The metabolic syndrome: common origins of a multifactorial disorder

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ABSTRACT

The metabolic syndrome (MetS) represents a combination of cardiometabolic risk determinants including obesity (central adiposity), insulin resistance, glucose intolerance, dyslipidaemia, non-alcoholic fatty liver disease and hypertension. MetS is rapidly increasing in prevalence worldwide as a consequence of the continued obesity "epidemic", and as a result will have a considerable impact on the global incidence of cardiovascular disease and type 2 diabetes. Currently, there is debate concerning whether the risk of cardiovascular disease is greater in patients diagnosed with MetS than that of the sum of the individual risk factors. At present, no unifying origin that can explain the pathogenesis of MetS has been identified and therefore no unique pharmacological treatment is available. This review summarises and critically evaluates the current clinical and scientific evidence supporting the existence of MetS as a multifactorial endocrine disease, for which maternal nutrition may be a common pathogenic mechanism. In addition, we suggest that ectopic fat accumulation (such as visceral and hepatic fat accumulation) and the proinflammatory state are central to the development of the MetS.

MetS are often criticised for their failure to identify a unifying pathogenic mechanism⁵ or single genetic cause, which in turn has prevented the formulation of a unique treatment.⁶ It is likely that a seemingly simple mechanism has not been identified because MetS has a highly complex aetiology including inherited genes, intrauterine environment, abnormal patterns of fat accumulation and physical inactivity.⁷ In this review, we will summarise and critically evaluate the current clinical and scientific evidence that supports the existence of MetS as a multifactorial endocrine disease and not a cluster of coincidental features. We will discuss the complex aetiology, pathogenesis and clinical outcomes of the syndrome and in doing so highlight its usefulness as a diagnostic tool. Finally, we will describe how many of the MetS components may share a common origin and how increased risk susceptibility may result from inappropriate maternal nutrition and developmental priming, therefore highlighting a common underlying pathophysiological process.⁸

DEFINITION OF MetS

There have been several definitions of MetS, but the most commonly used criteria for definition at present are from the World Health Organization (WHO),⁹ the European group for the study of Insulin Resistance (EGIR),¹⁰ the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III)¹¹ and the International Diabetes Federation (IDF)(2005).¹² Table 1 presents the diagnostic features of each definition. Although each definition possesses common features, there are several parameters that differ. For example, the WHO and EGIR classifications require the measurement of IR, which is determined by an oral glucose tolerance test and hyperinsulinaemic-euglycaemic clamp. As this method is labour intensive, it is primarily used in a research environment.¹³ In contrast, the ATP III definitions were developed to be applicable in the outpatient clinic and therefore have remained a backbone for subsequent classifications such as the IDF diagnostic criterion.¹³ It is plausible that alternative definitions have contributed to variations within the literature and questions surrounding the pedagogic capacity of the MetS. Nonetheless, the strength of associations between IR and abdominal obesity as a main contributing force driving the onset of MetS is potentially unifying the field. The fact the abdominal obesity is the only mandatory diagnostic criterion in the IDF classification clearly emphasises this.

In 1988, Reaven postulated that insulin resistance (IR) was the cause of glucose intolerance, hyperinsulinaemia, increased very-low-density lipoprotein (VLDL), decreased high-density lipoprotein (HDL) and hypertension.¹ Twenty years later, the insulin resistance syndrome has graduated to become the metabolic syndrome (MetS). MetS is thought to represent a combination of cardiovascular risk determinants, including obesity (especially central adiposity), glucose intolerance and IR, dyslipidaemia (including hypertriglyceridaemia, increased free fatty acids (FFAs) and decreased HDL-cholesterol) and hypertension, and more recently has also been associated with clinical manifestations such as polycystic ovarian syndrome (PCOS), atherosclerosis, proinflammatory state, oxidative stress and non-alcoholic fatty liver disease (NAFLD).

