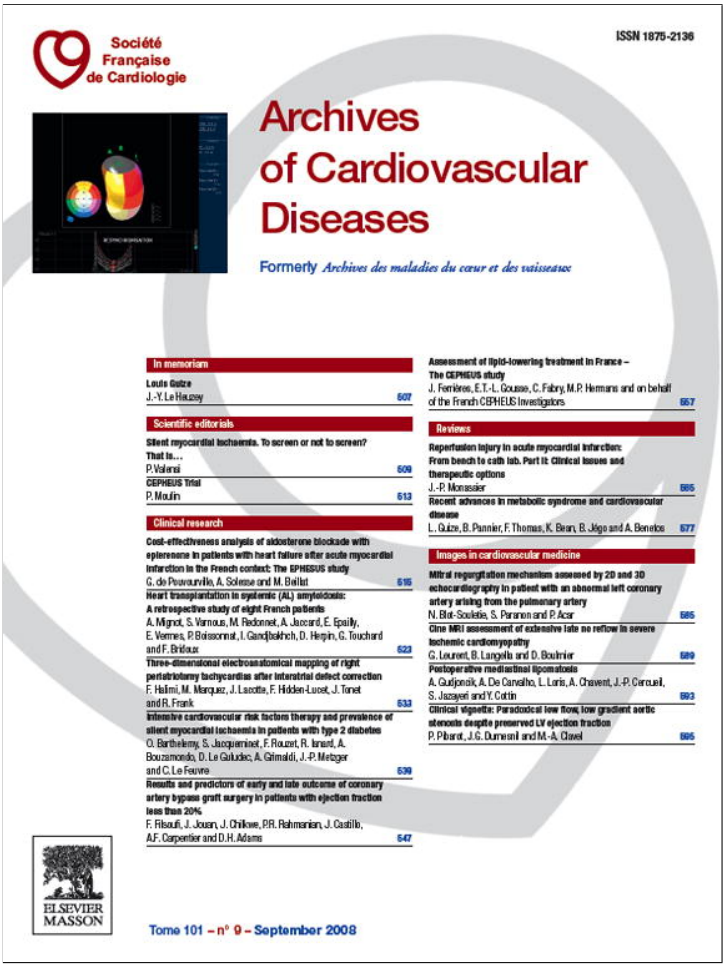

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REVIEW

Recent advances in metabolic syndrome and cardiovascular disease

Syndrome métabolique et maladies cardiovasculaires. Actualités

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Summary Metabolic syndrome is defined as an association of central obesity and several other cardiometabolic risk factors. Dysfunctional visceral adipose tissue and inflammatory status appear to be involved in its genesis. New definitions have decreased the threshold for glycaemia and one has lowered the threshold for waist circumference, leading to an increase in the prevalence of metabolic syndrome. However, the impact on mortality with these new definitions is lower than with the National Cholesterol Education Program—Adult Treatment Panel III 2001 definition. An increase in waist circumference, along with increased glycaemia, triglycerides and/or blood pressure is more highly associated with an increased risk of mortality than are other associations, while a decrease in high density lipoprotein cholesterol increases risk of coronary heart disease. The risk of sudden death and stroke is particularly notable with metabolic syndrome. Metabolic syndrome is associated with an increase in heart rate, pulse pressure, arterial stiffness and left ventricular hypertrophy, impairment of diastolic function, enlargement of the left atrium and atrial fibrillation. In the 2007 European recommendations for the management of high blood pressure, metabolic syndrome is now taken into consideration for both risk stratification and in selecting the optimal therapeutic strategy for arterial hypertension.

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MOTS CLÉS
Syndrome métabolique ;
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Résumé Le syndrome métabolique (SM) associe une obésité centrale et une constellation de plusieurs facteurs de risque cardiométaboliques. Les élévations du *plasminogen activator inhibitor-1* et de l'aldostérone paraissent jouer un rôle clé dans son développement. Les nouvelles définitions, ayant abaissé le seuil du glucose et l'une d'elles ayant abaissé les seuils du périmètre abdominal tout en exigeant ce critère, ont pour conséquence une prévalence accrue du SM, mais un impact sur la morbimortalité cardiovasculaire et totale moins élevé qu'avec la définition du National Cholesterol Education Program 2001. Le risque de mort subite est particulièrement marqué. L'augmentation du périmètre abdominal, associé à l'élévation du glucose, des triglycérides et/ou de la pression artérielle, comporte un risque de mortalité plus élevé que les autres associations des composants du SM ; la baisse du HDL-cholestérol accentue le risque coronaire. Le SM est associé à une augmentation de la fréquence cardiaque, de la pression artérielle pulsée, de la rigidité artérielle, une hypertrophie et une altération de la fonction diastolique ventriculaire gauche, une dilatation de l'oreillette gauche et une incidence accrue de fibrillation atriale. Le SM est pris en compte dans les recommandations européennes 2007 concernant la stratification du risque et la stratégie thérapeutique de l'hypertension artérielle.

