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Chapter 2

FUNCTIONAL CHANGES IN METABOLIC SYNDROME

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ABSTRACT

Metabolic Syndrome (MetS) is a condition characterized by the co-occurrence of several cardiovascular risk factors, including insulin resistance, obesity, dyslipidemia, and hypertension. The development of MetS is closely linked to visceral adiposity, which refers to fat accumulation around critical vital organs in the abdominal cavity. Visceral fat is metabolically active and produces adipokines, proteins that regulate energy balance and play a role in inflammation and atherosclerosis. Some adipokines, such as leptin and adiponectin, have beneficial effects on glucose homeostasis and are considered protective against MetS. However, other adipokines, such as visfatin and resistin, contribute to glucose intolerance and have pro-atherogenic properties. Visceral obesity also contributes to the development of MetS through its effects on blood pressure. It activates the sympathetic nervous system, the renin-angiotensin-aldosterone system, and insulin resistance, leading to elevated blood pressure.

Another critical factor in the development of MetS is the activation of the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1). LOX-1 is a protein that acts as a receptor for oxidized LDL on the cell surface. Its activation leads to the production of reactive oxygen species, a decrease in nitric oxide, and increased expression of molecules contributing to hypertension and vascular damage. LOX-1 is also involved in the development of other complications associated with MetS, such as nephropathy and left ventricular hypertrophy.

The renin-angiotensin-aldosterone system (RAAS) regulates blood volume, electrolyte balance, and vascular resistance. In patients with MetS, the activation of RAAS leads to increased levels of angiotensin II (Ang II) and aldosterone, which have various effects on blood pressure and sodium and water retention. Ang II also contributes to oxidative stress and inflammation in the vasculature.

Insulin resistance, a key feature of MetS, disrupts the insulin signaling process in adipose tissue, leading to increased lipolysis and elevated levels of circulating free fatty acids. These fatty acids further worsen insulin resistance and contribute to impaired glucose metabolism.

Oxidative stress, characterized by an imbalance between the production of reactive oxygen species and the body's antioxidant defenses, is closely associated with the development of MetS. Hyperlipidemia and hyperglycemia, standard features of MetS, are linked to increased oxidative stress and ROS production. Oxidative stress and the activation of RAAS and LOX-1 contribute to the progression of dyslipidemia, type 2 diabetes, hypertension, and cardiovascular diseases.

The oral-gut-liver axis is an emerging concept that suggests a relationship between oral infections, such as periodontitis, and metabolic dysfunction, including MetS and liver diseases. Periodontitis has been associated with chronic liver diseases, such as non-alcoholic fatty liver disease (NAFLD) and liver cirrhosis. The translocation of oral bacteria from the mouth to the gut may contribute to gut dysbiosis, increased intestinal permeability, and systemic inflammation, which can worsen liver functions.

Overall, the development of MetS involves the interplay of various factors, including visceral obesity, adipokines, LOX-1 activation, insulin resistance, oxidative stress, and the oral-gut-liver axis. Understanding these mechanisms is crucial for preventing and managing MetS and its associated complications. Further research is needed to fully elucidate the roles of individual factors and develop targeted interventions for MetS.

Introduction

Metabolic Syndrome (MetS) represents a complex constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increase the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality. This syndrome has emerged as a significant public health challenge worldwide, paralleling the rising epidemic of obesity and sedentary lifestyles. At its core, MetS is characterized by the co-occurrence of several cardiovascular risk factors, including insulin resistance, visceral obesity, atherogenic dyslipidemia, and hypertension[1].

The pathophysiology of MetS is multifaceted, involving an intricate interplay of various mechanisms. Central to this syndrome is visceral adiposity, which goes beyond mere fat accumulation to represent metabolically active tissue-producing adipokines—proteins that play crucial roles in energy homeostasis, inflammation, and atherosclerosis. The balance between protective adipokines (such as leptin and adiponectin) and those contributing to metabolic dysfunction (like visfatin and resistin) is critical in the progression of MetS[1,2,3].

Furthermore, the activation of the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) and the renin-angiotensin-aldosterone system (RAAS) contributes significantly to the development of hypertension and vascular damage associated with MetS [1, 4]. Insulin resistance, a hallmark of MetS, disrupts normal metabolic processes, leading to a cascade of events that further exacerbate the syndrome.

