Ann Natl Acad Med Sci (India), 42 (Suppl.) : 61-68, 2006
Edited by : J.S. Bajaj & K.K. Talwar

The Metabolic Syndrome and Cardiovascular Risk

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Introduction:

The term "Syndrome X" was coined by Prof. Gerald Reaven at the Banting lecture of the American Diabetic Association in 1988 for a constellation of abnormalities that had insulin resistance as the underlying abnormality. The term metabolic syndrome (MetS) has been in extensive use after WHO formulated diagnostic criteria in 1999 to denote this entity although the expression per se was in use since the late 1970s. The syndrome encompasses a cluster of metabolic risk factors associated with an increased risk for Type 2 Diabetes and cardiovascular disease (CVD). Several expert groups have attempted to produce diagnostic criteria to define metabolic syndrome (see Table 1).

Table 1 Definitions of the metabolic syndrome

ATP III definition (15)

Any three or more of the following criteria:

(1) Waist circumference > 102 cm in men and > 88 cm in women.

(2) Serum triglycerides > 150 mg/dl

(3) Blood pressure > 130/85 mm Hg

(4) HDL cholesterol < 40 mg/dl in men and < 50mg/dl in women

(5) Serum glucose (fasting) > 110 mg/dl

WHO definition (2)

Diabetes, IFG, IGT or insulin resistance (assessed by clamp studies) and at least two of the following criteria:

(1) Waist-to-hip ratio > 0.90 in men or >0.85 in women

(2) Serum triglycerides > 150 mg/dl or HDL cholesterol < 35 mg/dl in men and <40 mg/dl in women

(3) Blood pressure > 140/90 mm Hg

(4) Urinary albumin excretion rate >20ug/min or albumin to creatinine ratio >30 mg/g

International Diabetes Federation (IDF) definition (3)

Central obesity

(Defined as waist circumference =94cm for Europid men and = 80cm for Europid

women, with ethnicity specific values for other groups) plus any two of the following four factors:

(1) Raised TG level: =150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality

(2) Reduced HDL cholesterol: <40 mg/dL (1.03 mmol/L*) in males and <50mg/dL (1.29 mmol/L*) in females, or specific treatment for this lipid abnormality.

(3) Raised blood pressure: systolic BP =130 or diastolic BP =85 mm Hg, or treatment of previously diagnosed hypertension.

(4) Raised fasting plasma glucose (FPG) =100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes (If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.)

* These values have been updated from those originally presented to ensure consistency with ATP III cut points.

The most widely accepted of the definitions for MetS have been produced by the World Health Organization (WHO) and the National Cholesterol Education Program —Third Adult Treatment Panel (NCEP ATP III) (1, 2). Both groups agree on the core components: obesity, insulin resistance, dyslipidaemia and hypertension. Unlike the WHO definition, the ATP III definition does not obligatorily require impaired glucose regulation or insulin resistance as an essential component. In addition, the levels set for each component and the combination of components required to diagnose the MetS are slightly different in the two recommendations.

Pathophysiology of cardiovascular disease in the metabolic syndrome

Abnormal fat distribution

Population studies have shown an increase in the risk of chronic non-communicable diseases associated with a progressive increase in total adiposity as assessed by the body mass index (BMI). Among equally obese individuals, those with an increase in abdominal fat (assessed by waist circumference) are at increased risk of Type 2 diabetes and CVD. This is independent of the risk predicted by increased BMI. For instance, the INTERHEART study (4) studied patients with initial myocardial infarction worldwide in over 55 countries and identified nine important risk factors for myocardial infarction which accounted for over 9/10th of the worldwide myocardial infarction risk. One of these risk factors was abdominal obesity. Yusuf et al. (5) subsequently explored the associations between different measures of obesity and risk of myocardial infarction in this study. Four different measurements of obesity were examined: BMI, waist-to-hip ratio, waist circumference and hip circumference. The waist-to-hip ratio was the obesity

measurement most strongly associated with myocardial infarction. The cut-off value for waist circumference is likely to be population specific as there are clear differences across various ethnic populations in the relationship between overall adiposity, abdominal obesity and visceral fat accumulation. This has been noted by several studies in India (6). In this regard waist circumference criteria for South Asians suggest a cut-off of 94 cm for males and 80cm for females (7).

Thus, although Reaven's original description did not include it, abdominal obesity as assessed by waist circumference is an important cardiovascular risk marker and the primary target for the treatment of metabolic syndrome. The International Diabetes Federation (IDF) (3) places even more emphasis on central obesity. This new emphasis on central obesity as opposed to BMI is based on growing evidence that waist circumference has a closer association with cardiovascular disease and mortality.

