Should we have more definitions of metabolic syndrome or simply take waist measurement?

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Abstract

The disorder now known as metabolic syndrome has been recognized for 50 years, but its multiple definitions have led to some confusion and even doubt about its very nature. Metabolic syndrome is directly linked to the presence of android obesity, which indicates insulin resistance and lies at the root of all risk factors and early indications of type 2 diabetes. It is diagnosed by systematic measurements of waist size and its direct interpretation taking ethnic origin into account. This pragmatic approach avoids the uncertainties generated by differing definitions and is subtler than the presence or absence of metabolic syndrome in a given patient. Drug-free treatment of an android obese patient is inexpensive and effective, but this apparently simple approach masks difficulties of application. However, these are sociological problems.

Résumé

Faut-il multiplier les définitions du syndrome métabolique ou doit-on se contenter de mesurer le tour de taille ?

Connue depuis 50 ans, l'entité aujourd'hui dénommée syndrome métabolique a fait l'objet de multiples définitions qui ont amené une certaine confusion et même une remise en cause de son originalité. Le syndrome métabolique est étroitement lié à la présence d'une obésité androïde qui témoigne d'une insulinorésistance et se situe au confluent de tous les facteurs de risque et aux avant-postes du diabète de type 2. Son dépistage passe par la mesure systématique du tour de taille et par son interprétation directe en tenant compte de l'ethnicité considérée. Cette attitude pragmatique de clinicien évite les incertitudes liées à des définitions différentes et apporte plus de nuances que la présence ou non d'un syndrome métabolique chez un sujet donné. Face à une obésité androïde, les mesures thérapeutiques non médicamenteuses sont peu coûteuses et efficaces, mais sous cette simplicité apparente se cachent des difficultés de mise en œuvre qui constituent en fait un problème de société.

Keywords: Metabolic syndrome; Insulin resistance; Waist size; Cardiovascular risk; Review

Mots clés : Syndrome métabolique ; Insulinorésistance ; Tour de taille ; Risque cardiovasculaire ; Revue

1. Introduction

Several studies carried out over the past few decades have identified the risk factors responsible for cardiovascular accidents, which are the main cause of death and disability in the western countries. Reaven (1988) extended the work of Jean Vague about android obesity and used the term ‘syndrome X’ to describe an association of arterial hypertension, carbohydrate intolerance, dyslipidemia and hyperinsulinemia, indicating insulin resistance [1,2]. This condition, now known as metabolic syndrome, has had several definitions that have given rise to some confusion and even questions about its real nature [3]. Although it is now considered to be a disease in the United States [4], still some consider it to be no more than a collection of risk factors [5].
This raises several questions for clinicians, such as how should metabolic syndrome be defined: what are its clinical consequences? How it should be diagnosed, in practice? And how should a patient with metabolic syndrome be treated? The responses to these questions should clarify the medical response and lead to treatment with medication or by a change in life style.

2. Defining metabolic syndrome

Metabolic syndrome has also been called dysmetabolic syndrome, plurimetabolic syndrome and insulin resistance syndrome. These names indicate its multifaceted nature and hence the many definitions of metabolic syndrome.

2.1. Definitions

2.1.1. The WHO definition [6]

The definition adopted by the WHO in 1998 requires measurement of insulin resistance and can be applied to the whole population, both diabetic and non-diabetic (Table 1). This definition assumes that metabolic syndrome involves glucose intolerance, hyperinsulinemia and diabetes, plus at least two other clinical or biochemical abnormalities.

2.1.2. The EGIR definition

The Groupe européen pour l’étude de l’insulinorésistance (EGIR) adopted a definition in the following year, 1999 that was applicable only to non-diabetic subjects. This is based on the notion of insulin resistance and thus requires the measurement of fasting plasma insulin. The syndrome is indicated by a plasma insulin concentration found in the top quartile of the population plus two clinical or biochemical criteria that differ from those in the WHO definition [7].

2.1.3. NCEP ATP III definition

A group of experts from the United States National Cholesterol Program proposed a simplified version of the WHO definition in 2001. They replaced the parameter of insulin resistance with the presence of at least three of five criteria of equal value [8]. This has the advantage of being easy to use in clinical practice because the criteria are all readily available. However, the criteria in the original NCEP definition did not include the notion of treatment, which created some confusion in patients who were well controlled by treatment with antihypertensive or hypolipidemic drugs.

2.1.4. IDF definition

The most recent (2005) definition is that of the International Diabetes Foundation. It uses the NCEP criteria, but considers waist measurement to be the main, and essential, parameter. The normal measurement is reduced and varies with race. There must be two other clinical or biochemical criteria [9].

2.2. Differences and limitations

The above definitions give rise to some confusion, and this in turn complicates the practical application of the concept of metabolic syndrome in normal clinical practice. Whether or not a particular patient suffers from metabolic syndrome will depend on the definition used [10]. Hence, the prognostic value of metabolic syndrome will differ greatly, which makes it much less pertinent.

