Module 24.1

Diagnostic criteria for Metabolic Syndrome

Learning Objectives:

- Study the diagnostic criteria for Metabolic Syndrome;
- Define the components of Metabolic Syndrome;
- Know the prevalence of Metabolic Syndrome;
- Determine the cardiovascular and diabetes risk associated with Metabolic Syndrome;
- Compare the Metabolic Syndrome with other scales for cardiovascular risk.

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1. Definition of the Metabolic Syndrome
2. Diagnostic criteria for the Metabolic Syndrome
3. Components of the Metabolic Syndrome
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   - 3.2. Dyslipidaemia
   - 3.3. Hypertension
   - 3.4. Glucose Intolerance
   - 3.5. Proinflammatory State
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   - 3.7. Other manifestations
4. Prevalence of the Metabolic Syndrome
5. Metabolic Syndrome and Cardiovascular and Diabetes Risk
6. Comparison of the MS with other risk-prediction algorithms
7. Summary
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Key Messages:

- The Metabolic Syndrome is a clustering of metabolic alterations including central obesity, hypertension, dyslipidaemia and hyperglycaemia
- The Metabolic Syndrome carries increased risk of diabetes and long-term cardiovascular disease
- Short-term cardiovascular risk is better predicted by other means
1. Definition of the Metabolic Syndrome

The Metabolic Syndrome (MS) is a clustering of metabolic alterations including central obesity, hypertension, dyslipidaemia and hyperglycaemia that increase the risk of cardiovascular disease (CVD) and diabetes (1). The concept of the MS has existed for at least 80 years (2). In the 1920s two Austrian physicians (Karl Hitzenberger and Martin Richter-Quittner) and the Spaniard Gregorio Marañón observed the relationship between blood pressure and diabetes mellitus in some of their patients. At about the same time, Kylin described the hypertension-hyperglycaemia-hyperuricaemia syndrome. In 1947, Vague drew attention to upper body adiposity as the obesity phenotype that was commonly associated with metabolic abnormalities in patients with type 2 diabetes and CVD. In 1988, Reaven described “Syndrome X”. He formed the hypothesis that insulin resistance is the common aetiological factor for a group of disorders, consisting of impaired glucose tolerance, hyperinsulinaemia, dyslipidaemia and hypertension. The MS has also been referred to as the insulin resistance syndrome.

2. Diagnostic criteria for the Metabolic Syndrome

Various diagnostic criteria have been proposed by different organizations over the past decade. The first official definition of the MS was established by a working group of the WHO in 1998 (3). It identified MS as the presence of insulin resistance (IR) plus 2 of the following criteria (obesity, hypertriglyceridaemia, low levels of HDL-cholesterol, hypertension and increased urinary albumin excretion) (Table 1).

Table 1. WHO criteria for the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Insulin resistance identified as one of the following:</th>
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<tbody>
<tr>
<td>Type 2 diabetes mellitus</td>
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<tr>
<td>Impaired fasting glucose</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
</tr>
<tr>
<td>If FG &lt; 110 mg/dl (6.1 mmol/l), hyperinsulinaemic, euglycaemic clamp-uptake in lowest 25%</td>
</tr>
</tbody>
</table>

Plus 2 of the following:
- BMI > 30 kg/m² or waist-to-hip ratio > 0.9 (male) or 0.85 (female)
- Triglycerides ≥ 150 mg/dl (1.7 mmol/l)
- HDL-cholesterol < 35 mg/dl (0.9 mmol/l) (male) or < 39 mg/dl (1 mmol/l) (female)
- Blood pressure ≥ 140/90 mmHg or medication
- Urinary albumin excretion ≥ 20 µg/min or albumin/creatinine ratio ≥ 30 mg/g (3.5 mg/mmol)

