LUMEN ET VIRTUS

Metabolic syndrome: Current syndemic evidence, diagnosis, treatment and diet therapy

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ABSTRACT

Metabolic syndrome (MS) is a complex clinical condition characterized by the combination of cardiovascular and metabolic risk factors, such as abdominal obesity, hypertension, dyslipidemia, and insulin resistance. Faced with this challenging scenario, this review proposes to provide a comprehensive update on this critical public health problem. Through a syndemic approach, we seek to highlight the interrelationship between metabolic risk factors and their implications for public health, considering social and economic contexts. We addressed various diagnostic criteria from organizations such as WHO, EGIR, NCEP-ATP III, AACE/ACE, IDF, AHA/NHLBI and JIS, emphasizing the need for standardization to facilitate clinical screening. It is a narrative review and focused on evidence from the last 10 years, highlighting advances in drug and nutritional treatments. The use of the WHO, NCEP-ATP III, and IDF criteria is especially recommended, as they offer a comprehensive and consistent approach to the diagnosis of MS. In view of the current evidence, the importance of personalized drug therapy and dietary interventions is emphasized, highlighting the DASH and Mediterranean diets as effective strategies. It is concluded that MS shows a syndemic character, requiring urgent attention from public health policies. The standardization of diagnostic criteria, the training of health professionals for early identification, and the implementation of government programs are essential to mitigate this condition, especially in primary care, underscoring the need for integrated and sustainable approaches to address this significant global health challenge.

Keywords: Abdominal Obesity, Insulin Resistance, Cardiovascular Diseases.

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INTRODUCTION

Metabolic syndrome (MS) is a clinical condition associated with insulin resistance (IR), central obesity, dyslipidemia, and systemic arterial hypertension (SAH) that constitutes a significantly high risk for the development of cardiovascular diseases (CVD) and type 2 diabetes *mellitus* (DM2) [1]. It is also composed of physiological, biochemical, clinical and metabolic alterations directly related to heredity and lifestyle[2].

In Brazil, the epidemiological panorama of MS has been similar, according to a study presented by Oliveira et al.[3] pointed out a prevalence of 38.4%, whereas, dos Santos Vieira et al.Sánchez et al.[4] found a prevalence of 32% in a survey in the region of São Paulo. The prevalence of MS increases with age, with a predominance in the age group over 60 years, and is more observed in females (70% *vs.* 56%), which can be justified by hormonal changes present in menopause, which contribute to the increase in waist circumference[3,5].

The diagnostic criterion varies according to the reference used, and the main ones can be cited as the World *Health Organization* - WHO[6], *the National Cholesterol Education Program Adult Treatment Panel* III - NCEP-ATP III[7] and the *International Diabetes Federation* - IDF[8]. It is worth noting that all of them agree that MS is a condition intrinsically associated with IR[9].

There is no specific treatment for MS, but the main objective is to minimize and prevent the risk of major cardiometabolic complications, through strategies to change lifestyle, use pharmacological medications or combine both[10]. Studies have shown that diets rich in *natural foods*, such as DASH (*Dietary Approach to Stop Hypertension*) and Mediterranean, improve lipidemic profile, blood glucose, blood pressure levels and oxidative stress, providing health benefits[11,12].

In view of this, this review aims to provide a broad update on this critical public health problem, with syndemic epidemiological evidence, discussion of clinical aspects and various diagnostic criteria that hinder screening by health professionals, in addition to presenting current evidence on drug and nutritional treatments. It is worth mentioning that it also aims to contribute to a better clinical understanding and intervention strategies, examining not only its clinical manifestations, but also the diagnostic implications and diet therapy strategies.

SYNDEMIC OF THE MS

MS, originally described in the 1980s as Reaven's syndrome, was also recognized as syndrome X, or IR syndrome, or even identified as "the deadly quartet" [13]. His attempts at terminology aimed to detail the detailed clinical picture, considering the set of metabolic complications identified [2].

However, researchers and health organizations, in consensus, standardized the term to MS, characterized as a set of cardiometabolic disorders, including IR, atherogenic dyslipidemia, central

obesity and SAH, conditions with frequent association for increasing the risk of CVD and DM2, as well as overall mortality [1,3,14].

