The Metabolic Syndrome

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The metabolic syndrome (MetS), first introduced by Haller in 1975, was sometimes also known as insulin resistance syndrome, syndrome X, and plurimetabolic syndrome. In 1989, it was rechristened by Kaplan as the “Deadly Quartet” based on a consolidation of central obesity, impaired glucose tolerance, dyslipidemia, and systemic hypertension.

Keywords: metabolic syndrome ; glucose tolerance ; pathophysiology

1. Introduction

The rapid increase in metabolic syndrome (MetS) prevalence is emerging as a significant public health concern worldwide. The upward trend of urbanization, high caloric diet uptake, decreased physical activities, and central obesity compounded with a sedentary lifestyle are assigned as the influential underlying factors contributing to the epidemic upsurge of MetS. The significant increase in the prevalence of MetS and its future challenge to the national and world health scenario is very important. Various epidemiological studies have foisted the conclusion that MetS confers a five-fold increased risk of developing type 2 diabetes mellitus (type 2 DM) and a two-fold increase in the risk of developing a cardiovascular disorder over the next five to ten years [1]. Moreover, an individual with MetS is two to four times more susceptible to developing stroke and at a three- to four-fold risk of progressing myocardial infarction (MI) [2]. These events increase the risk of dying two-fold compared with those without MetS [3]. In 2001, the term MetS became institutionalized with the ICD-9 (International Code for Diseases-9) code 277.7 and was thought of as a first-order threat for the progression of atherothrombotic complications.

Visceral obesity and insulin resistance (IR) are recognized as the major intrinsic risk factors for MetS. Additionally, decreased physical activities, atherogenic dyslipidemia, calorie-rich dietary intake, and hormonal imbalance are risk factors for developing MetS [4]. The complete pathophysiology of MetS is still unclear. However, redundant adipose tissues-induced persistent low-grade inflammation is considered the crucial underlying cause of developing central obesity-related disorders, such as type 2 DM, cardiovascular diseases (CVDs), and IR [5]. The redundant adipose tissue-induced low-grade persistent inflammatory condition was found to be involved in the progression of diseases related to MetS, such as atherosclerosis, atherogenic dyslipidemia, hypertension, pro-thrombotic status, and impaired glucose tolerance [5].

2. Historical Background

Though Haller first introduced the term MetS in his scientific literature in 1975 [6], which was sometimes also known as IR syndrome and “Syndrome X” by Reaven in 1980 [7], the documented historical evidence of MetS begins with the Italian physician, Morgagni, around four decades earlier [8]. Morgagni noticed a significant association between central obesity, increased arterial blood pressure, atherosclerosis, elevated plasma uric acid, and obstructive sleep apnea. Paulescu observed an interconnection between obesity and diabetes and forwarded the statement “most frequently, obese people become glycosuric” in 1920 [9]. In 1927, a Spanish endocrinologist described hypertension and obesity as pre-diabetic conditions [10]. Since its origin, it has drawn the attention of many researchers worldwide. Later in 1947, Vague developed the concept that central obesity was commonly associated with the metabolic alteration observed in CVDs and type 2 DM [9].

The term plurimetabolic syndrome was introduced in the 1960s to describe the clinical condition of the frequent and concurrent presence of central obesity, dyslipidemia, Type 2 DM, and systemic increased arterial blood pressure [9][11]. In 1965, an abstract was presented at the European Association referencing the study in the diabetes annual meeting, which redefined the syndrome characterized by increased arterial blood pressure, hyperglycemia, and central obesity [11]. It is believed that the MetS field accelerated forward significantly after Reaven’s banting lecture, which came up with a cluster of risk factors for DM and CVDs. Reaven was the first to introduce the concept of IR associated with MetS [12]. However,

he astonishingly passed over the crucial component of visceral obesity, later considered a pivotal abnormality. Furthermore, regarding the history of MetS, in 1989, it was renamed the “Deadly Quartet” based on the combination of central obesity, increased blood glucose, hypertriglyceridemia, and hypertension described by Kaplan [13], and further, in 1992, it was retitled, the IR syndrome [14].