In 1999, the European Group for Study of Insulin Resistance (EGIR) suggested that a more appropriate term would be the insulin resistance syndrome and modified the criteria to require fasting hyperinsulinaemia plus 2 other factors using different cut-off points from those used by the WHO (Table 2)(4). The American Association of Clinical Endocrinologists (AACE) also recommended this term in a position statement, stressing that it places the individual at increased risk not only for type 2 DM and CVD, but also for other disease states associated with IR (polycystic ovary syndrome, non-alcoholic fatty liver disease, sleep apnoea and certain forms of cancer) (Table 3) (5).
Table 2. EGIR criteria for Insulin Resistance Syndrome

<table>
<thead>
<tr>
<th>Insulin resistance-hyperinsulinaemia: top 25% of fasting insulin values from non-diabetic population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus 2 or more of the following:</td>
</tr>
<tr>
<td>• Waist circumference ≥ 94 cm (male) or ≥ 80 cm (female) or BMI ≥ 30 kg/m²</td>
</tr>
<tr>
<td>• Fasting plasma glucose ≥ 110 mg/dl (6.1 mmol/l) and &lt; 126 mg/dl (6.9 mmol/l)</td>
</tr>
<tr>
<td>• Triglycerides ≥ 180 mg/dl (2 mmol/l) or HDL-cholesterol ≤ 40 mg/dl (1 mmol/l)</td>
</tr>
<tr>
<td>• Blood pressure ≥ 140/90 mmHg or medication</td>
</tr>
</tbody>
</table>

Table 3. AACE criteria for Insulin Resistance Syndrome

| Triglycerides ≥ 150 mg/dl (1.7 mmol/l) |
| HDL-cholesterol < 40 mg/dl (1 mmol/l) (male) or < 50 mg/dl (1.3 mmol/l) (female) |
| Blood pressure ≥ 130/85 mmHg or medication |
| 2h post OGTT-glycaemia > 140 mg/dl (7.7 mmol/l) and < 200 mg/dl (11.1 mmol/l) |

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) simplified the definition to make it more user-friendly for practitioners (6). The ATP III required any 3 of 5 risk factors: abnormal waist circumference, high triglyceride level, low HDL cholesterol level, high blood pressure, and high fasting plasma glucose concentration (Table 4). These criteria were updated in 2005 to correspond with the new American Diabetes Association (ADA) standard of a normal fasting glucose level of less than 100 mg/dl (<5.6 mmol/L)(7).

Table 4. ATP-III criteria for the Metabolic Syndrome

| Three or more of the following: |
| Abdominal obesity: waist circumference > 102 cm (male) or 88 cm (female) |
| Triglycerides ≥ 150 mg/dl (1.7 mmol/l) |
| HDL-cholesterol < 40 mg/dl (1 mmol/l) (male) or < 50 mg/dl (1.3 mmol/l) (female) |
| Blood pressure ≥ 130/85 mmHg or medication |
| Fasting plasma glucose ≥ 110 mg/dl (6.1 mmol/l) |

Although these classifications agree in the essential components of the syndrome (hyperglycaemia, obesity, hypertension and dyslipidaemia), they differ in some criteria and in the cut-off points. The WHO and EGIR definitions consider that IR and/or glucose intolerance is essential for the syndrome, in contrast to the ATP-III that considers it as just one criterion. Also, while people with DM are excluded in the EGIR and AACE classifications, they may be included in the others.

To unify the different classifications, the International Diabetes Federation (IDF) established a new definition of MS that includes central obesity as a necessary criterion, and creating for the first time cut-off points to define central obesity in different ethnic groups (Table 5) (8).

Table 5. IDF criteria for the Metabolic Syndrome

| Central obesity (WC > 94 cm for Europid men and > 80 cm for Europid women) |
| Plus any 2 of the following: |
| Triglycerides ≥ 150 mg/dl (1.7 mmol/l) or medication |
| HDL-cholesterol < 40 mg/dl (1 mmol/l) (male) or < 50 mg/dl (1.3 mmol/l) (female) |
| Systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or medication |
| Fasting plasma glucose ≥ 100 mg/dl (5.6 mmol/l)* or previously diagnosed type 2 diabetes |
*If above 100 mg/dl, OGTT is strongly recommended but is not necessary to define the syndrome.