Background

The main physiological processes underlying metabolic syndrome are insulin resistance [1,2] and inflammation [3—5]; lipotoxicity also appears to be a major component [6]. Metabolic syndrome associates abdominal obesity [7] and several metabolic factors with elevated blood pressure levels. It is associated with an increase in cardiovascular disease (CVD) and death, and in diabetes [8—10]. However, numerous debates have been generated over the disparity in the definitions used to describe metabolic syndrome and its lack of homogeneity, which may ultimately question the reality of this syndrome. The impact on morbidity and mortality of metabolic syndrome as a whole, of its individual components, and the limits chosen for each [11] remain important points of discussion.

After the widely used National Cholesterol Education Program—Adult Treatment Panel III (NCEP—ATP III) definition in 2001 [12], two new definitions were established by experts in 2005, one by the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (AHA/NHLBI) [13] and the other by the International Diabetes Federation (IDF) [14]. Both of these definitions increased the threshold of several components of metabolic syndrome, including waist circumference for the IDF definition. In 2007, the international consensus of the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) summarized the definition of metabolic syndrome as a specific association of three of the components found in each of the three previous definitions [15].

Numerous studies focus on the prevalence of metabolic syndrome and its components and on the morbimortality risks associated with it. Certain pathologies, associated with metabolic syndrome, have also been discovered recently and European recommendations pertaining to blood pressure (BP) management have been updated to take into account metabolic syndrome.

New definitions of metabolic syndrome

The AHA/NHLBI 2005 [13] definition is derived from the NCEP—ATP III 2001 definition [12] and requires at least three of the following criteria to be present:

- waist circumference greater than or equal to 102 cm in men and greater or equal to 88 cm in women (W);
- triglycerides greater than or equal to 1.50 g/L or a specific treatment for elevated triglycerides (TG);
- high density lipoprotein (HDL) cholesterol less than 0.40 g/L in men and less than 0.50 g/L in women or a specific treatment for reduced HDL cholesterol;
- systolic BP greater than or equal to 130 mmHg or diastolic BP greater than or equal to 85 mmHg or antihypertensive treatment (BP);
- fasting glucose greater than or equal to 1.00 g/L or drug treatment for elevated glucose (G).

The changes that were made in 2005 to the NCEP—ATP III 2001 definition slightly reduced the threshold for waist circumference (it had been strictly greater than 102 cm in men and greater than 88 cm in women) but significantly lowered the threshold for glucose (it had been greater than or equal to 1.10 g/L). Furthermore, individuals treated for dyslipidaemia, hypertension or hyperglycaemia were included. Consequently, based on this new definition, the number of subjects and, therefore, the prevalence of metabolic syndrome increased.

The IDF definition [14] requires the presence of abdominal obesity, defined as waist circumference greater than or equal to 94 cm in men and greater than or equal to 80 cm in women for Europids (W) and at least two of the following criteria:

- triglycerides greater than or equal to 1.50 g/L or a specific treatment for lipid abnormalities (TG);
- HDL cholesterol less than 0.40 g/L in men and less than 0.50 g/L in women or a specific treatment for lipid abnormalities (HDL);

- systolic BP greater than or equal to 130 mmHg or diastolic BP greater than or equal to 85 mmHg or antihypertensive treatment (BP);
- fasting glucose greater than or equal to 1.00 g/L or diabetes (G).

The IDF definition introduces fundamental changes in the requirements needed for defining metabolic syndrome; it significantly reduces the threshold for waist circumference and glucose and includes treated individuals and those with diabetes.