MS emerges as a global syndemic, connecting to attributed factors such as urbanization, changes in dietary patterns and population aging[15]. The prevalence of MS ranged from 20% to 25% worldwide, and was gradually increasing, reflecting the severity of this public health problem[8]. It is estimated that about a quarter of the world's population is affected by MS, with more alarming numbers in developing countries [16].

In Brazil, MS is a critical public health problem with a significant prevalence. Studies such as the one by Siqueira Valadarez[17] reveal that about 33% of the Brazilian population has this condition, with an increasing incidence, especially in urban areas. Another study, such as that by Saklayen[9], corroborates these findings and highlights the importance of early identification and appropriate management of MS to mitigate its adverse health consequences. Therefore, it is necessary to emphasize that these numbers may be underreported due to the lack of standardization in the diagnostic criteria used, which hinders the effective implementation of preventive and control strategies[18].

The lack of training of health professionals in the early identification of MS contributes to delays in diagnosis and, consequently, to the late initiation of appropriate interventions, compromising the quality of life and work capacity of affected individuals, in addition to substantial economic implications with the expenses associated with the adverse outcomes of MS, which can overload health systems and negatively impact public resources[18,19]. Therefore, investing in professional health training programs becomes imperative, promoting early recognition and adequate management of MS to reduce its prevalence and mitigate adverse effects[20].

MS is intrinsically associated with a low-grade inflammatory state, which plays a crucial role in its pathophysiology[2]. Several inflammatory components contribute to this condition, including proinflammatory cytokines such as TNF-α and IL-6, which are frequently elevated in individuals with MS[21].

The pathophysiological components of MS promote a cascade of events that compromise metabolic homeostasis[2,14,15]. Insulin resistance triggers a compensatory increase in insulin production, resulting in pancreatic dysfunction and chronic elevation of blood glucose[15,22]. Visceral obesity contributes to the inflammatory state by releasing pro-inflammatory adipokines that further exacerbate insulin resistance[22,23]. Dyslipidemia, characterized by high levels of triglycerides and low levels of HDL-c, perpetuates the inflammatory state[24]. Arterial hypertension, in turn, intensifies oxidative stress and vascular inflammation[14].

In addition to the traditional components, hormonal and metabolic aspects play significant roles in the pathophysiology of MS. Hormonal imbalance, including leptin resistance and

hyperactivity of the hypothalamic-pituitary-adrenal axis, contributes to inflammation and central obesity [25,26]. Metabolically, activation of the serine kinase signaling pathway and accumulation of intracellular lipids contribute to insulin resistance and metabolic dysfunction[22,23,25].

The consequences of these pathophysiological processes are vast and adversely impact the health of individuals with MS. Metabolic and hormonal imbalances contribute to the development of type 2 diabetes, atherosclerosis and cardiovascular diseases[9,15,18]. In addition, the chronic inflammatory state is associated with complications such as nonalcoholic fatty liver, psychiatric disorders and even cancer[14,22,24]. This complex interconnectedness of pathophysiological events highlights the need for integrated approaches to the management of MS, aiming to attenuate not only the traditional components but also the inflammatory, hormonal, and metabolic aspects.

DIAGNOSIS

The evaluation of MS involves the consideration of several diagnostic criteria proposed by different health organizations. The WHO[6] defined criteria that include high blood pressure, high fasting glucose, high triglycerides, low HDL cholesterol levels and abdominal obesity. The European Group for the Study of Insulin Resistance (EGIR)[27] focuses on insulin resistance as a central component, while the NCEP-ATP III[7] highlights abdominal obesity, in addition to other risk factors. The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE)[28] proposes more comprehensive criteria, including waist circumference and fasting blood glucose. The IDF[8] emphasizes abdominal obesity and introduces specific cut-off points for different populations. The American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI)[29] offers criteria similar to the NCEP-ATP III, whereas the Joint Interim Statement (JIS)[30] seeks to harmonize existing approaches. Despite this variety, three sets of criteria are commonly recommended: those of the WHO, NCEP-ATP III and IDF. These sets share a focus on abdominal obesity, fasting glucose, blood pressure, triglycerides, and HDL cholesterol, providing a broader and more consistent approach to diagnosing metabolic syndrome. This recommendation aims at uniformity in the identification of the condition, facilitating comparison between studies and ensuring clear guidelines for clinical practice. (Table 1).

Table 1. Main criteria adopted for the diagnosis of MS.

