A review of the metabolic syndrome

B. Balkau, P. Valensi, E. Eschwège, G. Slama

Abstract

While the concept of this syndrome has been described more than 60 years ago, and more formally almost 20 years ago, the controversy continues as to its utility, which of the various syndrome definitions should be used and their ability to predict diabetes and/or cardiovascular disease. The metabolic syndrome, of cardiovascular risk factors, provides an early warning of at risk subjects and emphasises the need to treat more aggressively (by at least lifestyle modification) patients with multiple abnormalities even though the abnormalities might be slight. Further, the syndrome can be easily used in clinical practice and when it is assessed against the background of the patient’s age, sex and smoking habits, it provides an evaluation of potential cardiovascular risk. Prospective intervention studies are the only means of definitively accepting or refuting the usefulness of the syndrome. The metabolic syndrome is an entity which merits attention from both the medical profession and public health authorities.

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Résumé

Le syndrome métabolique : revue générale

Voilà plus de 60 ans, le concept de syndrome métabolique a été identifié, et plus formellement décrit, il y a une vingtaine d’années. La controverse continue quant à l’utilité d’un tel syndrome, quant à la définition utilisée et à la capacité des différentes définitions à prédire le diabète et/ou les maladies cardiovasculaires. Le syndrome métabolique indique une alerte précoce pour traiter plus agressivement (au moins par des changements de comportement) les patients atteints d’anomalies multiples, même si ces anomalies sont modérées. De plus, le syndrome est facile à utiliser en clinique et devrait être mis en parallèle avec l’âge, le sexe et le tabagisme du patient pour l’évaluation du risque cardiovasculaire. Les études prospectives d’intervention sont les seules études qui fournissent la preuve de l’utilité du syndrome. Le syndrome métabolique mérite toute l’attention de la part du corps médical et des autorités de santé publique.

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Mots clés : Diabète ; Insulinorésistance ; Maladies cardiovasculaires ; Syndrome métabolique ; Revue générale

The metabolic syndrome groups insulin resistance, hyperinsulinaemia, hyperglycaemia, dyslipidaemia (hypertriglyceridaemia and/or hypo HDL-cholesterolaemia), high arterial blood pressure and central adiposity. Other abnormalities are also associated with this constellation – and may well also be part of this syndrome. A variety of names have been associated with this condition: the pluri-metabolic syndrome, the insulin-resistance syndrome, syndrome X, the dysmetabolic syndrome, the metabolic syndrome … In itself insulin resistance is not a disease, but rather a risk factor for the syndrome abnormalities...
and it has yet to be demonstrated that it is a risk factor for later cardiovascular disease or for diabetes as there are few prospective studies that have measured insulin resistance by a validated method.

At the request of the American Association of Clinical Endocrinologists, in October 2001 the Centre for Disease Control created the code number 277.7 for the dysmetabolic syndrome X in the International Classification of Diseases (ICD-9). This code was recommended to be noted if a physician considered that the syndrome was present in a given individual. However, a report from the United States indicates that the code is little used [1].

1. History of the syndrome

In 1988 Gerald Reaven presented the Banting Lecture at the American Diabetes Association meeting. The title of his lecture was “The Role of Insulin Resistance in Human Disease”, and the corresponding article was published in the same year [2]. He gave pathophysiological arguments for the existence of a “syndrome X”, in which he included insulin resistance, hyperinsulinaemia, hyperglycaemia, dyslipidaemia, arterial hypertension. Several years later, during the Claude Bernard Lecture of the European Society for the Study of Diabetes (EASD), Reaven included central adiposity in the syndrome, and noted the importance of free fatty acids [3]. While Reaven’s description was based on the pathophysiology of insulin resistance, the syndrome that he described was not precise and it was not possible to identify individuals as having the syndrome: the combination of abnormalities, the number of abnormalities, the thresholds defining the abnormalities were not given. The only abnormality Reaven quantified was insulin resistance, which he affirmed to be present in 25% of the adult population.

Reaven was not the first to propose such a syndrome. Kylin, in 1923, described the clustering of hypertension, hyperglycaemia and gout [4]. In France, Jean Vague, at the end of the 1940s, documented the association between central adiposity, diabetes, atherosclerosis and gout [5,6]. Later, in 1967, Avogaro et al. described a metabolic syndrome [7] and in 1985 Michaela Modan proposed that hyperinsulinaemia was the link between hypertension, obesity and glucose intolerance [8].

