The metabolic syndrome – a risk factor for diabetes and cardiovascular diseases

*B Balkau**

Summary

The metabolic, or insulin resistance, syndrome is a cluster of risk factors (hyperinsulinaemia, hyperglycaemia, hypertriglyceridaemia, hypo-HDL-cholesterolaemia, high blood pressure, abdominal adiposity) that are all associated with insulin resistance.

The syndrome has been proposed as the 'common soil' for both diabetes and cardiovascular disease. There have been a number of proposed definitions for the syndrome: the most documented comes from the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III).

While the syndrome is predictive of both conditions, the classical risk factors provide better predictive tools. Nevertheless, the metabolic syndrome remains a useful concept to be used as an additional criterion for screening subjects at long-term risk of cardiovascular disease and diabetes.

Eur Diabetes Nursing 2006; 3(3): 126–130.

Key words

Metabolic syndrome; diabetes; cardiovascular disease

Introduction

The concept of a clustering of risk factors has been discussed since the 1920s[1–3] and in 1988 Reaven provided a conceptual framework to link the various factors together: insulin resistance. He named the cluster syndrome X[4] and included insulin resistance, hyperinsulinaemia, hyperglycaemia, hypertriglyceridaemia, hypo-HDL-cholesterolaemia and high arterial blood pressure. Later, Reaven added abdominal adiposity to the cluster, and this has become a key component of the syndrome.[5]

This first work generated a lot of epidemiologic research, centred on showing that the various abnormalities did indeed cluster, and that they were correlated with hyperinsulinaemia, a surrogate marker of insulin resistance, as quantified by either the hyperinsulinaemic euglycaemic clamp or by the intravenous glucose tolerance test and the minimal model.[6–10]

Authors

B Balkau PhD, Director of Research, Institut national de la santé et de la recherche médicale (INSERM), France

***Correspondence to:**
B Balkau
INSERM U780-IFR69
16 Avenue Paul Vaillant Couturier
94807 Villejuif
France
e-mail: balkau@vjf.inserm.fr

Received: 27 February 2006
Accepted in revised form:
10 July 2006

In 1999 the World Health Organization (WHO) provided a definition of the metabolic syndrome in their guidelines for the diagnosis of diabetes.[11] For a subject to have the WHO syndrome, in addition to impaired regulation or insulin resistance, two other abnormalities (among high blood pressure, hypertriglyceridaemia, hypo-HDL-cholesterolaemia, micro-albuminuria, high waist–hip ratio and/or high body mass index) were required. This should have been a big step forward to enable prevalences in various groups to be evaluated, and compared, to provide a better understanding of the syndrome from the differences observed between various populations. However, the first criteria in this definition required subjects to have either impaired glucose regulation (diabetes, impaired glucose tolerance, impaired fasting glucose) or insulin resistance. Thus, for normal glucose-tolerant subjects to be considered to have the metabolic syndrome, they had to be insulin resistant, as evaluated by a hyperinsulinaemic clamp; this information is not routinely available however, neither from clinics nor in epidemiological studies. The definitions used in research papers often used hyperinsulinaemia or the homeostasis model assessment (HOMA) insulin resistance index (essentially fasting glucose multiplied by fasting insulin) as surrogate markers for insulin resistance. As there were no guidelines given for this, analyses used differing criteria, rendering comparison very difficult.[12]

The next major step in the metabolic syndrome story was the National Cholesterol Education Program – Adult Education Panel III (NCEP-ATP III),[13] which provided a more practical definition (Table 1), requiring only fasting blood samples and routinely available parameters. This definition

Three or more of the following risk factors:
• Abdominal obesity: waist circumference >102/88 cm (men/women)
• Triglycerides ≥150 mg/dl (1.69 mmol/l)
• HDL-cholesterol <40/50 mg/dl (1.04/1.29 mmol/l) (men/women)
• Blood pressure ≥130/≥85 mmHg
• Fasting glucose ≥110 mg/dl (6.1 mmol/l)

Table 1. NCEP-ATP III definition of the metabolic syndrome, 2001[11]

has the advantage of simplicity, but it can be criticised on a number of grounds:[14] each of the chosen thresholds is arbitrary; the five abnormalities are assumed to carry an equal weight in the syndrome; the lipids are included as two abnormalities, thus increasing the importance of dyslipidaemia; and the criteria for abdominal obesity results in there being more abdominally obese women than men, despite the fact that men are more susceptible to cardiovascular disease (CVD), and in some countries more susceptible to diabetes.

