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The metabolic syndrome

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Abstract

The metabolic syndrome (MS) is a cluster of metabolic abnormalities leading to increased risk for cardiovascular diseases and diabetes type 2. Its prevalence is increasing with aging. There exists actually an epidemic of MS. Visceral obesity and the resulting insulin resistance (IR) are the major determinant in the development of the MS. Abdominal obesity results in a low grade inflammation via the adipose tissue and macrophages secreted adipokines. This inflammation, via the generated pro-inflammatory molecules, interferes with the normal insulin signalling and thus contributes to the etiopathogenesis of the MS. Large clinical studies showed that CRP is increased in obese subjects and concomitantly to the number of existing component of the MS. Treatment of the MS is aimed to improve the IR by lifestyle changes including exercise and diet alone or in combination with medication targeting the individual components but having also anti-inflammatory actions. More research is needed to bring new therapies to be able to decrease the incidence and prevalence of the MS among the population and thus increasing their quality of life.

Keywords: Insulin resistance; Obesity; Inflammation; Adipose tissue; Cytokines; Aging innate immunity

1. Introduction

The metabolic syndrome (MS) was recently reintroduced in the medical common thinking by Reaven in 1988 [1]. This entity however was already described already in the 20s [2]. The MS consists of a deadly quintet factors namely diabetes, hypertension, abdominal obesity, lipid disorders and alterations in the thrombotic potential that are related to hyperinsulinemia and insulin resistance (IR). As simple and straightforward it could appear the definition of the MS there are great controversies and each association has its own definition and criteria [3]. Independently of its definition it is directly related to increased atherogenesis and death from myocardial infarction. The MS includes as criterion the abdominal accumulation of visceral adiposity due most probably to overeating and sedentarity, however genetic factors could certainly contribute. Nowadays, the MS is a real epidemic not only between middle-aged persons but also among adolescents and elderly (15–20% over 70 years). It is important to note that the prevalence of the MS is highly age-dependent. Thus, this is an important public health problem. Furthermore, the pathophysiological underlying cause is just starting to be unravelled as being related to the IR and consequently to a chronic inflammatory process. In this review we will describe the clinical approach to he MS, continuing with the basic pathophysiological process underlying this syndrome and finally, we will discuss new interventions avenues following our basic comprehension of the MS.

2. How to clinically define the MS?

The MS, which is considered as a constellation of cardiovascular risk factors, became one of the major public health challenges all around the world [4]. After the first conceptual approach of Reaven [1], the World Health Organisation (WHO) introduced the MS as a diagnostic category in 1999 [5]. Since that time other organisms or medical organisations emitted their own criteria for the MS including the European Group for the Study of Insulin Resistance (EGIR), the National

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Table 1
The various criteria for MS diagnosis

WHO 1999	ATPIII 2001	IDF 2005
Diabetes or impaired		Central obesity
Glucose tolerance or IR		Waist circumference
+ 2 or more of the following	3 or more of the following	+ any two of the following
1. Obesity: BMI>30 kg/m^2 or waist–hip ratio > 0.9 (M) > 0.85 (F)	1. Central obesity: waist circumference > 102 cm (M), > 88 cm (F)	1. Raised triglycerides > 150 mg/dl (1.7 mmol/l) or specific treatment for this abnormality
2. Dyslipidaemia: triglycerides > 150 mg/dl (1.7 mmol/l) or HDL-C < 0.35 mg/dl (0.9 mmol/l) (M) < 0.39 mg/dl (1.0 mmol/l) (F)	2. Hypertriglyceridaemia triglycerides>150 mg/dl (1.7 mmol/l)	2. Reduced HDL-C < 40 mg/dl (1.03 mmol/l) (M), < 50 mg/dl (1.29 mmol/l) (F) or specific treatment for this abnormality
3. Hypertension: blood pressure > 140/90 mmHg or medication	3. Low HDL-C < 40 mg/dl (1.03 mmol/l) (M), < 50 mg/dl (1.29 mmol/l) (F)	3. Hypertension: blood pressure>130/85 mmHg or medication
4. Microalbuminuria: albumin excretion > 20 μg/min or albumin: creatinine ratio > 30 mg/g	4. Hypertension: blood pressure> 130/85 mmHg or medication	4. Fasting plasma glucose > 5.6 mmol/l or previously diagnosed type 2 diabetes
	5. Fasting plasma glucose > 110 mg/dl (6.1 mmol/l)	

WHO: World Health Organisation; ATPIII: National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of high blood cholesterol in adults (adult treatment panel III), IDF: International Diabetes Federation, M: male, F: female.

