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Diagnostic criteria and management of metabolic syndrome: Evolution overtime

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SUMMARY

The beginnings of the Metabolic Syndrome (MetS) as a suspected, not yet recognized entity can be traced back to 1923 when a study concerning a particularly common clustering of metabolic entities observed in diabetic patients was first published. Years of research and endless debate yielded the currently accepted MetS definition and diagnostic criteria, even if some components and their cut-off points are still up for discussion. To date, MetS are defined as a clustering of metabolic risk factors that greatly increase the incidence of cardiovascular disease (CVD) and type 2 diabetes (T2D), while also being closely related to various potentially deadly comorbidities. Furthermore, since early detection and management of MetS have been shown to decrease the risk for CVD and T2D, current research has focused on unifying diagnostic criteria and proposing novel parameters to facilitate MetS identification, while also promoting a healthy lifestyle as a preventive measure. With a deeper understanding of MetS pathophysiology comes the broadening of therapeutic targets open for study, thus expanding and enhancing the treatment methods currently in use. This review aims to summarize the evolution of MetS as a concept, development of the diagnostic criteria, current management, and future directions.

***Key words**: Metabolic syndrome, diagnostic criteria, management, MetS updates, cardiovascular disease, type 2 diabetes.*

RESUMEN

Los inicios del síndrome metabólico (SM) como una entidad sospechada, si bien no reconocida, datan de 1923, cuando fue publicado un estudio sobre el agrupamiento bastante común de ciertas alteraciones metabólicas en pacientes diabéticos. En las décadas siguientes, la investigación y debates interminables resultaron en la definición y criterios diagnósticos del SM actualmente aceptados, aún si algunos de sus componentes y respectivos puntos de corte siguen en

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discusión. Hasta la fecha, el SM es definido como un aglomerado de factores de riesgo metabólico que aumentan de gran manera la incidencia de enfermedad cardiovascular (ECV) y diabetes mellitus tipo 2 (DM2), al tiempo que están íntimamente relacionados con diversas comorbilidades potencialmente mortales. Asimismo, debido a que la detección y manejo temprano del SM han demostrado disminuir el riesgo de padecer ECV y DM2, la investigación al respecto se ha enfocado en unificar los criterios diagnósticos y proponer nuevos parámetros que faciliten la identificación del SM, en conjunto con la promoción de un estilo de vida saludable como medida de prevención. El continuo estudio de las bases fisiopatológicas del SM va de la mano con la expansión de blancos terapéuticos a investigar, de esta manera fortaleciendo y mejorando las líneas de tratamiento actualmente en uso. El objetivo de esta revisión es el resumir la evolución del SM como un concepto y sus criterios diagnósticos, haciendo hincapié en su manejo actual y las actualizaciones en lo concerniente a nuevos parámetros diagnósticos y tratamientos innovadores aún en estudio.

Palabras clave: *Síndrome metabólico, criterios diagnósticos, manejo, actualizaciones de SM, enfermedad cardiovascular, diabetes mellitus tipo 2.*

INTRODUCTION

From the discovery and very first description of the Metabolic Syndrome (MetS) (1), it has been made clear that MetS represents an increasingly common and lethal prelude to various diseases that could be avoided if identified on time (2,3). MetS is not a disease, but rather a clustering of metabolic risk factors that have been proven to make the incidence of cardiovascular disease (CVD) at least twice as likely, and increase the possibility of suffering from type 2 diabetes (T2D) fivefold (4). MetS are also related to various comorbidities, such as pro-inflammatory, pro-thrombotic states (5-7).

At its core, the origin of MetS could be condensed to an energetic imbalance, where the intake of energy far surpasses what is consumed in the human metabolism; a vicious cycle associated with sedentary life and excessive food consumption (8-10).

It is worrying how MetS have recently become highly prevalent in modern society, not only in the USA, but also in Europe, some Asian countries, and Latin America (11,12). It has been reported that changes in lifestyle promoting exercise are key in preventing and managing MetS (13-15), supporting the theory of central obesity plays an important role in its pathophysiology (16-18). Considering how mere lifestyle changes could prevent MetS, early detection becomes a necessity to not only promote a healthier lifestyle as a whole, but also to devise clinical diagnostic methods aimed to easily identify people at risk, and therefore avoid possible MetS-associated CVD and T2D incidence (19-21).

Although leaps and bounds have been taken concerning the definition of MetS and its underlying pathophysiology (22), there is still a long way to go before it can be reliably and consistently used as an epidemiologic and preventive tool in assessing further risks and incidence of comorbidities in the general population (23,24). This review aims to concisely present how MetS came to be recognized as a tangible entity, and all current updates regarding management and early diagnosis of MetS designed to aid in the prevention and treatment of what is rapidly growing to be a 21st-century epidemic.

METABOLIC SYNDROME: DEFINITION, EPIDEMIOLOGY, AND RISK FACTORS

Defining MetS: in the pursuit of identity

The earliest recorded allusion to MetS as an entity came in 1923 when Swedish researcher Kylin published his observations on the commonly shared entities seen in T2D patients, a clustering of traits that he called the "hypertension-hyperglycemia-hyperuricemia syndrome" (25). However, it was only four decades later when the efforts concerning MetS initial recognition bore fruit. The 1960s marked a significant milestone in MetS research owed to Albrink and Meigs' recognition of obesity as an essential contributing factor to the development of dyslipidemia and hyperglycemia (26), while Welborn et al. correlated hyperinsulinemia with high blood pressure (HBP) and coronary heart disease (27). Additionally, Reaven uncovered various associations between altered glucose tolerance, hyperlipidemia, and myocardial infarction (28) whereas Camus termed the

clustering of T2D, gout, and hyperlipidemia as "metabolic syndrome" (29). On the other hand, the widely known Framingham Heart Study, the first long-term epidemiological study of its kind, reported critical findings that underscored the importance of high cholesterol, HBP, cigarette smoking, and obesity in the increase of heart disease risk (30).

