

The global burden of metabolic syndrome: A review of epidemiology and clinical challenges

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Abstract

Metabolic syndrome (MetS) is a multifaceted disorder defined by a cluster of interrelated risk factors, including central obesity, insulin resistance, dyslipidemia, and hypertension, which together increase the likelihood of developing type 2 diabetes, cardiovascular disease, and other chronic conditions. Its prevalence has escalated to alarming levels worldwide, with considerable variation across populations due to genetic background, lifestyle patterns, and socioeconomic differences. The underlying mechanisms of MetS involve visceral adiposity, insulin resistance, and persistent low-grade inflammation, further influenced by oxidative stress, hormonal imbalances, and endothelial dysfunction. Recent studies also point to the role of genetic susceptibility, alterations in the gut microbiome, and neuroendocrine stress responses in aggravating disease progression. Lifestyle interventions such as dietary modification, increased physical activity, and weight reduction remain the cornerstone of management, while adjunctive options including bariatric surgery, pharmacological agents, nutraceuticals, probiotics, and microbial metabolites such as butyrate are emerging as promising alternatives in resistant or advanced cases. Despite significant progress in elucidating the biological basis of MetS, challenges remain in establishing uniform diagnostic criteria, ensuring timely detection, and achieving sustainable long-term outcomes. This review brings together current insights on the epidemiology, pathophysiology, and management of MetS to provide a comprehensive understanding of the condition and identify future directions for research.

Keywords: Metabolic Syndrome; Insulin Resistance; Central Obesity; Dyslipidemia; Cardiovascular Risk; Inflammation; Gut Microbiota; Therapeutic Strategies

1. Introduction

Metabolic Syndrome (MetS) refers to a cluster of interrelated metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, and elevated blood pressure. Collectively, these factors significantly increase the likelihood of developing atherosclerotic cardiovascular disease (CVD).^[1] Both genetic predisposition and environmental influences contribute to the inflammatory processes underlying MetS, which ultimately lead to CVD. The global surge in obesity rates has made MetS a critical concern in modern healthcare.^[2] It is now recognised as one of the most pressing public health challenges due to its strong association with type 2 diabetes and heart disease. Rather than being a single condition, MetS encompasses a group of risk factors that health organisations have defined in varying ways over time.^[3]

According to recent guidelines by the Polish Society of Hypertension, the diagnosis of MetS requires the presence of obesity—determined by either a BMI greater than 30 kg/m² or waist circumference exceeding 88 cm for women and 102 cm for men—along with at least two of the following: elevated blood pressure, impaired glucose regulation, or increased levels of low-density and non-high-density lipoprotein cholesterol.^[4]

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The American Diabetes Association (ADA) further supports this diagnosis by specifying that insulin resistance is indicated by a fasting glucose level between 100–125 mg/dL, a 2-hour glucose value between 140–199 mg/dL following an oral glucose tolerance test, or an HbA1c level ranging from 5.7% to 6.4%.^[5] Additionally, a non-HDL cholesterol level above 130 mg/dL and blood pressure readings exceeding 135/85 mmHg in-office—or above 130/80 mmHg at home—are also considered diagnostic criteria. Use of medications to manage blood sugar, lipids, or blood pressure also qualifies.^[6] MetS is not limited to one system; it affects multiple organs due to overlapping mechanisms like ischemia, oxidative stress, inflammation, and hemodynamic imbalances.^[7] This increases the risk not only for cardiovascular diseases but also for chronic kidney disease, liver dysfunction (including non-alcoholic fatty liver disease), certain cancers, and neurological disorders.^[8] Historically, the World Health Organization (WHO) was the first to define metabolic syndrome in 1999, with an emphasis on insulin resistance and high blood sugar as the primary criteria.^[9]

1.1. Epidemiology

The global prevalence of Metabolic Syndrome (MetS) varies widely ranging from below 10% to as high as 84% depending on geographical location, urban versus rural settings, and differences in demographics such as age, gender, ethnicity, and lifestyle patterns. According to estimates by the International Diabetes Federation (IDF), more than one in four adults worldwide is affected by MetS. Numerous contributing factors influence its prevalence, including genetics, physical activity levels, dietary habits, smoking, educational background, and family history of diabetes. Research indicates that individuals with a sedentary lifestyle, high body mass index (BMI), or higher socioeconomic status are more likely to develop MetS. Findings from the National Health and Nutrition Examination Survey (NHANES) show that MetS is present in 5% of individuals with normal weight, 22% of overweight individuals, 60% of obese individuals.¹² Prevalence also increases with age, affecting 10% of people aged 20–29, 20% of those aged 40–49, 45% of individuals aged 60–69. Gender also plays a role. Based on criteria from the NCEP-ATP III (2001), the prevalence ranges from 7% to 56% in women and 8% to 43% in men, rising progressively from early adulthood into the sixth and seventh decades of life.

