The role of genetic variations in metabolic syndrome: insights into etiology, diagnosis, and management

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ABSTRACT

Metabolic syndrome (MetS) is a cluster of interrelated conditions primarily driven by excessive caloric intake, physical inactivity, and excess abdominal fat. Core features include abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure. MetS is also closely associated with several comorbidities, such as a prothrombotic state, systemic inflammation, nonalcoholic fatty liver disease, and reproductive abnormalities. Its global prevalence is rising rapidly, particularly in urbanized areas and developing nations, reflecting changing lifestyles and dietary patterns. This surge has significant public health implications, as individuals with MetS face a twofold higher risk of developing cardiovascular diseases and a fivefold increased likelihood of progressing to type 2 diabetes. Managing MetS requires a multifaceted approach, with lifestyle modification as the cornerstone. Sustainable weight loss, achieved through dietary changes, regular physical activity, and behavioral interventions, is essential. Concurrently, it is critical to address other cardiovascular risk factors aggressively, including hypertension, hyperlipidemia, and hyperglycemia, to mitigate long-term health complications. As the prevalence of MetS continues to grow, understanding its pathophysiology and implementing comprehensive management strategies are paramount to reducing its global burden and improving patient outcomes.

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Key words: metabolic syndrome, polymorphism, diabetes, cholesterol, abdominal obesity.

Contributions: all the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not applicable.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: all data underlying the findings are fully available

Funding: none.

Acknowledgments: the author would like to acknowledge the support from A' Sharqiyah University and Galgotias University.

Received: 10 January 2025.
Accepted: 17 February 2025.

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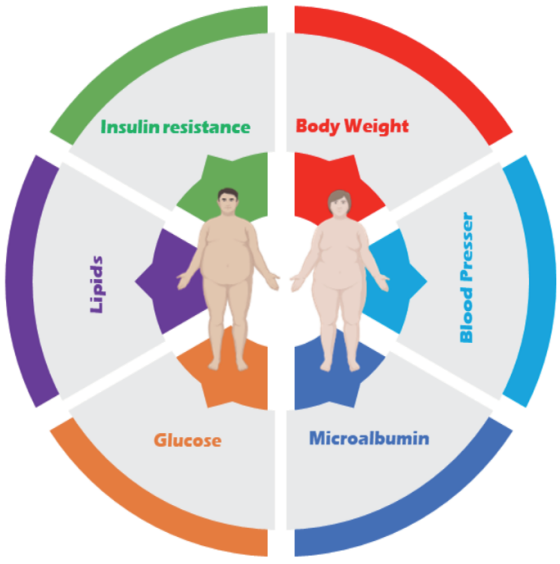
Licensee PAGEPress, Italy
Italian Journal of Medicine 2025; 19:1908
doi:10.4081/itjm.2025.1908

GRAPHICAL ABSTRACT



Introduction

The phenomenon of many metabolic abnormalities, such as dyslipidemia, dysglycemia, hypertension, central obesity, and insulin resistance, has been referred to as metabolic syndrome (MetS), which increases the danger of developing cardiovascular disease (CVD) and type 2 diabetes (T2D).[1,2] The clinical diagnosis of MetS involves the use of various indicators, such as measures of abdominal obesity, atherogenic dyslipidemia, hypertension, and glucose intolerance. To diagnose MetS according to the guidelines set by the World Health Organization, it is required to include the evaluation of fasting insulin levels or suitable alternatives, as well as the identification of indications suggesting the existence of insulin resistance. Nevertheless, the Adult Treatment Panel III of the US National Cholesterol Education Program (NCEP) proposed a simpler classification for therapeutic purposes, devoid of any consideration of insulin resistance. MetS is characterized by the existence of certain physiological markers, including elevated blood pressure levels exceeding 130/85 mm Hg, low levels of high-density lipoprotein (HDL) cholesterol below 1.04 mmol/L in men and 1.29 mmol/L in women, high levels of triglycerides exceeding 1.69 mmol/L, elevated fasting plasma glucose levels surpassing 6.1 mmol/L, and abdominal obesity indicated by a waist circumference greater than 102 cm in men and 88 cm in women. The International Diabetes Federation has lately put up a revised definition encompassing a spectrum of thresholds for waist circumference tailored to individuals of many ethnic backgrounds, with central obesity being a critical condition.[3]

