Metabolic syndrome

Thang S Han

Michael EJ Lean

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

Thang S Han *MA MB BChir PhD is a Consultant Physician with a Special Interest in Diabetes and Endocrinology at Ashford and St Peter's NHS Trust, UK. Competing interests: none declared.*

Michael EJ Lean *MA MB ChB MD FRCP is Professor of Human Nutrition at the University of Glasgow, UK, and Honorary Consultant Physician at Glasgow Royal Infirmary. Competing interests: in the last 5 years Professor Lean has received research funding, contributed to Advisory Boards and undertaken consultancy for a number of pharmaceutical and food companies, holds shares in Eat Balanced, and has given lectures sponsored by Cambridge Nutrition.*

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

Pragmatic suggestions for the management of elevated waist circumference in relation to cardiovascular disease risk (adapted from Lawlor et al.[4])

- Waist circumference below 80 cm in women and 94 cm in men — **low level of risk**
  - Requires no intervention; avoid weight gain and stay below these levels
- Waist circumference above 80 cm in women and 94 cm in men, and less than 10% CVD risk over next 10 years — **elevated risk**
  - Requires public health measures to check and prevent continued weight gain
- Waist circumference above 80 cm in women and 94 cm in men, and greater than 10% CVD risk over next 10 years — **high level of risk**
  - Requires effective treatment to lose 5—10% body weight and prevent further weight gain
- Waist circumference above 88 cm in women and 102 cm in men irrespective of 10-year CVD risk — **high level of risk** for other medical problems associated with obesity/intra-abdominal fat accumulation
  - Requires effective treatment to lose 5—10% body weight and to prevent further weight gain
- CVD risk based on Joint British Societies' guideline or equivalent (current prediction charts do not include a measure of obesity)

Table 3

obesity, and metabolic syndrome. Although only a small proportion of the variance in obesity (<2%) is observed to be attributable to common allelic 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 (>10) will gain extra body weight than those who carry lower number (1 or 2). It has become clear that the underlying genetic cause of obesity requires interaction with the environment. The lifestyle factors that increase intra-abdominal fat and metabolic risk factors are weight gain, a diet high in saturated fat, smoking, inactivity and excess alcohol intake.[6]

Pathophysiology

High glucose and insulin resistance: some of the links between components of the metabolic syndrome relate to insulin resistance, although about 30% of patients with the metabolic syndrome have normal insulin sensitivity. Insulin resistance is characterized by a high plasma insulin concentration that fails to suppress plasma glucose normally. The contributing factors are complex (Figure 1); a central feature is unresponsiveness to insulin at the cellular level because of changes in receptor binding or post-receptor mechanisms. Exposure to high free fatty acid (FFA) concentrations is a common mediator, related to an expanded intra-abdominal fat mass.

Insulin resistance varies between tissues and organs (e.g. subcutaneous/white and intra-abdominal/brown adipose tissues, muscle, liver, skin); this may be important in the clinical manifestation of insulin resistance, pancreatic β-cell defects and impaired insulin secretion. Insulin resistance is closely related to impaired glucose tolerance, diabetes and risk of CHD.

Elevated blood pressure and insulin resistance: compared with normotensive individuals, many hypertensive patients are glucose intolerant and hyperinsulinaemic. The relationship between insulin resistance and hypertension appears to be indirect, because:

- controlling hypertension does not improve either glucose tolerance or hyperinsulinaemia
- patients with insulinoma are not hypertensive.

Obesity contributes to both hypertension and hyperinsulinaemia, and weight loss usually improves these. Insulin resistance and hyperinsulinaemia could cause hypertension directly via an increase in catecholamine activity without a change in plasma glucose concentration. Raised blood pressure from increased insulin concentration may also result acutely from insulin-stimulated renal tubular reabsorption of sodium. Overweight and obese people need to eat more calories in order to avoid weight loss: their extra food consumption entails greater sodium consumption because salt is added to so many foods. However, hyperinsulinaemia probably does not account completely for the rise in blood pressure in the metabolic syndrome.