Table 1 Prevalence of Metabolic Syndrome by BMI and Age (NHANES Study)

Group	Prevalence (%)
Normal weight individuals	5%
Overweight individuals	22%
Obese individuals	60%
Age 20–29	10%
Age 40–49	20%
Age 60–69	45%

In postmenopausal women, the occurrence of MetS is notably high, with studies reporting prevalence rates between 32.6% and 41.5%. Even modest weight gain can significantly increase risk. For example, gaining more than 2.25 kg over 16 years correlates with a 45% greater risk of developing MetS. Similarly, every 11 cm increase in waist circumference is associated with an 80% higher risk of acquiring the syndrome within five years. It's also important to note that the presence of multiple MetS components simultaneously raises the risk of cardiovascular disease more than any individual factor alone. The more features of MetS a person has, the higher their overall health risk.^[10] The given table below emphasises that as individuals age and their BMI increases, the likelihood of developing metabolic syndrome also increases significantly.

1.2. Pathophysiology

1.2.1 Excess adiposity

The pathogenesis of cardiovascular-renal-hepatic metabolic syndrome (CRHM) is based on the reciprocal relationships between the development of renal, hepatic, and cardiovascular dysfunction and excess/dysfunctional adiposity and other cardio metabolic risk factors. The main cause of this syndrome process is excess adiposity, which is marked by persistent inflammation and promotes atherosclerosis, heart, kidney, and liver dysfunction in addition to other CRHM risk factors like arterial hypertension, type 2 diabetes, and dyslipidemia. Clinicians can better understand how adipose dysfunction and mild metabolic abnormalities might progress to severe heart failure, chronic kidney disease, and liver cirrhosis by being aware of these pathways ^[11-12]

Adiposity and insulin resistance

Increased immune cell infiltration, especially of M1 pro-inflammatory macrophages, and decreased angiogenesis are hallmarks of excess and particularly dysfunctional adipose tissue, particularly visceral. Local inflammation is made worse by these alterations, which produce hypoxia in adipose depots. Macrophages and defective adipocytes release pro-inflammatory cytokines such as interleukin (IL)-6, IL-1 β , and tumor necrosis factor- α (TNF- α). This metabolic dysregulation causes "meta-inflammation," an inflammatory inflammation that interferes with normal insulin signaling in peripheral organs such as muscle, liver, and adipose tissue. In particular, intracellular kinases like JNK and IKK- β are activated by pro-inflammatory cytokines, phosphorylating insulin receptor substrate (IRS) proteins on serine residues rather than tyrosine. Because of the disruption of downstream communication caused by this abnormal phosphorylation, peripheral organs such as skeletal muscle and adipose tissue absorb less glucose while increasing hepatic gluconeogenesis^[11-12]

Furthermore, more free fatty acids (FFAs) are released into the bloodstream by larger and malfunctioning adipose tissue. These FFAs cause lipotoxicity when they build up in muscle and liver cells. Metabolic inefficiency is exacerbated by this ectopic fat deposition, which directly affects insulin signaling and mitochondrial function.^[12]

Adipokine dysregulation is another characteristic of obesity. Leptin resistance results from the chronic overproduction of leptin, a hormone that controls satiety and energy balance, in obese people. This condition makes it harder for the brain to control hunger and energy expenditure, which contributes to weight gain. Insulin resistance development is tightly associated with leptin resistance. Furthermore, insulin resistance is made worse by resistin, an adipokine that is increased in obesity and encourages meta-inflammation. On the other hand, as obesity rises, adiponectin, an adipokine that is insulin-sensitising and anti-inflammatory, falls.^[13]

Adiposity and dyslipidemia

FFAs are continually released into the portal and systemic circulation by excess adipose tissue. These FFAs are used by the liver to create TGs, which are then encapsulated in very low-density lipoproteins (VLDLs). VLDL overproduction raises plasma TG levels, which is a defining feature of dyslipidemia linked to obesity. The cholesteryl ester transfer protein (CETP), which enables the interchange of triglycerides from VLDLs with cholesteryl esters from HDL, is activated by high amounts of triglyceride-rich VLDLs. Lower plasma HDL levels are the outcome of this process' depletion of HDL particles. Furthermore, the development of small dense low-density lipoprotein (sdLDL) particles, which are more atherogenic, is facilitated by the elevated presence of VLDLs. The dyslipidemic profile linked to obesity is exacerbated by insulin resistance, dysregulated adipokine profiles, and meta-inflammation, which all interfere with lipoprotein metabolism.^[14]

