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Review paper

Diagnostic criteria for metabolic syndrome: A historical overview

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Abstract

Introduction: Although attempts to establish a definition of metabolic syndrome (MS) intensified two decades ago, research into diseases co-occurring with MS was initiated as early as in the 17th century. The breakthrough came in 1988 with a study by Gerald M. Reaven, which combined so far unrelated conditions into X syndrome. In the 20th and 21st century, research focused on providing a definition applicable in clinical practice.

Aim: The following overview summarizes the history of MS, from early descriptions to the most recent attempts at defining it.

Material and methods: The literature was searched in PubMed, Scopus, and Google Scholar databases focusing on history of research on MS, criteria of diagnosis.

Results and discussion: Since 1998, while the concept of MS was accepted, the definition has evolved. Since the European Group for the Study of Insulin Resistance definition was announced, the essential components of diagnosing MS have not changed, they have only been specified to include a greater part of the population. It seems that MS is not only a pathophysiological term, but also a practical-clinical one. When diagnosed, it involves further medical treatment.

Conclusions: (1) The definition of MS has evolved, becoming simplified so that it can be used in clinical practice. (2) Main components of diagnosing MS have been specified to include a greater part of the population. (3) It seems that MS is not only a pathophysiological term, but also a practical-clinical one. (4) The construct of MS definition has inherent limitations which impact on its clinical usefulness. (5) The current definition might be subject to more modifications following new research studies.

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1. INTRODUCTION

Metabolic syndrome (MS) is broadly defined as co-occurrence of abdominal obesity, insulin resistance, disorders of carbohydrate and lipid metabolism, hypertension, increased levels of inflammation markers, excess production of cytokines and adipokines, as well as endothelial dysfunction.[1,2] Co-occurrence of these disorders considerably increases the risk of atherosclerosis, diabetes mellitus type 2 (DM2) and cardiovascular complications.[3–5]

Since 1988, when Reaven publicized his suggestion the insulin resistance played a role in syndrome X pathogenesis, the criteria to diagnose MS have undergone a number of modifications. In the light of a number of studies confirming the co-occurrence of MS and cardiovascular complications, it was attempted to create a uniform and clinically useful definition of the syndrome in order to differentiate patients with an increased risk of cardiovascular events and to include them in the primary or secondary prevention.[6–8]

A major criticism levelled at the MS has been that multiple competing definitions are at best confusing, and at worst represent a syndrome which nobody knows how to define. Just as the prevalence of component conditions such as obesity, hypertension, hyperglycelmia, and dyslipidemia is dependent on the definition, so is the prevalence of the syndrome as a whole. Many studies compare prevalences of MS using different criteria so that it shows the need for a standarised international definition. After agreement on definition of MS it is possible to compare the prevalence among population worldwide and its relationship with various health outcomes can be made.

2. AIM

The following overview summarizes the history of MS, from early descriptions to the most recent attempts at defining it.

3. MATERIAL AND METHODS

The literature was searched in PubMed, Scopus, and Google Scholar databases with no time limitation using metabolic syndrome, criteria, history in medical subject heading.

4. RESULTS AND DISCUSSION

4.1. First case studies

The first references to MS come from the ancient Egypt. Doctors there saw the reason behind 'stopping of the heart' in obesity and excessive energy supply. Detailed descriptions concerning MS can be found in the 17th and 18th centuries in contributions from doctors such as Nicolaes Tulp and Giovanni B. Morgagni.[9,10] The former presented a case of MS in *Observationes Medicae* in 1641. He enumerated such findings as: milky serum, obesity, excessive consumption of milk, while its consequences included blood coagulation disorders and sudden cardiac death. Morgagni, in turn, described a case of an obese man with insomnia (which was a symptom of obstructive sleep apnoea), headache (hypertension), peripheral oedema (cardiac insufficiency) and symptoms of biliary colic. The patient died most probably of a stroke. In the post-mortem examination the findings confirmed cholelithiasis and severe atherosclerotic lesions in arteries. The scholar postulated that vascular lesions were most probably related to excessive energy supply and they were the basis for the remaining diseases.