• **Central obesity: ethnic-specific**
– Europids ≥94/80 cm (men/women) (in the USA the ATP III [102 cm male, 88 cm female] are likely to be used for clinical purposes)
– South Asians ≥90/80 cm (men/women)
– Chinese ≥90/80 cm (men/women)
– Japan ≥85/90 cm (men/women)
– Ethnic Central and South Americans: use recommendations for South Asians
– Sub-Saharan Africans: use recommendations for Europids
– Eastern Mediterranean and Middle East (Arab): use recommendations for Europids
plus any two of the following four factors:
– Raised triglyceride level: >150 mg/dl (1.7 mmol/l) or a treatment specific for this lipid abnormality
– Reduced HDL-cholesterol: <40/50 mg/dl (1.03/1.29 mmol/l) (men/women) or a treatment specific for this lipid abnormality
– Raised blood pressure: systolic BP ≥130 or diastolic BP ≥85 mmHg or treatment of previously diagnosed hypertension
– Raised fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or previously diagnosed type 2 diabetes

Table 2. International Diabetes Federation consensus worldwide definition of the metabolic syndrome, 2005[15]

Defining the metabolic syndrome

Most of the epidemiological publications on the syndrome have been based on this NCEP-ATP III definition. More recent definitions come from the International Diabetes Federation (IDF)[15] and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI)[16] (Tables 2 and 3).

The first publications comparing the NCEP-ATP III and the IDF definitions[17,18] show the IDF definition to have a higher prevalence than the NCEP-ATP III definition: in the National Health and Nutrition Examination Survey (NHANES 1999–2002) the prevalence in persons aged over 20 years changed from 34% to 39%, and in an Australian study (subjects aged ≥18 years) from 19% to 26% in men and from 14% to 16% in women. In a French population, the frequency increased from 9% to 17% in women and from 10% to 21% in men (Table 4); the individual abnormalities that greatly increased in frequency were central obesity and hyperglycaemia, which result from the changes in thresholds between the two definitions. The increase in lipid abnormalities is due to lipid treatment. In contrast, including treatment for hypertension altered the frequency of high arterial blood pressure by only 1%.

Identifying at-risk patients

In the clinic, the syndrome enables the identification of subjects with a clustering of syndrome

abnormalities, each of which might be below the threshold for treatment, but the fact that they cluster implies a long-term risk of diabetes and/or cardiovascular disease. This is a similar concept to the 'global' or 'overall' cardiovascular risk, which emphasises that all risk factors should be taken into account when determining risk and hence treatment modalities.

The Framingham equations are the best-known risk equations, but other equations are used, including the European SCORE project equation.[19,20] The tables of coloured squares developed by the SCORE project are a practical way of evaluating the 'absolute' cardiovascular risk for an individual.[20] This does at least provide a risk ranking for the patient and his physician, for patient education and treatment. It appears that this approach has had mixed success – depending on the country, the context and the speciality of the physician.

The identification of the metabolic syndrome may be simpler for the practising physician; it just requires the counting of abnormalities. However, if the aim is to predict long-term cardiovascular risk, the syndrome does not include the important cardiovascular risk factors – age and smoking – and the dyslipidaemia included in the syndrome does not involve high LDL-cholesterol, except perhaps by the inclusion of lipid treatments. Many studies have shown that the syndrome does predict cardiovascular risk, and a meta-analysis using the NCEP-ATP III defined syndrome evaluated the relative risk as 1.6 in comparison to subjects without the syndrome; however, there are better methods of predicting cardiovascular risk than the syndrome.[21,22]

Similarly, for diabetes, while the syndrome is associated with a relative risk of 3.0, diabetes risk scores do perform better than the syndrome.[21,22] It would seem that the syndrome does identify men who might not be identified as being 'at risk' by a cardiovascular risk score; however the waist circumference alone provides a simple screening tool, with a similar hazards ratio for cardiovascular death as the syndrome, in men at low cardiovascular risk.[23]

Three or more of the following risk factors:
• Elevated waist circumference: ≥102/88 cm (men/women)
• Elevated triglycerides ≥150 mg/dl (1.7 mmol/l) or drug treatment for elevated triglycerides
• Reduced HDL-cholesterol <40/50 mg/dl (1.04/1.29 mmol/l) (men/women) or drug treatment for reduced HDL-cholesterol
• Elevated blood pressure ≥130 or ≥85 mmHg or drug treatment for hypertension
• Elevated fasting glucose ≥100 mg/dl (5.6 mmol/l) or drug treatment for elevated glucose