Parameters	**WHO (1998)[6]**	**EGIR (1996)[27]**	**NCEP-ATP III (2001)[7]**	**AACE (2003)[28]**	**IDF (2005)[8]**	**AHA/NHLBI (2005)[29]**	**JIS (2009)[30]**
No. of criteria	IG or IR or MD+ 2 criteria	RI + 2 critérios	3 or more criteria	Blood glucose + 1 criterion	Central obesity + > 2 criteria	3 or more criteria	3 or more criteria
Obesity	WHR > 0.9 H >0.85 M and/or BMI > 30 kg/m²	CC >94 H >80 M	CC >102 H >88 M	BMI> 25 kg/m² or CC> 100 H > 87.5 M	IMC > 30 kg/m² e CC >94 H >80 M	CC >102 H >89 M	Population and country-specific definitions

Glycemia	IG or YOUR RI OR DM	GJ >110 mg/dL IP >75% percentil	FPG > 100 mg/dL or use of DM medications	FPG > 100 mg/dL or use of DM medications	FPG > 100 mg/dL or diagnosis of DM	FPG > 100 mg/dL or use of DM medications	FPG > 100 mg/dL or use of DM medications
Dyslipidemia	HDL-c < 35 mg/dL H < 39 mg/dL M e/ou TGL >150 mg/dL	HDL-c < 39 mg/dL para H/M e/ou TGL >150 mg/dL	HDL-c < 40 mg/dL H < 50 mg/dL M and/or TGL >150 mg/Dl or pharmacological treatment	HDL-c < 40 mg/dL H < 50 mg/dL M and/or TGL >150 mg/Dl or pharmacological treatment	HDL-c < 40 mg/dL H < 50 mg/dL M and/or TGL >150 mg/Dl or pharmacological treatment	HDL-c < 40 mg/dL H < 50 mg/dL M and/or TGL >150 mg/Dl or pharmacological treatment	HDL-c < 40 mg/dL H < 50 mg/dL M and/or TGL >150 mg/Dl or pharmacological treatment
HAS	SBP/DBP >140/90 mmHg and/or use of antihypertensive medication	SBP/DBP >140/90 mmHg and/or use of antihypertensive medication	SBP/DBP >130/85 mmHg and/or use of antihypertensive medication	SBP/DBP >130/85 mmHg and/or use of antihypertensive medication	SBP/DBP >130/85 mmHg and/or use of antihypertensive medication	SBP/DBP >130/85 mmHg and/or use of antihypertensive medication	SBP/DBP >130/85 mmHg and/or use of antihypertensive medication
Other	Microalbuminuria (urinary excretion >20 ug/min)	-	-	IR Evidence	-	-	-

DM: diabetes mellitus; GI: glucose intolerance; IR: insulin resistance; WHR: waist-to-hip ratio; H: men; M: women; BMI: body mass index; TGL: triglycerides; SBP: systolic blood pressure; DBP: diastolic blood pressure; LG: fasting blood glucose; CC: waist circumference; HDL-c: high-density lipoprotein.

WORLD HEALTH ORGANIZATION – WHO

The first formalized definition for diagnosing MS was proposed by a group from the WHO[6], emphasizing that IR is the main underlying risk factor for the diagnosis of MS, as it contributes to obesity and hyperglycemia, mainly because they are factors that increase oxidative stress (reactive oxygen species – ROS; advanced glycation end products – AGEs; malonaldehyde – MDA; 8-hydroxy-deoxyguanosine – 8-OHdG; among others), and inflammatory processes, such as pro-inflammatory cytokines (Interleukin-6 - IL-6; Interleukin-1β - IL-1β; tumor necrosis factor - TNF-α; C-reactive protein - CRP; haptoglobin), and adipokines (such as leptin and resistin), and these can intensify the prevalence not only of CVD, but also of DM and obesity[14,22]. Thus, the diagnostic criteria according to the WHO establish that there is a need for an abnormality of glucose tolerance or IR, associated with two or more components: (1) obesity (waist-to-hip ratio – ORQ > 0.9 for men and 0.85 for women and/or body mass index – BMI, > 30 kg/m²), (2) dyslipidemia (decrease in High Density Lipoprotein - cholesterol (HDL-c) < 35 mg/dL in men and < 39 mg/dL in women and/ or elevated serum triglycerides (Tg) >150 mg/dL), (3) hypertension (systolic blood pressure - SBP / diastolic blood pressure - DBP >140/90 mmHg and/or use of antihypertensive medication) and (4) microalbuminuric (urinary excretion index >20 ug/min and/or albumin/creatinine ratio >30 mg/g)[6,31].