Oxidative stress, resulting from an imbalance between reactive oxygen species production and the body's antioxidant defenses, is another key player in the pathogenesis of MetS. This oxidative imbalance is closely linked to the lipid and glucose abnormalities characteristic of the syndrome[5, 6].

Recent research has also highlighted the potential role of the oral-gut-liver axis in metabolic dysfunction[7-10]. This emerging concept suggests a relationship between oral infections, particularly periodontitis, and the development of MetS and liver diseases, adding another layer of complexity to our understanding of this syndrome.

This chapter sets the stage for a deeper exploration of these mechanisms, their interactions, and their collective impact on the development and progression of Metabolic Syndrome. Understanding these pathways is crucial for developing effective strategies for prevention, early diagnosis, and targeted treatment of this increasingly prevalent condition.

Role of Visceral Fat and Adipokines (Adipocytes) in Metabolic Syndrome

Metabolic syndrome (MetS), also variously known as syndrome X, refers to the co-occurrence of several known cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia, and hypertension. The incidence of metabolic syndrome often parallels that of obesity. However, obesity does not always reflect MetS without other features such as insulin resistance, visceral obesity,

atherogenic dyslipidemia, and endothelial dysfunction[14,15]. Of these, the first two appear to be required for metabolic syndrome.

Visceral adiposity is crucial for the development of MetS. This type of fat is stored in the abdominal cavity around important internal organs such as the liver, pancreas, and intestines (Figure 1). The adipocytes of obese patients usually show increased sensitivity to the lipolytic action of catecholamines. This increased lipolytic response can lead to elevated levels of free fatty acids in the bloodstream, affecting lipid metabolism and contributing to dyslipidemia[1, 11, 12, 13].

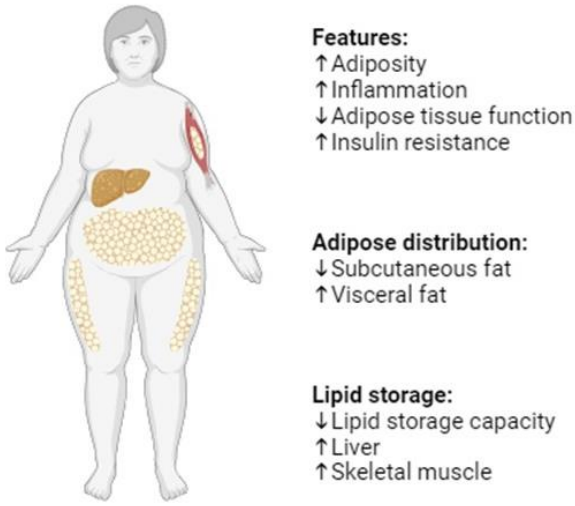

Figure 1. Metabolically unhealthy obesity

Visceral obesity can also elevate blood pressure. This is due to a variety of factors, including the activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the effects of insulin resistance[1, 12, 14].

Visceral fat is metabolically active and produces adipokines and secretes proteins called “adipocytokines,” which regulate the body’s energy homeostasis and play an essential role in pathophysiological events such as inflammation and atherosclerosis[15-18].They regulate lipolysis, lipogenesis, and lipid uptake in different tissues and contribute to the development of metabolic syndrome through various mechanisms. Adipokines, such as leptin, adiponectin, resistin, and visfatin, as well as pro-inflammatory and anti-inflammatory cytokines, such as TNF-α, IL-6, IL-1β, monocyte chemoattractant protein-1, and serum amyloid A, originate from visceral fat (Figure 2) [19, 20].

