Int J Cardiovasc Sci. 2023; 36:e20230101

REVIEW ARTICLE

One Size Does Not Fit All: The Need to Rethink the Metabolic Syndrome in Women

Maria Cristina Costa de Almeida,[1] Marildes Luiza Castro,[2] Larissa Neto Espíndola,[3] Luciana Nicolau Aranha,[4] Thaís Salim,[4,5] Gláucia Maria Moraes de Oliveira[4]

Centro universitário de Belo Horizonte (UNIBH), Belo Horizonte, MG – Brazil
IPEMED,[2] Belo Horizonte, MG – Brazil
Hospital Santa Izabel,[3] Salvador, BA – Brazil
Universidade Federal do Rio de Janeiro,[4] Rio de Janeiro, RJ – Brazil
Universidade de Vassouras,[5] Vassouras, RJ – Brazil

Abstract

Metabolic syndrome (MetS) is increasing at epidemic proportions worldwide. MetS and its components are frequent among Brazilian women (41.8%). Women are affected by changes in adipose tissue distribution, lipid profile, insulin resistance (IR), and vascular remodeling during their lives. These changes result from the lack of estrogen after menopause. There have been various attempts to propose a uniform origin for the clustering of the MetS components, including genetics, IR, obesity, lifestyle, sleep disturbances, inflammation, fetal and neonatal programming, and disturbed circadian rhythm of the body functions. The proinflammatory and prothrombotic state in MetS is well-defined. Socioeconomic and lifestyle-related factors are also essential triggers of MetS, which is associated with a higher risk for coronary artery diseases (CAD) and stroke in women. Population measures in health and community medicine, such as continuing education on the importance of lifestyle change to reduce cardiovascular risks from early childhood, are fundamental strategies. Statins reduce high-sensitivity C-reactive protein blood levels and treat high cholesterol. According to the patient, hypoglycemic agents, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1(GLP-1a), and sodium-glucose transport protein 2 (SGLT2) inhibitors, in addition to metformin, have their indication due to their beneficial cardiometabolic and vascular effects. Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin-receptor blocker (ARB) should be the first choice to treat hypertension in postmenopausal womem. The recognition of the different gender- and age-specific risk factors, allowing for specific and targeted interventions, is fundamental, especially for women.

Keywords

Women; Metabolic Syndrome; Drug Therapy; Children; Adolescent; Diagnosis.

Definition and Clinical Implications of Metabolic Syndrome (MetS)

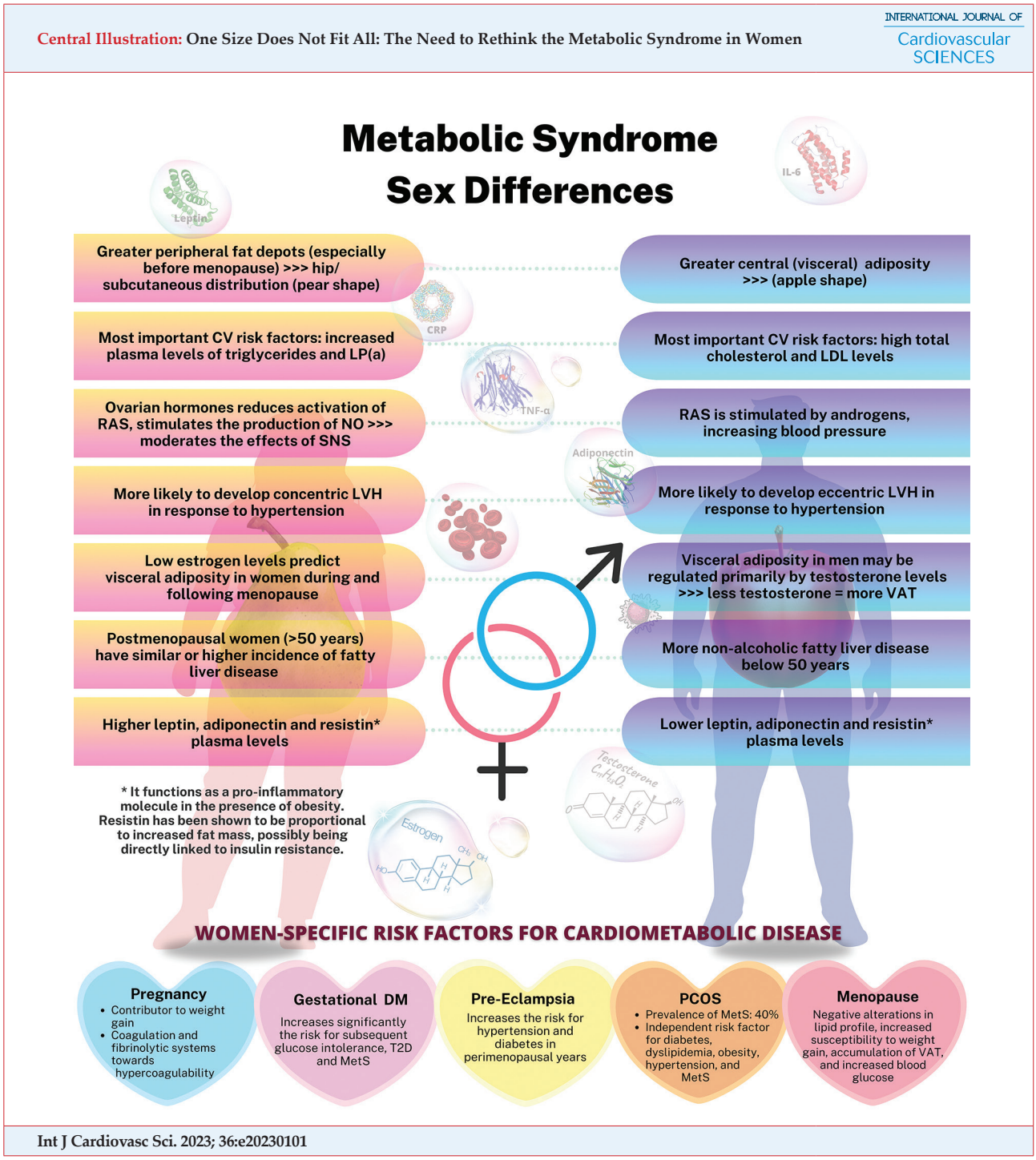
MetS represents a cluster of metabolic factors that may favor developing type 2 diabetes (T2D) and cardiovascular disease (CVD) in the future. Several definitions of MetS have been proposed, and some controversy exists about whether MetS is an actual syndrome or a mixture of unrelated phenotypes. In 2009, representatives of the International Diabetes Federation (IDF), American Heart Association (AHA), National Institutes of Health (NIH), International Atherosclerosis Society, World Heart Federation, and International Association for the Study of Obesity attempted to resolve the differences between the definitions of MetS.[1] The 'harmonized' MetS proposal has five components, and the presence of three abnormal findings out of those five would identify a person as having MetS. The risk of three associated factors does not exceed the risk of elevated blood pressure (BP) nor that of elevated plasma glucose alone. Table 1 shows the cut points defined for all components except waist circumference, for which national or regional cut points would be used.