Adiposity and arterial hypertension

Obesity-related meta-inflammation and dysregulated adipokine profiles can trigger the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), which can lead to endothelial dysfunction and decreased generation of nitric oxide (NO). Blood pressure rises as a result of these alterations, which also raise peripheral vascular resistance, heart rate, and adrenal aldosterone secretion. Peripheral vascular resistance is further increased by the promotion of smooth muscle hypertrophy in blood arteries by chronic stimulation of the RAAS and SNS. Furthermore, aldosterone secretion is directly stimulated by defective adipose tissue, which aggravates hypertension and causes salt retention.^[15]

Adiposity and renal dysfunction

Increased cardiac output (CO) and blood volume can raise the glomerular filtration rate (GFR) in the early stages of obesity and insulin resistance; this is referred to as "hyper filtration." Chronic glomerular hypertension and dysfunction are caused by this hyper filtration. Furthermore, neurohormonal stimulation raises intraglomerular pressure by increasing efferent arteriolar tone. Proteinuria and gradual nephron loss might arise from podocyte destruction, which is caused by the increased mechanical stress in the glomeruli. Podocytes are important cells in the kidney's filtration barrier. Furthermore, by directly harming tubular cells and encouraging fibrosis, persistent inflammation might exacerbate renal injury.^[16]

2. Coexistence of hypertension and Diabetes leads and progression to CKD chronic kidney disease. The harmful consequences of diabetes and hypertension on the kidneys are greatly increased when they coexist

2.1. Glomerular Hyper filtration

Both disorders worsen hyper filtration and raise glomerular pressure, hastening the deterioration of podocytes and other glomerular cells. Chronic hyperglycemias in diabetes causes the kidneys to filter more glucose. Renal tubules increase their reabsorption of salt and glucose to make up for this, which raises intraglomerular pressure and encourages hyper filtration. Similar to this, systemic hypertension causes the glomeruli to experience high pressure, which initially causes hyper filtration before developing into glomerular sclerosis (hardening and scarring) ^[17-18]

2.2. RAAS (Renin-Angiotensin-Aldosterone System)

RAAS activity, which is frequently increased in idiopathic arterial hypertension, can be exacerbated by insulin resistance and hyperglycaemia. Preferential constriction of the efferent arteriole due to elevated angiotensin II raises intraglomerular pressure. Chronic glomerular damage results from this pressure being exacerbated by increased aldosterone secretion as well as fluid and sodium retention. Damage caused by RAAS eventually leads to structural alterations in the renal vasculature, including hyper-plastic arteriosclerosis in more severe cases and hyaline arteriosclerosis in afferent arterioles ^[19-20-21]

2.3. Vascular Remodeling Vascular Remodeling

Long-term high blood pressure causes the walls of tiny renal arteries and arterioles to thicken, which narrows the lumen and reduces blood flow. Kidney disease is made worse by this ischemia damage to the nephrons. ^[20-21]

2.4. Advanced Glycation End Products (AGEs)

Long-term hyperglycaemia encourages the renal tissues to produce AGEs. These AGEs cause oxidative stress, fibrosis, and inflammation by changing protein structures like collagen in the glomerular basement membrane ^[20-21]

2.5. Chronic Inflammation and Endothelial Dysfunction

Pro-inflammatory cytokines and oxidative stress from diabetes and hypertension cause endothelial dysfunction, which harms renal vessels and glomeruli. Mesangial cells and fibroblasts are activated by chronic inflammation, which results in extracellular matrix deposition, nephron loss, and a progressive reduction in GFR ^[20-21]

3. Cardiovascular-Liver Interactions, the Impact of Heart Failure on the Liver

3.1. Diminished Hepatic Perfusion

Reduced CO results in decreased hepatic perfusion in cardiac failure, especially HF with reduced ejection fraction (HFrEF). This insufficient perfusion restricts the liver's ability to receive nutrients and oxygen, which stresses the hepatocytes' metabolism and leads to hepatocellular damage.^[22]

3.2. Congestive Hepatopathy

Another name for congestive hepatopathy is sinusoidal congestion, which occurs when high central venous pressure is transferred to the hepatic veins in heart failure. Additionally, HF triggers the RAAS, which increases water and sodium retention and exacerbates hepatic congestion. Chronic congestion reduces the amount of oxygen and nutrients that reach hepatocytes by interfering with hepatic microcirculation. Low-grade inflammation and sinusoidal congestion work together to activate hepatic stellate cells, which results in the deposition of extracellular matrix and the creation of collagen. This process may eventually lead to the formation of ascites and even evolve into severe fibrosis and "cardiac cirrhosis".^[23]

3.3. Neurohormonal Activation

An increase in systemic and splanchnic vascular resistance is linked to neurohormonal activation, which is the stimulation of the SNS and RAAS, and cardiac dysfunction, specifically HFrEF and to a lesser extent HFpEF. Low systemic vascular resistance is frequently linked to cirrhosis; nevertheless, HF-driven RAAS activation can upset this equilibrium,

exacerbating portal hypertension and ascites. In patients with chronic liver damage, aldosterone and angiotensin II may exacerbate hepatic fibrosis by contributing to tissue fibrosis.^[24-25]