In 1980, Ruderman et al. reported their findings on the "metabolic obesity" of normal weight subjects attributed to hyperinsulinemia and thus proposed the term "metabolically obese" (31), the use of which was heavily debated considering it would imply the existence of "metabolically healthy obese" (MHO) subjects, as well as "metabolically obese normal-weight" (MONW) subjects (32). It wasn't until 1988 when Reaven proposed the term "Syndrome X" to describe the intricate connection between insulin resistance (IR), hyperglycemia, hyperinsulinemia, increased triacylglycerol (TAG) levels, low HDL cholesterol (HDL-c), and high blood pressure (HBP). Reaven considered IR to be the basis of the said syndrome and that all the other factors derived from it, increasing the risk for CVD (33).

A year later in 1989, Kaplan emphasizes the role of obesity and made his contribution to the growing hypothesis, establishing what was termed at the time as the "deadly quartet" characterized by central obesity, glucose intolerance, hypertriglyceridemia, and HBP (34). Zimmet, in turn, coined the term "Syndrome X Plus" referring to a metabolic entity that included Syndrome X components and added central obesity, hyperuricemia, physical inactivity, and aging (35). Other authors such as DeFronzo and Ferrannini, and Ferrannini et al. in 1991, employed the term "insulin resistance syndrome", grouping non-insulin-dependent diabetes syndrome, obesity, HBP, dyslipidemia, and atherosclerotic CVD (36,37).

Further down the line, other contributions to the developing characterization of MetS were made. Such is the case with Shafrir in 1996, who formulated the hybrid term of "diabesity" alluding to the association between insulin resistance (IR) and obesity, based on the observation of animal models (38). A year later in 1997, Matsuzawa proposes the term "visceral fat syndrome" subscribing to the theory of Syndrome X and the deadly quartet, wherein the clustering of multiple factors might lead to the appearance of CVD. However, Matsuzawa's hypothesis focused on visceral fat accumulation and its contribution to the incidence of morbidities independently from IR (39).

At last, the World Health Organization (WHO) organizing committee published the official functioning definition of MetS in 1999, establishing the clustering of five main components as key: abdominal obesity, HBP, hypertriglyceridemia, low HDL-c levels, and altered glucose metabolism. Likewise, it emphasizes the importance of IR in the pathophysiology of MetS as it is considered to be the unifying causal factor between the syndrome components, and that these, in turn, are directly associated with the risk for cardiometabolic diseases (40). It is important to note that although the older terms are still currently being used, the term "MetS" is more widely accepted and commonly employed globally (41,42).

Metabolic Syndrome Epidemiology: A wide-reaching problem

The worldwide prevalence of MetS has steadily risen over the years, hand-in-hand with the development of industrialization and globalization (43,44). MetS have been currently estimated to affect approximately 30 % of the global population and is associated with an increased risk of morbidity and mortality that is two to three times higher compared to healthy subjects (45). MetS incidence seems to increase with age (46) and is inclined to affect women more frequently, which points out sex as an important intervening factor in its appearance (47).

The interest surrounding MetS prevalence has prompted many epidemiologic studies that report increasingly worrying numbers. In Africa, MetS prevalence is higher in North Africa (35.73 %) (48) and is closely followed by Central Africa (32.45 %) (49), opposite to Sub-Saharian Africa (11.1-23.9 %) (50). In Asian countries, the highest rate of MetS prevalence is found in India (33.5 %) (51), followed by Taiwan (32.8 %) (52), Korea (31.3 %) (53), China (24.2 %) (54), and lastly Indonesia (21.6 %) (55). On the other hand, a quarter of the European

population is reported to suffer from MetS (56), where Spain (27.8 %) (57), Russia (27 %) (58), Italy (26.5 %) (59), France (21.1 %) (60), and Germany (19.8 %) (61) have described their findings accordingly.

Regarding the American continent, Canada has the lowest MetS prevalence (18 %) (62), contrary to other North American countries. In this sense, a third of the USA's adult population suffers from MetS, amounting to 38.5 % of its population (63), whereas Mexico holds a close second at 36 % (64). The general prevalence of MetS in Central America rounds 30.3 %, with specific reports from Costa Rica (35 %), Belize (32 %), Guatemala (31 %), Nicaragua (30 %), and Honduras (23 %) (65). South America has its own MetS prevalence reports, among them Venezuela (35 %) (66), Chile (32 %) (67), Colombia (30.2 %) (68), Brazil (29.6 %) (69), and Argentina (27.5 %) (70).

Prevalence rates might vary greatly depending on the different criteria employed to diagnose MetS, as well as the very definition of the MetS components (71-73). Waist circumference (WC) is a prime example of this, with various cut-off points proposed worldwide (74-77) and even some countries like Venezuela identifying slight cut-off variations between regions of the same country (78,79). Therefore, these statistics need to be interpreted cautiously, considering the vast variability of global MetS prevalence owed not only to cultural, socio-economic, and ethnic factors unique to every region but also to the diverse diagnostic criteria currently used (11).

Factors associated with metabolic syndrome: A biopsychosocial approach

The direct association between certain genetic risk factors, lifestyle-related aspects, and MetS has been thoroughly documented. In this context, various genome-wide association (GWA) studies carried out along the years have identified some candidate genes capable of altering many metabolic pathways, such as insulin signaling, lipid metabolism, glucose uptake, and appetite regulation. These findings suggest that said genetic and epigenetic factors might directly or indirectly impact on MetS components and its incidence (80-83). Nonetheless, the genetic counterpart of MetS is yet to be clinically applicable in a widespread manner, marking its contribution to MetS prevention and management as humble at best (84).

Concerning lifestyle-related factors, certain dietary patterns arise as the likeliest to increase MetS incidence. The Western diet has long been singled out as the main culprit, characterized by high-sugar, high-fat food, with excessive red meat and refined flour consumption (10,85,86). The empty calorie diet is also responsible for increasing the risk for MetS, typically distinguished by alarmingly low fruit and vegetable intake added to high-fat food and refined sugar consumption (87,88). On the other hand, the Mediterranean diet has proven to be extremely beneficial towards avoiding MetS occurrence, significantly lowering the risks of MetS incidence in those that adhere to the said dietary pattern (89,90).