Several meta-analyses have evaluated the incremental risk of MetS. Ford[2] have performed a meta-analysis to

Mailing Address: Gláucia Maria Moraes de Oliveira
Universidade Federal do Rio de Janeiro. Rua Visconde de Pirajá, 330, Sala 1114. Postal code: 22410-000. Rio De Janeiro, RJ – Brazil
E-mail: glauciamoraesoliveira@gmail.com

DOI: https://doi.org/10.36660/ijcs.20230101

Manuscript received July 7, 2023; revised manuscript July 12, 2023; accepted July 12, 2023.



Some sex differences in MetS. CV: cardiovascular; LDL: low-density-lipoprotein cholesterol; LP: lipoprotein; LVH: left ventricular hypertrophy; MetS: metabolic syndrome; NO: nitric oxide; PCOS: polycystic ovary syndrome; RAS: renin-angiotensinogen system; SNS: sympathetic nervous system; T2DM: type 2 diabetes mellitus; VAT: visceral adiposity.

estimate the impact of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and WHO definitions of MetS on all-cause mortality, CVD, and T2D. They have reported similar relative risks for all-cause mortality (1.27–1.37) and CVD (1.65–1.93) for both MetS definitions. In addition, they have estimated that the population-attributable risk (PAR) fraction for MetS was 6–7% for all-cause mortality and 12–17% for CVD. In the INTERHEART study[3] (n = 26 903) involving 52 countries, MetS was associated with a 2.2- to 2.7-fold

Table 1 – The "harmonized" MetS: criteria for clinical diagnosis.[1]

MEASURE	CATEGORICAL CUT POINTS
Elevated waist circumference	Population- and country-specific definitions
Elevated triglycerides(*)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-cholesterol (*)	Males: <40 mg/dL (1.0 mmol/L) Females: <50 mg/dL (1.3 mmol/L)
Elevated blood pressure (*)	Systolic ≥130 and or Diastolic ≥85 mmHg
Elevated fasting plasma glucose (**)	≥100 mg/dL (≥5.6 mmol/L)

HDL: high-density lipoprotein. (*) Drug treatment for elevated triglycerides, elevated glucose, and reduced HDL-cholesterol is an alternative indicator. (**) Antihypertensive drug treatment in patients with a history of hypertension is an alternative indicator.

increased risk of myocardial infarction. The presence of MetS in people with or without diabetes also increases the risk for ischemic stroke or transient ischemic attacks.[4] A meta-analysis has suggested that women with MetS were more sensitive (relative risk - RR, 1.83) than men (RR, 1.47), and people with MetS had a significantly higher risk of ischemic (RR, 2.12) than hemorrhagic stroke (RR, 1.48).[5] Another meta-analysis has included reports from 12 studies (n = 6865) aiming at quantifying the risk of progression from mild cognitive impairment to frank dementia in people with and without T2D, and with and without MetS. Both T2D and MetS were associated with an increased incidence of dementia (1.53 x 2.95, respectively) when co-existing with mild cognitive impairment.[6]

There have been various attempts to propose a uniform origin for the clustering of the MetS components, such as genetics, insulin resistance (IR), obesity, lifestyle, sleep disturbances, inflammation, fetal and neonatal programming, and disturbed circadian rhythm of the body functions.[7]

Epidemiology

The prevalence of MetS is increasing at epidemic proportions in developed and developing countries. The global prevalence of this condition in the adult population is estimated at 20% to 25%.[8] In Latin America, the general prevalence found was similar, 24.9%, with a more significant predominance of women and age over 50 years.[9]

In Brazil, an analytical cross-sectional study that used data from the 2013 National Health Survey, a nationwide home-based survey (PNS, n = 64 348 household interviews and 60 202 individual interviews) including data on laboratory tests collected between 2014 and 2015 (n = 8952), has estimated the prevalence of MetS in a Brazilian population (waist circumference ≥ 80cm for females and ≥ 90cm for males). The authors have estimated the prevalence of MetS and its components with 95% confidence intervals, as well as the unadjusted and adjusted prevalence ratio (PR) with Poisson regression. MetS and its components were more frequent among women (41.8%), individuals with low schooling (47.5%), and older adults (66.1%). In the adjusted analysis, females (PR = 1.16; 95% CI, 1.08-1.24), older adults (PR = 3.69; 95% CI, 3.26-4.17), and low schooling (PR = 1.32; 95% CI, 1.17-1.49) were associated with MetS. Table 2 summarizes the results stratified by sex.[10]

A recent meta-analysis has aimed to determine the prevalence of MetS among the adult population in Brazil. The overall pooled prevalence among the general population of Brazil was 33%, and high heterogeneity was observed. By gender, the prevalence was 26% in males and 38% in females. Regarding the residence area, the prevalence was 34% in urban, 15% in rural, 28% in quilombola, and 37% in indigenous areas. Regarding the geographic region, the prevalence was 37% in the South, 30% in the Southeast, 38% in the North, 31% in the Northeast, and 39% in the West-Central. The pooled prevalence of MetS according to age range was as follows: <45 years, 43%; and ≥45 years, 42%. The pooled prevalence based on the year of study was 31% in 2015–2019, 35% in 2010–2014, and 28% in 2005–2009.[11]

Table 2 – Prevalence of individual components and diagnosis of MetS in the Brazilian adult population according to gender, PNS 2013, and PNS Laboratory 2014-2015 (Adapted from Oliveira et al.[10])

MetS components		Total n- %a (95% CI)	Female n- %a (95% CI)	Male n- %a (95% CI)
Blood Preassure	≥ 130/85 mmHg	8.858	32.3 (31.0-33.6)	31.2 (29.6-32.9)	33.6 (31.6-35.6)
Waist circumference	≥ 80cm female / ≥ 90cm male	8.854	65.5 (64.1-66.9)	74.1 (72.4-75.7)	56.0 (53.8-58.2)
HDL-cholesterol	< 50mg/dl female / < 40mg/dl male	8.512	49.4 (48.0-50.8)	55.2 (53.4-57.1)	42.9 (40.7-45.1)
Total cholesterol	≥200mg/dl	8.526	32.8 (31.5-34.1)	35.1 (33.4-36.9)	30.1 (28.1-32.1)
Glycated hemoglobin	≥ 5.6 mmol/L	8.552	30.0 (28.7-31.3)	31.5 (29.8-33.2)	28.3 (26.4-30.3)
Metabolic syndrome		8.199	38.4 (37.0-39.8)	41.8 (40.0-43.6)	34.6 (32.5-36.7)

a: Population estimate; 95% CI: 95% confidence interval; HDL: high-density lipoprotein; MetS: metabolic syndrome.