EUROPEAN GROUP FOR THE STUDY OF INSULIN RESISTANCE – EGIR

In 1996, a group from Europe suggested a modification of the definition made by the WHO, proposing the replacement of IR analysis by fasting insulin measurement, excluding microalbuminuria as one of the components of MS. In addition, this criterion also assessed obesity, based on waist circumference (WC) (>94 cm for men and > 80 cm for women), associated with fasting glucose (FPG) (>110 mg/dL) to identify glucose intolerance[27].

NATIONAL CHOLESTEROL EDUCATION PROGRAM ADULT TREATMENT PANEL III – NCEP-ATP III

In 2001, another group formalized the criteria for an individual to be diagnosed with MS, namely: occurrence of three of the five components indicated, in any order of grouping, (1) abdominal obesity (WC >102 cm in men and 88 cm in women), (2) HDL-c (>40mg/dL for men and >50 mg/dL for women), (3) HYPERTENSION (DBP/DBP of >130/85 mmHg and/or use of antihypertensive medication), (4) Tg (>150 mg/dL or pharmacological treatment), (5) fasting glucose (>100 mg/dL and/or use of MS medication)[7].

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDROCRINOLOGY – AACE/ACE

In 2003, the AACE/ACE[28] emphasized the importance of including glucose tolerance tests in the diagnosis, in addition to differentiating risk according to specific characteristics, such as (1) BMI > 25 kg/m²; (2) WC > 100 cm in men and > 87.5 in women; (3) sedentary lifestyle; (4) age > 40 years; (5) ethnicity (with a greater predisposition in Africans, Hispanics, Asians, and Native Americans); (6) family history of DM2, SAH, or CVD; (7) history of glucose intolerance or gestational diabetes; (8) Acanthosis nigricans; (9) polycystic ovary syndrome and (10) nonalcoholic liver disease.

INTERNATIONAL DIABETES FEDERATION – IDF

In 2005, the IDF proposed the unification of the existing diagnostic criteria, taking into account the presence of mandatory central obesity (BMI > 30 kg/m² and WC > 94 cm for men and > 80 for women) associated with the occurrence of two more parameters: (1) glucose > 100 mg/dL or diagnosis of diabetes; (2) HDL cholesterol < 40 mg/dL for men and < 50 mg/dL for women; (3) Triglycerides ≥ 150 mg/dL or pharmacological treatment (4); blood pressure ≥ 130/85 mmHg or antihypertensive treatment[8].

AMERICAN HEART ASSOCIATION/NATIONAL HEART, LUNG AND BLOOD INSTITUTE – AHA/NHLBI

In 2005, the American Heart Association (AHA) together with the National Heart, Lung and Blood Institute (NHLBI) released a report on the diagnosis and management of MS, thus proposing as a criterion the presence of 3 or more of the following criteria: (1) WC of 102 cm for men and 89 cm for women; (2) triglyceride level > 150 mg/dL or presence of pharmacological treatment; (3) HDL-c level <40 md/dL in men and <50 mg/dL in women or presence of pharmacological treatment; (4) blood pressure of 130/85 mmHg or presence of pharmacological treatment; (5) fasting glucose of 100 mg/dL or presence of pharmacological treatment[29,31].

JOINT INTERIM STATEMENT – JIS

The last definition proposed was in 2009, through a scientific declaration made by the merger of several organizations, which harmonized the criteria of the MS components to a definition: a single set of cutoff points would be used for all components, except CC([30].

There is no consensus on which combination of risk factors should be taken into account in the final diagnostic criterion for MS, however, in all of them, there is agreement regarding MS being a clinical condition associated with IR, obesity and CVD[15,18,31]. Among the groups, there was agreement on the need for at least three components to be present to close the diagnosis, however, for the WHO, EGIR and AACE, the presence of IR is indispensable, while for the IDF the mandatory condition is central obesity.

The lack of standardization in the parameters used for the diagnosis of metabolic syndrome represents a substantial challenge in the interpretation and comparison of epidemiological studies[18]. Different organizations and research groups adopt different criteria, which results in a considerable variation in risk factors and in the prevalence attributed to metabolic syndrome in different populations[9,17,31]. This disparity not only obscures the global understanding of the prevalence and impact of metabolic syndrome, but also hinders the formulation of effective public health strategies for its management[16].

