Metabolic syndrome

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Abstract

The metabolic syndrome is a condition characterized by the co-existence of several major risk factors for cardiovascular disease (CVD) — high blood pressure, hyperglycaemia, and dyslipidaemia (reduced high-density lipoprotein cholesterol or raised triglycerides). These components are related to insulin resistance and appear to be aetiologically linked, probably by genetic factors. In recent years genome-wide association studies (GWAS) have provided new insights into the genetic basis of obesity and metabolic syndrome. The appearance of the metabolic syndrome phenotype is provoked by weight gain, particularly if there was poor intra-uterine growth, and specifically by intra-abdominal fat accumulation with a large waist circumference. The metabolic syndrome is highly prevalent among individuals with partial lipodystrophy and spinal cord injury, suggesting that a lack of subcutaneous adipose tissue and muscle atrophy play critical roles in metabolic disturbances. Sleep disorders may cause metabolic disturbances by inducing neurohumoral changes and perhaps altered muscle fibre adaptation. Developing the metabolic syndrome doubles the risk of CVD and type 2 diabetes, but offers an effective treatment approach. Reducing weight by 5—10 kg, by diet and exercise or with anti-obesity drugs, reduces CVD risk substantially and reduces diabetes risk by over 50%. Some new anti-diabetic agents have been found to improve insulin resistance, and to reduce lipids and weight, and could potentially be used to treat metabolic syndrome.

Keywords Cardiovascular disease; diabetes; genetics; hypogonadism; insulin resistance; lipodystrophy; muscle atrophy; obesity; weight management

What's new?

- Genome-wide association studies (GWAS) have provided new insights into genetic basis of obesity and metabolic syndrome. Although only a small proportion of the variance in obesity is attributable to common variants, these risk alleles are considered likely to contribute to obesity in a polygenic manner such that people who carry a higher number of risk alleles will gain extra body weight
- Genetic factors, impaired fetal growth, and weight gain in adulthood all provoke manifestations of the metabolic syndrome
- Pro-inflammatory mediators released from adipose tissue increase with body fat mass and hypoxia, and may have a role in the development of the metabolic syndrome
- Identifying the metabolic syndrome allows intervention for weight management to prevent cardiovascular disease before reaching treatment thresholds for metabolic risk factors
- Weight loss is effective treatment, preventing progression to diabetes and to coronary heart disease
- New anti-diabetic agents have been shown to reverse metabolic abnormalities, through their actions within the hypothalamus or peripheral tissues, with substantial weight loss. These agents potentially provide additional options in the treatment of the metabolic syndrome

Individuals with coronary heart disease (CHD) or who have suffered a stroke often exhibit more than one major metabolic risk factor for these conditions. This has suggested that there are aetiological links between these components. The metabolic syndrome comprises a cluster of metabolic disorders listed in Table 1, all of which are risk factors for atherosclerotic cardiovascular disease (CVD) and all are revealed by weight gain and age. Certain medical conditions (e.g. type 2 diabetes mellitus, frank hypertension, polycystic ovary syndrome, Cushing's syndrome) could be considered extreme examples of the components of the metabolic syndrome insofar as they all need specific treatment and all increase CVD risk. The development and severity of all the components depend on age and weight (fat) gain, even within the 'normal range' of body mass index (BMI 18.5—25 kg/m^2). However, increased central fat accumulation (reflected in a large waist circumference) is a stronger contributing factor than total body fat, in both thin individuals and the overweight (see below).

The original risk scores for CHD (e.g. Framingham equations[1]) were developed before the epidemic of obesity, when the metabolic syndrome as now defined was less commonly seen. Neither BMI nor waist measurement was included in the original Framingham risk scores, whose components were not reversible. Identifying people with the metabolic syndrome approximately doubles the prediction of CVD but, more importantly, its components are all reversible, so its recognition offers a treatment — weight management.

