Biochemistry Letters, 19(1) 2023, pages 52-63

Scientific Research & Studies Center-Faculty of Science- Zagazig University- Egypt

Biochemistry Letters

Journal home page:

Metabolic syndrome: A Review Involving the Hedgehog Pathway, PGC-1α , and GLP Roles

Bassant Salah([1*]), Hani abdelsalam[(1)], Tarek Khamis[(2,3)], Abdelaziz Diab[(1)], Khalifa El-Dawy([4])

[(1)] Physiology- Zoology Department, Faculty of Science, Zagazig University, Zagazig, Egypt, 44511,

[(2)] Pharmacology Department, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt, 44511,

[(3)] Laboratory of Biotechnology, Faculty of Veterinary Medicine, Zagazig University, Zagazig Egypt, 44519,

[(4)] Biochemistry Department, Faculty of Veterinary Medicine, Zagazig University, Zagazig, Egypt, 44511,

ARTICLE INFO

Received : 17/7/2023
Accepted : 28/7/2023
Available online: 24/8/2023

Keywords:

Metabolic syndrome, hyperglycemia, dyslipidemia, hedgehog pathway, PGC-1α , and GLP.

ABSTRACT

Metabolic syndrome (MetS) is a kind of metabolic disorder, including abdominal obesity, hyperglycemia, dyslipidemia, hypertension, etc. The prevalence of MetS is increasing substantially, making it a major public health issue in many nations. The morphogen Hedgehog (HH) signaling system plays a crucial role in controlling many aspects of embryonic development. The potential for pharmaceutical manipulation of the Hh pathway to improve outcomes in metabolic disorders has been demonstrated by researchers. The peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) has a strong correlation with the development of MetS and its principal sequelae, including obesity, cardiovascular illness, and hepatic steatosis. Glucagon-like protein 1 (GLP-1) is an antiobesogenic hormone that promotes glucose-induced beta-cell insulin secretion and suppresses alpha-cell glucagon synthesis. As these signaling and related regulatory modalities for regulating metabolism become more complex, this work aims to give a comprehensive understanding of the key signaling events involved. Furthermore, it explores the potential methods required to treat metabolic illnesses effectively.

Introduction:

History of metabolic syndrome

Several metabolic abnormalities come together to generate metabolic syndrome (MetS), which includes insulin resistance (IR), central obesity, and hypertension. Type 2 diabetes (T2DM) and cardiovascular diseases (CVD) share a common etiological factor, IR, which was first hypothesized by Reaven in 1988. It's been noted by Reaven, and he called it "syndrome X," that IR often occurs in tandem with a group of

***Corresponding author email address: Salahbassant0@gmail.com**

anomalies (1). To distinguish Reaven's syndrome from the previously existing syndrome X in cardiology, the prefix "metabolic" was added. Overall, IR, dysglycemia, and hypertension make up MetS X, which is a risk factor for CVDs even in the absence of associated T2DM. Six indices, including waist circumference, fasting glucose levels, lipid profile levels, and blood pressure, are used to diagnose MetS (2).

Epidemiology

The Center of Disease Control and Prevention reports that the prevalence of MetS in the United States increased by 35% between the 1980s (when the name first appeared) and 2012. MetS prevalence parallels that of obesity and T2DM. MetS increases the risk of CVD, and approximately 85% of T2DM patients have it. About 12.2% of the adult population in the United States had T2DM in 2017. About a fifth of them didn't realize they had the illness. The prevalence of MetS was three times higher than expected, representing around one-third of the adult population in the United States. The good news is that current data from the National Health and Nutrition Examination Survey show decreased rates of the condition, with 24% in men and 22% in women (3).

Urbanization, excessive caloric intake, rising obesity, and a lack of physical activity have all contributed to the worldwide rise in the prevalence of the MetS, which poses a serious and growing public-health and clinical concern. The chance of acquiring T2DM is increased 5-fold and the risk of CVD is increased 2-fold in people with MetS over the next 5-10 years. Moreover, regardless of a prior history of cardiovascular events, patients with the MetS had a 2- to 4-fold greater risk of stroke, a 3- to 4-fold increased risk of myocardial infarction (MI), and a 2-fold increased risk of death from such an event compared with those without the syndrome (4).

