

Expert Views in Diabetes



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type 2 diabetes (mainly renal cardiovascular disease [CVD]). During the last 10 to 15 years, his primary interest has been type 2 diabetes and CVD with particular focus on prevention of type 2 diabetes, early detection and screening strategies for type 2 diabetes and early intervention in screen detected diabetic individuals.

Professor Borch-Johnsen initiated the DECODE and DECODE-Asia studies in collaboration with Dr Jaakko Tuomilehto (Finland) and the DETECT-2 diabetes database – a global database with many

of the same aims as the DECODE and DECODE-Asia studies, but with additional focus on development and validation of screening and early detection strategies for type 2 diabetes – in collaboration with Professor Stephen Colagiuri (Australia). He is responsible for the diabetes arm of the Danish Inter99 study, a population-based intervention study including 60,000 individuals aged 30–60 years. Professor Borch-Johnsen also initiated and is co-principal investigator of the ADDITION study, a population-based screening, early detection and intervention trial in type 2 diabetes including over 3,000 screen detected diabetic individuals in Denmark, The Netherlands and UK.

Professor Borch-Johnsen graduated in 1981 and worked as a research fellow at the Steno Diabetes Center until 1986 where he completed his thesis 'The prognosis of insulin dependent diabetes mellitus'. From 1993–1997 he was head of the research unit, Copenhagen County Center for Preventive Medicine. In 1997, Professor Borch-Johnsen became a consultant at the Steno Diabetes Center and in 2000 he assumed his current position as Director.

The Metabolic Syndrome Revisited

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In March 2005, the International Diabetes Federation (IDF) published their new definition of the metabolic syndrome.¹ This definition is the first attempt to modify the definition of the metabolic syndrome according to ethnic and regional variations in risk and risk factor distributions. This approach therefore acknowledges that what may be true for white Caucasians in Europe and North America, for example, may not be true in Sub-Saharan Africa, India or China or among native Indians or Inuit populations. Subsequently, the

American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have published a consensus statement posing many questions and issues for further reflection.²

This commentary will focus on the following:

- what is the metabolic syndrome?
- the different definitions – why the confusion, and what is new in the new definition?
- is the metabolic syndrome a clinically relevant entity?

- the IDF definition – the end of the road?
- the ADA/EASD consensus statement

What is the metabolic syndrome?

The metabolic syndrome is the nomenclature used to describe the clustering of cardiovascular (CV) risk factors in individuals with insulin resistance. This clustering was first described by Harry Himsworth in 1936, but the labelling of the clustering as a 'syndrome' was first used by Reaven in 1988,³ when he suggested that the

triad – hypertension, dyslipidaemia and diabetes – were all due in part to insulin resistance. As a result, Reaven identified a clustering, suggested the hypothesis that insulin resistance was the common denominator, and gave us a hypothesis that could be tested. Unfortunately, researchers went on to identify other potential CV risk factors that are statistically associated with insulin resistance, and they suggested that these new factors – including a variety of lipoproteins, haemostatic factors, hyperuricaemia and microalbuminuria – should also be added to the syndrome, thus leading to confusion rather than clarification. Indeed, this proliferation of definitive characteristics and inconsistency has prompted several international organisations to generate their own definitions of the metabolic syndrome over the last 6 years.

Definitions of the metabolic syndrome

In 1999, the World Health Organization (WHO) originated the first definition of the metabolic syndrome (Table 1).⁴ This definition was rapidly challenged for several reasons. The first reason was that it defined insulin resistance on the basis of a hyperinsulinaemic euglycaemic clamp, a test that is only used for scientific purposes, not as a clinical test, and is thus not feasible as a test for the classification of large groups of individuals. The second question raised related to the inclusion of microalbuminuria in the syndrome as data on this were conflicting in 1999 (and still are). In 2002, The European Group of Insulin Resistance (EGIR) recommended a revision of the definition.⁵ They did not include diabetic individuals in the definition, and they did not include microalbuminuria.