As a multicomponent condition, MetS imparts an approximate doubling of risk for atherosclerotic cardiovascular disease.² However, it is currently uncertain which component of the syndrome configures this risk. In fact, there is currently a controversial debate surrounding the identity of MetS and its pedagogic utility and diagnostic capacity.^{3,4} A criticism of MetS is its lack of weighting for the individual syndrome components, and consequently whether the syndrome as a whole counts more than the sum of its parts remains unclear.³ In addition, the proponents of

Table 1 Features of the World Health Organization (WHO), European Group for the Study of Insulin Resistance (EGIR), National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP-III) and International Diabetes Federation (IDF) definitions of metabolic syndrome

	WHO (WHO consultation, 1999). Impaired glucose tolerance or diabetes and/or insulin resistance and two other factors	EGIR (Balkau and Charles, 1999 ¹⁹). Presence of fasting hyperinsulinaemia (the highest 25%) and two other factors	ATP-III (NCEP Expert Panel on Detection, 2001). Three or more of the following factors (TAGs and HDL counted separately)	IDF. Central obesity and two other factors (www.idf.org)
Central obesity	WHR ≥ 0.9 (men), 0.85 (women) and/or BMI >30 kg/m ²	Waist ≥ 94 cm (men), ≥ 80 cm (women)	Waist ≥ 102 cm (men), >88 cm (women)	Waist >94 cm (European men), >90 cm (Asian men), >80 cm (women)
Blood pressure (mm Hg)	$\geq 140/90$	$\geq 140/90$ or treated for hypertension	$>130/85$ or treated for hypertension	≥ 130 SBP or ≥ 85 DBP or treated for hypertension
Dyslipidaemia (mmol/l)	TAGs ≥ 1.7 , HDL <0.9 (men), <1.0 (women)	TAGs ≥ 2.0 or HDL-cholesterol <1.0 or treated for dyslipidaemia	TAGs ≥ 1.7 , HDL-cholesterol: <1.0 (men), <1.3 (women)	TAGs ≥ 1.7 , HDL-cholesterol, <1.04 (men), <1.29 (women)
Dysglycaemia (mmol/l)	Fasting glucose ≥ 6.1 and/or 2 h post-challenge glucose ≥ 7.8 on diabetes	Fasting plasma glucose >6.1 , but non-diabetic	Fasting plasma glucose ≥ 6.1	Fasting glucose ≥ 5.6 or previous diagnosis of impaired glucose tolerance or diabetes
Insulin resistance	Glucose uptake during hyperinsulinaemic-euglycaemic clamp in lowest quartile for population	Presence of fasting hyperinsulinaemia (ie, among the highest 25% of the non-diabetic population)	Not applicable	Not applicable
Other factors	WHO (WHO consultation, 1999). Impaired glucose tolerance or diabetes and/or insulin resistance and two other factors)	EGIR (Balkau and Charles, 1999 ¹⁹). Presence of fasting hyperinsulinaemia (the highest 25%) and two other factors	Microalbuminuria (urinary albumin excretion rate >20 μ g/min or albumin/creatinine ratio >30 mg/g)	None

BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure; TAG, triacylglycerol; WHR, waist/hip ratio.

CORRELATION OF THE INCREASE IN MetS PREVALENCE WITH INCREASING OBESITY PREVALENCE

When Reaven originally developed the insulin resistance syndrome concept, he did not include any marker of obesity in his description. Many years later, it is clear that in most cases obesity, particularly visceral (or central) obesity, is important for the development of many of the other MetS components and downstream manifestations. In the USA, the prevalence of MetS is driven by the growing obesity “epidemic”, which is occurring throughout Western society and is particularly notable in south-eastern USA.¹⁴ In fact, MetS has reached epidemic proportions across the whole of the USA and, in unison, so has the expression of obesity, glucose intolerance, type 2 diabetes, vascular inflammation and a prothrombotic phenotype.⁶ It has been reported that the incidence of MetS increases with the severity of obesity and has been observed in 50% of obese adolescents.¹⁵ Type 2 diabetes is five to six times more common in obese people (body mass index (BMI) >30 kg/m²) than in those of normal weight.¹⁶ Even within diverse populations exposed to different environmental factors, increasing BMI is positively associated with prevalence of both impaired glucose tolerance and type 2 diabetes.^{17–19} In turn, this increasing BMI also correlates with other MetS components, including increasing total cholesterol, low-density lipoprotein (LDL)-cholesterol and triacylglycerols (TAGS) and decreasing HDL-cholesterol and hypertension.^{16–20}

