Revisiting the metabolic syndrome

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ABSTRACT

- Metabolic syndrome (MS) refers to the clustering of cardiometabolic risk factors — including abdominal obesity, hyperglycaemia, dyslipidaemia and elevated blood pressure — that are thought to be linked to insulin resistance. MS is associated with increased risk of cardiovascular disease and type 2 diabetes.
- MS is common, affecting a quarter to a third of adults, and its prevalence is rising, in parallel with increasing obesity and population ageing.
- Operational definitions of MS have been proposed by the World Health Organization and the National Cholesterol Education Program. Recently, the International Diabetes Federation proposed a global definition that emphasised the importance of central adiposity.
- In cardiovascular risk assessment, MS encapsulates the contribution of non-traditional risk factors and provides a clinically useful framework for early identification of people at increased long-term risk. It should be used in conjunction with standard algorithms based on conventional risk factors, which better predict short-term risk.
- Management of MS should emphasise lifestyle interventions (eg, physical activity, healthy diet and weight reduction) to reduce long-term risk of cardiovascular disease and diabetes. Those at increased short-term risk should also have individual risk factors treated according to established guidelines.

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Metabolic syndrome (MS) refers to the clustering of several cardiometabolic risk factors, including abdominal obesity, hyperglycaemia, dyslipidaemia and elevated blood pressure, that are likely to be linked to insulin resistance.[1] The clinical relevance of MS is that it identifies people who are at increased long-term risk of cardiovascular disease and type 2 diabetes, thus providing an opportunity for preventive lifestyle interventions.

Our article outlines our perspective on the evolving concept, definition and clinical spectrum of MS, with reference to several health issues specific to men. It focuses on the cardiometabolic risk of MS and associated management issues, as well as recent debate about the syndrome itself and its role in risk assessment.

Evolving concept and clinical spectrum

An association between hypertension, hyperglycaemia and hyperuricaemia was first reported over 80 years ago.[2] Subsequently, this cluster was expanded to include upper body ("android") adiposity[3] and dyslipidaemia, and was observed to be linked to atherosclerosis. In 1988, Reaven described a set of metabolic abnormalities (hypertension, hypertriglyceridaemia, low high-density lipoprotein (HDL)-cholesterol level and hyperinsulinaemia) associated with increased cardiovascular risk, which he termed "syndrome X", and postulated that impaired insulin action was the underlying pathophysiology.[4] The "insulin resistance syndrome" embodied a similar concept that also included obesity.[5]

Recent studies support the notion that these metabolic abnormalities do indeed cluster beyond the effect of chance,[6] and that a single factor may underlie the association.[7] That insulin resistance and abdominal obesity, key components of this cluster, are also associated with perturbations in plasma adipokine levels, altered fatty acid metabolism, endothelial dysfunction, procoagulant state and systemic inflammation underscores the breadth and complexity of the pathophysiology of this clustering, which is still poorly understood.[8]

In addition to cardiovascular disease and diabetes, insulin resistance is also associated with a wide spectrum of clinical disorders, including polycystic ovary syndrome, non-alcoholic fatty liver disease, sleep-disordered breathing, chronic kidney disease and certain cancers.[9] Insulin resistance and its related metabolic abnormalities may also be features of glucocorticoid excess and HIV-associated lipodystrophy.

In men, insulin resistance is associated with erectile dysfunction,[10] probably due to endothelial dysfunction. Elevated plasma levels of insulin and insulin-like growth factor 1 may have growth-promoting effects on hormonally-responsive prostate cells,[11] increasing the risk of hyperplasia and cancer. Hyperinsulinaemia also suppresses hepatic production of sex hormone-binding globulin, which reduces total plasma testosterone levels,[12] but whether free hormone levels are affected is less certain. Increased fat mass may also promote conversion of testosterone to oestradiol via aromatisation.[12]

Clinical definitions: a pragmatic approach

The first operational definition of MS was proposed by the World Health Organization,[13] with hyperglycaemia and/or insulin resistance as a central feature, associated with two or more related metabolic abnormalities (elevated blood pressure, dyslipidaemia, central obesity or microalbuminuria). Two other definitions of MS have since been proposed, based on readily assessable clinical and biochemical measures, to help identify people at risk (Box).

The National Cholesterol Education Program (NCEP) definition requires three or more of the following features: abdominal obesity, elevated triglyceride levels, reduced HDL-cholesterol level, elevated blood pressure or elevated fasting glucose level.[8] These criteria were updated recently to include people receiving medical treatment for dyslipidaemia or hypertension, and those with isolated systolic or diastolic hypertension. The threshold defining impaired fasting glucose was also revised, and consideration was given to using lower waist circumference cut-off points for individuals prone to insulin resistance.