Dyslipidaemia: high triglycerides and low high-density lipoprotein (HDL) cholesterol are features of the metabolic syndrome. Elevated plasma small dense low-density lipoprotein (LDL) cholesterol, the most atherogenic subfraction of LDL, has been identified as a key feature in association with elevated triglyceride and low HDL cholesterol in susceptible individuals who gain weight. Several studies have shown that individuals with high concentrations of these particles are at greater myocardial risk. Concentrations of small dense LDL are also increased in individuals with greater abdominal fat accumulation (large waist circumference). The mechanism is related to excess accumulation of intra-abdominal fat. Elevated total and LDL cholesterol, whilst common, are mainly related to saturated fat consumption, and not so strongly to weight gain and obesity.

Polycystic ovaries and depression: women with the metabolic syndrome are more likely to have polycystic ovary syndrome and depression, which may be partly explained by disturbances in insulin, cortisol and sex hormones, with reduced sex hormone-binding globulin.

Large waist circumference and intra-abdominal fat accumulation: the structure and function of adipose tissues vary between anatomical sites (Figure 2). Intra-abdominal fat (mainly omental and retroperitoneal) exhibits higher rates of lipolysis and glycolysis than subcutaneous fat, and greater mitochondrial density (reflecting its origin as brown adipose tissue). It appears to be primarily involved, not in fat storage, but in high-turnover fatty acid provision to the liver and elsewhere. Problems seem to occur when intra-abdominal fat becomes used as fat storage. Increased abdominal fat mass (particularly the intra-abdominal

Factors related to the metabolic syndrome and coronary heart disease through obesity, central fat distribution and muscle mass (sources: Bouchard[5] and Han et al.[6])

	Obesity (large waist circumference and high BMI)	Central fat accumulation (larger waist circumference than expected for given BMI)	Muscle paucity or atrophy (smaller hip circumference than expected for given BMI)
Genetic	++	+++	+
Physical inactivity	+++	+++	++
High-fat diet	+++	++	–
Low socioeconomic status	+++	+++	+
Smoking	–	++	+
Heavy alcohol consumption	++	++	+
Age	++	++	++
Obesity	–	++	+
Relative deficiency of type I (oxidative) muscle fibres	+	+	+

Table 4

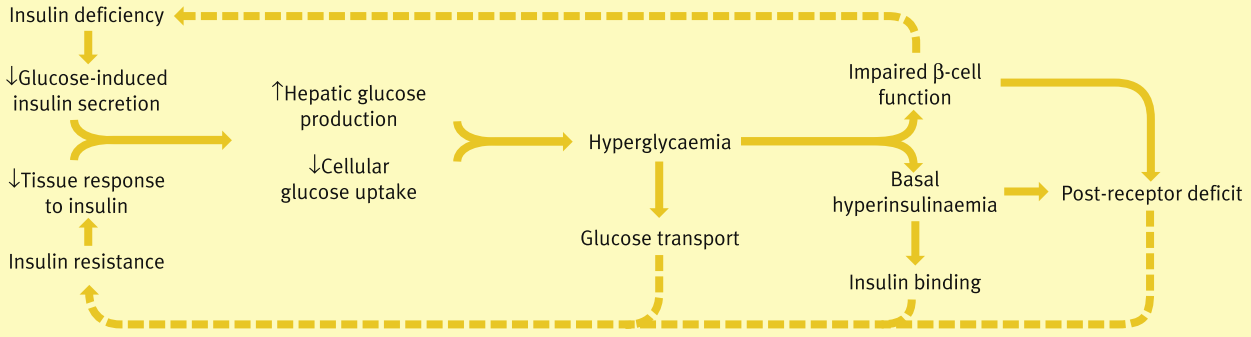
fat depot) is easily recognized as an 'apple-shaped' torso and may have a direct intermediary role in the development of the metabolic syndrome (Figure 3). It has been suggested that the large amounts of FFAs released via the portal system into the liver by the highly metabolically active intra-abdominal (visceral) fat mass may interfere with insulin clearance by the liver.