Pathophysiology

The exact underlying mechanisms of MetS are still not completely understood. It is not clear whether the individual elements represent distinct pathologies or if they are manifestations of a complex common pathogenic mechanism. Nevertheless, critical lifestyle and environmental factors, such as overeating and lack of physical activity, have been identified as significant contributors.

The adipose tissue is recognized as a crucial regulator of cardiovascular health mediated by the secretion of several bioactive substances, and visceral adiposity (VAT) is considered the primary trigger for most of the pathways involved in MetS, releasing the three "key factors" responsible for increasing CVD risk: insulin resistance (IR), chronic inflammation, and neurohormonal activation. The final pathway is a proinflammatory state that explains the elevation of various inflammatory markers, such as interleukin 6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-α), seen in individuals with MetS.[12]

The enlarged VAT exposes the liver to high levels of free fatty acids (FFA) that impair hepatic lipid and carbohydrate metabolism, particularly in the postprandial state, which contributes to increased hepatic glucose production and β-cell dysfunction, resulting in decreased insulin secretion. The result of this pathway is IR that also contributes to the development of hypertension and a prothrombotic state, in addition to the release of proinflammatory cytokines, all of which contribute to increase the risk of CVD.[13]

IL-6 is a cytokine produced by adipocytes and immune cells, and its increased production is associated with increased body fat and IR. It raises the production of acute phase reactants, including CRP, and fibrinogen levels, resulting in a prothrombotic state. In addition, IL-6 promotes adhesion-molecule expression by endothelial cells and activation of the local renin–angiotensinogen system (RAS) pathways, leading to vascular wall atherosclerosis, inflammation, and dysfunction.[13,14]

TNF-α is another cytokine produced within the adipose tissue, mainly by macrophages, and its production varies proportionally to the adipose tissue mass and correlates with IR. TNF-α also contributes to IR by inducing hepatic lipolysis, which increases FFA load and inhibits adiponectin release, thus increasing the cardiovascular risk.[13,15] It is essential to emphasize the importance of neurohormonal activation in the MetS pathophysiology, which occurs through some pathways.

The increase in VAT promotes a clear imbalance in the levels of adipokines as follows: high leptin levels (promotes a proinflammatory immune response by activating the Th1 pathway) and reduced adiponectin levels (affects the nuclear factor kappa-light-chain enhancer of activated B cells [NF-κB], has anti-atherogenic properties, decreases both vascular reactivity and smooth muscle proliferation, improves plaque stability, and its effects oppose those of leptin; thus, it has been considered a protective factor against the development of diabetes, hypertension, and acute myocardial infarction). That imbalance increases the risk of CVD.[14,15]

Angiotensin II (Ang II) is also produced by the adipose tissue. VAT and IR are associated with an increased production of Ang II, leading to the generation of

reactive oxygen species (ROS), which precipitates a cascade of effects, such as LDL oxidation, endothelial injury, platelet aggregation, and expression of NF-κB and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) on the endothelium and vascular smooth muscle cells. This RAS, ROS, and LOX-1 activation initiates a vicious cycle of inflammation, endothelial damage, and fibroblast proliferation, resulting in the development of hypertension, dyslipidemia, diabetes, cardiac hypertrophy, and, finally, CVD.[15]

To summarize, there are well-known triggers of several proatherogenic pathways that culminate in a proinflammatory state, systemic oxidative stress, and IR, leading to increased activation of other downstream signaling cascades that culminate in atherogenesis, tissue fibrosis, and, finally, cardiometabolic risk and CVD.

The individual components that define MetS are known to be the same in women and men, but data indicate that the cardiovascular risk conferred by MetS is highly dependent on gender and sex hormone status throughout life. Therefore, understanding individualized MetS development based on gender is of clinical importance, and some of these differences deserve to be highlighted (Figure 1).[16,17]

Sexual hormones may regulate the adipose tissue distribution and BP. Androgens lead to an increase in BP by activation of the RAS, whereas ovarian hormones have the opposite effect, reducing plasma renin and angiotensin-converting enzyme activity, resulting in a decrease in BP. In addition, the differences in BP control between men and women could be explained by the sex hormones' effects on renal sodium reabsorption and vascular resistance. Estrogens seem to induce structural beneficial effects on the arterial wall that reduce vascular stiffness, maintain normal endothelial function by stimulating the production of nitric oxide (NO), and moderate the sympathetic nervous system effects.[17]

Testosterone is associated with adipose-regulating effects. VAT in men may be regulated primarily by testosterone levels, with low serum testosterone associated with reduced subcutaneous and increased abdominal adiposity in men.[17]

Women are affected by changes in the adipose tissue distribution, lipid profile, IR, and vascular remodeling during their lives, and these changes result from the decreased protective effect of estrogens as the result of menopause. Premenopausal women tend to have greater peripheral fat depots, accumulating in the gluteus–femoral area ("pear-shaped"). However, during the perimenopausal period, fat deposition tends to increase centrally, and the decreased protective effect of estrogens contributes to endothelial dysfunction, inflammatory state, and arterial stiffness, resulting in increased CVD risk. Furthermore, postmenopausal women have the tendency to reach higher levels of total cholesterol, LDL-cholesterol, triglycerides, and lipoprotein(a), as well as lower HDL-cholesterol levels compared with premenopausal women, which represents a change to a proatherogenic and procoagulatory lipid profile strongly connected with the increase in visceral fat mass and classically important risk factors for CVD.[17,18]

Although considered a single syndrome for men and women, MetS is a heterogeneous entity, with biological variations related to age and gender that can impact its clinical presentation, and, therefore, the cardiovascular outcomes. It is of fundamental importance to recognize the different risk factors specific to each gender and age, which allows for specific and targeted interventions, mostly with preventive purpose (Central Illustration).

