MINI-REVIEW:
EXPERT OPINIONS

The Metabolic Syndrome

More Than the Sum of Its Parts?

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The prevalence of obesity has risen dramatically in the United States.[1] This has led to a marked increase in the metabolic syndrome (MetSyn), a clustering of atherosclerotic cardiovascular disease risk factors characterized by visceral adiposity, insulin resistance, low HDL cholesterol (HDL-C), and a systemic proinflammatory state.[2] In the United States, the MetSyn affects roughly 25% of adults over the age of 20 and up to 45% of the population over 50. These observations have focused attention on the role of metabolic derangements in the development of cardiovascular disease. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines highlighted the key features of this syndrome and proposed a clinical definition to facilitate diagnosis and preventive interventions.[3] This binary definition is based on having at least 3 of 5 criteria (Table). The diagnosis of the MetSyn appears to identify substantial additional cardiovascular risk above and beyond the individual risk factors.[4] Therefore, the clinical diagnosis of MetSyn may be a valuable tool for identification of the elusive high-risk patient.

Distinct pathophysiological components of the MetSyn need to be defined if we are to identify the life-style and pharmacological interventions that will succeed in modulating the primary abnormalities of the disorder. Factor analysis has been applied to data from epidemiological studies to reduce the large number of related metabolic variables into a smaller set of core factors.[5] Such studies suggest that key components of the MetSyn include central obesity, insulin resistance, dyslipidemia, and hypertension, in addition to chronic inflammation, procoagulation, and impaired fibrinolysis.[6] However, current clinical MetSyn guidelines do not incorporate inflammatory or hemostatic factors. In fact, a situation is evolving in clinical practice in which the use of traditional risk factors, absolute risk quantification, diagnosis of the MetSyn, and consideration of inflammatory biomarkers are being considered without global integration of their impact on cardiovascular risk. One approach to dealing with these apparently conflicting needs is to build a broad and inclusive framework of the underlying molecular mechanisms of the MetSyn and to use this as a point of reference for patient-oriented experiments, epidemiological and genetic studies, randomized clinical trials, and clinical practice.

Obesity: What Measures Are the Best Predictors of Metabolic and Cardiovascular Complications?

Although obesity is a powerful risk factor for type 2 diabetes mellitus (DM-2) and cardiovascular diseases across populations, substantial heterogeneity exists in the relationship between metabolic and cardiovascular abnormalities and the degree of obesity.[7] A significant minority of subjects who are defined as obese by current guidelines do not develop insulin resistance; conversely, insulin resistance can be present in lean individuals.[8] Genetic and environmental factors may have a major impact on the metabolic and cardiovascular consequences of obesity, although the mechanisms by which genetic factors modify the effects of obesity are largely unknown. A major challenge for MetSyn research remains

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MetSyn Features, Measurement of These Features, and Features Included in the Current NCEP ATP III MetSyn Guidelines

MetSyn Feature	Clinical Measures	Research Measures	NCEP ATP III Criteria
Obesity	Waist	Displacement techniques	Waist
	Body mass index	Bioelectrical impedance	
		DEXA scanning	
		CT	
		MRI	
		Plasma leptin, adiponectin, resistin	
Insulin Resistance	Fasting plasma glucose	Plasma insulin	Fasting plasma glucose
	Oral glucose tolerance testing	HOMA/QUICKI	
		Intravenous glucose tolerance testing	
		Hyperinsulinemic clamp	
Hypertension	Systolic and diastolic BP	Vascular compliance/stiffness	Systolic and diastolic BP
	Ambulatory BP	Microalbuminuria	
		Angiotensin II	
		Endothelin	
Lipoproteins	TG, VLDL	Transfer proteins and enzyme activity	TG
	HDL	Cholesterol efflux assays ex vivo	HDL
	Small dense LDL	Postprandial lipoprotein responses	
		Lipoprotein turnover studies	
Inflammation	White cell count	Serum amyloid A	NA
	C-reactive protein	Fibrinogen, factor VIII	
		Sialic acid	
		Cytokines IL-6, TNF-α, IL-10	
		Soluble adhesion molecules: ICAM-1, VCAM, E-selectin	
		Evoked inflammatory responses	
Prothrombotic, fibrinolytic		Plasma PAI-1, D-dimer	NA
		Plasma FPA, F1–2	
		Urinary 11-dehydroTXB	
Oxidant stress		Oxidized LDL	NA
		Isoprostanes	
		DNA /protein adducts	
Genetics		Candidate gene single nucleotide polymorphisMetSyn (SNPs)	NA
		Genome-wide scan—linkage analysis	

BP indicates blood pressure; DEXA, dual-energy X-ray absorptiometry; HOMA, Homeostasis Model Assessment (HOMA); QUICKI, Quantitative Insulin Sensitivity Check Index ; IL, interleukin; TNF, tumor necrosis factor; ICAM, intercellular adhesion molecule; VCAM, vascular cellular adhesion molecule; PAI, plasminogen activator inhibitor; and NA, not applicable.

the identification of features of adiposity that best reflect increased risk of developing the MetSyn.