In 2005, the International Diabetes Federation (IDF) proposed a definition of MS similar to that of the NCEP, but with increased waist circumference as a necessary requirement, emphasising the central importance of abdominal obesity.[14] Importantly, because of racial differences in the relationship between level of adiposity and risk of comorbidities, ethnic-specific cut-off points were proposed for waist measurements.

The various MS definitions include the same core criteria of central obesity, hyperglycaemia, dyslipidaemia and high blood

Clinical definitions of the metabolic syndrome

	World Health Organization[13]	National Cholesterol Education Program (NCEP) (Adult Treatment Panel III)*[8]	International Diabetes Federation (IDF)[14]
Criteria required	Hyperglycaemia/insulin resistance plus two or more of four other criteria	Three or more of five criteria	Central obesity plus two or more of four other criteria
Central obesity	Waist/hip ratio > 0.9 (men), > 0.85 (women) and/or body mass index > 30 kg/m^2	Waist circumference: Caucasian: ⩾ 102 cm (men), ⩾ 88 cm (women) Asian: ⩾ 90 cm (men), ⩾ 80 cm (women) Consider lower cut-offs (⩾ 94 cm [men], ⩾ 80 cm [women]) for some non-Asian adults with strong genetic predisposition to insulin resistance	Waist circumference (ethnic-specific): Europid, Sub-Saharan African, Eastern Mediterranean and Middle Eastern (Arab): ⩾ 94 cm (men), ⩾ 80 cm (women) South Asian, Chinese, South/Central American: ⩾ 90 cm (men), ⩾ 80 cm (women) Japanese: ⩾ 85 cm (men), ⩾ 90 cm (women)
Hyperglycaemia	Insulin resistance: diabetes, impaired fasting glucose, impaired glucose tolerance or hyperinsulinaemic euglycaemic clamp glucose uptake in lowest 25% of the population	Fasting plasma glucose level ⩾ 5.6 mmol/L or current drug treatment for elevated glucose level	Fasting plasma glucose level ⩾ 5.6 mmol/L or previous diagnosis of type 2 diabetes
Dyslipidaemia†	Triglyceride levels ⩾ 1.7 mmol/L *and/or* HDL-cholesterol level < 0.9 mmol/L (men), < 1.0 mmol/L (women)	Triglyceride levels ⩾ 1.7 mmol/L or current drug treatment for hypertriglyceridaemia	Triglyceride levels ⩾ 1.7 mmol/L or current drug treatment for hypertriglyceridaemia
		HDL-cholesterol level < 1.0 mmol/L (men), < 1.3 mmol/L (women) or current drug treatment for low HDL-cholesterol level	HDL-cholesterol level < 1.0 mmol/L (men), < 1.3 mmol/L (women) or current drug treatment for low HDL-cholesterol level
Elevated blood pressure	Blood pressure ⩾ 140/90 mmHg	Systolic blood pressure ⩾ 130 mmHg, diastolic blood pressure ⩾ 85 mmHg or current drug therapy for known hypertension	Systolic blood pressure ⩾ 130 mmHg, diastolic blood pressure ⩾ 85 mmHg or current drug therapy for known hypertension
Other	Microalbuminuria: urinary albumin excretion rate > 20μg/min or urinary albumin/creatinine ratio > 3.5 mg/mmol		

HDL = high-density lipoprotein. * As modified in the American Heart Association/National Heart, Lung and Blood Institute Scientific Statement 2005.[8]
† Elevated triglycerides and low HDL-cholesterol are considered separate criteria in the NCEP and IDF definitions. ◆

pressure, but differ in the cut-off points for individual criteria, in specific mandatory requirements (eg, abdominal obesity or insulin resistance) and in the inclusion of additional factors (eg, microalbuminuria). Hence, they identify broadly similar, but not identical, groups of individuals with MS.[15]

Epidemiology: MS a growing problem

Whichever definition is used, large epidemiological surveys show that MS is common. The National Health and Nutrition Examination Survey 1999–2002 estimated the age-adjusted prevalence of MS in US adults aged 20 years and over to be between 34.6% (NCEP) and 39.1% (IDF).[15] Unpublished data from the AusDiab study (1999–2000) showed an adjusted estimated MS prevalence of between 23.9% (NCEP) and 26.0% (WHO) in Australian adults, although a lower prevalence was found in a smaller Australian community sample (15.0% [NCEP] and 22.8% [IDF]).[16]

MS is more prevalent with increasing age, affecting half of adults aged 60 years and over.[15] It is more common in men when WHO or IDF criteria are used, but there is little difference between the sexes when the NCEP definition is used.[15,16] Ethnicity also influences MS prevalence.[15]

The prevalence of MS is increasing,[17] in parallel with population ageing and "epidemic" obesity. The rise in childhood obesity presents a challenging problem for the future.[18]

Cardiovascular risk: is the whole greater than the sum of the parts?