Following the description of the syndrome by Reaven, it has become a major theme of research and of public health interest. The number of publications on the subject is ample evidence of the importance given to the syndrome by clinicians and researchers (over 18,000 citations to the “metabolic syndrome” in PubMed, December 2006 – with more than 3000 citations in 2006 alone).

2. Arguments for the existence of a syndrome

The fact that this cluster of abnormalities exists has been well validated by epidemiological studies: the abnormalities cluster more frequently than what would be observed if they clustered by chance [9].

3. Definitions of the metabolic syndrome

In the absence of a diagnostic test, a number of definitions of the syndrome have been proposed (Appendix A). They come from the World Health Organisation (WHO) [10], the European Group for the study of Insulin Resistance (EGIR) [11], J-P Després’ group [12], the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) [13]. In 2003, the American Association of Clinical Endocrinologists and the American College of Endocrinologists provided a position statement of what they entitled the “insulin resistance syndrome” [14], but they did not give a precise definition, leaving it to a clinician to decide whether a given individual had the syndrome. They recognised that there was no experimental evidence to define diagnostic criteria for the syndrome and consequently their definition could not be precise. They conclude, that the more abnormalities, the more likely that an individual is insulin resistant.

These various definitions include different factors and different thresholds for them. For example the first definition, from the WHO, included microalbuminuria, which does not appear in the later definitions [10]. The EGIR definition [11] did not include diabetic patients, for two reasons – these patients should already be in the health care system, and have their health monitored so identification of the syndrome should not be necessary, and secondly, long standing diabetic patients have lower insulin levels, which do not reflect the level of insulin resistance, a key element of this definition. Finally the simple definition of the “hypertriglycerceridemic waist” was originally defined only for men, and it has not generally been used as a definition of the syndrome.

The most recent definitions, both in 2005, are from the International Diabetes Federation (IDF) [15,16] and from the American Heart Association/National Heart, Lung, and Blood Institute AHA/NHLBI [17,18].

The differences between these definitions are essentially the thresholds for the parameters to define a syndrome abnormality, the number of abnormalities before the syndrome is deemed to be present, and whether there is a compulsory abnormality, which is required to be present.

Reavens’ arguments were centred around insulin resistance, and the definitions proposed by the WHO, EGIR and the IDF have taken this into account – WHO because the presence of either insulin resistance or glucose dysregulation were required, EGIR because hyperinsulinaemia was a mandatory factor and for the IDF central obesity (as quantified by the waist circumference) is mandatory, because of the close association between insulin resistance and central adiposity.

The IDF definition, with its differing thresholds for waist circumference according to ethnic group, is likely to become the international norm, as it is supported by several international bodies, however, the more recent American definition will probably be used in the United States.

To define any diagnostic criteria is not easy (for diabetes, the criteria have changed over the years). For a syndrome it is even more complicated – what parameters, what thresholds,
what combinations should be used to define it? In fact a score to evaluate the severity of the syndrome, using a combination of continuous variables would be more logical than a syndrome defined with arbitrary thresholds.

4. Frequency of the syndrome and of its abnormalities

The frequency of the syndrome differs according to the definition, country, sex, age, and even according to the region in France. From the French MONICA study, the frequency of the NCEP-ATP III defined syndrome, in men aged 35–65 years was 26% in Lille, 22% in Strasbourg and 16% in Toulouse; in women, the corresponding frequencies were 26%, 24% and 13% [19]. (The definition used included subjects treated by drugs for hypertension and/or for diabetes). In comparison, in the French D.E.S.I.R. Study, of men and women aged 30–64 years, the corresponding frequencies were 9% and 6% and if treatment for diabetes and for hypertension were also included, the frequencies increased to 15% and 10%, respectively [20].