Furthermore, they defined insulin resistance on the basis of fasting hyperinsulinaemia. Common to the WHO and EGIR definitions is the fact that *both include measures of insulin resistance as mandatory elements in the definition.*

This is in contrast with the American National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) definition (Table 1)⁶ and the recent IDF definition (Table 2).¹ Neither of these definitions includes measures of insulin resistance as components of the metabolic syndrome. Thus the ‘syndrome’ is now a clustering of CV risk factors rather than a clustering of risk factors around a common possible explanatory factor – ie insulin resistance. The three definitions from WHO, EGIR and NCEP ATP-III are all based predominantly on epidemiological studies conducted in white Caucasian populations. Nevertheless, all definitions have been used in relation to non-white Caucasian populations. This presents a serious problem given the fact that numerous studies have shown that the association between obesity and other CV risk factors and glucose intolerance varies between ethnic groups. Individuals from Central and South East Asia develop dyslipidaemia, hypertension and diabetes at much lower levels of BMI than Europeans and North Americans, while in native Indians and Inuit populations, higher levels of BMI are needed to develop the same level of dyslipidaemia, hypertension and glucose intolerance. For this reason, the recent IDF definition from 2005 (Table 2)¹ has been modified according to ethnic and regional variations in risk and risk factor

WHO definition of the metabolic syndrome

Diabetes, impaired glucose regulation (IGT or IFG) or insulin resistance in combination with two or more of the following factors:

- hypertension ($\geq 140/90$ mmHg)
- dyslipidaemia (triglycerides >1.7 mmol/l or HDL-cholesterol <0.9 mmol/l in males, <1.0 mmol/l in women)
- central or overall obesity (waist to hip ratio >0.9 in males, 0.85 in females or BMI >30 kg/m²)
- microalbuminuria

NCEP ATP-III definition of the metabolic syndrome

Three or more of the following components occurring simultaneously:

- central obesity (>102 cm in males, >88 cm in females)
- raised triglycerides (>1.7 mmol/l)
- low HDL-cholesterol (<1.0 mmol/l in males, 1.3 mmol/l in females)
- high blood pressure ($\geq 130/85$ mmHg)
- fasting hyperglycaemia (FPG ≥ 6.1 mmol/l)

Table 1: WHO and NCEP ATP-III definitions of the metabolic syndrome^{4,6}

The IDF definition of the metabolic syndrome

Central obesity (based on local/regional/ethnic definition and on waist circumference) in combination with two or more of the following:

- high triglycerides (≥ 1.7 mmol/l or treatment for dyslipidaemia)
- low HDL-cholesterol (< 1.0 mmol/l in males, < 1.3 mmol/l in females or treatment for dyslipidaemia)
- high blood pressure ($\geq 130/85$ mmHg)
- hyperglycaemia (FPG ≥ 5.6 mmol/l or previously diagnosed diabetes)

individual risk factors, is minimal or non-existent. This does in fact question the clinical relevance of the currently available definitions of the metabolic syndrome.

The IDF definition – the end of the road?

The present IDF definition represents the fourth 'official' definition of the metabolic syndrome. It is the first definition to really attempt to adapt to ethnic variability, but it still seems to be far from the end of the road. Indeed, the present definition fails to predict development of CVD any better than the previous definitions. The IDF definition has abandoned BMI as a measure of obesity and uses waist circumference as the only measure of obesity despite the fact that very few studies in non-white Caucasian populations have looked at this measure of obesity in relation to CV risk. Recent studies in Inuit from Greenland and populations from South India have shown that BMI is a better, easier and more precise measure of obesity than waist circumference.⁹ In addition to this, the recent definitions of the metabolic syndrome are used as markers of CVD. In this respect, the relevant comparison would be some of the existing CV risk scores. There are several of these including the Framingham risk score, the Dundee risk score, the PreCard Score, the Procarn Score and the Heart Score amongst others. These risk scores all follow the guidelines from the European and American Societies of Cardiology, assessing CV risk based on multiple risk factors, and for each risk factor assuming that the risk of CVD increases with the actual value of the risk factor. Comparative studies of these CVD risk scores indicate that they perform almost equally well in white Caucasian populations, and

Table 2: The IDF definition of the metabolic syndrome¹

distributions. This definition is the first to provide local standards for central obesity, thus acknowledging that studies performed in white Caucasians from Europe or North America cannot automatically be applied to all populations worldwide.

Is the metabolic syndrome a clinically relevant entity?

