FEATURED EDITORIAL

Metabolic syndrome, dysglycaemia and vascular disease: making sense of the evidence

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“ ‘Diagnosis’ of metabolic syndrome by any current criteria is not needed and adds little to clinical practice. Attention and resources should be focused on the major modifiable risk factors and more should be done to engender sustainable lifestyle changes in all with vascular disease”

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Since the Framingham Risk Score (FRS) became available, clinicians have had at their disposal a tool for cardiovascular risk prediction. Robust evidence linking classical risk factors to incident vascular end points and proof that effective treatment of major modifiable risk factors (hypercholesterolaemia, hypertension, smoking) reduces primary and secondary risk, are some of the significant advances in recent medical history. More recently, other risk prediction models (QRISK,¹ ASSIGN²) have been proposed which take into account additional risk factors such as family history and social deprivation, although their validation and future use is not yet certain. Regardless, any newly proposed risk predictor faces stiff competition before acceptance into routine clinical practice. To be of value, any new risk predictor or criterion should be more effective than current risk predictors and should include features which, when treated, are known to reduce risk. The evolution of the metabolic syndrome, however, seems to have evaded these requirements, and has caused more confusion than clarity.^{3–4}

It is first necessary to specify what is meant when referring to the metabolic syndrome. The term may refer either to a specific condition (ICD9 code 277.7) diagnosed according to specified criteria, or, alternatively, to a pathophysiological entity made up of a cluster of related metabolic findings. It is the former use which is the source of current debate and on which we will focus. The knowledge that certain cardiovascular risk factors, some weak and some strong, cluster together was recognised decades ago. In 1988 Reaven proposed an association between underlying insulin resistance, and hypertension and dyslipidaemia, as an explanation for the excess cardiovascular risk in patients with diabetes.⁵ In an attempt to group these features together, the World Health Organisation, National Cholesterol Education Panel (NCEP) and International Diabetes Federation (IDF) have each subsequently issued different, but overlapping, diagnostic criteria for the metabolic syndrome, a diagnosis aimed at identifying insulin-resistant people at risk of

vascular disease but not adequately identified by conventional risk factor analysis. The NCEP⁶ and IDF⁷ criteria, in particular, have led to an explosion of papers linking metabolic syndrome to incident vascular events and, of interest, more recently, to new onset type 2 diabetes.

WHAT ARE THE CRITERIA?

The different definitions of metabolic syndrome require different combinations of the following criteria: dysglycaemia, low high-density lipoprotein (HDL) cholesterol, hypertriglyceridaemia, obesity or increased waist circumference, hypertension, microalbuminuria and hyperinsulinaemia (table 1). The most obvious weakness is the lack of inclusion of known major risk factors for vascular disease such as age, total or low-density lipoprotein (LDL) cholesterol and smoking status in any of these criteria. The committees designing all criteria were perhaps too focused in their desire to include only insulin resistance-related factors to the detriment of vascular risk prediction. In some respects the goal of the metabolic syndrome criteria—that is, simultaneous vascular and diabetes risk ascertainment—was unrealistic, since these two end points and their risk factor patterns are different.⁸

HOW USEFUL ARE THE METABOLIC SYNDROME CRITERIA IN PREDICTING VASCULAR EVENTS?

The various definitions of metabolic syndrome are certainly associated with future cardiovascular events as confirmed in numerous studies.^{9–10} This is neither a surprising finding nor the relevant observation to make since the criteria include low HDL cholesterol and blood pressure (BP), two established risk factors. A proposed risk prediction model or change to an existing model should appreciably improve prediction beyond what is achievable by the existing model. In this regard metabolic syndrome has simply not made the grade. On its own it is inferior to the FRS and, more importantly, in the best conducted studies it adds nothing to risk prediction—as measured by receiver operating characteristic analyses—beyond the FRS.^{11–13} Nor is the whole greater than the sum

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Abbreviations: BP, blood pressure; EASD, European Association for the Study of Diabetes; ESC, European Society of Cardiology; FRS, Framingham Risk Score; HDL, high-density lipoprotein; HR, hazard ratio; IFG, impaired fasting glycaemia; IDF, International Diabetes Federation; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; NCEP, National Cholesterol Education Panel; OGTT, oral glucose tolerance test