Prospective studies have established that MS is associated with a doubling of the risk of cardiovascular disease.[19] Importantly, this risk also extends to people with MS who do not have diabetes. Moreover, the presence of MS in non-diabetic individuals markedly increases the likelihood of developing future type 2 diabetes (about sevenfold), further augmenting cardiovascular risk.[19]

By definition, MS incorporates some established risk factors (eg, hypertension and diabetes) that contribute to its association with cardiovascular disease. Although there is conflicting evidence about whether MS itself may predict cardiovascular risk more strongly than its individual components,[20,21] data showing that MS is associated with increased coronary risk independent of Framingham risk score category suggest that MS is associated with risk not entirely accounted for by traditional vascular risk factors.[22] This highlights the important association between MS and other non-traditional atherogenic risk factors linked to insulin resistance (eg, elevated triglyceride-rich lipoproteins, small dense low-density lipoprotein (LDL) particles, postprandial lipaemia, endothelial dysfunction, low-grade inflammation and prothrombotic state)[9] that are not routinely measured in clinical practice.

Nevertheless, the Framingham risk assessment tool seems to be a better predictor of short-term (10-year) cardiovascular risk than

MS.[23] This is not surprising, as it includes potent cardiovascular risk factors (such as age, sex, smoking and total cholesterol level) that are not included in the MS definition. On the other hand, MS may be a useful tool for clinicians for identifying, at an early stage, people who are at increased long-term risk of cardiovascular disease and diabetes, particularly when traditional risk assessment may indicate low short-term risk (eg, younger patients without diabetes who have abnormal glucose metabolism and atherogenic dyslipidaemia). Such patients can then be targeted for early lifestyle interventions, aggressive risk factor management and close follow-up. Hence, global cardiometabolic risk should be assessed using both MS and conventional risk algorithms.

Management: what is the evidence?

Management of MS is aimed primarily at reducing longer-term risk of cardiovascular disease and diabetes. Current guidelines recommend initial focus on intensive therapeutic lifestyle interventions (such as increased physical activity, dietary modification and modest weight reduction) that address many of the metabolic risk factors in MS, including insulin resistance.[1,8] Cardiovascular risk should also be assessed using established algorithms (eg, the Framingham risk assessment tool) to guide clinical management of individual risk factors. If necessary, pharmacological agents should be used to achieve recommended therapeutic targets.

Resistance exercise training can improve insulin sensitivity, reduce visceral adiposity, lower blood pressure and improve dyslipidaemia.[24] In people with impaired glucose tolerance, exercise and weight reduction have been shown to reduce the incidence of both MS[25] and diabetes.[26] Adjunctive use of orlistat for weight reduction lowered metabolic risk factors and diabetes risk in obese subjects, many of whom had MS.[27] In obese patients with type 2 diabetes, weight loss with sibutramine improved glycaemic control and reduced waist circumference, with favourable effects on dyslipidaemia, albeit with a small increase in diastolic blood pressure.[28] Bariatric surgery may result in long-term improvements in diabetes, hypertension and dyslipidaemia in the severely obese.[29]

Statin therapy reduces cardiovascular risk across a wide range of high-risk groups, including people with diabetes,[30] but there are no studies specifically relating to MS. While statins alone may lower cardiovascular risk in the presence of low HDL-cholesterol levels, they do not substantially elevate HDL-cholesterol levels. However, fibrates may be useful in treating the atherogenic dyslipidaemia associated with MS. A recent large randomised controlled trial suggested that fenofibrate may reduce total cardiovascular events in patients with type 2 diabetes,[31] and retrospective analyses of an earlier trial showed that gemfibrozil reduced cardiovascular events in people with diabetes and insulin resistance.[32]

Lowering blood pressure was shown to reduce cardiovascular events in patients with type 2 diabetes,[33] but this has not been studied in patients with MS. Risk reduction appeared to be related more to the degree of blood pressure reduction than to any specific agent, with multiple drugs usually required to achieve adequate control.