Intra-abdominal fat is now recognized as an active endocrine organ secreting a range of cytokines (adipokines), including leptin, adiponectin, resistin, interleukins (IL) such as IL-1 and IL-6, and tumour necrosis factor alpha (TNF-α), which are important factors in energy regulation. Excessive amounts of these substances released by an expanded intra-abdominal fat mass are associated with increased metabolic disorders.

It is difficult to interpret the association between visceral fat and risk factors for CVD because there are many confounding factors (e.g. subcutaneous fat and skeletal muscle mass, lifestyle and hormonal factors). Specific subcompartments of intra-abdominal fat (e.g. intraperitoneal and retroperitoneal, because of their proximity to the portal system) may be important but it is difficult to study these depots separately from the total intra-abdominal fat mass, or even total abdominal fat. However, observations of high incidence of the metabolic syndrome, in individuals with partial lipodystrophy or those with spinal cord injury, have brought to light the important roles of subcutaneous adipose tissue and skeletal muscle in the development of metabolic disturbances (*vide infra*).

Partial lipodystrophy and the metabolic syndrome: the relative contributions of subcutaneous adipose tissue to the metabolic syndrome have become more apparent from studies on individuals with partial lipodystrophy. These subjects have rare loss-of-function mutations of the peroxisome proliferator-activated receptor gamma (PPARγ) gene, resulting in atrophy

Development of insulin resistance in type 2 diabetes mellitus



Note that, whether the primary defect that initiates glucose intolerance resides in β-cells or in peripheral tissues, insulin resistance eventually develops or is aggravated, respectively.

Positive feedback loop resulting in self-perpetuation of primary defect.

Figure 1

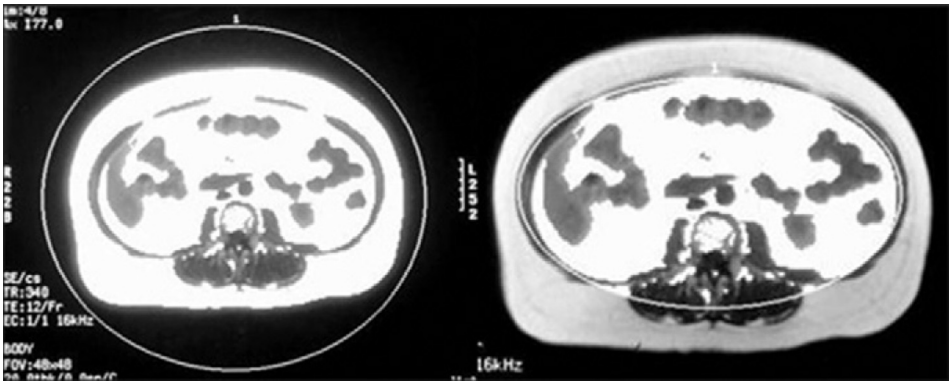


Figure 2 Magnetic resonance imaging showing different adipose compartments. The outer elliptic ring signifies both subcutaneous and intra-abdominal fat. The inner elliptic ring signifies intra-abdominal fat.

of subcutaneous adipose tissue with a high incidence of severe insulin resistance, diabetes, dyslipidaemia, hepatic steatosis and polycystic ovary syndrome in females[7]; most of these features can be reversed by leptin therapy.[8]

Skeletal muscle atrophy and the metabolic syndrome: a high waist-to-hip circumference ratio is found in individuals with a large waist (high abdominal fat accumulation), small hips (small amounts of gluteal fat or low muscle mass) or both (Figure 3). Muscle atrophy occurs progressively with inactivity and age, but may be accelerated by a host of conditions that interfere with hormonal and neuromuscular signalling, or adversely affect the potential of the myofibre degeneration–regeneration process. Several studies have proposed that reduced muscle mass, and thus a low capacity for fat oxidation, is important in metabolic disorders. A relatively low hip circumference is now known to be connected with many components of the metabolic syndrome in both men and women. In cross-sectional studies, type 2 diabetes is related more strongly to waist-to-hip ratio than to waist circumference alone, and low hip circumference and high waist circumference both, independently, predict type 2 diabetes (in longitudinal studies, waist circumference alone is the best predictor of type 2 diabetes).

