Rzeszów University Press 2025
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2025.3.18

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2025; 23 (3): 776–785

REVIEW PAPER

Genetic determinant of metabolic syndrome – a review

Haritha Nagarajan, Santhini Gopalakrishnan S.

Department of Biochemistry, Center for Health Research and Innovation, Chennai, India

ABSTRACT

Introduction and aim. Metabolic syndrome is a pathological condition that is a combination of insulin resistance, hypertension, dyslipidemia, and abdominal obesity. Every metabolic syndrome trait has an estimated hereditary factor greater than fifty percent. Many mutations related to distinct traits have been successfully identified through genetic studies. With respect to the advancements in our knowledge of the genetics of obesity, it is a major contributor to metabolic syndrome.

Metabolic syndrome is associated with many diseases and is closely related to overweight / obesity and lack of activity. Genetic predisposition also plays an important role in it. Therefore, lifestyle modification is the initial and main intervention that can be implemented for such a population. This review pinpoints the literature on the definition of metabolic syndrome, epidemiology, pathogenesis, and its gene polymorphism and treatment approach comprising metabolic syndrome.

Material and methods. The literature review was carried out using databases such as PubMed, Scopus, Google Scholar and the Web of Science for studies looking into metabolic syndrome and its complications. This review provides a comprehensive analysis of the role of genetic and lifestyle changes in the development of metabolic syndrome.

Analysis of the literature. Metabolic syndrome is a collection of diseases that include lower levels of high-density lipoprotein (HDL), increased triglyceride levels (TG), high blood pressure, more waist circumference, and elevated fasting blood glucose. It is closely related to overweight / obesity and lack of activity. Genetic predisposition also plays an important role in it. So lifestyle modification is the initial and main intervention that can be implemented for this population.

Conclusion. Genetic, lifestyle changes, and other environmental changes contribute to the development of metabolic syndrome. Metabolic syndrome leads to many health issues; for a better healthy outcome, lifestyle modifications such as healthy dietary habits, following regular physical activity, quitting smoking and alcohol, balanced weight, stress management are required.

Keywords. genetics, lifestyle modification, metabolic syndrome, obesity

Introduction

Metabolic syndrome is a collection of elevated risk factors for cardiovascular disease (CVD) and diabetes. These include decreased levels of high-density lipoprotein (HDL) cholesterol, obesity, increased triglyceride (TG), high blood pressure, and glucose level.[1]

Metabolic syndrome is one of the greatest threats to type 2 diabetic mellitus (T2DM) and CVD in this twenty-first century. In addition, a sedentary lifestyle, increased food intake, and the ensuing abdominal obesity may be the basic cause of metabolic syndrome. However, it is now understood that metabolic syndrome is a frequent, complicated reality rather than an illness.[2]

Obesity is associated with an increased risk of comorbidities and difficulties caused by being overweight. Hypertension and metabolic abnormalities, such as elevated TG, fasting blood sugar (FBS) levels, and decreased HDL levels, are linked to the deposition of fat.[3,4] Individuals with abdominal obesity, particularly those who have more of visceral or intra-abdominal adipose tissue, ex-

Corresponding author: Santhini Gopalakrishnan S., e-mail: santhinidept@gmail.com

Received: 7.11.2024 / Revised: 8.04.2025 / Accepted: 27.04.2025 / Published: 30.09.2025

Nagarajan H, Gopalakrishnan SS. Genetic determinant of metabolic syndrome – a review. *Eur J Clin Exp Med.* 2025;23(3):776–785. doi: 10.15584/ejcem.2025.3.18.

hibit metabolic abnormalities associated with insulin resistance.[5] The prevalence of obesity and type 2 diabetes often correlates with the prevalence of metabolic syndrome.[6]

The components of the metabolic syndrome produce a cardiovascular illness. But there is still a risk associated with overweight that includes various types of heart disease, such as microvascular dysfunction, coronary atherosclerosis, myocardial infarction, cardiac dysfunction, and heart failure.[7]

The complete etiology of metabolic syndrome has yet to be discovered. Studies on genetic associations could shed insight into the precursors of metabolic syndrome. According to research, the risk of metabolic syndrome is primarily hereditary. The epidemiological study states that only a minor portion of the genetic variance in metabolic syndrome is explained by the single nucleotide polymorphism (SNP) for which a genetic association with metabolic syndrome has been demonstrated. Consequently, there are still many genetic variations to be found. SNPs linked to lipid levels, insulin resistance, and abdominal obesity in the genome-wide association study (GWAS) are probably candidates for a relationship with the metabolic syndrome itself.[8]

Now, metabolic syndrome has become a problem for public health and it is concerned of its high prevalence. The estimated prevalence with 95% uncertainty interval of metabolic syndrome is 1.4% to 6.7% among children and 4.8% among teenagers. This corresponds to approximately 25.8 million children (around 12.6 to 61 million) and 35.4 million teenagers (around, 21.3 to 63 million) are affected by metabolic syndrome. This prevalence of metabolic syndrome has been estimated worldwide in 2020 at 2.8%. This prevalence has differed among countries based on the income of that country.[9] Research has indicated that the adjusted prevalence of metabolic syndrome in urban Indian populations was found to be around 25% (roughly 31% in women and 18.5% in men).[10] It clearly shows that metabolic syndrome is quite common nowadays and is in the position of rising prevalence worldwide, this emphasizes the increase in obesity and sedentary lifestyle.[1]

Modifications in lifestyle habits, such as increased exercise and decreased calorie consumption, are essential for both preventing and treating metabolic syndrome. Due to the fact that its pathophysiology involves a positive energy balance, it is stressed to achieve optimal body weight, so that excess fat does not deposit in the body.[11]

It has come to know that obesity as a primary cause of metabolic syndrome, linking it to metabolic complications such as insulin resistance and lipid abnormalities. It also clearly shows that obesity is a key determinant of insulin resistance and CVD risk. Here it is mentioned that the genetic basis of metabolic syndrome suggested that SNP associated with insulin resistance, lipid metabolism, and obesity may contribute to disease susceptibility. Although genetic predisposition plays a role, lifestyle factors such as poor dietary habits and physical inactivity are also predominant contributors to the development of metabolic syndrome.