Regarding psychobiological habits, some interesting findings have been reported. Low to moderate alcohol consumption is linked to a lower prevalence of MetS, and has a favorable effect on some metabolic aspects, resulting in a significant HDL-c increase (91,92). However, as is the usual fare with many substances, the key lies in regulating the quantity consumed, seeing as excessive alcohol intake negatively affects said metabolic variables, increasing WC, TAGs, BP, and IR (93-95). Similarly, coffee consumption faces an equivalent pattern, where low (1 or 2 cups) to moderate (3 to 5 cups) daily coffee intake is related to a lower risk for MetS, contrary to those with high (over 5 cups) coffee consumption (96,97). Additionally, smoking is also consistently associated with MetS incidence, as the risk for MetS rises with the number of cigarettes smoked (98).

Conversely, decreased daily physical activity in healthy young adults has been associated with negative metabolic consequences, including a drop in insulin sensitivity, and an alarming increase of visceral fat (99). Likewise, physical inactivity and sedentary behavior are directly linked to MetS incidence by increasing the risk of obesity, HBP, and IR at any given age (100-102). Therefore, it is clear that MetS is a common consequence of leading an unhealthy lifestyle, rife with physical inactivity, high-calorie diet,

smoking and/or drinking habits, added to pre-existent genetic and epigenetic factors that further tip the balance in favor of MetS (3,103,104).

METABOLIC SYNDROME DIAGNOSIS

Over the years, several attempts at defining MetS have been made in the search for the most fitting terminology to be employed among researchers, particularly given MetS' great importance concerning CVD and other various comorbidities. Overall, the proposed definitions bear the following comprising metabolic components in common: impaired glucose tolerance or T2D, obesity (105), HBP, and/or dyslipidemia (106–108). To study these components systematically and diagnose MetS as accurately as possible, many variations have been suggested regarding some cut-off points according to sex, ethnicity, and other factors. The most commonly applied variations and requirements can be found in Table 1.

Table 1

Five definitions of metabolic syndrome

Parameters	WHO 1999	EGIR 1999	AACE 2003	ATP III 2005*	IDF 2009¶
Required	Insulin resistance in top 25 %; fasting glucose ≥6.1 mmol/L (≥110 mg/dL); 2-hour glucose ≥ 7.8 mmol/L (≥140 mg/dL)	Insulin resistance or fasting hyperinsulinemia	High risk of insulin resistance or BMI ≥ 25 kg/m^2 or waist ≥ 102 cm (men) or ≥88 cm (women)		
Number of alterations	And ≥ 2 of:	And ≥2 of:	And 2 ≥ of:	≥ 3 of:	≥ 3 of:
Glucose		Fasting glucose: 6.1-6.9 mmol/L (110-125 mg/dL)	Fasting glucose: ≥6.1 mmol/L (≥110 mg/dL); 2-hour glucose ≥ 7.8 mmol/L (≥140 mg/dL)	Fasting glucose: ≥6.1 mmol/L (110 mg/dL) or pharmacological treatment for elevated blood glucose	Fasting glucose: ≥6.1 mmol/L (110 mg/dL) or diagnosed diabetes
HDL colesterol	Men: <0.9 mmol/L (<35 mg/dL) Women:	< 1.0 mmol/L (<40 mg/dL) for	Men: < 1.0 mmol/L (<40 mg/dL) Women:	Men: < 1.0 mmol/L (<40 mg/dL) Women: <1.3 mmol/L (<50 mg/dL)	Men: < 1.0 mmol/L (<40 mg/dL) Women: <1.3 mmol/L (<50 mg/dL)

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Parameters	WHO 1999	EGIR 1999	AACE 2003	ATP III 2005*	IDF 2009¶	
	<1.0 mmol/L (<40 mg/dL)	both men and women	<1.3 mmol/L (<50 mg/dL)	Or pharmacological treatment for low HDL cholesterol	Or pharmacologica treatment for low HDL cholesterol	
Triacylglycerols	Elevated triacylglycerols ≥1.7 mmol/L (≥150 mg/dL)	Elevated triacylglycerols ≥2.0 mmol/L (≥180 mg/dL) or pharmacological treatment for dyslipdemia	Elevated triacylglycerols ≥1.7 mmol/L (≥150 mg/dL)	Elevated triacylglycerols ≥1.7 mmol/L (≥150 mg/dL) or pharmacological treatment for high triacylglycerols	Elevated triacylglycerols ≥1.7 mmol/L (≥150 mg/dL) or pharmacological treatment for high triacylglycerols	
Obesity	BMI ≥ 30 kg/m^2 or Waist/hip ratio: Men: >0,9 Women: >0,85	Waist circunference: Men: ≥ 94 cm Women: ≥ 80 cm		Waist circunference: Men: ≥ 102 cm Women: ≥ 88 cm	USA, Europe, Sub-Saharan Africans, Eastern Mediterranean and Middle East (Arab) populations: Waist ≥ 94 cm (men), ≥ 80 cm (women)	Asia, Ethnic South and Central Americans: Waist ≥ 90 cm (men), ≥ 80 cm (women)
Blood Pressure	≥ 140/90 mmHg	≥ 140/90 mmHg Or pharmacological treatment for hypertension	≥ 130/85 mmHg Or pharmacological treatment for hypertension	≥ 130/85 mmHg Or pharmacological treatment for hypertension	≥ 130/85 mmHg Or pharmacological treatment for hypertension	
Microalbuminuria	Urinary albumin excretion index ≥ 20 mg/min or ≥ 30 mg/g of creatinine-albumin ratio					

WHO: World Health Organization; **EGIR:** European Group for Study of Insulin Resistance; **AACE:** American Association of Clinical Endocrinologists; **ATP III:** National Cholesterol Education Program (NCEP) Adult Treatment Panel III; **IDF:** International Diabetes Federation; **BMI:** Body Mass Index; **USA:** United States of America. *: Last update after American Heart Association/National Health, Lung and Blood Institute modification. ¶: Last update after harmonized criterion.