Variation in human body fat distribution in men and women

	Male A Pear-shaped body	Male B Apple-shaped body	Female A Pear-shaped body	Female B Apple-shaped body
Body mass index	29	21	30	30.5
Waist-to-hip ratio	0.90	1.10	0.70	1.20

In each pair of men and pair of women (subjects A and B), the body mass indices are similar. However, the waist circumference and waist to hip ratios of subjects B are much higher, indicating a greater distribution of body fat around the abdomen as well as a decreased amount of muscle mass around the hips.

Figure 3

How the metabolic syndrome relates to skeletal muscle mass remains unclear but it has been observed to occur earlier in individuals with spinal cord injury. The association could be partly a consequence rather than a causal link, but loss of muscle mass (and thus glucose oxidation capacity) may precipitate type 2 diabetes. Muscle is a major site of insulin action, and of fat and glucose oxidation, and both type 2 diabetes and the metabolic syndrome are associated with a relative deficiency of type I (oxidative) muscle fibres. Findings from various studies support the hypothesis that an increase in the proportion of white, type IIB (glycolytic) muscle fibres and a decrease in red, oxidative type I muscle fibres are associated with metabolic complications. Individuals with a genetic preponderance of type IIB muscle fibres and lack of type I fibres may experience a chronic need for glucose, to overcome the lack of lipolytic capacity that results from the relative reduction in the proportion of type I muscle fibres. As a consequence, their capacity for aerobic endurance exercise is limited (despite the availability of FFAs) and extra sources of glucose must be consumed while circulating FFAs are spared, leading to an increase in body fat storage. Increased circulating FFAs in such individuals may lead to desensitization of insulin in peripheral tissues and reduced hepatic insulin clearance; these lead to hyperinsulinaemia and eventual exhaustion of β-cell insulin.

One of the many actions of the anabolic hormone, testosterone, is to stimulate the growth and function of skeletal muscle and it has been shown to alter body fat distribution favourably. Testosterone secretion declines progressively with age, a process in which can be accelerated by various diseases. Sufficiently low serum concentrations of testosterone (hypogonadism) result in muscle atrophy, consequent physical disability and a range of health impairments, ranging from sexual to psychological dysfunctions.[9] A low serum testosterone is associated with the metabolic syndrome in cross-sectional studies and predicts the development of the metabolic syndrome in apparently healthy men in longitudinal studies.[10]

Sleep disorders, hypoxia and the metabolic syndrome: obesity is the main cause of obstructive sleep apnoea (OSA). Individuals with OSA have an increased risk of the metabolic syndrome and

are at particularly high risk of hypertension, probably as a result of increased sympathetic activity, driven by hypoxia. Among people with diabetes, those with OSA are more likely to have microvascular disease. Small studies employing continuous airway pressure (C-PAP) therapy for individuals with OSA have shown reductions in CRP and leptin concentrations, and improvement in insulin sensitivity. It is generally postulated that intermittent hypoxia and sleep fragmentation induce oxidative stress, leading to inflammation with neurohumoral changes and subsequent metabolic disturbances.[11] A 20-year prospective study of 4434 British men has shown that restrictive impairment of lung function as indicated by reduced forced expiratory volume in 1 s increases the incidence of type 2 diabetes. The authors of the study suggested that traditional and metabolic risk factors as well as inflammation could partly explain this relationship.[12] Alternative explanations to the above suggestions include adaptation of myocytes to chronic hypoxic states. In order to generate energy non-oxidatively under hypoxic conditions, increased populations of glycolytic type IIB muscle fibres are required. This may be achieved by hypertrophy or proliferation, or alternatively by transformation from the oxidative type I muscle fibres. This hypothesis requires interventional studies, involving muscle biopsies and histological examination of the muscle fibres.

