The metabolic syndrome: Pie in the sky?

Brian Karet

This article decribes how the metabolic syndrome came to enter our vocabulary, what it really means and whether it really is something that could help us to look after our patients better, or perhaps its just another cumbersome tool that produces a lot of heat but no light.

The association or clustering of abnormal physical and biochemical findings has been observed for a long time. Over 80 years ago it was noted that people with gout had high blood pressure and raised blood sugar levels. In 1988 an American, Gerald Reaven, noted that people with type 2 diabetes developed cardiovascular disease (heart attacks, strokes and peripheral vascular disease) more often than would have been expected by chance. He used the term "syndrome X" to postulate an association between the emerging concept of insulin resistance, hypertension and the abnormal lipid pattern of low high-density lipoprotein (HDL) cholesterol, high low-density lipoprotein (LDL) cholesterol and raised triglyceride levels (dyslipidaemia) seen in type 2 diabetes, to explain this excess cardiovascular risk (Reaven, 1988).

The association of these and other risk factors became known as the metabolic syndrome. Between 1998 and 2005 the metabolic syndrome was the focus of intense discussion, debate and research which continues to this day. So much so that four different definitions emerged from, in turn, the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the American National Cholesterol Education Programme Adult Treatment Panel III (ATP III) and, lastly, the International Diabetes Federation (IDF). The purpose of all of these definitions was to help healthcare professionals, (who already had the Framingham Risk Score [FRS]) more accurately identify people who were at increased risk of developing cardiovascular disease and type 2 diabetes.

Before we look at why there are four different definitions and which one is most helpful, it might be interesting to see how many people are covered by this relativele new "disease". In the UK it has been estimated that as many as 25% of the population have significant evidence of the metabolic syndrome and this prevalence is much higher in Afro-Caribbean and South Asian populations as well as women with polycystic ovary syndrome and those with non-alcoholic fatty liver disease (Tonkin, 2004).

What is the point of the metabolic syndrome?

There is no doubt that in today's world, hypertension, hyperglycaemia, dyslipidaemia and most of all obesity – particularly central obesity – pose an enormous threat to public health. It has emerged over the last 15 years or so, that a key mechanism linking these abnormalities is the inability of the body to effectively utilise its own insulin production, now termed insulin resistance. There is little doubt that people with insulin resistance are at a much higher risk of developing type 2 diabetes but some of

Article points

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2. There is no doubt that in today's world, hypertension, hyperglycaemia, dyslipidaemia and, most of all, obesity – particularly central obesity – pose an enormous threat to public health.
3. If we need a comprehensive cardiovascular disease risk assessment, Framingham-based analyses including those of the Joint British Societies and the very recent QRISK seem to do the job better than the metabolic syndrome.

Key words

- Metabolic syndrome
- Insulin resistance
- Waist circumference

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1. Between 2001 when the ATP III definition appeared and the latest IDF version in 2005, insulin resistance assumed much greater importance in the causation of type 2 diabetes and CVD due to discoveries about fat cells.
2. It emerged that fat cells, especially fat cells inside the abdomen around organs, so called visceral fat, is not just an inert storage system but is highly metabolically active producing chemicals (pro-inflammatory cytokines) which can inflame the lipid laden plaques which line blood vessels causing them to rupture resulting in strokes and heart attacks.

them are also at significant risk of developing cardiovascular disease (CVD; Wannamethee et al, 2005).

It was an attempt to pick out which people should have particular attention focused on them that led the WHO to define and classify the metabolic syndrome. Their definition was rather complex and involved a "pick-and-mix" algorithm needing any marker of insulin resistance (for example, diabetes, impaired fasting glucose) combined with any two elevations of triglycerides, blood pressure or microalbuminurea; or a marker of obesity, specifically increased waist-to-hip ratio, body mass index or both.

Simple and easy to use it was not, and it is not surprising that pretty soon clinicians from the US devised a more straightforward definition focusing on primary prevention of CVD in people with multiple risk factors. Interestingly, their definition was a simple any 3 out of 5 for raised fasting glucose, blood pressure, triglycerides an increased waist circumference, and low HDL-cholesterol levels, so it was quite possible to have the ATP III metabolic syndrome without being obese or having a raised blood glucose level.