3.4. Oxidative stress and chronic inflammation

ASCVD (atherosclerotic cardiovascular disease); and HF (heart failure) are linked to higher levels of oxidative stress markers and pro-inflammatory cytokines (such as TNF- α and IL-6). These mediators can prolong the cycle of hepatic damage and fibrosis and worsen underlying liver disease.^[26-27]

4. The Impact of Hepatic Dysfunction on the Heart

4.1. Hyper-dynamic Circulation

A hyper dynamic circulatory state with decreased systemic vascular resistance is caused by the overproduction of vasodilatory mediators like NO, especially in the splanchnic circulation, in advanced liver cirrhosis. In order to maintain perfusion, the heart adapts by raising CO even while arterial blood pressure may decrease. This cardiac stress can eventually lead to heart failure, also known as "cirrhotic cardiomyopathy," which is characterised by decreased contractility and cardiac remodeling.^[28]

4.2. Neurohormonal Activation

In cases of severe liver disease or cirrhosis, the splanchnic circulation produces an excessive amount of vasodilatory mediators, such as NO, which, when combined with hypoalbuminemia and lowered oncotic pressure, results in a significantly decreased effective arterial blood volume. The RAAS and SNS are then activated in a compensatory manner. Chronic left ventricular pressure overload is caused by RAAS activation, which also causes vasoconstriction and raises after load. This may cause or worsen myocardial fibrosis and left ventricular hypertrophy, which may lead to the onset of "cirrhotic cardiomyopathy." Furthermore, increased aldosterone causes water and sodium retention, which results in volume overload.^[24-25]

4.3. Ascites

Tense ascites can exacerbate heart failure symptoms by impairing cardiac filling and venous return.^[29]

4.4. Toxic Metabolite Accumulation

Ammonia and other metabolic wastes build up because the liver is unable to effectively remove them when there is liver failure. In addition to increasing the risk of arrhythmias, these toxins can induce atherosclerosis, oxidative stress, systemic inflammation, and the development of "cirrhotic cardiomyopathy".^[30]

4.5. Chronic Inflammation and Oxidative Stress

Pro-inflammatory cytokines (e.g., TNF- α , IL-6) and oxidative stress are released when Kupffer cells and other immune cells are activated by chronic liver disease, such as cirrhosis. This can cause direct harm to endothelial cells and cardiomyocytes, which can lead to atherosclerosis and the emergence of "cirrhotic cardiomyopathy"^[31]

Promoting Dyslipidemia and Insulin Resistance in MASLD Patients with MASLD have dysregulated hepatic lipid metabolism and decreased hepatic insulin sensitivity due to factors like lipotoxicity and meta-inflammation. They also have hyperglycemia due to increased glycogenolysis and gluconeogenesis, which are important risk factors for atherosclerosis.^[31]

4.6. Cardiovascular-kidney interaction

The Impact of Cardiovascular Disease on the Kidneys

- Impaired Renal Perfusion: Reduced CO causes impaired renal perfusion in cardiac failure, especially HFrEF. The cardiorenal syndrome is characterised by this decrease in GFR, which can also result in persistent ischemia renal injury and atrophy.^[31]
- Congestive nephropathy: Renal congestion is caused by elevated central venous pressure that travels backward into the renal veins as a result of cardiac failure. Renal congestion is made worse by HF's activation of the RAAS, which encourages water and sodium retention. The transrenal pressure gradient is diminished by high venous

pressure, which hinders glomerular filtration. Fibrosis and increasing nephron loss may result from this mechanism over time.[32]

- **Neurohormonal Activation:** Neurohormonal activation, or the stimulation of the SNS and RAAS, is linked to cardiac dysfunction, specifically HFrEF, and to a lesser degree, HFpEF. This leads to an increase in systemic and splanchnic vascular resistance. Prolonged RAAS activation is linked to glomerular injury, which causes increasing nephron loss, fibrosis, and proteinuria. Renal vasoconstriction is made worse by chronic SNS activation, which lowers GFR and encourages ischemia renal damage,[33]
- **Oxidative stress and chronic inflammation:** ASCVD and HF are linked to higher levels of oxidative stress markers and pro-inflammatory cytokines (such as TNF- α and IL-6). Renal impairment may result from these mediators' direct harm to blood vessels and renal tubular cells.[33]