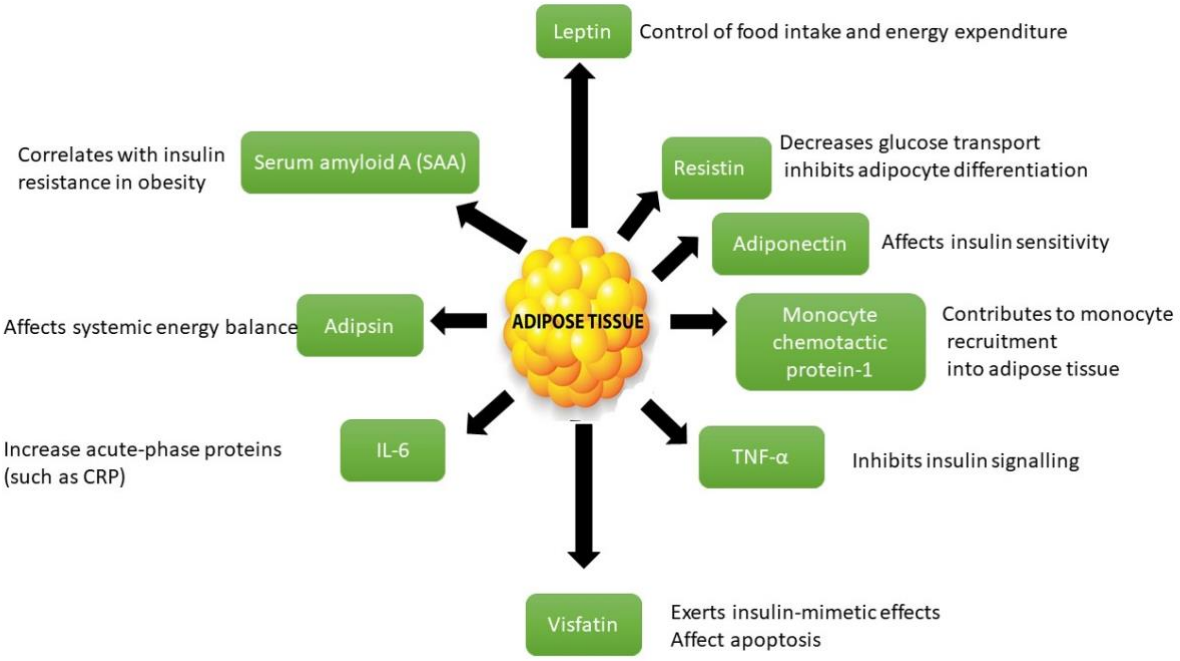

Figure 2. Major adipokines and their functions

Adipokines such as leptin and adiponectin are involved in glucose homeostasis and lipid metabolism. Leptin and adiponectin improve insulin sensitivity, increase fatty acid oxidation, and prevent foam cell formation. These adipokines have beneficial effects on glucose homeostasis and are generally considered protective against metabolic syndrome[20].

On the other hand, adipokines like visfatin, fetuin-A, resistin, and plasminogen activator inhibitor-1 (PAI-1) are mentioned as contributors to the development of glucose intolerance and have pro-atherogenic properties[3, 21]. These adipokines may have harmful effects on metabolic syndrome.

Furthermore, chronic inflammation in adipose tissue, driven by elevated levels of cytokines and chemokines, recruits monocytes and produces vascular adhesion molecules. This process can result in hepatic fibroinflammatory injury, insulin resistance, and other complications associated with metabolic syndrome[17-23].

It is important to note that the contributions of individual adipokines to the pathophysiological features of metabolic syndrome are still a topic of debate, and further research is needed.

Obesity is a key feature of MetS, a state of chronic low-grade inflammation that contributes to insulin resistance and other metabolic abnormalities with increased levels of pro- and anti-inflammatory markers. These pro-inflammatory mediators trigger monocytes to differentiate macrophages in the adipose tissue, releasing cytokines.

However, the recruitment of monocytes into adipose tissue is not fully understood.

Role of Lectin-Like Oxidized Low-Density Lipoprotein (LOX) Activation

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is a membrane protein that acts as a receptor for oxidized low-density lipoprotein receptor-1 (LOX-1) is a membrane protein that acts as a receptor for oxidized LDL (ox-LDL) on the cell surface. LOX-1 activation produces reactive oxygen species, decreases nitric oxide from vascular endothelial cells, and increases expression of endothelin-1, AT1R, and cell adhesion molecules[24, 25]. All of these factors contribute to both hypertension and vascular damage. In the case of high blood pressure, the expression of LOX-1 is increased in vascular smooth muscle cells[26]. Elevated concentrations of LOX-1 have been reported in adults with conditions such as hypertension, diabetes, and hyperlipidemia and cause oxLDL-induced apoptosis of endothelial cells. It can be down-regulated by Angiotensin I receptor blockers and statins[27, 28].