Historical review

As was mentioned before, it wasn't until 1999 when the scientific community agreed in regards to MetS definition and diagnostic criteria (40), with the WHO working towards the unifying concept of MetS and suggesting its use over "Syndrome X" to avoid confusion with the microvascular angina syndrome of the same name (109). Although the WHO considered IR to be the pathophysiological link between all MetS components, it is important to note that the combination of the other components might increase the risk for macrovascular disease, which suggests that MetS management should not be merely focused on glucose control, but also in the devising of strategies aimed to reduce CVD risk factors. Additionally, the WHO was the first organization to include microalbuminuria as a required component for MetS diagnosis, while sidelining hyperuricemia, coagulation disorders, and elevated plasminogen activator inhibitor-1 (PAI-1) by considering them unnecessary in MetS diagnosis (40).

Some months later in 1999 (110), the European Group for the Study of Insulin Resistance (EGIR) subscribed to the WHO's perspective on IR being crucial in the development of MetS and so, to further emphasize its importance, suggested the term "insulin resistance syndrome" to be used instead. This proposal is explained by the high number of non-diabetic insulin-resistant subjects, amounting to 25 % of the population of those not diagnosed with T2D. Therefore, the EGIR introduced new MetS diagnostic criteria to include non-diabetic subjects: obligatory IR or fasting hyperinsulinemia added to 2 other MetS parameters, such as high fasting plasma glucose (FPG), HBP or in pharmacological treatment for HBP, dyslipidemia without sex distinction (elevated TAGs or low HDL-c levels) or in pharmacological treatment for dyslipidemia, and central obesity measured by WC based on European studies cut-off points according to sex (111,112).

Moreover, the EGIR also considered that Body Mass Index (BMI) was not appropriate to measure obesity in the context of MetS identification and that microalbuminuria should not be considered as a valid criterion due to its direct correlation to insulin levels. Nevertheless, these modifications in diagnostic criteria did not achieve the expected international recognition, owing to its minimal differences when compared to the previously established WHO criteria (113).

Three years later in 2002, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) proposed simpler, more practical diagnostic measures for MetS, citing the need for widely accepted criteria in the midst of MetS rising prevalence and lack of consensus concerning definitions among organizations. Contrary to the previously published WHO criteria, the NCEP ATPIII considered routine tests for IR to be unnecessary, seeing as it was assumed that most subjects with 3 or more MetS components would also be insulin-resistant, thus shifting the therapy target from IR management to decreasing LDL levels instead. The microalbuminuria component was also rejected by the NCEP ATPIII, while other components such as WC, sex-dependent cut-off points for HDL levels, and high TAGs were accepted (114).

Furthermore, although the NCEP ATPII did consider pro-inflammatory and pro-thrombotic states as MetS components bearing in mind their contribution to Coronary Heart Disease (115,116), no diagnostic criteria were proposed regarding said aspects.

The American Association of Clinical Endocrinologists (AACE) made their stand on the topic known in 2003, preferring the use of "insulin resistance syndrome" over MetS, just as the EGIR did before them (117). The NCEP ATPIII MetS criteria were considered as the most accurate, thus the lipids and blood pressure (BP) cut-off points were accepted without contest. However, the AACE did not consider it necessary to specify any number of criteria for MetS diagnosis but rather suggested relying on clinical judgment instead. The AACE also proposed some modifications, such as a 2-hour glucose tolerance test (140-200 mg/dL) considering fasting glucose measuring limitations, the use of BMI (≥25 kg/m^2) to measure obesity, and screening for various non-specific risk factors, while excluding T2D patients from the IR definition. Nonetheless, researchers continued to prefer the definition and diagnostic criteria proposed by the NCEP ATPIII due to its simple nature and clinical applicability.

The persistent conflict surrounding consistent MetS diagnostic criteria and globally accepted cut-off points led to the International Diabetes Federation (IDF) publishing their own MetS definition in 2005 after reaching consensus following various meetings on the issue (118). The goal was to present unified, practical MetS diagnostic criteria easily used by medical practitioners, and to provide a list of "platinum standard" parameters for additional metabolic measurements (Table 2) to aid in MetS research, epidemiological, or otherwise. The IDF emphasized central obesity as an essential MetS component, assigning specific WC cut-off points according to sex and race. Additionally, a minimum of two other parameters as needed to meet the MetS diagnostic criteria, among them elevated TAGs levels (≥150 mg/dL) or history of dyslipidemia treatment, low HDL-c levels (<40 mg/dL in males, <50 mg/dL in females), HBP (≥ 130/85 mmHg) or currently in treatment for previously diagnosed HBP, and high FPG (≥ 100 mg/dL) or previously diagnosed T2D.

After numerous discussions with the IDF that very same year to combine their proposals, the American Heart Association (AHA) and National Heart, Lung and Blood Institute (NHLBI) published their contribution to the field, modifying the NCEP ATPIII MetS criteria, specifically concerning the WC cut-off point, settling at ≥ 102 cm for males and ≥ 88 cm for females regardless of ethnicity, unlike the IDF cut-off points (4).

Table 2

IDF 2006 "Platinum Standards"for additional metabolic measurements

PARAMETER	TEST/MEASUREMENT
Abnormal body fat distribution	General body fat distribution (DEXA) Central fat distribution (CT/MRI) Adipose tissue biomarkers: leptin, adiponectin Liver fat content (MRS)
Atherogenic dyslipidemia (beyond elevated triacylglycerols and low HDL)	ApoB (or non-HDL-c) Small LDL particles
Dysglycemia	Oral Glucose Tolerance Test
Insulin resistance (other than elevated fasting glucose)	Fasting insulin/proinsulin levels HOMA-IR Insulin resistance by Bergman Minimal Model Elevated free fatty acids (fasting and during OGTT) M value from clamp
Vascular dysregulation (beyond elevated blood pressure)	Measurement of endothelial dysfunction Microalbuminuria
Pro-inflammatory state	Elevated high sensitivity C-reactive protein Elevated inflammatory cytokines (e.g: TNF alpha, IL-6) Decrease in adiponectin plasma levels
Pro-thrombotic state	Fibrinolytic factors (PAI-1, etc.) Clotting factors (fibrinogen, etc.)
Hormonal factors	Pituitary-adrenal axis