VISCERAL OBESITY IS A MECHANISTIC LINK BETWEEN THE MetS COMPONENTS

In response to these observations, it can be feasibly argued that the most common contributor to the rise in MetS is excessive body fat accumulation.²¹ However, more specifically, one of the most important causal components of MetS is the accumulation of “ectopic” fat. This often results in a pathophysiological condition that has recently been termed “adiposopathy”, and is defined as pathogenic adipose tissue that is promoted by a

positive energy balance and sedentary lifestyle in genetically and environmentally susceptible patients.^{22–24} Adiposopathy is thought to be clinically manifest through a combination of adipocyte hypertrophy, adipose tissue growth, ectopic fat distribution and, especially, visceral adipose tissue accumulation, all of which may cause adverse immune and metabolic disturbance²⁴ and may contribute to the development of MetS. There are a number of epidemiological studies to support the notion of adiposopathy and, in particular, to support a coherence between visceral obesity and the prevalence of increased MetS leading to increased CVD.^{25–26} Waist/hip ratio, which is used as a marker of visceral obesity, correlates positively with fasting plasma glucose and is consequently a risk factor for the development of type 2 diabetes,²¹ which is independent of, and additive to, BMI.²⁷ Another marker of central obesity—increased waist circumference—has also been shown to significantly increase the risk of CVD, through a positive effect on systolic and diastolic blood pressure increase.²⁸ Although the association between visceral fat and MetS is strong, the mechanism is not fully elucidated.

FAT AND INFLAMMATION

The most challenging aspect to unifying the MetS components is understanding and identifying common cellular mechanisms that provide a pathophysiological link between each metabolic abnormality and the development of disease.¹³ It has been hypothesised that visceral fat may be at the centre of an underlying mechanism, primarily through its release of substances that are causal to metabolic abnormalities. A study of extremely obese subjects (mean (SD) BMI 54.7 (12.6) kg/m²) showed that mean plasma interleukin (IL)-6 concentrations were significantly raised in the portal vein and correlated directly with C-reactive protein (CRP), suggesting that visceral fat provides a mechanistic causal link to systemic inflammation.²⁹ In fact, CRP has been shown to strengthen the relationship between MetS and coronary heart disease events.³⁰

Atherosclerosis is also hypothesised to have a proinflammatory pathogenesis and results from a combination of the innate and adaptive immune system effectors pathways.³¹ Ectopic fat accumulation may directly affect these pathways via the release of immune factors. In addition, dietary fat intake per se may also directly influence inflammatory pathways. Recent studies have shown that high dietary fat intake is associated with oxidative stress and activation of the proinflammatory transcription factor nuclear factor kappa-beta (NFκB).³² In contrast, a diet rich in fruit and fibre has no inflammation-inducing capacity compared with a high-fat diet even if it has the same calorie content.³³

ROLE OF ADIPOCYTOKINES IN MetS

In support of the role of ectopic fat as central to the pathogenesis of MetS, there are several lines of evidence to suggest that ectopic fat may be involved in the genesis of IR. Adipose tissue is now regarded as an endocrine organ secreting a number of hormones and bioactive substances termed adipocytokines (adipokines). The best characterised of these adipokines are leptin, adiponectin, tumour necrosis factor alpha (TNFα) and IL-6.^{34–37} Several other adipokines, including visfatin, plasminogen activator inhibitor-1, angiotensin, resistin and glucocorticoids, have been identified.³⁷ Specifically, it is thought that elevated production of the proinflammatory adipokines due to expanded visceral adiposity (and increased macrophage infiltration) contributes to the development of IR, type 2 diabetes and increased risk of CVD.³⁷ However, there is a complex interplay between these molecules and the pathogenic mechanisms leading to IR. For example, obesity-induced TNFα may contribute to IR by stimulating the release of other proinflammatory cytokines into the circulation. In addition, both resistin and visfatin, although initially associated with the development of IR, have now been shown to have opposing expression in different models of obesity. For a detailed review of the role of adipokines in IR, see *Adipose tissue and adipokines in health and disease*.³⁸