5. The Impact of Renal Dysfunction on the Cardiovascular System

5.1. Neurohormonal Activation and Volume Overload

Reduced salt supply to the distal tubule causes renin release, which in turn activates the RAAS as kidney function deteriorates. Chronic left ventricular pressure overload is caused by RAAS activation, which also causes vasoconstriction and raises after load. This can cause or worsen myocardial fibrosis and left ventricular hypertrophy, which can stiffen the ventricular walls and encourage diastolic dysfunction. Furthermore, increased aldosterone causes water and sodium retention, which raises right ventricular preload and results in volume overload. Through the leftward displacement of the inter ventricular septum, this volume overflow may cause inter ventricular contact, lowering left ventricular preload and, ultimately, CO. Moreover, pulmonary oedema may be exacerbated or caused by excessive fluid retention.[34]

5.2. Accumulation of Uremic Toxins

In advanced chronic kidney disease (CKD), urea and indoxyl sulfate are examples of uremic toxins that can directly affect cardiac function. In addition to promoting vasoconstriction, inflammation, atherosclerosis, and arrhythmogenesis, these toxins also affect endothelial function by decreasing NO generation.[35]

5.3. Anemia of CKD

Normocytic anemia is the result of failing kidneys producing less erythropoietin (EPO), which causes anemia in chronic kidney disease (CKD). Additionally, red cell apoptosis is increased by the uremic toxin indoxyl sulfate, which exacerbates anemia in CKD. To meet peripheral oxygen demands, the heart responds by trying to raise the CO, which might raise left ventricular filling pressures and result in dyspnea. The heart is under stress from chronic hyper dynamic circulation brought on by CKD (chronic kidney disease) anemia, which may result in a deterioration in cardiac function. Severe anemia can also lower the oxygen flow to the heart, which can lead to ischemia and worsen heart function, which can lead to a type 2 myocardial infarction.[36-37]

5.4. Oxidative stress and chronic inflammation

CKD is linked to higher levels of oxidative stress markers and pro-inflammatory cytokines (such as TNF- α and IL-6). One important endotheliotoxin that contributes to the development of cardiovascular disease in people with chronic kidney disease is indoxyl sulfate. It causes thrombosis, inflammation, and oxidative stress in endothelial cells, all of which are crucial for atherosclerosis, cardiac dysfunction, and endothelial dysfunction.[38-39-40]

6. Other er Modifying Factors in CRHM Syndrome Pathophysiology

Adiposity is the primary cause and first event in the onset and evolution of the CRHM syndrome. Nevertheless, the etiology and development of the condition are also significantly influenced by aging, sex hormone dynamics, environmental stresses, and hereditary factors. Increased frailty, systemic low-grade inflammation (also known as "inflammaging"), and mitochondrial dysfunction are all fundamentally associated with aging and aggravate metabolic, cardiovascular, renal, and hepatic dysfunction [ml-omics].[41-42-43-44-45]

Frailty exacerbates organ failure by causing sarcopenic obesity, poor glucose metabolism, and decreased physiological reserves.[46-47-48]

Another level of intricacy is introduced by sex dimorphism, which is caused by variations in sex hormones. For instance, estrogen has protective effects on metabolic, hepatic, and cardiovascular health; its decrease in postmenopausal women

is linked to higher risks of systemic inflammation, visceral obesity, and dyslipidemia. Similarly, insulin resistance, decreased lean mass, and increased cardiovascular risk are associated with testosterone deprivation in men. [49-50]

Through common pathways like oxidative stress, endothelial dysfunction, and chronic inflammation, environmental stressors such as smoking, air pollution, physical inactivity, and chronic psychosocial stress can further accelerate the advancement of CRHM. It has been demonstrated that exposure to environmental pollutants and fine particulate matter (PM_{2.5}) aggravates hepatic steatosis, renal damage, and atherosclerosis. [51]

Lastly, epigenetics and genetic variables are also quite important. It is commonly known that some people who are not obese go on to get type 2 diabetes, while others who have minor abdominal obesity do so, and some people who have severe, chronic obesity do not develop type 2 diabetes. This variation in susceptibility demonstrates how genetic predispositions and epigenetic changes impact the effects of obesity. A more thorough grasp of the interrelated processes causing the CRHM condition can be obtained by acknowledging these other aspects.

6.1. Treatment

6.1.1 Lifestyle modification

Treatment for lifestyle modification should be provided by a team of doctors and nonphysicians using a multidisciplinary approach. experts, including dietitians and those holding master's degrees in behavioural psychology, exercise physiology, or health education⁸⁰. Lifestyle therapy has the advantage of producing a moderate reduction in all metabolic risk factors, even though it might not alter any one risk factor as much as a specific medication. [52-53]

6.1.2 Weight reduction

There are four methods for losing weight: calorie restriction (e.g., 500 kcal/d deficiency), more exercise, behavioural changes, and, in FDA-approved medications for weight loss in the right persons⁸¹ A 10% drop in body weight within the first six months to a year is advised by a number of experts, and weight loss should continue until the BMI falls below 25. Exercise and dietary modifications that can lower blood pressure and enhance lipid levels will further improve insulin resistance even in the absence of weight reduction, even though many patients find it difficult to lose weight. [52].