At last, in 2009, new efforts to achieve worldwide consensus were made. The IDF Task Force on Epidemiology and Prevention, NHLBI, AHA, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity agreed and published an international "harmonized" joint statement of appropriate MetS criteria, standardizing BP, lipids levels, and hyperglycemia cut-off-point values. The only difficulty faced during these discussions focused on central obesity, concluding that it should not be a pre-required component, while WC would continue to be a useful preliminary screening tool, applying IDF cut-off points by sex, ethnicity, and region until more data became available (119,120). However, the on-going discussion did not come to an end in 2009, and only a year later the WHO and NHLBI suggested the MetS definition to be reconsidered, arguing that it is an educational concept focused on health problems as a pre-morbid condition rather than a clinical diagnosis, also stating that it has limited utility in clinical practice and treatment, only being applicable in epidemiological studies of MetS criteria comparison (23).

MetS diagnostic methods: what's new?

Over the years, several researchers have reported various correlations between biological markers, anthropometric measurements, and MetS as an entity and/or its traditional markers, breaching the possibility of new studies focused on early identification of this pre-morbid state. In this vein, the homeostasis model assessment of insulin resistance index (HOMA-IR) is a key marker of IR (121), just as adiponectin, ghrelin, and free fatty acids (FFAs), which may also predict IR (122,123) and coronary heart disease (124). Also, apolipoprotein A1 and B have been proposed as atherogenicity and CVD risk predictors (125), while cystatin C (126), and aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (127) have been associated with increased risk for MetS incidence.

As has been previously mentioned, MetS are strongly associated with pro-thrombotic and pro-inflammatory states, leading researchers to propose additional markers of MetS risk factors accordingly, among them white blood cell count and high-sensitivity C-reactive protein (CRP) as markers of inflammation (128,129); homocysteine as a marker of endothelial dysfunction (130); and uric acid and γ-glutamyl-transferase (GGT) as markers of oxidative stress (131,132).

There is mounting evidence found in cellular biomarkers studies that consider micro RNAs (miRNAs), DNA, and proteins contained in extracellular vesicles to be useful in MetS diagnosis (133). Some of the plasma and serum biomarkers studied to date are neprilysin and adiponectin messenger RNAs (mRNA) (134,135). Adiponectin gene polymorphisms have been identified as related to obesity, T2D, and coronary heart disease susceptibility (136). Additionally, miRNAs let-7 and miR-122 circulating serum levels have been reported to be increased when four out five MetS components are also present (137), while miR-17, miR-197, miR-509-5p, and miR-92a sequences were found in extracellular vesicles at higher quantities in MetS subjects (138). However, these studies have not yet proven to be conclusive enough to formulate a compelling statement, and their use might be restricted to epidemiological rather than clinical studies.

Conversely, alternative anthropometric measurements other than WC and BMI have been linked to MetS definition, such as the index of central obesity (ICO), also known as waist to height ratio (WHtR), or a waist-to-stature ratio (WSR), defined as the ratio of WC and height with a common cut-off point of 0,5 (139). ICO has shown a good correlation with central adiposity, tissue glucose utilization, lipids profile, oxidative stress, and increased cardiovascular risk, which makes it an ideal alternative MetS parameter (140-143).

One of the other alternative parameters studied is the visceral adiposity index (VAI), a sex-specific mathematical index based on WC, BMI, TAGs, and HDL-c levels that indirectly measure visceral adipose function and insulin sensitivity, showing excellent results as an accurate MetS predictor (144,145). Lastly, the lipid accumulation product (LAP) is a parameter based on WC and fasting TAGs levels estimations to reflect lipids accumulation by sex. It has shown to be a good predictor of

CVD and T2D, thus being suggested as useful in MetS identification (146,147), although it may not prove to be better or more accurate than the other parameters mentioned in MetS diagnosis. The persisting conflict concerning these measurements stands in their lack of universality, considering how they tend to vary between individuals depending on sex, age, race, and age, emphasizing the need for a unified cut-off point criterion encompassing all contributing factors across regions.

THE STANDARD IN METABOLIC SINDROME MANAGEMENT

The foundations of MetS management are essentially lifestyle modifications, like changes in dietary and exercise habits (148). Moreover, current evidence supports that diet and exercise, along with pharmacologic and surgical interventions, may inhibit the progression of MetS to T2D or CVD (149-151). Before providing the evidence that every physician should consider when approaching a patient with metabolic syndrome, it is worth mentioning that proper management is focused on each altered component. For purely academic purposes, therapeutical strategies will be subdivided into pharmacological and non-pharmacological.

Non-pharmacological management

A healthy lifestyle is the pillar of MetS treatment. Diet, physical activity, sleep, emotion control, and avoidance of tobacco and other drugs that affect satiety or body weight are crucial targets, each of which requires a systematic evaluation and a patient-centered intervention (150).

Diet

Lifestyle modifications and weight loss are considered the most important initial steps of MetS treatment. Westernized diets are strongly associated with a higher risk of developing metabolic syndrome (152). Conversely, different diets like Mediterranean-style diets, characterized by high dairy, fish, wine, and cereal grain intakes seem to be associated with lower risk and, possibly, MetS resolution in already diagnosed patients, especially when combined with exercise programs (153,154). Regarding wine consumption, epidemiologic studies suggest that moderate wine intake may protect against MetS onset (155). Besides, diets that promote fruits, vegetables, and low-fat dairy products consumption such as the DASH (Dietary Approaches to Stop Hypertension)–style diet, show positive effects lowering BP and may lower the risk of stroke and CVD (156); what is more, even modest adherence to the DASH diet is associated with a lower risk of all-cause mortality (157).