The current clinical approach to the MetSyn uses sex-specific waist circumference criteria to define the body mass component contributing to the MetSyn. The rationale for the use of waist criteria arises partly from data showing that measures of overall obesity, such as body mass index, are relatively insensitive indicators of the risk for metabolic and cardiovascular complications of obesity, as compared with measures of central or abdominal adiposity.[9] Waist circumference reflects both abdominal subcutaneous adipose tissue (SAT) and abdominal visceral adipose tissue (VAT) and is a general index of central (trunk) fat mass. VAT has been proposed as the major determinant of metabolic and cardiovascular complications of obesity.[10] However, this remains controversial, and it is unclear whether more accurate measures of total body fat, trunk fat mass, or specific abdominal SAT or VAT compartments (including CT and MRI) provide superior information regarding obesity complications.[11] Alternatively, the use of novel biochemical measures of adipose mass and function may be a more practical way to incorporate additional adipose readouts into large epidemiological studies

and clinical practice. Adipose tissue is an active secretory organ that elaborates a variety of molecules known as adipocytokines, including tumor necrosis factor α, interleukin-6, leptin, adiponectin, and resistin, that may mediate many of the metabolic changes in the MetSyn.[12] Some of these fat-derived factors may be directly atherogenic. Plasma leptin, which is largely derived from adipose tissue, increases in obesity and insulin-resistant states. Leptin deficiency in mice protects against atherosclerosis despite causing massive obesity,[13] and plasma leptin levels were found to be predictive of cardiovascular events, independent of traditional risk factors, body mass index and C-reactive protein (CRP) levels.[14] In contrast, plasma levels of adiponectin are reduced in obesity and DM-2, and early evidence suggests that this molecule may have antiatherosclerotic properties in mice models and in humans.[15,16] Whether these measures of adipose tissue hormonal activity will be superior markers of cardiovascular risk over anatomic measures of obesity remains to be determined.

Insulin Resistance: Should We Incorporate Measures of Insulin Resistance Into Clinical Practice?

Many researchers believe that insulin resistance is the pathophysiological process underlying the clustering of cardiovascular risk factors in the MetSyn.[8] Indices of insulin resistance predict atherosclerosis and cardiovascular events independent of other risk factors including fasting glucose and lipid levels.[17] Current NCEP ATP III guidelines use impaired fasting glucose (>110 mg/dL) as one criterion for identifying subjects with MetSyn. However, many subjects with normal fasting glucose levels have insulin resistance.[8] The recent application of the ATP III MetSyn criteria to subjects studied at the third National Health and Nutrition Examination Survey (NHANES) showed that impaired fasting glucose criteria were only met in ≈10% of MetSyn subjects, consistent with a significant underestimation of insulin resistance using this approach.

Various measures have been used to define insulin sensitivity. The hyperinsulinemic clamp is considered the gold standard but requires prolonged insulin infusion and repeated blood sampling. Similarly, glucose tolerance testing–based approaches require repeated blood sampling. However, surrogate measures of insulin sensitivity, including the Homeostasis Model Assessment (HOMA) and Quantitative Insulin Sensitivity Check Index (QUICKI), have been developed that can be applied to single measurements of fasting insulin and glucose. These surrogates have been shown to correlate with direct gold-standard measures[18] and are useful in defining the MetSyn and in predicting the development of cardiovascular disease and DM-2.[17,19] Therefore, it may be time to consider the routine inclusion of these simple indices of insulin sensitivity into clinical MetSyn guidelines.

Important questions regarding the pathophysiological role of insulin resistance in the MetSyn and cardiovascular risk remain to be answered. Recent evidence suggests that innate immunity and inflammation play a role in the development of insulin resistance and predict the development of DM-2.[20,21] Thus, the pathophysiology of insulin resistance, the MetSyn cluster, and atherosclerotic cardiovascular events may have a common proximal inflammatory basis (Figure). It remains to be determined whether measures of insulin sensitivity will provide independent information regarding cardiovascular risk when measures of inflammation and adipose tissue metabolic activity are included in predictive models.

