

The metabolic syndrome – does it exist?



The association between type 2 diabetes mellitus (T2DM), obesity, hypertension, dyslipidaemia, hyperuricaemia and coronary vascular disease (CVD) was recorded more than 70 years ago, and in 1977 Haller coined the term metabolic syndrome (MS) to describe this group of disorders.¹ In his Banting Lecture of 1988, Gerald Reaven emphasised the central role of insulin resistance in the development of what he termed syndrome X.^{2,3} Subsequently a number of other conditions such as microalbuminuria (MA), non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS) and certain obesity-related cancers have been included in the syndrome.

Today, an emotional controversy rages as to whether the syndrome exists at all – some even suggesting that the condition was invented by industry to create new markets! The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) remain sceptical as to whether the MS serves a useful purpose, while the International Diabetes Federation (IDF) and a large part of the cardiovascular community are convinced that it does.⁴⁻⁶

Diagnostic criteria for MS have been proposed by numerous organisations (the World Health Organization (WHO), National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII), American Association of Clinical Endocrinologists (AACE), European Group for the Study of Insulin Resistance (EGIR), IDF and others). Criticism that these criteria are often imprecise and ambiguous is certainly valid. The NCEP/ATPIII criteria, originally published in 2001, were updated in 2004³ and currently differ from the IDF criteria announced in 2005⁴ only in that (i) the IDF employs ethnicity-specific values for *abdominal obesity* which must be met to secure a diagnosis of MS, whereas the presence of abdominal obesity is optional according to the ATPIII; and (ii) the IDF accepts a *history of a previous diagnosis of T2DM or treatment of hypertension or the specific dyslipidaemias* which occur in MS, as valid criteria. Both definitions therefore largely identify the same subjects. In fact, in a recent small local study of black subjects with established CVD, both definitions appeared to generate similar estimates of the MS.⁷

What is the evidence to support the existence of a syndrome?

There is ample evidence from cluster analyses that the prevalence of obesity, dysglycaemia, lipid abnormalities, hypertension and CVD occur together

more readily than would be predicted from pure chance. We are therefore, per definition, dealing with a syndrome.

There is also some evidence to suggest that major role players like hypertension and dyslipidaemia are synergistic in their predisposition to CVD risk – i.e. risk increases exponentially and not in a linear fashion. There is, however, no convincing evidence to suggest that the combination of the specific components of the MS confers an exponential increase in risk. The MS, as initially developed by the WHO and the NCEP, was intended as an operational definition for CVD risk. It did not include recognised major CVD risk factors like age, gender, physical inactivity, smoking, a family history of CVD or low-density lipoprotein (LDL)-cholesterol, and was not intended as a measure of *absolute risk*, but rather as an *addition* to global risk. Not surprising therefore is the observation that established risk assessment models like the Framingham Risk Score or the Diabetes Risk Model have generally, although not consistently, outperformed the MS in predicting either incident CVD or diabetes. If the aim of the MS is to remind care physicians of these additional/hidden CVD risk factors, it raises the question as to whether other related risk parameters (C-reactive protein (CRP), plasminogen activator inhibitor 1 (PAI-1), alanine aminotransferase (ALT)) should not be included in the diagnostic criteria of the MS (*vide infra*).

Another argument that would strengthen the case for a true syndrome involves *approaches to therapy*. There is no doubt that drugs required to treat one component of the MS may impact on another component. Examples include the well-known *deleterious effects* of certain antihypertensive drugs on the lipid profile (β -blockers) or glucose tolerance (thiazides). The converse, namely *beneficial effects* of drugs used to treat one component of MS or another, is less well established. Although metformin has been convincingly shown to decrease CVD in patients with established diabetes, data showing that this also occurs in the setting of the MS are still lacking. Initial trials suggesting that angiotensin-converting enzyme inhibitors (ACEIs) may delay/prevent the development of diabetes (CPT, HOPE, ALLHAT) have not been confirmed by more recent studies, e.g. DREAM (although progression to impaired glucose tolerance was significantly decreased). To date, most authorities therefore emphasise that treatment of MS should focus on lifestyle change and on the individual components, if the former fails. The lack of evidence-based data from large randomised

clinical trials should not, however, be regarded as synonymous with data to the contrary. Therefore, while ACEIs are clearly not indicated for the prevention of T2DM *per se*, it seems prudent to employ these drugs, which not only lower blood pressure but also increase adiponectin levels, decrease insulin resistance, improve endothelial function and reduce circulating markers of inflammation, when treating hypertension in subjects with the MS. Analogous arguments could be made for the potential benefit of metformin in PCOS, or thiazolidenediones in NAFLD.

Whereas a full understanding of the underlying cause(s) of a condition is certainly not a prerequisite to give it a name or to call it a syndrome, there is little doubt that improved insights into the pathogenesis of the MS will go a long way towards resolving the debate. In this regard, much progress has been made in recent years, with two or three major hypotheses emerging – insulin resistance, hyperinsulinaemia and visceral obesity.