Individuals diagnosed with MetS and possessing a Framingham risk score exceeding 20% exhibit an elevated probability of experiencing notable coronary events within the subsequent 10-year period, in contrast to individuals without MetS but possessing an equivalent risk score. Furthermore, it is worth mentioning that the Framingham risk score is derived from several factors, such as age, serum levels of low-density lipoprotein LDL and HDL cholesterol, blood pressure, cigarette smoking, and diabetes mellitus. However, it primarily focuses on predicting the occurrence of CVD. On the other hand, MetS is capable of predicting the growth of both diabetes and CVD.[4]

Metabolic syndrome-associated disorders

MetS is associated with various systemic disorders; the most commonly occurring are cardiovascular disorders, diabetes mellitus, cognitive disorders, polycystic ovary syndrome (PCOS), various cancers, and liver disorders (Figure 1). Non-alcoholic fatty liver disease (NAFLD) is a prevalent ailment frequently associated with MetS. It is characterized by an accumulation of fat in the liver, mostly linked to insulin resistance rather than other established etiologies such as alcohol consumption, viral infections, or drug-induced effects. The occurrence of MetS and NAFLD exhibits a positive association with obesity. Both illnesses can also be caused by excessive consumption of simple sweets and a lack of physical activity. Both illnesses are associated with an increased risk of developing T2D, CVD, non-alcoholic steatohepatitis, and hepatocellular cancer.[5]

Recent cross-sectional research has indicated a negative association between MetS and cognitive function in terms of overall cognitive abilities and specific cognitive domains. The observed correlation in the bulk of research varied based on the specific neuropsychological assessment employed, with certain tests demonstrating greater sensitivity than others. Individuals diagnosed with MetS exhibited diminished cognitive abilities in various areas, such as memory, executive function, attention/speed, and global cognition, compared to individuals without MetS. Mild cognitive impairment and dementia are two distinct cognitive disorders frequently encountered in clinical settings.[6]

The relationship between obesity, MetS, and cancer has been extensively examined in the academic literature; nonetheless, there remains ongoing debate regarding their relationship. Evidence indicates a correlation between body mass index (BMI) and the prevalence of several kinds of cancer, including endometrial, colorectal, gastric, liver, bladder, and prostate cancer. The underlying processes of this correlation have also been examined. A hypothesis suggests that chronic inflammation, as influenced by obesity, may contribute to the creation of tumors. Additionally, it is postulated that insulin resistance may directly or indirectly impact cell proliferation, possibly exacerbating this process. Furthermore, some studies indicate that there may be a correlation between an elevated BMI and the growth of cancer, possibly involving metabolic disruptions similar to those associated with MetS. Nevertheless, a correlation exists between higher body weight and improved overall prognosis in individuals with advanced illness, frequently referred to as the obesity paradox. This conundrum has lately been analyzed within the domain of urological malignancies, including bladder, prostate, and kidney cancer.[7]

MetS has been observed to have a link with CVD. However, its independent danger for microvascular disease remains uncertain. Retinopathy, chronic renal disease, microalbuminuria, and neuropathy are observed in around 8-10% of patients with impaired fasting glucose and impaired glucose tolerance but do not have diabetes. Individuals diagnosed with diabetes are at an elevated risk of developing various forms of microvascular illness when they also have MetS. Nevertheless, a recent analysis conducted after the fact of the United Kingdom Perspective Diabetes Study failed to identify a higher probability of

