REVIEW ARTICLE

Lifestyle Modifications and Nutraceutical Interventions in the Prevention and Management of Metabolic Syndrome

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Abstract

Abdominal obesity, dyslipidemia, hypertension, and hyperglycemia are metabolic risk factors that are grouped together to define metabolic syndrome (MetS). It is now widely recognized that MetS is linked to a higher risk of type 2 diabetes (T2DM) and cardiovascular disease (CVD). Overall, the pathophysiology of MetS initiated by the imbalance of nutrition intake and physical activity. It involves a complex interplay of insulin resistance (IR), inflammation, dysregulated adipocyte function, and genetic susceptibility, all of which contribute to the metabolic dysfunction. Lifestyle modifications play a crucial role in managing and preventing MetS. Key strategies include adopting a balanced diet like Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH), or caloric restriction (CR), engaging in regular physical activity, and maintaining a healthy weight. Nutraceuticals, including polyphenols and CR-mimetic agents, improve insulin sensitivity, reduce inflammation, lower blood pressure and cholesterol levels, reducing oxidative stress, and promoting autophagy. In addition to lifestyle changes, drug therapy may be necessary for some individuals to manage specific risk factors, such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), calcium channel blockers, and beta blockers for hypertension; biguanides, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide 1(GLP-1) receptor agonists, sodium-glucose co-transporter 2 (SGLT2) inhibitors, and thiazolidinediones for hyperglycemia; and statins for dyslipidemia. Early diagnosis, including waist circumference and blood pressure measurement, serum cholesterol and glucose testing, and intervention, is essential to effectively manage MetS and prevent the progression of associated diseases. In conclusion, understanding the risk factors and associated risks of MetS, along with the implementation of lifestyle modifications such as dietary and nutraceutical interventions including polyphenols and CR-mimetic agents, is vital for reducing the burden of this syndrome. Early diagnosis and proactive management are key to improving long-term health outcomes.

KEYWORDS: metabolic syndrome, abdominal obesity, insulin resistance, diet, nutraceuticals

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Introduction

The metabolic syndrome (MetS) or metabolic dysfunction has become a silent major global public health concern with estimated prevalence of almost half (~40-46%) of the adult population and keep increasing. The syndrome includes a group of metabolic conditions known as the "deadly quartet" including central obesity, insulin resistance (IR), dyslipidemia, and hypertension.(1,2) Each component of the quartet significantly contributes to increase metabolic dysfunction. Excess abdominal fat in central obesity is

closely linked to IR and inflammation, which are key drivers of MetS. IR impairs the body's ability to use insulin effectively, leading to elevated blood glucose levels and a higher risk of type 2 diabetes mellitus (T2DM). Dyslipidemia, which involves elevated triglyceride levels and reduced high-density lipoprotein (HDL) cholesterol, plays a major role in the development of atherosclerosis and cardiovascular disease (CVD).(3,4) Additionally, high blood pressure strains the cardiovascular system, increasing the risk of heart disease and stroke. Individuals with MetS are at 2-5 times greater risk for developing T2DM, stroke, myocardial infarction (MI), CVD, and increased mortality over the next 5 to 10 years.(3)

However, environmental factors, such as diet and sedentary behavior, alongside genetic predisposition, play a major role in the development of MetS.(3) The global adoption of Western dietary patterns, along with increasing sedentary lifestyles, have significantly contributed to the rising prevalence of MetS worldwide. This leads to a challenge in creating a firm definition of MetS that best predicts the risk of subsequent cardiovascular events.(5) To effectively prevent and manage MetS, early diagnosis and intervention are essential.(6) While pharmaceutical treatments, such as metformin for insulin resistance, statins for dyslipidemia, and antihypertensives for hypertension, are commonly used to address the individual components of MetS, these therapies focus on symptom management rather than the root causes.

Nutraceuticals, especially polyphenols, have emerged as promising adjuncts in managing MetS. These bioactive compounds, found in various fruits, vegetables, and teas, possess antioxidant and anti-inflammatory properties that improve insulin sensitivity, lower blood pressure, enhance lipid metabolism, as well as activate autophagy. This integrative approach, combining nutraceuticals with lifestyle modifications and conventional pharmacotherapy, offers a more holistic strategy for mitigating MetS risk factors and improving overall health outcomes. In this regard, the current natural treatments and lifestyle that may help in its management with few adverse effects as a promising avenue for the creation of innovative treatments will be discussed in this review article.

Metabolic Syndrome: Definition and Controversies

The concept of MetS, initially referred to as 'Syndrome X' by Reaven, was first proposed as a central factor in the development of T2DM and CVD mainly due to IR in target tissues.(7) Since its initial description, MetS has been redefined multiple times, leading to inconsistencies in its diagnosis. These variations are evident in studies that employ different criteria, particularly in how abdominal obesity is interpreted as summarized in Table 1.(8-13)

Visceral obesity has been known to induce a state of chronic low grade inflammation and releases fatty acids, inflammatory cytokines, and hormones that can lead to IR and dyslipidaemia, as the initial cause of MetS.(14) Different organizations use varying ranges of waist circumference (WC) to determine due to different population, different thresholds based on the specific health risks associated with waist circumference in their target populations, and practical aspects such as ease of measurement and the ability to implement these measurements in various healthcare settings (Table 1).(15)

IR is a central feature of MetS and occurs when cells in the body become less responsive to insulin. This impairs glucose uptake, leading to elevated blood glucose (hyperglycemia) and increased insulin production (hyperinsulinemia), which contribute to lipid abnormalities and hypertension, the core components of MetS. While IR is a central feature of the syndrome, some diagnostic criteria, especially those focusing on central obesity, do not require the presence of IR for diagnosis.(16)

However, unlike the World Health Organization (WHO), American Association of Clinical Endocrinology (AACE) and European Group for the Study of Insulin Resistance (EGIR) definitions, other criteria do not technically require the existence of IR in their criteria, which may make them more specific to CVD than to T2DM.(17) Given the variety of other non-traditional criteria that were suggested for MetS study, the International Diabetes Federation (IDF) definition is an intriguing contender.(5,17) Despite of all agreement on MetS definition, to predict the risk of MetS since earliest is still become current challenge.

MetS Pathophysiology and Predisposing Factors

Adipose tissue (AT) has a significant role in central metabolic diseases (18,19), but its pathophysiology is complex and the intricate interactions between the numerous variables are still unknown. Oxidative stress and low-grade chronic inflammation contribute as potential causes, leading to IR and an increased flow of fatty acids, which are considered key pathways underlying the pathophysiology of MetS.(20)

Table 1. MetS definition based on different organization. The presence of any three out of five components qualifies for a diagnosis of MetS.(8-13)

Criteria	NCEP-ATP III, NHLBI, and AHA	WHO	IDF	AACE	EGIR	IAS
Central Obesity	WC: ≥102 cm (men), ≥88 cm (women)	BMI: >30 kg/m² or WHR: >0.90 (men), >0.85 (women)	WC: ≥94 cm (men), ≥80 cm (women) (Europid); WC ≥90 cm (men), ≥80 cm (women) (South East Asia)	WC: ≥102 cm (men), ≥88 cm (women)	WC: >94 cm (men), >80 cm (women)	WC based on population-specific definitions
Insulin Resistance (IR)	Not required	Required: Impaired glucose tolerance, diabetes, or IR	Not required	Required: Impaired glucose tolerance, diabetes, or IR	Required: Fasting insulin levels above the 75th percentile for the population.	Not required
Dyslipidemia	Triglycerides: ≥150 mg/dL; HDL-C: <40 mg/dL (men), <50 mg/dL (women)	Triglycerides: ≥150 mg/dL; HDL-C: <35 mg/dL (men), <39 mg/dL (women)	Triglycerides: ≥150 mg/dL; HDL-C: <40 mg/dL (men), <50 mg/dL (women)	Triglycerides: ≥150 mg/dL; HDL-C: <40 mg/dL (men), <50 mg/dL (women)	Triglycerides ≥150 mg/dL or HDL cholesterol <39 mg/dL.	Triglycerides ≥150 mg/dL; HDL Cholesterol <40 mg/dL (men), <50 mg/dL (women)
Blood Pressure	≥130/85 mmHg	≥140/90 mmHg	≥130/85 mmHg	≥130/85 mmHg	≥140/90 mmHg	≥130/85 mmHg
Blood Glucose	Fasting glucose: ≥100 mg/dL	Fasting glucose: ≥110 mg/dL or diagnosed diabetes	Fasting glucose: ≥100 mg/dL	Fasting glucose: ≥110 mg/dL or diagnosed diabetes	Fasting glucose: ≥110 mg/dL but <126 mg/dL.	Fasting glucose: ≥100 mg/dL
Other Criteria		Microalbuminuria: Urinary albumin excretion rate ≥20 µg/min or albumin:creatinine ratio ≥30 mg/g				

NCEP-ATP III: National Cholesterol Education Program Adult Treatment Panel III; NHLBI: National Heart, Lung, and Blood Institute; AHA: American Heart Association; WHO: World Health Organization; IDF: International Diabetes Federation; AACE: American Association of Clinical Endocrinology; EGIR: European Group for the Study of Insulin Resistance; IAS: International Atherosclerosis Society; WC: waist circumference; WHR: waist-to-hip ratio; IR: insulin resistance; BMI: body mass index. HDL-C: HDL cholesterol; LDL-C: LDL cholesterol.