Moreover, LOX-1 is highly expressed in macrophages in human atherosclerotic lesions, and high glucose concentrations enhance LOX-1 expression in human macrophages. Endothelial dysfunction, in addition to disturbances in cholesterol metabolism, is associated with the development of atherosclerosis[26]. Endothelial cells, which form a single layer on the blood vessels' innermost surface, release molecules such as vasodilator nitric oxide, vasoconstrictor endothelin-1, adhesion molecules, and chemokines. Oxidized LDL (Low-Density Lipoprotein) causes the dysregulation of endothelial function proinflammatory, prothrombotic, or proatherogenic through the LOX-1 receptor[29]. Urged by the endothelin-1, up-regulation of LOX-1 causes lipid accumulation in the coronary arteries of ApoE. By means of passivization through superoxide production and phosphorylation of endothelial synthase of endothelial nitric oxide, LOX-1 activation hinders nitric oxide discharge[30]. Depressed levels of NO also lead to increased endothelin-1 levels. In addition, LOX-1 stimulates various cellular signaling pathways such as rho and rac small GTPases, p38 MAP kinase, protein kinase C beta II, and NF-kB, thereby activating the expression of chemokines and molecules that facilitate the adhesion of leukocytes [31].

In addition to complications that are associated with diabetes and hypertension, LOX-1 is also associated with nephropathy and left ventricular hypertrophy. Depending on the extent of tubulointerstitial damage and urine protein concentrations, high LOX-1 expression is observed in tubulointerstitial regions in diabetic nephropathy[32]. Moreover, LOX-1 has been demonstrated to play a critical role in reforming cardiac myocytes as opposed to angiotensin II. Serum levels of soluble LOX-1 (sLOX-1) are elevated in the presence of ventricular hypertrophy in the pathophysiology of essential hypertension[27, 32].

The role of LOX-1 in visceral fat is thought to be associated with inflammation (Figure 3). It is suggested that elevated serum oxidized LDL (ox-LDL) levels in obesity demonstrating systemic oxidative stress due to escalating production of reactive oxygen species (ROS) by adipose tissue mitochondria[33].