The definition from the ESC/ESH consensus [15] requires at least three of the following five criteria to be present:

- waist circumference greater than 102 cm in men and greater than 88 cm in women (W);
- systolic BP greater than or equal to 130 mmHg or diastolic BP greater than or equal to 85 mmHg (BP);
- HDL cholesterol less than 0.40 g/L in men and less than 0.46 g/L in women (HDL);
- triglycerides greater than or equal to 1.50 g/L (TG);
- fasting glucose greater than or equal to 1.0 g/L (G).

The ESC/ESH definition includes a combination of criteria from the NCEP–ATP III 2001 definition (i.e., abdominal obesity, BP and TG) and new thresholds for HDL cholesterol in women and for glycaemia since it does not include treatment for hypoglycaemia or diabetes. The lack of epidemiological data available for this definition is most likely to be attributed to the fact that it was published only recently.

Concerns and criticisms pertaining to the lack of homogeneity among these definitions remain. Lowering the thresholds for several of the components and the inclusion of treated subjects require further studies to determine the impact of these components on morbidity and mortality risk for subjects identified as having metabolic syndrome according to these new definitions.

Prevalence of metabolic syndrome and its components according to recent definitions

Differences in the prevalence of metabolic syndrome according to recent definitions are reported in numerous publications [16–28]. For instance, in the Investigations préventives et cliniques (IPC, Paris) cohort [29–31], which included 39,998 men (52.6 ± 8.3 years) and 20,756 women (54.7 ± 9.2 years) who volunteered for a free health check-up and who had no personal history of CVD, the more recent definitions were associated with a higher prevalence of metabolic syndrome. With the AHA/NHLBI definition, the prevalence was 20.0% in men and 13.5% in women; with the IDF definition, the prevalence was 26.0% in men and 18.4% in women; and with the NCEP–ATP III 2001 definition, the prevalence was 11.7% in men and 7.5% in women [29]. In other studies, the prevalence varied from 8 to 37% with the NCEP–ATP III 2001 definition, from 26 to 45% with the AHA/NHLBI definition, and from 18 to 57% with the IDF definition [16–28,32,33]. The prevalence of metabolic syndrome often increases by approximately 50% when the IDF definition is used compared with the NCEP–ATP III 2001 definition. The AHA/NHLBI definition provides an intermediate value. Lorenzo et al. compared the prevalence of metabolic syndrome in different populations and showed that the impact of the different definitions on prevalence varied depending on the population characteristics [21]. There is no doubt that this complicates the interpretation of results found in the numerous studies that have examined metabolic syndrome. Several studies have continued to use the NCEP–ATP III 2001 definition because it has been validated the most.

Subjects classified as having metabolic syndrome using the NCEP–ATP III 2001 definition, especially in France, were included based on BP values for which the thresholds were relatively low [29–33]. This underlines the importance of the role played by this particular parameter in the risk associated with metabolic syndrome [34]. The thresholds for high BP have not been modified in the recent definitions, unlike blood glucose, which has been lowered, treated subjects have been included, and waist circumference which is a required component for the IDF definition and which includes lower thresholds for Europids. To validate these definitions, they must be compared using robust criteria, such as all-cause and cardiovascular mortality. In the IPC population, Benetos et al., very recently, suggested that the two new definitions (AHA/NHLBI and IDF), although they increase the prevalence of metabolic syndrome, they do not enable the identification of new subjects at risk when compared with the NCEP–ATP III 2001 definition [35]. Further studies are needed to clarify this important point.

Even though it is possible for metabolic syndrome to include five different components, the recent definitions only require three of the five to be present. This leads to a significant disparity among subjects who have been diagnosed with metabolic syndrome and creates confusion. For example, in the IPC population, the percentage of subjects who were included based on the different three-component combinations varied from 6.0 to 55.5% depending on the combinations and definitions used [29]. According to the NCEP–ATP III 2001 definition, only 2.4% of the subjects had four of the metabolic syndrome components and 0.5% had all five [29,30]. These observations clearly show the lack of homogeneity among patients diagnosed with metabolic syndrome.

Cardiovascular morbidity and mortality associated with metabolic syndrome according to recent definitions

Using previous definitions, morbidity associated with metabolic syndrome has been clearly established [8–10], resulting in an increase in incidence of cardiovascular disease, coronary disease and cerebrovascular disease [9]. These definitions have also had an impact on ischaemic strokes, particularly in women, and have shown a higher mortality rate in women than in men [10,36,37]. The impact of the newer definitions is, however, not quite as clear. Morbimortality related to metabolic syndrome is systematically lower when the newer definitions are used compared to the NCEP–ATP III 2001 definition [18–20,24–29].