Figure 1 summarizes the complex interactions between different biological processes that lead to the primary pathophysiological pillars of MetS. Increased visceral adipose tissue (VAT) mass due to over eating and lack of physical activity releases bioactive molecules secreted by adipose tissue (adipose cytokines, or adipokines) like leptin and adiponectin, which are involved in regulating appetite and insulin sensitivity. In addition, imbalance condition of free fatty acis (FFAs) that which contributing to IR and inflammation; inflammatory markers including tumor necrosis factor (TNF)-α, interleukin (IL)-6, C-reactive protein (CRP), and fibrinogen which promote chronic inflammation; reactive oxygen species (ROS) which lead to oxidative stress and further metabolic disturbances; as well as renin-angiotensin-aldosterone system (RAAS) which contributing to hypertension, might lead to hyperglycemia and further cause MetS.(21) These factors collectively contribute to neurohumoral activation, chronic inflammation, and IR, ultimately resulting in MetS characterized by increased gluconeogenesis, lipogenesis, and elevated triglycerides in the liver (Figure 1).(22) The intricate and multidimensional pathophysiology of MetS is constructed by combining those "current" clinical characteristics with genetic vulnerability and the traditional pathogenic components.(23)

It is still up for debate whether the many elements of MetS are indications of a single disease process or separate disorders. The significant geographic variance in MetS distribution in developing countries highlight the significance of lifestyle and environmental variables, including excessive calorie intake and inactivity as a major causative factor for MetS, as it has been shown that visceral adiposity is a fundamental trigger for the majority of the pathways involved.(24)

VAT's positive correlation with IR is stronger than that of overall obesity, making its role in metabolic diseases

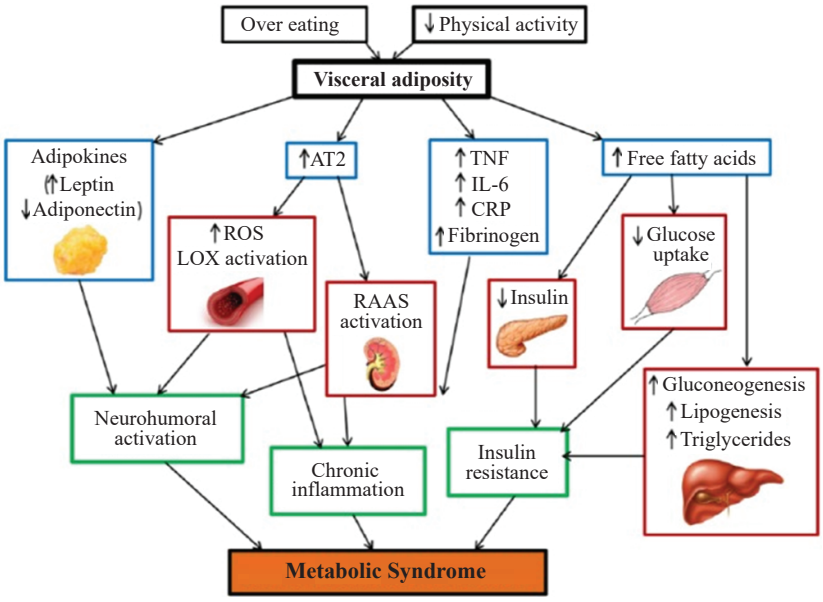

Figure 1. Pathophysiological mechanisms in metabolic syndrome.(21) (Adapted with permission from Sage Publications).

associated with MetS widely acknowledged.(25) Based on its endocrine capacity (26), the VAT noxious ability has been extensively addressed, but appears to be focused on hormonal (26) and immunological regulation (27,28) in overweight and obesity situations. VAT acts as an endocrine organ, releasing adipokines such as leptin, adiponectin, and resistin. Furthermore, it seems that visceral adiposity is the main source of FFA, which first travels to the liver and then to the circulatory system.(29)

The pathophysiology of obesity-associated MetS involves dysregulated production of both "defensive" adipocytokines, such as adiponectin and leptin, and "offensive" adipocytokines, such as plasminogen activator inhibitor (PAI-1), TNF-α, IL-6, monocyte chemotactic protein (MCP)-1, and angiotensinogen.(30) Indeed, high fatty acid levels in cultured adipocytes exacerbated oxidative stress, leading to dysregulated adipocytokine (fat-derived hormone) production, including adiponectin, PAI-1, IL-6, and MCP-1. Chronic inflammation, IR, and the risk of CVD may be influenced by a number of hormones generated from AT that are released into the bloodstream, including resistin and adiponectin.(31) Lower levels of adipokines are linked to beneficial effects, while increased proinflammatory cytokines and adipokines linked to atherogenesis and IR are also associated with obesity. Therefore, metabolic disturbances linked to obesity may be mostly influenced by an adipokine composition unique to obesity.(32)

Obesity and IR-induced systemic stress oxidative, increases the activation of downstream signaling cascades that result in tissue fibrosis and atherogenesis. A prothrombotic condition is induced, serum viscosity rises, and pro-inflammatory cytokines are released from AT as a result of IR, all of which raise the risk of CVD.(33) The pathophysiology of CVD is significantly influenced by inflammation, and patients with MetS have been found to have higher levels of several inflammatory markers.(34) It is still debatable whether these markers represent the cause of the inflammation or merely its bystanders.(21)

Through immune system activation, inflammation appears to constitute the pathogenic connection between obesity and MetS.(35) The number of immune cells in AT including macrophages and CRP was modulated in a chronic low inflammation state, thus increased the expression of pro-inflammatory cytokines.(36) Hepatic damage such as cirrhosis, sepsis, and even acute liver failure due to regenerative capacity reduction, as well as failing insulin generation and secretion related to β-cell loss and muscle IR, have been progressively connected to the loss of inflammatory homeostatic control.(37)

MetS hypertension may result from a number of potential causes, including visceral obesity, IR, oxidative stress, endothelial dysfunction, activation of the renin-angiotensin system (RAS), elevated inflammatory mediators, and obstructive apnea.(38) In order to preserve glucose homeostasis, compensatory hyperinsulinemia is determined by resistance to insulin-mediated glucose elimination. This adaptive mechanism may ultimately contribute to hypertension and a number of atherogenic processes.(39)

Since the nutrients' digestion might result in biological molecules that cause an inflammatory response, they may naturally have a pro-inflammatory character in addition to

being directly tied to the energy balance.(40) Therefore, the development of MetS is significantly influenced by diet. (41) Excessive nutrient intake, such as the Western Diet, a dietary pattern is being characterized by excessive calorie intake and high levels of red meat, fat, and processed carbs, may worsen the inflammatory process in addition to causing overweight and obesity.(42) Substituting monounsaturated and/or polyunsaturated fats for saturated fat in the diet might improves metabolic control by lowering LDL cholesterol levels, improving the postprandial lipid profile, lowering blood pressure, and improving insulin sensitivity. (43) Mediterranean diet, which is rich in fruits, vegetables, whole grains, legumes, nuts, and olive oil, with moderate consumption of fish and poultry, and low intake of red meat and sweets, has been shown to reduce the incidence and severity of MetS by improving lipid profiles, reducing inflammation, and enhancing insulin sensitivity. Key components like high intake of monounsaturated fats (from olive oil) and omega-3 fatty acids (from fish) contribute to these benefits.(44)

Low-carb diets are beneficial for managing MetS. By lowering carbohydrate intake, the body reduces insulin levels and improves insulin sensitivity, which is crucial for MetS management. Oppositely, refined sugars and high glycemic index (GI) foods cause rapid spikes in blood glucose and insulin levels. These spikes can lead to insulin resistance over time, a key factor in the development of MetS. High GI foods include white bread, white rice, and sugary snacks, which are quickly digested and absorbed, leading to rapid increases in blood sugar.(45,46) Meanwhile, intermittent fasting (IF) involves cycling between periods of eating and fasting. The most common IF methods include the 16/8 method (16 hours of fasting and 8 hours of eating) or the 5:2 method (eating normally for 5 days and restricting calories for 2 days). IF has been shown to improve insulin sensitivity, reduce inflammation, and promote weight loss, which can help manage MetS.(47)

Lipotoxicity refers to the harmful effects caused by the accumulation of lipid intermediates, such as diacylglycerol and ceramides, in non-adipose tissues like the liver, heart, kidneys, and skeletal muscle. This lipid buildup occurs when the storage capacity of adipose tissue is exceeded, leading to the spillover of excess fatty acids into other tissues and disrupt normal cellular functions.(48) Chronic high-calorie intake based on high saturated-fat intake is linked to intracellular fat storage and fat-derived lipotoxins that can cause IR (49), particularly in skeletal muscle, hepatic, and pancreatic tissue, which are key organs for postprandial glucose uptake and the maintenance of homeostatic glucose levels (50). Although they differ, the damage mechanisms resulting from insulin signaling pathways and the ensuing glucose metabolic disorders linked to lipotoxicity are comparable in those tissues. Ceramide molecules build up as a result of an excess of muscle oxidative capability, but the accumulation of hepatic fatty acids inhibits their conversion to triglyceride, resulting in the formation of diacylglycerol (DAG).(51,52)

AT Distribution, Inflammation and Its Metabolic Consequence

AT is crucial for maintaining metabolic balance, particularly in regulating glucose and lipid metabolism. Dysregulation of AT, especially in obesity, leads to a cascade of inflammatory processes, IR, and metabolic dysfunction. This review explores the distribution, inflammatory roles, and metabolic consequences of different adipose tissue depots, including white, brown, and beige fat, and their impact on obesity-related diseases such as T2DM and CVD.(53)

WAT can be broadly categorized by location, with the two main categories being visceral/omental (found intra-abdominally, next to internal organs) and subcutaneous (found beneath the skin). Numerous cell types that make up AT emit a variety of cytokines, chemokines, and hormones in unison. Chemokines are a type of cytokine, which are small signaling proteins secreted by cells. Their primary function is to act as chemoattractants, guiding the movement of immune cells, such as white blood cells, to sites of infection, inflammation, or injury. Chemokines play a crucial role in immune responses, helping to direct immune cells to where they are needed most. They are also involved in various biological processes, including tissue maintenance, development, and wound healing.(54) Adipocytes make up around one-third of the cells in AT; the other cells are made up of pre-adipocytes, fibroblasts, endothelial cells, macrophages, stromal cells, and immune cells. WAT is restricted to specific depots in the majority of healthy, slim people. However, WAT mass can rise ectopically in places that may affect the vulnerability to comorbidities like diabetes and atherosclerosis in circumstances like obesity and lipodystrophy. Visceral fat, which mostly belongs to the group of ectopic fat, is not found in significant quantities in lean, healthy people. FFA are continuously released into the portal circulation by visceral fat, which has a high metabolic activity.(55) In contrast to subcutaneous fat, visceral fat is highly metabolically active, and its dysregulation contributes to IR and systemic inflammation. The following