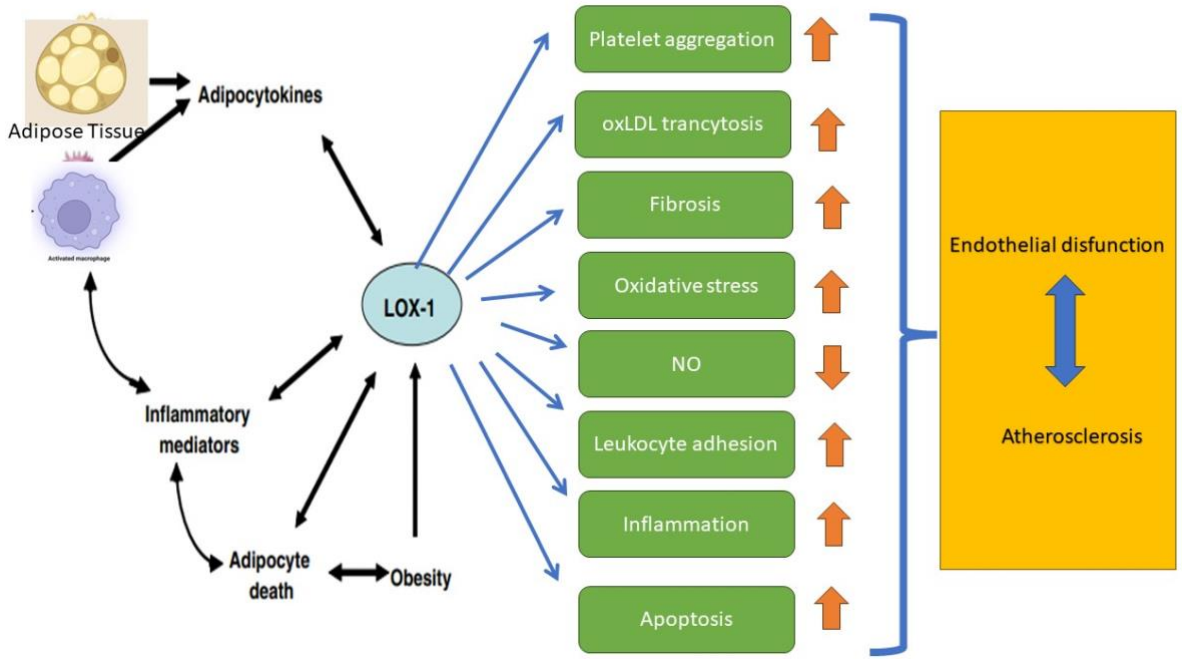

Figure 3. Role of LOX-1 in MetS

Angiotensin II and Lox (lectin-like oxidized low-density lipoprotein) activation

The renin-angiotensin-aldosterone system (RAAS) regulates blood volume, electrolyte balance, and systemic vascular resistance. In patients with overactivated RAAS, pathological events promoting vascular disease are initiated. In type 2 diabetes, increased glucose levels initiate the activation of RAAS, which leads to increased levels of angiotensin II (Ang II) and aldosterone[34]. Ang II has various effects on blood pressure, including vasoconstriction, sympathetic nervous system stimulation, and sodium and water retention promotion through aldosterone release. Ang II's pathologic effects on the vasculature occur via oxidative stress by generating reactive oxygen species (ROS). The overproduction of Ang II, the activation of NAD(P)H oxidases, and the generation of ROS contribute to the pathophysiology of type 2 diabetes (Figure 4) [35].

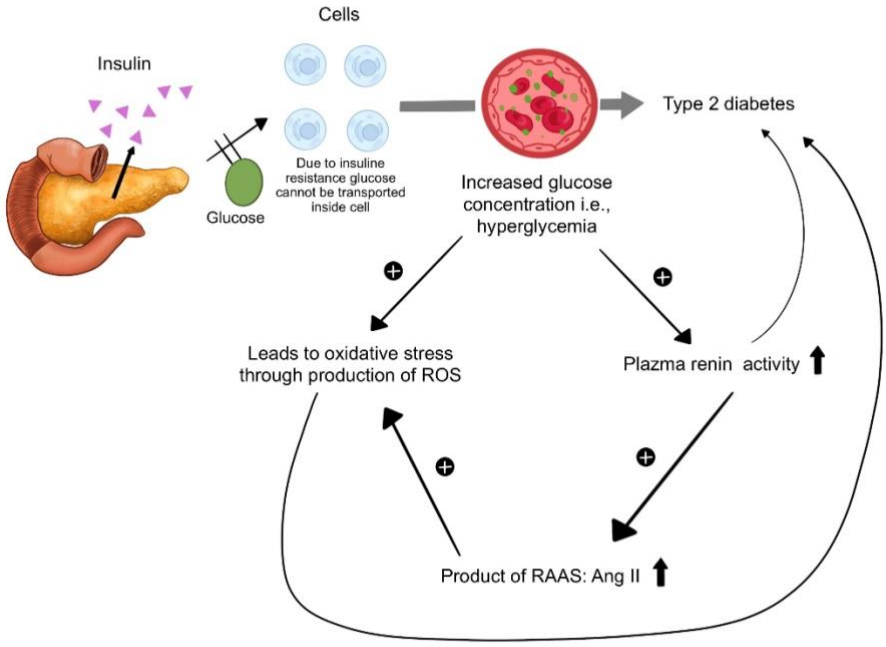

Figure 4. The role of Ang-II and ROS generation in diabetes type 2 pathophysiology

The Angiotensin type 1 receptors (AT1R) are widely distributed in all organs and mediate most of the physiological effects of Ang II, such as blood pressure elevation, vasoconstriction, increased cardiac contractility, renal sodium retention, water reabsorption, and aldosterone release from the adrenal gland. AT1R expression in vascular smooth muscle cells is upregulated by LDL, insulin, progesterone, and erythropoietin and downregulated by epidermal growth factor, platelet-derived growth factor, thyroid hormone, nitric oxide, forskolin, angiotensin II, interferon-gamma, estrogen, vitamin A and HMG (3-hydroxy-3-methyl-glutaryl) CoA reductase inhibitors. Both native LDL and oxidized LDL (ox-LDL) increase the expression of AT1R, which mediates most of the recognized cardiovascular effects of Ang II[29, 36].