Even a modest 5–10% reduction in body weight can significantly lower TGs and raise HDL-C⁵³ A slight decrease in body weight can significantly lower blood pressure in people with hypertension and those at risk of acquiring it.^[54] Fasting blood glucose, insulin, and haemoglobin A1c can also be decreased with a little weight loss.⁵⁵ Regular exercise seems to be crucial for reducing abdominal fat during weight maintenance (i.e., energy balance)^[55-56]

6.1.3 Physical activity

Exercise routines that are realistic, consistent, and moderate are advised by the most recent physical activity guidelines^[57]

The typical recommended for exercise is 30 minutes or more each day of moderate-intensity exercise. Nonetheless, 60 minutes of brisk, moderate-intensity walking is preferred, to be complemented by other exercises.^[58] The latter includes several quick (10 to 15 minute) bursts of activity (e.g., walking breaks during work, gardening, or housework), using basic exercise equipment (e.g., treadmills), jogging, swimming, biking, golfing, team sports, and resistance training.^[59]

It's also recommended to stay away from common Sedentary pastimes like watching television and playing video games. The most recent AHA recommendations demand that before starting a new exercise program, a clinical evaluation of the risk of future ASCVD occurrences be conducted. For patients at high risk (such as those who have recently experienced acute physical exercise under a doctor's supervision if you have coronary symptoms or recent revascularization. Taking into account the obstacles (such as arthritis and time limits) that may hinder a successful increase in physical activity, clinicians should assess what kind of activity is practical for the patient. As a result, they ought to help patients create a plan for physical activity based on the results of the initial evaluation. Nonetheless, physical activity of any kind must be promoted. To prevent excessive tiredness, muscle soreness, strains, or injuries, lifestyle activity should be gradually increased in time and intensity (by 5 minutes per session/week), beginning with low-intensity exercise (<3 metabolic equivalent) in sedentary people.^[60]

6.1.4 Bariatric surgery

For those who are exceedingly obese (BMI > 40 kg/m²) and do not react to weight loss diets or drugs, surgery is advised.), or if they have one or more comorbid illnesses and a BMI greater than 35 to 40 kg/m²^[61] Improvements in

the metabolic profile have been reported, most likely as a result of adiposity redistribution.⁶² In addition to Roux-en-Y and other types of gastric bypass, bariatric surgical procedures that use laparoscopic adjustable banding of the stomach are now preferred for obesity that is extreme and morbid.^[63] In patients with diabetes and hypertension, it causes a 25–30% reduction in body weight and a quick return to normal blood pressure and glucose management. 95% of individuals are clear of the syndrome one year following surgery. ^[63-64]

6.1.5 *Nutraceuticals*

The use of nutraceuticals in the treatment of MetS is being evaluated by recent studies. In the treatment of people with MetS, a number of plant extracts, spices, herbs, and essential oil extracts appear to be beneficial. These compounds are currently being studied and cannot be regarded as a pharmacotherapy substitute, despite some advantages having been reported. Nonetheless, the use of nutraceuticals, which are widely accessible and have few side effects, to treat MetS.^[65]

6.1.6 *Probiotics*

These days, there is proof that the development of insulin resistance may be influenced by gastrointestinal dysbiosis, which is the alteration of the gastrointestinal microbiota research have demonstrated the negative impacts of low oratypical gut bacterial load on insulin resistance, obesity, inflammatory markers, and dyslipidemia. ^[66-67]

Furthermore, exposure to the bacterial LPS, the primary cause of metabolic endotoxemia associated with MetS, was one of the pathways.^[68]

Research has demonstrated that obese people have a lower ratio of Bacteroidetes\ Firmicutes than people of normal weight. ^[69] It's interesting to note that one strain in particular (Lactobacillus reuteri V3401) has drawn interest in the literature and produced positive outcomes in animal experiments. Therefore, 53 persons with MetS participated in a randomized, placebo-controlled crossover research.^[70]

And the participants were split into two groups: one group was given a placebo along with a healthy lifestyle suggestion, while the other group received the probiotic Lactobacillus reuteri V3401 for 12 weeks while simultaneously following a hypocaloric diet and engaging in physical exercise. The group treated with Lactobacillus reuteri V3401 showed no differences in clinical characteristics of MetS; however, alterations in anthropometric measurements, inflammatory biomarkers, and microbiome composition were noted: a decrease in IL-6 and VCAM-1 levels, an improvement in anthropometric parameters, and an increase in the proportion of Verruco microbia phylum. ^[70]

There have been conflicting findings about the effectiveness of probiotics in treating MetS. The different doses, strains, and study designs are most likely the cause of these contradictory findings. Hence, more research is needed to prove the positive effects of probiotics and further examine their mechanism of action.^[71]