It is uncertain whether specifically treating hyperglycaemia or insulin resistance improves cardiovascular risk in MS. However, in subjects with impaired glucose tolerance, metformin can reduce the incidence of MS[25] and diabetes,[26] and thiazolidinediones can slow the progression to diabetes.[34,35] Acarbose, targeting postprandial glycaemia, has been shown to reduce the incidence of diabetes and hypertension in people with impaired glucose tolerance, with retrospective analyses suggesting a reduction in cardiovascular events.[36,37] Metformin reduces macrovascular events in obese patients with type 2 diabetes,[38] and a recent randomised controlled trial of pioglitazone in high-risk patients with type 2 diabetes suggested benefit in reducing the secondary composite endpoint of death, non-fatal myocardial infarction and stroke.[39]

Intensive multiple risk factor management, employing behaviour modification and pharmacological therapy, has been demonstrated to improve cardiovascular outcomes in patients with type 2 diabetes and microalbuminuria,[40] suggesting that a similar approach may also be effective in people with MS.

The recent debate and the way forward

There has been considerable debate recently about the definition and pathogenesis of MS and the clinical utility of MS as a concept. Some of the discussion has centred on the distinction between the concept of an "insulin resistance syndrome" (as a pathophysiological construct that explains the clustering of metabolic risk factors) and the pragmatic definition of MS as a clinical matrix for identifying people at increased cardiovascular risk.[9] There is concern that focusing on whether the diagnostic criteria for MS are strictly met may shift attention away from management of important individual risk factors that might otherwise be overlooked.

A joint statement by the American Diabetes Association and the European Association for the Study of Diabetes[41] has highlighted concerns that, in the context of poor understanding of the underlying pathophysiology, the criteria for defining MS are ambiguous and incomplete, and may not include other relevant vascular risk factors. Issues were raised about the validity of applying a dichotomous classification to risk factors that are continuously related to atherosclerosis, and the lack of distinction between individuals with different degrees of MS and risk burden. The joint statement[41] suggested that MS did not predict cardiovascular risk any better than individual risk factors. As treatment for the syndrome was the same as that for individual factors, the clinical value of defining MS was vigorously challenged.

A subsequent joint scientific statement from the American Heart Association and National Heart, Lung and Blood Institute has re-emphasised the important role of MS, not in the assessment of short-term cardiovascular risk (where use of standard risk algorithms is more appropriate), but in identifying people at increased long-term cardiometabolic risk who could benefit from early intensive lifestyle management.[8] The focus on lifestyle change to prevent cardiovascular disease and diabetes in these at-risk individuals was also strongly supported by the IDF.[14]

Active debate about MS and re-examination of its clinical role has highlighted the need for further research into its underlying pathophysiology. Despite recognition of MS as a clinical entity, it is still not known whether the central cause is insulin resistance, inflammation or some other abnormality linked to abdominal adiposity.[8] Greater insight into the basic science of why factors cluster in MS and how they modulate cardiometabolic risk will help to refine its clinical definition and improve its utility in risk prediction. It may also provide specific therapeutic targets that address the key central abnormality in MS. Progress is being made not only in understanding the complex gene–environment interactions and associated developmental origins of MS and obesity,[42] but also in characterising the signalling mechanisms involved in

regulating energy balance and glucose homeostasis.[43] Active research into novel ways of treating obesity has seen emergence of the endocannabinoid system[44] and the enzyme 11-β-hydroxysteroid dehydrogenase type 1[45] as potential therapeutic targets. In the broader public health context, development of population-wide strategies to curtail the obesity "epidemic" that is driving MS should target not only individuals but also the "obesogenic" environment that promotes overnutrition and underactivity.

Conclusion

MS is common, and the associated risk burden of diabetes and cardiovascular disease is a major public health problem. It is therefore imperative that efforts are made to recognise individuals with MS early, so they may be targeted for intensive lifestyle and risk factor management to reduce cardiometabolic risk. Despite their limitations, criteria-based definitions of MS provide a simple, practical tool for clinicians to identify the interaction of multiple metabolic abnormalities that contribute to atherosclerosis, including the "unmeasured" non-traditional risk factors associated with central obesity and insulin resistance. Use of MS in cardiovascular risk assessment is therefore adjunctive, rather than alternative, to traditional risk algorithms. Because the presence of diabetes already identifies individuals at high cardiovascular risk, it may be that identifying MS is most relevant in those *without* diabetes. It is these people, many of whom have abnormal glucose metabolism (eg, impaired glucose metabolism or impaired fasting glucose), who are likely to benefit most from early lifestyle interventions to prevent the development of both diabetes and vascular disease. Finally, beyond its clinical and public health importance, MS continues to provide increasingly challenging avenues for medical research.

Competing interests

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