Table 1 World Health Organisation (WHO), International Diabetes Federation (IDF) and National Cholesterol Education Panel (NCEP) criteria for diagnosing metabolic syndrome

Criteria	WHO criteria (modified)	IDF criteria	NCEP ATP III criteria
Essential criterion	Fasting hyperinsulinaemia (highest 25% in non-diabetic population) or Type 2 diabetes mellitus or impaired glucose tolerance or FPG ≥ 6.1 mmol/l	Men ≥ 94 cm (Europoid) Women ≥ 80 cm (Europoid), or Sex- and ethnic-specific waist circumference	–
Central obesity	Plus at least 2 of: BMI > 30 kg/m ² or waist/hip ratio > 0.90	Plus at least 2 of: –	At least 3 of: Waist circumference: Men > 102 cm Women > 88 cm
Fasting plasma glucose	–	≥ 5.6 mmol/l or previously diagnosed type 2 diabetes mellitus	≥ 6.1 mmol/l
Blood pressure	$\geq 140/90$ mm Hg or receiving treatment	$\geq 130/85$ mm Hg or receiving treatment	$\geq 130/85$ mm Hg or receiving treatment
Triglycerides (fasting)	≥ 2.0 mmol/l or	≥ 1.7 mmol/l or receiving specific treatment	≥ 1.7 mmol/l
HDL cholesterol	HDL < 1.0 mmol/l	Men < 1.04 mmol/l Women < 1.29 mmol/l or receiving specific treatment	Men < 1.04 mmol/l Women < 1.29 mmol/l

BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein.

of the parts. For example, in the British Women's Heart and Health Study,¹⁴ the BP cut-off point alone trumped the risk prediction of the syndrome. Other studies have concurred and found individual components to be at least or more powerful than the sum.^{15–16} Compare this with the FRS which better predicts cardiovascular events than its components (age, gender, total and HDL cholesterol, BP, smoking, diabetes).¹⁷

The confusion in the literature arises from the critical difference between independent association and useful prediction. Thus, although metabolic syndrome is associated with enhanced risk after adjusting for conventional risk factors (hazard ratio (HR) of around 1.5 in meta-analysis),¹⁰ the level of risk is simply too weak to enhance risk prediction. As discussed by Lloyd-Jones *et al*¹⁸ using the example of C reactive protein, a risk marker added to an existing risk score requires a multivariate odds ratio of > 3.0 to improve risk prediction significantly. Therefore, suggested C reactive protein cut-off points, like metabolic syndrome, both with odds ratios of ~ 1.5 , fail to improve risk stratification beyond simpler and more accepted FRS-based algorithms.

WHERE DOES THE METABOLIC SYNDROME FAIL?

There are multiple reasons. The most important are:

- First, and as mentioned above, the metabolic syndrome criteria lack three of the most important cardiovascular risk factors. To illustrate this major deficiency, consider the case examples listed in table 2. Although both are hypertensive, Mr A fulfils all the criteria for metabolic syndrome, unlike Mr B. Nonetheless, Mr B is at considerably greater risk of vascular disease because he is older, has much higher LDL cholesterol and smokes.
- As metabolic syndrome includes factors linked to insulin resistance, it is actually more strongly associated with incident type 2 diabetes than vascular events.^{9–13} In the NCEP criteria, for example, equal weighting is given to five criteria known to not contribute equally to the development of vascular disease. Take, for example, raised fasting plasma glucose in the non-diabetic range—that is, impaired fasting glycaemia (IFG). This is not linked convincingly to incident vascular events; in the West of Scotland Coronary Prevention Study, as in other studies, an increase in fasting plasma glucose > 5.0 mmol/l was not significantly associated with

incident vascular events (HR ~ 1.1) but was a strongly associated with future type 2 diabetes (adjusted HR ~ 10).¹⁹ The cases of body mass index and hypertriglyceridaemia are analogous. Thus three of the five variables in the NCEP criteria are more strongly linked to diabetes. However, metabolic syndrome criteria themselves are also unlikely to be used to predict future risk for diabetes, which is a complex issue as discussed previously.⁸

- Dichotomous variables: The increase in vascular risk related to a risk factor is continuous, rendering threshold values inappropriate and overly simplistic. Furthermore, the use of a dichotomous variable based on a measure such as fasting serum triglyceride, which has a particularly high within-subject biological variability of 20%,²⁰ might easily label one as having or not having metabolic syndrome depending simply on the day of sampling.