Whereas the circulating concentrations of the proinflammatory cytokines are raised in obese people,³⁹ adiponectin, which is exclusively secreted by adipose tissue, appears to be reduced.³⁷ Although the precise physiological role of adiponectin is not fully elucidated, it is considered to be a marker of insulin sensitivity,^{40–42} and plasma concentrations of adiponectin correlate negatively with IR.^{43–44} In mice, administration of adiponectin has been shown to improve insulin sensitivity via a decrease in hepatic glucose output and increased fatty acid oxidation in muscle.^{45–47} Conversely, patients with type 2 diabetes have lower plasma concentrations of adiponectin than BMI-matched control subjects.⁴⁸ Similarly, hypertensive patients also have low concentrations of adiponectin.⁴⁹

Adiponectin exists in three molecular-mass forms in the circulation. However, the specific biological action of these different molecular forms and how they react with the adiponectin receptors remain to be clarified. It is paradoxical that obese subjects have low adiponectin concentrations compared with lean people, as they have more fat and therefore should produce greater amounts of adipokines. In fact, adiponectin appears to be under the control of adipokine-initiated signalling pathways. For example, adiponectin expression and secretion in adipocytes has been shown to be reduced by TNFα.⁵⁰ It is possible that a change in fat distribution and quantity may deregulate otherwise crucially balanced adipokine concentrations, which may play a key role in the development of a proinflammatory state and increased CVD and IR.

IR AND MetS

IR is the most clinically accepted causal component of MetS. It is classically defined as an impaired glucose response to insulin in key insulin-sensitive tissues, such as adipose tissue, liver and skeletal muscle, and more recently cardiovascular tissue.⁵¹ IR is associated with CVD, and meta-analyses have shown an independent positive association between fasting plasma insulin concentrations and the risk of CVD mortality.⁵⁵ Although the precise mechanisms leading to IR in each tissue type have not yet been fully determined, potential pathways leading to IR have been attributed to either pre-receptor or post-receptor defects.³⁴ For example, impaired cellular signalling events that occur post-receptor, within the target tissue, result in impaired glucose transport and a compensatory increase in insulin to overcome the defect.³⁴ Although any imbalance in the insulin signalling pathway may lead to metabolic disturbance, the most studied is the phosphatidylinositol-3-kinase and protein kinase B (Akt) pathway. Upon insulin binding, the insulin receptors rapidly activate (via phosphorylation) several intracellular protein cascades, such as insulin receptor substrate 1, which recruits and activates phosphatidylinositol-3-kinase. Activation of this pathway is crucial in all insulin-sensitive tissue, including cardiovascular tissue, and therefore disruption may result in IR and hyperinsulinaemia.³⁴ This IR may have a direct adverse effect on dietary nutrient exchange (eg, glucose) in key tissues such as skeletal muscle, contributing to other components of MetS such as hyperglycaemia.⁵²

VISCERAL OBESITY AND FFAs

Increased concentrations of visceral fat may also contribute to an IR state, because, by its nature, it is more resistant to the metabolic effects of insulin than subcutaneous fat.⁶ Instead, it is more responsive to lipolytic hormones, glucocorticoids and catecholamines.^{53–54} The most dramatic abnormality in the FFA metabolism of visceral fat is the failure to suppress FFA concentrations through adipose tissue lipolysis normally in response to hyperinsulinaemia.⁵⁵ This results in an increased CVD risk profile, with impaired endothelial dysfunction, vascular smooth muscle cell proliferation, and alteration of circulating LDL-cholesterol and HDL-cholesterol.⁵⁶ This constantly increased release of FFA into the portal system also provides increased substrate for hepatic production of TAGs,⁵³ a situation that is likely to contribute to the development of non-alcoholic fatty liver and IR. In addition, FFAs themselves contribute to IR. The intracellular accumulation of FFAs in non-adipose tissues in high quantities may induce the overproduction of damaging metabolites and structural abnormalities and ultimately induce necrosis and systemic inflammation, which again is associated with the development of CVD.