In the IPC population, the risk of all-cause mortality was lower when the new definitions were used; this was

especially true with the IDF definition, but remained significant nonetheless. Compared to subjects without metabolic syndrome (those with fewer than three criteria) and after adjustment for age, sex, tobacco consumption, low-density lipoprotein cholesterol, declared physical activity and socioeconomic status, mortality risk associated with the presence of metabolic syndrome was higher with the NCEP–ATP III 2001 definition (hazard ratio [HR]: 1.79; 95% confidence interval [CI]: 1.35–2.38) than with the AHA/NHLBI (HR: 1.46; 95% CI: 1.14–1.88) or IDF (HR: 1.32; 95% CI: 1.04–1.67) definitions [29]. Corresponding values reported by Katzmarzyk et al. were 1.36 (1.14–1.62), 1.31 (1.11–1.54) and 1.26 (1.07–1.49), respectively [19]. In the IPC population, the risk of all-cause mortality was 1.44 (1.11–1.87) when the ESC/ESH definition was used [29]. Similar findings were reported for normotensive and hypertensive patients [38].

Katzmarzyk et al. reported higher HRs for cardiovascular mortality: 1.79 (95% CI: 1.35–2.37), 1.67 (1.27–2.19) and 1.67 (1.27–2.20) for the NCEP–ATP III 2001, AHA/NHLBI, and IDF definitions, respectively [19]. In the diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe (DECODE) study, the observed hazard ratios were 1.74 (95% CI: 1.31–2.30), 1.72 (1.31–2.26) and 1.51 (1.15–1.99), respectively, in men and 1.39 (0.89–2.18), 1.09 (0.70–1.69) and 1.53 (0.99–2.36), respectively, in women [20]. In the IPC study, risk of cardiovascular mortality was 2.05 (95% CI: 1.28–3.28) for the NCEP definition and 1.77 (95% CI 1.18–2.64) for the IDF definition [35]. Occasionally, the IDF definition does not predict coronary heart disease risk, even though with the NCEP–ATP III 2001 definition this risk is significant [24,27].

Results from the Paris Prospective Study I recently showed an increased risk of sudden death related to metabolic syndrome in a population of 6678 men. When the NCEP–ATP III 2001 definition was used, the risk of sudden death increased by 68% (95% CI: 1.05–2.70), whereas the risk of non-sudden death only increased by 38% (95% CI: 0.95–2.01). When the IDF definition was used, the hazard ratios were 2.02 (1.30–3.14) and 1.69 (1.20–2.38), respectively [39].

Cardiovascular morbidity and mortality according to different combinations of metabolic-syndrome components

Several studies have suggested that the impact of certain combinations of metabolic syndrome components are more deleterious than others, such as abdominal obesity and elevated TGs [40–42]. In the Framingham study, however, Wilson et al. [43] did not find any significant difference in cardiovascular morbimortality risk between the various combinations of metabolic syndrome components. Wang et al. found that certain components by themselves were as predictive of cardiovascular disease as was metabolic syndrome itself [44].

Several recent studies have revealed some very interesting information [29,45,46]. Protopsaltis et al. [45] showed that among diabetic subjects without known coronary heart disease (CHD), the combination of metabolic syndrome components consisting of diabetes plus hypertension plus low HDL cholesterol was associated with an increased risk of coronary events. Hong et al. [46] found three metabolic syndrome component combinations that led to the highest risk of CHD:

- increased BP and increased glycaemia combined with lower HDL cholesterol;
- an increase in BP, glycaemia and TGs;
- increased BP and TGs associated with lower HDL cholesterol.