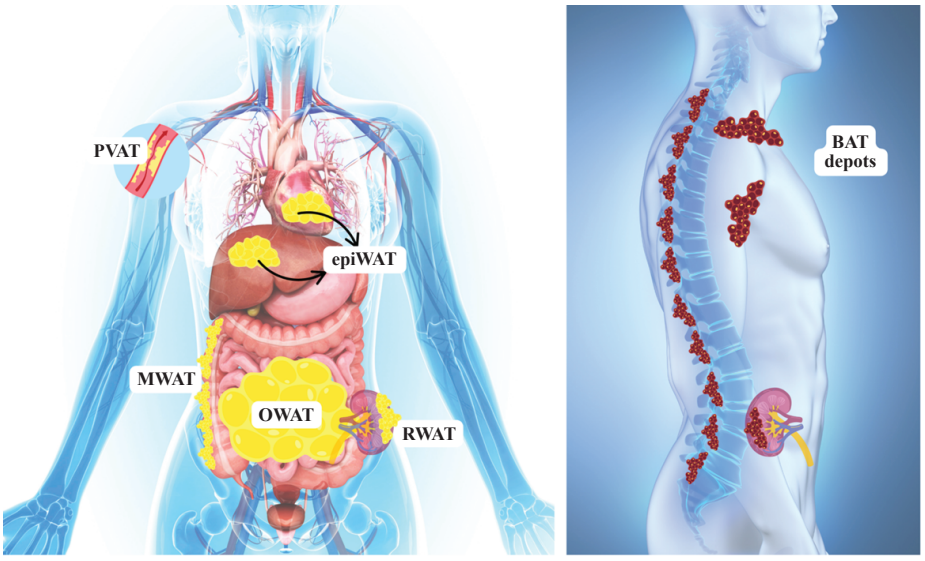

Figure 2. Various adipose tissue depots. Left: white adipose tissue (WAT) depots; Right: brown adipose tissue (BAT) depots. Beige adipose tissue was induced from WAT. PVAT: perivascular visceral adipose tissue; MWAT: mesenteric visceral adipose tissue; epiWAT: epicardial visceral adipose tissue; OWAT: omental visceral adipose tissue; RWAT: retroperitoneal visceral adipose tissue.

sections will explore how various AT depots (Figure 2), particularly visceral fat, contribute to these processes.

The primary ectopic WAT in the visceral cavity can be found as mesenteric fat (MWAT) which surround the area of intestines, omental fat (OWAT) which stretches almost all abdominal cavity, covering the intestines and also liver. Another VAT are intrahepatic epicardial (epiWAT) which located within the liver and around the heart, perivascular (PVAT) which can be found around the major blood vessels (vascular), and retroperitoneal fat (RWAT, surrounding the kidneys) are examples of such ectopic WAT areas, which are primarily found within the visceral cavity. With increased levels of fatty acid intake and fatty acid release from lipolysis, epiWAT is believed to be roughly twice as metabolically active as other WAT depots because of its close proximity to the heart.(56) The term "visceral fat" will be used to refer to the last three depots (MWAT, OWAT, and RWAT) collectively, and they were embryo origin. (57) Some cytokines like adiponectin, resistin, vascular endothelial growth factor (VEGF) that affect the surrounding myocardium are secreted by epiWAT.(58) Apart from WAT depots, BAT is a unique form of AT that is distinguished by its architecture and function. Its brown appearance is attributed to concentrated mitochondria. A third novel type of AT is represented by beige fat, where brown adipocytes are seen in traditional WAT depots.

PVAT is the type of fat that envelops blood vessels. It is now known that PVAT is thought to be an active player in vascular homeostasis and shares traits with both BAT and WAT.(59) Adipokines (*e.g.*, leptin, adiponectin, omentin, visfatin, resistin, and apelin), cytokines/chemokines (*e.g.*, IL-6, TNFα, and MCP-1), and vasoactive molecules (*e.g.*, nitric oxide, prostacyclin, and angiotensin II) are among the numerous bioactive molecules that PVAT produces and that affect vascular reactivity.(60) Therefore, PVAT can promote the maintenance of vessel structure while also directly influencing vascular tone. While PVAT in the abdominal aorta demonstrates characteristics of both BAT and WAT, it has been proposed that PVAT in the thoracic aorta resembles BAT.(60) Therefore, PVAT can go from having an atheroprotective function to encouraging atherosclerosis if it malfunctions in the context of obesity.

Subcutaneous WAT serves as a physiological buffer for excess energy intake during periods of reduced energy expenditure more than any other depot. Excess lipid accumulation is metabolically "sunk" by subcutaneous WAT. (61) Fat starts to accumulate ectopically in areas outside the subcutaneous WAT when this storage capacity is exceeded, either because there are not enough new adipocytes to be produced (limited hyperplasia) or because there are not enough adipocytes to expand existing ones (limited hypertrophy). Furthermore, subcutaneous WAT serves as a barrier against skin infection, an cushion to stop heat loss, and a cushion to protect against physical stress from the environment.(62) There are several ways that subcutaneous WAT has been shown to improve glucose metabolism. The "upper" and "lower" parts of subcutaneous WAT, which are mostly found in the trunk and gluteo-femoral regions, respectively, can be further separated.(63)

Once thought to be a simple organ for storing energy, AT is now understood to be a major endocrine system that secretes chemokines, growth factors, cytokines, and adipokines. The paracrine/autocrine actions of adipokines within specific AT depots appear to be reliant on the energy

status of the adipose depot and appear to differ by adipokine secretion pattern. Adipokines take part in many major metabolic pathways in active tissues especially the process of glucose metabolism, and fat metabolism.(64)

Progress in The Identification of Different Obesity Phenotypes

As obesity progresses, AT undergoes changes in both size and number of adipocytes. These alterations lead to dysfunction within the AT, which is a key characteristic of obesity and contributes to various metabolic disturbances. Interestingly, not all individuals with obesity exhibit the same metabolic profile. Some individuals, despite having a high BMI, maintain normal insulin sensitivity and exhibit fewer signs of metabolic dysfunction, a phenotype referred to as 'metabolically healthy obesity' (MHO). In contrast, 'metabolically unhealthy obesity' (MUHO) is associated with a greater risk for metabolic disorders such as T2DM and CVD.(6,65)

Although there is disagreement about a precise diagnosis, MHO is frequently described as having two or fewer MetS characteristics or as being based on having homeostatic model assessment of insulin resistance (HOMA-IR) measurements less than 2.5.(66) This indicates that despite having obesity, these individuals maintain normal insulin sensitivity and do not exhibit the metabolic disturbances commonly associated with obesity. As a result, some people who are diagnosed with MHO really fall somewhere in the middle of the metabolically healthy and unhealthy categories. Furthermore, along with time, people with "MHO" may develop to have MetS characteristics.(67) Subjects with MUHO will display a predisposition to T2DM, IR, AT and systemic inflammation, a thrombogenic profile (a set of characteristics or conditions that increase the likelihood of thrombus formation within the blood vessels including endothelial dysfunction, hypercoagulability, hemodynamic change and inflammation), dyslipidemia (defined as hypertriglyceridemia, a preponderance of small, dense low-density lipoprotein (LDL) particles, and reduced HDL-cholesterol levels), hypertension, metabolic dysfunction-associated fatty liver disease (MAFLD), and dysglycemia (a general term that refers to an abnormality in blood sugar stability) which are all linked to visceral adiposity and adipose distribution.(68) These will affect the adipokines secretion which in the end, MUHO subjects have higher CVD risk correlated to VAT which is further worse when overt diabetes arises as a result of insulin production not being able to sufficiently offset IR compared to MHO (Figure 3).

There have been reports of notable variations in the adipokine profiles of MHO and MUHO participants, which may increase their risk of developing T2DM and CVD, respectively. Leptin levels were greater in MUHO than MHO obese Chinese children.(69) Other study showed that even though both groups have lower levels of adiponectin than metabolically healthy lean controls, it has been repeatedly demonstrated that people with MHO have higher levels than those with MUHO.(70) The MUHO population often has higher levels of fibroblast growth factor (FGF)21 and resistin.(70) There has been conflicting evidence about whether omentin levels are different in MHO and MUHO participants. One study found that omentin levels are higher in MUHO subjects than in MHO subjects (71), while another found a negative correlation between omentin levels and the MetS (72). However, MUHO individuals fund to have higher pro-inflammatory cytokines.(70)

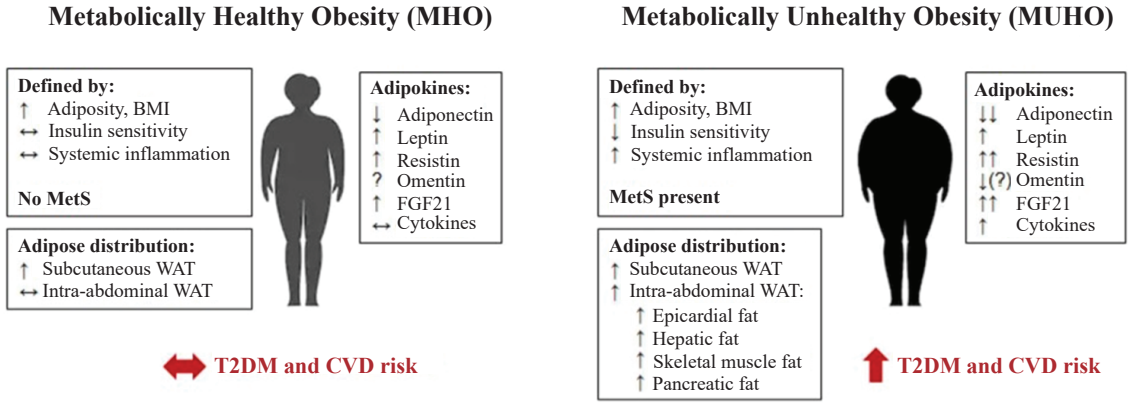

Figure 3. The character and risk of obesity both MHO and MUHO compared to lean subjects.(53) (Adapted with permission from Frontiers).

