Guidelines Review

Definition of Metabolic Syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference on Scientific Issues Related to Definition

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Most individuals who develop cardiovascular disease (CVD) have multiple risk factors. Some risk factors that commonly cluster together (like dyslipidemia, hypertension and hyperglycemia) have been termed the *metabolic syndrome*. Recently the National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) defined criteria used to identify patients with the metabolic syndrome. The selected criteria differ from those of other organisations and therefore, the National Heart, Lung, and Blood Institute, in collaboration with the American Heart Association, convened a conference to examine scientific issues related to definition of the metabolic syndrome.

Clinical Outcomes of Metabolic Syndrome

ATP III viewed CVD as the primary clinical outcome of the metabolic syndrome. Most people with this syndrome have insulin resistance, which confers an increased risk of type 2 diabetes. When diabetes becomes clinically apparent, CVD risk rises sharply. Apart from CVD and type 2 diabetes, individuals with metabolic syndrome are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer.

Components of the Metabolic Syndrome

ATP III identified six components of the metabolic syndrome that relate to CVD: abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance ± glucose intolerance, proinflammatory and prothrombotic states. The pathogenesis of the metabolic syndrome is not known but there seem to be three potential etiological categories: obesity and disorders of adipose tissue, insulin resistance and a number of independent factors that mediate specific components of the metabolic syndrome.

Criteria for Clinical Diagnosis of Metabolic Syndrome

At least 3 organisations have recommended clinical criteria for the diagnosis of the metabolic syndrome. The criteria used are similar in many respects, but there are significant differences.

ATP III

Criteria of ATP III are shown in Table 1. When a subject has three of the five listed criteria, a diagnosis of the metabolic syndrome can be made. The primary clinical outcome of metabolic syndrome was identified as CHD (coronary heart disease)/CVD. ATPIII defined the metabolic syndrome essentially as a clustering of metabolic complications of obesity. The criteria listed include abdominal obesity, determined by increased waist circumference, raised triglycerides, reduced HDL, elevated blood pressure, and raised plasma glucose. Insulin resistance is not required for the diagnosis; however, most subjects meeting ATP III criteria will be insulin resistant. The presence of type 2 diabetes does not exclude a diagnosis of metabolic syndrome.

World Health Organization (WHO)

The WHO guidelines (Table 2) also viewed CVD as the primary outcome of the metabolic syndrome. However, unlike the ATP III criteria insulin resistance is required for the diagnosis along with two other risk factors from high blood pressure, raised triglycerides, low HDL and increased BMI (or increased waist:hip ratio) and microalbuminuria. A higher

Table 1. ATP III Clinical Identification of the Metabolic Syndrome.

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference*†	
Men	>102 cm
Women	>88 cm
Triglycerides	≥1.7 mmol/L
HDL cholesterol	
Men	<1.04 mmol/L
Women	<1.30 mmol/L
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥6.1 mmol/L

*Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated BMI. Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.
†Some males can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g. 94 to 102 cm. Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life style, similarly to men with categorical increases in waist circumference.

Table 2. WHO Clinical Criteria for Metabolic Syndrome.

Insulin resistance, identified by one of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- or for those with normal fasting glucose levels (<6.1 mmol/L), glucose uptake below the lowest quartile for the background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any two of the following:

- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides ≥1.7 mmol/L
- HDL cholesterol <0.9 mmol/L in men or <1.0 mmol/L in women
- BMI >30 kg/m^2 and/or waist:hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥20 µg/min or albumin:creatinine ratio ≥3.4 mg/mmol

blood pressure was required than for the ATPIII criteria. Like the ATP III criteria, the presence of type 2 diabetes does not exclude a diagnosis of metabolic syndrome. A potential disadvantage of the WHO criteria is that special testing of glucose status beyond routine clinical assessment may be required.

American Association of Clinical Endocrinologists (AACE)

The AACE has proposed a third set of criteria for the *insulin resistance syndrome* (Table 3). These criteria appear to be a mixture of the ATP III and WHO criteria except that no defined number of risk factors is specified and the diagnosis is left to clinical judgement. When a person develops diabetes, the term *insulin resistance syndrome* no longer applies. In patients without impaired fasting glucoseIFG , a 2-hour post-glucose challenge is recommended when an abnormality is suspected. Finding an abnormal 2-hour glucose will improve prediction of type 2 diabetes.

Metabolic Syndrome as a Predictor of CVD

Individuals with the metabolic syndrome are at increased risk for CHD. Studies published on the Framingham population have shown the metabolic syndrome alone predicted approximately 25% of all new-onset CVD cases. In the absence of diabetes, the metabolic syndrome generally did not raise ten year risk for CHD to >20%. Ten year risk in men with the metabolic syndrome generally ranged from 10% to 20%. Framingham women with the metabolic syndrome had relatively few CHD events during the eight year follow-up, possibly due to the high proportion of women who were under 50 years of age. Although the metabolic syndrome in these women appeared to be accompanied by higher risk for CVD/CHD, the differences were not statistically significant.