Diagnosis

Although some people are genetically prone to developing MetS, others develop it due to their lifestyle or other factors. Factors that increase the risk for MetS are obesity/overweight, and excessive fat in and around the abdomen is most strongly associated with MetS and IR. Some people are genetically predisposed to IR. For example, Black men are less likely than White men to have MetS, and Black women are more likely than White women. The risk of developing MetS increases with age.[7]

In a study with 302 individuals, half of the sample had a body mass index (BMI) of 27 to 30 kg/m² and the other half had a BMI > 30 kg/m², 45% being women. That study has reported that MetS was associated with an increased inflammatory profile that profoundly differed between women and men: women with MetS showed a lower concentration of anti-inflammatory adiponectin, whereas men showed increased levels of several proinflammatory markers, such as IL-6 and leptin. Adipose tissue inflammation showed similar sex-specific associations with these markers. Peripheral blood mononuclear cells isolated from men, but not women, with MetS showed enhanced cytokine production capacity.[12] Figure 2 summarizes the diagnostic findings of MetS.

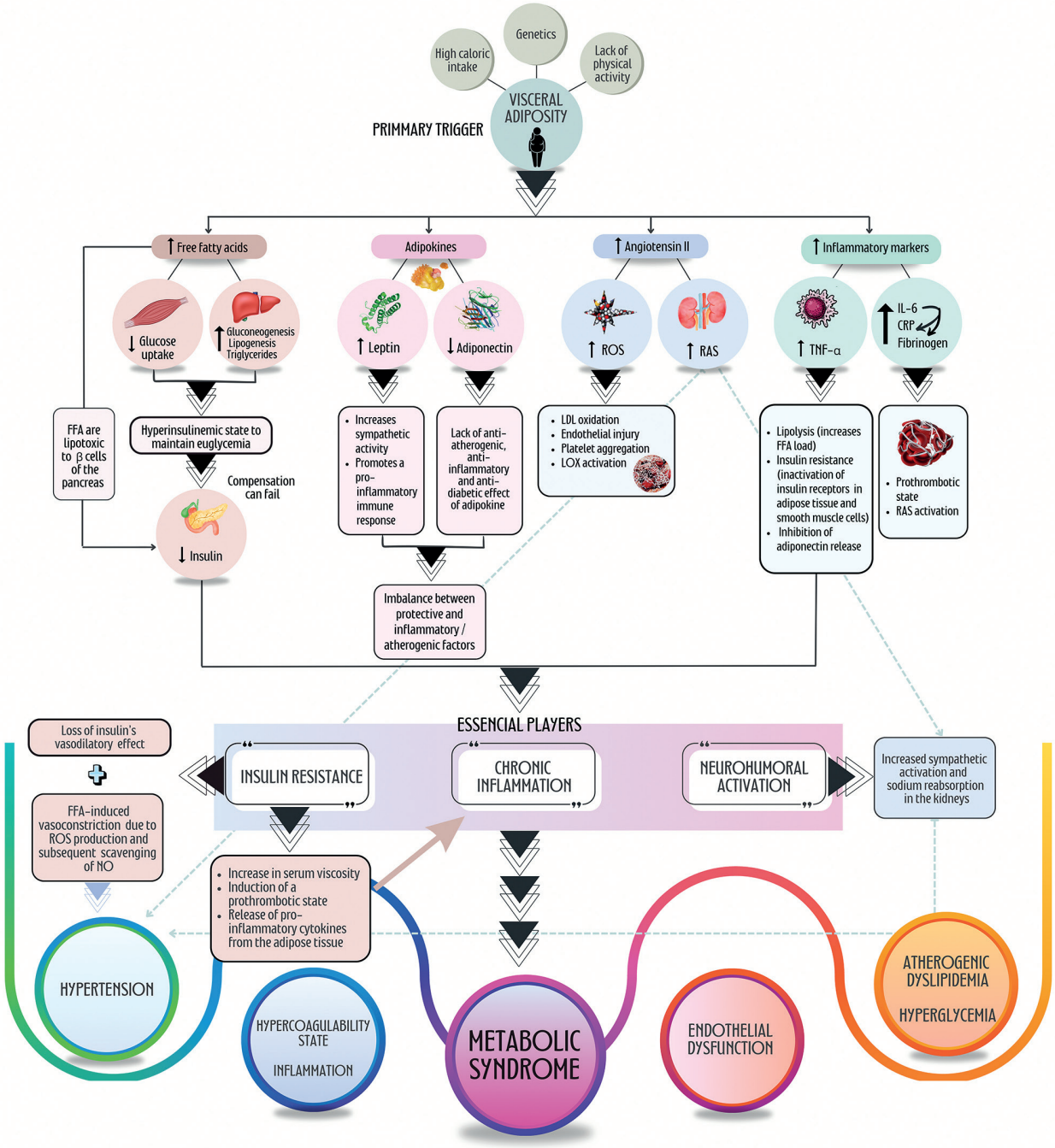


Figure 1 – The complex pathophysiology of MetS with its primary trigger, three mean players, and other components of this clustering of risk factors that, in fact, result in cardiovascular risk increase.
CRP: C-reactive protein; FFA: free fatty acids; IL-6: Interleukin 6; LDL: low-density lipoprotein cholesterol; LOX: lectin-like oxidized low-density lipoprotein receptor-1; NO: nitric oxide; RAS: renin-angiotensinogen system; ROS: reactive oxygen species; TNF-α: tumor-necrosis factor alpha.

