The metabolic syndrome—a new worldwide definition

The metabolic syndrome (visceral obesity, dyslipidaemia, hyperglycaemia, and hypertension), has become one of the major public-health challenges worldwide.[1] There has been growing interest in this constellation of closely related cardiovascular risk factors. Although the association of several of these risk factors has been known for more than 80 years,[2] the clustering received scant attention until 1988 when Reaven described syndrome X: insulin resistance, hyperglycaemia, hypertension, low HDL-cholesterol, and raised VLDL-triglycerides.[3] Surprisingly, he omitted obesity, now seen by many as an essential component, especially visceral obesity.[1] Various names were subsequently proposed, the most popular being metabolic syndrome.[1]

The cause of the syndrome remains obscure. Reaven proposed that insulin resistance played a causative role,[3] but this remains uncertain. Lemieux et al suggested visceral obesity and the hypertriglyceridaemic waist phenotype as a central component,[4] but this too has been contested. Several different factors are probably involved, many related to changes in lifestyle.[1]

The ultimate importance of metabolic syndrome is that it helps identify individuals at high risk of both type 2 diabetes and cardiovascular disease (CVD). Several expert groups have therefore attempted to produce diagnostic criteria. The first attempt was by a WHO diabetes group in 1999, which proposed a definition that could be modified as more information became available.[5] The criteria had insulin resistance or its surrogates, impaired glucose tolerance or diabetes, as essential components, together with at least two of: raised blood pressure, hypertriglyceridaemia and/or low HDL-cholesterol, obesity (as measured by waist/hip ratio or body-mass index), and microalbuminuria. The European Group for the Study of Insulin Resistance[6] then produced a modification of the WHO criteria excluding people with diabetes and requiring hyperinsulinaemia to be present. Waist circumference was the measure of obesity, with different cutoffs for the other variables.

A fresh approach came from the US National Cholesterol Education Program: Adult Treatment Panel III in 2001, with a focus on cardiovascular disease risk.[7] The specific remit was to facilitate clinical diagnosis of high-risk individuals. It was less glucocentric than the definition from WHO and the European Group for the Study of Insulin Resistance, requiring the presence of any three of five components: central obesity, raised blood pressure, raised triglycerides, low HDL-cholesterol, and fasting hyperglycaemia.

The different definitions inevitably led to substantial confusion and absence of comparability between studies. One difficulty has been that the conceptual framework used to underpin the metabolic syndrome (and hence drive definitions) has not been agreed on. Opinions have varied as to whether the metabolic syndrome should be defined to mainly indicate insulin resistance, the metabolic consequences of obesity, risk for CVD, or simply a collection of statistically related factors. Prevalence figures for the syndrome have been similar in any given population regardless of which definition is used, but different individuals are identified.[8] What matters, of course, is which produces the best prediction of subsequent diabetes and CVD. Thus Adult Treatment Panel III was superior to WHO in the San Antonio Study, but WHO gave better prediction of CVD in Finnish men.[9,10]

Another problem with the WHO and the Adult Treatment Panel definitions has been their applicability to different ethnic groups, especially as relates to obesity cutoffs.[11] For example, the risk of type 2 diabetes is apparent at much lower levels of adiposity in Asian populations than in European populations.[12] With current metabolic syndrome definitions, particularly Adult Treatment Panel III, suspiciously low prevalence figures in Asian populations resulted,[12] suggesting the need for ethnic-specific cutoffs, at least for obesity.

The International Diabetes Federation (IDF) felt there was a strong need for one practical definition that would be useful in any country for the identification of people at high risk of CVD, but also diabetes. This definition would also allow comparative long-term studies, which could then be used, if necessary, to refine the definition on the basis of solid endpoints. As a result, an IDF consensus group met in 2004, with representatives from the organisations that had generated the previous definitions and members from all IDF regions. Their recommendations are now available.[13]

There was consensus that the components identified by Adult Treatment Panel III were a sensible starting point. It was also agreed that diabetes and insulin resistance had been overemphasised as core measurements in the earlier

definitions. Measurement of insulin resistance was deemed impractical, although it is clear that several metabolic syndrome components, especially waist circumference and triglycerides, are highly correlated with insulin sensitivity.[4]