These cytokines increase systemic chronic low-grade inflammation in MUHO subjects, impair insulin signaling, leading to insulin resistance; promote chronic low-grade inflammation, which damages blood vessels and contributes to atherosclerosis; influence lipid metabolism, resulting in dyslipidemia; impair endothelial function, causing hypertension and atherosclerosis; and cause adipose tissue dysfunction, creating a pro-inflammatory, hyperlipidemic, and insulin-resistant environment. Fat distribution plays a crucial role in distinguishing between MHO and MUHO since most pro-inflammatory cytokines were secreted by VAT. MUHO individuals typically have higher amounts of visceral fat and lower subcutaneous fat, leading to a pro-inflammatory state and impaired metabolic function. In contrast, MHO individuals tend to have more subcutaneous fat, which is less metabolically harmful and better at storing excess lipids, thereby reducing ectopic fat deposition and associated metabolic risks. Understanding fat distribution and managing adipokine levels and improving metabolic health are crucial to reducing risk associated with obesity.(71)

Gut Microbiota and Immune Crosstalk in Metabolic Syndrome

The gut microbiota is a trend area of study that has drawn interest for its impact on health.(73) It is now known that gut microbiota and MetS are related, and various therapeutic approaches have been put out to enhance the gut microflora's makeup in order to support the best possible metabolic health.(74,75)

According to recent research, probiotics, prebiotics, and synbiotics may be able to modify the gut microbiota, which could be a potential strategy for treating MetS.(76,77) Prebiotics are indigestible oligosaccharides that have a positive impact on the colon by promoting the growth or activity of good bacteria, serve as food for probiotics, like inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS). Probiotics are live microorganisms that, when consumed in adequate amounts, confer health benefits to the host. Probiotics are found in the human colon and intestines, where they influence immunological responses and gastrointestinal microbiota. While synbiotics are combination of prebiotics and probiotics that work synergistically to enhance the survival and colonization of beneficial bacteria in the gut which have the potential to be even more beneficial than each one by itself.(78) In obese, T2DM, and dyslipidemic mice and humans, some probiotic species and prebiotic kinds have been shown to enhance lipid profiles and glycemic indicators.(79,80)

The molecular foundations of the compromised immune system and the compromised microbiome should be taken into account when developing treatments for long-term, metabolic abnormalities. Through microbiota transfer experiments, the causative effect of gut microbiota on metabolic illnesses has been demonstrated in humans (81) and rodents (82), showing that the microbiota from a healthy donor could enhance the glycemia and body weight of an obese and diabetic recipient, respectively induce a holobiont (an assemblage of human as the host and its associated microbiome which function as a single biological entity) adaptation. It would need specific processes of the host's adaptation to the microbiota alteration. The innate immune system is the first to adjust to changes in the microbiome, by adapting the quickest in a general and non-specific way. The adaptive immune system comes next, giving the dysbiotic microbiome specialization, speed, and memory. In light of the holobiont definition, this crosstalk between human as the host and the microbiome may be the first idea to combine the effects of the host's genetic makeup with the environment (social, nutritional, chemical, and behavioral) to explain metabolic illness development and diversity. The idea that the holobiont, which includes the immune system and microbiome as the master regulatory mechanism, is a complex creature that has evolved to its surroundings, should be taken into account when developing and treating metabolic diseases. Metabolic disease may occur as a result of environmental changes that affect the microbiome and the host. Within the context of metabolic disease, the immune system's function as a crucial adapter to environmental influences on the microbiome will be explored.(83)

Modulating gut microbiota can significantly impact IR and inflammation through several interconnected pathways. The gut-brain axis plays a crucial role, where gut microbiota influence central nervous system functions, affecting stress responses and metabolic regulation. Nuclear factor-kappaB (NF-κB) signaling, a major inflammatory pathway, is activated by gut-derived pro-inflammatory cytokines, contributing to insulin resistance by impairing insulin signaling. Insulin signaling itself is disrupted by inflammatory mediators like cytokines TNF-α or IL-6, leading to decreased insulin sensitivity and increased blood glucose levels. Additionally, the AMP-activated protein kinase (AMPK) pathway, which regulates energy balance, can be modulated by gut microbiota to suppress inflammation and improve insulin sensitivity. Together, these pathways

illustrate the complex interplay between gut microbiota and host metabolic health. On the other side, chronic activation of NF-κB can exacerbate conditions like irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), further influencing the gut-brain communication.(84)

Beneficial bacteria like *Lactobacilli* and *Bifidobacteria* grow more when prebiotics are used. Additionally, by regulating hunger, increasing the synthesis of GLP-1 and peptide YY (PYY), decreasing ghrelin, and fatty acid storage, *Lactobacilli* and *Bifidobacteria* help lower body weight and adipocyte size.(85) However, there appears to be conflicting evidence about how prebiotics affect satiety, body weight, GLP-1, and the production of peptide YY.(86)

According to clinical targets based on the biological thresholds described in National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III), probiotics and synbiotics have reduced the prevalence of additional MetS components over the intervention period. (87) Integrating probiotics, prebiotics, and synbiotics into clinical practice for treating MetS involves leveraging their ability to modulate gut microbiota, which can influence metabolic health. These interventions include improved gut barrier function, reduced systemic inflammation, and better regulation of blood glucose levels. However, limitations in real-world settings include variability in individual responses due to differences in gut microbiota composition, the need for personalized treatment plans, and the challenge of maintaining consistent long-term adherence. Additionally, the efficacy of these interventions can be influenced by factors such as diet, age, and overall health status.(88) Nevertheless, further studies involving important pathways such as the gut-brain axis, NF-κB route, insulin signaling pathway, and AMPK pathway are needed before we can recommend prebiotics to manage metabolic diseases.(89)

Epigenetics, MicroRNA and MetS

Epigenetic changes, including DNA methylation and histone modifications, play a crucial role in the development and progression of MetS by influencing the expression of genes involved in metabolic pathways.(90,91) For instance, an epigenome-wide association studies (EWASs) analysis revealed that the overall MetS phenotype and elevated metabolic risk were associated with decreased methylation of carnitine palmitoyltransferase 1A (*CPT1A*), a gene that plays a crucial role in controlling mitochondrial fatty acid oxidation (FAO).(91) Decreased *CPT1A* methylation leads to increased activity enhances the production of the CPT1A enzyme, which is crucial for transporting long chain fatty acids (LCFA) into mitochondria for oxidation. While this might seem beneficial, excessive FAO can disrupt normal metabolic processes and induce IR.(92)

MetS was also consistently linked to elevated methylation in the ATP-binding cassette transporter A1 (*ABCG1*) gene, which encodes a protein in the ATP-binding cassette transporter family and is implicated in lipid transport and intracellular and extracellular signaling. (90,93) Increased methylation of the *ABCG1* gene can lead to decreased production of the ABCG1 protein. With lower *ABCG1* activity, the body's ability to manage cholesterol and phospholipids is impaired and lead to an accumulation of lipids in cells.(94) Global DNA methylation of long interspersed nuclear element-1 (LINE-1) has been linked to glucose metabolism and metabolic decline in VAT of people with and without MetS.(95) These individuals also showed strong correlations between their MetS status and the methylation of some genes related to inflammation and substrate metabolism, including lipoprotein lipase (LPL) and peroxisome proliferator-activated receptor alpha (PPARA).(95)

Histone modification changes have been found to be crucial elements of epigenetic networks that regulate energy homeostasis and modify adipocyte thermogenesis, both of which contribute to the pathophysiology of MetS. (96,97) For instance, a study using mice lacking the enzyme human double minute (HDM)2a, which demethylates histone H3 lysine-9 (H3K9), revealed that the deficient mice developed adult-onset obesity, hypertriglyceridemia, hypercholesterolemia, and IR in comparison to the wild type.(97) Furthermore, it has been revealed that IR positively correlates with histone deacetylase 3 (HDAC3) activity and *HDAC3* mRNA levels in T2DM patients' peripheral blood mononuclear cells.(98) Sirtuins (SIRT), a type of HDACs, function as metabolic regulators of glucose homeostasis and inflammation also linked to IR.(99) The development of MetS has been shown to correlate with the lack of SIRT1-, SIRT2-, and SIRT6-dependent deacetylation and activation of specific adipose gene programs, thus histone modifications should take part in the etiology of these disorders.(100) In short, the fact that the pathophysiology of MetS is significantly impacted by the epigenome, which is constantly in feedback with an organism's genotype and phenotype (101) describes that environmental factors, like as nutrition and diet, can cause the epigenetic regulatory alteration and underlies the pathophysiology of MetS. Therefore, MetS and associated metabolic disorders would

be made possible managed by creating therapies to change the epigenetic changes.

MicroRNAs (miRNAs) expression dysregulation has been demonstrated to alter pathological pathways implicated in the onset of a number of diseases, including T2DM, cancer, and CVD. For example, elevated levels of miR-122-5p in obese individuals are associated with higher insulin resistance. This occurs because the inhibition of pyruvate kinase M2 (PKM2) by miR-122-5p interferes with insulin signaling pathways, making it harder for cells to respond to insulin effectively.(102) miR-15a-5p can alter the expression of proteins involved in the insulin signaling pathway, affecting insulin sensitivity, while miR-17-5p has a protective effect on pancreatic β-cells, which are responsible for insulin production. It inhibits the Thioredoxin-interacting protein (TXNIP)/ NOD-like receptor protein 3 (NLRP3) inflammasome pathway, reducing inflammation and cell death in β-cells. High glucose levels can decrease miR-17-5p expression, impairing insulin secretion.(103,104) Therefore, miRNAs may be useful as a biomarker or diagnostic tool for both healthy and diseased conditions.(105)

Pharmacological treatments, epigenetic diets, any methods for manipulating the epigenome, therapies and diagnostics based on miRNA are examples of epigenetic-based approaches. Dietary variables and bioactive substances have been identified as important mediators of epigenetic reprogramming.(106) "Epigenetic diets" are diets or dietary components that have been found to mediate metabolic programming through epigenetic changes. They can alter epigenetic via DNA methylation and histone modifications, which are the traditional epigenetic mechanisms, and also interact with miRNAs, which means they play a role in the dynamic regulation of gene expression and the control of cellular phenotypes associated with the prevention and advancement of disease phenotypes.(107) Some epigenetic diets that can affect DNA methylation including foods rich in folate, vitamin B12, and choline (*e.g.*, leafy greens, eggs, and legumes) which provide methyl groups necessary for DNA methylation. Proper methylation can help regulate gene expression and protect against diseases like cancer and cardiovascular conditions.(108)