The discussion on the epidemiology reinforces metabolic syndrome among children, adolescents, and adults, and highlights its widespread impact across age groups in different demographic groups. This emphasizes the increasing prevalence of metabolic syndrome due to increasing obesity rates, sedentary lifestyle, and genetic predisposition. This sets the stage for further exploration of its pathophysiology, risk factor, and guess that are associated with metabolic syndrome.

Aim

This review pinpoints the literature on the definition of metabolic syndrome, epidemiology, pathogenesis, and its gene polymorphism and treatment approach comprising metabolic syndrome.

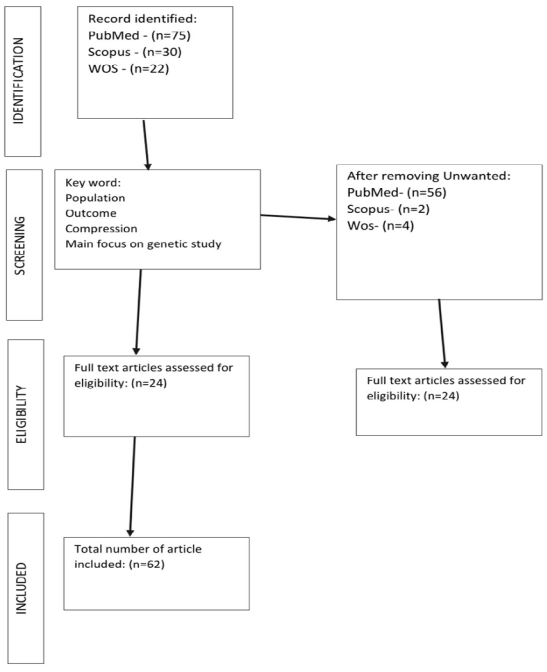

Fig. 1. PRISMA flow chart

Material and methods

The literature review was carried out using databases such as PubMed, Scopus, Google Scholar and the web of science for studies looking into metabolic syndrome and its complications. This review provides a comprehensive analysis of the role of genetic and lifestyle changes in the development of metabolic syndrome. Inclusion criteria: peer-reviewed review paper,, research paper and meta-analysis papers relevant to metabolic syndrome. Studies with various study designs. Studies

involving various age group related with metabolic syndromes. Studies published in the last 15 years, with exception of older highly relevant studies and studies that suggest interventions and preventive measures for metabolic syndrome. Exclusion criteria: Studies that are irrelevant to this review article. Poor methodology and high risk of bias. The selection and inclusion of papers have been mentioned in Figure 1.

Table 1. Criteria proposed for the clinical finding of metabolic syndrome*

Clinical tests	WHO (1998)	EGIR (1999)	NCEP:ATPIII (2001)	AACE (2003)	IDF (2005)	IDF, AHA, NHLBI definition
Insulin resistance	IGT, IFG (>100 mg/dL), T2DM, and with any 2 of the following criteria	Insulin resistance >75th percentile of non-diabetic patients, with two of the following	Nothing, but any 3 of the following criteria	IGT or IFG with any of the following criteria	None	None, but any 3 of the following criteria
Abdominal obesity	Waist-to-hip ratio: >0.9 in men and >0.85 in women, BMI: >30 kg/m^2	WC 94 cm in men and ≥80 cm in women	WC > 100 cm and above in men, and >88 cm and above in women	BMI ≥25 kg/m^2	BMI >30 kg/ m^2. And following 2 criteria	WC 102 cm or more for men, and for women 88 cm or more
Blood pressure	140/90 mmHg or above that	BP 140/90 mmHg or higher or on hypertensive drugs	130/85 mm Hg and more	BP 130/85 mmHg or higher.	BP- 130/85 mmHg or more	BP 130/85 mmHg or more
Lipid profile	TG 150 mg/dL and more than that and High-density lipoprotein (HDL) cholesterol <40 mg/dL in men and <50 mg/dL in women	TG 150 mg/dL or greater and / or high density lipoprotein-cholesterol <39 mg/dL	TG 150 mg/dL or higher. HDL cholesterol <40 mg/dL in men and <50 mg/dL in women	TG 150 mg/dL and higher and HDL cholesterol <40 mg/dL in men and <50 mg/dL in women	TG 150 mg/ dL or more and HDL <40 mg/dL or more	TG 150 mg/ dL and higher, and HDL cholesterol <40 mg/dL in men and <50 mg/dL in women
Glucose	IGT, IFG or T2DM	IGT or IFG (but non-diabetes)	FBS 110 mg/ dL and more	IGT and IFG	FBS 100 mg/dL or more	FBS 100 mg/ dL or more
Others	Microalbuminuria: Urinary excretion of >20 mg/min or albumin: creatinine ratio of >30 mg/g	–	–	Insulin resistance	–	–

* WHO World Health Organization, EGIR – European Group for the Study of Insulin Resistance, NCEP: ATPIII – The National Cholesterol Education Program: adult Treatment Panel III, IDF – International Diabetes Foundation, NHLBI – National Heart, Lung, and Blood Institute, AHA – American Heart Association), T2DM type 2 diabetes Miletus, TG triglyceride, HDL – high density lipoprotein, WC waist

Analysis of the literature

Pathophysiology

The primary pathophysiological feature of metabolic syndrome involves excessive abdominal fat accumulation that results in obesity and insulin resistance, fasting glucose is affected and decreased glucose tolerance, which may alter the gene leading to single nucleotide polymorphism.[12] This shows the dietary changes such as high calorie intake, high fat diet, and life style changes like lack of physical activity, these two are the main contributor to the development of metabolic syndrome (Fig. 2). This determines that visceral adiposity is the main cause of most of the pathways linked to metabolic syndrome.[13] The patient's metabolic disarray becomes a syndrome if they exhibit any three of these conditions showed in the Table 1.