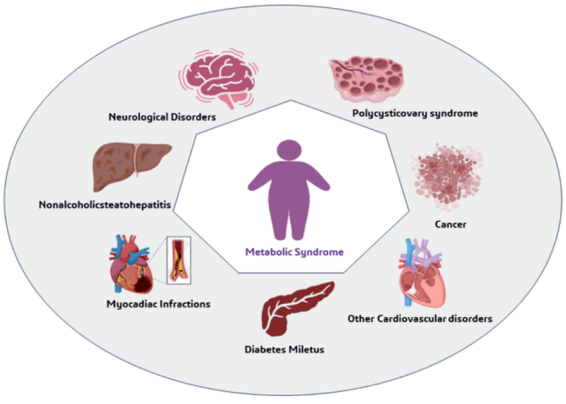


Figure 1. Associated disorders related to metabolic syndrome.

microvascular illness in persons diagnosed with T2D.[8] PCOS is a clinical disease characterized by anovulation, excessive testosterone levels, and insulin resistance. Women diagnosed with PCOS have challenges related to their reproductive capabilities, the social stigma associated with excessive testosterone levels, and insulin resistance. These variables contribute to an elevated propensity to develop T2D and various risk factors associated with CVD. There is a notable convergence between PCOS and MetS, whereby MetS tends to be prevalent among women with PCOS who are obese. The precise pathophysiology of PCOS remains uncertain, while it is widely accepted that the ovary, hypothalamic-pituitary axis, and insulin resistance are all implicated in its development and progression. A correlation exists between insulin resistance and obesity in women diagnosed with PCOS and an elevated propensity to CVD and metabolic diseases. A significant proportion, namely more than two-thirds, of women diagnosed with PCOS exhibit varying levels of glucose intolerance, rendering them very susceptible to the growth of diabetes.[8]

Genetic polymorphism

Both lifestyle and genetic factors influence obesity. Twin studies and adoption studies demonstrate that genetic factors significantly impact BMI, with parental obesity being a significant risk factor for obesity in offspring. Nearly 150 genetic variants have been recognized as significantly associated with body size or obesity risk, but much remains unknown. A single nucleotide polymorphisms related to MetS is listed in Table 1.[9-31]

Table 1. Genetic polymorphism associated with metabolic syndrome.

S.no	Gene Name	Position	Methodology	Reference
1	Interleukin-6 (rs1800796)	-	RT-PCR	9
2	*HSPA1B*	1267 (A>G)	PCR-RFLP	10
3	Interleukin-18 gene (rs187238 and rs1946518)	137 (G>C), 607 (C>A)	ARMS-PCR.	11
4	*ABCG1*	-	PCR-RFLP	12
5	TNF-α (rs1800629)	308 (G>A)	PCR-RFLP	13
6	*CYP2R1* (rs12794714 and rs10741657)	-	RT-PCR	14
7	*VDR* (rs7975232)	-	RT-PCR	14
8	DRD2(rs1799732, rs4436578)	-	SEQUENOM mass ARRAY	15
9	VEGF	-	ARMS-PCR	16
10	SREBF2 (rs1052717 and rs4822064)	-	(MALD-TOF)	17
11	TRPM5 gene rs4929982	578 (A>G)	RT-PCR	18
12	FTO (rs9939609)	-	Allelic discrimination assay	19
13	FTO (rs9939609)	-	TaqMan SNP Genotyping Assay	20
14	eNOS	894 (G>T)	PCR-RFLP	21
15	PAI-1 4G/5G	-	Allele-specific PCR	22
16	ACE ID	-	PCR-RFLP	23
17	OXTR (A>G)	-	PCR-RFLP	23
18	CAT-21A/T	-	PCR-RFLP	23
19	ATR1 A1166C	-	PCR-RFLP	23
20	SOD1	35 (A>C)	PCR-RFLP	23
21	eNOS 4a/b	-	PCR-RFLP	23
22	*ADIPOQ* (rs2241766 and rs1501299)	45 (T>G), 276 (G>T)	PCR-RFLP	24
23	GSTT1	-	RT-PCR	25
24	GSTM1	-	RT-PCR	25
25	GSTP1	-	RT-PCR	25
26	ADRB3 (rs4994) and	-		26
28	ADRA2A (rs1800544, rs553668)	-		26
29	PLIN	6209 (T>C) 11482 (G>A) 3041(A>G) 4995(A>T)	TaqMan assay	27
30	*PLCL2 (rs4685423 and rs4618210)*	-	Improved multiplex ligation detection reaction	28
31	Tumor necrosis facto-α	308(G>A)	PCR-RFLP	29
32	Interleukin-1β	511(C>T)	PCR-RFLP	30
33	*NOS2*-c.	1823 (C>T)	PCR-RFLP	31