6.1.7 *Butyrate and microbiota-targeted therapy*

In animal models of MetS, butyrate has recently been shown to increase insulin sensitivity, body weight, composition, glycemia, and lipid profile. Butyrate's positive effects on adipose tissue, intestinal cells, skeletal muscle, pancreatic islets, hepatocytes, and blood vessels were examined in vitro, highlighting the interaction of genes and pathways. There has been evidence of a connection between human microbiome components and obesity. However, these findings rely on experimental research conducted with relatively small and discrete volunteer or model animal groups. Furthermore, the overall and relative amounts of butyrate are controlled by dietary intake and microbial components. ^[72] Faecalibacterium prausnitzii, Eubacterium rectale, and Roseburia intestinalis are the three principal species of the many and phylogenetically distinct group of bacteria that create butyrate in the colon. Subjects with diabetes and those at risk for the disease have lower levels of these microorganisms.^[73] Lean people's microbiota exhibits higher relative amounts of butyrate-producing bacteria, and when they are transferred to subjects with MetS, insulin sensitivity improves.^[74]

There are several different ways that butyrate works, and one of them is by blocking histone deacetylase, which controls gene expression epigenetically. ^[75]

Histone N-terminal tail acetylation is thought to enhance gene transcription in epigenetic.. Environmental influences, including food components, can modify the acetylation and deacetylation of histones, potentially reduce disease and promote health. Furthermore, PGC-1 α activity can be stimulated by butyrate-induced AMPK activation and histone deacetylase (HDAC) inhibition.^[76] Butyrate is thought to have a significant impact on metabolism and appetite suppression by binding to and activating the intestinal enteroendocrine cells' G protein-coupled free fatty acid receptors (FFAR), FFAR2 and FFAR3. ^[77]

Surprisingly, it has been demonstrated that butyrate supplementation or a diet rich in fiber, along with an increase in gut bacteria, can prevent or lessen insulin resistance and obesity [78]

Butyrate may decrease hunger and weight by inducing FFARs in the gut. Peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) are released in response to FFAR activation (Figure 2). PYY will decrease appetite and slow stomach emptying, while GLP-1 will boost insulin secretion and suppress glucagon secretion. [79] Butyrate also inhibits the release of the hunger hormone ghrelin. By lowering increases in adiposity, butyrate supplementation reduced weight gain in rats fed high-fat diets (HFD). Butyrate did not change weight, adiposity, glycemia, or insulinemia in mice on a non-HDF, according to Matheus et al. [80]

However, these parameters were significantly improved in mice on an HFD, suggesting that butyrate mitigates the negative effects of an HFD. Fermentable fibers and resistant starches also exhibit the positive benefits of butyrate supplementation. [81]