In the first half of the 20th century, MS patients became the focus of Eskil Kylin from Sweden and a Polish doctor Jakub Węgierko.[11,12] Kylin claimed that hypertension, hyperuricemia and hyperglycaemia, which often coexist, could be seen as a separate syndrome. A similar conviction can be attributed to Węgierko, who noticed co-occurrence of diabetes and hypertension, obesity, gout, cholelithiasis and vascular atherosclerosis. A French scientist Jean Vague described various types of obesity, and concluded that abdominal obesity was a factor which contributed more significantly to the development of atherosclerosis and diabetes than gynoid obesity.[13]

4.2. Year 1988 – syndrome X according to Reaven's definition

In 1988, Gerald M. Reaven published in *Diabetes* a study entitled 'Role of insulin resistance in human disease,' in which he determined the so called 'X syndrome.' It encompassed so far unrelated disorders: hypertension, disorders of carbohydrate metabolism (abnormal glucose tolerance) and lipid metabolism (increased VLDL concentration, low HDL-cholesterol concentration). He referred to insulin resistance as a possible cause of these disorders. Despite a number of studies into a correlation between insulin resistance and visceral obesity, Reaven did not enumerate abdominal obesity among the components of MS; he assumed that insulin resistance appeared also in people with normal body weight.[14] In a study from 2005, he emphasized that the syndrome was not differentiated for epidemiological reasons, but to draw the public's attention to an increased cardiovascular risk in seemingly healthy people.[15]

4.3. Year 1998 – World Health Organization

In 1998, for the first time in history the World Health Organization (WHO) adopted the term 'metabolic syndrome' and announced criteria of diagnosing it.[16] They included DM2, abnormal glucose tolerance or abnormal fasting glycaemia, as well as insulin resistance diagnosed directly in the hyperinsulinemic-euglycemic clamp technique. Additional criteria of the diagnosis included central obesity, dyslipidaemia, hypertension and microalbuminuria. This definition of MS focused on proving insulin resistance, including it in the diagnosis criteria. On the other hand, it required extending the set of biochemical tests to determine MS, which caused doubts as to its clinical usefulness. The WHO indicated that there was a higher risk of cardiovascu-

lar events in patients with MS than it was assumed on the basis of separate risk factors.

4.4. Year 1999 – European Group for the Study of Insulin Resistance

Another definition of MS was presented by the European Group for the Study of Insulin Resistance (EGIR) in 1999.[17] MS was called 'an insulin resistance syndrome,' and for it to be diagnosed, one of the following criteria had to be met: insulin resistance or hyperinsulinism (serum insulin level-more than 75 percentile). Additional criteria required for MS to be diagnosed in line with this definition included two out of four following criteria: abdominal obesity, dyslipidaemia, hypertension, fasting glycaemia of at least 110 mg/dL (≥ 6.1 mmol/L) or impaired glucose tolerance. This definition focused especially on insulin resistance, which lowered its clinical applicability. On the other hand, it resigned from the criterion of microalbuminuria, required to diagnose MS according to the WHO. At the same time, recognizing abdominal obesity on the basis of waist circumference was a more convenient approach, better correlating with the amount of visceral adipose tissue. Additionally, the HDL-cholesterol criterion was unified – which might be cause reservations in the light of current reports on differences in HDL-cholesterol concentration depending on the sex. What is more, among patients with glycaemia disorders there were no people with diagnosed diabetes, while insulin resistance plays a key role in DM2 pathogenesis and DM2 patients present also with other MS features.[18]

Both definitions did not become clinical standards because they required performing complicated tests to confirm insulin resistance.[19]

4.5. Year 2001 – National Cholesterol Education Program — Adult Treatment Panel III Program

In 2001, experts of the Third Report of the National Cholesterol Education Program – Adult Treatment Panel III (NCEP–ATP III) proposed another modification of the MS definition.[20] This definition differentiated five criteria of diagnosis, which were equally important, without emphasizing the most significant criterion: abdominal obesity as an increased waist circumference, hypertriglyceridemia, low HDL-cholesterol concentration, blood pressure of at least 130/85 mmHg, fasting glucose of at least 110 mg/dL (≥5.6 mmol/L). In order to diagnose MS, it was necessary to meet three out of five of the above criteria.