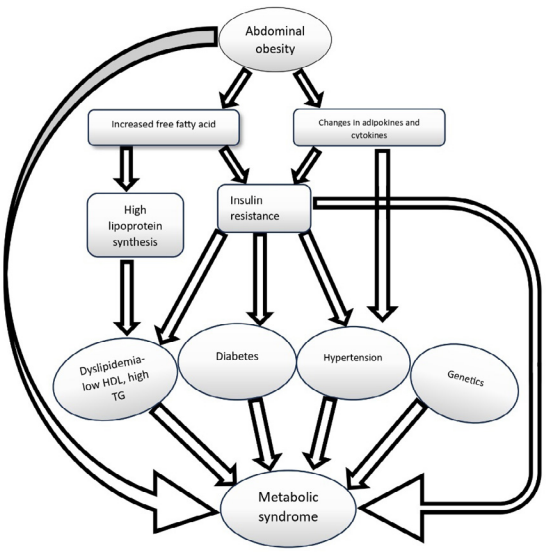

Fig. 2. Characteristics and cause of metabolic syndrome

Obesity

Obesity is a non-communicable disease, which has become a major health issue around the world.[14] According to the World Health Organization (WHO), health is at risk when obesity or overweight is due to unusual or extra fat deposition in the body.[15] When body mass index (BMI) falls under 25 to <29 is considered overweight, and if the BMI is more than 30, is considered as obesity. A person with obesity is at high risk of central obesity, high blood pressure, dyslipidemia, cardiovascular disease (CVD), diabetes, gastrointestinal disorder, muscle and joint problems, respiratory problems, sleeping disorder, and ultimately leads to metabolic syndrome,[16] as obesity is one of the co-occurrence of metabolic syndrome. The overview of obesity is that, it is caused due to the body stores surplus energy than its energy expenditure,[17] lack of physical activity, overconsumption of high calorie and high fat foods, and genetics also plays a major role in developing obesity. Among the components of metabolic syndrome, abdominal obesity is found to be more prevalent than the central obesity.

Anthropometric measurements such as waist hip ratio and BMI help in the partial prediction of metabolic syndrome, as this will show whether the person in having obesity and abdominal obesity proved that the best

anthropometric measure for identifying metabolic syndrome differed depending on the subsets of age and sex subsets.[18]

Insulin resistance

Insulin resistance, characterized by reduced biological activities of the insulin stimulant of target tissue, especially adipose tissue, muscle, and liver. In this phase, it decreases glucose disposal leading to an increase in beta cells and subsequently causes hyperinsulinemia.[19] Insulin resistance is one of the root causes of more pathophysiology problem in the process and development of many non-communicable diseases, including dyslipidemia, T2DM, obesity, hypertension, CVD, sleep problem, cancer, nonalcoholic fatty liver disease (NAFLD), poly cystic ovary disease (PCOD), commonly it contributes to metabolic syndrome.[20,21] Mostly Insulin resistance will be present in the person having metabolic syndrome. The body produces insulin to transport glucose into cells for its process of producing energy, so people with metabolic syndrome are mainly obese, which makes it more difficult for cells to response to the insulin. says that the researcher has observed that most patients with high level of plasma insulin and insulin resistance also had hypertension.[22] Insulin resistance and diabetes also cause many kinds of heart disease.

In the diagnosis of metabolic syndrome by gender, the insulin resistance area under the curve for the homeostatic model assessment of insulin resistance (HOMA-IR) in men with metabolic syndrome are (0.7000) and for women with metabolic syndrome (0.6779). for the quantitative insulin sensitivity check index (QUICKI) (0.7016) and (0.65779) in men and women with metabolic syndrome. The prediction accuracy is similar for men, indicating effective performance in both HOMA-IR and QUICKI. For women both show lower area under the curve value suggesting predictive capability. Sensitivity and specificity differ between sexes.[23,24]

Dyslipidemia

Dyslipidemia is a fundamental part of metabolic syndrome. It refers to an unusual level of lipid in the bloodstream. Increased triglyceride, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and reduced level HDL. The criteria for metabolic syndrome are that increased triglycerides 150 mg/dL or more per dL of blood and reduced HDL cholesterol, below 50 mg/dL and 40 mg/dL in women and men, both define hypertriglyceridemia.[25]

Recently, many findings have shown that people with metabolic syndrome are more prone to heart-related diseases such as cardiovascular disease, myocardial infraction, stroke, coronary heart disease. The highly atherogenic lipid profile is often the result of having an unhealthy eating habit and unhealthy lifestyle changes such as smoking, alcohol, lack of physical activity, leading sedentary life or genetic predisposition.[26,27]

Genetic predisposition to dyslipidemia and type 2 diabetes share more phenotypic feature of metabolic syndrome such as (insulin resistance, hypertension, abdominal obesity, and abnormal cholesterol levels). Mostly, it seems to present a higher risk of cardiovascular disease. Therefore, according to the guidelines, diabetic patents are also treated for dyslipidemia.[28]

Hypertension

Hypertension is one of the other components of metabolic syndrome. Hypertension is highly correlated with dyslipidemia, insulin resistance, obesity, which are considered as metabolic syndrome.[29] Hypertension is one of the basic reasons for the complication of diabetes, atherosclerosis, CVD and other heart-related problems, and even depression.[30] Nowadays, it is more common among adults due to their frequent stress, unhealthy eating habits, obesity, sedentary life style, high salty foods and processed food are the main cause for the cause of hypertension.[31] Many studies have found that genetic predisposition causing hypertension, where pathways and other molecular mechanism has impact on blood pressure which influences metabolic syndrome.[32]

Role of genetics in the development of metabolic syndrome

Genetics

In particular, lifestyle changes, environmental factors, diet, and exercise are the primary source for the onset of metabolic syndrome. However, genetic factors contribute a crucial role in the onset of metabolic syndrome. Researchers have found that many genes are associated with obesity, dyslipidemia, insulin resistance.[33] However the genetic research to examine metabolic syndrome is much less. Family-based studies have been concerned with identifying the genetic factors that contribute to various diseases such as metabolic syndrome.[34] As the sedentary lifestyle is more common these days. The increasing incidence of metabolic syndromes among young adults and children is more prevalent. Deeper understanding of the genetics that are related to metabolic syndrome will give proper insight into the inception of the disease.[35] Different countries and various clinical findings have different criteria to find metabolic syndrome, in addition to genetic, will also help in finding the metabolic syndrome and prevent future complications. This genetic study may be more consistent. Recent GWAS have allowed the identification of many polymorphisms associated with metabolic syndrome. Genetic markers can be used for early detection of metabolic syndrome as a biomarker for screening for the development of its related diseases. Here are some genes associated with various diseases interlinked with metabolic syndrome that are mentioned below.