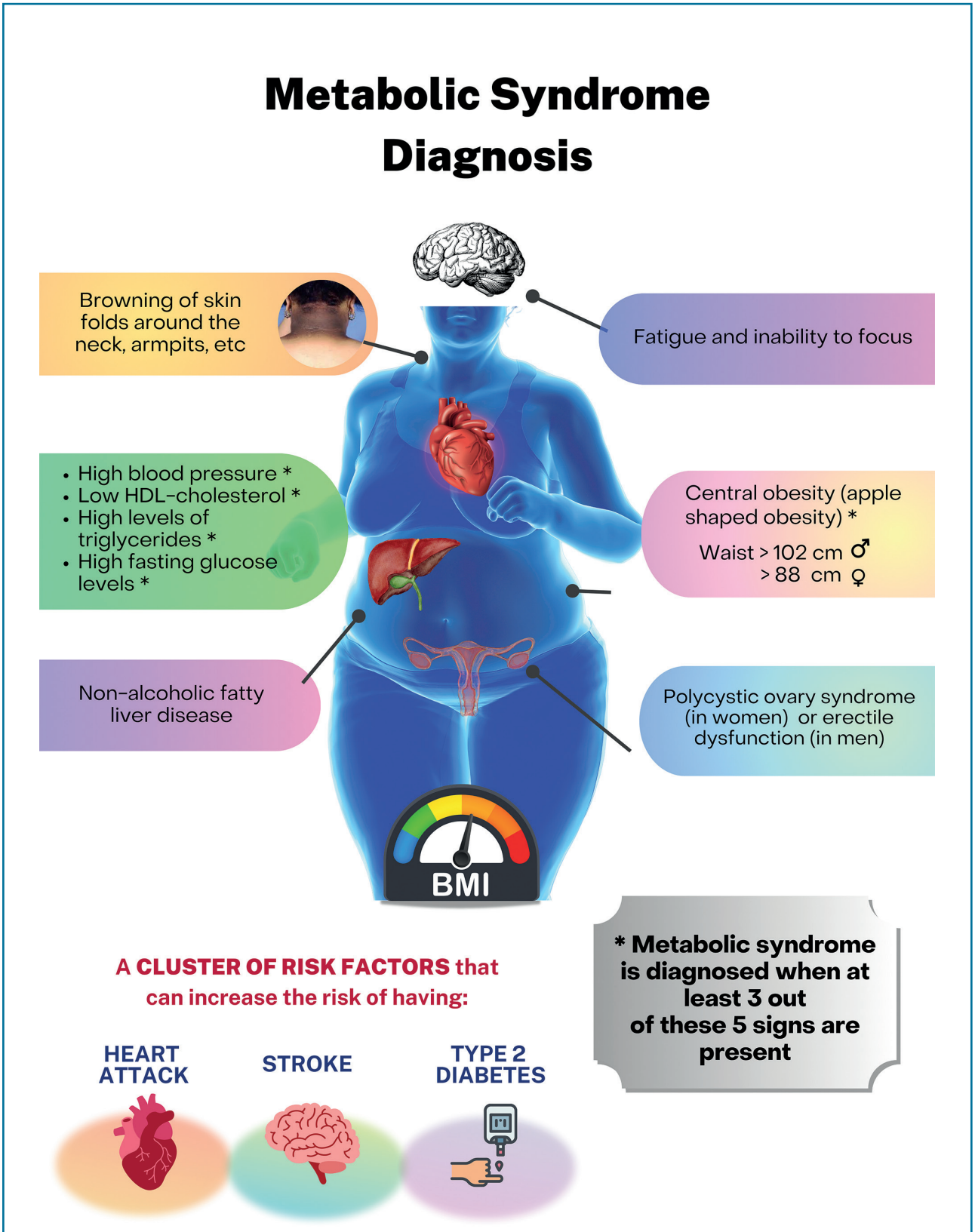


Figure 2 – Diagnostic findings of MetS.

MetS in children and adolescents

MetS in childhood and adolescence still lacks consistent diagnostic criteria.[19] Characteristics, such as glucose metabolism disorder, arterial hypertension, dyslipidemia, and abdominal obesity, raise diagnostic suspicion. However, the definitions of cut-off values are still heterogeneous in the pediatric population and vary with age.[19-21] Several studies have linked the early development of MetS to a higher risk of CVD, T2D, obstructive sleep apnea, and sudden death.[22-26] In 2017, the American Academy of Pediatrics proposed screening for and treatment of individual risk factors of MetS defined for adults.[20] Given that the set of risk factors for the MetS components shares pathophysiology and many common lifestyle modification-based treatment approaches, this can also be applied to the pediatric population. It is estimated that approximately 40% of obese children and adolescents have MetS.[21] This should heighten the attention of healthcare professionals caring for this population, as the global prevalence of obesity in childhood and adolescence doubled in the last decade.[21] In the United States, obesity affects one in six teenagers, with an increase of nearly 3% when comparing years before the COVID-19 pandemic (2018-2019) with the 2020-2021 period.[21] According to the Global Obesity Atlas and the World Health Organization (WHO), Brazil is projected to rank 5th in the number of children and adolescents with obesity by 2030.[21,27,28] The Cardiovascular Risk in Adolescents (ERICA) study was the first national school-based cross-sectional study conducted in Brazil, including 73 399 adolescents.[22] The prevalence of obesity in that study was 8.4%, and, among the obese, there was a higher prevalence of hypertension, 28.4% (95% CI, 25.5-31.2), as compared to overweight adolescents, with a fraction of hypertension attributable to obesity of 17.8%.[23]

The factors that contribute to MetS in adulthood originate either during the prenatal and early postnatal period,[20,24,29] such as maternal gestational diabetes, low birth weight and rapid weight recovery during growth associated with glucose metabolism disorders, arterial hypertension, and obesity in adulthood,[29] or throughout childhood and adolescence, such as socioeconomic factors, parental obesity, and behavioral health factors (sedentary lifestyle, smoking, dietary habits, and screen usage).[20,24,27,28] (Figure 3)

The American Diabetes Association and the AHA recommend the prevention and treatment of obesity in childhood and adolescence as the main approach to reduce cardiometabolic risk.[20] The diagnosis of obesity in children and adolescents is based on anthropometric data, such as weight, height, and BMI, which should be measured at each medical visit and classified according to age and sex using charts: Weight-for-Age, Height-for-Age, and BMI-for-Age.[19,20,28] Children with a BMI at or above the 95th percentile or a Z-score of +3 should be referred to a multidisciplinary weight control program.[20,28]

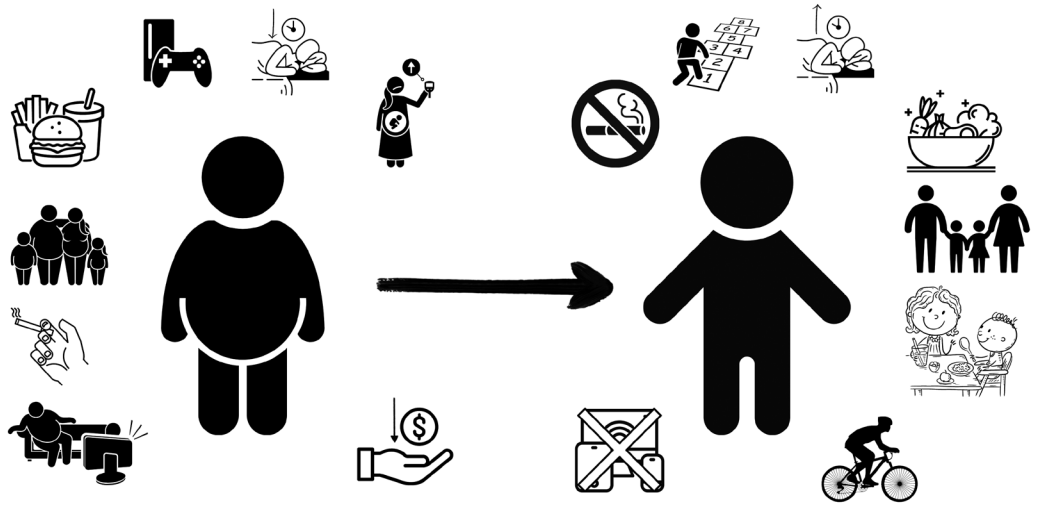


Figure 3 – Risk factors and preventive measures in children and adolescents for MetS in adults.