NAFLD: A NOVEL COMPONENT OF MetS

The liver is an organ that is vulnerable to ectopic fat accumulation. Currently, the incidence of NAFLD mirrors the prevalence of obesity and MetS, and NAFLD is now one of the most common causes of chronic liver disease worldwide.^{57–60} Approximately 33% of the American adult population have NAFLD.⁵⁹ Recent estimates of prevalence in the USA are 20–30% for hepatic steatosis and 3.5–5% for non-alcoholic steatohepatitis, and up to 80% of people with type 2 diabetes may have some form of NAFLD.⁵⁹ Notably, NAFLD is not a single disease entity, but describes a spectrum of liver conditions. The disorder ranges from simple fatty liver (steatosis) to more severe steatosis coupled with marked

Main messages

- ▶ The metabolic syndrome (MetS) represents a combination of cardiometabolic risk determinants including obesity (central adiposity), insulin resistance, glucose intolerance, dyslipidaemia, non-alcoholic fatty liver disease and hypertension.
- ▶ MetS is rapidly increasing in prevalence worldwide as a consequence of the continued obesity “epidemic”.
- ▶ There is debate about the pedagogic capacity and usefulness of MetS as a diagnostic tool. The main reason for this centres around the apparent lack of a unifying pathogenic mechanism and the variability in the diagnostic criteria.
- ▶ The International Diabetes Federation criteria puts emphasis on central obesity and may be the most clinically accessible method to date.
- ▶ One of the most important causal components of MetS is the accumulation of “ectopic” fat, seen as increased visceral adiposity.
- ▶ Ectopic fat occurring in the viscera may be at the centre of an underlying mechanism, primarily through a paracrine effect to decrease tissue insulin sensitivity in key tissues such as liver. In addition, the release of substances such as adipokines from ectopic fat may act to promote a proinflammatory state, decrease insulin sensitivity and, in turn, adversely modify cardiovascular risk factors.
- ▶ The liver is particularly susceptible to ectopic fat accumulation, and non-alcoholic fatty liver disease (NAFLD) is now considered to be the hepatic manifestation of MetS. NAFLD may progress in susceptible people with increasing steatohepatitis and progressive liver fibrosis.
- ▶ NAFLD may be developmentally “primed” through exposure of the developing offspring in utero to inappropriate maternal nutrition during pregnancy. Therefore, we suggest that this developmental origin may provide a unifying mechanism to explain MetS susceptibility and the broad spectrum of the MetS phenotype extending from dysglycaemia to increased blood pressure, dyslipidaemia, central obesity and NAFLD.

inflammation termed non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, and subsequently to liver cirrhosis (15–17%), liver failure (3%) and hepatocellular carcinoma.⁶¹

Interestingly, all components of MetS correlate with liver fat, as determined by ¹H-magnetic resonance spectroscopy, and, although these measures increase with obesity, they remain significant even when adjusted for BMI.⁶² Therefore it is not surprising that NAFLD is considered the hepatic manifestation of MetS.^{63–65} In support of this, recent epidemiological studies have shown that severe NAFLD is linked to an increased risk of CVD, independent of underlying cardiometabolic risk factors.⁶⁶ These studies suggest that NAFLD may be actively involved in the pathogenesis of CVD, potentially through the increased release of pro-atherogenic factors from the liver (CRP, fibrinogen, plasminogen activator inhibitor-1 and other inflammatory cytokines). Alternatively, NAFLD is involved in whole-body IR and dyslipidaemia. For example, once significant hepatic steatosis occurs, the liver becomes insulin-resistant and overproduces both glucose and VLDL, which in turn leads to hyperglycaemia, hypertriglyceridaemia and low HDL concentrations.⁶⁷ However, whether IR precedes ectopic fat deposition or whether fat accumulation is a consequence of IR remains an unanswered question.