Adiponectin (ADIPOQ)

It controls glucose metabolism and lipid metabolism, enhances insulin sensitivity, manage food intake, and body weight. The ADIPOQ gene is located on the 3q27 chromosome and this locus is susceptible for it to be associated with cardiovascular risks such as hypertension, diabetes, LDL-C and TG.[36,37] SNP in adiponectin gene negatively correlated with HDL, body weight, waist circumference, fasting insulin, TG, insulin resistance and HOMA IR. show the association with adiposity, insulin secretion and T2DM. The study conducted with the Caucasian population found that high triglycerides, low adiponectin concentration, and insulin resistance are associated with the GG rs17300539 genotype, which will lead to a higher risk of metabolic syndrome.[38] Punjabi population concludes that, ADIPOQ -3971A>G (rs22396) and +276G>T (rs1501299) SNP could be clinically helpful in assessing metabolic syndrome and its related problem among that population.[39] Investigation done with the Crimean individuals in the population of Crimean has found that GT genotype is more prevalent variant of ADIPOQ (rs2241766) among patients with metabolic syndrome. It is also associated with high systolic blood pressure and high BMI. Whether high diastolic blood pressure, high HBA1c glucose value, high value are associated with the ADIPOQ individuals carrying the genotype (rs2241766). Their finds show that this genetic variant is very closely linked to metabolic syndrome in this population (Fig. 3).[40]

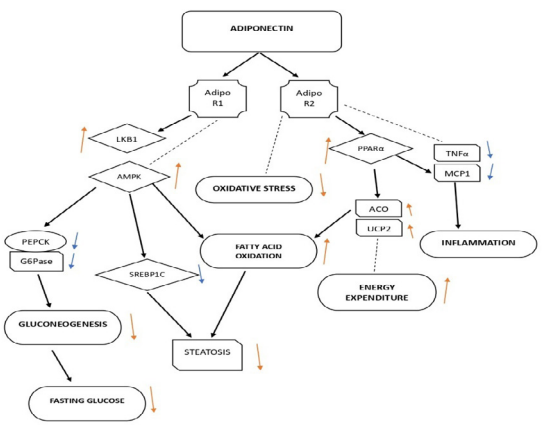

Fig. 3. Mechanism of adiponectin (AdipoR1 – adiponectin receptor 1, AdipoR2 – adiponectin receptor, LKB1 – liver kinase B, AMPK – AMP-activated protein kinase, PEPCK – phosphoenolpyruvate carboxy kinase, G6Pase – glucose-6-phosphatase, SREBP1c – sterol regulatory element binding protein 1c, PPARα – peroxisome proliferator-activated receptor alpha, ACO – acyl-CoA oxidase, UCP2 – uncoupling protein 2, TNFα – tumor necrosis factor alpha, MCP1 – monocyte chemoattractant protein 1)

Peroxisome proliferator – activated receptor gamma co-activator 1 – alpha (PPARGC1A)

Shows the association with adiposity, insulin secretion indexes, and type 2 diabetes.[41] SNP in PPARGC1A, became more inflexible and may have altered the protein's catalytic activity and structural structure.[42] It may also have caused coronary artery disease (CAD), nonalcoholic fatty liver disease (NAFLD), and T2DM. According to the genotype, the parameters among the 2-study group do not show any significant variation. Therefore, statistical significance does not show the risk of metabolic syndrome.[43] The Gly482Ser polymorphism (rs8192678) may facilitate in the onset of metabolic syndrome, but the effect might be less. A meta-analysis performed using data collected from Asian, African and European populations concludes that the PPARGC1A gene locus might be one of the risk factors for type 2 diabetes (Fig. 4).[44]

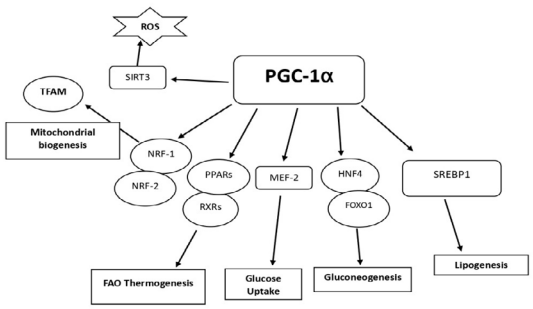

Fig. 4. Mechanism of PPARGC1A (SIRT3 sirtuin 3, ROS – reactive oxygen species, nuclear respiratory factors NRF-1 and NRF-2, mitochondrial transcription factor A, TFAM mitochondrial transcription factor A, PPAR peroxisome proliferator activated receptors, RXRs – retinoid X receptors, FAO fatty acid oxidation, MEF-2 – myocyte enhancer factor 2, HNF4 nuclear factor 4, FOXO1 – fork head box protein O1 SREBP1 sterol regulatory element-binding protein 1)

Fat mass obesity associated (FTO)

Studies have shown that the FTO gene is very much associated with obesity. FTO is present in the hypothalamus, so it is associated with energy expenditure and in regulation of food intake.[45] FTO is located on the chromosome at 16q12.2. The first gene that is associated with obesity is FTO, which was found by GWAS. As diabetes and obesity is characteristics of metabolic syndrome, it is believed that FTO gene polymorphism might be linked to the risk of metabolic syndrome. A study found that the SNP of FTOrs9939609 gene was correlated with the risk among the Temiar subtribe.[46] A study done with the FTO rs9939609 gene, their results show that, the subjects with AA allele have significantly low HDL cholesterol levels than subjects with TT allele. Therefore,

they concluded that the FTO rs9939603 gene is one of the causes of genetically risk factor for metabolic syndrome among the Egyptian population. And they also highlight that the HDL component may be the reason for this association.[47] FTO gene (rs9939609) is used to study the southern Italian polymorphism in the population among the subjects with Metabolic Syndrome, their results show that, TA allele heterozygous the SNP of FTO gene (rs9939609) is significantly correlated among the individuals with metabolic syndrome.[48]