Pathophysiology

There are still many unresolved questions about the MetS's pathogenesis. Whether the various components of MetS are independent diseases or belong to a similar, overarching pathologic process is still up for dispute. In addition to genetic and epigenetic variables, environmental and behavioural ones have been identified as important contributors to the emergence of metabolic syndrome (5).

Overeating can be considered a cause of MetS since it leads to visceral adiposity, which is a known pathway activator. Several mechanisms have been postulated to explain how MetS might lead to CVDs and T2DM, but IR, chronic inflammation, and neurohormonal activation stand out as key contributors (6).

Glucose uptake in the liver, muscles, and adipose tissues is increased, whereas lipolysis and hepatic gluconeogenesis are suppressed thanks to insulin, a peptide hormone secreted by pancreatic beta cells in response to elevated blood glucose levels. The capacity of insulin to inhibit lipolysis is diminished as adipose tissue develops resistance. The subsequent rise in circulating free fatty acids (FFAs) exacerbates

IR because of alterations in the insulin signalling cascade in a number of organs (7).

Reduced GLUT-4 translocation to the surface and, by extension, decreased glucose uptake is the result of the effect of FFAs on insulin receptor substrate-associated PI3K activity in skeletal muscle. Fatty acids stimulate both gluconeogenesis and lipogenesis in the liver. The end outcome is a hyperinsulinemic condition where glucose levels are tightly controlled. The lipotoxic impact of FFAs on pancreatic beta cells contributes to the decline in insulin levels once the compensatory mechanisms fail. When compared to subcutaneous fat, visceral fat deposits are a more significant contributor to IR. This is because visceral lipolysis increases the flow of FFAs directly to the liver via the splanchnic circulation (8).

In addition, high levels of FFAs promote the synthesis of cholesterol esters and TAG, leading to more very low-density lipoproteins (VLDLs) that are enriched in TAGs. These then stimulate cholesterol ester transfer protein, which increases HDL clearance and reduces HDL concentrations by encouraging the transfer of TAGs from VLDL to HDL. In addition, lipoprotein or hepatic lipase hydrolyzes TAG-rich LDL, which is generated following exchange for LDL cholesterol ester, resulting in cholesterol-depleted small dense LDL particles. Atherogenic dyslipidemia, brought on by IR in MetS, is characterized by these changes in lipoproteins' concentrations (9).

Hypertension develops in response to IR because of the loss of insulin's vasodilatory effect and because of FFA-induced vasoconstriction due to reactive oxygen species production and subsequent scavenging of nitric oxide. Renin-induced salt reabsorption in the kidneys and enhanced sympathetic activation are two additional pathways. Additional risk factors for CVDs and T2DM include IR-related increases in serum viscosity, prothrombotic status, and adipose tissue-derived proinflammatory cytokine release (10).

It has been postulated that liver enzymes may be potential candidate biomarkers for MetS and associated clinical effects because of their sensitivity as a serum biomarker for detecting NAFLD. Changes in GGT and ALT levels can be utilised as a predictor of hepatic fat deposition, and thus changes in visceral fat (11,12).

The metabolic syndrome, insulin resistance, atherosclerosis, and other cardiovascular diseases all followed when PPAR was inactivated, leading to alterations in visceral fat. Liver enzymes, despite their limited sample size, have been recommended in previous epidemiological research as showing strong sensitivity to metabolic diseases (13,14).

Researchers found that ALT and the AST: ALT ratio could foretell the onset of MetS. Another study found that ALT in the higher quartile of the normal range indicated future diabetes, independently of the other components of MetS (15,16).