Dyslipidemia: What Is the Pathophysiology of Dyslipidemia in the MetSyn?

Dyslipidemia is a hallmark of the MetSyn and is characterized by elevated triglycerides (TG) and low levels of HDL-C.[22,23] Plasma LDL cholesterol (LDL-C) levels are often normal in patients with the MetSyn. A common finding, however, is that LDL particles are smaller and denser than normal,[22,23] a state believed to be associated with increased cardiovascular risk.

What drives the elevated TG levels in the MetSyn? Conventional wisdom, based primarily on studies in cell culture, is that the increased flux of free fatty acids from the periphery to the liver in the insulin-resistant state drives hepatic TG synthesis, which in turn promotes the assembly and secretion of TG-containing VLDL.[23] Studies in animals and humans are needed in which the impact of hepatic TG synthesis on VLDL TG production is carefully assessed. It is likely that the causes of elevated TG levels in the MetSyn are multifactorial and not simply a function of increased free fatty acid flux to the liver.

Low HDL-C levels in patients with the MetSyn are often ascribed as secondary to elevated TG, at least in part because of increased transfer of TG to HDL and cholesterol from HDL, mediated by the cholesteryl ester transfer protein.[22,23] However, HDL-C levels are often reduced in patients with insulin resistance even when fasting TG levels are normal. This suggests that other mechanisms contribute to the low HDL-C levels. One possibility is that even persons with normal fasting TG levels have impaired postprandial responses to dietary fat, and that increased cholesteryl ester transfer protein–mediated lipid exchange occurs during the postprandial state. Altered lipid flux in the liver due to insulin resistance could reduce the hepatic production of apolipoprotein A-I (apoA-I). Furthermore, nascent apoA-I must acquire cholesterol from peripheral tissues to avoid rapid degradation. ATP-binding cassette transporter 1 is a key molecule in lipidating apoA-I and may be generally downregulated in insulin resistance, resulting in less lipidation of HDL and reduced HDL-C levels.

Activation of innate immunity offers a potential unifying pathophysiology for insulin resistance and dyslipidemia in the MetSyn. In animal models, activation of innate immunity