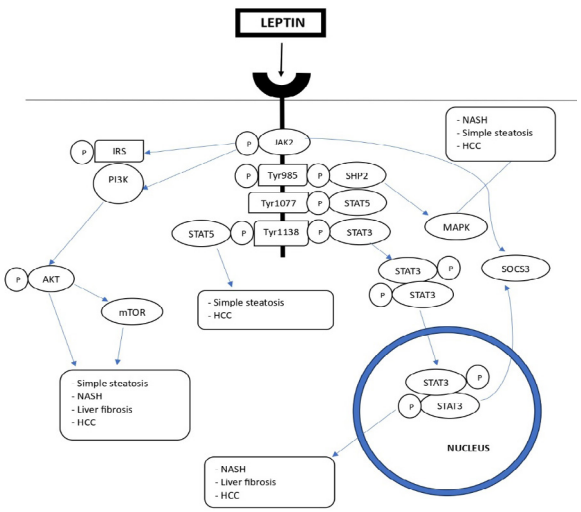

Fig. 5. Mechanism of leptin (JAK2 phosphorylates Tyr985, Tyr1077, and Tyr1138 residues on Ob-Rb, STAT signal transducers and activators of transcription, SOCS3 suppressor of cytokine signaling 3, PI3K – phosphoinositide 3-kinase. IRS – insulin receptor substrate. AKT – protein kinase B, mTOR – mammalian target of rapamycin, P – phosphorylation, NASH - nonalcoholic steatohepatitis, HCC – hepatocellular carcinoma)

Leptin (LEP)

When obesity develops, plasma LEP levels increase and when weight is lost, they drop. The hypothalamus and brain stem contain the majority of leptin receptors, and signals from these receptors regulate neuroendocrine function, energy expenditure, and satiety. Therefore, many overweight people will have leptin resistance.[49] Adiposity and plasma leptin concentrations are associated, and hyperleptinemia is in fact believed to be a separate risk factor for CVD and also nonalcoholic steatohepatitis (NASH).[50] Research carried out in Kyrgyz population, the leptin receptor gene shows the association with a higher level of insulinemia and glycemia, therefore, this gene may be the marker of insulin resistance.[51] Their research shows that LEP AA genotype carriers has the higher incidence of Metabolic Syndrome and the G2548A gene of leptin polymorphism BMI and FBS is correlated with the G2548A gene of leptin polymorphism. So, the research confirms that Leptin G2548A loci will alone be the risk factor for Metabolic Syndrome. Their findings show that the homozygous genotype LEP 2548AA is a risk factor for developing high cholesterol levels (Fig. 5).[52]

Lipoprotein lipase (LPL)

The LPL gene is located on the human chromosome 8p22 and helps in the transport and metabolism of lipoprotein. The SNPs for each gene were associated with an increased risk of obesity, and the LPL protein interacts functionally to regulate lipid metabolism. The study shows that the C allele and the CC allele of the rs13702 C/T SNP of LPL gene is significantly correlating with type 2 diabetes. Their research states that this may be due to increased level of LPL that will be leading to insulin resistance.[53] An interventional study was conducted in Taiwan among metabolic syndrome, who are subjected to do aerobic exercise. Their result shows that the polymorphism of the LPL gene (rs3779788) expressed in TT carrying individuals who did aerobic exercise shows the improvement in metabolic syndrome compared with CC/CT carrying individuals.[54]

Apolipoprotein A1 (APOA-1)

Apoa1 gene is located in chromosome 11q23. the main protein found in HDL particles, which provides protection against CVD risk. The SNP in the APOA-I gene affects the HDL level, leading to many CVD risks.[55] A study conducted with 1000 adult obese, states that, Apoa1 rs570 gene has an influence on glucose, HOMA-IR, insulin and anthropometric measurement. Central obesity, low HDL levels, diabetes are shown in males without A alleles.[56] Studies conducted in the Malaysian population states that patients with DM2, Apoa1 -75G>A genetic polymorphism can be considered as susceptibility to myocardial infraction. The variation of the Apoa1 gene is also associated with arterial stiffness, since the Apoa1 gene is involved in the synthesis, transport, and HDL process.[57] Research conducted in Tehran shows that, individual who are regularly eat the western diet pattern and fat-sweet dietary pattern are associated with Apoa1 gene polymorphism linked with Metabolic Syndrome risk.[58]

Apolipoprotein A2 (APOA-2)

Apoa2 is the second most abundant protein in HDL. Apoa2 appears to affect the process of reverse cholesterol transport and the antioxidant role of HDL cholesterol, which is consistent with the observation that increased Apoa2 levels and SNP in this gene promote the development of atherosclerosis and other CVD risks. Research done in Egypt states that CC genotype SNP is associated with insulin resistance.[59] Study conducted among Egyptian adolescents, results show that, after adjusting for multivariate, individuals with homozygous CC genotype exhibit higher levels of body fat percentage, more

WC, visceral adipose tissue, and HDL cholesterol when compared to the TT or TC genotype. In common, these individuals were consuming more food, so they conclude that individuals with homozygous C allele have more risk of obesity than the individuals with T allele. And they mentioned the link between Apoa2 c.-492T >C SNP and food intake.[60] Apoa2 rs5082 polymorphism can serve as marker to forecast the effectiveness of digital healthcare and lifestyle interventions, where genotype-based personalized medicine is required.[61]

Genetics causes various changes in the body, especially by increasing certain diseases or due to inherited genetic factors. Genetic predisposition is the probability of having a high risk of metabolic syndrome. Therefore, genetic screening is also highly important to predict metabolic syndrome and its related disease. A limitation of these studies is that they are often population-specific.

The limitations of these studies are often population-specific, focusing on particular ethnic groups. The findings may not be generalizable to other populations with different genetic backgrounds, lifestyle factors, or environmental exposures. Results from these populations may not apply to larger and more diverse populations. Depending on the study, sample sizes may be relatively small, limiting the ability to detect the effects of genetic variants on metabolic syndrome. Smaller sample sizes also increase the risk of type I or type II errors, leading to negative results. Genetic variants may not have uniform effects among individuals within the same population due to genetic heterogeneity. The influence of specific SNPs may vary based on other genetic factors, making it difficult to predict individual responses to these variants. Environmental factors, including lifestyle choices (eg, diet, exercise), environmental exposures, and other external factors, can interact with genetic factors in influencing metabolic outcomes. If these factors are not properly considered, they could confound the observed genetic associations. Genotyping technologies and the choice of SNPs may vary between studies, potentially leading to inconsistencies in the results. Additionally, the relevance of certain SNPs might be influenced by gene-environment interactions or epigenetic modifications that are not captured in these studies.