Obesity, metabolic syndrome, and chronic kidney disease (CKD) are linked due to shared genetic and environmental causes. As a good

biomarker of early stage CKD, serum creatinine (Cr) is widely utilized to detect subtle changes in glomerular filtration rate. Increased risk of CVD, obesity, and hypertension were all linked to elevated Cr levels in the blood. Similar to how high serum uric acid (UA) levels are a risk factor for hypertension and CVD, they are also a sign for diminished renal function. Research also shows that serum UA is an excellent predictor of T2DM in the absence of any potential confounding variables (16).

Increased risk was seen across the board for the MetS when serum UA/Cr levels were higher. Earlier studies found that hyperuricemia was strongly linked to obesity, dyslipidemia, and hypertension. There was a correlation between elevated serum Cr levels and the MetS components. MetS is characterized by low-grade inflammation, which is caused by the endocrine imbalance in adipose tissue that hyperuricemia causes. Pro-inflammatory cytokines, including as C-reactive protein and tumour necrosis factor, are produced in response to UA, suggesting that this compound may be used to regulate chronic inflammatory processes. The rising prevalence of MetS coincides well with the observed increase in the consumption of fructose and purine-rich diets over the past few decades, both of which may lead to increased serum uric acid levels (17).

Serum UA has been demonstrated to be associated with metabolic syndrome and its components, but this association is largely influenced by renal function. The purine metabolic byproduct UA is primarily excreted in the urine. Therefore, greater levels of serum UA are related with renal impairment, namely decreased eGFR and higher serum creatinine. In this research, a positive and statistically significant correlation was found between serum UA and creatinine. The presence of metabolic syndrome or cardiovascular disease has been proven to be an independent predictor of elevated blood uric acid levels. A serum UA/Cr ratio, which is adjusted for renal function and reflects net UA production, may therefore prove to be a useful marker in the etiology of MetS and similar illnesses (18).

Many physiological processes rely on lipids, such as cholesterols and TAG. Cholesterols are found in the plasma membrane and have a role in controlling the membrane's permeability, thickness, and internal curvature. Cholesterols serve as a regulator in neuronal signalling pathways and are also necessary for the synthesis of bile acids and steroid hormones. However, muscle and adipose tissues rely on TAG for fuel. Lipoproteins and chylomicrons are responsible for transporting TAG and cholesterol due to their hydrophobic properties. The carriers are made up of phospholipids, free cholesterol, and apolipoproteins, with a hydrophobic core holding a varying quantity of cholesterol esters and TAG (19).

Even while lipids play a crucial role in the body, excessive lipid levels, also known as dyslipidemia, are harmful because they raise the risk of numerous diseases, such as cerebrovascular and cardiovascular disorders. MetS is characterized by an increase in the risk of cardiovascular illnesses, although each component of the lipid profile

is a separate risk predictor for MetS. Independent correlations between total cholesterol, LDL, and HDL and cardiovascular illness, including MI, have been documented in a number of population studies (20).

MetS mostly consists of dyslipidemia, which is marked by increased levels of free fatty acids (FFAs), TAG, LDL-C, and apolipoprotein B, and decreased levels of HDL. Visceral adipocytes become more sensitive to lipolytic hormones in response to insulin resistance, which is associated with elevated fasting blood glucose. Under these circumstances, FFA are transported to the liver, where they further stimulate hepatic TAG production and increase the development of ApoB. Lipoprotein lipase (LPL), found mostly in skeletal muscle and adipose tissue, is a key mediator in dyslipidemia, as it is responsible for the production of LDL. Each of the MetS characteristics may be affected in different ways by these activities, which may be an indication of the interplay between different cellular structures during MetS development (21).

The recently discovered endocrine activity of adipose tissue provides novel insights into the aetiology of MetS, in addition to its usual roles as a thermoregulator and lipid storage facility. Interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), visfatin, omentin, and chemerin are all inflammatory cytokines that are released and play important roles in the pathophysiology of insulin resistance (IR) and metabolic syndrome (MetS) (22).