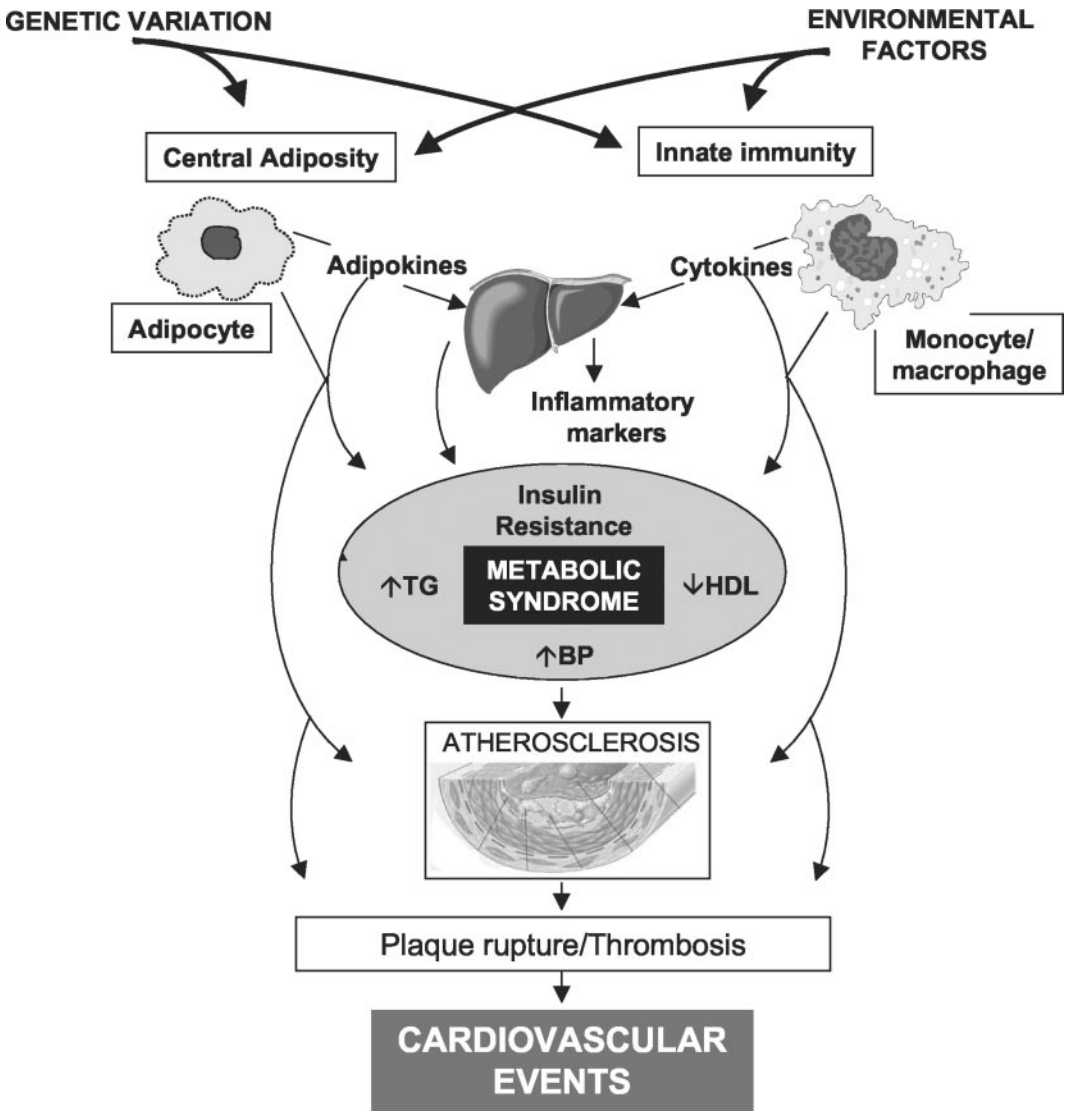

Figure 1. Pathophysiology of atherosclerotic cardiovascular disease in the metabolic syndrome. Central adiposity and innate immunity play key roles in the development of insulin resistance, chronic inflammation, and metabolic syndrome features through the effects of adipokines (eg, leptin, adiponectin, resistin) and cytokines (eg, tumor necrosis factor-α, interleukin-6) on liver, skeletal muscle, and immune cells. In addition, monocyte/macrophage and adipocyte-derived factors may have direct atherothrombotic effects that promote the development of atherosclerotic cardiovascular events. Common genetic variants and environmental factors may impact the development of atherosclerosis at multiple levels through influences on central adiposity, innate immunity, glucose and lipoprotein metabolism, and vascular function.

leads to changes in lipoproteins, enzymes, transfer proteins, and receptors with an increase in atherogenic lipoprotein particles.[24] These changes are similar to those seen in human MetSyn and include increased hepatic VLDL production, reduced VLDL clearance, increased small and dense LDL, reduced HDL, and alteration in HDL composition. One possible contributor to the changes in HDL during inflammation is the increased production of lipases that act on HDL phospholipids, thus reducing the lipid content of HDL and promoting its catabolism.[25] Careful studies of evoked inflammatory, metabolic, and dyslipidemic changes in response to controlled inflammatory stimuli are needed to address the relative contributions of obesity, insulin resistance, and inflammation to the dyslipidemia in MetSyn.

Inflammation: Is Activation of Innate Immunity a Proximal Pathophysiology in the MetSyn?

Chronic subclinical inflammation is part of the MetSyn.[26] The current clinical approach to the MetSyn does not incorporate measures of inflammatory activity that could provide additional insights into the risk of clinical complications. In fact, inflammatory markers are predictors of cardiovascular events and progression to DM-2 in healthy human populations,

underscoring the proximal links between inflammation, metabolic disorders, and cardiovascular disease.[20,21,27,28] Currently, there is discussion about the incorporation of plasma CRP levels into clinical algorithms regarding cardiovascular risk in healthy subjects.[29] However, integration of inflammatory marker data and MetSyn criteria into a single algorithm that also includes traditional risk factors is likely to prove the most useful approach to risk prediction.

Plasma CRP levels provided additional prognostic information regarding subsequent cardiovascular risk in apparently healthy women at all levels of severity of the MetSyn.[30] However, it remains unclear whether plasma levels of CRP are predictive of cardiovascular events after adjustment for insulin sensitivity indices or more accurate measures of adipose tissue mass/activity. Whether markers of increased coagulation, impaired fibrinolysis, and oxidant stress will provide incremental information regarding MetSyn complications remains to be determined. The practical question of how to integrate all of these related markers of cardiovascular risk into a single clinical algorithm remains a major challenge.