Table 1 shows the means and standard deviations of syndrome parameters from a general French population, recruited in Preventive Health Examination Centres in the central western part of France. More details of the reference values, and centiles are given in the online version (Appendix B). These data are for subjects aged 20–74 years, and are given by 5-year age classes and by sex; they are from a sample of 130 882 consultants at IRSA (an Institute which provides health screening examinations which are financed by the French social security system). In the tables, the column on the right gives the reference values in a population of 19,126 men and 19,874 women with the same age structure as the French population in the 1999 census, for subjects aged between 20 and 74 years.

In this French population, the frequency of the NCEP-ATP III defined syndrome was 10% in the men and 9% in the women, for the IDF definition 21% and 17% and for the AHA/NHLBI definition 18% and 14%, respectively (Table 2).

Note that central adiposity is more common in women than in men – because of the choice of the thresholds (Table 2). The NCEP thresholds for the waist circumference > 102/88 for men/women were defined because of their relation with obesity, a BMI ≥ 30 kg/m² and/or a high waist–hip ratio > 0.95/0.80 men/women [21], and not in relation with the diseases associated with the syndrome, diabetes and cardiovascular disease. The IDF waist thresholds were chosen for the sensitivity/specificity to screen for a BMI ≥ 25 kg/m² [21].

Hypo HDL-cholesterolaemia was also defined according to sex, and is more frequent in women than in men.

It has already been noted that in the French DESIR study [20], high arterial blood pressure is more commonly present than in the United States, where the NCEP-ATP III definition was conceived: in men 67 versus 38% and in women 44 versus 29%. Such differences have been documented in a collaborative study where the prevalence’s of hypertension were 28% in North American countries in comparison to 44% in Europe [22].

For the IDF definition of the metabolic syndrome, in comparison with the NCEP-ATP III definition, the definitions of all abnormalities are changed, with an increase in frequency for each abnormality, in comparison with the NCEP-ATP III definition (Table 2). The result is a doubling of the syndrome frequency. The most marked increases in frequency are associated with the waist circumference and fasting glucose (Table 2) where the thresholds have been lowered. For high blood pressure and dyslipidaemia, the changes in frequency are due only to the inclusion of the corresponding treatments – little change for high blood pressure, and a close to doubling for both lipid abnormalities; it must be noted that all lipid treatments were included in this analysis, as there was no information as to whether the lipid-lowering therapy was prescribed for treatment of LDL-cholesterol or for triglycerides/HDL-cholesterol.

The AHA/NHLBI definition is similar to the NCEP-ATP III, with the major difference being the lowering of the glucose threshold, and in consequence a more than three-fold increase in hyperglycaemia.

5. Consequences of the syndrome

Reaven described the consequences of the syndrome as cardiovascular disease and diabetes [2].

A meta-analysis of prospective studies quantified the risks of all cause mortality, of morbidity or mortality from cardiovascular diseases and of diabetes from the metabolic syndrome as defined by NCEP-ATP III [23]. The relative risks were estimated as: 1.3 (95% CI: 0.9–1.8), 1.6 (1.3–2.0) and 3.0 (1.9–4.6), respectively. These are certainly dependent on the subjects in the study, and if diabetic subjects are included, the risk associated with cardiovascular disease is higher than when they are excluded [24].

There are a number of more recent analyses, one from the Framingham Offspring Cohort showed age-adjusted relative risks for CVD, CHD and type 2 diabetes of 2.9, 2.5 and 6.9 for men, and 2.2, 1.5 and 6.9 for women [25]. In France the D.E.S.I.R. study has shown that the syndrome is predictive of both cardiovascular events and diabetes [26], and in the PRIME study of men from France and northern Ireland, the IDF defined syndrome carried a relative risk for coronary heart disease of 1.41, the WHO 1.40 and the NCEP 1.46 [27].

While these relative risks may be statistically significant, a risk equation for cardiovascular morbidity or mortality, for example the Framingham or the SCORE risk equations [28, 29], are better predictors [30]. However, in the European DECODE study, in men at low risk, with an estimated 10-year risk of cardiovascular mortality under 5%, the metabolic syndrome had a relative risk of cardiovascular mortality of 2.5 (1.2–5.0) [31,32]. Thus the syndrome provides additional predictive information on CVD risk, over and above that given by a CVD risk score, and involved 9% of the men. Of the men at high CVD risk (more than 5% over 10 years, and involving 41% of the men), the syndrome was present in only one third...
Table 1
Means and standard deviations (S.D.), according to age, of parameters included in the metabolic syndrome in a population of 130 882 consultants, 65 372 men and 65 510 women, in 2002–2004 at the “Institut inter Régional de la Santé”, (IRSA) an Institute in central-western France which provides health examinations. The last column shows the reference values for a population aged 20–74 years with the same age structure as the French population in the 1999 census. More complete information with the distribution of the percentiles is available in the online version (Appendix B)