Obesity and total body fat have both been shown to be correlated with the hormone leptin. When a person's energy reserves are full, leptin signals the body to slow its metabolism and cut back on food consumption. The inability of high leptin levels to restore metabolic balance in obesity, however, may be due to "leptin resistance," a condition in which tissues have decreased sensitivity to leptin. There is evidence that leptin promotes a proinflammatory immune response by activating the Th1 pathway and counteracting the immunosuppression caused by fasting. The correlation between elevated leptin levels and elevated cardiovascular risk and inflammation is strengthening evidence that leptin is a crucial link between obesity, MetS, and CVDs (23).

In contrast to leptin, the adipokine adiponectin has been shown to have anti-inflammatory, and anti-diabetic properties. Adiponectin has a number of health benefits, including increased insulin sensitivity, decreased proliferation of vascular smooth muscle cells (VSMCs), and stabilisation of plaque formation. MetS is more likely to occur in those with genetic hypoadiponectinemia caused by a missense mutation (24).

Higher amounts of circulating chemerin have been identified in persons with MetS in several small cohort studies. This was true even after taking into account measures of obesity such as waist size and body mass index (BMI). After controlling for waist size, the chemerin/adiponectin ratio is not significant, but the chemerin/HDL-C ratio may be a superior biomarker and better predictor of nascent MetS (25,26).

Increased levels of IL-6, C-reactive protein (CRP), and TNF-α are observed in people with MetS, which can be explained by the pro-inflammatory state that results from the several pathogenic pathways that contribute to MetS development. IR and obesity have been demonstrated to raise levels of IL-6, a cytokine generated by both macrophages and adipocytes. In fact, IL-6 is known to mediate IR through a variety of complex pathways, including regulation of fat and glucose metabolism (27).

Obesity's metabolic consequences can be traced back to this cytokine and its actions on multiple tissues. Acute phase reactants, such as CRP, are produced at a higher rate in the liver when IL-6 is present. The highest association between CRP levels above the normal range and cardiac events, T2DM, and MetS has been shown in multiple investigations. By raising fibrinogen levels, IL-6 also promotes a prothrombotic condition. VSMCs and endothelial cells are among the other tissues that IL-6 targets to enhance the expression of VCAMs and local RAS pathway activation, all of which contribute to the development of atherosclerosis, inflammation, and dysfunction in the vascular wall (28,29).

MetS is characterised by a persistent inflammatory state, and this condition is maintained in part by toll-like receptors (TLRs) and other components of the innate immune system. TLRs have a role in pathogen recognition and influence the innate immune response by activating downstream inflammatory signalling pathways that culminate in the release of several cytokines (TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein-1). Lipopolysaccharide (LPS) and other pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) generated by inflamed host tissues are examples of ligands for TLRs. Saturated fatty acids, modified low-density lipoproteins, advanced glycation end-products, extracellular matrix degradation products, heat shock proteins, and other DAMPs are all recognised by TLRs, especially TLR2 and TLR4 (30,31).

The role of hedgehog pathway in MetS

Patched1 (PTCH1), the first HH receptor discovered, binds to Smoothened (SMO) to inhibit its activity in the absence of an HH ligand. Suppressor of Fused (SOF) is a protein that is bound to the tip of the primary cilium and is shortened by protein kinases such as protein kinase A, glycogen synthesis kinase 3, and Glioma-associated oncogene homolog 1 (GLI1). However, the inhibitory effect of PTCH1 on Smo was diminished after HH bound to it. Once the GLI-SuFu complex is broken down, GLI enters the nucleus as a transcription activator (GLIA) and begins to promote the transcription of downstream target genes. The activation of SMO is followed by its transfer to the primary cilia (32).

The morphogen Hedgehog and its downstream signals have only lately been linked to metabolic regulation. The sonic hedgehog (Shh) signalling system plays a crucial role in controlling many aspects of embryonic development. Many physiological and pathological processes, such as adipocyte

differentiation, cancer, diabetes, and obesity, have been linked to the deregulation of the Shh pathway. Pharmacological manipulation of the Shh system has been shown to have potential for improving patient outcomes in metabolic diseases. The molecular nature of the Shh Pathway in Metabolic Disorders and its therapeutic implication were investigated by a thorough examination using multiple search engines (33).