Other weaknesses which have been levelled at the diagnostic criteria and limit its acceptability include the following:

- Estimates suggest that fully a quarter of the US or UK population would meet the NCEP criteria. Do we really wish to medicalise 1 in 4 of the population?
- Whereas fasting samples are required to “diagnose” metabolic syndrome, key cardiovascular risk factors (including total and HDL cholesterol) can be measured at any time. Note the recent Joint British Societies guidelines encourage opportunistic screening with an initial non-fasting sample in all over 40 years of age.²¹
- Making the “diagnosis” does not indicate any new proven treatment options (see below).
- It is possible that attention may be diverted away from the major modifiable risk factors.

SO HOW SHOULD WE TREAT PATIENTS WITH VASCULAR DISEASE AND FEATURES OF THE METABOLIC SYNDROME IN WHOM MAJOR RISK FACTORS ARE ALREADY TREATED?

We are all faced with patients with persistently low HDL cholesterol who are hypertriglyceridaemic, overweight and dysglycaemic despite adequate control of their BP and LDL cholesterol. We know they are at higher than average

Table 2 Who is at greater cardiovascular risk? Mr A or Mr B?

Characteristics	Mr A	Mr B
Waist circumference (cm)	105	80
Triglyceride (mmol/l)	2.2	1.3
HDL cholesterol (mmol/l)	0.9	1.2
Fasting blood glucose (mmol/l)	6.2	5.0
Blood pressure (mm Hg)	145/90	145/90
Metabolic syndrome?	Yes (5/5 criteria)	No (1/5 criteria)
Age (years)	40	60
Smoker	No	Yes
LDL cholesterol (mmol/l)	3.0	6.0
Framingham risk score? (%)	8	42

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

cardiovascular risk.¹⁵ But can we reduce this risk by mechanisms other than potential further reductions in cholesterol and blood pressure? Relevant outcome trial data for drugs which aim at lowering triglycerides or increasing HDL cholesterol are either sparse or unconvincing. Those with IFG, impaired glucose tolerance (IGT) or early type 2 diabetes are not routinely prescribed glucose-lowering agents. Should we treat the apparent upstream insulin resistance, and if so how? The only option which the clinician can currently “offer” is lifestyle modification, usually to a poorly receptive audience! Most would accept that lifestyle modification (increased activity and improved diet) is the best and safest means to target insulin resistance and that it has multiple other benefits. Randomised trials convincingly show that modest lifestyle improvements delay development of type 2 diabetes in those with IGT.²² Clearly, lifestyle improvement should be an important goal for all those at increased risk of vascular events, regardless of their glycaemic status. Yet significant improvement remains difficult to achieve and sustain outside the research environment. Why this should be the case is not a question easily answered. Lifestyle improvement requires that patients take some responsibility for their own health and that clinicians take the time to advise them. Perhaps part of the solution lies in better communicating more achievable and, critically, sustainable goals to the patients.²³

Targeting insulin resistance may yet yield useful results. Admittedly, thiazolidinediones look unlikely candidates given that they increase weight, can exacerbate fluid retention and that rosiglitazone may increase vascular risk in patients with diabetes.²⁴ This should not necessarily signal the end of the road for insulin sensitisers. Metformin remains an inexpensive and safe drug with evidence for cardiovascular benefit in the UK Prospective Diabetes Study.²⁵ It may also lower weight. Thus it is generally considered the first-line treatment for patients with diabetes. A properly powered prospective randomised trial of metformin in non-diabetic subjects with cardiovascular disease would therefore be of significant value.