<table>
<thead>
<tr>
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Table 2
Frequency of the metabolic syndrome abnormalities and frequency of the syndrome defined according to the NCEP-ATP III, the IDF and the AHA/NHLBI definitions, in a sample of consultants from IRSFA (French Health Examination Centres) in 2002–2004. These men and women, aged 20–74 years, had the same age structure as the French population in the 1999 census

<table>
<thead>
<tr>
<th>NCEP-ATP III defined metabolic syndrome</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference &gt; 102/88 cm</td>
<td>12%</td>
<td>20%</td>
</tr>
<tr>
<td>Fasting glucose ≥ 1.10 g/l</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Blood pressure ≥ 130/85 mmHg</td>
<td>66%</td>
<td>43%</td>
</tr>
<tr>
<td>Triglycerides ≥ 1.50 g/l</td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td>HDL-cholesterol &lt; 0.40/0.50 g/l</td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td>NCEP-ATP III syndrome present</td>
<td>10%</td>
<td>9%</td>
</tr>
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<table>
<thead>
<tr>
<th>IDF defined metabolic syndrome</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference ≥ 94/80 cm</td>
<td>33%</td>
<td>40%</td>
</tr>
<tr>
<td>Fasting glucose ≥ 1.00 g/l or previously diagnosed type 2 diabetes</td>
<td>35%</td>
<td>18%</td>
</tr>
<tr>
<td>Raised blood pressure:</td>
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</tr>
<tr>
<td>SBP ≥ 130 or DBP ≥ 85 mmHg or treatment of previously diagnosed hypertension</td>
<td>67%</td>
<td>44%</td>
</tr>
<tr>
<td>Raised triglycerides ≥ 1.5 g/l or a specific treatment for this lipid abnormalitya</td>
<td>23%</td>
<td>14%</td>
</tr>
<tr>
<td>Reduced HDL-cholesterol &lt; 0.4/0.5 g/l</td>
<td>18%</td>
<td>24%</td>
</tr>
<tr>
<td>(men/women) or a specific treatment for this lipid abnormalityb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDF syndrome presentb</td>
<td>21%</td>
<td>17%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AHA/NHLBI defined metabolic syndrome</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference ≥ 102/88 cm</td>
<td>14%</td>
<td>22%</td>
</tr>
<tr>
<td>Fasting glucose ≥ 1.00 g/l or previously diagnosed type 2 diabetes</td>
<td>35%</td>
<td>18%</td>
</tr>
<tr>
<td>Raised blood pressure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP ≥ 130 or DBP ≥ 85 mmHg or drug treatment for hypertension</td>
<td>67%</td>
<td>44%</td>
</tr>
<tr>
<td>Raised triglycerides ≥ 1.5 g/l or drug treatment for elevated triglycerides</td>
<td>23%</td>
<td>14%</td>
</tr>
<tr>
<td>Reduced HDL-cholesterol &lt; 0.4/0.5 g/l (men/women) or drug treatment for reduced HDL cholesterol</td>
<td>18%</td>
<td>24%</td>
</tr>
<tr>
<td>AHA/NHLBI syndrome presentb</td>
<td>18%</td>
<td>14%</td>
</tr>
</tbody>
</table>

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

of them. The hazards ratios of men at high risk of CVD, whether they had the syndrome or not, and those at low risk with the syndrome, were very similar: 2.5, 2.2 and 2.5, respectively, after adjustment for age and the recruitment centre. For women there were fewer cardiovascular events, there was no relation, and the relative risk was 1.3 (0.4–4.2). However, the waist alone, with the NCEP-ATP III thresholds, was associated with higher cardiovascular mortality: 2.2 (1.1–4.8) in men and 2.3 (0.8–6.7) in women, after adjustment for age and recruitment centre, and these two risks were not significantly different.