Current research questions

- ▶ Do the metabolic syndrome (MetS) criteria require further review to appraise the thresholds for each of the five simple features of the syndrome, as used in the International Diabetes Federation and Adult Treatment Panel III criteria?
- ▶ Should the simple easily measurable individual features of MetS be considered as part of a continuum of increasing risk for type 2 diabetes, cardiovascular disease and non-alcoholic fatty liver disease?
- ▶ Should the term dysglycaemia replace the term “type 2 diabetes” to (a) acknowledge the evidence that increasing glucose concentrations increase the risk of microvascular complications, (b) move away from the notion that type 2 diabetes reflects a single disease entity, and (c) allow the treatment of glucose concentrations to be considered as the management of a continuously distributed risk factor within a population?
- ▶ What are the precise pathogenic mechanisms linking ectopic fat accumulation to the other MetS components?
- ▶ What makes an individual more susceptible to ectopic fat distribution?
- ▶ What are the mechanisms underlying the developmental priming of the MetS components?

As previously described, ectopic fat is an important source of inflammatory factors, cytokines and adipokines. It is possible that adipose tissue inflammation plays a role in the pathogenesis of NAFLD. Indeed, analysis of adipose tissue from subjects with severe liver steatosis has suggested that inflamed adipose tissue characterises people with a high liver fat content.^{68–69} In mice, the overexpression of an inflammatory marker in adipose tissue (CCL2/MCP1) is thought to lead to macrophage infiltration and hepatic steatosis.⁷⁰ However, it is also possible that hepatic inflammation may precede that of other insulin-sensitive tissues, as the hepatic activation of NFκB via overexpression of IκB kinase β can induce IR in the liver and muscle in addition to an increase in signs of systemic inflammation (IL-6).⁷¹ This study also reported that the same situation arises in response to a high-fat diet. In response to these findings, we can draw similarities between hepatic fat and more traditional sites of proinflammatory, adiposopathic ectopic fat, predominantly influenced by a high-fat diet. Therefore, liver with a more severe form of NAFLD (NASH) may play an even larger role in the whole-body inflammatory state, because the liver itself is in an advanced state of inflammation. It is also possible to hypothesise that, in some people, liver fat per se may act as the adiposopathic ectopic fat (potentially independent of visceral fat) contributing to the development of MetS.

DEVELOPMENTAL ORIGINS OF NAFLD

NAFLD clearly plays an important role in the development of MetS components and the inflammatory state. But how does hepatic lipid accumulate to abnormal concentrations in the first place is the primary and crucial question. Several events may result in a fatty liver, particularly in the context of IR. These include increased FFA delivery due to increased lipolysis from both visceral and subcutaneous adipose tissue, and/or increased intake of dietary fat, coupled with decreased oxidation and increased de novo hepatic lipogenesis.⁷² Analysis of hepatic TAG content has shown that fatty acids contributing to TAG

accumulation were derived from a plasma supply of FFAs (59%), de novo hepatic lipogenesis (26%) and the diet (15%).⁷³ These data may seem counter-intuitive, as fatty liver largely appears to be a consequence of diet-induced obesity. However, we have recently tested in mice the hypothesis that exposure to a maternal high-fat diet during pregnancy can predispose the offspring to develop a progressive fatty liver phenotype in adulthood.⁷⁴ We have shown that this appears to occur through two distinct mechanisms. The prenatal high-fat exposure upregulates the gene expression of key enzymes involved in hepatic de novo lipogenesis and TAG synthesis. We hypothesise that this increased supply of lipids from the prenatal high-fat diet developmentally “primes” the offspring’s metabolic pathways to cope with exogenous lipids. Upon secondary exposure to a diet high in fat in postnatal life, these “primed” metabolic pathways readily accumulate fat within the liver, resulting in ectopic fat storage and a NASH-like phenotype. We observe this phenomenon at a developmental time point equivalent to early adulthood, before the onset of IR, but after the onset of obesity.⁷⁵ This timeline suggests that, in our animal model, ectopic fat accumulation may precede NASH, which in turn may precede IR.