Criteria

The most widely used criteria for the metabolic syndrome are those of the National Cholesterol Education Program ATP III.[2] They incorporate cut-offs of blood pressure, HDL cholesterol, fasting triglycerides and fasting glucose — all set at levels below their individual treatment thresholds but which in combination greatly increase the risks of type 2 diabetes and of premature CHD. These criteria also included a cut-off of waist circumference and require the presence of three of the components for 'diagnosis'. More recently, a group from the International Diabetes Federation (IDF) has proposed a simpler set of criteria (Table 2), which requires a large waist circumference (set at a slightly lower

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Features of the metabolic syndrome

Endocrine and biochemical abnormalities	Overt pathophysiological conditions
• Glucose intolerance	• Type 2 diabetes mellitus
• Hyperinsulinaemia	• Coronary heart disease
• Insulin resistance	• Polycystic ovary syndrome
• Hypercortisolism	• Central fat distribution
• Hypertriglyceridaemia	• Morbid obesity
• Reduced HDL	• Stress and depression
• Raised small dense LDL cholesterol	• Hypertension
	• Non-alcoholic steatohepatitis

Table 1

level than ATP III) plus two other criteria.[3] The IDF criteria are directed at diabetes prevention as well as CVD prevention, and so use lower cut-offs of waist circumference and fasting blood glucose. The purpose of applying these diagnostic criteria, aside from epidemiological surveys, is to initiate preventive interventions for an individual patient's weight management in order to prevent diabetes and CVD. The main disadvantage to a practical application of metabolic syndrome is the need for a fasting blood sample. However, since weight management has multiple clinical and personal benefits, with no appreciable hazards, there is an argument for offering evidence-based weight management to all patients with large waists, irrespective of the other components. A new proposed management-directed algorithm is shown in Table 3.[4]

A range of other metabolic abnormalities may co-exist, such as the presence of inflammation (e.g. raised serum C-reactive protein (CRP), uric acid and cytokines) and a prothrombotic state (e.g. plasminogen activator inhibitor 1 (PAI-1)). A variety of other terms have been used more or less interchangeably in the literature for the metabolic syndrome:

- syndrome X (NB: this term is also used by cardiologists to denote angina in association with reversible ECG signs of ischaemia and angiographically normal coronary arteries, which is often found in obesity)
- plurimetabolic syndrome
- Reaven's syndrome (in 1988, Reaven first drew attention to the clustering of key metabolic abnormalities in certain patients, and coined the term 'syndrome X')
- insulin resistance syndrome (it has become clear that not all components of the metabolic syndrome can be attributed to insulin resistance).

Aetiology

The metabolic syndrome is strongly linked to a 'Westernized' lifestyle characterized by physical inactivity and an unlimited supply of high-fat foods. Childhood obesity is a risk factor for the metabolic syndrome in adults. A role for psychosocial stress has been postulated, and many components are more prevalent in deprived populations. Not all individuals develop the metabolic syndrome, however, and the existence of genetic factors is now well established for both the components of the syndrome (e.g. type 2 diabetes, dyslipidaemia) and body composition (fat and muscle mass). It is estimated that genetic factors contribute about 30–40% of the observed variance in BMI and about 70% of the variance in fat distribution that relates more to the metabolic syndrome (Table 4).[5] In recent years, genome-wide association studies (GWAS) have provided new insights into the genetic basis of obesity. In 2007, the first single nucleotide polymorphism (SNP) associated with increased BMI was mapped to a gene now known as *FTO* (fat mass and obesity associated). The *FTO* gene affects obesity by regulating appetite and energy expenditure. The use of SNPs has since identified over 40 genetic variants that are associated with BMI, fat distribution or risk of

Criteria for diagnosis of the metabolic syndrome as defined by ATP III of the National Cholesterol Education Program (NCEP)[2] and more recent proposals from the International Diabetes Federation (IDF)[3]

	Defining level	
	ATP III NCEP proposals: any three features	IDF proposals: large waist plus two other features
Increased waist circumference		
• Men	≥102 cm (40 in)	≥94 cm (37 in)
• Women	≥88 cm (35 in)	≥80 cm (32 in)
Raised triglycerides	≥1.7 mmol/L (150 mg/dL)	≥1.7 mmol/L (150 mg/dL)
Reduced HDL cholesterol		
• Men	<1.03 mmol/L (40 mg/dL)	<1.03 mmol/L (40 mg/dL)
• Women	<1.29 mmol/L (50 mg/dL)	<1.29 mmol/L (50 mg/dL)
Raised blood pressure	≥130/≥85 mmHg	≥130/≥85 mmHg
Raised fasting plasma glucose	≥6.1 mmol/L (110 mg/dL)	≥5.6 mmol/L (100 mg/dL)

All individual components are below treatment thresholds, but combined in the metabolic syndrome, coronary heart disease risk is doubled. If body mass index ≥30 kg/m^2 then assume waist circumference is above treatment level.

Table 2

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