When these programs are not available, physicians should initiate intervention strategies to reduce obesity. In addition to obesity screening using BMI, children should be screened annually for high BP in primary care, with BP measurement by auscultatory method starting at 3 years of age or earlier in the presence of hypertension risk factors.[20,27] Screening for dyslipidemia with laboratory tests should be performed between 9 years and 11 years of age and in all patients, regardless of age, who are classified as obese or overweight. Screening for glucose metabolism abnormalities should be carried out in children and adolescents with risk factors for T2D, namely obesity or overweight, belonging to a high-risk racial and/or ethnic group, family history of T2D, physical signs of IR (*acanthosis nigricans*), polycystic ovary syndrome (PCOS), dyslipidemia, or hypertension.[20]

The treatment of MetS is multifactorial and involves individual and family behavioral measures, such as adopting a healthy diet, increasing outdoor activities and physical exercise, weight loss or reducing the rate of weight gain, adequate sleep duration for each age group, and reducing screen time.[20,24,27,28] In some cases, pharmacological measures may be necessary for the treatment of obesity, hypertension, dyslipidemia, and glucose metabolism abnormalities.[19,20,27] Regular follow-up with a healthcare professional is important to monitor progress, prevent future cardiometabolic disease risk, and its complications.

Non-pharmacological treatment

Lifestyle modification is the primary and effective strategy to control each MetS component and improve CVD prognosis.[30,31] Recommendations include weight reduction in overweight and obese patients, adherence to a healthy eating pattern, physical activity, smoking cessation, sleep hygiene, and stress management.[30-32] Salas-Salvadó et al. have evaluated the effectiveness of an intensive lifestyle intervention for weight loss based on energy-restricted Mediterranean diet (Med-diet), physical activity promotion, and behavioral support in participants of the *Prevención con Dieta Mediterránea* (PREDIMED)-Plus study. The participants were overweight/obese and had MetS. After a 12-month follow-up, the following was observed: a reduction in weight and waist circumference; improvement in glycemic parameters and lipid profile; and a reduction in inflammatory markers, such as IL-18 and monocyte chemoattractant protein-1 (MCP-1).[33] In addition, some reference studies that evaluated adult individuals with glucose intolerance, such as The Finnish Diabetes Prevention Study[34] and the Da Qing Diabetes Prevention Outcome Study,[35] have demonstrated that lifestyle interventions, including diet and/or physical activity with the aim of reducing body weight, decreased the risk of diabetes by 58%, incidence of cardiovascular events by 26%, microvascular complications by 35%, cardiovascular mortality by 33%, and all-cause mortality by 26%, in addition to increasing survival by 4.82 years and life expectancy by 1.44 year.[35]

A reduction ≥ 5% of the baseline body weight has been recommended for overweight or obese individuals at metabolic risk.[30-32] A systematic review conducted with randomized clinical trials has shown that interventions, such as weight loss, significantly reduced systolic and diastolic BP, LDL-cholesterol, triglycerides, fasting plasma glucose, and hemoglobin A1C over 6-12 months, and these changes remained after two years for several risk factors.[36] It is known that successful weight loss and weight maintenance depend on adherence to lifestyle intervention components, which include dietary changes, physical activity goals, and self-monitoring, thus highlighting the importance of the follow-up of these individuals by health professionals.[30]

Dietary interventions should be based on healthy foods and adequate total energy intake to achieve weight control.[37] Several dietary patterns can be used to treat MetS, emphasizing Mediterranean diet, vegetarian diet, and Dietary Approaches to Stop Hypertension (DASH).[7,38,39] In general, these dietary patterns emphasize the consumption of whole grains, fruits and vegetables, healthy sources of protein (mainly plants, fish and seafood, and low-fat dairy products), liquid vegetable oils, and minimally processed foods, in addition to limiting alcohol and ultra-processed beverages, foods with added high sugar and salt contents. Healthy and balanced diet patterns can affect MetS components due to their high content of dietary fiber, omega 3 and 9 fatty acids, complex carbohydrates, antioxidants, minerals, vitamins, and bioactive substances, such as polyphenols. These contents can regulate the intestinal microbiota and block the signaling and expression of NF-kB, thus reducing oxidative stress and inflammation, which may lead to increased insulin sensitivity, improved lipid metabolism, and reduced BP.[38]

Physical activity is part of a healthy lifestyle and has many benefits in the treatment of MetS. A systematic review and meta-analysis study evaluating the effects of aerobic, resistance, and combined exercises on the MetS parameters has shown that resistance exercise was more

effective in reducing body fat, LDL-cholesterol, and BP. In contrast, aerobic exercise improved BMI and HDL-cholesterol, suggesting that combined exercise is the most effective measure in improving MetS parameters and reducing cardiovascular risk.[40] The guidelines recommend practicing aerobic physical activity at least 150 minutes per week, cumulative moderate-intensity or vigorous-intensity aerobic physical activity 75 minutes per week, or encouraging some type of physical activity for those who do not follow these recommendations.[30,31,32]

Smoking cessation and stress management through methods based on relaxation and cognitive-behavioral techniques may benefit individuals at metabolic risk since these are risk factors of CVD.[30,31]

It has been shown that both short-duration sleep (<6 hours) and long-duration sleep (>8 hours) are associated with an increased risk of MetS.[41] The most suitable sleep duration for health ranges from 7 to 9 hours for adults and 7 to 8 hours for elderly.[42] As sleep disturbances are prevalent in individuals with MetS, it is essential for healthcare professionals to investigate this diagnosis in the clinical evaluation.[42] Figure 4 summarizes the non-pharmacological measures in the treatment of MetS.