Between 2001, when this ATP III definition appeared, and the latest IDF version in 2005, insulin resistance assumed much greater importance in the causation of type 2 diabetes and CVD due to discoveries about fat cells. It emerged that fat cells, especially those inside the abdomen around organs, so called visceral fat, is not just an inert storage system but is highly metabolically active producing chemicals (pro-inflammatory cytokines) which can inflame the lipid-laden plaques which line blood vessels causing them to rupture resulting in strokes and heart attacks. The collective wisdom of the IDF therefore came up with their definition of the metabolic syndrome which made central obesity a core component and for the first time specified ethnicity-specific values for waist circumference which has emerged as the preferred marker of obesity in terms of cardiovascular risk. The IDF definition is completed by the core presence of central obesity along with any two of raised blood pressure, triglycerides and fasting blood sugar and low HDL levels. A direct comparison

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 criteria	Fasting hyperinsulinaemia (highest 25% in non-diabetic population) or type 2 diabetes or impaired glucose tolerance or FPG ≥6.1 mmol/L	Men ≥94cm (Europoid) Women ≥80cm (Europoid) or Sex- and ethnic-specific waist circumference	-
	Plus at least 2 of:	*Plus at least 2 of:*	*At least 3 of:*
Central obesity	BMI>30kg/m^2 or waist/hip ratio >0.90	-	Waist circumference: Men >102 cm Women >88cm
Fasting plasma glucose	-	≥5.6 mmol/L or previously diagnosed type 2 diabetes	≥6.1 mmol/L
Blood pressure	≥140/90 mmHg or receiving treatment	≥130/85 mmHg or receiving treatment	≥130/85 mmHg 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-c<1.0 mmol/L	Men <1.04 mmol/L Women <1.29 mmol/L or treatment	Men <1.04 mmol/L Women <1.29 mmol/L

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

WHO data from Alberti and Zimmet (1998), IDF data from International Diabetes Federation (2006), NCEP ATP III data from National Institute of Health (2001).

of these 3 definitions is shown in *Table 1*.

Do the differences matter?

Despite some major similarities among the three definitions discussed, it is clearly quite easy to describe individuals who have the metabolic syndrome by using one definition but not another. For instance, a non-obese male with a waist circumference under 94cm but with a low HDL-cholesterol, high blood pressure and diabetes does not have IDF metabolic syndrome but does have ATP III metabolic syndrome. You will see, additionally, that two of the biggest risk factors for CVD, namely age and smoking, are not included at all in any of the definitions.

There is also some suggestion that in people at risk of developing CVD and diabetes, many of the components of the metabolic syndrome are seen together in any event and having one component makes it highly likely individuals will have another. For example, it is known that people with low grades of glucose intolerance (impaired fasting glycaemia) also have higher blood pressure, higher triglycerides and lower HDL-cholesterol than people with normal glucose tolerance (Zavaroni, 1989) – four components of both the IDF and ATP III definitions but essentially one abnormality: insulin resistance. Also, people with hypertension tend to be more insulin resistant than people without hypertension (Ferranini et al, 1987) and even more interestingly this also applies to first degree relatives of people with hypertension (Ferrari et al, 1991).

It is also clear that having isolated components of the metabolic syndrome do not significantly increase the risk of CVD. A big study looking at almost 3000 men without any history of CVD in Copenhagen reported in 2001, divided them into 3 groups depending on their lipid profile while recording their blood pressure as well (Jeppesen et al, 2001). Men with a bad lipid profile of high triglycerides and low HDL-cholesterol were in one group and those with a good profile of low triglycerides and high HDL-cholesterol in another. The third group was those with intermediate levels. Results showed that over 8 years, cardiovascular risk was not significantly increased in men with high blood pressure if the lipid profile was good and this also applied to those who had high LDL-cholesterol levels, low levels of physical activity or were smokers. Those at greatest risk of CVD were hypertensive and had a poor lipid profile.

Although the more obese someone is the more likely they are to be insulin resistant, there are also lots of overweight and obese people who do not have other components of the metabolic syndrome and studies have shown that people with obesity on its own without signs of insulin resistance (hypertension, dyslipidaemia, impaired fasting glycaemia) are not at significant risk of developing CVD or diabetes (Abbasi et al, 2002).

Should we treat the metabolic syndrome?