In 2009, the IDF, the American Heart Association (AHA) and the National Heart Lung and Blood Institute reached a consensus on criteria for the MS (Table 6) that uses different cut-off points for waist circumference according to the ethnic group (Table 7) and considers the burden of all criteria equally to define the syndrome (9).

Table 6. Consensus criteria for the Metabolic Syndrome: IDF-AHA/NHLBI

<table>
<thead>
<tr>
<th>Any 3 of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference: population- and country-specific definitions</td>
</tr>
<tr>
<td>Blood pressure: Systolic ≥ 130 and/or diastolic ≥ 85 mmHg or drug treatment</td>
</tr>
<tr>
<td>Fasting glucose: ≥ 100 mg/dl (5.6 mmol/l) or drug treatment</td>
</tr>
<tr>
<td>Triglycerides: ≥ 150 mg/dl (1.7 mmol/l) or drug treatment</td>
</tr>
<tr>
<td>HDL-cholesterol: &lt; 40 mg/dl (1 mmol/l) (male) or &lt; 50 mg/dl (1.3 mmol/l) (female) or drug treatment</td>
</tr>
</tbody>
</table>

Table 7. Recommended waist circumference thresholds for abdominal obesity by organization

<table>
<thead>
<tr>
<th>Population</th>
<th>Organization</th>
<th>WC (men)</th>
<th>WC (women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europid</td>
<td>IDF</td>
<td>≥ 94 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Caucasian</td>
<td>WHO</td>
<td>≥ 94 cm*</td>
<td>≥ 80 cm*</td>
</tr>
<tr>
<td>United States</td>
<td>AHA/NHLBI (ATP III)*</td>
<td>≥ 102 cm</td>
<td>≥ 88 cm**</td>
</tr>
<tr>
<td>Canada</td>
<td>Health Canada</td>
<td>≥ 102 cm</td>
<td>≥ 88 cm</td>
</tr>
<tr>
<td>European</td>
<td>European CV Societies</td>
<td>≥ 102 cm</td>
<td>≥ 88 cm</td>
</tr>
<tr>
<td>Asian (including Japanese)</td>
<td>IDF</td>
<td>≥ 90 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Asian</td>
<td>WHO</td>
<td>≥ 90 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Japanese</td>
<td>Japanese Obesity Society</td>
<td>≥ 85 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>China</td>
<td>Cooperative Task Force</td>
<td>≥ 85 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Middle East, Mediterranean</td>
<td>IDF</td>
<td>≥ 94 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Sub-Saharan African</td>
<td>IDF</td>
<td>≥ 94 cm</td>
<td>≥ 80 cm</td>
</tr>
<tr>
<td>Ethnic Central and South American</td>
<td>IDF</td>
<td>≥ 90 cm</td>
<td>≥ 80 cm</td>
</tr>
</tbody>
</table>

*Increased risk, **still higher risk.

*Recent AHA/NHLBI guidelines for MS recognize an increased risk for CVD and DM at WC thresholds of ≥ 94 cm in men and ≥ 80 cm in women and identify these as optional cut-points for individuals or populations with increased risk.

Although the definition of MS in children and adolescents is outside the scope of this work, the criteria used in paediatric studies have been variably adapted from adult standards. A multidisciplinary American group has prepared an excellent review of this topic (10).
3. Components of the Metabolic Syndrome

The main aetiological factors of the MS are IR and central obesity. The ATP-III classification considers six components of the MS (Fig. 1). Each one of them is related to an increased risk for CVD (11). However, the ATP III criteria do not provide a sensitive approach to identification of insulin-resistant individuals (sensitivity 46%, specificity 93%, positive predictive value 76%). The individual components vary both in terms of their utility in making a diagnosis of the metabolic syndrome and in their relationship to IR, with the obesity and lipid criteria being most useful (12).