The metabolic syndrome and fetal growth: the 'thrifty phenotype' and 'programming' hypotheses: there are striking relationships between markers of poor early growth (birth weight, length, weight at one year) and features of the metabolic syndrome in later life. Two hypotheses, the 'thrifty phenotype' and 'programming', have been used to describe these. Early exposure to adverse conditions, including fetal undernutrition and perinatal nutritional depletion (e.g. infection), produces a small child who becomes a relatively small adult (a *thrifty phenotype*) but who is possibly capable of surviving adverse conditions with limited food. However, these adaptive changes may predispose (*programme*) individuals to chronic diseases (e.g. respiratory disease) and the features of the metabolic syndrome when high-energy food is overprovided and physical activity is not required. During our evolution, we had to survive famines but food excess was not an important factor: obesity is a post-evolutionary stress. Four underlying principles of 'programming' have been established, based on animal studies.

- undernutrition in early life has permanent effects
- undernutrition has different effects at different times in early life
- rapidly growing fetuses and neonates are more vulnerable to undernutrition
- permanent effects of undernutrition include reduced cell numbers, altered organ structure and resetting of hormonal axes.

Barker and colleagues applied the thrifty and programming hypotheses to explain the association between body size at birth and chronic disease in later life, suggesting that poor nutrition in fetal and early life has an adverse effect on the structure and function of vital organs.[13] Because the brain develops early in the fetus, it is most severely affected when undernutrition occurs in the first trimester. In contrast, the musculoskeletal, endocrine and cardiovascular systems develop later and are more severely affected by undernutrition in the later trimesters, resulting in disproportionate body morphology, diabetes and CHD in later life. Such individuals would remain unaffected if they remained in an environment of reduced nourishment, but suffer ill health when exposed to certain stimuli (e.g. abundant food, corticosteroids or stress). Adult influences (including obesity, ageing and physical inactivity) determine the time of onset and severity of the disease. The thrifty phenotype hypothesis may be applied to the development of type 2 diabetes:

- undernourishment during fetal or early life has an adverse effect on the structure and/or function of pancreatic β-cells and peripheral tissues (primarily skeletal muscle mass)
- this limited glucose–insulin metabolism can cope in an undernourished environment
- in an abundant nutritional environment, the deficiencies in β-cell function and diminished peripheral tissue sensitivity to insulin action are exposed, resulting in the development of impaired glucose tolerance and diabetes.

The thrifty phenotype and programming hypotheses help explain the high incidence of obesity, especially the increased abdominal fat accumulation, CHD and type 2 diabetes observed in immigrants to the UK from the Indian sub-continent.

Inflammation and the metabolic syndrome: CRP is a mediator of inflammation. Chronic mild elevation, even within the clinically 'normal' range, is independently predictive of future cardiovascular events. The mechanism of the increase in circulating CRP in apparently healthy individuals is not clearly established. Recent studies have shown that elevated CRP correlates significantly with features of the metabolic syndrome, including adiposity, hyperinsulinaemia and insulin sensitivity index, hypertriglyceridaemia, low HDL cholesterol and type 2 diabetes.[14] A recent study has also demonstrated that a high CRP is related to increased accumulation of visceral and subcutaneous fat depots measured by computerized tomography. Other pro-inflammatory mediators, including white blood cell count, serum albumin, serum amyloid A and fibrinogen, have been shown to predict type 2 diabetes in large prospective studies.