In order to diagnose MS in a simpler way the authors of this definition resigned from marking insulin resistance, because they believed that it was too complicated for clinical practice. Oral glucose tolerance test was no longer performed, as it was stated it was not a routine procedure, which could become an obstacle in recognizing MS in everyday clinical practice. In the commentary to the definition, it was, however, emphasized that MS was closely related to insulin resistance. It was the aim of the simplified definition of MS to foreground actively looking for people with an increased risk of cardiovascular diseases so that to implement preventative measures in these groups of patients as soon as possible. The authors of the NCEP-ATP III MS definition emphasized the role of abdominal obesity in insulin resistance, and the values of waist circumference which indicated abdominal obesity were repeated in line with the guidelines of the National Institute of Health for the USA population. This approach definitely limited the definition, since neglecting racial and ethnic differences in diagnosing abdominal obesity unnecessarily excluded people with a higher risk of cardiovascular diseases, e.g. Asian people.[21]

4.6. Year 2003 – American Association of Clinical Endocrinologists

In 2003, another MS definition was provided by experts of the American Association of Clinical Endocrinologists (AACE).[22] One more time the role of insulin resistance was reiterated. Criteria to be met to diagnose MS comprised abnormal glucose tolerance or fasting glycaemia. Additional criteria were: obesity or abdominal obesity (diagnosed on the basis of BMI), hyperglyceridaemia and/or low HDL-cholesterol concentration, increased systolic blood pressure or other risk factors, such as history of DM2 in the patient's family, polycystic ovary syndrome (PCOS), sedentary lifestyle, elderly age, belonging to an ethnic group with a high DM2 risk. In order to diagnose MS, both the basic and additional criteria had to be met. However, this definition was rather imprecise and left much space for clinical interpretation, additionally excluding patients with diabetes.

4.7. Year 2005 – International Diabetes Federation

Yet another definition originated in 2005, as a modification of the NCEP–ATP III definition, which is supported by clinicians.[23] It was authored by a group of experts of the International Diabetes Federation (IDF). The *sine qua non* condition to diagnose MS consisted here in abdominal obesity understood as an increased waist circumference. Values typical of other ethnic groups were also distinguished. Additional criteria comprised: hypertriglyceridemia, low HDL–cholesterol concentration, blood pressure of at least 130/85 mmHg, fasting hyperglycaemia or treatment for DM2. The IDF introduced abdominal obesity as a prerequiste of the diagnosis of MS, with particular emphasis on waist measurement as a simple screening tool. For MS to be diagnosed, the criterion of abdominal obesity and two out of four additional criteria were required to be met.

It was a considerable advantage of this definition that it took into account ethnic and racial differences in diagnosing abdominal obesity. It was also praiseworthy that the level of fasting glycaemia was lowered to be at least 100 mg/dL, a value recommended by the American Diabetes Association (ADA).[24]

NCEP–ATP III and AACE definitions met the need to diagnose MS in epidemiological studies, while the WHO and EGIR definitions were applicable mainly in scientific research. It was the IDF definition that corresponded to the needs of both scientists and clinicians.