![Components of the Metabolic Syndrome](image)

**Figure 1. Components of the Metabolic Syndrome**

3.1. Central or Abdominal Obesity

Increased adiposity is related to unfavourable levels of other CVD risk factors. A BMI greater than 25 kg/m² increases the risk of CVD events. Overweight and obesity are associated with IR. However, abdominal obesity (measured with the waist circumference or the waist to hip ratio) is more strongly associated with the metabolic risk factors than the body mass index (BMI). With increases in intra-abdominal or visceral adipose tissue, a higher rate of flux of adipose tissue-derived free fatty acids (FFA) to the liver through the splanchnic circulation would be expected, whereas increases in abdominal subcutaneous fat would release lipolysis products into the systemic circulation and avoid more direct effects on hepatic metabolism (e.g., glucose production, lipid synthesis, and secretion of prothrombotic proteins such as fibrinogen and plasminogen activator inhibitor-1) (Figure 2) (13).

3.2. Dyslipidaemia

The atherogenic dyslipidaemia of the MS is characterized by hypertriglyceridaemia and low levels of HDL-cholesterol (13). There are also other alterations in the lipoproteins: an increase in the remnant particles, in apo-B lipoproteins, and the presence of small dense LDL particles.
In the setting of IR, the increase in FFA flux to the liver produces an increase in the production of apo-B-containing triglyceride-rich, very low-density lipoproteins (VLDL) (Figure 2). In addition, IR could also reduce the concentrations of lipoprotein lipase (LPL) in peripheral tissues (i.e., in adipose tissue more than muscle). This alteration in LPL, however, seems to contribute less to the hypertriglyceridaemia than does the overproduction of VLDL.

The reduction in HDL-cholesterol is a consequence of changes in HDL composition and metabolism. In the setting of hypertriglyceridaemia the HDL particles lose cholesterol and gain triglycerides, making the particle smaller and denser. This change in lipoprotein composition results in an increased clearance of HDL from the circulation.

The composition of LDL is also modified in a similar way, appearing instead as small dense LDL particles that may be more atherogenic.

Lower HDL-cholesterol and higher triglyceride levels accompany greater adiposity during adulthood, but the variability of triglyceride determinations limit its importance as a predictor or precursor of CVD. The triglyceride effects have consistently been shown to be more highly related to cardiovascular outcomes in women than in men (11).

Figure 2. Pathophysiology of the Metabolic Syndrome

3.3. Hypertension

Hypertension has been the most controversial element of the IR syndrome, implying that other physiological processes are involved in its aetiopathogenesis. It is important to note that insulin is a vasodilator when given intravenously to people of normal weight, with secondary effects on sodium reabsorption in the kidney. In the setting of IR, the vasodilatory effect of insulin can be lost, but the renal effect on sodium reabsorption is preserved. Fatty acids themselves can mediate relative vasoconstriction. Insulin also increases the activity of the sympathetic nervous system (SNS), an effect that might also be preserved in the setting of IR (13).
On the other hand, obesity probably leads to hypertension through different mechanisms: increased vascular tone created by a reduced bioavailability of NO because of increased oxidative stress, increased asymmetric dimethylarginine concentrations, increased sympathetic tone, and increased expression of angiotensinogen by adipose tissue leading to an activation of the renin-angiotensin system (14).

3.4. Glucose Intolerance

Glucose levels have been related to the development of CVD in population settings. The majority of the studies have included information from fasting blood glucose levels, but data from oral glucose tolerance testing have shown that post-challenge glucose levels provide additional information which may be helpful in the prediction of CVD. In men aged 35-64 years with type 2 DM, the risk for most CVD events is at least double that for non-diabetic men, and diabetic women are at even higher risk (threelfold risk compared to non-diabetics) (11). Therefore, due to the CVD risk that diabetes carries itself, some authors consider that it is probably nonsense for patients with type-2 diabetes to know if they fulfill the criteria of the MS, considering that these patients should be excluded of the MS definitions.

The defects in insulin action in glucose metabolism include deficiencies in the ability of the hormone to suppress glucose production by the liver and kidney, and to mediate glucose uptake and metabolism in insulin sensitive tissues (i.e., particularly muscle and adipose tissue). To compensate for defects in insulin action, insulin secretion increases, with the development of hyperinsulinaemia. On the other hand, insulin resistance is also present in pancreatic beta cells, implying that the signals that generate glucose-dependent insulin secretion have been adversely modified, and fatty acids are the prime candidates for this (lipotoxicity). Clinically these abnormalities are manifested across different stages: impaired fasting glucose, impaired glucose tolerance and type 2 diabetes (13).