It is imperative to call for standardization of the diagnostic criteria for metabolic syndrome, with special emphasis on the need to address underreported diagnosis. Many cases of metabolic syndrome can go unnoticed due to the lack of uniformity in the diagnostic criteria, resulting in an underestimation of the true prevalence of the condition[30]. This underreporting can have significant implications for public health, since individuals who are not correctly diagnosed may miss the opportunity for preventive interventions and appropriate treatments[3,32]. The standardization of diagnostic criteria would not only improve the comparability between epidemiological studies, but would also ensure that all cases are identified consistently[33].

Therefore, it is essential to recognize the urgency of establishing uniform diagnostic criteria for metabolic syndrome, not only to improve consistency in epidemiological studies, but also to ensure that all affected individuals are accurately identified[32]. Standardization would provide a solid foundation for more effective public health approaches, addressing the need for early diagnosis and personalized interventions. This call for uniformity in diagnostic criteria aims to improve the accuracy and comprehensiveness of research, as well as to optimize clinical management and the implementation of preventive strategies [31,33].

SM COMPONENTS

INSULIN RESISTANCE - IR

IR is characterized by a deficiency in the action of insulin in peripheral target tissues, especially in skeletal muscles and adipose tissue, in an attempt to maintain normal blood glucose levels, the pancreas produces large concentrations of insulin, which results in compensatory hyperinsulinemia, but this mechanism further aggravates IR, especially in obese individuals[22,23].

In normal physiological function, insulin binds to the insulin receptor resulting in the phosphorylation of tyrosine and the activation of pathways, such as phosphoinositide 3-kinase (PI3K). In cases of hyperinsulinemia, tyrosine residues attach to the PI3K binding sites, generating IR in sensitive tissues[13]. In adipose tissue, IR causes increased concentrations of free fatty acids (FFA) through insulin-mediated inhibition of lipolysis, impairing the insulin signaling cascade. In addition, FFA affect the action of PI3K, which decreases the translocation of glucose transporter 4 (GLUT-4) to the surface, leading to a decline in glucose uptake, especially in skeletal muscles[25].

The gold standard for evaluating IR is the euglycemic hyperinsulinemic clamp (CHE), which is a direct quantification method that consists of the administration of exogenous insulin through continuous intravenous infusion, causing hyperinsulinemia, the sensitivity of insulin action is quantified by the glucose infusion rate, demonstrating the tissue action of insulin, the disadvantage is the high cost and the need for a technique to perform it[34]. However, other methods are used to assess this condition, such as: *Homeostasis Model Assessment* (HOMAR-IR), Oral Glucose Tolerance Test (OGTT) and *Quantitative Insulin Sensitivity Check Index* (QUICKI).

The HOMAR-IR evaluates insulin sensitivity through a mathematical formula that requires fasting glucose and insulinemia, based on the degree of fasting hyperglycemia caused by pancreatic beta cell deficiency and IR[35]. It is possible to calculate the value of the RI through the equation:

$$HOMA - IR: \frac{\text{Glicemia em jejum } \left(\frac{\text{mmol}}{\text{L}}\right) \; x \; \text{Insulina em jejum } \left(\frac{\text{uU}}{\text{mL}}\right)}{22.5}$$

It is considered a tool that is easy to apply and perform, and is widely used in the clinical and epidemiological spheres, however, the lack of standardization in reference values makes it difficult to obtain reliable values[35].

OGTT is performed through blood samples before and after oral ingestion of 75g of glucose diluted in 300 mL of water in five minutes, the conventional protocol consists of the determination of glucose and insulin every 30 minutes for 2 or 3 hours[35]. It is worth noting that glucose tolerance reflects information about the body's metabolic capacity after an oral glucose overload and not about IR, which is why it is frequently used in clinical practice to identify glucose intolerance and DM2[35].

The QUICKI evaluates insulin sensitivity by a logarithmic calculation made to normalize the variability of the values obtained by a fasting glucose and insulin measurement, through the correlation of both[34], in the following formula:

$$\text{QUICKI: } \frac{1}{\log(\text{insulina em jejum } \left(\mu \frac{\text{U}}{\text{mL}}\right) + \log(\text{glicose em jejum } (\frac{\text{mg}}{\text{dL}})}$$

This method is widely used in population studies, in addition to helping to observe the progression of DM2 (Chart 2).