Compounds found in fruits, vegetables, tea, and red wine (*e.g.*, resveratrol, quercetin) can modify histones, affecting how tightly DNA is wound around them. This can either promote or inhibit gene expression, impacting processes like inflammation and aging.(108) Catechin, epicatechin, and its oligomers proanthocyanidin and epigallocatechin-3-gallate (EGCG) are examples of natural phenolic substances that are thought to be biological modulators of MetS.(109,110) Catechins have been demonstrated to lower levels of inflammatory cytokines and decrease dyslipidemia and IR in both human and animal models of obesity.(111–113) Catechins partially mediate these benefits via altering epigenetic pathways such DNA methyltransferase (DNMT) inhibition, boosting HDAC activity, or inhibiting histone acetyltransferases (HAT) activity.(114,115) Sulforaphane, an isothiocyanate that has been shown to lower hepatic glucose production and enhance glucose management in people with obesity and T2DM, is an example of one of the key ingredients in the Mediterranean diet was associated with regulation of HDAC and DNA methylation activity affect in glucose control. (116) Turmeric's polyphenolic component, curcumin, is another example of dietary-derived HAT. By lowering HAT activity, curcumin has been shown to reduce the cytokine generation in monocytes brought on by hyperglycemia. (106,117) Resveratrol, a little polyphenolic substance, is one of the histone deacetylase activators that has been found to enhance hepatic gluconeogenesis in IR circumstances by influencing the energy metabolism pathway through the translocation of HDAC4 from the nucleus to the cytoplasm. (118,119) Since then, a number of human clinical studies have demonstrated the beneficial health effects of resveratrol administration in people with T2DM, MAFLD, or obesity. (118,120)

Some epigenetic diets example including n-3 PUFAs which found in fatty fish, flaxseeds, and walnuts can influence the production of non-coding RNAs, which regulate gene expression by interacting with coding RNAs. They alter the expression of miRNAs implicated in important metabolic processes, including inflammation and lipid metabolism like miR-34a-5p, a negative regulator of insulin receptor substrate 2 (IRS2).(121) It has also been demonstrated that both short-term and long-term Mediterranean diets alter miRNA expression linked to the pathophysiology of MetS, including adipogenesis, atherogenic processes, and inflammatory gene regulation.(122,123) A study that examined how people with MetS responded to an 8-week hypocaloric Mediterranean diet found that their expression of miRNAs important in the pathophysiology of CVD was altered (decreased miR-155 and increased let-7b). (124) Moreover, polyphenols have been shown to alter the expression of miRNAs that control the genes and pathways that underlie MetS.(125) For instance, it was demonstrated using a model of mice fed a high-fat diet (HFD) that after consuming green tea for 12 weeks, the mice's adipose miR-335 decreased along with their energy expenditure,

AT inflammation, and IR-associated gene expression.(126) Resveratrol consumption can downregulate miR-155 while upregulate miR-21, miR-181b, miR-663, and miR-30c. Other studies demonstrated a negative correlation between the expression of inflammatory cytokine genes and the elevated miRNAs.(127)

When taken as a whole, epigenetic diets could be useful supplements to MetS treatment. By improving the pathophysiology of MetS, including inflammation, obesity, glucose intolerance, and insulin insensitivity, epigenetic diet supplements would improve metabolic homeostasis. Finding new and efficient therapeutic targets may be aided by knowledge of the pathophysiology of metabolic diseases and the molecular targets of epigenetic diets in connection to preserving metabolic balance.(128)

MAFLD and MetS

Because of its increasing influence on global health, MAFLD and its more advanced stage, metabolic dysfunction-associated steatohepatitis (MASH), have become a major focus of research and clinical attention. Around 38.8% of adult people worldwide are thought to have MAFLD, with the Middle East and South America having the highest frequency and Africa having the lowest. (129) MAFLD is diagnosed in individuals with fatty liver who are either obese, have T2DM, or meet at least two of the seven criteria for MetS.(130) MAFLD is the updated term for non-alcoholic fatty liver disease (NAFLD), which is now more inclusive and better define the cause, cover the neglection of lean MAFLD subjects, and to emphasize the role of inflammation and metabolic dysfunction in fatty liver disease pathophysiology both in lean and non-lean patients. MAFLD acknowledges that metabolic dysfunction can coexist with mild to moderate alcohol consumption, which was not considered in the NAFLD definition.(131)

MASH is a more severe process involving inflammation and hepatocyte destruction (steatohepatitis). The progression from MAFLD to MASH involves a combination of lipid accumulation, lipotoxicity, oxidative stress, ER stress, chronic inflammation, and fibrosis. These processes are interconnected and contribute to the worsening of liver health, ultimately leading to more severe liver conditions such as cirrhosis and hepatocellular carcinoma. A liver biopsy is the only way to definitively diagnose MASH, though imaging and clinical characteristics (such as the presence of metabolic comorbidities and abnormal lab tests) can raise a person's suspicions of either MAFLD or MASH.(132) Other subgroups of MASH have also been identified recently. In contrast to individuals with MAFLD alone, those with MASH have a higher risk of liver and perhaps non-liver-related complications (133), individuals with MAFLD alone have a very low risk of being cirrhosis, liver failure, and hepatocellular carcinoma compared to MASH, while increased CVD and cancer are the main causes of non-liver-associated adverse outcomes.(134,135) MAFLD and MASH involving varying rates of disease progression and clinical symptoms. The various yet convergent effects of the environment, metabolism, comorbidities, microbiota, and genetic risk factors are reflected in the very heterogeneous natural history of MAFLD and MASH. Studies showing a higher incidence of fibrosis among family members of patients with MASH have highlighted the significance of genetic and maybe microbiome-related risk factors in the onset and severity of MASH.(136,137) More precise forecasting of the course of the disease and more efficient treatments based on unique disease drivers may result from elucidating the genetic and other variables that contribute to the many subtypes of MAFLD.(138)

MetS, particularly in relation to T2DM and hypertension, is known as the greatest risk factor for MAFLD and MASH.(139) The relationship between MAFLD and MetS characteristics may be reciprocal, since not only does MetS raise the risk of MAFLD, but MAFLD may also improve some MetS characteristics and comorbidities. Therefore, enhancing the characteristics of MetS may be an added advantage of effectively treating MASH.(140,141) Up to 75% of people with T2DM also have MAFLD, making T2DM the MetS trait having the strongest physiologic correlation to the development of MAFLD. The frequency of MASH and advanced fibrosis is similarly higher among people with diabetes and MAFLD than among nondiabetics with MAFLD even when having normal level of blood aminotransferases.(142–144) It has long been known that IR plays a crucial role in the pathophysiology of MAFLD (145) and that it gets worse as the condition progress. While reducing IR helps MASH, it might not be enough to slow the progression of MASH on its own. Additionally, incident diabetes is more likely to occur in patients with MAFLD.(146)

Following the triglycerides lipolysis in AT, which is a process that is controlled by insulin's effects on adipocytes, the fatty acids are mostly transported from the circulation to the liver. Through dysregulated lipolysis that results in an increased supply of fatty acids to the liver, impaired insulin post-receptor signaling in AT contributes to MASH.

(143) During inflammation, adipocytes' phosphorylation of c-Jun N-terminal kinases (JNKs) substantially reduces post-receptor insulin signaling.(147) Therefore, the pathophysiology of MASH may be driven by inflammatory and metabolic processes in AT which may also be suitable targets for treatment.(148,149)

AT IR causes dysregulated lipolysis, which releases fatty acids inappropriately and further impairs insulin signaling throughout the body. Research has indicated that there is metabolic overlap between the liver and AT. In the liver, adiponectin, IL-6, and other peptides secreted by AT have both pro-inflammatory and preventive effects. (150,151). Dipeptidyl peptidase 4 (DPP-4) is an enzyme that can contribute to IR and may be another connection between liver and AT impairment. DPP-4 secreted by the liver activates M1 macrophages in mice's VAT. IR is known to be exacerbated by this effect, highlighting the critical interactions between the liver and other organs that underlie metabolic dysregulation in MAFLD.(152) In humans, modest weight loss also improves IR and homeostasis in AT, which may help with MASH.(153)

For a number of years, a "two-hit" explanation was proposed to explain the pathophysiology of nonalcoholic steatohepatitis (NASH). The first hit is involves the accumulation of fat in the liver (hepatic steatosis). The fat-laden liver becomes more susceptible to additional damage and induce the second hit includes oxidative stress, mitochondrial dysfunction, and inflammatory cytokines. These factors cause liver cell injury, inflammation, and fibrosis, progressing to NASH. NASH is considered as the most severe form of NAFLD.(154) By updating the term into MASH, the multiple-hit hypothesis has replaced the two-hit hypothesis to better explain the complex pathogenesis by considering a broader range of factors that contribute to the disease progression. This newer model considers a variety of factors, including genetic susceptibility, epigenetic changes, IR, oxidative stress, and gut dysbiosis as the signaling pathways related to hepatic lipid metabolism, as described in Figure 4.(155) It is unclear whether MAFLD always comes before MASH because there are numerous molecular mechanisms that lead to the development of MASH. Recent studies suggest that dysbiosis, or microbial imbalance in the gut, may contribute to inflammation and insulin resistance, both of which are critical factors in the development of MAFLD and MASH. For instance, patients with MASH often exhibit reduced microbiome diversity compared to healthy individuals, and interventions aimed at modulating the microbiome, such as probiotics or dietary changes, have shown promise in improving liver health. (156) Furthermore, not every patient is likely to have the same pathogenic factors. As a result, there is a great deal of variation in both the mechanisms causing disease and its clinical presentations.(157)

Glucose and fructose can be another main source of fatty acids via *de novo* lipogenesis (DNL). DNL is primarily responsible for the rise in hepatic lipid content in patients with MAFLD.(158) Fructose induces DNL by bypassing glycolytic regulation, activating lipogenic enzymes, and

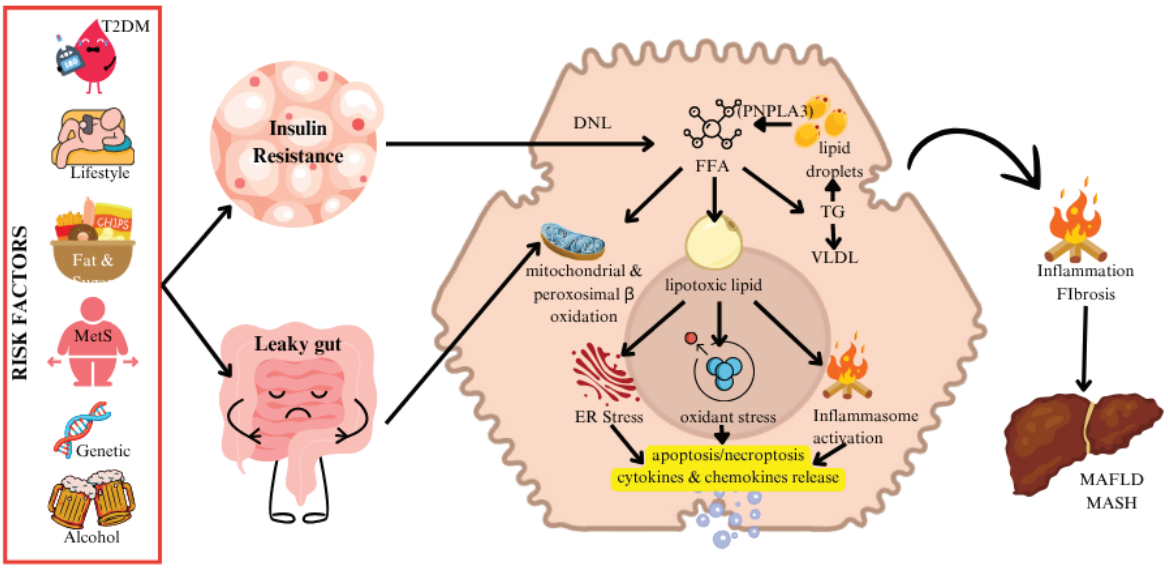

Figure 4. The substrate-overload liver injury model of MAFLD and MASH pathogenesis. T2DM: Type 2 Diabetes Mellitus; MetS: metabolic syndrome; DNL: de novo lipogenesis; PNPLA3: patatin-like phospholipase domain containing 3 gene; FFA: free fatty acids; TG: triglyceride; VLDL: very low-density lipoprotein; ER: endoplasmic reticulum.