3.5. Pro-inflammatory State

The association of the MS with inflammation is well documented and is clinically characterized by high levels of C-reactive protein (CRP). The level of CRP is an independent predictor of new CVD events (13). In a recent study 18 loci associated with CRP levels were identified in a genome-wide association analysis (15).

The adipocyte produces inflammatory cytokines (e.g. TNF-alpha, IL-6) that stimulates the synthesis of CRP in the liver. There is evidence that the macrophages that reside in the adipose tissue might also be responsible for the secretion of these cytokines both locally and into the systemic circulation. Also, the levels of adiponectin (a hormone secreted by the adipocyte that improves insulin sensitivity and which has antiinflammatory effects) are decreased in patients with the MS.

3.6. Prothrombotic State

Patients with the MS have a prothrombotic state characterized by high levels of plasminogen activator inhibitor-1 (PAI-1) and fibrinogen. The last of these is an acute-phase protein, whose hepatic synthesis is stimulated by the proinflammatory cytokines (13).

3.7. Other Manifestations

Patients with the MS are more susceptible to several diseases, such as polycystic ovarian disease, hyperuricaemia, obstructive sleep apnoea, and non-alcoholic fatty liver disease (NAFLD), amongst others (13). The spectrum of NAFLD ranges from asymptomatic steatosis through to non-alcoholic steatohepatitis (NASH) and cirrhosis. Up to 20% of patients with NASH may develop
cirrhosis. Hepatic steatosis occurs when FFAs, released in the setting of IR and MS, are taken up by the liver. Additional biochemical insults, including oxidative stress, up-regulation of inflammatory mediators, and dysregulated apoptosis, can combine to result in inflammation (producing NASH) and cirrhosis (16).

4. Prevalence of the Metabolic Syndrome

The prevalence of the MS is increasing rapidly throughout the world, in parallel with the increasing prevalence of diabetes and obesity, thus to be considered as a major public health problem. The prevalence of the MS varies from 4% to 84% depending on the criteria employed to define it, as well as on other parameters such as age, sex, study populations, and ethnic differences (17). Recently, Cameron and others have published a detailed review about the prevalence of the syndrome in different countries (18) (Fig. 3).

![Prevalence of Metabolic Syndrome in different countries](image)

**Figure 3.** Prevalence of Metabolic Syndrome

Despite differences in the design of these studies, certain inferences can be made. For example, there is wide variation in prevalence in both sexes. In those studies that include people 20-25 years and older, the prevalence varies in urban populations from 8% (India) to 24% (USA) in men, and from 7% (France) to 43% (Iran) in women. An interesting example of the effect of ethnic origin on the MS is a comparison of the prevalence of the syndrome in the USA with lower prevalence in non-Hispanic white people compared with Mexican Americans, and in African American men compared with non-Hispanic white and Mexican American men.

A very consistent finding is that the prevalence of the MS is highly age-dependent. In the NAHNES III the prevalence of MS in USA was around 23%; it increased from 7% in participants aged 20-29 years to 44% and 42% for those aged 60-69 years and at least 70 years, respectively (19). In that survey the prevalence of the MS in the 12-19 years
age-group was 4.2% with ATP-III criteria modified for adolescents. The overall prevalence of the metabolic syndrome in non-diabetic adult Europeans is 15% (20).