The metabolic syndrome carries a much higher risk for diabetes than for CVD. To predict incident diabetes, the traditional risk markers of diabetes, such as glucose concentrations perform better than the metabolic syndrome [30,33]. But in the Framingham Offspring Study [25], while high fasting glucose carried a hazards ratio of 12.5 (9.1–17.3) for high glucose alone, the syndrome had a hazards ratio of 11.0 (8.1–14.9), and the hazards ratio was still high, 5.0 (3.7–6.8) if the syndrome was present, but the glucose level low < 6.1 mmol/l.

Other consequences of the syndrome are hypertension, polycystic ovary syndrome, non-alcoholic steatosis and chronic renal disease.

6. Treatment of the syndrome

As the syndrome does not have a known cause, the cause is not able to be treated.

To delay the appearance of the syndrome or its manifestations, insulin sensitivity could be targeted, by lifestyle modification – loss of weight, increase in physical activity, a healthy diet or by pharmacological intervention. There are several medications which target insulin sensitivity (thiazolidinediones, metformin... and others which help in weight loss (orlistat, sibutramine, rimonabant). In the future, there will be more evidence to elucidate whether these treatments are effective in delaying the appearance of the metabolic syndrome and in the patients with the syndrome, in preventing CVD and diabetes.

To treat the abnormalities of the metabolic syndrome, the first step is lifestyle modification and modest weight may be effective [34]. Drug treatment should be used for the specific abnormalities according to current guidelines, and a more aggressive approach may be appropriate when more than one abnormality is present.

7. Statement from the European Association for the Study of Diabetes and the American Diabetes Association, 2005

This joint statement gave a "critical appraisal" of the metabolic syndrome [35]. It concluded: "Until much-needed research is completed, clinicians should evaluate and treat all CVD risk factors without regard to whether a patient meets the criteria for diagnosis of the "metabolic syndrome". The review aimed to argue four points, which are given below along with our responses, given in italics:

- “the metabolic syndrome is not nearly as well defined and characterized as is often assumed”
  RESPONSE: The syndrome is certainly not well defined, and it was Reaven who was initially (perhaps deliberately) vague with his description of the syndrome [2]. The multiplicity of definitions for the syndrome has resulted in confusion and has led to a lack of credibility for the concept as a whole.

- “the notion that it is a useful marker of CVD risk above and beyond the risk associated with its individual components is uncertain”
  RESPONSE: That the individual components of the syndrome may carry a similar or even higher risk than the syndrome has been illustrated in the DECODE study [32]; these analyses also show that men at lower estimated risk of cardiovascular death (< 5% in 10 years according to the
SCORE risk equations), who have the syndrome, are at high risk of fatal CVD, of equivalent risk to those at higher risk of CVD death, according to the European CVD SCORE equation. Thus, the syndrome – or at least the components in the syndrome that are not included in a classical CVD risk score (waist circumference in particular) – identifies a group of men at risk. This was not the case in the women, but waist circumference was a good marker of fatal CVD risk, in the women at low risk (< 5% in 10 year). While CVD risk scores appear to be more closely related with CVD outcomes than the syndrome [30], they are rarely used in clinical practice. The syndrome is an easy concept enabling a physician to identify patients at risk, with routinely available measures. The thresholds of the various parameters enable a quick categorisation of patients, with a large waist circumference being a clear first step, which should prompt the search for the cluster of metabolic abnormalities. If age, sex and smoking are taken into account along with the syndrome abnormalities, the cardiovascular risk can be assessed. An evaluation needs to be made of the severity of the various abnormalities, and each one may not carry the same importance. Further, the promotion of the concept of the metabolic syndrome has drawn attention to the fact that patients diagnosed with diabetes, hypertension or lipids, should be investigated for other abnormalities in the metabolic syndrome cluster.

- “although certain CVD risk factors undoubtedly occur together more often than expected, the underlying pathophysiology of the syndrome is unclear”

RESPONSE: The clustering of the CVD risk factors, the syndrome abnormalities cannot be disputed – and research is needed to elucidate the reasons for this clustering. Given current knowledge, drug treatment can only be factor by factor, with appropriate care to choose the treatments, which do not aggravate the other abnormalities. Research will provide more information, and may also provide new molecules to treat the syndrome as a cluster, rather than treating the individual abnormalities. In the meantime, the outcome is treated, without consideration of the physiology, which has led to the condition. Treatment should target insulin sensitivity: increase in physical activity and weight loss, and possibly some drugs in the future.