Lifestyle modification

As sedentary lifestyle is more common these days, the rising incidence of metabolic syndrome among young adults and children is more prevalent. Lifestyle changes in daily life will help in preventing various diseases. Metabolic syndrome is one of the diseases, where it can be treated by altering individual lifestyle habits like, regular physical activity, quitting smoking and alcohol, following healthy diet patterns, reducing or managing stress, maintaining healthy weight, having good quality of sleep, regular ingestion of medication, in case of hypertension, diabetes, dyslipidemia. Lifestyle modification plays a key role in the metabolic syndrome.[62]

Conclusion

Metabolic syndrome is the characterization of a combination of physiological, biochemical, clinical, metabolic factors, genetic factors, diet and lifestyle modification, and environmental changes. This will increase the risk of hypertension, obesity, cardiac related problems, insulin resistance, T2DM, dyslipidemia, genetic predisposition and stress. Metabolic syndrome can be treated by lifestyle modifications such as healthy eating habits, following regular physical activity, quitting smoking and alcohol, balanced weight, and stress management. Lifestyle modification is required to overcome metabolic syndrome. medications will be required if the metabolic syndrome is not treated. Genetic predisposition is the major factor in developing metabolic syndrome. Many studies are undergoing to find various genetic polymorphism markers to detect the risk of metabolic syndrome risk. In general, it provides a strong foundation for discussing metabolic syndrome by demonstrating its significance in both clinical and public health contexts.

Declarations

Funding

This study was self-funded by the authors.

Author contributions

Conceptualization, H.N. and S.G.; Methodology, H.N.; Software, H.N.; Validation, S.G. and H.N.; Formal Analysis, S.G.; Investigation, S.G.; Resources, H.N. and S.G.; Data Curation, H.N.; Writing – Original Draft Preparation, H.N.; Writing – Review & Editing, H.N.; Visualization, H.N.; Supervision, H.N.; Project Administration, H.N.; Funding Acquisition, H.N. and S.G.

Conflicts of interest

The authors declared no conflicts of interest.

Data availability

The dataset supporting the finding of this study are derived from publicly available database and articles, which are cited in the reference list.

Ethics approval

Ethical approval was not required for this study as it is a review of previously published literature and does not involve human participants or animal subjects.

References

1. Alberti KGMM, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: A joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood

institute; American heart association; World heart federation; International atherosclerosis society; And international association for the study of obesity. *Circulation*. 2009;120(16):1640-1645. doi: 10.1161/CIRCULATIONAHA.109.192644
2. Wang HH, Lee DK, Liu M, Portincasa P, Wang DQH. Novel insights into the pathogenesis and management of the metabolic syndrome. *Pediatr Gastroenterol Hepatol Nutr*. 2020;23(3). doi: 10.5223/PGHN.2020.23.3.189
3. Gobato AO, Vasques AC, Zambon MP, Barros Filho Ade A, Hessel G. Metabolic syndrome and insulin resistance in obese adolescents. *Rev Paul Pediatr*. 2014;32(1):55-62. doi: 10.1590/s0103-05822014000100010
4. Kleinrok A, Głowa B. The obesity and its meaning in cardiovascular diseases Part 1. Obesity as a risk factor. *Prz Med Uniw Rzesz Inst Leków*. 2015;13(2):165-172. doi: 10.15584/przmed.2015.2.9
5. Després JP, Lemieux I, Bergeron J, et al. Abdominal Obesity and the Metabolic Syndrome: Contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol*. 2008;28(6):1039-1049. doi: 10.1161/ATVBAHA.107.159228
6. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep*. 2018;20(2):12. doi: 10.1007/s11906-018-0812-z
7. Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. *Translational Research*. 2017;183:57-70. doi: 10.1016/j.trsl.2017.01.001
8. Povel CM, Boer JM, Onland-Moret NC, Dollé ME, Feskens EJ, van der Schouw YT. Single nucleotide polymorphisms (SNPs) involved in insulin resistance, weight regulation, lipid metabolism and inflammation in relation to metabolic syndrome: an epidemiological study. *Cardiovasc Diabetol*. 2012;11:133. doi: 10.1186/1475-2840-11-133
9. Noubiap JJ, Nansseu JR, Lontchi-Yimagou E, et al. Global, regional, and country estimates of metabolic syndrome burden in children and adolescents in 2020: a systematic review and modelling analysis. *Lancet Child Adolesc Health*. 2022;6(3):158-170. doi:10.1016/S2352-4642(21)00374-6
10. Bhalwar R. Metabolic syndrome: The Indian public health perspective. *Med J Armed Forces India*. 2020;76(1):8-16. doi: 10.1016/j.mjafi.2019.12.001
11. Pérez-Martínez P, Mikhailidis DP, Athyros VG, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: An international panel recommendation. *Nutr Rev*. 2017;75(5):307-326. doi: 10.1093/nutrit/nux014
12. Rana S, Ali S, Wani HA, Mushtaq QD, Sharma S, Rehman MU. Metabolic syndrome and underlying genetic determinants-A systematic review. *J Diabetes Metab Disord*. 2022;21(1):1095-1104. doi: 10.1007/s40200-022-01009-z
13. Rochlani Y, Pothineni NV, Kovelamudi S, Mehta JL. Metabolic syndrome: Pathophysiology, management, and modulation by natural compounds. *Ther Adv Cardiovasc Dis*. 2017;11(8):215-225. doi: 10.1177/1753944717711379
14. Dhawan D, Sharma S. Abdominal Obesity, Adipokines and Non-communicable Diseases. *J Steroid Biochem Mol Biol*. 2020;203:105737. doi: 10.1016/j.jsbmb.2020.105737
15. Safaei M, Sundararajan EA, Driss M, Boulila W, Shapi'i A. A systematic literature review on obesity: Understanding the causes & consequences of obesity and reviewing various machine learning approaches used to predict obesity. *Comput Biol Med*. 2021;136. doi: 10.1016/j.compbiomed.2021.104754
16. Fruh SM. Obesity: Risk factors, complications, and strategies for sustainable long-term weight management. *J Am Assoc Nurse Pract*. 2017;29:S3-S14. doi: 10.1002/2327-6924.12510
17. Lin X, Li H. Obesity: Epidemiology, Pathophysiology, and Therapeutics. *Front Endocrinol (Lausanne)*. 2021;12:706978. doi: 10.3389/fendo.2021.706978
18. Guo X, Ding Q, Liang M. Evaluation of eight anthropometric indices for identification of metabolic syndrome in adults with diabetes. *Diabetes Metab Syndr Obes*. 2021;14:1431-1443. doi: 10.2147/DMSO.S294244
19. Freeman AM, Acevedo LA, Pennings N. Insulin Resistance. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; August 17, 2023.
20. Bhattacherjee S, Guha S, Banerjee I, Nath I, Banerjee R, Ray K. A study of insulin resistance and its clinico-metabolic associations among apparently healthy individuals attending a tertiary care hospital. *Ann Med Health Sci Res*. 2014;4(5):823. doi: 10.4103/2141-9248.141572
21. Mahaki H, Mansourian M, Meshkat Z, et al. Nanoparticles Containing Oxaliplatin and the Treatment of Colorectal Cancer. *Curr Pharm Des*. 2023;29(38):3018-3039. doi: 10.2174/0113816128274742231103063738
22. Brosolo G, Da Porto A, Bulfone L, et al. Insulin Resistance and High Blood Pressure: Mechanistic Insight on the Role of the Kidney. *Biomedicines*. 2022;10(10). doi: 10.3390/biomedicines10102374
23. Fahed G, Aoun L, Zerdan MB, et al. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. *Int J Mol Sci*. 2022;23(2):786. doi: 10.3390/ijms23020786
24. Motamed N, Miresmail SJ, Rabiee B, et al. Optimal cutoff points for HOMA-IR and QUICKI in the diagnosis of metabolic syndrome and non-alcoholic fatty liver disease: A population based study. *J Diabetes Complications*. 2016;30(2):269-274. doi: 10.1016/j.jdiacomp.2015.11.019
25. Haile K, Haile A, Timerga A. Predictors of lipid profile abnormalities among patients with metabolic syndrome in southwest ethiopia: A cross-sectional study. *Vasc Health Risk Manag*. 2021;17:461-469. doi: 10.2147/VHRM.S319161
26. Blaton VH, Korita I, Bulo A, et al. How is metabolic syndrome related to dyslipidemia? *Biochemia Medica*. 2008;18(1):14-24.
27. Janani J, Lakshmanan K, Gopalakrishnan S. Unveiling the atherogenic lipoprotein particle: A case-control study. *Rom J Diabetes Nutr Metab Dis*. 2023;30(4):398-402. doi: 10.46389/rjd-2023-1384