As the essential element in the WHO definition is abnormal glucose regulation all patients so defined are at risk of developing type 2 diabetes even though they are not yet diabetic. The inclusion of diabetics in the metabolic syndrome, as may occur using the IDF definition, obscures the message, as these patients should be classified as being at high risk for cardiovascular disease.

In contrast, abnormal glucose regulation is only one element used in the NCEP definition of metabolic syndrome. Hence, a
patient with metabolic syndrome may have no symptom of abnormal glucose regulation. This definition undoubtedly is a better reflection of cardiovascular risk even though it does not include the plasma LDL cholesterol concentration, which is an important element in it [11]. Quite apart from these fundamental differences, the definitions differ in several other ways. Thus the criteria used to define obesity vary. The WHO uses two measurements: the waist/hip ratio and the body mass index, while the NCEP ATP III, EGIR and IDF definitions use only waist measurement. The threshold of abdominal obesity is thus lower in the EGIR and IDF definitions than in that of the NCEP. Abdominal obesity, which is the essential criterion of the IDF definition, is modulated by the patient’s race. Epidemiological studies on Chinese subjects in Hong Kong clearly showed that the risk of arterial hypertension, abnormal blood glucose or elevated plasma triglycerides are linked to a smaller waist measurement than in Europeans [12,13]. The normal values for parameters such as arterial pressure and the biochemical values vary from one definition to another. The idea of whether or not there is any treatment for metabolic syndrome needs clarification. There is nowhere any indication of the consequences of treating metabolic syndrome with hypolipemiant drugs in terms of the two blood lipid parameters in the IDF definition. Should a subject whose lipid metabolism has been normalized with fibrate be considered to have one or two of the criteria in the definition? Lastly, the WHO definition includes an assay of microalbuminuria, which is rarely measured in non-diabetics.

The above comments clearly show the uncertainties accompanying any attempt to unambiguously identify metabolic syndrome using criteria readily used in clinical practice. These multiple definitions have made it difficult to compare epidemiological studies, even though the main objective of a definition of metabolic syndrome is to facilitate early diagnosis of the disorder in subjects at high cardiovascular risk. These problems cast doubt on the practical used or even existence of metabolic syndrome, although its consequences for cardiovascular risk and diabetes seem to have been well established.

3. Importance of metabolic syndrome: reasons for diagnosis

The importance of metabolic syndrome for public health involves two elements: its increasing frequency and its clinical consequences.

3.1. Prevalence of metabolic syndrome

The prevalence of metabolic syndrome varies with the country, ethnic origin and the definition used. The NHANES III (Third National Health And Nutrition Examination Survey) epidemiological study carried out from 1988 to 1994 on 8608 subjects over 20 years old found that the overall prevalence of metabolic syndrome in the United States was 23.9% using the NCEP criteria and 25.1% using the WHO definition [14,15]. The apparent homogeneity indicated by the fact that 86.2% of the participants did or did not suffer from metabolic syndrome according to the two definitions masks any differences that might be important in certain subgroups. Thus the prevalence in men of Afro-American origin was 24.9% using the WHO definition and only 16.5% using that of the NCEP. Certain ethnic groups, such as Mexicans, particularly women, were especially susceptible. The importance of metabolic syndrome is indicated by the clear increase in its prevalence in American adults; it increased from 24.1% in 1988–1994 to 27% in 1999–2000. Thus about 55 millions Americans were suffering from metabolic syndrome in 2000 [15].

The EGIR group also showed great variation in the frequency of metabolic syndrome in Europe; it depended on the population studied and the definition used [16]. Using the WHO definition, 7–36% of men and 5–22% of women aged 40–55 suffered from metabolic syndrome. The DECODE prospective European study on non-diabetic individuals (6156 men and 3356 women) aged 30–89 years, defined 11 cohorts [17]. The median follow-up was 8.8 years. The prevalence of metabolic syndrome was 15.7% in men and 14.2% in women, adjusted for age, using the EGIR definition.

There are no published data for the whole of France.

The MONICA multicenter study was done in 1995–1998 on populations in Lille, Strasbourg and Toulouse. The 1700 men and 1700 women were randomly selected from the voter lists [18]. The results showed that 22.5% of men and 18.5% of women aged 35–65 suffered from metabolic syndrome. But these figures mask the considerable geographic variation: metabolic syndrome was almost twice as frequent in the North of France as in the South.

The DESIR (Données épidémiologiques sur le syndrome d’insulinorésistance) study on 4293 subjects aged 30–64 found that 10% of men and 7% of women suffered from metabolic syndrome using the NCEP definition [19]. When medical treatment was included in the definition of the abnormalities the frequencies were 16% of men and 11% of women. But only 12% of the men and 8% of the women had the syndrome at inclusion and after 3 years, which is prevalence 2.5 times lower than in the United States.