Likewise, other current popular diets have been related to MetS parameters improvement. Such is the case of ketogenic diets, which can be defined as the calculated limitation of dietary carbohydrate intake to boost ketones production and promote a metabolic effect that balances glycemia and minimizes insulin requirements (158). Beneficial effects of a "well-formulated" ketogenic diet are known to be weight loss (159-161), significant total cholesterol reduction, increased HDL-c, and a shift in size and volume of LDL particles (162,163), a phenomenon that appears even more robust in patients with diabetes (164).

Physical Activity

Exercise is considered to be one of the main interventions to treat MetS. Currently, physical activity recommendation is at least 150-175 min/week, in conjunction with dietary energy restriction, targeting weight loss of 5 %-7 %. The latter has demonstrated reductions of 40 %-70 % in the risk of developing T2D in people with impaired glucose tolerance (165). Also, exercises can be of moderate-intensity for at least 30 minutes at a time, 5 days per week (ideally, 7 days per week), and maintaining long-term adherence (165). Along these lines, a recent systematic review of 53 studies that evaluated 66 lifestyle intervention programs reported that, compared with usual care, diet and physical activity promotion programs reduced T2D incidence, body weight, and fasting blood glucose while improving other cardiometabolic

risk factors (166).

Recent research point out that excessive sitting and other behaviors that carry out low activity and energy expenditure may trigger unique cellular responses that contribute to MetS development (167). Also, The ADA (American Diabetes Association) established recommendations about sedentary time, which are as follows: 1. All adults, and particularly those with T2D, should decrease the amount of time spent in daily sedentary behavior. 2. Prolonged sitting should be interrupted with bouts of light activity every 30 min for blood glucose benefits, at least in adults with T2D, and 3. the recommendation number 1 and 2, are additional to, and not interchangeable for, increased structured exercise and incidental movement. These sets of recommendations are based on studies that show an association between high sedentary time and increased mortality and morbidity, mostly independent of physical activity in people at risk for developing T2D (165,168,169).

Surgical treatment

Bariatric surgery (BS) and transcatheter bariatric embolotherapy, are the two surgical options that have demonstrated positive effects on obesity or MetS management (170,171). The first is a therapeutic alternative for obesity, which is comprised of several surgical procedures able to generate structural and metabolic changes in the digestive system, hence allowing weight loss (172). In addition, the main indications for BS in adults are patients aged between 18 and 55 years, BMI ≥40 kg/m^2 or BMI between 35-39.9 kg/m^2 in combination with some obesity-related comorbidity (T2D, HBP, obstructive apnea sleep) and history of therapeutic failure in weight loss or the inability to maintain it for ≥ 18 months after the administration of pharmacological and non-pharmacological treatment under specialized supervision (173,174); that is to say, this is one of the last options to manage MetS, which implies that the patient must be morbidly obese, but at the same time it is essential to highlight that improvement in those comorbidities, can reach up to remission of T2D in 55 to 85 %, and of HBP in 68 % to 79 % of the cases (175,176). Therefore, this is a great option for those who fit the latter indications; notwithstanding, no surgical intervention for MetS has been widely accepted if the patient is not morbidly obese.

The following technique is the transcatheter bariatric embolotherapy (TBE), which is a minimally invasive approach that uses a custom occlusion balloon microcatheter and robotic manifold to inject beads to the left gastric artery affecting energy homeostasis by decreasing ghrelin production (a food intake-stimulating hormone secreted by the stomach), providing sustained weight loss without serious adverse effects among obese patients (177). However, despite not having the risks of a major intervention such as bariatric surgery, the technique *per se* is still under study (178). Within the most relevant studies, one is especially noteworthy, a metanalysis which evaluated 47 subjects with overweight/obesity and assessed their weight loss after embolization showing a mean ± SD of 8.1 % ± 1.5 % and 8.85 kg ± 1.24 kg (both P<0.001) after a mean 12-month follow-up (179). These results were similar to a recent review of clinical data suggesting an average weight loss of about 8-9 kg (ranging 7.6-22.0 kg), corresponding to 8-9 % (ranging 4.8-17.2 %) of the patients' baseline weight (180). Providing that further studies prove a long-term success, bariatric embolization represents a potential minimally invasive approach to treat obesity after setting specific indications.

Pharmacological management

As mentioned above, pharmacologic interventions may lessen the contribution of MetS to T2D, coronary diseases, stroke, and other disabilities, but it is not the kickoff (181).

Hypertension

Current hypertension treatment is based on the recommendations of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) guidelines, to achieve a goal blood pressure (BP) of less than 140/90 mmHg or less than 130/80 mmHg in T2DM

patients (182). However, the 2014 report of the Eighth Joint National Committee (JNC-8) has recommended less stringent goals for drug therapy, resulting in 140/90 mmHg for most populations and 150/90 mmHg for patients aged 60 or older, maintaining an emphasis on the importance of promoting healthy diet and exercise behaviors (183). Similarly, the statements above are identical to those recently published by The International Society of Hypertension (ISH) where the essential objective is BP reduction by at least 20/10 mmHg, ideally less than 140/90 mmHg, and the optimal goal in <65 years is <130/80 mmHg if tolerated (but >120/70 mmHg), and in those ≥65 years the target BP is <140/90 mmHg if tolerated, but it is advised to consider an individualized BP target in the context of frailty (184).

Furthermore, some authors encourage to use angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) rather than diuretics or beta-blockers when medication is indicated, given that the latter may induce insulin resistance, weight gain, and increase the risk of hyperglycemia because of the decreased perfusion to skeletal muscle (185-187). On the other hand, studies have led to propose a role of adiponectin-improving insulin sensitivity in hypertensive patients under ACEI or ARB treatment (187). Respectively, as part of the Heart Outcomes Prevention Evaluation (HOPE) Study demonstrated (in 9,297 high-risk patients) a risk reduction of 33 % to develop diabetes, myocardial infarction by 22 %, stroke by 33 %, cardiovascular death by 37 %, and overt nephropathy by 24 % in the group treated with ramipril 10 mg/day vs. placebo (188). In light of the above and other studies, the ADA suggests the administration of ACEIs or ARBs in patients with pathologies, hypertension, and diabetes (189).