RT-PCR, reverse transcription polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; ARMS-PCR, amplification-refractory mutation system polymerase chain reaction; MALD-TOF, matrix assisted laser desorption ionization-time of flight mass spectrometry; SNP, single nucleotide polymorphism; PCR, polymerase chain reaction.

Vitamins in metabolic syndrome

Vitamin D plays a significant role in the development of MetS. A notable correlation exists between decreased levels of 25-hydroxyvitamin D and an elevated probability of MetS and insulin resistance in individuals of middle-aged and elderly populations. Additionally, postmenopausal women possess prospective risk factors for the growth of MetS.[32-39] The administration of vitamin D on a daily basis for 12 weeks, along with moderate endurance physical activity, may play a crucial role in regulating parathyroid hormone and serum calcium levels. Additionally, this intervention has been observed to substantially elevate vitamin D concentration and significantly reduce lipid profile among individuals with MetS.[40,41] Higher intake of vitamins B1, B2, niacin, B6, and DFE were all associated with reduced risk of MetS.[42,43]

Mitochondrial alterations in metabolic syndrome

Mitochondria play an important role in energy production and several cellular functions, such as apoptosis, proliferation, regulation of redox status, and synthesis of heme and steroids. Dysfunction can result in cellular demise, impairment of organs, and, ultimately, organ system failure. The link between mitochondrial dysfunction and MetS, including insulin resistance and non-alcoholic fatty liver disease. Although certain studies have indicated the existence of mitochondrial dysfunction in cases of insulin resistance, the results from other investigations have been equivocal.[44] Insulin resistance has been linked to mutations and haplotypes in mitochondrial DNA. However, variances in this association are observed across diverse ethnic groups, primarily attributable to discrepancies in nuclear genetic variables. Evidence suggests a correlation between insulin resistance and environmental exposure, including pesticides and herbicides that target mitochondria. Mitochondrial dysfunction has been targeted by therapeutic interventions such as the execution of mitochondrial uncoupling and the administration of substances such as berberine, resveratrol, and MitoQ.[45]

Diagnostic and prognostic markers for metabolic syndrome

Diagnostic markers such as uric acid, γ-glutamyl transferase (GGT), ferritin, and C-reactive protein (CRP) play crucial roles in diagnosing and managing MetS. Uric acid is the last product of purine catabolism, wherein purines, chemical compounds introduced into the bloodstream through food digestion or the natural deterioration of some cells in the body, are broken down. There is a positive correlation between elevated uric acid levels and conditions such as obesity, T2D, CVD, and MetS, as supported by limited research evidence.[46-49] GGT is an enzyme produced in almost all human organs like the kidney, pancreas, liver, spleen, heart, and brain. This enzyme is a precursor to the antioxidant and metabolic substrate glutathione and a diagnostic marker for hepatobiliary disease, diabetes, hypertension, and stroke risk. Evaluate alcohol consumption and MetS; increasing the biological value above 27 IU/L for men and 17 IU/L for women are markers for the MetS. Ferritin is a vital iron storage protein that regulates iron homeostasis and can reflect the degree of acute and chronic inflammation, abnormally increasing up to two to threefold the ferritin associated with MetS.[50,51] CRP is a commonly employed biomarker for the differential diagnosis or classification of inflammatory diseases such as rheumatic diseases and is used as a prognostic marker. Increasing the biological value to more than 2.5mg/L also showed a likelihood of MetS.[52,53] Leptin, an endocrine hormone, plays a crucial role in regulating energy metabolism through its ability to inhibit food consumption and enhance energy expenditure. Abdominal obesity and insulin resistance, both crucial factors in the growth of MetS, have been observed to be linked with this condition. MetS was correlated with reduced levels of adiponectin in the bloodstream, as evidenced by the low serum concentrations of 2.65 g/mL.