- “the list of risk factors comprising the cluster is not grounded by well-defined criteria”

They then state that “the manuscript is a cautionary reminder to practitioners, and an urgent call for further research.”

RESPONSE: The abnormalities proposed for the definitions of the syndrome have been chosen following Reaven [2], and other components have been added or proposed because of their close correlation with insulin concentrations or insulin resistance indexes. As argued above, the choice of the components, their thresholds or the number of them required for the syndrome is all rather arbitrary. Each of the syndrome parameters has a continuous relation with cardiovascular disease incidence, thus it is difficult to define a threshold on this basis. The combination of abnormalities is also difficult to justify, as is the inclusion of other possible related abnormalities.

8. Other arguments pro- and con- for the syndrome

In a similar vein, a recent article by Reaven is entitled “The Metabolic Syndrome: Requiescat in Pace” [36]. His arguments are targeted on insulin resistance and its relation with clinically significant disease with the aim of understanding the pathophysiology. Insulin resistance can exist without metabolic clustering. However, Reaven does argue that there is a benefit in diagnosing a syndrome to initiate lifestyle changes, but that the use of a precise definition, given the arbitrary nature of the thresholds, may not be appropriate. The diagnosis of diabetes relies on somewhat arbitrary, consensual thresholds, and has long proved its usefulness.

Greenland poses the clinical question as to whether patient outcome is improved by identification of the syndrome – rather than by a classical global CVD risk score [37].

The American Heart Association, in particular Grundy et al. [17,18,38], and Eckel et al. [39], have argued both in scientific journals and in internet newsletters about the utility of the syndrome and provided guidelines for its management.

9. Conclusion

While awaiting further knowledge on the causes of the abnormalities of the metabolic syndrome and of the metabolic syndrome itself, the metabolic syndrome should be recognized as an entity, which deserves attention from the medical profession and public health authorities. The metabolic syndrome provides an early, simple and cheap warning of patients at risk of cardiovascular disease and diabetes, and emphasizes the need to treat more aggressively those with multiple abnormalities, even though individually these abnormalities may be slight. While there is no clinical trial evidence for the efficacy of such an approach, it is in line, for example, with recommendations for the more aggressive treatment of lipids and hypertension in diabetic patients. In all the cases, the first-line treatment consists of lifestyle modification. Drug treatments should be used according to current recommendations for each individual risk factor. Additional research is needed to identify new targets for treatments to prevent cardiovascular disease, in particular other lipid goals, such as increasing HDL-cholesterol levels once the LDL-cholesterol goal is achieved.

In clinical practice either the NCEP-ATP III or the IDF or the AHA/NHBLI definitions of the syndrome could be used: the fact that the thresholds and the combinations of abnormalities might be arbitrary does not prevent the use of the concept. For epidemiological studies, it would be preferable to report frequencies and outcomes for all three definitions. The AHA/NHBLI definition, which retains the higher thresholds values for waist circumference is likely, to be adopted in the United States [17,18]. Certainly, the recognition of a high waist cir-
cumference as a first abnormality, as in the IDF definition of the syndrome, will enable a quick screening of subjects at risk for cardiovascular disease and for diabetes.

Acknowledgements

The data and the analyses determining the reference values of the parameters of the metabolic syndrome components and the syndrome itself, have been provided by J. Tichet and S. Vol from the Institut inter Régional pour la Santé (IRSA, France).

Appendix A

A.1. Definitions of the syndrome

WHO definition of the metabolic syndrome, 1999 [10].
Glucose intolerance, IGT or diabetes mellitus and/or insulin resistance together with two or more of the other components listed below:

- impaired glucose regulation or diabetes;
- insulin resistance (under hyperinsulinaemic, euglycaemic conditions, glucose uptake below lowest quartile for background population under investigation);
- raised arterial pressure ≥140/90 mmHg;
- raised plasma triglycerides (≥1.7 mmol/l (1.5 g/l) and/or low HDL-cholesterol (<0.9 mmol/l (0.35 g/l) men; <1.0 mmol/l (0.39 g/l) women);
- central obesity: (men: waist to hip ratio > 0.90; women: waist to hip ratio > 0.85 and/or BMI > 30 kg/m²);
- microalbuminuria (urinary albumin excretion rate ≥20 µg/min or albumin:creatinine ratio ≥30 mg/g).