Dyslipidemia

The management of elevated LDL-C brings into consideration all of the statins. Statins are a class of drugs that, in their active hydrolyzed form, are specific inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is responsible for catalyzing the conversion of HMG-CoA to mevalonate, an early rate-limiting step in the cholesterol biosynthesis pathway (190). Interestingly, there are several presentations of these drugs that vary in dose and potency, all of which improve the lipid profile, but the treatment scheme should be individualized and titrated to achieve guideline-recommended goals. Accordingly, in patients with a high risk of atherosclerotic cardiovascular disease (ASCVD) maximally tolerated statin therapy to reduce LDL-C levels by ≥50 % is recommended (191). Notably, statin therapy is associated with a modest increase in the risk of new-onset diabetes; thus, patients should be reassured that the benefits of statins in preventing cardiovascular disease events far outweigh the potential risk of hyperglycemia (192). Contrarily, the case of reduced HDL-c treatment remains controversial. However, it can be addressed with lifestyle changes, and niacin might be included, which not only raises low HDL-c levels and reduce cardiovascular events but can also exacerbate hyperglycemia, especially in high doses, so constant follow-up is recommended (193).

Cholesterol guidelines from the American College of Cardiology emphasize the use of statins over non-statin therapies (194). The main recommendations concerning the usage of statins are as follows; 1. In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL) without calculating 10-year ASCVD risk, begin high-intensity statin therapy. 2. In adults aged between 40 to 75 years evaluated for primary ASCVD prevention, they must have a clinician-patient risk discussion before starting statin therapy**.** Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1c, and calculated 10-year risk of ASCVD); 3. In adults of 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL, at a 10-year ASCVD risk of ≥7.5 %, start a moderate-intensity statin if the discussion of treatment options favors statin therapy. Finally, 4. In adults of 40 to 75 years of age without diabetes mellitus and 10-year risk of 5 -19.9 %, along with risk-enhancing factors that favor the initiation of statin therapy.

These factors include persistent elevations of triglycerides ≥175 mg/dL, in which case the peroxisome proliferator-activated receptor agonists, such as fibrate therapy may serve as

an important adjuvant, especially in overweight patients with elevated triglyceride and low HDL-c levels (a combination known as atherogenic dyslipidemia) (195,196).

Hyperglycemia and obesity

Typically, hyperglycemia management in patients with metabolic syndrome starts with lifestyle changes and an insulin-sensitizing agent, such as metformin (197,198). Moreover, in patients with metabolic syndrome who are also in the highest-risk quartile of progression to diabetes, metformin 850 mg, twice a day, reduces the risk by about 20 % over 3 years. In contrast, intensive lifestyle modification over 10 years reduces the absolute risk of diabetes by 34 % and metformin reduces the risk by 18 % for all patients at increased risk (199). As a consequence, it is suggested that metformin may overturn changes in MetS. Accordingly, the combination of metformin with lifestyle changes (199,200) or with fibrates (201) and thiazolidinediones (eg, pioglitazone) (202,203) may produce favorable metabolic modifications as in patients with MetS (204). Additionally, metformin enhances weight reduction and improves lipid profile, by modestly reducing cholesterol and triglyceride levels and vascular integrity; hence, it can be considered as the first-choice drug in diabetics with a BMI greater than 27 % (205). Notably, weight loss goals in non-diabetic patients with a BMI >30 kg/m^2 or with a BMI> 27 kg/m^2 alongside comorbidities is > 5 %; conversely, in diabetic patients a > 3 % weight loss is expected after a 3-month treatment (206). In the case that these conditions are not met, the anti-obesity medication should be discontinued (206).

Orlistat and liraglutide are two of the treatments approved for clinical use in obesity. The former is a potent and selective pancreatic lipase inhibitor that reduces intestinal fat absorption (207) and visceral abdominal fat (208). The later, liraglutide, is a glucagon-like peptide 1 analog (GLP-1), a hormone with satiety function already used to treat T2D and obesity. A recent retrospective study compared treatment with both drugs significantly reduced weight, fasting plasma glucose, and LDL-C during a follow-up period of 7 months. Nonetheless, liraglutide-associated weight loss (-7.7 kg) was significantly greater than the observed with orlistat (-3.3 kg), and more individuals lost at least 5 % of their baseline weight with liraglutide (64.7 %) than with orlistat (27.4 %). In summary, liraglutide showed an overall better performance (209).

Future perspectives for MetS management

Dysregulation of cortisol and MetS

Ultimately, metabolic syndrome has been associated with abnormal cortisol levels (210). Therefore, the dysregulation of cortisol action could have a crucial action in metabolic syndrome onset, but this is yet to be confirmed (211). Therefore, it is expected that glucocorticoid antagonist drugs, like mifepristone, may be able to act as an insulin sensitizer, as seen in studies where mifepristone increases insulin-dependent glucose absorption, improving insulin sensitivity in obese animals (212). In addition, it improves glucose tolerance in knockout mice for the macrophage migration inhibitory factor (213); also, it improves diabetes symptoms in ob/ob mice (213). Consequently, it has been reported to reduce lipid alterations and insulin resistance in mice fed with a high fructose diet (214). All in all, these studies exhibit a potential therapeutic target to tackle MetS, with more on-going investigations looking forward to discovering a possible metabolic pathway, which has been suggested to involve skeletal muscle and mitochondrial-AMPK pathway (215,216). For that reason, more studies are required to accept the use of mifepristone not only in Cushing syndrome but also in MetS patients.

Sarcopenic obesity and MetS

Recently, MetS have been related to the loss of lean mass (217), bringing to context a relevant concept from the health perspective that is not new by any means, sarcopenic obesity. Sarcopenic obesity is defined as the simultaneous presence of skeletal muscle mass two standard deviations below the mean for the young population along with a corporal fat percentage above the median (218). This entity is considered to be multifactorial, in which there is a combination of genetic and environmental factors, like physical

activity, caloric intake, oxidative stress, and hormonal profiles (219).