promoting the transcription of lipogenic genes, resulting in increased fatty acid synthesis and lipid accumulation in the liver. In contrast to the highly regulated entrance of glucose into the DNL pathway, the liver phosphorylates and commits almost all fructose to DNL without regulation after removing it from portal circulation. It is unclear how much fructose that is consumed makes it to the hepatic portal circulation because research on mice has revealed that gut enterocytes play a role in fructose (159), and research on humans has revealed that the gut epithelium has a limited capacity to absorb fructose (160). The critical role of dietary factors in MAFLD progression was assumed to be via the mechanisms of dietary fructose that contributes to the increased hepatic fat accumulation and the development of IR in humans.(161) Both humans and animals experience hepatic ATP depletion as a result of the phosphorylation of fructose in hepatocytes after a high fructose load, which may exacerbate cellular stress.(162) That's how consuming sugar-sweetened beverages that include either sucrose (which the gut converts to fructose and glucose) or a combination of fructose and glucose is epidemiologically linked to the development of liver fat and MASH.(163,164) Ceramides (165,166), lysophosphatidylcholine species (167), and diacylglycerols (165,168) are examples of potential lipotoxic lipids. A high-cholesterol diet is used in various mouse and rat models of MASH and cholesterol build up in the liver may worsen the disease.(169,170)

Increasingly sedentary lifestyle and a diet high in fructose, sucrose, and saturated fats, combine with antibiotic-induced dysbiosis have been mainly blamed for the sharp rise in MAFLD in the industrialized world over the past 25 years. Many studies in human showed that the gut microbiota of MASH patients is less varied than that of healthy individuals, and weight reduction may change the microbiome.(171) While lifestyle interventions, such as weight loss and exercise, remain the cornerstone of MAFLD treatment, emerging pharmacotherapies targeting metabolic dysfunction, including PPAR agonists and GLP-1 receptor agonists, may offer additional treatment options for patients with MASH.(172)

Lifestyle Modification as MetS Early Prevention and Treatment Strategy

Energy from good nutrition is fundamental for development, regeneration, and maintenance of the body, and maintaining wellbeing involves a balanced diet rich in beneficial foods while limiting the intake of harmful ones. Excessive calorie intake especially diet rich in refined sugar and unhealthy fat, lack of fiber and micronutrient can contribute to IR and leaky gut which lead to MetS. Dietary, urbanization and lifestyle changes, aging population, and socioeconomic changes contribute to the sharp increases in recent decades MetS prevalence.(3)

Since MetS involves a number of risk factors for CVD, poor physical and mental health-related quality of life (QoL), the main goal of therapeutic care is to reduce the incidence of major cardiovascular events (stroke, infarction). The first line treatment of MetS emphasize on lifestyle modifications to address obesity, physical inactivity, and unhealthy diets including quitting smoking, engaging in physical activity (30–60 minutes per day), to reach ideal BMI (<25 kg/m2), and adopting the Mediterranean diet regardless of reducing calorie intake, the diet itself already has lower sugar, alcohol, salt, and saturated or trans fats intake.(173) It has been shown to not only reduce weight, but benefit people with MetS, reduce anxiety, and improve peripheral IR.(174,175) A study in overweight men showed that after an 8-week program, pre-diabetic patients men showed greater reductions in weight and metabolic markers compared to women, who had a decrease in bone mineral content and fat-free mass.(173) Frequent exercise helps improve lipid problems, including lowering triglycerides and increasing HDL, as well as assist people lose weight and lower their blood pressure.(176,177) It has been suggested that one of the most observable benefits of consistent exercise is to improve IR.(20) A balanced diet with appropriate caloric intake and high-fiber foods stabilizes blood sugar levels, lowers cholesterol, and reduces inflammation. Regular physical activity burns calories, enhances insulin sensitivity, strengthens the heart, and lowers inflammatory markers. Together, the interconnection of both lifestyle modifications create a caloric deficit, improve glucose utilization, reduce the risk of heart disease, and manage inflammation, leading to effective prevention and management of MetS.

In terms of metabolomics, a 1-year non-surgical weight loss program was associated with lower levels of methyladenosine, alanine, proline, trans-cinnamic acid, tyrosine, and branched-chain amino acids (BCAA) in serum, as well as baseline xylitol levels in serum, which were predictive of achieving ≥10% weight loss.(178) To predict future weight gain, a metabolic risk score based on 42 metabolites showed to be linked to a change in BMI in another study. In particular, a lower weight gain was linked to a rise in the levels of 35 metabolites, while a bigger weight gain was linked to the remaining seven metabolites. The likelihood of future weight gain was finally determined to be

predicted by eight metabolites, notably triacylglycerol 56:6 and 56:2, malate, niacinamide, sphingomyelin 24:0, uridine, tyrosine, and xanthine.(179) Using five distinct metabotypes (metabolic profiles based on specific combinations of oxidative stress, inflammation, carbohydrate metabolism, lipid metabolism, and gut microbiota metabolism) from blood, urine, and saliva samples, the PREVENTOMICS project is creating a tailored nutrition algorithm, and the results showed that personalized dietary plans delivered a generally healthy diet compare to generic diet especially in IR and lipid profile, although not statistically significant.(180) The participants experienced several benefits, including improved metabolic health, better weight management, enhanced blood sugar control, and reduced inflammation. These personalized plans helped participants adopt healthier lifestyle habits and achieve sustained improvements in their overall health.(181)

Recent meta-analyses and single site trials indicate that variables underlying the MetS may be improved by exercise training as the improvement of IR, cardiorespiratory fitness, and body composition. Aerobic and resistance training, dramatically improves health outcomes for individuals who fit the MetS criteria. Exercise still shown to improve risk markers in certain people to the point where they no longer fit the MetS criteria. These positive effects of physical activity or structured exercise regimens can be attributed to variety of physiological, lifestyle, and hereditary variables including inflammation, adipose fuel metabolism, IR, and epigenetic variables. It would seem that incorporating physical exercise as a key component of MetS treatment plans would significantly lessen the negative health effects of the illness.(182)

Pharmacology treatments are commonly prescribed for MetS including antihypertensive agents like ACE inhibitors (*e.g.*, lisinopril), ARBs (*e.g.*, losartan), calcium channel blockers (*e.g.*, amlodipine), and diuretics (*e.g.*, hydrochlorothiazide) to help lower blood pressure by relaxing blood vessels and removing excess sodium and water. Lipid-lowering agents like Statins (*e.g.*, atorvastatin) reduce LDL cholesterol, fibrates (*e.g.*, fenofibrate) lower triglycerides and increase HDL cholesterol, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (*e.g.*, evolocumab) enhance LDL removal from the blood. Antidiabetic agents including Metformin improves insulin sensitivity, SGLT2 inhibitors (*e.g.*, canagliflozin) help kidneys remove glucose, and GLP-1 receptor agonists (*e.g.*, liraglutide) enhance insulin secretion and control blood sugar. Anti-obesity medications, orlistat, reduces fat absorption, and phentermine-topiramate decreases appetite and increases energy expenditure. Often, multiple medications are used together to address various aspects of MetS, requiring careful management to avoid interactions. Current research is developing multi-target drugs to simplify treatment and improve adherence. Pharmacogenetics and pharmacokinetics ensure treatments are tailored to individual genetic and metabolic profiles for optimal effectiveness and safety.(183) Therefore, a treatment approach to MetS requires dietary and physical exercise protocols, lifestyle modifications, and frequently pharmaceutical medication. Incorporating personalized nutrition and regular physical activity may reduce negative health impacts and prevent MetS-associated complications as described in Figure 5.

Dietary Strategy for MetS

The association between food patterns and components of MetS demonstrated that a diet centered on nutritious food selections, like cereals, seafood, fruits, and vegetables, correlates with a more favorable metabolic profile and

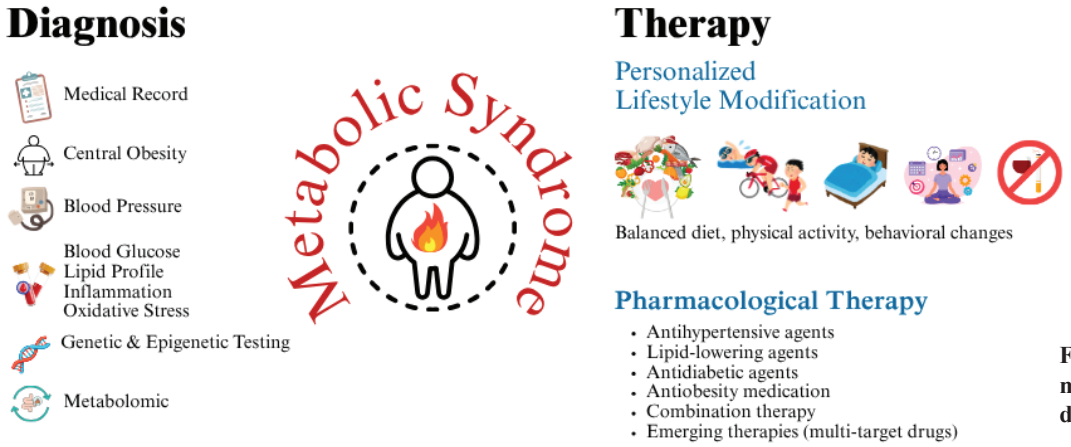

Figure 5. Strategies to manage MetS, including diagnosis and therapies.