Management of the metabolic syndrome

Management of the metabolic syndrome focuses on lifestyle changes to reduce risks (Table 5), and maintain healthy weight and body fat distribution (waist circumference <94 cm in men, <80 cm in women). The upper end of the normal BMI range is associated with a substantial increase in the risk of the metabolic syndrome. Maintaining BMI at 21–22 kg/m^2 is optimal for those at risk for genetic or other reasons. However, quite modest weight loss (5–10%) brings major benefits in all metabolic risk factors for people who are overweight. Physical activity has benefits above its role in weight control.

Several drugs appear to improve more than one component of the metabolic syndrome and may give clues to the underlying biochemical disorders. Thiazolidinediones shift intra-abdominal fat to the metabolically favourable subcutaneous fat depot with an associated increase in glucose tolerance and improvement of lipid profile. This is probably because of an expansion in the subcutaneous fat depot (acting via PPARγ), which serves as a metabolic sump for glucose and lipid disposal. Metformin improves glucose tolerance and lipid profile, and has been used in

Management of the metabolic syndrome

Daily core foods

- Five portions of fruit or vegetables
- Two cup-sized helpings of potatoes, pasta or rice
- One glass of low-fat milk
- Bread — six slices for men, five slices for women
- One bowl of cereal with low-fat milk

Weekly core foods

- Two portions of fish or fish products
- Two servings of cheese (more if no meat)
- Three portions of meat
- Limit butter and margarine (maximum 85—110 g)
- Alcohol <21 units for men, <14 units for women

Minimize physical inactivity

- Restrict television viewing/computer use, avoid motor transport for short journeys, activity-oriented holidays and leisure time

No smoking

- Advice and support for cessation including drugs

Daily moderate exercise

- Swimming, climbing stairs, brisk walking, dancing, household chores

Drugs

- Metformin
- PPARγ agonists/thiazolidinediones (e.g. pioglitazone)
- Dipeptidyl peptidase inhibitors (e.g. sitagliptin, vildagliptin)
- GLP-1R agonists (e.g. exenatide, liraglutide)
- Dopamine D2 receptor agonist (e.g. bromocriptine mesylate)
- Tetrahydrolipstatin (e.g. orlistat)

Table 5

conditions other than diabetes, such as polycystic ovary syndrome, to regulate oligomenorrhoea and increase fertility. However, its effect on body fat distribution is unknown, and it does not modify all components of the metabolic syndrome.

Anti-obesity drugs achieve weight loss and, more importantly, reduce weight regain in the long term, which tends to reverse or delay most features of the metabolic syndrome.

Two classes of insulin secretagogues have recently been licensed for the treatment of type 2 diabetes with sufficient residual β-cell function. The oral agents dipeptidylpeptidase-4 (DPP-4) inhibitors ('gliptins') act by prolonging the half-life of the naturally occurring ligand, glucagon-like peptide-1 (GLP-1), secreted from the intestinal L cells; and the injectable GLP-1 receptor (GLP-1R) agonists, exenatide and liraglutide directly activate GLP-1R expressed in the pancreatic β-cells, leading to enhanced insulin synthesis and secretion in the presence of elevated plasma glucose. GLP-1R agonists have major effects on the gut—brain axis by delaying gastric emptying and promoting hypothalamic satiety, resulting in weight loss[15] and reduction in hepatic fat content, but evidence of their long-term effects on metabolic disturbances is not yet available.

In 2009, the FDA approved an ergot derivative, bromocriptine mesylate, as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes. This agent is a quick-release formulation of bromocriptine, a centrally-acting dopamine D_2 receptor agonist. Randomized controlled trials of overweight patients with type 2 diabetes, using bromocriptine mesylate as monotherapy and as dual therapy with a sulfonylurea, have shown significant reduction in HbA_{1c} but no change in body weight.[16] Lipid profile has also been shown to improve in obese patients with type 2 diabetes.[17] The mechanism is not yet elucidated but it is thought that bromocriptine mesylate acts by resetting the abnormal hypothalamic circadian organization of monoamine neuronal activities,[18] thereby reversing the hypothalamic-driven increases in plasma glucose, triglyceride and FFA concentrations in fasting and postprandial states in insulin-resistant patients; this agent could be considered in the future for treating the metabolic syndrome.