The EPIMIL (Étude épidémiologique des facteurs de risque et du syndrome métabolique en milieu militaire) study on 2045 male military personnel aged 38.6 ± 8.8 years based in the Paris region found that 185 (9%) of them had at least three of the five NCEP ATP III criteria, thus satisfying the definition of metabolic syndrome [20].

3.2. Clinical consequences of metabolic syndrome

The main objective of the concept of metabolic syndrome is to help identify subjects at high risk of cardiovascular disease or of developing type 2 diabetes.

3.2.1. Cardiovascular risk

All the cohort studies have shown that subjects with metabolic syndrome are at relatively great risk of a cardiovascular
The 3.9 year old Botnia study on 4483 Finnish people aged 35–70 found that the relative risk of cardiovascular disease was particularly high in diabetics with metabolic syndrome as defined by the WHO. The presence of metabolic syndrome tripled the risk of a coronary event and increased the likelihood of death from a cardiovascular accident 1.8-fold [21].

The Kuopio Ischaemic heart disease risk factor study on 1209 Finns aged 42–60 suffering from metabolic syndrome but having no history of cardiovascular disease or diabetes showed that metabolic syndrome was associated with increased frequency of death due to coronary disease and any cause [22]. The relative risk of such a death was 4.26 using the NCEP definition and 3.32 with the WHO definition. The absolute risk of coronary disease indicated by metabolic syndrome was about 10% over 10 years.

The NHANES III study on a representative American population showed a relative risk of a coronary accident of 2.07 in subjects with metabolic syndrome using the NCEP definition [23]. Similarly, the 11-year ARIC study on 12,000 white and Afro-American adults found that metabolic syndrome was associated with a 1.5-fold greater risk of coronary disease in men, regardless of their ethnic origin. But it was even greater (double) in women [24]. The 6447 Scottish men monitored in the WOSCOPS study had an absolute risk of cardiovascular disease over 10 years of 20%, while the relative risk of a coronary accident was 1.71 in subjects with metabolic syndrome using the NCEP definition [25]. A more recent prospective American study on 6255 subjects (54% women) aged 30–75 found that the relative risk of coronary disease in patients with metabolic syndrome was 2.02, but it was 4.19 for those with a history of cardiovascular disease [26]. Lastly, the San Antonio Heart Study showed that the increased prevalence of metabolic syndrome from 1979–1982 to 1984–1988 could be used to explain the increase in cardiovascular accidents [27].

These studies are all in general agreement, that a person with metabolic syndrome, as defined by the NCEP ATP III criteria, are at two-fold greater risk of cardiovascular disease. Thus the absolute risk due to metabolic syndrome is 10–20% after 10 years, depending on the age of the subject, which is high but less than that due to type 2 diabetes.

### 3.2.2. Risk associated with type 2 diabetes

The increased cardiovascular risk due to type 2 diabetes is hardly surprising in a subject suffering from metabolic syndrome whose abdominal obesity indicates insulin resistance. The WHO definition, which includes abnormal blood glucose, undoubtedly increases the risk of developing type 2 diabetes. The findings of the Paris Prospective Study on 5042 men show that moderate fasting hyperglycaemia is significantly linked to increased prevalence of type 2 diabetes after a median follow-up of 3 years [28].

The WOSCOPS study shows that the risk of diabetes is 3.5-fold greater in subjects with metabolic syndrome, as defined by the NCEP criteria. The presence of four of the five criteria considerably increased the risk of diabetes. A hs-CRP concentration ≥ 3 mg/l was associated with increased risk of diabetes.

The EPIMIL study found that plasma insulin and the HOMA index defining insulin resistance increased significantly with the number of metabolic syndrome criteria. Plasma insulin increased from 6.6 ± 4 mIU/l in subjects with no criteria to 20.6 ± 13 mIU/l in those with four criteria. Although insulin secretion slightly increased at the same time, the increase was not significant, clearly indicating the development of type 2 diabetes because the most important increase of insulin resistance (Fig. 1).

Lastly, several national studies in the United States have shown that subjects with metabolic syndrome are 7 to 9 times more likely to develop type 2 diabetes than are healthy subjects [29].

### 4. Diagnosis of metabolic syndrome in practice

A pragmatic approach is required to overcome the paradox of the importance of metabolic syndrome in public health and the practical problems of its diagnosis.

Abdominal obesity appears to be associated with an increased cardiovascular risk, as shown by the Paris Prospective Study [30]. J.-P. Després more recently defined the « high blood sugar waist measurement » that diagnoses 80% of cases at risk [31]. Abdominal fat and a fatty liver are the causes of this phenomenon, as the removal of subcutaneous abdominal fat by liposuction does not reduce the cardiovascular risk [32].