The HH molecular pathway was so named because mutant HH genes in fruit flies produce a "hedgehog"-like spiky process with denticles on their dorsal surface. Most metabolic diseases, including those involving fat storage, carbohydrates, and amino acids, are brought on by alterations in cellular processes and enzyme shortages. More than a billion people throughout the world are affected by the health problems associated with obesity and diabetes. Hypertension, IR, high cholesterol levels, and an increased risk of clotting make up the hallmarks of MetS, which affect 20-30% of the population in developed nations (34).

Throughout embryonic development, Hh signalling is essential for cell differentiation. Disruption of Hh signalling contributes to the onset of cancer in many tissues. This includes the liver, pancreas, skeletal muscle, and others. The expression of several ligands and effector proteins is upregulated, while Human hedgehog-interacting protein (HHIP) is downregulated in various hepatoma cell lines, demonstrating constitutive activation of the Hh pathway. Different cellular activities are controlled by signalling pathways, which are composed of regulatory proteins and other gene products (35).

The HHIP has a crucial role in embryonic tissue regeneration. It has a crucial role in pancreatic endocrine and exocrine function. Negatively regulating the hedgehog pathway, HHIP is a trans-membrane glycoprotein with 700 amino acid residues. HHIP was first discovered as an inhibitor of the HH ligand, which can regulate cell activities such pathologic angiogenesis and muscle growth through traditional or non-classical HH pathways. By causing islet ß cell dysfunction, HHIP has been shown to reduce insulin production in HFD-fed animals. Furthermore, a diabetes-related genome-wide database analysis revealed an upregulation of HHIP mRNA expression in the islets of ob/ob mice compared to lean mice. In addition, a recent study indicated that patients with impaired fasting glucose, impaired glucose tolerance, and newly diagnosed T2DM had significantly elevated serum HHIP concentrations. In addition, circulating HHIP concentration was independently linked with both HbA1c and fasting blood glucose levels. Therefore, there is a link between high levels of HHIP in the serum and diabetes and metabolic disorders (36).

Peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α and MetS

The PGC-1α has been called a master regulator of mitochondrial biogenesis and function. PGC-1α is overexpressed in tissues that have a high need for energy, and it has been linked to the development of MetS and its major consequences such obesity, T2DM, heart disease, and hepatic steatosis. Inflammation is often accompanied by metabolic abnormalities, and both are made worse by PGC-1α dysregulation. Reduced levels of PGC-1α during

inflammation are associated with an increase in oxidative stress, mitochondrial antioxidant gene downregulation, and nuclear factor kappa B activation. PGC-1α dysregulation alters the metabolic characteristics of tissues in MetS, which is characterized by chronic low-grade inflammation, by modifying mitochondrial function and encouraging buildup of reactive oxygen species (37).

Since PGC-1α functions as a major node integrating metabolic regulation, redox control, and inflammatory pathways, it is an exciting therapeutic target that may have substantial benefits for a range of metabolic ailments. The PGC-1α was initially identified as a result of its association with the nuclear receptor peroxisome proliferator-activated receptor- in response to decreased environmental heat. In addition to its role in adaptive thermogenesis, PGC-1α is now understood to be a master regulator of mitochondrial biosynthesis and function, including oxidative phosphorylation and reactive oxygen species detoxification (38).

PGC-1α is responsible for the nutritional status of the organism and is a potent regulator of both cellular and systemic metabolisms. In this setting, abnormalities in PGC-1α activity may alter tissue metabolic characteristics and contribute to a variety of metabolic diseases. Obesity, diabetes, and high blood pressure have all been linked to variations in the human PGC-1 gene. The role of PGC-1 in the onset of MetS is well-documented. The loss of PGC-1 function can lead to an inflammatory process and an associated shift in redox control, both of which may play a role in the emergence of metabolic diseases across a variety of tissues (39).