Another agent with potential for treating metabolic syndrome is testosterone. Other than its well-known property in promoting muscle hypertrophy, testosterone has many effects on skeletal muscles, including the attenuation of muscle fibre transformation to a fast-twitch, glycolytic, insulin-resistant type IIB fibre.[19] Testosterone and oestrogen therapy have also been proposed as neuroprotective agents in spinal cord injury, on the basis of their possible anti-inflammatory effect.[20,21] Sex hormones, therefore, may be an important factor in modifying metabolic disturbances. In small clinical trials in individuals with low concentrations of testosterone, testosterone replacement has been shown to reduce intra-abdominal fat, increase muscle mass, and improve insulin sensitivity and other features of the metabolic syndrome.[22,23] However, the use of testosterone replacement to treat the metabolic syndrome requires more evidence from double-blind control trials, particularly in those with extreme muscle atrophy such as individuals with spinal cord injury.

Prevention

Whereas there are encouraging developments in the management of the metabolic syndrome, the greater need is for prevention. Although metabolic disturbances naturally progress with age, many modifiable factors can be removed in order to prevent acceleration of this process. At-risk individuals can be identified from their family history and large waist circumference. Serious tissue damage has already occurred by the time diabetes has developed. Regular physical activity (brisk walking for 2—4 hours per week) is likely to prevent most instances of metabolic syndrome and, even after it has developed, modest weight loss (about 5 kg) can reverse all its components, thereby reducing its prevalence and its future incidence, as well as preventing about 60% of new cases of diabetes. Modest weight loss with orlistat has been shown to reduce the incidence of metabolic syndrome and of diabetes by 30—40%.[24] Although metformin can prevent progression of pre-diabetes, it reverses metabolic syndrome in only 5% of cases.[25] Other agents, such as PPARγ agonists and GLP-1R agonists, may also be considered: liraglutide can produce a mean sustained weight loss of 10 kg, associated with reversal of pre-diabetes and metabolic syndrome in some 70% of cases. ◆

REFERENCES

1 Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham study. *Am J Cardiol* 1976; **38:** 46—51.