Insulin resistance

Insulin resistance is central to the pathophysiology of the metabolic syndrome and has been postulated as its underlying cause. It correlates univariately with the risk of Type 2 diabetes and CVD; however the association with hypertension is weak. The mechanisms underlying the link between insulin resistance and CVD still need further investigation but there is evidence that excess free fatty acids are involved. A recent meta-analysis (8) examined the relationship between plasma insulin and cardiovascular mortality in nondiabetic adults based on data from 11 prospective studies. After adjusting for various risk factors including age and smoking, the hazard ratio of cardiovascular mortality was highest in the subgroup with the highest fasting insulin. Although there is overwhelming evidence suggesting that the metabolic syndrome is significantly associated with insulin resistance, the ATP III definition of the metabolic syndrome does not include a measurement of insulin resistance.

Obesity and inflammation

Inflammation clearly plays a major role in atherogenesis (9). Several inflammatory markers: Tumour necrosis factor (TNF) α, Interleukin-6 (IL-6), fibrinogen and C-reactive protein (CRP) have often been found to be elevated in studies of patients with MetS. The most extensively studied inflammatory marker is high sensitivity C-reactive protein (CRP). It has been shown to be a predictor of both diabetes and cardiovascular disease risk. A proinflammatory state recognized by elevated C-reactive protein (CRP) levels is commonly present in people with the MetS . There is a significant relationship between plasma CRP levels and measures of adiposity and of insulin resistance. One contributory mechanism to this association is obesity, as adipocytes and macrophages release inflammatory cytokines which promote an inflammatory state.

CRP has also been shown to be an independent predictor of cardiovascular

events and its predictive value has been said to equal that of metabolic syndrome (10). The predictive strength of CRP levels on cardiovascular disease has, however, been questioned by Danesh et al. (11), who reported CRP levels in 2459 patients with major adverse cardiovascular events in comparison with a matched cohort of 3969 individuals. After adjusting for many known risk factors, CRP showed an odds ratio of only 1.45 for coronary artery disease. At present the American Heart Association (AHA) does not recommend using CRP for population screening or to monitor treatment.

Obesity and atherogenesis: multiple signals

Adipose tissue is not an inert organ but an important player in the integration of endocrine, metabolic, and inflammatory signals for the control of energy homeostasis. Several substances are secreted and several receptors have been identified on adipocytes. One important adipocytokine identified is adiponectin. Levels of adiponectin have been shown to have a strong and consistent inverse association with insulin resistance and inflammation (12,13). Adiponectin levels possibly, may be a marker for atherosclerosis and coronary heart disease. In a large case-control study that examined adiponectin levels it was found that men with the lowest quintile of adiponectin levels had a significantly decreased risk of myocardial infarction (relative risk 0.39) (14). Adiponectin may have anti-inflammatory effects that provide protection against atherosclerosis development, particularly in those clinical situations associated with low plasma concentrations of adiponectin. The future may possibly see recombinant adiponectin used in the prevention or treatment of cardio-vascular disease in selected patients.

Leptin and resistin are other markers associated with obesity. Obese individuals have been demonstrated to have elevated leptin concentrations (15). The West of Scotland Coronary Prevention Study (WOSCOPS) (16) showed that leptin independently increased the relative risk of coronary artery disease. The role of resistin in obesity and insulin resistance in humans is debated. Obese individuals have higher serum levels of resistin than lean individuals (17) but serum resistin has not been shown to be a significant predictor of insulin resistance (18,19).

Atherogenic dyslipidaemia

The dyslipidaemia associated with the MetS includes raised TGs and low concentrations of HDL-cholesterol. A more detailed analysis usually reveals other lipoprotein abnormalities, including elevated apolipoprotein B (Apo B), increased number of small dense low-density lipoprotein (LDL) particles and small HDL particles. All of these abnormalities are independently atherogenic.

Elevated blood pressure

MetS is usually associated with raised blood pressure. However, the strength of

association varies considerably from one population to another.

Prothrombotic state

Components of the MetS are associated with both coagulation and fibrinolytic proteins, with a link to an elevated plasminogen activator inhibitor-1 (PAI-1) and fibrinogen being the most consistent findings.

Endothelial dysfunction

There is evidence that patients with MetS have elevated mononuclear cell adhesion, and diminished endothelial-dependent vasodilata-tion that are markers of endothelial dysfunction and associated with cardiovascular adverse events.