The role of glucagon-like peptide-1 (GLP-1) in MetS

Intestinal L cells release a hormone called glucagon-like peptide-1 (GLP-1) from the prepro-glucagon molecule. Not only does it prevent acid release in the stomach in vivo, but it also stimulates glucose-induced insulin secretion to an unprecedented degree. Fasting rats had a significant decrease in intracerebroventricular GLP-1. The suppressive effect of GLP-1 on food intake was also reversed by injection of a particular antagonist of GLP-1. Any function of the GLP-1 receptor, including reduction of insulin secretion, suppression of appetite, and inhibition of gastric motor activity, has a hypoglycemic impact, and it is expressed everywhere except in cells of the pancreas. A GLP-1 analogue was found to be more effective on obese patients than the prior anti-obesity medication olristat in a recent trial. For individuals with diabetes, MetS, and atherosclerotic predisposition, treatment with GLP-1 mimetic drugs such as DPP-4 inhibitors and GLP-1 analogues may represent a unique therapeutic option (40).

T2DM and MetS have both been treated with insulin-sensitizing medications and those that increase insulin production from pancreatic β-cells. Others improve insulin sensitivity and insulin secretion; examples include dipeptidyl peptidase-4 inhibitors and GLP-1 receptor agonists. Since GLP-1 is a naturally occurring hormone with multiple roles in normal physiology, including increasing insulin sensitivity, biosynthesis, and

secretion, GLP-1 receptor agonists are an appealing therapy option for MetS. GLP-1 receptor agonists also improve cardiac function in chronic heart failure and decrease neointimal development following vascular injury, and they lessen the size of myocardial infarcts after ischemia/reperfusion injury (41).

Different methods exist for primary and secondary prevention of MetS, abdominal obesity, and inflammation, including exercise and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (42).

Conclusion:

It is estimated that between 40 and 46 percent of the global population suffers from metabolic disorders including diabetes and obesity, which are closely linked to an increased risk of developing cardiovascular illnesses. The management of energy metabolism is one of the most difficult physiological processes yet is essential for good health. The relevance of environmental and social factors cannot be overstated in light of the widespread distribution of metabolic syndrome and the following catch-up in the developing world.

References:

1. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, Assi HI. Metabolic syndrome: Updates on pathophysiology and management in 2021. Int J Mol Sci. 2022;23(2):786.

2. Saklayen MG. The global epidemic of the metabolic syndrome. Curr Hypertens Rep. 2018; 20(2): 1-8.

3. Nilsson PM, Tuomilehto J, & Rydén L. The metabolic syndrome–what is it and how should it be managed?. EJPC. 2019;26(2): 33-46.

4. Moore JX, Chaudhary N, Akinyemiju T. Peer reviewed: Metabolic syndrome prevalence by race/ethnicity and sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. PCD. 2017;14.

5. Jha BK, Sherpa ML, Imran M, Mohammed Y, Jha LA, Paudel KR, Jha SK. Progress in Understanding Metabolic Syndrome and Knowledge of Its Complex Pathophysiology. Diabetol. 2023;4(2):134-59.

6. Dizaji BF, Rivandi M, Javandoost A, Karimian MS, Raei A, Sahebkar A, Ferns G, Mobarhan MG, Pasdar A. Association of genetic polymorphisms of PON1 and CETP with the presence of metabolic syndrome; the effects of genotypes on their serum activity and concentrations. EJMHG. 2018;19(1):43-8.

7. James DE, Stöckli J, Birnbaum MJ. The aetiology and molecular landscape of insulin resistance. Nat Rev Mol Cell Biol. 2021;22(11):751-71.

8. Manavi SP, Amiri T, Mozafaryan MJ. Role of Flavonoids in Diabetes. J Res Med Sci. 2021;1(3):149-61.

9. Alnami A, Bima A, Alamoudi A, Eldakhakhny B, Sakr H, Elsamanoudy A. Modulation of Dyslipidemia Markers Apo B/Apo A and Triglycerides/HDL-Cholesterol Ratios by Low-Carbohydrate High-Fat Diet in a Rat Model of Metabolic Syndrome. Nutrients. 2022;14(9):1903.

10. Schinzari F, Tesauro M, Cardillo C. Obesity-related changes in the vascular actions of insulin. Endo and Metab Sci. 2021;2:100075.