2 Expert Panel on Detection. Evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the

National Cholesterol Education Program (NCEP) expert panel detection, evaluation, and treatment of high blood cholesterol adults (Adult Treatment Panel III). *J Am Med Assoc* 2001; **285:** 2486–97.
3 International Diabetes Federation. The IDF consensus worldwide definition of the metabolic syndrome [article online: www.idf.org].
4 Lawlor DA, Lean ME, Sattar NA. Obesity and a wider impact on vascular disease. *BMJ* 2006; **18:** 1060–3.
5 Bouchard C. Genetics and the metabolic syndrome. *Int J Obes* 1995; **19**(suppl 1)**:** S52–9.
6 Han TS, Bijnen FC, LeanME Seidell JC. Separate associations of waist and hip circumference with lifestyle factors. *Int J Epidemiol* 1998; **27:** 422–30.
7 Semple RK, Chatterjee VK, O'Rahilly S. PPAR gamma and human metabolic disease. *J Clin Invest* 2006; **116:** 581–9.
8 Guettier JM, Park JY, Cochran EK, et al. Leptin therapy for partial lipodystrophy linked to a PPAR-gamma mutation. *Clin Endocrinol* 2008; **68:** 547–54.
9 Wu FCW, Tajar A, Beynon JM, et al. for the EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med* June 16, 2010; **363:** 123–35.
10 Kupelian V, Hayes FJ, Link CL, Rosen R, McKinlay JB. Inverse association of testosterone and the metabolic syndrome in men is consistent across race and ethnic groups. *J Clin Endocrinol Metab* 2008; **93:** 3403–10.
11 Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. *Proc Am Thorac Soc* 2008; **5:** 207–17.
12 Wannamethee SG, Shaper AG, Rumley A, et al. Lung function and risk of type 2 diabetes and fatal and non-fatal major coronary heart disease events: possible associations with inflammation. *Diabetes Care* 2010; **33:** 1990–6.
13 Barker DJP. Fetal and infant origins of adult disease. London: Springer Publishing, 1992.
14 Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean Haffner SM. Prospective study of C-reactive protein in relation the development of diabetes and the metabolic syndrome in city diabetes study. *Diabetes Care* 2002; **25:** 2016–21.
15 Astrup A, Rossner S, Van Gaal L, et al. NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 2009; **374:** 1606–16.
16 Scranton RE, Gaziano JM, Rutty D, Ezrokhi M, Cincotta A. A randomized, double-blind, placebo-controlled trial to assess safety and tolerability during treatment of type 2 diabetes with usual diabetes therapy and either cycloset or placebo. *BMC Endocr Disord* 2007; **7:** 3.
17 Cincotta AH, Meier AH, Cincotta Jr M. Bromocriptine improves glycaemic control and serum lipid profile in obese type 2 diabetic subjects: a new approach in the treatment of diabetes. *Expert Opin Investig Drugs* 1999; **8:** 1683–707.
18 Pijl H, Edo AM. Modulation of monoaminergic neural circuits: potential for the treatment of type 2 diabetes mellitus. *Treat Endocrinol* 2002; **1:** 71–8.
19 Gregory CM, Vandenborne K, Huang HF, Ottenweller JE, Dudley GA. Effects of testosterone replacement therapy on skeletal muscle after spinal cord injury. *Spinal Cord* 2003; **41:** 23–8.
20 Ogata T, Nakamura Y, Tsuji K, Shibata T, Kataoka K. Steroid hormones protect spinal cord neurons from glutamate toxicity. *Neuroscience* 1993; **55:** 445–9.
21 Sribnick EA, Wingrave JM, Matzelle DD, Ray SK, Banik NL. Estrogen as a neuroprotective agent in the treatment of spinal cord injury. *Ann N Y Acad Sci* 2003; **993:** 125–33.
22 Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. *J Androl* 2009; **30:** 726–33.
23 Haider A, Gooren LJ, Padungtod P, Saad F. Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate. *Exp Clin Endocrinol Diabetes* 2010; **118:** 167–71.
24 Didangelos TP, Thanopoulou AK, Bousboulas SH, et al. The orlistat and cardiovascular risk profile in patients with metabolic syndrome and type 2 diabetes (ORLICARDIA) study. *Curr Med Res Opin* 2004; **20:** 1393–401.
25 Nieuwdorp M, Stroes ES, Kastelein JJ, Fenofibrate/Metformin Study Group. Normalization of metabolic syndrome using fenofibrate, metformin or their combination. *Diabetes Obes Metab* 2007; **9:** 869–78.

FURTHER READING

Abu-Hamdah R, Rabiee A, Meneilly GS, Shannon RP, Andersen DK, Elahi D. Clinical review: the extrapancreatic effects of glucagon-like peptide-1 and related peptides. *J Clin Endocrinol Metab* 2009; **94:** 1843–52.
Björntorp P, ed. International textbook of obesity. Chichester: Wiley, 2001.
Fall T, Ingelsson E. Genome-wide association studies of obesity and metabolic syndrome. *Mol Cell Endocrinol* 2014; **382:** 740–57.
Gooren L, Meryn S, Shabsigh R. The metabolic syndrome: when is testosterone treatment warranted. *J Mens Health* 2008; **5:** S40–5.
Lucas A. Programming by early nutrition in man. In: Bock GR, Whelan J, eds. The childhood environment and adult disease. Chichester: Wiley, 1991; 38–55.
Reaven GM. Banting Lecture. Role of insulin resistance in human disease. *Diabetes* 1988; **1988:** 1595–607.
Sattar N, Lean MEJ. ABC of obesity. London: BMJ Books, 2007.