Genetics: How Do We Define the Role of Higher-Order Genetic Influences on the MetSyn and Its Complications?

A "thrifty genotype hypothesis" implicates the evolutionary selection of metabolic genes in the development of the MetSyn in the setting of a modern environment of physical inactivity and dietary excess. Indeed, family studies suggest a complex but significant genetic basis to individual components of the MetSyn. However, identifying a genetic profile that defines an increased risk of developing a complex disease trait, such as the MetSyn or atherosclerosis, remains one of the most difficult challenges facing research in human diseases. Important gene-environment interactions in the MetSyn may only be identified through the use of a patient-oriented approach that defines metabolic responses to specific evoked challenges in subjects selected on the basis of individual genotypes.

Is the MetSyn Itself a Target for Established and New Therapies?

After the appropriate "therapeutic life-style changes" have been instituted, what constitutes appropriate therapy for patients with the MetSyn? If the MetSyn does in fact represent a condition associated with substantially greater risk than the sum of its parts, then pharmacological therapy to reduce cardiovascular risk would seem appropriate in most patients. LDL-C levels are not elevated in most patients with the MetSyn, and there is no consensus on the appropriate LDL-C target in the MetSyn. Prospective epidemiological studies that compare, and integrate, the cardiovascular risk associated with traditional risk factor scoring, absolute risk quantification, MetSyn components, and inflammatory biomarkers are urgently needed to define relative cardiovascular risk and appropriate LDL-C goals. It is likely that the MetSyn, particularly in the presence of additional traditional risk factors (eg, family history or smoking) or newer risk factors (eg, elevated level of plasma CRP), may represent a cardiovascular disease equivalent. In this setting, the appropriate target LDL-C may be $<$100 mg/dL, and statin therapy is a logical choice.

There remains substantial uncertainty about pharmacological therapy for the metabolic dyslipidemia and insulin resistance in MetSyn. For the high TG and low HDL-C levels, a fibrate or niacin might reasonably be considered. Certainly some data exist, particularly with fibrates, to suggest that cardiovascular risk is reduced in patients with the MetSyn.[31] For insulin resistance, metformin or a thiazolidinedione (TZD) might be considered. Although metformin has been shown to reduce the risk of progression to DM-2 in subjects with impaired glucose tolerance, this has not yet become standard clinical practice. The combination of fibrates with either metformin or a TZD is conceptually attractive in patients with MetSyn because it simultaneously addresses both the dyslipidemia and the insulin resistance, but there is a paucity of data regarding the effects of such combinations.

A major question is whether the MetSyn is a discrete entity that constitutes a viable, registrable indication for new pharmacological therapies. An example of such a therapy is the category of so-called "dual peroxisome proliferator-activated receptor (PPAR) agonists" currently under development. These agents target both PPARγ and PPARα, thereby simultaneously improving insulin resistance, glucose intolerance, elevated TG, and low HDL-C levels. Will it be necessary to demonstrate reduction in hard clinical cardiovascular end points, or will significant improvements in several aspects of the MetSyn be sufficient for approval of a new therapy? The answer to this question will be key to the pace at which new therapies for the MetSyn are developed and approved for clinical use.

Summary and Conclusions

Major challenges remain for the integration of the key MetSyn features into clinical practice in identifying high-risk populations and individuals. These include (1) developing an optimal definition of the MetSyn that better identifies insulin resistance and integrates markers of systemic inflammation, (2) defining the utility of these MetSyn criteria in providing incremental information regarding the risk of diabetes and cardiovascular events independent of the individual components, and (3) identifying subgroups within the MetSyn that are associated with the greatest risk and therefore warrant the most aggressive interventions. In addition, important research questions remain to be addressed including (1) identification of dynamic features of the MetSyn, such as postprandial lipemic, glycemic, and adipocytokine responses, that provide further information regarding the risk of metabolic and cardiovascular complications; (2) defining gene-gene and gene-environment interactions that further predict MetSyn

and cardiovascular risk; (3) use of MetSyn criteria as end points for clinical trials; and (4) clinical trials of combinations of therapeutic interventions specifically targeted toward the MetSyn. In summary, some evidence suggests the MetSyn is indeed "more than the sum of its parts," but we have only just begun to explore its pathogenic basis and therapeutic implications.

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