For that reason, drugs that can increase the total lean mass have been studied, mainly in the elderly, because of their inherent loss of skeletal muscle (220). Like the case of testosterone which is known to increase muscular protein synthesis, a phenomenon is directly regulated by genetic, nutritional, and behavioral factors like exercising (221,222). Furthermore, randomized controlled trials (RCTs) have demonstrated the beneficial effects of testosterone therapy regarding sexual function, quality of life, glycemic control, insulin sensitivity, bone density, and skeletal muscle and fat mass; hence, diminishing long term morbidity and mortality (223).

Antirheumatic drugs and MetS

Several epidemiologic studies have shown that MetS is linked to a variety of diseases, rheumatic diseases among them, including osteoarthritis (OA) and systemic lupus erythematosus (SLE) (224,225). Currently, the pathways connecting MetS and rheumatic entities are yet to be described; nonetheless, low-grade chronic inflammation and oxidative stress seem to play a role in this matter. Specifically, adipose tissue hypertrophy and hyperplasia, as a consequence of obesity, can lead to insufficient blood supply; thus, inducing hypoxia and necrosis (226,227). Consequently, hypoxia leads to the production of proinflammatory mediators and adipokines like leptin, IL-6, TNF-α, PAI-1, and CRP. Similarly, rheumatic diseases are characterized by high proinflammatory cytokines production and the synthesis of autoantibodies (228). Moreover, some adipokines might play an essential role in the development and progression of these entities, particularly SLE (229).

In light of the above, the relation between MetS and rheumatic disorders is plausible. Interestingly, adipokine inhibitors do not take part in T2D treatment (230). However, they are included in the treatment of rheumatic diseases (231), which introduces several questions about the possible implementation of these anti-rheumatic drugs in the management of MetS.

Firstly, glucocorticoids are widely used to manage rheumatic disorders; however, as a result of their ability to induce hepatic gluconeogenesis and disturb the excretion of insulin these drugs are not a viable option to use in MetS patients (232). Contrarily, through a study with 400 patients diagnosed with rheumatoid arthritis (RA), it was demonstrated that those who took methotrexate had a lower prevalence of MetS and also lower fasting glucose levels compared to the control group (233). On the other hand, a low dosage of methotrexate was evaluated in the prevention of atherosclerotic events in 4.786 patients with previous myocardial infarction or multivessel coronary disease, along with T2D or MetS. After a 2 year follow-up, methotrexate did not exhibit any benefits in lowering pro-inflammatory cytokines or improving MetS parameters compared to the placebo group (234), suggesting that methotrexate could improve metabolic profiles in patients with rheumatic disease, but not in those with cardiometabolic diseases.

Along these lines, hydroxychloroquine is also used as an option for rheumatic diseases; also, it has some favorable qualities regarding glucose metabolism. Moreover, hydroxychloroquine therapy was associated with a significant decrement in T2D incidence (HR: 0,54; CI 95 %: 0,36-0,80) (235). Besides, when compared to methotrexate, hydroxychloroquine showed a greater reduction in HbA1c levels, approximately 54 % (P=0.04) (236). For that reason, it should be considered in patients with a combination of rheumatic and metabolic disorders.

Furthermore, there is ongoing evidence concerning biological anti-rheumatic treatment. For instance, a research with 61 patients diagnosed with RA treated with infliximab, a TNF-α antagonist, were evaluated for 12 weeks and showed significantly lower levels of HOMA-IR and higher levels of QUICKI by the end of the study (237).

Apart from that, IL-1 antagonists are also a potential therapeutic target in these regards, because low concentrations of these cytokines for a short time can induce insulin secretion, whereas long-term stimulation induces apoptosis (238). In a randomized, double-blind study with 70 T2D patients, the effect of anakinra, a recombinant and slightly modified version of the human interleukin 1 receptor antagonist protein, was assessed in 34

of them, against 36 placebo patients. After 13 weeks, results showed that anakinra patients had significantly lower levels of HbA1C, CRP, IL-6, and proinsulin/insulin ratio (239).

Lastly, IL-6 tends to have high serum concentrations in T2D, making IL-6 antagonists a feasible target to modulate the pathophysiology in T2D and MetS (240). Concretely, 11 non-diabetic patients with RA showed significantly lower levels of HOMA-IR after 3 months of treatment with tocilizumab, an IL-6 inhibitor, at a dose of 8 mg/kg (241). Also, after 6 months of tocilizumab therapy, HbA1C levels decreased significantly in diabetic patients as well as in non-diabetic patients (242). In light of all the above, biological anti-rheumatic drugs show several potential mechanisms and favorable aspects regarding the management of MetS in rheumatic individuals; nevertheless, further research is still needed to support the application of these drugs for this sole purpose.

CONCLUSION

Obesity has undoubtedly become what could be termed as a 21st-century epidemic, with no end in sight to its seemingly ceaseless expansion in the near future and carrying with it multiple risk factors for various avoidable diseases and their resulting clustering into MetS. The road that led to MetS recognition and study was arduous, and the discussions to reach consensus on its diagnostic criteria were even more so, which is to be expected when there are five very dynamic components to be measured accordingly. It is no surprise then, that the need for universal diagnostic criteria remains and is still being discussed to date.

Seeing as many of the diseases heralded by MetS could be avoided if identified on time, numerous efforts are being made to aid in the early clinical identification of MetS, with studies pointing to novel biomarkers and alternative anthropometric measurements as grounds for further research, even if many agree that MetS should only remain as a pedagogical concept and its diagnosis useful only in the context of epidemiological studies.

MetS first-line initial management is deeply entrenched in lifestyle modifications, owed to the vast amount of evidence supporting the many benefits of healthy habits and their role in avoiding MetS progression. Additionally, as stipulated by various organizations, MetS pharmacological and surgical treatment focuses on each component individually, collectively aiming to lower risk for CVD and other comorbidities. Current research in the search for unexplored MetS treatment methods goes hand-in-hand with the deepening understanding of MetS pathophysiology, and so with the underlying cause of MetS being closely investigated, new therapeutic targets arise and open the field for continuous research.

CONFLICT OF INTEREST

These authors declare that they have no competing interests.

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