When Reaven first proposed the clustering of risk factors around insulin resistance as a syndrome, he did not intend to define it as clinical syndrome, but as a hypothesis based on scientific evidence that could (and should) be tested and explored. Unfortunately, once defined as a 'syndrome', it attracted an overwhelming amount of interest that led to confusion rather than clarification. Thus we are now facing two problems:

1. There are four definitions – do they identify the same individuals?
2. Utility of the definitions – do they predict development of cardiovascular disease (CVD) and/or diabetes?

The answer to the first question is evidently no. There are numerous studies showing that, whatever population we are looking at in Europe, USA, Asia or the Pacific

Islands, the agreement between the definitions, when it comes to classifying an individual as having the metabolic syndrome or not, is generally poor to moderate. This is understandable as they use different cut-off points for the different components of the syndrome, and the factors included in the definitions are not automatically the same. The second question is even more relevant. Do the different definitions predict development of CV disease and diabetes? Not surprisingly, the answer to this question is yes. This is indeed unsurprising as the factors included are established CV risk factors, and thus it would be surprising if they did NOT predict development of CVD. Therefore, the really relevant questions would be: does the presence of the syndrome predict development of CVD and diabetes over and above what is predicted by each of the risk factors included in the syndrome? Only a few studies have tested this, but data from the San Antonio Heart Study⁷ show that the syndrome, as such, has no additional predictive power. Data from the DECODE study⁸ are not quite as clear but they also indicate that the additional predictive power of the metabolic syndrome, on top of the

the few comparisons with the metabolic syndrome indicate that they perform markedly better than the metabolic syndrome as predictors of CVD risk. This again is not surprising. The metabolic syndrome is based on dichotomisation of the individual risk factor, putting an individual with systolic blood pressure of 131 mmHg at equal risk as someone with a blood pressure of 185 mmHg. This approach ignores the fact that the probability of a fatal CVD event in the latter individual is five times higher than that in the first (adjusting for all other risk factors).

Therefore, in conclusion, the IDF definition has a minor advantage compared with previous definitions in that it acknowledges the fact that risk varies with ethnicity and geographical region. However, this does not compensate for the fact that the generalisability of the definition across ethnic groups remains questionable, that the definition – if used to identify individuals at risk of CVD – is a very poor predictor of CVD compared with existing CV risk scores, and that the definition does not necessarily identify insulin resistant individuals. Meanwhile, if we adapt the IDF definition, we will define 25% of the world's adult population – or between 1 and 1.5 billion individuals – as having the metabolic syndrome without having proper and evidence-based strategies to reduce the (hypothetical) increased risk of CVD in these individuals.

Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes

This review argues that the metabolic syndrome is not as well defined or characterised as is often believed, and that the notion that

it is a useful marker of CVD risk, beyond the risk associated with its individual components, is uncertain. For this reason, the review represents a milestone in several respects. The metabolic syndrome – originally suggested as an entity with insulin resistance as the common denominator – has become a popular hypothesis over the last 5–10 years but, unfortunately, it has also apparently become a misleading and misunderstood term. The 'syndrome' is now one of the best-selling arguments for papers in scientific reviews, in relation to grant applications and for new pharmaceutical compounds. This review is one of the first to really analyse in depth the relevance of the syndrome and, in addition to this, as a joint publication by key persons in the ADA and EASD, has good reason to be one of the most highly cited papers in the future. The authors (and thereby the ADA and EASD organisations) summarise their concerns regarding the metabolic syndrome as follows:

1. Criteria are ambiguous and incomplete. Rationale for thresholds are ill defined
2. Value of including diabetes in the definition is questionable
3. Insulin resistance as the unifying aetiology is uncertain
4. No clear basis for including/excluding other CVD risk factors
5. CVD risk value is variable and dependent on the specific risk factors present
6. The CVD risk associated with the 'syndrome' appears to be no greater than the sum of its parts
7. Treatment of the syndrome is no different to the treatment of each of its components
8. The medical value of diagnosing the syndrome is unclear.

There is no doubt that this is a paper that all of us, whether in clinical practice or research, will be confronted with at future meetings and in ongoing discussions. Thus, rather than commenting on it further, I can only give you one piece of advice, read it in depth in your own time!

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