4.8. Year 2005 – Amarican Heart Association and National Heart, Lung, and Blood Institute

Experts of the American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI) expanded the NCEP–ATP III definition to include another change in 2005, still not differentiating the leading criterion necessary to recognize MS. This definition suggested an adjustment of waist circumference to lower threshols only in some ethnic gropus, such as Asians and kept the factor of fasting glycaemia to be at least 100 mg/dL, unlike previously, when it was 110 mg/dL.[25]

4.9. Year 2009 – the International Diabetes Federation modification

The most recent change in the definition of MS was introduced in 2009 in the version provided by the IDF.[26] After a meeting of experts of a few organisations (IDF, AHA, WHO) it was established that all the criteria would remain equally important, and in order to diagnose MS it would be necessary to recognize three out of five on the following: abdominal obesity, hypertriglyceridemia, low HDL concentration, increased blood pressure, fasting hyperglycaemia or medication for DM2. The numerous race- and gender-specific waist circumference cutoffs has further confused the definition of MS. A correction of the issue of the repeatedly raised problem was introduced, namely the diagnosis of MS in people without abdominal obesity. It was noted that even lean individuals may develop features of MS.

4.10. Limitations of MS definition

Over the years, the main components of diagnosing MS evolved and became simplified for ease of use in clinical practice. It includes some of the most frequently occurring chronic disorders, which are also major risk factors for cardiovascular disease, the leading cause of mortality in the Western world. It is suggested that MS is a systemic predisease state beyond DM2 and cardiovascular disease and can be used as a guide to clinical managment decisions. It has been shown to predict cardiovascular disease morbidity, cardiovascular disease mortality, DM2 and all-cause mortality in a number of populations worldwide.[27–29] MS associations with apparently unrelated diseases such as polycystic ovary syndrome are described.[30] Currently, the two most widely used definitions are NCEP-ATP III and IDF focusing specifically on waist circumference which is an indicator of abdominal obesity. In contrast, the WHO, EGIR and the AACE definitions are all largely focused on insulin resistance and carbohydrate metabolism disorders. The definition of MS might be subject to more modifications following new research studies.[31–36] After agreement on definition of MS it is possible to compare the prevalence among population worldwide and its relationship with various health outcomes can be made.

The ongoing discussion into defining MS has its opponents, who believe there is no impact of diagnosing MS on the clinical practice. MS is presented as an educational concept that focuses attention on complex multifactorial health problems and a pre-morbid condition rather than clinical diagnosis. It is said that citeria of MS and rationale for threshold of MS components ale not scientific enough. The metabolic syndrome should be considered a pre-morbid condition, exluding idividuals with establisher diabetes or known cardiovascular disease. The construct of MS criteria has inherent limitations which impact on its clinical usefulness such as:

(1) Dichotomisation of the diagnosis of MS and of risk factos used to difine MS;
(2) Omission of established risk factors such as age, sex, family history, socioeconomic status, ethnicity, current treatment, smoking, physical activity;
(3) Heterogeneity among individuals diagnosed with the MS;
(4) MS describes relative risk as opposed to absolute risk;
(5) The cardiovascular disease risk associated with MS appears to be no greater than the sum of its parts;
(6) Treatment of MS is no diffrent than the treatment for each of its component;
(7) Superiority of waist circumference to BMI is notscientifically established for defining obesity;
(8) Value of including DM2 in MS definition is questionable.[37,38]

Moreover prognostic capability of pediatric metabolic syndrome criteria is pretty low due to its sensitivity. Therefore obese adolescents not met diagnostic level for metabolic syndrome by IDF criteria could be falsely excluded from the cardiovascular risk group.[39]

However, it seems that MS is not only a pathophysiological term, but also a practical-clinical one. Diagnosis of MS requires introduction effective approaches to treat it. The diagnosis and treatment of the underlying risk factors for the metabolic syndrome should be an important strategy for the reduction of all-cause mortality associated with metabolic syndrome in the general population.

6. CONCLUSIONS

(1) The definition of MS has evolved, becoming simplified so that it can be used in clinical practice. 2. Main components of diagnosing MS have been specified to include a greater part of the population.
(3) It seems that MS is not only a pathophysiological term, but also a practical-clinical one.
(4) The construct of MS definition has inherent limitations which impact on its clinical udefulness.
(5) The current definition might be subject to more modifications following new research studies.

Conflict of interest

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