Ethnic group	Waist circumference (as measure of central obesity)
Europids*	
Men	⩾94 cm
Women	⩾80 cm

Central obesity, as assessed by waist circumference, was agreed as essential (panel), because of the strength of the evidence linking waist circumference with cardiovascular disease and the other metabolic syndrome components, and the likelihood that central obesity is an early step in the aetiological cascade leading to full metabolic syndrome. The waist circumference cutoff selected was the same as that used by European Group for the Study of Insulin Resistance, and lower than the main Adult Treatment Panel III recommendations, because most available data suggest an increase in other cardiovascular disease risk factors in Europids (white people of European origin, regardless of where they live in the world) when the waist circumference rises above 94 cm in men and 80 cm in women.[1] Ethnic-specific waist circumference cutoffs have been incorporated into the definition (table), and have been based on available data linking waist circumference to other components of the metabolic syndrome in different populations.[12,14,15] The levels of the other variables were as described by Adult Treatment Panel III, except that the most recent diagnostic level from the American Diabetes Association for impaired fasting glucose (5·6 mmol/L [100 mg/dL]) was used.[16] Although this new definition will still miss substantial numbers of people with impaired glucose tolerance (because an oral glucose-tolerance test is not required), it retains the simplicity of the instrument.

The consensus group also recommended additional criteria that should be part of further research into metabolic syndrome, including: tomographic assessment of visceral adiposity and liver fat, biomarkers of adipose tissue (adiponectin, leptin), apolipoprotein B, LDL particle size, formal measurement of insulin resistance and an oral glucose-tolerance test, endothelial dysfunction, urinary albumin, inflammatory markers (C-reactive protein, tumour necrosis factor α, interleukin 6), and thrombotic markers (plasminogen activator inhibitor type 1, fibrinogen). These factors should be combined with assessment of CVD outcome and development of diabetes so better predictors can be developed.

Researchers and clinicians should use the new criteria for the identification of high-risk individuals and for research studies. Preventive measures are obviously needed in the people identified. Mounting evidence suggests that lifestyle modification with weight loss and increased physical activity will be beneficial, although specific studies in metabolic syndrome are needed. There

are suggestions from the Finnish Diabetes Prevention Study that individuals with metabolic syndrome show less development of diabetes with lifestyle advice.[17] In many people, however, pharmacological intervention will be needed. There is no specific treatment for the metabolic syndrome so individual abnormalities will have to be attended to. Again, long-term studies will help establish whether existing or newer agents, such as agonists for the peroxisome-proliferator-activated α/γ receptors or cannabinoid-1 receptor blockers,[18] could be of specific benefit.

Recently, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have published a provocative discussion paper on the syndrome.[19] They raise several interesting questions, based on a critique of the earlier WHO and Adult Treatment Panel III criteria: 1) is it indeed a syndrome, particularly as the precise cause is unknown, 2) does it serve a useful purpose, and 3) is it labelling (and medicalising) people unnecessarily? Additionally, it has been suggested in an editorial that recognition of the metabolic syndrome has been largely driven by industry to create new markets.[20]

A major part of the ADA/EASD[19] stance is based on pure semantics, but the IDF (and the cardiovascular community) feel strongly that this clustering of closely related risk factors for CVD and type 2 diabetes is indeed a very good basis for calling this a syndrome. Many examples exist of conditions being given a name even when the precise underlying cause or causes, are unknown (eg, type 2 diabetes). The IDF feels that it serves a useful purpose to focus on people, in both the community and clinical settings, who are at high risk of developing CVD and type 2 diabetes, particularly using the new IDF criteria proposed above.