In obesity, increased body weight results in elevated cardiac output [33].As a result, an increased metabolic rate due to functional vasodilatation causes greater tissue oxygen consumption. The exact mechanisms responsible for the harmful effects of obesity on the blood vessels have not been completely clarified. However, these effects likely result from complex interactions among various factors, including elevated blood pressure, inflammation, hyperglycemia, the accumulation of lipids leading to "lipotoxicity" through non-beta oxidative metabolism of fatty acids, oxidative stress, and the activation of various neurohumoral systems. Visceral obesity causes excessive secretion of pro-inflammatory and vasoactive adipokines such as angiotensinogen, Ang II, aldosterone, and resisting, along with increased plasma renin activity, which has been implicated in blood pressure control. RAAS activation occurs despite NaCl retention, volume expansion, and hypertension, which typically suppress renin secretion

and Ang II formation[32, 34, 37]. Multiple mechanisms activate RAAS activation in obesity, including kidney compression and increased sympathetic nervous system activation. Although angiotensinogen is produced in adipocytes, the importance of adipose tissue as a source of Ang II formation remains unclear. An essential role for Ang II in stimulating renal NaCl reabsorption and in mediating obesity hypertension is supported by studies in experimental animals demonstrating that Ang II receptor blockade or ACE inhibition attenuates sodium retention, volume expansion, and increased BP. Activation of the RAAS may contribute to glomerular injury and nephron loss associated with obesity not only by increasing but also through intrarenal effects.

Many of these effects have been observed in experimental models of obesity-related hypertension that exhibit the characteristics of metabolic syndrome. Specific metabolic syndrome factors, such as high cholesterol levels, elevated blood sugar levels, and obesity, as indicated by an increased waist circumference, regulate the expression of components of the renin-angiotensin system (RAAS). This activation of the RAAS leads to the production of Ang II in specific tissues and cell types. The mechanisms mediated by Ang II contribute to the development of metabolic syndrome by exacerbating pathologies in various organs, including the vascular system (smooth muscle cells, endothelial cells), adipocytes, liver, pancreas, and kidney (Figure 5) [24, 26, 27, 32].

The role of insulin resistance and adipose tissue

In healthy individuals, insulin signaling plays a crucial role in regulating the synthesis and storage of triacylglycerol in adipose tissue. However, insulin's ability to inhibit lipolysis in adipose tissue is impaired when insulin resistance develops. This leads to an increase in the levels of circulating free fatty acids, which further worsens insulin resistance by disrupting the insulin signaling process in various organs (Figure 5). The elevated levels of circulating fatty acids and triacylglycerol are strongly associated with impaired insulin signaling and glucose intolerance in obesity and type 2 diabetes[1, 31, 35, 37]. Dysfunctional lipid metabolism is considered the primary underlying cause of metabolic diseases. The accumulation of fat in non-adipose tissues, such as the liver and muscles, has been identified as a significant predictor of type 2 diabetes mellitus. In muscles, free fatty acids affect insulin receptor substrate (IRS-1), leading to reduced glucose uptake. In the liver, free fatty acids stimulate the production of glucose and fats. As a result, there is an increased demand for insulin to maintain normal blood glucose levels.