Table 2. Comparison of methods for determining insulin resistance.

Method	Reference value	Advantages	Disadvantages
CHE	5.3 mg/kg (performed at 80 mU/m² min)	Direct method under stable conditions	Experienced operators; risk of hypoglycemia; frequent collection of blood samples; need for insulin infusion; high cost; accomplishment.
HOMA-IR	> 2.5 U/mLμ	Simple, minimally invasive, it provides blood glucose and insulin values in a state of homeostasis	SI at the hepatic level is equal to peripheral SI, poor precision, does not obtain reliable results in individuals with a deficit of secretion by pancreatic beta cells; lack of standardisation of reference values.
TOTG	140-199 mg/dL (glucose tolerance) >200 mg/dL (T2DM) in 2 measurements after 120 min	Simple	Useful for assessing glucose tolerance, but not IR.
QUICKI	<0,3310,010 for obese± <0.3820.007 for non-obese± <0.3040.007 for diabetics±	Consistent, precise and minimally invasive	Interlaboratory variations in the method of insulin measurement.

SI: insulin sensitivity; IR: insulin resistance.

ATEROGENOUS DYSLIPIDEMIA

Atherogenic dyslipidemia refers to the group of alterations in the dyslipidemic profile characterized by the elevation of TG, apolipoprotein B (apo-B) and small and dense particles of low-

density lipoprotein (LDL), as well as the reduction in HDL cholesterol particles and concentration, these alterations are strongly linked to MS([36].

IR induces lipolysis, which consequently increases FFA concentrations in the liver, serving as substrates in TG production and stimulating the synthesis of very low-density lipoproteins (c-VLDL), in addition, there is a reduction in lipoprotein-lipase activity, which is responsible for VLDL clearance, which contributes to hypertriglyceridemia[24,36]. This condition increases the activity of the cholesterol ester transfer protein (CETP) that transfers TG from VLDL to HDL in exchange for cholesterol esters, resulting in TG-enriched HDL particles that are substrates for hepatic lipase that promotes the metabolization of small and dense, extremely atherogenic LDL particles that amplify oxidative stress[36]. In addition, hyperglycemia is also responsible for the increase in the prothrombotic and inflammatory state, together with IR, causing endothelial alterations that can lead to the formation of atherosclerosis plaques due to reduced blood flow[15,37].

CENTRAL OBESITY

Adipose tissue, in addition to being an energy reserve, is a significant risk factor because it triggers numerous changes in the body through metabolically active endocrine function due to adipokines, which results in metabolic and hormonal imbalances, enabling the development of other pathologies such as IR and SAH[18,23].

Obesity is characterized by the excessive accumulation of body fat, with a sedentary lifestyle and positive energy balance as the main factors, in addition to having a great genetic influence. With emphasis on central or visceral obesity, which is the one in which excess fat is located primarily in the upper region of the body, with an important correlation in IR due to poor fat distribution[25].

It is noteworthy that there are three types of adipose tissues – brown (found in the neck, interscapular and supraclavicular areas); white (subcutaneous and visceral regions); and beige (supraclavicular region, in the inguinal canal, near the carotid sheath and the long neck muscle) –, white has expressed greater concern, since it is related to the increase in cytokines, adipokines, and reactive oxygen species (ERONs) [38].

Leptin is a hormone that stimulates eating behavior and energy intake, it is released by adipokines and its concentrations are directly related to the amount of body fat, that is, in obesity, levels will be strictly high, but they do not suppress appetite, characterizing the condition of leptin resistance and promoting a pro-inflammatory response[36].

Resistin is an adipokine secreted predominantly by adipocytes, which can negatively influence insulin signaling, triggering a state of insulin resistance associated with obesity. In addition, resistin can also modulate inflammation and energy metabolism, which contributes to the pathogenesis of MS([39].

Proinflammatory cytokines, such as IL-6, IL-1β, TNF-α, CRP, and haptoglobin, are released by adipose tissues, immune cells, and other sites affected by obesity, exacerbating chronic inflammation and contributing to IR and dyslipidemia, thus, these molecules play crucial roles in instigating and maintaining the inflammatory state associated with MS[21,26].