Not surprisingly when a new condition is described, someone has to come up with a cure and so far, the list includes the usual suspects such as metformin and the glitazones, as well as the weight reducing drugs acarbose and orlistat and the new kids on the block, rimonabant (an endocannabinoid receptor blocker) and the incretin drugs, exenatide and the DPP-IV (dipeptidyl peptidase IV) inhibitors, sitagliptin and vildagliptin.

Given that we are looking for people at increased risk of CVD and diabetes it makes sense to try and do something about it at an early stage. As mentioned above, however, it is quite possible to have people with type 2 diabetes, hypertension and dyslipidaemia who do not have IDF metabolic syndrome or people with obesity, hypertension and dyslipidaemia who do not have WHO metabolic syndrome. In reality what the metabolic syndrome has done, no matter which definition is used, is to make healthcare professionals aware that risk factors clump together and to look more assiduously for associated abnormalities when one risk factor is diagnosed.

However, it is also clear that although abnormalities such as hypertension and dyslipidaemia are useful population-based risk factors, they are poor predictors of an individual person's risk of CVD and whether that person is likely to benefit from treatment. This needs a comprehensive risk assessment and it is doubtful if the metabolic syndrome is the right tool to

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1. in groups where no therapeutic intervention was made, a quarter of people with so called pre-diabetes reverted to normal.
2. The real question is not whether people diagnosed with the metabolic syndrome are at increased risk of CVD – it would be most surprising if they were not, given the component parts – it is whether we can predict individual risk better and more accurately and even more importantly decide on the use and intensity of therapeutic interventions including lifestyle interventions.
3. If we need a quick risk assessment, a tape measure around the abdomen is all we need. The metabolic syndrome has served us well in highlighting the clustering of cardiovascular risk factors.

help us decide on therapeutic interventions. In addition not only are measurements of triglyceride notoriously variable, even on a fasted blood sample, but trials looking at lowering triglycerides particularly with fibrate drugs have not shown any benefit (Keech et al, 2005). Also, drug trials looking at raising HDL-cholesterol levels have had to be halted prematurely because of increased cardiovascular events. Even more concerning is the prospect of treating those who have impaired glucose tolerance with blood glucose lowering agents. We know from large lifestyle intervention trials (Knowler et al, 2002) that even in groups where no therapeutic intervention was made, a quarter of people with so called pre-diabetes reverted to normal. We are all also still smarting from the rosiglitazone debate where a drug that undoubtedly reduces insulin resistance may increase cardiovascular events (Nissen and Wolski, 2007). Aside from the widely proffered and even more widely ignored mantra of diet and exercise, to date metformin is the only drug we have that reduces insulin resistance and shows any degree of cardiovascular benefit (Gray et al, 2000).

Can we live without it?

Since the metabolic syndrome came to the fore there have been a profusion of papers (over 1000 in the last year alone!) examining the predictive benefit of the syndrome for vascular events and diabetes and indeed vascular events in people with diabetes. The real question is not whether people diagnosed with the metabolic syndrome are at increased risk of CVD – it would be most surprising if they were not, given the component parts – it is whether we can predict individual risk better and more accurately and even more importantly decide on the use and intensity of therapeutic interventions including lifestyle interventions. Also, given that the core abnormality of the metabolic syndrome is insulin resistance, it is again not surprising that it is more than twice as good a predictor of diabetes than CVD. Insulin resistance and central obesity has been discussed extensively and there is a lot of evidence as to its central role in both the development of CVD and diabetes. The huge Nurses Health Study looking at over 40 000 nurses in the USA found a direct correlation between the development of type 2 diabetes and waist circumference (Carey et al, 1997). The more recent INTERHEART study looked at 27 000 participants in 52 countries and found a strong correlation between waist circumference and myocardial infarction risk (Yusuf et al, 2004).

The bottom line

The metabolic syndrome has certainly grabbed the headlines and we have all got used to looking at overweight people with hypertension and giving them another label. But aside from telling us what we probably already know (that they are at increased risk of developing CVD and diabetes) what other information have we gained?

For 30 years we have had the Framingham risk score (FRS) and more recently in the UK we have the Joint British Societies (JBS) risk score, heavily based on FRS, to guide us for people in need of primary prevention. If we need a comprehensive CVD risk assessment, FRS-based analyses including JBS and the very recent QRISK seem to do the job better than the metabolic syndrome. If we need a quick risk assessment, a tape measure around the abdomen is all we need. The metabolic syndrome has served us well in highlighting the clustering of cardiovascular risk factors. However, it is time to move on. ■

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