However, certain recent criticisms have raised doubts about the contribution of metabolic syndrome in terms of the importance of its component risk factors. Current definitions do not seem to identify all the subjects at risk and appear to be no
better at predicting cardiovascular risk than systems like the Framingham equation. The risk equations are rarely used in routine clinical practice and doctors are more likely to view problems of obesity, blood pressure, plasma glucose and plasma lipids as somewhat separate problems. Thus a combination of minor symptoms like moderate overweight, slightly elevated blood pressure or moderately elevated fasting blood glucose can be underestimated, misleading the recognition of metabolic syndrome.

This concept facilitates the recognition of patients at risk and establishes a link between the slightly theoretical idea of insulin resistance and cardiovascular risk in routine clinical practice by simply measuring the waistline [33]. The InterHeart study also considered the waist measurement to be of some importance as it accounts for 20% of the attributable risk of suffering a myocardial infarct [34].

Many reports have shown no clearly identifiable boundary between normality and disease. These observations apply equally to cardiovascular risk, whatever formula is used. Thus the link between the criteria for metabolic syndrome and cardiovascular complications is indicated by the increase in risk indicators like hs-CRP or microalbuminuria [35,36].

It thus appears to be necessary to diagnose these patients and to practically quantify their insulin resistance. Assaying blood insulin and calculating a Homa index may seem attractive, but there are problems of assay cost and difficulty. The EPIMIL study, like many others, showed that there is an excellent correlation between waist measurement and plasma insulin and the other components of metabolic syndrome [20] (Fig. 2 and Table 2). This simple, inexpensive and highly reproducible measurement should become routine in clinical practice. It is already routine in many departments, along with calculation of the BMI and measurement of arterial pressure. It should be interpreted based on its unweighted absolute value, providing a simple, rapid approximate estimate of a patient’s insulin resistance [37].

5. Three practical questions that clinicians should ask

5.1. Which parameter best predicts the onset of type 2 diabetes?

Fasting blood glucose is fundamental because the definitions of metabolic syndrome vary so greatly: those that include this parameter seem to be the most effective. Thus the WHO definition is the most sensitive, but the NCEP definition is most specific [29]. Measuring HbA1c seems to be less sensitive and less specific that fasting blood sugar. It is useful for identifying those patients who need close monitoring [40].

5.2. Of what predictive value is metabolic syndrome for vascular risk?

Here again the variety of definitions of metabolic syndrome results in a range of responses. Some studies have found that the presence of metabolic syndrome need not be more informative than the sum of its risk factors [41,42]. But the Interheart study [34] found that waist measurement is a predictive element for myocardial infarct. In the light of these results, waist measurement appears to be an independent risk indicator; hence, its measurement should be a fundamental component of any clinical examination. Other parameters such as moderate fasting hyperglycaemia, high arterial blood pressure or dyslipidaemia, no matter how slight, can only strengthen the predictive value of the waist measurement for a cardiovascular accident. Thus the «waist measurement-hypertriglyceridemia » concept of Després fits our definition perfectly [31,43].

5.3. Should abdominal obesity be reduced?

All the relevant pathophysiological theories hold that abdominal visceral obesity is central to the development of diabetes and cardiovascular accidents, even though the mechanisms involved are not yet fully understood. Every effort should thus be made for the early management of this type of obesity even if there are not other clinical or biological abnormalities. Many studies have shown the advantages of physical exercise and diet. Lastly the recent discovery of the role of the endocannabinoid system has shed new light on the possibilities for treating abdominal obesity and the resulting risk factors [43]. The next few years should show just how rimonabant fits into the overall picture.
6. Management of a patient with metabolic syndrome

Diagnosis should lead to effective management that breaks the links between deleterious features: abdominal obesity, metabolic syndrome and increased risk of cardiovascular disease and type 2 diabetes [38]. Several intervention studies have shown that altering life style is effective, with improved eating habits and increased physical exercise [39]. Several drugs have also been found effective when one of the parameters of metabolic syndrome is abnormal enough for treatment. Metformin, glitazones, statins, ACE inhibitors and aspirin have all be used to treat specific patients, and other drugs like the endocannabinoid inhibitors are being evaluated.

7. Conclusion

Metabolic syndrome, with android obesity indicating insulin resistance, is a fundamental precursor of all the cardiovascular risk factors and a predictor of type 2 diabetes [44]. This potentially serious syndrome can be effectively managed if it is accurately diagnosed. This is done by the routine measurement of the waist and its direct interpretation, taking ethnic origin into account [45]. This clinical condition is readily treated by drug-free, inexpensive changes of life style. Unfortunately this apparent simplicity masks considerable difficulties that are far greater than the purely medical aspects; they are in fact a fundamental problem of society [46].

References