Another mechanism that leads to developmentally primed NAFLD is mitochondrial dysfunction. Mitochondrial dysfunction has been previously described in animal models and in people with NASH.^{63, 76–81} Our data show that offspring of dams that were exposed to a high-fat diet have reduced mitochondrial electron transport chain (ETC) enzyme complex activity, which persists until adulthood. The ETC is responsible for oxidative phosphorylation and is intimately linked to the citric acid cycle and β -oxidation, therefore its impairments must further reduce the offspring’s hepatic capacity to deal with superfluous dietary fats, thus contributing to hepatic lipid accumulation. In addition, a decrease in ETC activity may lead to imbalanced membrane potential, which prolongs the half-life of electron carriers and

increases the generation of reactive oxygen species.⁸² This effect would initiate lipid peroxidation and activate NF κ B inflammatory pathways and exacerbate the existing “inflammatory state”.

Mitochondrial dysfunction has also been implicated in several other studies investigating the developmental programming of MetS. For example, recent findings have shown that diet-induced obesity leads to mitochondrial impairment.⁸³ In addition, studies using a transgenerational animal model of IR have shown that mitochondrial dysfunction (observed as a reduction in mitochondrial DNA) is developmentally programmed in response to maternal nutrition.⁸⁴ In simple invertebrate model systems, it has been established that very early stresses during the initial stages of development cause persistent changes to mitochondrial activity,⁸⁵ thus establishing a precedent for “programming” mitochondria. Mitochondria are central to lipid homeostasis, are maternally inherited, act as a vector for dietary-induced stress, and produce changes that persist into adulthood; collectively, this implies that mitochondrial dysfunction may be a key common mechanism contributing to increased susceptibility to MetS.

A COMMON “DEVELOPMENTAL” ORIGIN FOR MetS

A candidate underlying mechanism that could unify the apparently disparate components of MetS, and which follows a similar socioeconomic trend, is maternal obesity or the maternal diet during pregnancy. Recent estimates in the USA are that about one-third of women are obese when they reach child-bearing age.⁸⁶ This presents a major health burden, as maternal obesity at conception alters gestational metabolism and affects placental, embryonic and fetal growth and development.⁸⁷ In addition, a wealth of evidence is accumulating to suggest that an inappropriate maternal diet can influence the susceptibility of the offspring to develop components of MetS in adult life.^{84, 88–92}

Originally, much of the early focus of this research was on retrospective clinical studies in which early life measurements have been undertaken in people who have been studied in adulthood. These studies detailed the relationship between low birth weight and subsequent adult CVD and led Barker and colleagues^{93, 94} to hypothesise that adverse environmental factors in early life cause disruption of normal growth and development, which became known as the “developmental origins of health and disease” hypothesis (DOHaD).

Recent experimental studies in animals support the DOHaD hypothesis and its role in the development of other components of MetS in addition to CVD. Specifically, it has been shown

Figure 1 Schematic diagram of the metabolic syndrome (MetS) with suggested mechanisms linking the MetS components. The maternal environment can developmentally prime the metabolic capacity of key tissues, and this, combined with the “genetic code”, establishes the individual’s susceptibility to developing MetS. The expression of the final adult MetS phenotype is dependent on the relative influences of the severity of the developmental priming, genetic code variation and environmental factors throughout life. We also suggest that ectopic fat accumulation per se (as occurs in non-alcoholic fatty liver disease (NAFLD) in addition to visceral fat accumulation) and the proinflammatory state are key to the development of MetS. CVD, cardiovascular disease.

