondence and requests for reprints to: Scott M. Grundy, M.D., Ph.D., Center for Human Nutrition, Department of Clinical Nutrition, and Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Y3.206, Dallas, Texas 75390-0952. E-mail: Scott.Grundy@UTSouthwestern.edu.

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