SHOULD WE SCREEN FOR DIABETES IN ALL WITH CARDIOVASCULAR DISEASE? IF SO, HOW?

Given the marked increase in cardiovascular risk associated with diabetes and the high prevalence of undiagnosed type 2 diabetes in those with cardiovascular disease, recent consensus guidelines from the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC)²⁶ correctly recommended diabetes screening for all with cardiovascular disease. The diagnosis of diabetes in this population should herald lower BP and cholesterol targets. In addition, earlier diagnosis and treatment will reduce the incidence of microvascular disease.

But what is the best method for screening? The ESC/EASD guidelines recommend the usual oral glucose tolerance test (OGTT),²⁶ which has the questionable added “advantage” of identifying IGT and IFG. Disadvantages of the OGTT include the huge numbers of people who would require it, the inconvenience of, and poor adherence to, the test protocol which requires fasting and lengthy morning attendance, and the poor reproducibility of the key 2-hour glucose concentration. It is also an expensive test. As an alternative, serious consideration should be given to a two-stage process with the initial use of HbA_{1c} in all—and note that like cardiovascular risk screening, HbA_{1c} does not require fasting—followed by an OGTT in a minority with HbA_{1c} between certain limits.

Despite concerns about the use of HbA_{1c} as a screening test for diabetes, it was shown in the AusDiab study²⁷ that in an apparently healthy population with at least one risk factor for developing diabetes, using an HbA_{1c} cut-off point of 5.3% and an OGTT as follow-up would give a sensitivity and specificity for diagnosing diabetes of 80%, comparable with the other protocols tested. In a small study in New Zealand,²⁸ when an HbA_{1c} >6.1% was used for screening, only 10% of new diagnoses were missed. The value of identifying particularly IFG (included in all metabolic syndrome diagnostic criteria) and, we would suggest, also IGT is unconvincing. IFG is not convincingly or unequivocally associated with an increased risk of vascular events. Although IGT is associated with incident vascular events, the risk is appreciably lower than with known or new diabetes. Moreover, not all studies are consistent. In a recent trial only known or newly detected diabetes, but not impaired glucose regulation (either IFG or IGT), had a negative influence on 1-year outcome in patients with coronary artery disease.²⁹ More data are clearly needed in this area. Furthermore, although lifestyle improvements for the prevention of diabetes are recommended for those with IFG and IGT, surely the same treatment plan is relevant to all with vascular disease regardless of glycaemic status.

CONCLUSIONS

We conclude that the “diagnosis” of metabolic syndrome by any current criteria is not needed and adds little to clinical practice. Attention and resources should be focused on the major modifiable risk factors and more should be done to engender sustainable lifestyle changes in all with vascular disease, regardless of glycaemic status. Identification of diabetes in those with vascular disease, however, is warranted but the best methods to do so require further study.

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IMAGES IN CARDIOLOGY

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Cardiac amyloid by cardiovascular magnetic resonance

A 45-year-old Afro-Caribbean man presented with a 1-year history of progressive fatigue, myalgia, chest pain and dyspnoea. A physical examination was normal. There were non-specific precordial ST- and T-wave changes by ECG and mild biventricular hypertrophy and diastolic dysfunction with pseudo-normalised left ventricular filling by echocardiography. Cardiovascular magnetic resonance (CMR) demonstrated reduced long-axis function and global left ventricular subendocardial delayed enhancement suggestive of cardiac

amyloid (panels A, B). Because of the CMR findings, a right ventricular biopsy was performed (panel C), which confirmed cardiac amyloid, with κ light chains on immunostaining. Initial serum electrophoresis results were equivocal, but over the subsequent months, a clear monoclonal band developed. Together with a bone marrow trephine, the final diagnosis was of IgG κ -secreting plasma cell dyscrasia presenting as cardiac amyloidosis. Treatment was started with thalidomide-based chemotherapy with a view to consideration of cardiac

transplantation before an autologous bone marrow stem cell transplant.

This case illustrates the clinical utility of contrast CMR and demonstrates that the recognition of specific patterns of CMR myocardial delayed enhancement may guide diagnostic procedures, here leading to a rapid diagnosis of cardiac amyloid.

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