5. Metabolic Syndrome and Cardiovascular and Diabetes Risk

The main objective of a diagnosis of the MS is to identify people with increased cardiovascular and diabetes risk in order to implement modifications in their lifestyle. In a recent systematic review and meta-analysis including 87 studies with 951,083 patients with MS according to ATP-III 2001 (63 studies) and ATP-III 2005 criteria (33 studies), the MS was associated with an increased risk of CVD (RR 2.35; 95% CI 2.02-2.73), CVD mortality (RR 2.40; CI 95% 1.87-3.08), all-cause mortality (RR 1.58; 95% CI 1.39-1.78), myocardial infarction (RR 1.99; 95% CI 1.61-2.46), and stroke (RR 2.27; 95% CI 1.80-2.85) (21). This means that the MS is associated with a 2-fold increase in adverse cardiovascular outcome and a 1.5-fold increase in all-cause mortality. MS was associated with higher cardiovascular risk in women relative to men. After synthesizing the results of studies conducted in patients without type 2 DM, the MS remained associated with a high cardiovascular risk, ranging from RR 1.62 (95% CI 1.31-2.01) for myocardial infarction, to RR 1.86 (95% CI 1.10-3.17) for stroke. The risk for all-cause mortality in patients without type 2 DM was however accompanied by a wide and inconclusive confidence interval as it was reported by only 2 studies (RR 1.32; 95% CI 0.65-2.67).

In another systematic review that used the ATP-III 2001 definition of the MS, the RR of developing diabetes was 2.99 (95% CI 1.96-4.57) (22). Based on these data it seems that the MS is a better predictor of diabetes than of cardiovascular disease.

Recent studies have added evidence about the risk associated with MS in regard to the new classifications of the syndrome, and to the MS in the elderly. In a large population study in France in middle-aged people without previous CVD, the use of the IDF and the ATP-III 2005 definitions dramatically increased the prevalence of MS from 10% according to the ATP-III 2001 definition to > 21% according to the IDF definition and > 16% according to the ATP-III 2005. However, the subjects identified as having MS using the 2 recent definitions, but not the original ATP-III definition, were not at higher risk for all-cause and CVD mortality (23).

In two prospective studies, Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) and the British Regional Heart Study (BRHS), the MS and its components were associated with type 2 DM but have weak or no association with vascular risk in elderly populations (24). However, in the Three-City Study the MS was associated with a 50% increased risk for all-cause mortality in the elderly (25). Also in this study, the MS and several of its components had a negative impact on global cognitive decline and specific cognitive function in older persons (26).

We need studies to investigate whether or not the prognostic significance of the MS exceeds the risk associated with the sum of its individual components. In the INTERHEART study (n= 26,903 subjects) the risk of myocardial infarction conferred by MS was significantly higher than that of low HDL cholesterol or abdominal obesity evaluated singly, but virtually the same as the risk conferred by diabetes or hypertension alone (27).

In conclusion, the MS increases CVD outcomes 2-fold, all-cause mortality 1.5-fold, and triples diabetes risk. The risk associated with the earlier definitions of the syndrome (mostly ATP-III 2001) was higher than with the more recent ones. In the elderly, the MS carries an increased risk of diabetes which is proportionately higher than the risk of CVD. We need more studies to determine if the risk associated with the MS is higher than the risk of the sum of its components.

6. Comparison of the MS with risk-prediction algorithms

The MS carries increased long-term risk both for CVD and diabetes. Importantly, the MS is not a reliable tool for global risk assessment for CVD in the short term (i.e., 10-year risk) (28). The MS may however increase the short-term cardiovascular risk in people.
with intermediate risk (29). The explanation for this apparent paradox could be that it does not include all risk factors contained in standard risk-prediction algorithms (e.g., age, gender, total cholesterol, cigarette smoking). Thus, 10-year risk assessment is better carried out with algorithms such as Framingham Risk Score, the SCORE, and the PROCAM scales.

The Framingham Risk Score (FRS) estimates the risk of coronary heart disease (30). It was developed in a community sample of white subjects drawn from a suburb west of Boston. It includes the gender, age, levels of LDL-cholesterol or total cholesterol, HDL-cholesterol, blood pressure, diabetes, and smoking status. In general, people are classified as low, intermediate or high risk if their 10-year CHD risk is < 10%, 10-20%, and > 20%, respectively.

The SCORE (Systematic Coronary Risk Evaluation) risk estimation system offers direct estimation of total fatal cardiovascular risk (31). It was developed according to the European Society of Cardiology and the Second Joint Task Force as a risk estimation system based on a large pool of representative European data sets that would capture the regional variation in risk. This scale includes gender, age, smoking status, total cholesterol or total cholesterol: HDL-cholesterol ratio, and systolic blood pressure.