The Framingham investigators also determined if the metabolic syndrome carried an incremental risk beyond the usual risk factors of the Framingham algorithm. The results indicated that there was no advantage gained in risk assessment by adding the unique risk factors of the ATP III metabolic

Table 3. AACE Clinical Criteria for Diagnosis of the Insulin Resistance Syndrome.*

Risk Factor Components	Cutpoints for Abnormality
Overweight/obesity	BMI ≥25 kg/m^2
Elevated triglycerides	≥1.70 mmol/L
Low HDL cholesterol	
Men	<1.04 mmol/L
Women	<1.30 mmol/L
Elevated blood pressure	≥130/85 mm Hg
2-Hour post-glucose challenge	>7.8 mmol/L
Fasting glucose	6.1 to 6.9 mmol/L
Other risk factors	Family history of type 2 diabetes, hypertension, or CVD. Polycystic ovary syndrome. Sedentary lifestyle Advancing age Ethnic groups having high risk for type 2 diabetes or CVD

*Diagnosis depends on clinical judgement based on risk factors.

syndrome to the usual Framingham risk factors. It is likely that most of the risk associated with the metabolic syndrome is captured by age, blood pressure, total cholesterol, diabetes, and HDL. Other risk factors such as obesity, triglycerides, and glucose levels (in the absence of diabetes) provided little additional power of prediction. Serum CRP might have additional predictive power in this model.

Metabolic Syndrome as a Predictor of Diabetes

When the risk for new-onset diabetes was examined for the Framingham cohort, in both men and women, the presence of metabolic syndrome was highly predictive of new-onset diabetes. Almost half of the population-attributable risk for diabetes could be explained by the presence of the ATP III criteria.

Diabetes as a Predictor of CVD

Framingham data showed that most men with diabetes had a ten year risk for CHD >20%, whereas, women rarely exceeded the 20% level. Some investigators believe that improved risk assessment in individuals with diabetes would be clinically useful in risk management. The UK Prospective Diabetes Study (UKPDS) investigators have developed a risk engine (www.dtu.ox.ac.uk/riskengine), which differs from the Framingham algorithm in that it includes a measure of glycaemia and the duration of diabetes. The investigators found that the Framingham equations underestimate the risk for CHD and stroke, whereas the UKPDS Risk Engine provides a more robust estimate.

Therapeutic Implications of Obesity and Body Fat Distribution as Targets of Therapy

ATP III recommended that obesity should be the primary target of intervention for the metabolic syndrome. Front line therapy should be weight reduction and increased physical activity. Weight loss lowers serum cholesterol, triglycerides, CRP and PAI-1, raises HDL, lowers blood pressure, glucose, and reduces insulin resistance.

Insulin Resistance as Target of Therapy

Apart from weight reduction and increased physical activity, two classes of drugs are available that reduce insulin resistance. These are metformin and the insulin sensitizers thiazolidinediones (TZDs). Metformin is used for treatment of type 2 diabetes and in the UKPDS, it reduced new-onset CHD in obese patients with diabetes. In the Diabetes Prevention Program, metformin therapy prevented (or delayed) onset of type 2 diabetes in persons with impaired glucose tolerance. TZDs are also used for the treatment of type 2 diabetes and they are known to reduce insulin resistance, modify several metabolic risk factors, and reverse abnormal arterial responses. However, there are no clinical trial data that document beneficial CVD risk reduction with the use of either metformin or TZDs. Therefore, neither drug can been recommended for the purpose of reducing CVD risk in subjects with the metabolic syndrome.

Conclusions

Conference participants agreed that CVD is the primary clinical outcome of the metabolic syndrome. In addition the risk for type 2 diabetes is higher, and diabetes is a major risk factor for CVD. The conference did not specifically recommend one criteria over another for the definition of the metabolic syndrome but suggest the ATP III criteria provided a practical tool to identify patients at increased risk for CVD. The WHO and AACE criteria do the same but require oral glucose testing if IFG and diabetes are absent.

Regardless of the diagnostic criteria used, there was agreement that weight reduction and increased exercise are the front-line therapy for the metabolic syndrome. Drug treatment to directly reduce insulin resistance is promising, but no drugs have been recommended for the purpose of reducing CVD risk in subjects with the metabolic syndrome. In patients where lifestyle changes have failed to reverse the metabolic risk factors, the specific abnormalities should be treated with drugs according to current guidelines.