Pharmacological Treatment

MetS is a set of risk factors that can lead to future cardiovascular complications: abdominal obesity, arterial hypertension, hyperglycemia, lipid profile changes. The therapeutic strategy must address these factors, which implies polypharmacy. The primary intervention is lifestyle change, with dietary change and physical activity, as described above. However, in more advanced cases, pharmacological treatment becomes necessary.[43]

There is no single drug to treat MetS. The approach must be individualized, with the management of each metabolic alteration and its associated comorbidity: statins, hypoglycemic agents, antihypertensive drugs, and antiplatelet drugs for those with increased prothrombotic risk.

There has been increasing interest in the involvement of the circadian system, an important regulator of many aspects of the metabolism and endocrine function. Growing evidence connects circadian rhythm disturbances with the main components of MetS: BP, lipids, glucose, and adipose tissue. Some drugs would have their greatest benefit if taken respecting the circadian cycle.[44]

Recent research is evaluating the role of nutraceuticals in the treatment of MetS. Various plant extracts, spices, herbs, and essential oil extracts have apparent benefits in treating patients with MetS. Butirates, probiotics (gastrointestinal dysbiosis, which is the modification of the gastrointestinal microbiome can participate in the IR development); coconut oil (elevated medium-chain fatty acid) has antioxidant effect, decreasing oxidative

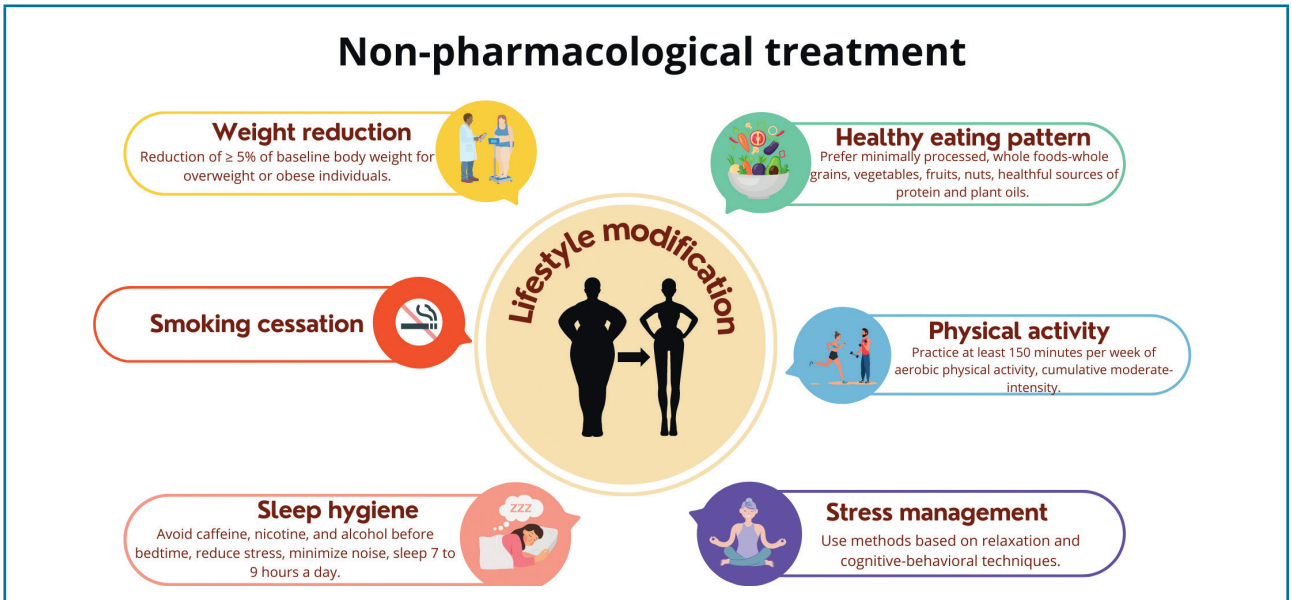


Figure 4 – Non-pharmacological treatment of MetS.

stress; curcumin (with anti-oxidative effect and anti-inflammatory properties, increases NO production) has beneficial effects on arterial stiffness and can control the weight of individuals with MetS.[14] Although some benefits have been documented, these agents are still under investigation and cannot be considered an alternative to pharmacotherapy.

Human physiology depends on omega-3 polyunsaturated fatty acids (n-3 PUFAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Fatty fish and seaweed are their main nutritional sources. The ability of these essential fatty acids to reduce plasma triglyceride levels are related to decreased plasma levels of the proinflammatory cytokines IL-6 and TNF- α, as well as CRP.[45]

The MetS treatment, in general, is similar in men and women, except for the use of some drugs in women of childbearing age (due to the risk of teratogenicity) and in those who need concomitant hormonal treatment. Apart from pharmacotherapy, there are no significant gender differences, except for metformin and thiazolidinediones in women with MetS and PCOS. Metformin is an insulin-sensitizing agent, fundamental to treat anovulation in infertile patients with PCOS and MetS as it lowers insulin levels and alters the insulin-stimulated effect of ovarian androgen synthesis. Thiazolidinediones are another alternative to improve IR and anovulation, as they attenuate ovarian androgen production and produce ovulation.[46]

Dipeptidyl dipeptidase-4 (DPP-4) expression showed a positive correlation with the extent of central obesity, VAT, and inflammation. Sitagliptin, a DPP-4 inhibitor, has been shown to decrease VAT and maximal response to an oral glucose tolerance test in women with PCOS.[14]

Sodium-glucose linked transporter 2 (SGLT2) inhibitors were associated with improvement in all MetS components, reducing blood glucose, systolic BP, and waist circumference. They seem to play a role in patients with MetS, regardless of the presence of T2D and heart failure.[47] In addition to reducing appetite and delaying gastric emptying, glucagon-like peptide-1 (GLP-1) appears to have direct antiatherosclerotic action by decreasing plaque formation and progression.

In postmenopausal women with hypertension and MetS, treatment is suggested to start with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB).[46]

Figure 5 sumarizes the pharmacological treatment of MetS.

Prognostic and future perspectives

As MetS is an important risk factor for the development of T2D and CVD, one of the most important measures is to identify patients at high metabolic risk. These patients need aggressive preventive actions, such as lifestyle change, especially physical activity and weight loss.