Indeed, the ADA has just reinvented and redefined the condition of "prediabetes" for people who only have a 50% chance of developing diabetes.[20] We also emphasise most strongly in our longer article[13] that treatment must be focused on life r our thnedF criyWQ9FCD0chanzDCU0uvascular2ɣU0ub8riy3S 22ɣU0utst2ɣckDSkY7eZ0aKDdUDC90and 2QUkD3KDdUD 2QDz9

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Developing an open relationship with the drug industry

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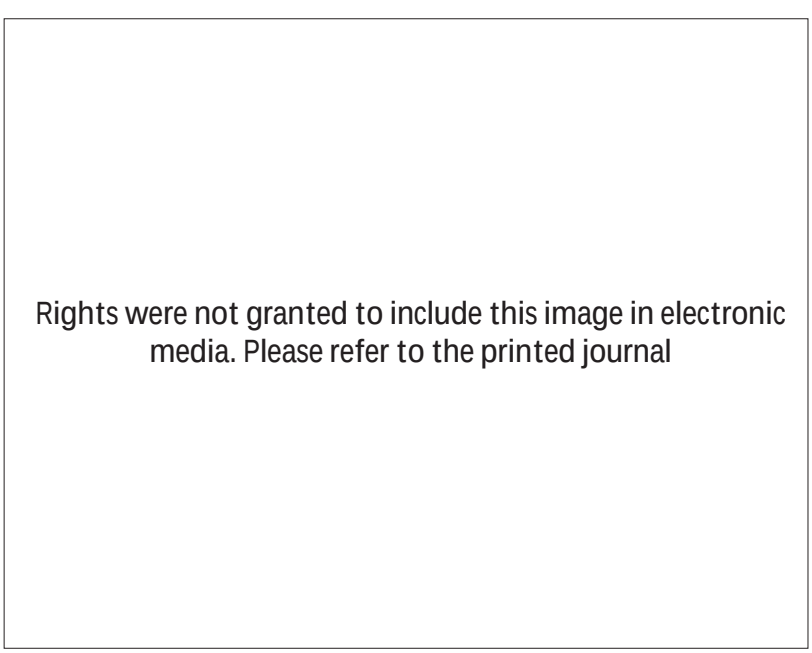
Last year I joined the research advisory board of the drug company GlaxoSmithKline and get paid for that work. I was asked to write this article by *The Lancet* and my fee for writing will be diverted to a charity. You need to know these things before you read on.

A ward round can reveal that many patients are taking ten or more drugs. A scan of a newspaper identified no fewer than six stories suggesting therapeutic breakthroughs. Therapeutic interventions, central to the practice of medicine, have spilled over into daily news—ranging from the adoption of fluoxetine as a drug for well-being in the 1990s to the pursuit of cardiovascular disease prevention resulting in 2003 for calls for a "polypill" for the entire population.[1] Yet despite this enthusiasm for drugs from doctors and patients, paradoxically the reputation of the drug industry is at an all time low—the industry is often portrayed as aiming for profit above all else. And it is not just the moral highgrounders who are voicing concern. Read this, from the business section of a major newspaper: "most drug failures are a by-product of the way the industry is structured: it develops drugs as fast as possible and employs an army of salesmen to sell like crazy before the patent expires. It ignores the fact that the side-effects of a drug are often not known until it has been taken by hundreds of thousands of patients."[2] If this picture is correct, is industry alone to blame or are the medical profession and academia complicit in helping industry pursue profit above all else? This question is the theme of a report by Carl Elliott.[3]



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Let us get one thing straight: the drug industry works within a system that demands it makes a profit to satisfy shareholders. Indeed it has a fiduciary duty to do so. The best way to make a lot of money is to invent a drug that produces a dramatically beneficial clinical effect, is far more effective than any existing options, and has few unwanted effects. Unfortunately most drugs fall short of this ideal. Does this stop doctors from prescribing them, or patients' groups from demanding availability for all? Clearly not. Even if we consider novel drugs rather than me-too products, recent examples provide some insights: the interferons for multiple sclerosis, drugs for dementia, and the inhibitors of cyclo-oxygenase 2 (COX-2).

Interferon β was potentially an exciting scientific advance and seemed to produce detectable biological effects in patients with multiple sclerosis. However, you needed an MRI to detect the change and the extent to which structural changes translated into clinical benefit, and improvement in quality of life, was unclear. In 2000, the UK National Institute for Clinical Excellence[4] released an early statement that "on the basis of a very careful consideration of the evidence their [the interferons] modest clinical benefit appears to be outweighed by their very high cost". The outcry was immediate, loud, and successful. Doctors, nurses, carers, and a patients' group lobbied Government and the drug was made available within the UK National Health Service (NHS), albeit with