Pathogenesis of the metabolic syndrome

Insulin resistance

This hypothesis, originally advanced by Reaven, suggests that genetic defects and/or acquired factors (e.g. obesity) cause insulin resistance. Since the discovery that the insulin receptor is an insulin-stimulated protein tyrosine kinase enzyme, Ron Kahn and others have shown that following the activation of the receptor kinase, several intracellular substrates are activated through tyrosine phosphorylation (serine phosphorylation, inhibits signalling). Best studied are a family of high molecular proteins called the insulin receptor substrates (IRS). These phosphorylated IRS proteins serve as intracellular docking molecules capable of attracting and binding enzymes (e.g. PI-3 kinase) and adaptor proteins (e.g. Grb-2, SOS), and link insulin to two major intracellular cascades – one mediated by the enzyme PI-3 kinase, and the other mediated by the raf-ras-MAPK pathway. Via the glucose transporter proteins (GLUTs), the former largely mediates the 'metabolic' actions of insulin, whereas the latter mediates the 'mitogenic' effects of the hormone. Furthermore, insulin-induced, nitric oxide (NO)-mediated vasodilatation is known to be mediated via the PI-3 kinase pathway. Insulin, however, also acutely stimulates the secretion of the potent vasoconstrictor endothelin-1 (ET-1) from endothelial cells – an effect that is mediated by MAPK-dependent, but not PI-3 kinase-dependent, pathways.⁸⁻¹¹

Numerous defects in insulin signalling (e.g. involving the insulin receptor, the IRS proteins, PI-3 kinase, the GLUTs, etc.) (see ① to ⑤ in Fig. 1) have been documented which result in insulin resistance. Insulin resistance is characterised by pathway-specific impairment in PI-3 kinase-dependent signalling. It

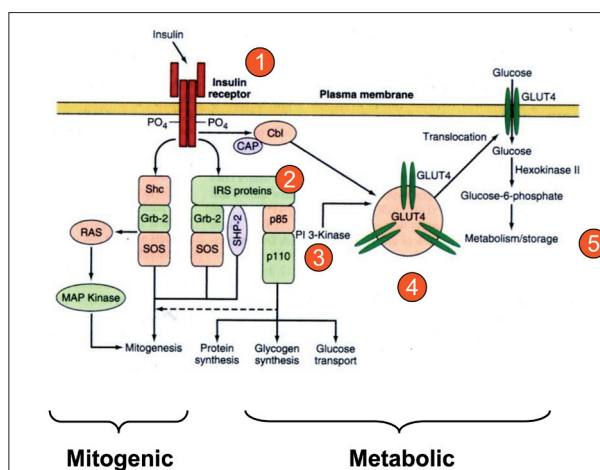


Fig. 1. Insulin resistance: defects in signalling.

is conceptually attractive to postulate, and mounting experimental evidence exists (see Muniyappa *et al.*¹⁰ for review), that a defect in the 'metabolic' limb of this signalling cascade may result in hyperglycaemia, hyperinsulinaemia and overstimulation of the intact 'mitogenic' pathway, resulting in proliferation of skin (acanthosis nigricans), ovaries (PCOS), and endothelial and vascular smooth-muscle cells (endothelial dysfunction and atherosclerosis). Hyperinsulinaemia may also be associated with hypertension (fluid retention, adrenergic stimulation) and dyslipidaemia (increased hepatic very-low-density lipoprotein (VLDL) production leading to hypertriglyceridaemia and a decrease in high-density lipoprotein (HDL)).

Whereas there is full agreement on an association of these disorders, the mechanism of their interrelationship remains unclear. Moreover, insulin resistance cannot be confirmed in a significant number of patients with MS.

Visceral obesity

An alternative, unifying hypothesis proposes that visceral (abdominal) obesity is the major cause of the MS. Visceral obesity is certainly an independent risk factor for all the components of the syndrome. Obese (hypertrophic) adipocytes liberate free fatty acids (FFAs) that trigger the activation of serine/threonine kinases (initiated by protein kinase C (PKC) isoforms and JNK-1). This results in increased serine phosphorylation of IRS-1 which reduces the ability of IRS-1 to bind and activate PI-3-K, resulting in reduced insulin-stimulated glucose transport and other events downstream of PI3K.

In addition, adipocytes produce a number of adipokines – some known to improve (adiponectin, leptin, visfatin) and others to decrease (TNF- α , IL-1, resistin, MCP-1) insulin sensitivity and to create an inflammatory milieu. Of the adipose-derived inflammatory markers studied, adiponectin deserves particular mention, since a strong inverse association between adiponectin and insulin resistance, blood pressure, triglycerides,

LDL-cholesterol and CVD risk has been consistently documented.^{12,13}

The enzyme AMP-activated protein kinase (AMPK) plays a major role in the regulation of cellular intermediary metabolism and is the target not only of adipokines like adiponectin and leptin, but also such stimuli as exercise, changes in fuel availability, and drugs that alter insulin sensitivity.

Hyperinsulinaemia

Insulin resistance usually, but not invariably, results in hyperinsulinaemia. In fact a recent review suggests that when insulin resistance, fat mass and distribution, and hyperinsulinaemia are simultaneously assessed in a large study population, no one factor stands out as the sole driving force of the cardiovascular risk factor cluster.¹¹

So, does a MS exist?

- There is substantial evidence that a constellation of CVD risk factors occurs together more often than would be predicted from chance alone. Whether we call this a syndrome or not is semantic.
- This 'syndrome' should clearly not be regarded as a comprehensive checklist to assess CVD risk. It intentionally excludes major CVD risk factors (like smoking, LDL-cholesterol), and serves to remind care physicians of 'additional' risk factors (obesity, non-LDL lipids, 'prediabetes') that had not previously received the attention they deserved. In this regard it has certainly succeeded admirably!
- Diagnostic criteria to identify the MS, especially those based on laboratory tests, remain problematic since a compromise between clinical efficacy (in predicting risk) and cost is sought. Criticisms that diagnostic criteria are imprecise, ambiguous, and not adequately weighted are certainly valid. The original contention to include only parameters that

would be 'routinely' obtained by care physicians, excludes important risk factors, notably the procoagulant and inflammatory markers, and should probably be revisited.

- Current treatment should emphasise lifestyle changes and of course involve management of all risk factors, whether these fit into a 'syndrome' or not. Due cognisance should, however, be taken of possible deleterious, as well as potentially beneficial, drug effects.
- Clearly more research on the underlying cause(s) and precise definition of this condition and the most appropriate way to manage it is required.

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