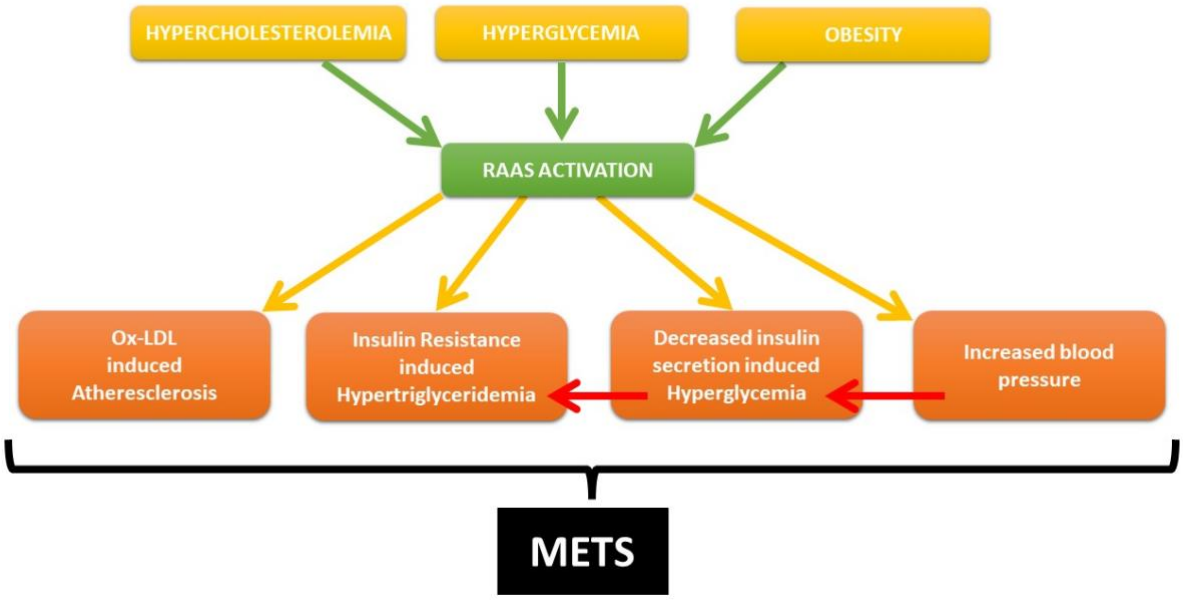

Figure 5. The interplay between RAAS components and other specific factors (hypercholesterolemia, hyperglycemia, obesity) regarding the development of metabolic syndrome.

Role of oxidative stress

Oxidative stress is a state of imbalance between the oxidative and anti-oxidative systems of cells and tissues, resulting in the overproduction of reactive oxygen species (ROS). Excessive oxidative stress is implicated in metabolic syndrome-related manifestations, including obesity, type 2 diabetes, hypertension, and cardiovascular diseases. In addition to increased oxidative activity, a reduced antioxidant state strongly correlates with MetS occurrence.

Hyperlipidemia and hyperglycemia are highly associated with oxidative stress and increased ROS production. ROS has multiple pleiotropic effects in the vascular system, including endothelial injury, LDL oxidation, and LOX-1 expression[32]. Increased ROS production, together with RAAS and LOX-1, contribute to the progression of dyslipidemia, type 2 diabetes, hypertension, and cardiovascular diseases. Total body fat and waist circumference are positively associated with oxidative stress-mediated endothelial dysfunction. Ang II is a principal NAD(P)H oxidase activator expressed in vascular smooth muscle cells and fibroblasts[35-39]. This oxidase system, similar to neutrophil oxidase, is a significant source of ROS in the vascular system. In hyperlipidemia and atherosclerosis, endothelial nitric oxide synthase may become dysfunctional and produce large amounts of superoxide.

Possible contributors to oxidative stress in obesity include hyperglycemia, hyperlipidemia, chronic inflammation, endothelial dysfunction, vitamin and mineral deficiencies, hyperleptinemia, increased muscle activity to carry excessive weight, impaired mitochondrial function, and diet. The relationship between oxidative stress and obesity is bidirectional and multifaceted. Oxidative stress can be a trigger and the outcome of obesity[35]. Obesity is highly associated with reduced antioxidant status due to

continuous overeating, especially high-calorie, low-nutrient foods, which overwhelms the body's metabolic processes. This excess nutrient intake can lead to the production of ROS that the body's antioxidant defenses can neutralize, resulting in oxidative stress.

It is well documented that reducing visceral adiposity (waist circumference) through lifestyle modifications such as dietary changes and physical activity positively impacts overall health, specifically concerning metabolic syndrome and oxidative stress.

Role of the Oral-Gut-Liver Axis in Metabolic Dysfunction

Obesity, metabolic syndrome, and oral infections are some of the most prevalent non-communicable diseases, and a substantial body of evidence from the published studies substantiates the correlation among these conditions. It is estimated that 3.5 billion people worldwide live with oral diseases[38]. Dental caries and periodontitis are the most prevalent oral infections, impacting approximately 35% and 11% of the worldwide population[39]. Extensive research has delineated plausible mechanisms elucidating how these conditions can detrimentally influence one another, indicating a mutually adverse relationship. The oral cavity hosts the second largest and most diverse microbiota, comprising more than 770 bacterial species engaging with diverse microbial populations at distinct anatomical sites within the human body, including the gut and liver. It is estimated that a person swallows up to 1.5 L of saliva each day, which can contain 10^8–10^{12} oral bacteria in the presence of periodontitis[40]. Although there is a growing body of knowledge regarding the dissemination of oral bacteria to distant organs via hematogenous and enteral routes, the functional impact of oral bacteria in the pathogenesis of intestinal and liver disorders remains relatively understudied.