3. Definition and Diagnostic Criteria

The term syndrome derives from the Greek word “Sundromos” (Sun-syn + dromos = to run), meaning to run together. MetS is characterized by a complicated modification of the metabolism, which involves modification of lipid metabolism (dyslipidemia and obesity), carbohydrate metabolism (glucose intolerance), along with increased arterial blood pressure (hemodynamic disturbance with a metabolic starting point) [15]. Recently, pro-inflammatory, pro-thrombotic, and hormonal factors have been reported to be involved in MetS [16]. These modifications of metabolism are interconnected to each other and are found to be involved in increasing the risk of coronary heart diseases (CHDs), cardiovascular atherosclerotic diseases, and type 2 DM and causing mortality [17].

Several documented pieces of evidence reveal that many international organizations and expert groups have attempted to coin the criteria to diagnose MetS. The first attempt was made by the World Health Organization (WHO) in 1998 to define the diagnostic criteria for MetS, followed by the Europe Group for the Study of IR (EGIR), The National Cholesterol Education Program Adult Treatment Panel (NCEP: ATP III) (**Table 1**), the American Association of Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF). The first criteria developed by the World Health Organization (WHO), in 1998, with the inclusion of the presence of IR, impaired glucose tolerance (IGT), or type 2 DM as absolutely required factors of MetS with at least two of the following factors: waist/hip ratio—male > 0.9 cm, female > 0.85 cm—or body mass index (BMI) > 30 kg/m^2; fasting blood sugar (FBS)—≥110 mg/dL—or IR or type 2 DM or triglycerides (TG) ≥ 150 mg/dL; high-density lipoprotein–cholesterol (HDL-C)—male < 40 mg/dL, female < 50 mg/dL; blood pressure (BP)—diastolic ≥ 140 and systolic ≥ 90 mmHg, respectively; and microalbuminuria [18] (**Table 1**). Within a year, the European Group for studying IR (EGIR) challenged the above-mentioned diagnostic criteria. It modified the WHO definition by excluding microalbuminuria as an essential component of MetS and included hyperinsulinemia instead [19]. The EGIR considered IR as the substantial cause of MetS and gave much more importance to obesity than the WHO; while excluding persons with type 2 DM, the EGIR defines MetS as hyperinsulinemia or IR along with two extra parameters as FBS ≥ 108.11 mg/dL; BP diastolic ≥ 140 and systolic ≥ 90 mmHg; TG ≥ 150 mg/dL; and HDL-C < 39 mg/dL. Shortly after that, in 2001, the National Cholesterol Education Program Adult Treatment Panel (NCEP: ATP III) released its new criteria for MetS, which included waist circumference, blood lipid level, BP, and FBS (**Table 2** and **Table 3**). These differed from both the WHO and EGIR definitions. The NCEP did not consider IR as a mandatory component of the diagnostic criteria and stated that any three of the factors (waist circumference ≥ 102 cm in males and ≥88 cm in females; TG: ≥150 mg/dL and/or on drug treatment; HDL-C < 40 mg/dL in males and <50 mg/dL in females; BP diastolic ≥ 130 and systolic ≥ 85 mmHg and/or on drug treatment; and FBS ≥100 mg/dL and/or on drug treatment) would suffice for a diagnosis of MetS [20].

Table 1. Diagnostic criteria of metabolic syndrome elucidated over the years by different organizations.

Clinical Parameters	Criteria						
	Central Obesity	FBS	↑ TG	↓ HDL-C	↑ BP	Other	Diagnosed as MetS, If
WHO (1998) [19]	Waist/hip ratio Male: >0.9 cm Female: >0.85 or BMI > 30 kg/m^2	≥110 mg/dL or IR or T2DM or Rx	≥150 mg/dL	Male: <40 mg/dL Female: <50 mg/dL	Diastolic ≥ 140 and systolic ≥ 90 mmHg	Microalbuminuria	Absolutely required IR plus ≥ 2 criteria
EGIR (1999) [20]	WC Male: ≥94 cm Female: ≥80 cm	≥108.11 mg/dL	≥150 mg/dL	<39 mg/dL	Diastolic ≥ 140 and/or systolic ≥ 90 mmHg or Rx		Absolutely required IR plus ≥ 2 criteria
IDF (2005) [21]	WC defined in terms of ethnicity specific values	≥100 mg/dL or Rx	≥150 mg/dL or Rx	Male: <40 mg/dL Female: <50 mg/dL	Diastolic ≥ 130 and/or systolic ≥ 85 mmHg or Rx		Absolutely required central obesity plus ≥ 2 criteria