11. Goessling W, Massaro JM, Vasan RS, D'Agostino Sr RB, Ellison RC, Fox CS. Aminotransferase levels and 20-year risk of metabolic syndrome, diabetes, and cardiovascular disease. J Gastroenterol. 2008;135(6):1935-44.

12. Kain K, Carter AM, Grant PJ, Scott EM. Alanine aminotransferase is associated with atherothrombotic risk factors in a British South Asian population. JTH. 2008;6(5):737-41.

13. Lee K, & Yang, JH. Which liver enzymes are better indicators of metabolic syndrome in adolescents: the Fifth Korea National Health and Nutrition Examination Survey, 2010. Metab Syndr Relat Disord. (2013);11(4), 229-235.

14. Zhang L, Ma X, Jiang Z, Zhang K, Zhang M, Li Y, Zhao X, Xiong H. Liver enzymes and metabolic syndrome: a large-scale case-control study. Oncotarget. 2015;6(29):26782.

15. Hanley AJ, Williams K, Festa A, Wagenknecht LE, D'Agostino Jr RB, Haffner SM. Liver markers and development of the metabolic syndrome: the insulin resistance atherosclerosis study. Diabetes. 2005;54(11):3140-7.

16. Sattar N, Scherbakova O, Ford I, O'Reilly DS, Stanley A, Forrest E, MacFarlane PW, Packard CJ, Cobbe SM, Shepherd J. Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the west of Scotland coronary prevention study. Diabetes. 2004;53(11):2855-60.

17. Baldwin W, McRae S, Marek G, Wymer D, Pannu V, Baylis C, Johnson RJ, Sautin YY. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. Diabetes. 2011;60(4):1258-69.

18. Al-Daghri NM, Al-Attas OS, Wani K, Sabico S, Alokail MS. Serum uric acid to creatinine ratio and risk of metabolic syndrome in Saudi type 2 diabetic patients. Sci Rep. 2017;7(1):12104.

19. Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us?. Am J Med. 2005;118(8):816-26.

20. Gutch M, Rungta S, Kumar S, Agarwal A, Bhattacharya A, Razi SM. Thyroid functions and serum lipid profile in metabolic syndrome. Biomed J. 2017;40(3):147-53.

21. Yadav D, Mishra M, Tiwari A, Bisen PS, Goswamy HM, Prasad GB. Prevalence of dyslipidemia and hypertension in Indian type 2 diabetic patients with metabolic syndrome and its clinical significance. PHRP. 2014;5(3):169-75.

22. Lavie CJ, Milani RV, O'Keefe JH. Dyslipidemia intervention in metabolic syndrome: emphasis on improving lipids and clinical event reduction. AJMS. 2011;341(5):388-93.

23. Recinella L, Orlando G, Ferrante C, Chiavaroli A, Brunetti L, Leone S. Adipokines: new potential therapeutic target for obesity and metabolic, rheumatic, and cardiovascular diseases. Front Physiol. 2020;11:578966.

24. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ, Gojobori T, Isenovic ER. Leptin and obesity: role and clinical implication. Front Endocrinol. 2021;12:585887.

25. Jung HN, Jung CH. The role of anti-inflammatory adipokines in cardiometabolic disorders: Moving beyond adiponectin. Int J Mol Sci. 2021;22(24):13529.

26. Buechler C, Feder S, Haberl EM, Aslanidis C. Chemerin isoforms and activity in obesity. Int J Mol Sci. 2019;20(5):1128.

27. Shafer-Eggleton J, Adams-Huet B, Jialal I. Chemerin ratios to HDL-cholesterol and adiponectin as biomarkers of metabolic syndrome. Endocr Res. 2020;45(4):241-5.

28. Reddy P, Lent-Schochet D, Ramakrishnan N, McLaughlin M, Jialal I. Metabolic syndrome is an inflammatory disorder: A conspiracy between adipose tissue and phagocytes. Clin Chim Acta. 2019;496:35-44.