28. Carr MC, Brunzell JD. Abdominal obesity and dyslipidemia in the metabolic syndrome: Importance of type 2 diabetes and familial combined hyperlipidemia in coronary artery disease risk. In: *Journal of Clinical Endocrinology and Metabolism*. 2004;89:2601-2607. doi: 10.1210/jc.2004-0432
29. Stanciu S, Rusu E, Miricescu D, et al. Links between Metabolic Syndrome and Hypertension: The Relationship with the Current Antidiabetic Drugs. *Metabolites*. 2023;13(1):87. doi: 10.3390/metabo13010087
30. Lalwani RK, Shah JD, Chatterjea T, Nadakuduru PR, Erande S. Prevalence of depression in Indian patients with type 2 diabetes mellitus and/or hypertension: DEPTH Study. *Eur J Clin Expl Med*. 2019;17(4):315-325. doi: 10.15584/ejcem.2019.4.5
31. Soleimani M, Barone S, Luo H, Zahedi K. Pathogenesis of Hypertension in Metabolic Syndrome: The Role of Fructose and Salt. *Int J Mol Sci*. 2023;24(5):4294. doi: 10.3390/ijms24054294
32. Chaimati S, Shantavasinkul PC, Sirivarasai J, Sritara P. Effects of AGT and AGTR1 Genetic Polymorphisms and Changes in Blood Pressure Over a Five-Year Follow--Up. *Risk Manag Healthc Policy*. 2023;16:2931-2942. doi: 10.2147/RMHP.S442983
33. Ho CY, Lee JI, Huang SP, Chen SC, Geng JH. A Genome-Wide Association Study of Metabolic Syndrome in the Taiwanese Population. *Nutrients*. 2024;16(1):77. doi: 10.3390/nu16010077
34. Wan JY, Goodman DL, Willems EL, et al. Genome-wide association analysis of metabolic syndrome quantitative traits in the GENNID multiethnic family study. *Diabetol Metab Syndr*. 2021;13(1):59. doi: 10.1186/s13098-021-00670-3
35. Nagrani R, Foraita R, Gianfagna F, et al. Common genetic variation in obesity, lipid transfer genes and risk of Metabolic Syndrome: Results from IDEFICS/I.Family study and meta-analysis. *Sci Rep*. 2020;10(1):7189. doi: 10.1038/s41598-020-64031-2
36. Gu HF. *Biomarkers of Adiponectin: Plasma Protein Variation and Genomic DnA Polymorphisms*. 2009. http://www.la-press.com.http://www.la-press.com. Accessed June 20, 2024.
37. Ghoshal K. Adiponectin: Probe of the molecular paradigm associating diabetes and obesity. *World J Diabetes*. 2015;6(1):151. doi: 10.4239/wjd.v6.i1.151
38. de Luis Roman D, Izaola Jauregui O, Primo Martin D. The Polymorphism rs17300539 in the Adiponectin Promoter Gene Is Related to Metabolic Syndrome, Insulin Resistance, and Adiponectin Levels in Caucasian Patients with Obesity. *Nutrients*. 2023;15(24):5028. doi: 10.3390/nu15245028
39. Kaur H, Badaruddoza B, Bains V, Kaur A. Genetic association of ADIPOQ gene variants (-3971A>G and +276G>T) with obesity and metabolic syndrome in north Indian punjabi population. *PLoS One*. 2018;13(9):e0204502. doi: 10.1371/journal.pone.0204502
40. Shramko II, Ageeva ES, Maliy KD, et al. Association between Adiponectin and Leptin Receptor Genetic Polymorphisms and Clinical Manifestations of Metabolic Syndrome. *J Diabetes Res*. 2022;2022. doi: 10.1155/2022/9881422
41. Santos JL, Krause BJ, Cataldo LR, et al. PPARGC1A gene promoter methylation as a biomarker of insulin secretion and sensitivity in response to glucose challenges. *Nutrients*. 2020;12(9):1-15. doi: 10.3390/nu12092790
42. Taghvaei S, Saremi L, Babaniamansour S. Computational Analysis of Gly482Ser Single-Nucleotide Polymorphism in PPARGC1A Gene Associated with CAD, NAFLD, T2DM, Obesity, Hypertension, and Metabolic Diseases. *PPAR Res*. 2021;2021. doi: 10.1155/2021/5544233
43. Csép K, Szigeti E, Vitai M, Korányi L. The ppargc1a - Gly482Ser polymorphism (RS8192678) and the metabolic syndrome in a central romanian population. *Acta Endocrinol (Copenh)*. 2017;13(2):161-167. doi: 10.4183/aeb.2017.161
44. Du F, Yang KJ, Piao LS. Correlation between PPARGC1A gene rs8192678 G>A polymorphism and susceptibility to type-2 diabetes. *Open Life Sci*. 2019;14(1):43-52. doi: 10.1515/biol-2019-0006
45. Qi Q, Kilpeläinen TO, Downer MK, et al. FTO genetic variants, dietary intake and body mass index: insights from 177,330 individuals. *Hum Mol Genet*. 2014;23(25):6961-6972. doi: 10.1093/hmg/ddu411
46. Harun NS, Wan Jusoh AF, Rohin MAK, Yahaya R, Nik Him NAS, Zahary MN. The contribution of FTO rs9939609 and RETN rs1862513 polymorphisms in predisposing resettled indigenous (Orang Asli) Temiar to metabolic syndrome. *Egyptian Journal of Medical Human Genetics*. 2023;24(1):44. doi: 10.1186/s43042-023-00425-x
47. Khella MS, Hamdy NM, Amin AI, El-Mesallamy HO. The (FTO) gene polymorphism is associated with metabolic syndrome risk in Egyptian females: A case- control study. *BMC Med Genet*. 2017;18(1):101. doi: 10.1186/s12881-017-0461-0
48. Liguori R, Labruna G, Alfieri A, et al. The FTO gene polymorphism (rs9939609) is associated with metabolic syndrome in morbidly obese subjects from southern Italy. *Mol Cell Probes*. 2014;28(4):195-199. doi: 10.1016/j.mcp.2014.03.004
49. Al-Hussaniy HA, Alburghaif AH, Naji MA. Leptin hormone and its effectiveness in reproduction, metabolism, immunity, diabetes, hopes and ambitions. *J Med Life*. 2021;14(5):600-605. doi: 10.25122/jml-2021-0153
50. Chen MC, Wang JH, Lee CJ, Hsu BG. Association between hyperleptinemia and cardiovascular outcomes in patients with coronary artery disease. *Ther Clin Risk Manag*. 2018;14:1855-1862. doi: 10.2147/TCRM.S172231
51. Mirrakhimov E, Bektasheva E, Isakova J, et al. Association of leptin receptor gene Gln223Arg polymorphism with insulin resistance and hyperglycemia in patients with metabolic syndrome. *Archives of Medical Science*. 2024;20(1):54-60. doi: 10.5114/aoms/170121