Clinical Parameters	Criteria						
	Central Obesity	FBS	↑ TG	↓ HDL-C	↑ BP	Other	Diagnosed as MetS, If
AHA/NHLBI (2005) [22]	WC Male: ≥102 cm Female: ≥88 cm	≥100 mg/dL or Rx	≥150 mg/dL or Rx	Male: <40 mg/dL Female: <50 mg/dL	Diastolic ≥ 130 and/or systolic ≥ 85 mmHg or Rx		≥3 criteria
AHA/NHLBI and IDF:2009 [23]	WC defined in terms of population- and country-based specific definition	≥100 mg/dL or Rx	≥150 mg/dL or Rx	Male: <40 mg/dL Female: <50 mg/dL	Diastolic ≥ 130 and/or systolic ≥ 85 mmHg or Rx		≥3 criteria

Table 2. Ethnic-specific values for waist circumference (IDF guideline 2005) [21].

Country/Ethnic group	Waist Circumference	
	Male	Female
Europids	≥94 cm	≥80 cm
South Asians Based on Chinese, Malay, and Asian–Indian population	≥90 cm	≥80
Chinese	≥90 cm	80 cm
Japanese	≥90 cm	≥80 cm
Ethnic South and Central Americans	Use South Asian recommendation until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available.	
Eastern Mediterranean and Middle East (Arab) population	Use European data until more specific data are available.	

Table 3. Waist circumference thresholds for abdominal obesity by different organizations.

Population	Organization	Recommended Waist Circumference	
		Male	Female
Caucasian	WHO	≥94 cm (increased risk) ≥102 cm (still higher risk)	≥80 cm (increased risk) ≥88 cm (still higher risk)
United States, Canada, and European	AHA/NHLBI (“ATP III”), Health Canada, and European Cardiovascular Societies	≥102 cm	≥88 cm
Japanese	Japanese Obesity Society	≥85 cm	≥90 cm
China	Cooperative Task Force		≥80 cm
Middle East, Mediterranean, Europid, Asian, and Sub-Saharan African	IDF	≥94 cm	≥80 cm
Ethnic Central and South American		≥90 cm	

More than one diagnostic criterion for MetS has created confusion for the diagnosis and research of the former. To address the confusion and with the motto to conclude a single definition for MetS, the International Diabetes Federation (IDF) proposed criteria that could be included in diagnostic criteria and epidemiological studies as well as in research on MetS in April 2005 [24]. Although the pathology of MetS, including its other essential causes, is not entirely understood, central obesity and IR are, however, considered the major causative factors [21]. According to the new IDF definition, for a person to be characterized as having MetS, they essentially have central obesity (defined as waist circumference with ethnicity-specific values) plus any two of the following four factors, i.e., a raised TG level, reduced HDL cholesterol, and raised BP and FBS. In the same year, the American Heart Association (AHA) and the National Heart, Lung, and Blood

Institute (NHLBI) of the United States introduced other criteria for MetS with the consideration of central obesity adopted by the IDF. They focused on the inflation of metabolic risk factors. According to the AHA/NHLBI criteria, a person possessing any three criteria of the following five will be characterized as having MetS: waist circumference ≥ 102 cm in males and ≥88 cm in females; TG ≥ 150 mg/dL and/or on drug treatment; HDL-C < 40 mg/dL in males and <50 mg/dL in females; BP diastolic ≥ 130 and systolic ≥ 85 mmHg and/or on drug treatment; and FBS: ≥100 mg/dL and/or on drug treatment [25] (**Table 2** and **Table 3**). Moreover, in 2009, a joint scientific statement by the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity was published with a common consensus to define MetS. According to a joint statement, for a person to be characterized as having MetS, they must have any three criteria out of the following five: central obesity (population- and country-based specific definition), TG ≥ 150 mg/dL and/or on drug treatment; HDL-C < 40 mg/dL in males and <50 mg/dL in females; BP diastolic ≥ 130 and systolic ≥ 85 mmHg and/or on drug treatment; and FBS ≥ 100 mg/dL and/or on drug treatment [22].

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