The increase in the production of ROS, advanced glycation end products (AGEs), 8-hydroxydeoxyguanosine (8-OHdG) and malondialdehyde (MDA) is intrinsically linked to the oxidative stress observed in MS([38]). These molecules contribute to cellular damage and modifications in proteins and lipids, triggering inflammatory responses and impairing cell function[40].

Chronic stress caused by obesity promotes the activation of the hypothalamic-pituitary-adrenal (HPA) axis and consequently the increase in cortisol levels. Studies highlight the complex interaction between cortisol in response to adrenocorticotropic hormone (ACTH) and metabolic syndrome[41]. The somatotrophic axis, which involves hormones such as insulin and insulin-like growth factor type 1 (IGF-1), plays a crucial role in the regulation of growth, development and metabolism, so the imbalance in this hormonal axis can contribute to the metabolic dysfunction observed in insulin resistance and metabolic syndrome[42].

The diagnosis of obesity, based on the parameter defined by the WHO – refers to the BMI, obtained from the ratio between body weight (kg) and height squared (m²) of individuals, where those whose BMI is equal to or greater than 30 kg/m² in adults are considered obese[6]. However, the most applied forms of measurement of abdominal adiposity in clinical practice and epidemiological research are: WC and waist-to-hip ratio (WHR). Table 3 shows the cut-off points for abdominal obesity (Chart 3)[43].

Table 3. Cut-off points for abdominal obesity.

Indicator	Men	Women
CC	>94 cm	>80 cm
WHR	>0.90	>0.85

Cc: waist circumference; WHR: waist-to-hip ratio.
Fonte: Cardinal, *et al.* 2018.

SYSTEMIC ARTERIAL HYPERTENSION - HYPERTENSION

According to Barroso et al.[44] SAH is a multifactorial clinical condition characterized by elevated and persistent blood pressure levels, with blood pressure equal to or greater than 130 x 80 mmHg, measured on at least two different occasions in the absence of antihypertensive drugs.

SAH is a polygenic syndrome and its development is related to constitutional and environmental factors, being determined by the product of cardiac output (CO) with peripheral vascular resistance (PVR), which are regulated by coordinated actions between the cardiovascular, renal, neural and endocrine systems, in addition to genetic and environmental aspects[44].

Renal functions influence blood pressure through adjustments of renal sodium excretion, renal autoregulation, and activation of the renin-angiotensin-aldosterone system (RAAS). According to Silva et al.[45] When some alterations occur, such as reduced blood flow, dietary sodium restriction (<100mEq/day), or/and reduction in plasma aldosterone concentration, the kidneys are stimulated to increase the release of the renin enzyme that converts angiotensinogen into angiotensin I, which is immediately converted into angiotensin II by angiotensin-converting enzyme. angiotensin II promotes vasoconstrictor action that results in the release of aldosterone, catecholamines, adrenaline, in addition to increasing muscle tone and stimulating sodium reabsorption[44,45].

TREATMENT

There is no specific treatment for MS, but the main objective is to minimize and prevent the risk of major cardiometabolic complications, through strategies to change lifestyle, use pharmacological medications, or combine both[10].

Drug treatment is performed by individualization and appropriate management of each of the components of MS according to their particularity, through a meta-analysis Guzmán et al. Vasconcelos et al.[46] showed that the use of some drugs (aspirin, statins, beta-blockers, thiazides, and alpha-glucosidase inhibitors) has a 3.39-fold (CI 0.81 – 9.99) probability of reversing MS, although strategies aimed at diet and physical activity are more effective.

Evidence indicates that lifestyle modifications improve MS and reduce the incidence of all components, so the primary strategy for the treatment and prevention of MS is lifestyle changes, highlighting diet and physical activity as essential, as regular physical exercise and the adoption of a balanced diet corroborate weight loss[11,12,46].

Weight reduction of 5% to 10% helps to reduce blood pressure and lipid levels, contributing to an improvement in IR and, consequently, in MS components. The association of a balanced diet and regular physical activity, at least 3 times a week, with an average of 30 minutes or >10,000 steps/day through the use of the pedometer, plays an important role in the loss of abdominal fat[11,47].

DIET THERAPY

Some dietary approaches can help regulate the components of MS, such as sodium intake of < 65 to 100 mmol/day, associated with potassium intake of 90 to 120 mmol/day, in the regulation of blood pressure[11]. The consumption of mono/polyunsaturated fatty acids and the intake of soluble fibers have a cardioprotective effect, in addition to improving dyslipidemias[11,46]. In addition, a diet rich in complex carbohydrates with a low glycemic index contributes to the reduction of hyperglycemia and hyperlipidemia[46].