52. Ortega FL, Camberos AM, Arredondo MI, Magallanes NG, Meraz EA. LEP (G2548A-G19A) and ADIPOQ (T45G-G276T) gene polymorphisms are associated with markers for metabolic syndrome. *Diabetol Metab Syndr*. 2023;15(1). doi: 10.1186/s13098-023-01215-6
53. Hatefi Z, Soltani G, Khosravi S, Kazemi M, Salehi A, Salehi R. Micro R-410 Binding Site Single Nucleotide Polymorphism rs13702 in Lipoprotein Lipase Gene is Effective to Increase Susceptibility to Type 2 Diabetes in Iranian Population. *Adv Biomed Res*. 2018;7(1):79. doi: 10.4103/abr.abr_286_16
54. Hsu CS, Chang ST, Nfor ON, et al. Association of metabolic syndrome with aerobic exercise and lpl rs3779788 polymorphism in taiwan biobank individuals. *Diabetes Metab Syndr Obes*. 2021;14:3997-4004. doi: 10.2147/DMSO.S328308
55. Bora K, Pathak MS, Borah P, Hussain MI, Das D. Single nucleotide polymorphisms of APOA1 gene and their relationship with serum apolipoprotein A-I concentrations in the native population of Assam. *Meta Gene*. 2016;7:20-27. doi: 10.1016/j.mgene.2015.10.005
56. de Luis DA, Izaola O, Primo D, Aller R. Implication of the rs670 variant of APOA1 gene with lipid profile, serum adipokine levels and components of metabolic syndrome in adult obese subjects. *Clin Nutr*. 2019;38(1):407-411. doi: 10.1016/j.clnu.2017.12.007
57. Supajaree P, Chanprasertyothin S, Chattranukulchai Shantavasinkul P, Sritara P, Sirivarasai J. Association between ApoA1 Gene, Plasma Lipid Profile, hsCRP Level, and Risk of Arterial Stiffness in Thai Elderly. *Adv Prev Med*. 2022;2022:1-8. doi: 10.1155/2022/4930033
58. Hosseini-Esfahani F, Mirmiran P, Daneshpour MS, et al. Dietary patterns interact with APOA1/APOC3 polymorphisms to alter the risk of the metabolic syndrome: the Tehran Lipid and Glucose Study. *Br J Nutr*. 2015;113(4):644-653. doi: 10.1017/S0007114514003687
59. Zaki ME, Amr KS, Abdel-Hamid M. Evaluating the association of APOA2 polymorphism with insulin resistance in adolescents. *Meta Gene*. 2014;2(1):366-373. doi: 10.1016/j.mgene.2014.04.007
60. Zaki ME, Amr KS, Abdel-Hamid M. APOA2 polymorphism in relation to obesity and lipid metabolism. *Cholesterol*. 2013;2013:1-5. doi: 10.1155/2013/289481
61. Kim M, Lee S, Cho E, Hong KW, You SJ, Choi HJ. CETP and APOA2 polymorphisms are associated with weight loss and healthy eating behavior changes in response to digital lifestyle modifications. *Sci Rep*. 2023;13(1):21615. doi: 10.1038/s41598-023-48823-w
62. Giulio Marchesini G. Lifestyle modification in the management of the metabolic syndrome: achievements and challenges. *Diabetes Metab Syndr Obes*. 2010;3:373-385. doi: 10.2147/dmsott.s13860