29. Roy S, Bhowmik DR, Begum R, Amin MT, Islam MA, Ahmed F, Hossain MS. Aspirin attenuates the expression of adhesion molecules, risk of obesity, and adipose tissue inflammation in high-fat diet-induced obese mice. Prostaglandins Other Lipid Mediat.2022;162:106664.

30. Mongraw- Chaffin M, Hairston KG, Hanley AJ, Tooze JA, Norris JM, Palmer ND, Bowden DW, Lorenzo C, Chen YD, Wagenknecht LE. Association of Visceral Adipose Tissue and Insulin Resistance with incident metabolic syndrome independent of obesity status: the IRAS family study. Obesity. 2021;29(7):1195-202.

31. Li B, Leung JC, Chan LY, Yiu WH, Tang SC. A global perspective on the crosstalk between saturated fatty acids and Toll-like receptor 4 in the etiology of inflammation and insulin resistance. Prog Lipid Res. 2020;77:101020.

32. Lim PS, Chang YK, Wu TK. Serum lipopolysaccharide-binding protein is associated with chronic inflammation and metabolic syndrome in hemodialysis patients. Blood Purif. 2019;47(1-3):28-36.

33. Xu S, Tang C. Cholesterol and hedgehog signaling: Mutual regulation and beyond. Front Cell Dev Biol. 2022:886.

34. Garg C, Kaur A, Singh TG, Sharma VK, Singh SK. Therapeutic implications of sonic hedgehog pathway in metabolic disorders: Novel target for effective treatment. Pharmacol Res. 2022:106194.

35. Verdelho Machado M, Diehl AM. The hedgehog pathway in nonalcoholic fatty liver disease. Crit Rev Biochem Mol Biol. 2018;53(3):264-78.

36. Wróblewski A, Strycharz J, Świderska E, Drewniak K, Drzewoski J, Szemraj J, Kasznicki J, Śliwińska A. Molecular insight into the interaction between epigenetics and leptin in metabolic disorders. Nutrients. 2019;11(8):1872.

37. Zhou X, Wang Y, Chen W, Zhang H, He Y, Dai H, Hu W, Li K, Zhang L, Chen C, Yang G. Circulating HHIP Levels in Women with Insulin Resistance and PCOS: Effects of Physical Activity, Cold Stimulation and Anti-Diabetic Drug Therapy. J Clin Med. 2023;12(3):888.

38. Rius-Pérez S, Torres-Cuevas I, Millán I, Ortega ÁL, Pérez S. PGC-1α, inflammation, and oxidative stress: an integrative view in metabolism. Oxid Med Cell longev. 2020; 1452696.

39. Vandenbeek R, Khan NP, Estall JL. Linking metabolic disease with the PGC-1 α Gly482Ser polymorphism. J Endocrinol . 2018;159(2):853-65.

40. Wu H, Deng X, Shi Y, Su Y, Wei J, Duan H. PGC-1α, glucose metabolism and type 2 diabetes mellitus. J Endocrinol. 2016;229(3):R99-115.

41. Yamaoka-Tojo M, Tojo T, Takahira N, Matsunaga A, Aoyama N, Masuda T, Izumi T. Elevated circulating levels of an incretin hormone, glucagon-like peptide-1, are associated with metabolic components in high-risk patients with cardiovascular disease. Cardiovasc Diabetol. 2010;9:1-9.

42. Dineen SL, McKenney ML, Bell LN, Fullenkamp AM, Schultz KA, Alloosh M, Chalasani N, Sturek M. Metabolic syndrome abolishes glucagon-like peptide 1 receptor agonist stimulation of SERCA in coronary smooth muscle. Diabetes. 2015;64(9):3321-7.

43. Sandsdal RM, Juhl CR, Jensen SB, Lundgren JR, Janus C, Blond MB, Rosenkilde M, Bogh AF, Gliemann L, Jensen JE, Antoniades C. Combination of exercise and GLP-1 receptor agonist treatment reduces severity of metabolic syndrome, abdominal obesity, and inflammation: a randomized controlled trial. Cardiovasc diabetol. 2023;22(1):41.