Novel treatment and strategies for treating metabolic syndrome

Given that MetS arises from a multifactorial etiology, it is imperative to undertake clinical diagnosis and therapy to effectively manage and treat individuals affected by MetS. Metabolic syndrome can be effectively managed with the execution of lifestyle modifications, such as weight reduction, dietary adjustments, and consistent engagement in physical exercise.[54] Effective pharmacological therapy, such as medication prescription to reduce blood pressure, blood glucose, or cholesterol levels.[55] In handling risk factors associated with MetS, it is suggested that physicians adhere to the prevailing treatment guidelines established by authoritative bodies such as the NCEP, the Seventh Joint National Commission for Blood Pressure Management, the American Diabetes Association, the American Heart Association, and the National Institute of Health Obesity Initiative.[56-59]

Hypertension arose due to hyperglycemia and hyperinsulinemia in MetS.[60] This occurrence can be ascribed to the initiation of the renin-angiotensin system *via* an upregulation of angiotensinogen expression.[61] Furthermore, it has been observed that this phenomenon also triggers the initiation of the sympathetic nervous system, leading to enhanced sodium reabsorption by the kidneys, increased cardiac output by the heart, and vasoconstriction in the arteries, ultimately resulting in hypertension.[62] To manage the advancement of atherosclerosis and CVD, pharmacological interventions that specifically address LDL cholesterol, HDL cholesterol, and triglyceride levels, alongside antihypertensive treatments, are employed. Viable choices for reducing LDL cholesterol levels include hydroxymethylglutaryl-CoA reductase inhibitors, which can be employed to increase HDL cholesterol levels, while fibrates effectively lower triglyceride levels.[63]

To mitigate the impacts of MetS, it is imperative to manage hyperglycemia effectively. Fortunately, various pharmaceutical choices may already be administered orally or subcutaneously to tackle this condition. Several medications that have been approved by the Food and Drug Administration (FDA) for the treatment of T2D warrant particular attention owing to their potential positive impacts on both glycemic

control and weight management. Metformin is a pharmacological agent used in the treatment of diabetes mellitus. Its mechanism of action involves the decrease in hepatic glucose synthesis and the improvement of peripheral glucose uptake. Metformin is commonly prescribed for treating T2D in obese patients owing to its potential for inducing weight loss. This medication does not contribute to weight growth and is often associated with a modest decrease in body weight. The ingestion of this medication leads to hypoglycemia, a condition that necessitates the administration of an oral hypoglycemic agent, alongside a range of accompanying adverse reactions.[64,65] Pharmacological agents such as glucagon-like peptide 1, exenatide, and sitagliptin can be used for regulating satiety, hunger, and weight by influencing not just hormones derived from the liver and adipose tissue.[62] For weight loss, FDA-approved drugs such as orlistat and sibutramine can be used.

Conclusions

In summary, MetS represents a significant clustering of cardiometabolic risk factors primarily linked to excess weight and obesity. Despite its recognized clinical importance, the syndrome remains a topic of debate due to differing classification criteria proposed by various international medical organizations. Nonetheless, there is broad consensus that MetS seeks to encapsulate the core pathophysiological processes, including visceral obesity, dyslipidemia, insulin resistance, and hypertension. As research advances and new therapeutic interventions emerge, there is an increasing emphasis on understanding additional clinical components relevant to the syndrome, such as steatohepatitis, microalbuminuria, endothelial dysfunction, and systemic inflammation. This expanding knowledge underscores the importance of a comprehensive approach to managing MetS, focusing on both its primary drivers and associated complications, to mitigate its far-reaching health.

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