Table 3. American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) diagnostic criteria for metabolic syndrome 2005[16]

Highlighting health problems

The syndrome has provided another topic for public education messages, and it highlights one of the great health problems of our modern society: obesity and in particular, central obesity. The emphasis is placed on abdominal adiposity, and the identification of other risk factors associated with it. The precise definition used for abdominal obesity has been rather arbitrarily chosen, as the frequencies of metabolic abnormalities increase with abdominal adiposity in a linear fashion, making the choice of threshold for the waist difficult.[24]

Describing the syndrome as a pathology implies that there is an underlying cause for all the abnormalities that it encompasses, and it follows that there should be a single treatment. It has yet to be shown that insulin sensitisers are effective in treating the metabolic syndrome, and the current recommendations are to treat the syndrome abnormalities one by one.[25]

Towards the end of 2005, doubts on the use of the syndrome arose following an appropriate cautionary and well-documented joint statement by the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA). In summary this statement commented that:[25]

- The metabolic syndrome is not nearly as well-defined and characterised as is often assumed
- The notion that it is a useful marker of cardiovascular risk above and beyond the risk associated with its individual components is uncertain
- Although certain cardiovascular risk factors undoubtedly occur together more often than expected, the underlying pathophysiology of the syndrome is unclear
- The list of risk factors comprising the cluster is not grounded by well-defined criteria.

	NCEP-ATP III syndrome	Men	Women	IDF syndrome	Men	Women	AHA/NHLBI syndrome	Men	Women
Central obesity	Waist >102/88cm (men/women)	12%	20%	Waist ≥94/80 cm (men/women)	33%	40%	Waist ≥102/88 cm (men/women)	14%	22%
Hyperglycaemia	Fasting glucose ≥110 mg/dl (6.1 mmol/l)	12%	6%	Fasting glucose ≥100 mg/dl (5.6 mmol/l) or diabetes treatment	35%	18%	Fasting glucose ≥100 mg/dl (5.6 mmol/l) or diabetes treatment	35%	18%
Raised blood pressure (systolic/diastolic)	≥130/85 mmHg	66%	43%	≥130/85 mmHg or hypertension treatment	67%	44%	≥130/85 mmHg or hypertension treatment	67%	44%
Hypertriglyceridaemia	≥150 mg/dl (1.69 mmol/l)	17%	7%	≥150 mg/dl (1.69 mmol/l) or specific treatment for this lipid abnormality†	23%	14%	≥150 mg/dl (1.69 mmol/l) or specific treatment for this lipid abnormality†	23%	14%
Hypo-HDL cholesterolaemia	<40/50 mg/dl (1.03/1.29 mmol/l)	10%	18%	<40/50 mg/dl (1.03/1.29 mmol/l) or specific treatment for this lipid abnormality†	18%	24%	<40/50 mg/dl (1.03/1.29 mmol/l) or specific treatment for this lipid abnormality†	18%	24%
Syndrome prevalence		10%	9%		21%‡	17%‡		18%‡	14%‡

† Any lipid treatment was included here
‡ If treated for lipids, only counted for the hypertriglyceridaemia abnormality

Table 4. Frequency of the National Cholesterol Education Program – Adult Treatment Panel (NCEP-ATP) III, the International Diabetes Foundation (IDF) and the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) metabolic syndromes and of their constituent abnormalities, in 19 126 men and 19 874 women recruited in French health examination centres in central western France, Inter-Regional Institute for Health (IRSA), from 2001 to 2003; the age structure is representative of the 1999 French population of men and women aged 20–74 years

It then states that 'the manuscript is a cautionary reminder to practitioners, and an urgent call for further research'. The final statement in their abstract is: 'treat all cardiovascular risk factors without regard to whether a patient meets the criteria for diagnosis of the metabolic syndrome'.

Conclusion

The metabolic syndrome remains a useful concept to be used as an additional criteria for screening subjects at long-term risk of cardiovascular disease and diabetes, along with the classical risk factors. Central adiposity is the characteristic physical sign of many who have metabolic abnormalities, and after taking a patient's blood pressure, medical practitioners should prescribe blood tests for the biological risk factors.

In a French population, we have proposed that the more centrally obese 30% of patients should be further tested – corresponding to ≥96 cm and ≥83 cm in men and women respectively.[26] However, as a caution, not all patients with the syndrome have central adiposity.

To repeat the above warning from the EASD and the ADA, all CVD risk factors should be taken into account: high blood pressure, high LDL cholesterol, high triglycerides, low HDL cholesterol, smoking, hyperglycaemia (especially diabetes), and central adiposity.