In the IPC population, we found that the most deleterious associations pertaining to all-cause mortality risk were, regardless of definition used, elevated waist circumference, glycaemia and triglycerides and/or BP [29]. Our findings clearly show that an accumulation of metabolic syndrome components is related to an increase in mortality risk. For example, when compared to subjects with no components of metabolic syndrome, the hazard ratio increased from 1.37 (NS) in the presence of elevated BP alone to 3.10 when BP and glycaemia were associated, to 3.95 when elevated waist circumference was included, and to 4.65 when elevated BP, glycaemia, waist circumference and TGs were associated (NCEP–ATP III definition) [34]. These observations are similar to those made by Andreadis et al. with regard to hypertensive subjects [47]. Liu et al. showed that, among subjects with either high blood glucose levels or with diabetes, an increase in risk of CVD was strongly related to the coexistence of multiple cardiometabolic disorders [48]. Kadota et al. found that glucose intolerance played an important role in CVD mortality and that the combination of certain factors was deleterious, even without the presence of obesity [49]. Lastly, Mozzafarian et al. suggested that metabolic syndrome itself is of less importance than elevated BP or elevated glycaemia in assessing the overall or cardiovascular prognosis in patients with metabolic syndrome who are over 65 years of age [50].

Other cardiovascular pathologies associated with metabolic syndrome

Several recent studies have examined the relationships between BP, pulse pressure, arterial stiffness and metabolic syndrome [30,50–57]. The rise in pulse pressure, observed in the presence of metabolic syndrome [30,52], increases CHD mortality in women and may well be a new metabolic-syndrome component. In untreated hypertensive subjects, the presence of metabolic syndrome leads to an increase in aortic stiffness, as determined by pulse-wave velocity, independently of age and systolic BP [55], confirming the works of Schillaci et al. [54]. In Japanese patients with metabolic syndrome, arterial stiffness was not associated with the number of coronary artery lesions [56].

Left ventricular hypertrophy increases in the presence of metabolic syndrome, independently of hypertension [58–62]. Alterations in left ventricular diastolic function appear prematurely and are independent of ventricular mass [60,61]. There is an increased risk of cardiovascular events and mortality in the presence of left-ventricular hypertrophy and metabolic syndrome, primarily, due to BP and glycaemia [61,62].

There is a greater prevalence of subclinical CVD, arterial and renal disease among subjects with metabolic syndrome and this association increases the risk of developing underlying CVD illnesses.

Metabolic syndrome is associated with risk of atrial fibrillation [63,64]. In the IPC population [29—31], metabolic syndrome is more frequent among subjects with atrial fibrillation than among those without and, even more so, among women than among men: 34.2% versus 7.7% in women, 19.3% versus 10.9% in men. Metabolic syndrome is a risk factor for atrial fibrillation as shown in a large prospective observational study [65]. In addition to the metabolic syndrome components known to increase the incidence of atrial fibrillation (hypertension, obesity, hyperglycaemia), other factors, such as an increase in pulse pressure [66], hypertrophy and alterations in left ventricular diastolic function, atrial dilation [58,64] and sleep apnoea [67,68] may also be contributing factors.

Various elements, resulting from cardiac abnormalities associated with stimulating the sympathetic nervous system [69], as noted by an increase in heart rate [29,30], could explain the increase in incidence of sudden death [39].

Two biomarkers, plasminogen activator inhibitor-1 (PAI-1), a fibrinolysis inhibitor, and aldosterone play a role in the development of metabolic syndrome [70]. PAI-1 is expressed largely in visceral adipose tissue rather than in subcutaneous adipose tissue and is inducible by different factors, more or less implicated in the components of metabolic syndrome [71]. Elevated levels of PAI-1 are significantly associated with a progressive increase in glucose, systolic BP and triglycerides. Elevated-aldosterone levels are significantly associated with increased BP and lower HDL cholesterol [70].

New European recommendations for BP management

The data pertaining to the risk associated with metabolic syndrome were taken into account for the new European recommendations for the management of BP [15]. In these new recommendations, metabolic syndrome is included in the risk stratification in the same manner as is the presence of three or more of the more traditional risk factors (age, tobacco, dyslipidaemia, heredity) and subclinical target organ disease (cardiac, arterial, renal) and is at the same level of importance as the presence of diabetes. Bitherapy is recommended as first-line antihypertensive treatment for high risk hypertensive subjects, but the use of beta blockers, especially with a thiazide diuretic is not advised in patients with metabolic syndrome.

Conclusions

Metabolic syndrome, with all its diverse definitions, both old and new, remains heterogeneous as a whole. The clinical- and subclinical-cardiovascular consequences of this syndrome are numerous and its impact on cardiovascular morbidity and mortality has been confirmed. It is, however, important to specify the combinations of the most deleterious components of metabolic syndrome, which vary depending on the population and the definition used and which can be very useful in clinical practice.

Conflicts of interest

None.

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