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that maternal undernutrition during critical periods can prime adipose tissue deposition to give rise to later obesity, especially when challenged postnatally with a hypernutritional diet.⁹⁵ There is also evidence to suggest that it may have a detrimental effect on glucose homeostasis. For example, manipulation of the fetal energy supply (low protein) has been shown to modify the process of islet cell expansion, leading to small β -cell mass at birth, which becomes even more pronounced when the protein-restricted diet is maintained until weaning.⁹⁶ Experimental findings from models of overnutrition are more limited and are beginning to come into the field. Preliminary studies have shown that overfeeding during the preweaning period permanently increases adipocyte hypertrophy.⁹⁷ Increased body weight and a twofold increase in the visceral fat depot weight in adult offspring of fat-fed dams (24% fat by weight; lard) has also been reported.⁸⁴ In addition, our studies have shown that high-fat-induced developmental priming of body fat accumulation is exacerbated when dietary challenge continues in the post-weaning phase.⁷⁵ This concept is illustrated in fig 1. Collectively, these data suggest that maternal diet may be a common origin and support the notion that early development may “prime” increased susceptibility to the multifactorial disorder that is MetS in later life (fig 1).

SUMMARY

MetS is a highly complex multifactorial endocrine disorder, which shares not one, but several common underlying mechanisms (fig 1), which include ectopic fat accumulation, impaired insulin sensitivity and increased systemic inflammation. We suggest that ectopic fat accumulation per se (as occurs in NAFLD in addition to visceral fat accumulation) and the proinflammatory state are key to the development of MetS. The pathophysiological effects that result as clinical disease are diverse (eg, type 2 diabetes, NAFLD, PCOS, CVD), and their phenotypic presentation depends on the relative extent to which each of the person's cues, either developmental and genetic or environment, influence the metabolic capacity of key tissues contributing to the onset of MetS in later life. Regardless of its variable presentation, and the ongoing debate on the validity of dichotomous thresholds on continuous variables, the MetS is a simple diagnostic tool. It has important use for the clinician and can emphasise the need to provide lifestyle advice to the patient. Moreover, identification of individual MetS features that are below the threshold for individual pharmacological treatment indicates the need to estimate cardiovascular risk, and highlights the need for specific treatment such as statins to decrease cardiovascular risk. The recent JUPITER trial has shown that statin treatment decreases the incidence of major cardiovascular events in people with “normal” LDL-cholesterol concentration and a marker of inflammation (increased CRP concentrations)⁹⁸ that is often present in MetS. However, in the follow-up period, an increase in physician-reported incident diabetes was observed. Although there was no difference in median fasting plasma glucose in the rosuvastatin and placebo arms of the study, there was a 0.1% increase in HbA1c in the rosuvastatin arm of the study versus the placebo. Although the cardiovascular benefits of statin treatment most likely outweigh the marginal adverse effects on glucose metabolism in these patients, the data suggest the need for routine monitoring of glucose concentrations in statin-treated patients with MetS. We suggest that identification of MetS in susceptible people may prompt the early diagnosis of other previously undetected MetS components such as NAFLD and PCOS, ultimately to the benefit of the patient.

MULTIPLE CHOICE QUESTIONS (TRUE (T) OR FALSE (F); ANSWERS AFTER THE REFERENCES)

1. Simple ATPIII and IDF criteria for identifying metabolic syndrome utilise the following measurements:

- A. age
- B. sex
- C. smoking status
- D. plasma triacylglycerols
- E. blood pressure

2. Metabolic syndrome is associated with increased risk of:

- A. type 1 diabetes
- B. type 2 diabetes
- C. ischaemic heart disease
- D. cerebrovascular disease
- E. foot ulcers

3. Metabolic syndrome is associated with increased fat in the following sites:

- A. liver
- B. abdomen
- C. hips
- D. bone
- E. lungs

4. Ectopic fat is associated with:

- A. anti-inflammatory state
- B. proinflammatory state
- C. release of anti-inflammatory cytokines
- D. release of proinflammatory cytokines
- E. release of proinflammatory adipocytokines

5. A predisposition to the development is thought to be due to:

- A. exposure to a balanced diet during development
- B. exposure to a poor diet during development
- C. genetic factors
- D. lifestyle factors
- E. all of the above

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Answers

1. (A) F; (B) F; (C) F; (D) T; (E) T
2. (A) F; (B) T; (C) T; (D) T; (E) F
3. (A) T; (B) T; (C) F; (D) F; (E) F
4. (A) F; (B) T; (C) F; (D) T; (E) T
5. (A) F; (B) T; (C) T; (D) T; (E) T