Acknowledgement

J Tichet and S Vol (Inter-Regional Institute for Health [IRSA])are

thanked for providing data on the frequency of the metabolic syndrome.

Conflict of interest statement:

Beverley Balkau did not receive any commercial funding to write this article; however, she does have commercial funding for her research work from Lilly, France; Sanofi-Aventis, France and Astra-Zeneca.

References

1. Kylin E. Studien über das Hypertonie-Hyperglykämie-Hyperurika miesyndrom. *Zentralbl Inn Med* 1923; **44:** 105–127.
2. Avogaro P, Crepaldi G, Enzi G, *et al.* Associazione di iperlipidemia, diabete mellito e obesita de medio grado. *Acta Diabetol Lat* 1967; **4:** 36–41.
3. Modan M, Halkin H, Almog S, *et al.* Hyperinsulinaemia. A link between hypertension, obesity and glucose intolerance. *J Clin Invest* 1985; **75:** 809–817.
4. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988; **37:** 1595–1607.
5. Reaven GM. The fourth musketeer – from Alexandre Dumas to Claude Bernard. *Diabetologia* 1995; **38:** 3–13.
6. Edwards KL, Austin MA, Newman B, *et al.* Multivariate analysis of the insulin resistance syndrome in women. *Arterioscler Thromb* 1994; **14:** 1940–1945.
7. Haffner SM, Valdez RA, Hazuda HP, *et al.* Prospective analysis of the insulin-resistance syndrome (syndrome X). *Diabetes* 1992; **41:** 715–722.
8. Ferrannini E, Haffner SM, Mitchell BD, *et al.* Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia* 1991; **34:** 416–422.
9. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; **237:** E214–E223.
10. Bergman RN. Lilly lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach. *Diabetes* 1989; **38:** 1512–1527.
11. World Health Organisation. *Definition, diagnosis and classification of diabetes mellitus and its complications.* Report of a WHO consultation, 1999.
12. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 1999; **16:** 442–443.
13. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA* 2001; **285:** 2486–2497.
14. Balkau B, Vernay M, Mhamdi L, *et al*, D.E.S.I.R. Study Group. The incidence and persistence of the NCEP (National Cholesterol Education Program) metabolic syndrome. The French D.E.S.I.R. study. *Diabetes Metab* 2003; **29:** 526–532.
15. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome – a new worldwide definition. *Lancet* 2005; **366:** 1059–1062.
16. Grundy SM, Cleeman JI, Daniels SR, *et al.* Diagnosis and management of the metabolic syndrome. An American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112:** 2735–2752.
17. Adams RJ, Appleton S, Wilson DH, *et al.* Population comparison of two clinical approaches to the metabolic syndrome: implications of the new International Diabetes Federation consensus definition. *Diabetes Care* 2005; **28:** 2777–2779.
18. Ford ES. Prevalence of the metabolic syndrome defined by the International Diabetes Federation among adults in the U.S. *Diabetes Care* 2005; **28:** 2745–2749.
19. Wilson PW, D'Agostino RB, Levy D, *et al.* Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; **97:** 1837–1847.
20. Conroy RM, Pyorala K, Fitzgerald AP, *et al*; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003; **24:** 987–1003.
21. Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 2005; **20:** 1769–1778.
22. Stern MP, Williams K, Gonzalez-Villalpando C, *et al.* Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care* 2004; **27:** 2676–2681.
23. Balkau B, Qiao Q, Tuomilehto J, *et al.* Does the metabolic syndrome detect further subjects at high risk of cardiovascular death, or is a conventional cardiovascular risk score adequate? *Diabetologia* 2005; **48:** A119.
24. Bertrais S, Balkau B, Vol S, *et al.* Relationships between abdominal body fat distribution and cardiovascular risk factors: an explanation for women's healthier cardiovascular risk profile. The D.E.S.I.R. Study. *Int J Obes Relat Metab Disord* 1999; **23:** 1085–1094.
25. Kahn R, Buse J, Ferrannini E, *et al.* The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005; **28:** 2289–2304; *Diabetologia* 2005; **48:** 1684–1699.
26. Balkau B, Sapinho D, Petrella A, *et al;* the D.E.S.I.R. Study Group. Prescreening tools for diabetes and obesity-associated dyslipidaemia: comparing BMI, waist and waist-hip ratio. The D.E.S.I.R. study. *Eur J Clin Nutr* 2006; **60:** 295–304.