Cholesterol Education Program—Third Adult Treatment Panel (NCEP ATP III) [6], The International Diabetes Federation (IDF) [7,8]. There are continuous updates to the already existing definitions [9] (Table 1). Through these various approaches a methodological switch occurred in the diagnosis of the MS namely from the pathophysiologically oriented approach, requiring somehow the assessment of the IR [5] to more clinically oriented approach, based on assessment of parameters available to any doctors [6,7].

The first official definition of the MS was made by the WHO in 1999. The central feature of this definition was glucose. The patients should have diabetes or glucose intolerance or IR. The IR could be measured by euglycaemic clamp. Moreover, the patients should also have two other features from high blood pressure, dyslipidaemia (hypertriglyceridaemia and/or low-HDL-cholesterol), obesity or microalbuminuria. The obesity could be measured either by waist–hip ratio or by BMI. It was quite quickly recognised that the determination of IR with a euglycaemic clamp was almost impossible to realise. However, nowadays hyperinsulinemia (10 mIU/l) or the homeostatic model assessment (HOMA) index is widely used in clinical settings as a surrogate of IR in large clinical and populational studies [10,11]. Nevertheless, it became evident that the criteria of the WHO are not enough simple to be applied in clinical settings that is why other association like EGIR proposed modifications. It relied basically on fasting insulin levels instead of the euglycaemic clamp to measure the IR [12]. Interestingly enough this definition is still based on the IR as an essential component arguing that IR is the underlying pathophysiological phenomenon of the MS.

Next emerged the ATPIII definition in 2001 [6]. The authors again wanted a simple definition which ultimately will include those with and without IR to prevent CVD and type 2 diabetes. Designed to have a direct clinical utility it was centred on glucose and all components became equal. Paradoxically, the most important critic however to this clinically oriented definition is the exclusion of those suffering from IR [13]. The modification proposed by the American Association of Clinical Endocrinology tried to compensate for this exclusion. They retained four key factors such as elevated TG, reduced HDL-C, elevated BP and elevated fasting and post-load sugar levels. All the other factors became only risk factors. It is noteworthy that central obesity was not included in this definition and deserved much criticism. However, it is clear while obesity is an important contributor to the development of CVD and type 2 diabetes its presence is not compulsory. All obese would not become diabetic and not all diabetic of type 2 are obese. This is a major contributing factor through inflammation leading to IR, but not as determinant that it seemed at first view.

So the question arises what elements are common to the MS independently of the parent elaborations of criteria. It seems that obesity, raised blood sugar, dyslipidaemia and elevated blood pressure are compulsory part of the MS. The most important differences reside on the concept of the driving force of the MS. According to the WHO and EGIR IR is considered as the driving force for this syndrome, while NCEP ATP III emphasised heavily the importance of central obesity (waist circumference). All the other new definitions of the MS put at the central stage the abdominal central distribution of obesity which became a prerequisite for the MS [8]. It was shown that the central obesity is strongly associated to the other parameters of the MS. It became also evident that central obesity is highly correlated with IR. Thus central obesity can be a surrogate for IR.

It is clear that the use of these many definitions create some difficulty to standardise the actual clinical practice. The most important question is actually which of these definitions can be used the most successfully to achieve the original goal i.e. preventing the CVD and type 2 diabetes. It seems that the most performing in this objective remains the definition of the WHO. Why it could be so? This definition is including the IR which is actually recognised as the underlying cause of diabetes type 2 and a risk factor for any CVD. Thus, it seems that the IR should be included, however the ever bothering question remains i.e. how to measure it accurately. In the same line of thinking the measure of the obesity is also controversial as there are no consensuses whether it should be measured by the widely used BMI or by the waist circumference and what should be the cut-off threshold.