a reduced risk of MetS. This suggested the contribution of diverse diets and their components in the prevention or management of MetS. plant-based foods, legumes and seeds, omega-3 fatty Acids, antioxidant-rich foods, and healthy fats are among recommended diets for MetS management.(184)

Plant-Based Foods

A plant-based diet primarily focuses on foods derived from plants. This includes not only fruits and vegetables, but also nuts, seeds, oils, whole grains, legumes, and beans. Numerous plants have been examined throughout the years to assess their beneficial effects on MetS. One study utilizing plant seeds from pumpkin (*Cucurbita pepo* L.) and flax (*Linum usitatissimum* L.) significantly improved MetS. Pumpkin seeds contain significant levels of protein (14.3–38%) and fat (21.9–54.9%). They also serve as a substantial supply of amino acids, providing 17 of the 20 amino acids essential for human protein synthesis.(184) The magnesium and zinc contain in pumpkin seeds known to improve insulin sensitivity.(185)

One RCT study administered garlic (*Allium sativum* L.) pills exhibited an enhancement in the symptoms of MetS, including blood pressure (BP), WC, triglycerides, and HDL. A significant reduction in γ-glutamyltransferase (GGT), fatty liver index (FLI), and HOMA-IR was seen. Allicin in garlic has potent anti-inflammatory and antioxidant properties. While S-allyl cysteineknown to improve lipid profile. The garlic-treated group exhibited an enhancement in satiety and a reduction in hunger, appetite, and eating capacity.(186)

Ginger (*Zingiber officinale* Roscoe) is another plant of significant importance owing to its numerous positive characteristics for human health. Ginger known to have antibacterial, antioxidant and anti-inflammatory properties. It also demonstrated benefit for CVD, obesity and TDM risk. The predominant bioactive components in ginger include phenolics (gingerols, shogaols, and paradols) and terpenes (β-bisabolene, α-curcumene, zingiberene, α-farnesene, and β-sesquiphellandrene). Ginger also contains polysaccharides, lipids, organic acids, and raw fibers. The results indicate that ginger has advantageous effects, possibly influencing glucose metabolism in rats on a high-calorie diet, implying that ginger may be useful in avoiding the onset of MetS and T2D.(187)

Legumes and Seeds

Legumes are a sustainable and cost-effective source of nutrition since they are rich in essential amino acids and complex carbohydrate. In several regions globally, beans are esteemed as a substitute for meat. Legumes also contain flavonoids, flavanols, flavan-3-ols, isoflavones, anthocyanins, tocopherols, condensed tannins, and lignans. The intake of legumes has been linked to several advantageous health benefits.(188)

Isoflavones in soybean can help improve lipid profiles, reduce blood pressure, and enhance insulin sensitivity. Subjects who took soy-protein diets showed improved lipid profiles and glycemic control compared to standard diets. (189) An RCT study assessed the impact of replacing animal protein diet with 30 g/day of soy protein on subjects with MetS, and found that the incorporation of whole-soy meals in a lipid-lowering diet markedly enhanced a pertinent array of biomarkers linked to cardiovascular risk. At the conclusion of the treatment period, TC, LDL cholesterol, and non-HDL cholesterol levels in the soy food group were considerably lower than those in the control group.(190)

Cereals, grains (wheat, rye, rice, barley, millet, and oats), and tubers (ginger, potatoes, sweet potatoes, cassava, and sunchokes) constitute the predominant staple foods globally. The consumption of various grains differs globally and is influenced by multiple variables, including native plant species, traditions, and customs. The primary components of the six cereal types are relatively consistent: starch serves as the predominant available carbohydrate, protein content ranges from 7 to 15% (albeit with limited essential amino acids), mono- and polyunsaturated fatty acids are abundant, and mineral and trace element concentrations diminish from the outer to the inner cells.(191)

Omega-3 Fatty Acids

Long-chain polyunsaturated fatty acid (PUFAs) are vital components of a healthy, balanced diet. The primary categories of PUFAs are omega-3 (n3) and omega-6 (n6) fatty acids. PUFAs have elongated carbon chains including a carboxyl group at one terminus and a methyl group at the opposite terminus. n3-PUFAs possess a carbon–carbon double bond commencing at the third carbon from the methyl terminal of the chain. There are various unique n3-PUFAs; however, the three most widespread and abundant in dietary sources are: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids, including ALA, EPA, and DHA, are crucial for cell function, inflammation regulation, and overall energy production. n3-PUFAs are present in particular foods, including fish and seafood (especially cold-water fatty fish like salmon, mackerel, sardines, tuna, and herring), nuts and seeds (such as chia seeds, flaxseed, and walnuts), plant oils

(including flaxseed oil, soybean oil, and canola oil), and fortified products (such as eggs, yogurt, juices, milk, soy beverages, and infant formulas). n3-PUFAs acids provide structural functions as constituents of cell membrane phospholipids, functional roles through eicosanoid production, and energy roles via oxidation. In addition to their nutritional function, substantial data indicates that the consumption of n3-PUFAs diminishes the risk of several chronic illnesses, including CVD, inflammatory disorders, and T2DM. Various original papers, reviews, and meta-analyses (192) have examined the relationship between dietary and circulating n-3 fatty acids and the risk of MetS, although the findings remain incongruous (193).

Antioxidant-Rich Foods

Recent research over the past decade have underscored the advantageous benefits of natural antioxidants and their possible role in controlling MetS. In addition to berries, the impact of bergamot, a yellow citrus fruit rich in different phytochemicals, flavonoids, and other health-enhancing substances, has also been documented.(194) Bergamot exhibits a distinctive flavonoids and glycosides profile across its several forms including rutin, naringin, neohesperidin, and neoeriocitrin.(195) Bioactivities of the bergamot-derived polyphenolic fraction on LDL cholesterol, total cholesterol, triglycerides, and blood glucose levels were already examined and reported.(196) A cohort of 237 individuals with isolated or mixed hyperlipidemia, with or without hyperglycemia, received oral administration of bergamot extract for 30 consecutive days. Bergamot extract use lowers total and LDL cholesterol levels,triglycerides levels, and significantly reduces blood glucose levels.

Healthy Fats

Olive oil contains monounsaturated fat, which reduces total cholesterol and LDL cholesterol levels.(197) The polyphenol concentration in olive oil varies according on olive maturity, agronomic conditions, and extraction process, ranging from 50 to 1000 mg/kg. The polyphenols contain in olive oil comprise of phenolic acids, flavonoids, and oleuropein. The derivate of oleuropein by hydrolysis known as hydroxytyrosol become the most potent antioxidant in olive oil.(198)

Adopting the Mediterranean diet can have significant positive effects on metabolic syndrome. It helps improve lipid profiles by lowering triglycerides and LDL cholesterol while increasing HDL cholesterol. The diet enhances insulin sensitivity and helps regulate blood glucose levels, contributing to better blood sugar control. Rich in antioxidants and anti-inflammatory compounds, the Mediterranean diet reduces inflammation, which is a key factor in MetS. Furthermore, it promotes satiety and supports healthy weight management, reducing central obesity. The diet also lowers blood pressure and improves overall heart health, reducing the risk of CVD.(199)

Dietary Approaches to Stop Hypertension (DASH) is designed to help prevent and manage high blood pressure, but it also benefits MetS. It emphasizes fruits and vegetables, whole grains, low-fat dairy, lean proteins, and limits sodium, saturated fats, and added sugars. The diet includes 4-5 servings of fruits and vegetables, 6-8 servings of whole grains, 2-3 servings of low-fat dairy, and lean meats, poultry, and fish, with limited sodium intake. Adopting the DASH diet not only effectively lowers blood pressure, but also improves lipid profiles by reducing LDL cholesterol and triglycerides while increasing HDL cholesterol, and enhances insulin sensitivity for better blood sugar control. The diet promotes satiety, supporting healthy weight management and reducing central obesity. Additionally, its high antioxidant content helps reduce inflammation, a key factor in MetS.(200,201) Figure 6 illustrates how combinations of these three diets can affect MetS condition.

Several supplements can help improve MetS by addressing its key risk factors. Omega-3 fatty acids from fish oil can improve lipid profiles and reduce inflammation. (201) Magnesium supports glucose metabolism and insulin sensitivity and improve sleep.(202,203) Vitamin D helps regulate blood sugar levels and improve insulin function. (203) Fiber supplements, like psyllium husk, can aid in weight management and improve cholesterol levels.(204) Probiotics enhance gut health, which can positively impact metabolic processes.(205) Coenzyme Q10 has antioxidant properties that reduce oxidative stress and improve cardiovascular health.(206) Recent data has shown the effects of polyphenols on the prevention and treatment of MetS. Incorporating these supplements into a balanced diet can be beneficial for managing and preventing MetS.

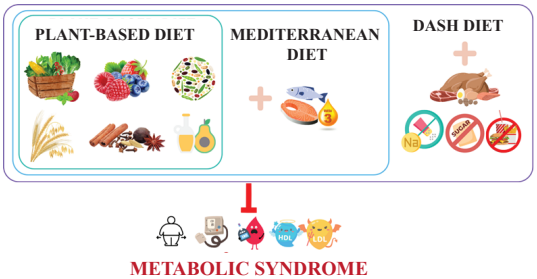

Figure 6. Diet strategy to prevent or improve metabolic syndrome.