Relationship to predictability of cardiovascular disease and diabetes mellitus

Cardiovascular disease

Since the metabolic syndrome comprises accepted CVD risk factors, it would be expected that the syndrome is a strong predictor of CVD. A substudy of the Botnia study, which involved over 4000 Finnish and Swedish adults, demonstrated that those with the MetS, as defined by the 1999 WHO criteria, were thrice as likely to have a history of CHD compared with those without the syndrome. Moreover, the presence of the syndrome was associated with a significantly increased cardiovascular mortality (12% vs. 2%) (20). Observational studies that have confirmed that the risks of developing CVD, cardiovascular mortality and all-cause mortality, are increased by the presence of the MetS, include the European DECODE study (8), the Finnish Kuopio study (21) and the San Antonio Heart Study (22). Similar findings are also reported from clinical trials, including the WOSCOPS trial, and, at least for insulin resistance, the VA-HIT study. Nonetheless, other studies have disputed whether the MetS gives any additional information over and above the individual well-known CVD risk factors (23). This may relate to an inadequate definition of the MetS; (clear measurements of inflammation are not included) and the cut-points used, rather than a problem with the overall concept. Indian studies have documented the prevalence of abnormal lipid distribution and waist-hip ratio (6); however, the predictive value of MetS for cardiovascular events has not yet been validated.

Diabetes

Non-diabetic people with the MetS are at a very high risk for the development of Type 2 diabetes. In one study, the risk for diabetes was five fold higher in patients with the syndrome (22). However, glucose dysregulation (IFG or IGT) is often already present in patients with MetS. Importantly, the greatest impact of diabetes is the two to four times greater risk of CHD and stroke.

Management

Lifestyle modification

The management of metabolic syndrome lies in the early detection and

treatment of the underlying risk factors which make up the syndrome, mainly abnormal blood pressure and glucose levels, dyslipidemia, being overweight and abdominal obesity. In individuals with a normal fasting glucose, the presence of IGT is a good surrogate marker for insulin resistance, and is easily measured using the oral glucose tolerance test. Once a clinical diagnosis is made, decreasing energy intake and increasing physical activity remains the cornerstone of therapy. Decreasing dietary glucose by reducing the intake of high-glycemic beverages and replacing refined grain products and potatoes with minimally processed plant based foods such as whole grains, fruits and vegetables may reduce coronary heart disease incidence among people with metabolic syndrome.

Mega doses of dietary antioxidants have not demonstrated protection against CV disease or diabetes. Smoking increases the risk of adverse CVD events and should be strongly discouraged.

Exercise has the potential to bring about weight loss, increase insulin sensitivity, alter the plasma lipoprotein profile and improve fibrinolytic activity. These favourable effects likely result from changes in the activity of insulin sensitive glucose transporters and of skeletal muscle lipoprotein lipase. The health benefits of regular physical activity as a primary preventive measure is beyond doubt. Accumulating at least 30 min of daily physical activity of moderate intensity is probably enough to maintain body weight.

Drug therapy

Appropriate drug therapy should be initiated to manage elevations in blood pressure and dyslipidemia among patients with the metabolic syndrome. The choice of medications prescribed should be based on the established guidelines for the management of these conditions. ACE inhibitors are a reasonable choice for the management of hypertension given its renal protection for patients with diabetes, and the possibility that it may prevent diabetes among patients with IGT. Statins or fibrate therapy should be initiated depending on the type of dyslipidemia.

Modulation of insulin resistance is possible by thiazolidinediones and metformin. Apart from their glucose lowering effects, the thiazolidinediones have multiple nonglucose metabolic effects. They also reduce insulin resistance through binding to and activation of the nuclear receptor, peroxisome proliferators-activated receptor - gamma (PPAR gamma), with subsequent effects on glucose and lipid homeostasis. Thus, diabetic patients must be treated with insulin sensitizers whenever possible. ACE-inhibitors should be the first-choice antihypertensives in patients with hypertension associated with the metabolic syndrome.

Other drugs that have the potential to control glucose abnormalities associated with the metabolic syndrome include the prandial oral antidiabetic agents such as alpha glucosidase inhibitors (Acarbose, voglibose, miglitol) and the rapidly acting

insulin secretagogues (Nateglinide, Repaglinide). These drugs improve the control of postprandial hyperglycemia.

The approach of treating patients with IGT with medications to prevent or delay diabetes is rapidly evolving and their benefits need to be confirmed in large prospective clinical trials.

Patients with diabetes derive substantial benefit from aspirin. Apart from its use in diabetics the role of aspirin in nondiabetics with metabolic syndrome is uncertain.

Antiobesity drugs

When attempts at lifestyle modification are inadequate, the use of anti-obesity drugs is warranted. Drug treatment is often indicated but is somewhat limited by the small number of safe and well tolerated drugs that are proven to have long-term efficacy in maintaining body weight loss. The currently available drugs, sibutramine and orlistat, appear modestly effective in promoting weight loss. Blockade of the endocannabinoid system with rimonabant appears to be a promising new strategy.

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