The PROCAM (Prospective Cardiovascular Münster) scoring scheme estimates the risk of acute coronary events in men (32). It was developed in Münster and includes age, LDL-cholesterol levels, HDL-cholesterol, triglycerides, smoking status, diabetes, family history of myocardial infarction and systolic blood pressure.

The NCEP (ATP-III) risk assessment tool uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death) in adults aged 20 years and older who do not have heart disease or diabetes. This tool includes age, gender, total cholesterol, HDL cholesterol, smoking status and systolic blood pressure/ hypertension treatment. The calculator can be downloaded from www.nhlbi.nih.gov/guidelines/cholesterol.

Individuals with type 2 diabetes have a 2- to 4-fold higher risk of developing CVD than persons without diabetes, and their risk is comparable with people with previous cardiovascular events. Nevertheless, the ADA has recognized that absolute risk for CVD varies among individuals with diabetes and has recommended the use of designed models and algorithms to estimate risk, especially in younger patients (< 40 years). For people with type 2 DM, the FRS is inaccurate, and several algorithms and models have been designed specifically for the assessment of cardiovascular risk in this population, including the DECODE equation, the UKPDS risk engine and the DPHD (33).

The DECODE (Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe) equation provides a score that predicts fatal cardiovascular risk. It takes into account the fasting plasma glucose and/or the glucose tolerance state. However it does not include important cardiovascular risk factors such as HDL cholesterol, triglyceride levels or an index of abdominal adiposity (34).

The United Kingdom Prospective Diabetes Study group has developed mathematical models for the estimation of 10-year risk of non-fatal and fatal CHD (UKPDS 56) and stroke (UKPDS 60) in men and women with newly diagnosed type 2 diabetes (35, 36). It includes age, sex, ethnicity, total cholesterol, HDL cholesterol, systolic blood pressure, smoking status, duration of DM and levels of glycated haemoglobin.

The DPHD (Diabetes Personal Health Decisions) was developed by the ADA as a cardiometabolic risk calculator based on the Archimedes model (37). It incorporates age, race, sex, weight, family history, smoking status, physical activity and medications, in addition to fasting blood glucose (glycated haemoglobin if DM), serum lipids and blood pressure. It estimates the current risk of developing DM, CVD, and foot and eye complications or the effects of treatment after developing DM or CVD.

At least three attempts have been made to compare the predictive ability for cardiovascular disease of the MS with the FRS (22). In two of them, the MS was not found to improve the risk prediction beyond that achieved by the FRS. In addition, the Diabetes Prediction Model was found to be superior to the MS in predicting risk for diabetes (22).
Therefore, attempts to use the presence of the MS as a risk assessment tool to estimate short-term (< 10-year) risk is a clear misuse of the diagnosis. Instead, its presence identifies a person with relatively high long-term risk, and thus calls for intensified lifestyle therapy. At the same time, if the patient with the MS has a high-risk condition, such as CVD or diabetes, drug therapies will be required to supplement lifestyle therapies for the purpose of reducing risk. Drug therapies also may be required if persons without these conditions are found to be at higher risk by FRS.

7. Summary

The metabolic syndrome is a clustering of metabolic abnormalities including central obesity, hypertension, dyslipidaemia and hyperglycaemia that increase the risk of CVD and diabetes. IR and central adiposity are important factors in the aetiology of the syndrome. The prevalence of the syndrome is increasing alongside the worldwide increase in the incidence of obesity and DM. There have been important advances in defining the criteria for the syndrome over the last decade among different Medical Associations, although some of them still maintain doubts on the existence and the value of the syndrome (38-41). The MS is a better predictor of DM than CVD. It increases long-term cardiovascular risk, but short-term risk is better estimated by other scales (FRS, SCORE, PROCAM). In people with diabetes, the CVD risk is better estimated by specific scales (DEC0DE equation, UKPDS risk engine, DPHD).

8. References