The MetS is a strong predictor of stroke and coronary artery disease (CAD) apart from T2D. In a systematic review and meta-analysis of longitudinal studies, MetS had an RR of cardiovascular events and death of 1.78 (95% confidence interval 1.58-2.00).[48] This association was stronger in women, even after adjustment for traditional cardiovascular risk factors,[49] as demonstrated in a study from the MORGAM Project, with a 12.2-year follow-up.[50] That study showed a difference between men and women: in men, the CVD risk was higher independently of age, whereas, in women, total CAD risk decreased significantly and the total stroke risk tended to increase with older age. In summary, in women, MetS was associated with higher RR for CAD events that decreased with age, whereas RR for stroke tended to increase.[50,51] It is important to emphasize that diabetes is a stronger independent risk factor for CVD in women, as it alone increases the risk of CVD by about two times, and that MetS is one of the most prevalent conditions that predispose to diabetes.[52] The association between MetS and diabetes is a consequence of IR and hypertension, dyslipidemia, and central obesity, and commonly coexist with T2D. These characteristics further aggravate the risk, which is highest in people with T2D and MetS features.[53]

A systematic review and meta-analysis has concluded that patients with MetS without diabetes were still at high cardiovascular risk (two-fold increase in cardiovascular outcomes) and mortality risk (1.5-fold increase in all-cause mortality), showing that the prognosis of MetS exceeds the risk associated with the sum of its individual components.[54]

Epigenetic components are known to influence the outcome of cardiometabolic diseases, such as diabetes and MetS. It has been proposed that understanding the interactions among genetic, epigenetic, environmental, and metabolic factors can lead to many explanations about this disease.[55] Therefore, it is important to recognize the risk factors to make interventions as preventive measures early from the intrauterine phase, avoiding unwanted outcomes in adult life.

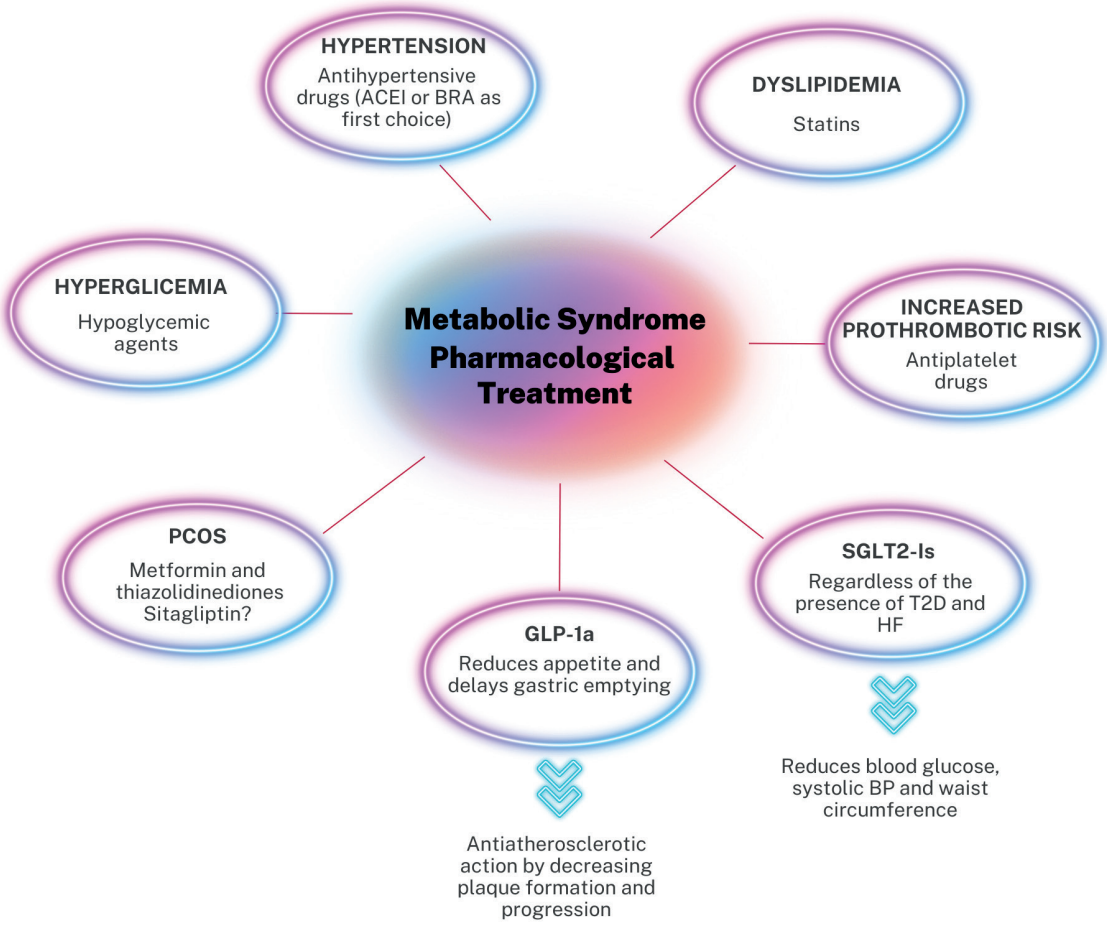


Figure 5 – Pharmacological treatment of MetS.
SGLT2-Is: sodium-glucose linked transporter-2 inhibitors; T2D: type 2 diabetes; HF: heart failure; BP: blood pressure; GLP-1a: glucagon-like peptide-1; PCOS: polycystic ovary syndrome; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker.

An important example is gestational diabetes, which shows great association with metabolic disorders in both the mother and newborn throughout their lives, associated with an increased risk of developing obesity, hypertension, and other CVD.[24,29] Preventive care for maternal and child health from the pre- and postconception period, such as maternal weight control, healthy lifestyle, such as adequate nutrition, physical activity, and others, can contribute to a healthy embryonic and fetal development.[7]

Socioeconomic and lifestyle-related factors, such as sedentary lifestyle, smoking, and dietary errors, are also important triggers of metabolic disorders. Population measures in health and community medicine, such as continuing education aimed at providing the population with information on the importance of lifestyle change to reduce cardiovascular risks from early childhood, are fundamental strategies in public health.[27]

New perspectives on the pathophysiology understanding include the role of circadian rhythm disturbances related to the MetS components, such as BP, metabolism of glucose, lipids, and adipose tissue. Another new concept is that the gastrointestinal microbiota diversity has an important function in health starting from birth and early life. Thus, this opens another opportunity for prevention, such as a healthy diet in childhood and young life, including breastfeeding.[7]

Author Contributions

Conception and design of the research: Almeida MCC, Oliveira GMM; acquisition of data, writing of the

manuscript: Almeida MCC, Castro ML, Espíndola LN, Aranha LN, Salim TR, Oliveira GMM; critical revision of the manuscript for intellectual content: Almeida MCC, Castro ML, Espíndola LN, Oliveira GMM; illustrations: Espíndola LN, Aranha LN; project coordination: Oliveira GMM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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