Several dietary strategies collaborate in weight loss, such as: the caloric deficit of 500 to 1000 calories/day, in addition, the use of the Mediterranean diet and the DASH diet, both have similar characteristics such as the high consumption of fresh foods (fruits, vegetables, legumes, grains), the intake from this food group improves the lipid profile and glycemia, in addition to bringing benefits to quality of life[10,11,12].

DIETA DASH

The DASH diet is a dietary approach recognized for its benefits in blood pressure control, and more recently for its potential impact on MS components[47]. Based on balanced nutritional principles, DASH emphasizes the consumption of foods rich in potassium, calcium, magnesium and fiber, such as fruits, vegetables, whole grains and low-fat dairy products[48].

The combination of the consumption of these foods favors the attenuation of MS components, such as SAH, due to the increase in sodium intake, which favors renal sodium excretion, consequently attenuating water retention[47]. The consumption of foods such as fish, nuts and olive oils contribute to the reduction of total cholesterol levels and the improvement of insulin sensitivity, as they have in their composition anti-inflammatory compounds that attenuate the systemic inflammatory response and polyunsaturated and monounsaturated fatty acids, which positively influence the lipid synthesis and transport pathways[11,47].

In addition, adherence to this strategy can act on glycemic control through a balance between complex carbohydrates, fibers and proteins, as a result, a modulation in the postprandial hormonal response is observed, favoring insulin sensitivity and positively influencing the intestinal microbiota[47,48].

MEDITERRANEAN DIET

The Mediterranean diet is a traditional dietary pattern with roots in Mediterranean regions, such as Greece, Italy and Spain, and is characterized by abundant consumption of fruits, vegetables, legumes, olive oil, fish, seafood, nuts and seeds, as well as moderation in the consumption of red meat, dairy products and red wine[48]. Scientific studies have consistently associated the Mediterranean diet with several benefits in promoting metabolic health[12,49].

Regarding the components of MS, the Mediterranean diet has emerged as a promising approach for the management and prevention of this condition. Recent epidemiological studies, such as those conducted by Hernandez et al.[Vasconcelos et al.(49)] have highlighted the benefits of the Mediterranean diet in reducing the incidence and improving the components of MS, such as abdominal obesity, IR, dyslipidemia, and SAH.

The high content of fiber, antioxidants, and monounsaturated fatty acids present in this diet can modulate inflammation, improve insulin sensitivity, and regulate lipid profile. In addition, the bioactive compounds present in foods such as olive oil and fish can positively influence energy metabolism, glycemic and lipidemic homeostasis[49,50].

FINAL CONSIDERATIONS

In view of the comprehensive analysis of MS, it becomes evident that this condition has a syndemic character, transcending the exclusive boundaries of physical health to encompass social and economic aspects. The complex interrelationship between metabolic risk factors, such as obesity, hypertension, and dyslipidemia, reflects the need for an integrated approach in public health. The steady increase in MS estimates highlights the urgency of preventive and therapeutic actions, since the condition not only compromises individual quality of life, but also exerts significant pressure on health systems.

Among the various diagnostic criteria proposed by different organizations, the set suggested by the NCEP-ATP III stands out due to its wide acceptance and simplicity in clinical application. The emphasis on waist circumference and other markers, such as high triglycerides, low HDL cholesterol, and high blood pressure, make this set of criteria a practical and effective tool for identifying MS in different clinical settings.

In the therapeutic field, current evidence highlights the importance of an individualized approach, considering the specific components altered in each patient. Drug therapy should be targeted according to compromised metabolic parameters, while dietary interventions play a crucial role. Among dietary approaches, the DASH and Mediterranean diets emerge as the most recommended due to their proven efficacy in improving risk factors associated with MS.

Given this complex scenario, it is imperative that metabolic syndrome be recognized as a critical public health problem. The implementation of effective public policies becomes crucial, including training and sensitization programs for health professionals, with an emphasis on early identification and appropriate management in primary care. In addition, the creation of government patient registration and follow-up programs aims not only to mitigate the effects of MS, but also to prevent long-term complications, providing a comprehensive and sustainable approach to address this global health challenge.

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