Effects of Dietary Polyphenols on MetS

Polyphenols are secondary metabolites naturally present in plants, renowned for their potential in preventing and treating diseases associated with IR, oxidative stress, inflammation, and dyslipidemia, all of which are key contributors to MetS. These compounds exhibit strong antioxidant and anti-inflammatory properties, which play a crucial role in mitigating oxidative stress and inflammation, central to the pathogenesis of MetS. By neutralizing free radicals and reducing inflammatory responses, polyphenols help protect against the cellular damage and metabolic disturbances that characterize MetS, thereby supporting overall metabolic health. Many plant species have been shown to have around 8000 polyphenolic chemicals.(207)

Polyphenols compounds have a common chemical structure, which are benzene derivatives with one or more hydroxyl groups attached to the ring. Because of their structure, these compounds can actively operate as reducing agents, pro-oxidant metal chelators, scavengers to stabilize free radicals, and quenchers to generate singlet oxygen.(208) Based on the amount of phenolic rings and the structural components that hold these rings together, polyphenols are classified into two primary classes: flavonoids and non-flavonoids (phenolic acids, stilbenes, and lignans). Dietary polyphenols' bioavailability and absorption are significantly influenced by their structural configuration, degree of polymerization, and conjugation with other phenolics. (209) For example, quercetin in onion and apple has higher bioavailability when it is in its glycoside form (bound to a sugar molecule) compared to its aglycone form (without sugar). Polyphenols can exist as monomers or polymers. Proanthocyanidins found in chocolates and grapes are absorbed more efficiently in their monomeric form than their polymeric forms. When polyphenols are bound to other phenolic compounds, their absorption can be altered. Conjugation can either enhance or inhibit bioavailability depending on the specific interactions. When chlorogenic acid binds to proteins, these complexes can protect chlorogenic acid from degradation in the digestive tract, potentially enhancing its bioavailability.(210)

Flavonoids, a subclass of polyphenolic molecules, are naturally found in fruits, vegetables, and beverages like wine, tea, and coffee. Their unique positive effects on MetS are primarily due to their structural variation. The fundamental structure of flavonoids consists of a central skeleton of 15 carbon atoms arranged into three rings: two benzyl rings (A and B) and one heterocyclic ring (C). Based on their chemical structure, flavonoids are categorized into six classes: anthocyanins, flavones, flavonols, isoflavones, flavanones, and flavanols (including catechins and proanthocyanidins).(209)

Flavonoid consumption lowers the risk of MetS. The primary mechanism against MetS is thought to be the anti-oxidative and anti-inflammatory.(211,212) It is known that some flavonoids raise the expression of endothelial nitric oxide synthase (eNOS), which in turn increases the generation of nitric oxide.(213) Because it controls vessel wall tone and elaxation response, this substance secreted by endothelial cells is crucial. Vasodilation decreases as nitric oxide production declines, potentially resulting in CVD. Additionally, endothelial cells are shielded from the malfunction that might result in vascular regulation disease by the anti-inflammatory and anti-oxidative properties.(213,214)

Apigenin and naringenin, prominent flavonoids, diminish the phosphorylation of protein kinase C ßII (PKCßII) and the production of ROS in endothelial cells subjected to high glucose concentrations, thereby mitigating the occurrence of endothelial dysfunction.(215) Apigenin decreases NF-κB phosphorylation in endothelial cells, Bax expression, caspase-3 activity, and high-glucose-induced apoptosis. Apigenin stops lipopolysaccharide (LPS)-induced apoptosis by blocking the generation of ROS and caspase-3 activity.(216) Because of these characteristics, apigenin is a great substance that can prevent endothelial dysfunction and regulate mitochondrial function in inflammatory conditions. Chlorogenic acid, a primary phenolic acid found in coffee and various fruits, is formed by the combination of caffeic acid and quinic acid. As a member of the hydroxycinnamic acid family, it is bound by an ester link at the C5 position, hence its name 5-O-caffeoylquinic acid (5-CQA). Chlorogenic acid is known for its numerous benefits, including anti-inflammatory, hypolipidemic, antidiabetic, antioxidant, and antihypertensive effects, making it a vital component in the prevention and treatment of MetS. 5-CQA was shown to have action against MetS.(217) In a reported *in vivo* study, 40 male Sprague-Dawley rats were divided into four groups based on their diets: normal, high-fat, low-chlorogenic acid (20 mg/kg body weight), and high-chlorogenic acid (90 mg/kg body weight) combined with high-fat. For 12 weeks, chlorogenic acid was administered orally once a day, dissolved in sterile saline. The chlorogenic acid reduced weight gain from visceral and body fat, as well as hepatic FFA induced by a high-fat diet, in a dose-dependent manner. Additionally, chlorogenic acid has been shown to help prevent diabetes in both humans and animals.(218)

Chlogenic acid's effects on glucose metabolism have also been linked to its anti-obesity and antidiabetic qualities. The 5-CQA can reduce intestinal glucose transport and release by blocking hepatic glucose-6-phosphatase activity. (219,220) and it can also prevent glucose absorption in the small intestine by blocking glucose-6-phosphate translocase 1. As a result, there is less glucose in the blood, which increases the amount of fat stores used as an energy source. Fatty deposits diminish as a result of decreased insulin action brought on by a drop in blood glucose levels.(221) Several studies demonstrated that chlorogenic acid can protect people from CVD risk.(193)

Resveratrol, a polyphenol found in grapes, berries, and peanuts, has shown promising effects in treating MetS. It possesses strong antioxidant and anti-inflammatory properties, which help reduce oxidative stress and inflammation, the key factors in MetS. Resveratrol activates SIRT1 that plays a crucial role in regulating metabolic processes, thus improves insulin sensitivity, lowers blood pressure, and enhances lipid metabolism, thereby mitigating the risk factors associated with MetS.(222,223)

Quercetin, abundant in apples, onions, and berries, is another polyphenol with potential benefits for MetS. It modulates various pathways involved in insulin sensitivity, lipid metabolism, and inflammation. Quercetin's antioxidant properties help reduce oxidative stress, while its anti-inflammatory effects can alleviate chronic inflammation associated with MetS. Quercetin activates AMPK. When AMPK is activated, it enhances glucose uptake in cells by promoting the translocation of glucose transporter type 4 (GLUT4) to the cell membrane. This process bypasses the traditional insulin signaling pathway, allowing for improved glucose uptake even in insulin-resistant conditions. Quercetin influences the p38 MAPK pathway, which is downstream of AMPK and further aids in glucose metabolism. Studies have shown that quercetin can improve glucose metabolism, reduce blood pressure, and positively impact lipid profiles, making it a valuable candidate for managing MetS.(223)

Curcumin, the active compound in turmeric, has been extensively studied for its therapeutic effects on MetS. Curcumin modulates the phosphoinositide 3-kinase (PI3K)/ protein kinase B (Akt) signaling pathway, and inhibits NF-κB pathway, which is involved in inflammation. Similar to quercetin, curcumin activates AMPK. Curcumin improves insulin sensitivity, reduces blood glucose levels, and enhances lipid metabolism. It also helps lower blood pressure and mitigate obesity-related inflammation. These multifaceted effects make curcumin a promising natural agent for preventing and treating MetS.(224)

As demonstrated for cocoa flavanols, all intervention study data suggest that dietary polyphenols can enhance endothelium dilatory function linked to increased nitric oxide bioavailability. Combining high polyphenols plant-based polyphenols with Mediterranean Diet (green-MED Diet), result in a significantly greater reduction in VAT—14% compared to 7% with the traditional Mediterranean diet. This suggests that the additional polyphenols in the green Mediterranean diet enhance its effectiveness in reducing visceral fat and potentially improving metabolic health.(225,226)

The relationship between polyphenols and microbiota may be taken into consideration in the dietary management of MetS (227,228), as gut microbiota has been shown to be important in the development of multiple pathologies (229), and in particular, it has recently been identified as a potential new risk factor for CVD (230). Only 5–10% of the total amount of polyphenols consumed is thought to be absorbed in the small intestine.(228) Alongside conjugates released into the intestinal lumen via bile, the residual polyphenols (90–95% of total polyphenol intake) may accumulate in the large intestine lumen to millimolar concentrations, where they encounter the enzymatic activities of the gut microbiota.(228) Through selective prebiotic effects and antimicrobial activities against gut pathogenic bacteria, recent studies have actually suggested that both the aromatic metabolites produced and the phenolic substrates provided to gut bacteria through varying dietary intake patterns may modulate and cause fluctuations in the composition of the microflora populations, potentially influencing their involvement in health issues. Therefore, investigating the possible involvement of polyphenols in metabolic balance and weight loss may be an intriguing focus on the gut microbiota.(231)

Polyphenols are recognized for their potent antioxidant and anti-inflammatory effects, which help mitigate MetS. Despite these promising findings, further research is needed to fully understand the long-term benefits of polyphenols, especially their impact on gut microbiota and overall metabolic balance. Generally, long-term polyphenol supplementation is considered safe for most people when consumed in moderate amounts. However, excessive intake can lead to potential side effects such as iron depletion, interference with thyroid hormone metabolism, and gastrointestinal issues. Chronic high doses may also exert pro-oxidant effects, which can be harmful. Polyphenols can interact with various medications, potentially altering their effectiveness. For example, curcumin may enhance the effects of anticoagulants like warfarin, increasing the

risk of bleeding. Quercetin can inhibit enzymes involved in drug metabolism, affecting the efficacy of medications such as cyclosporine. Resveratrol may interact with drugs metabolized by cytochrome P450 enzymes, altering their plasma levels. Polyphenols can also interact with other dietary components. For instance, polyphenols can inhibit iron absorption, which may be problematic for individuals with marginal iron stores. Additionally, the presence of proteins and fats can affect the bioavailability of polyphenols. Polyphenols bound to proteins may have altered absorption rates.(232) Future studies should focus on exploring any possible interactions between polyphenols either with another compounds or with gut microbiome to better understand their role in managing MetS. This includes investigating how polyphenols' interactions contribute to the regulation of metabolic pathways and inflammation. Understanding these mechanisms could pave the way for new therapeutic strategies targeting MetS through dietary polyphenols and gut microbiota modulation.

Conclusion

Measurements of basic indicators, including WC, blood pressure, HDL cholesterol, triglycerides, and blood glucose, are frequently used to diagnose MetS. Early diagnosis is crucial for effective management and prevention of MetS and its associated comorbidities. Adipose tissue depots play a significant role in the development of MetS, with VAT releasing proinflammatory cytokines that induce IR, as the fundamental aspect for MetS. An epigenetic approach to reduce MetS risk factors can be translated as lifestyle modifications, including increasing physical activity and adopting a balanced diet like a plant-based diet, Mediterranean diet, or DASH diet. Additionally, certain metabolites, particularly those associated with polyphenols, have shown benefits in reducing inflammation and oxidative stress thus improve MetS. Therefore, implementing suitable lifestyle changes, optimizing the gut microbiota, and adding supplements with a high content of polyphenols are considered key strategies for preventing and treating MetS and its associated comorbidities.

Authors Contribution

AM drafted the original manuscript and critically revised the manuscript manuscript. NMD edited and revised the manuscript. AW proposed and concepted the manuscript topic, and gave critical suggestions to the final draft. All authors have agreed with the final revisions of the manuscript.

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