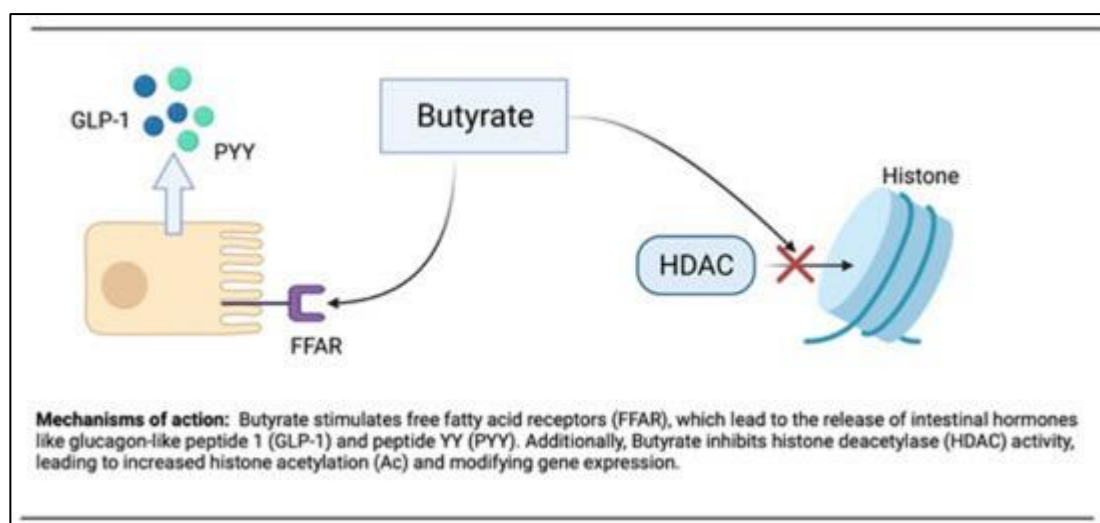


Figure 1 Mechanism of Action

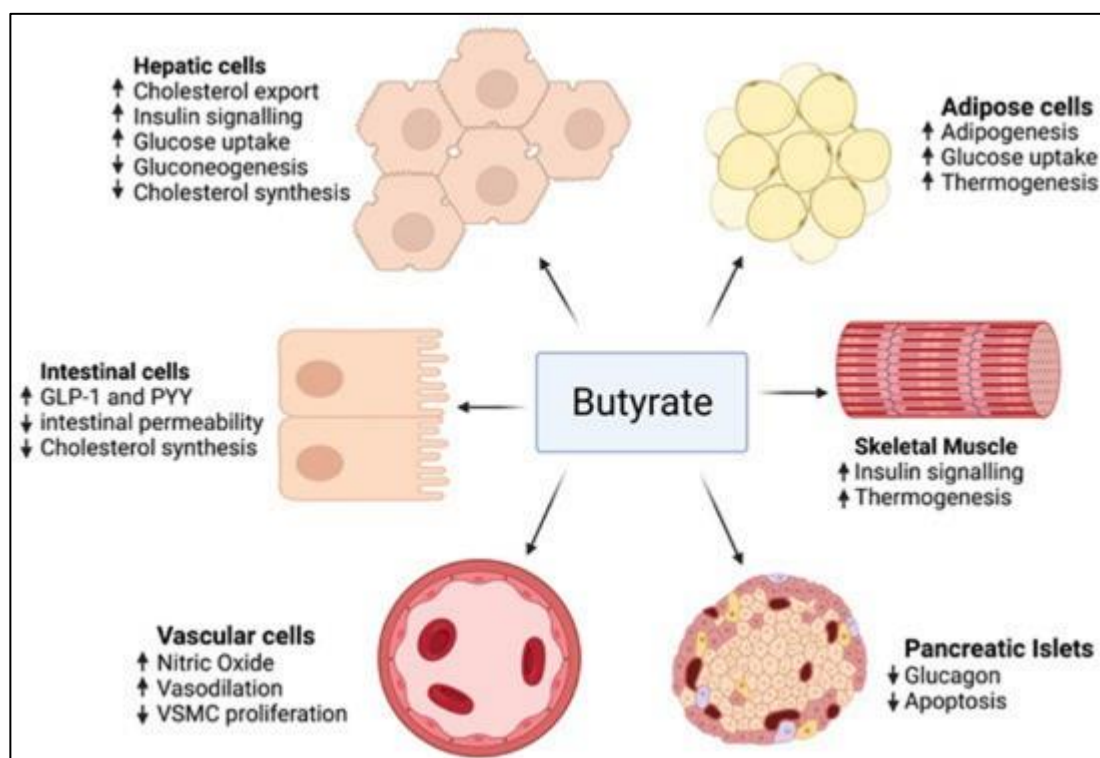


Figure 2 The effect of butyrate on adipose tissue, intestinal cells, skeletal muscle, pancreatic islets, hepatocytes, and blood vessels

Currently, the majority of human clinical trials have examined the effects of butyrate whether taken orally or rectally for intestinal illnesses. Diverticulitis [82] Crohn's disease [83] ulcerative colitis [83-84] and traveler's diarrhoea [85] have all improved in a number of these trials. It was well tolerated and no significant adverse effects were reported. The particular issue was that butyrate taken orally caused foul-smelling belching. However, the benefits of butyrate in MetS were not sufficiently investigated in human clinical trials. There were only two minor tests carried out. There was no improvement in fasting insulin, fasting blood glucose, cholesterol, or triglyceride levels in type 2 diabetics treated with 100 mg sodium butyrate six times a day for 45 days, according to a randomized placebo-controlled clinical trial [86]. However, there was an increase in GLP-1 and a decrease in diastolic blood pressure. The second experiment was not placebo-controlled and had a limited sample size. It investigated the effects of four grams of sodium butyrate taken orally every day for four weeks. Lean males, as opposed to obese males, showed an improvement in peripheral and hepatic insulin sensitivity [87]. The function of butyrate in MetS is summed up in Figure.

7. Conclusion

Metabolic syndrome is a major global health concern because of its strong association with type 2 diabetes, cardiovascular disorders, and other chronic diseases. Its development is driven by a multifactorial interaction of genetic predisposition, lifestyle patterns, and environmental influences, with central obesity, insulin resistance, and persistent low-grade inflammation at the core. Lifestyle measures such as balanced diet, physical activity, and weight management remain the foundation of prevention and treatment, yet complementary approaches including bariatric surgery, probiotics, nutraceuticals, and gut-derived metabolites like butyrate are gaining attention. Future research should focus on refining diagnostic criteria, identifying novel therapeutic targets, and advancing personalized interventions. Coordinated efforts from clinicians, nutritionists, scientists, and policymakers are essential to curb the rising global burden of metabolic syndrome and its complications.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

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