Defined only for non-diabetic subjects.
Insulin-resistance (defined by hyperinsulinaemia - above the third quartile of the fasting insulin concentration in non-diabetic subjects, sexes and all ages combined) plus two abnormalities among:

- central obesity: waist circumference ≥94/80 cm (men/women);
- dyslipidaemia: high triglycerides: ≥2.0 mmol/l (1.8 g/l) and/or low HDL-cholesterol: <1.0 mmol/l (0.40 g/l) or treatment for dyslipidaemia;
- hyperglycaemia: fasting plasma glucose ≥6.1 mmol/l (1.1 g/l), but < 7.0 mmol/l (1.26 g/l);
- hypertension: systolic/diastolic ≥140 and/or 90 mmHg or treatment for hypertension.

Desprès’ Group, the hypertriglyceridemic waist, 2000 [12].
Defined only for men, both abnormalities:

- waist ≥90 cm;
- triglycerides ≥2.0 mmol/l (1.75 g/l).

NCEP-ATP III definition of the metabolic syndrome, 2001 [13].
Three or more of the following risk factors:

- abdominal obesity: waist circumference >102/88 cm (men/women);
- triglycerides ≥1.50 g/l (1.69 mmol/l);
- HDL-cholesterol <0.40/0.50 g/l (1.04/1.29 mmol/l) (men/women);
- blood pressure ≥130/85 mmHg;
- fasting glucose ≥1.10 g/l (6.1 mmol/l).

American Association of Clinical Endocrinology, American College of Endocrinology (ACE) [14],
ACE Position Statement on the insulin resistance syndrome*, 2002:

- abnormalities of the insulin resistance syndrome;
- triglycerides ≥1.50 g/l (1.7 mmol/l);
- HDL-cholesterol <0.40/0.50 g/l (1.04/1.29 mmol/l) (men/women);
- blood pressure >130/85 mmHg;
- glucose: fasting 1.10–1.25 g/l (6.1–6.9 mmol/l), 2 h post-glucose challenge 1.40–2.00 g/l (7.8–11.1 mmol/l).

*The diagnosis of the insulin resistance syndrome must be based on the professional opinion of the physician.

International Diabetes Federation (IDF) [15,16]. Consensus worldwide definition of the metabolic syndrome, 2005, plus any two of the following four factors:

- raised triglycerides level: ≥1.50 g/l (1.7 mmol/l) or a specific treatment for this lipid abnormality (given as >1.50 g per day in [15]);
- reduced HDL-cholesterol: <0.40/0.50 g/l (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 mm Hg or treatment of previously diagnosed hypertension;
- raised fasting plasma glucose ≥1.00 g/l (5.6 mmol/l) or previously diagnosed type 2 diabetes.

*Central obesity waist circumference – ethnic specific. Europids ≥94/80 cm (men/women) (In the USA, the ATP III (102 male, 88 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 South Asians recommendations.
Sub-Saharan Africans: use Europid recommendations.
Eastern Mediterranean and Middle East (Arab): use Europid recommendations.
American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) diagnostic criteria for Metabolic Syndrome 2005 [17,18].

Three or more of the following risk factors:

- elevated waist circumference: $\geq 102/88$ cm (men/women);
- elevated triglycerides $\geq 1.50$ g/l (1.7 mmol/l) or drug treatment for elevated triglycerides;
- reduced HDL-cholesterol $< 0.40/0.50$ g/l (1.03/1.30 mmol/l) (men/women) or drug treatment for reduced HDL-cholesterol;
- elevated blood pressure $\geq 130$ or $\geq 85$ mmHg or drug treatment for hypertension;
- elevated-fasting glucose $\geq 1.00$ g/l (5.6 mmol/l) or drug treatment for elevated glucose.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://www.sciencedirect.com, doi:10.1016/j.diabet.2007.08.001.

References