Cross-sectional studies have found associations between periodontitis and the onset and progression of chronic liver diseases such as non-alcoholic fatty liver disease (NAFLD) and liver cirrhosis[8, 41, 42]. Common risk factors such as diabetes, smoking, and alcohol use partially explain the connexions between these conditions. NAFLD is the most widespread chronic liver condition globally, with a notable rise in cases among individuals with metabolic syndrome. Population-based health examination surveys in the USA, Asia, and Europe indicated that advanced forms of periodontitis were linked to a heightened risk of developing NAFLD[9, 43, 44]. Salivary *P. gingivalis* is more frequently detected in saliva in patients with NAFLD than in controls[45]. Potentially, swallowed periodontal bacteria can translocate to the gut and cause gut dysbiosis, increased intestinal permeability, and subsequent systemic inflammation. Moreover, individuals with NAFLD showed elevated serum antibody levels against periodontitis-related bacteria such as *P. gingivalis and A. actinomycetemcomitans*. Periodontopathic bacteria may aggravate NAFLD by affecting lipid and glucose metabolism and altering the gut microbiota in experimental periodontitis models[10]. In a mouse model inducing NAFLD via a high-fat diet, intravenous *P. gingivalis* treatment led to notable increases in body and liver weight compared with NAFLD controls[45]. More interestingly, oral bacteria are overrepresented in the fecal microbiome of patients with liver cirrhosis[46]. Oral bacteria have been observed to infiltrate and persist within immune cells, suggesting that they may exploit host immune cells as Trojan horses for transportation from the

oral mucosa to the gut mucosa[47]. The exact mechanism by which oral bacteria contribute to the pathogenesis of liver diseases remains elusive (Figure 6). Once periodontitis is established, oral bacteria can invade the gut, spreading adverse events to the intestinal microbiome and likely affecting liver functions. This may not be surprising as the liver has very close anatomical proximity and physiological interdependence with the intestine via metabolic exchange and translocation of bacteria. Ectopically colonized oral bacteria may contribute to the worsening of liver functions through the combined effects of two separate mechanisms: triggering mucosal inflammatory responses directly and acting as specific antigens for migrated oral T cells indirectly.

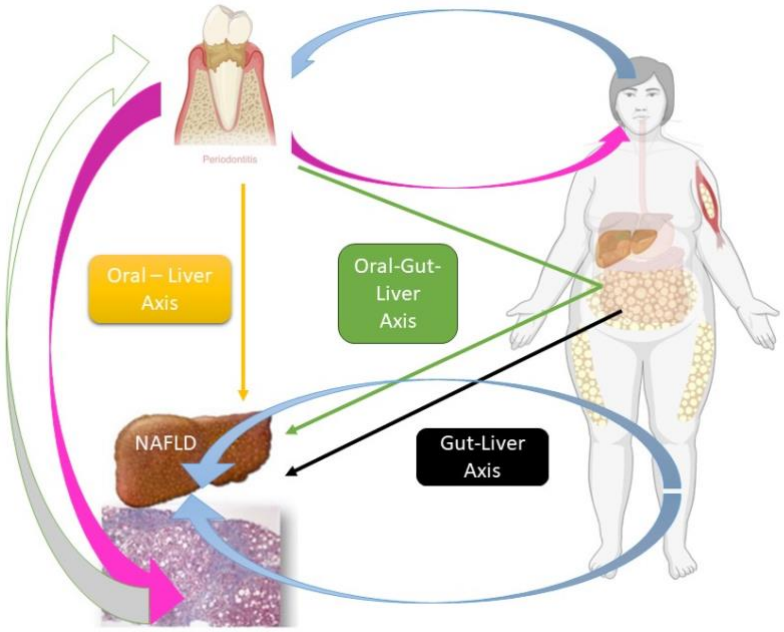

Figure 6. The interplay between the gut, liver, and mouth.
Direct transfer occurs from mouth to gut due to impaired intestinal permeability. An imbalanced microbiota causes gut dysbiosis, and inflammatory mediators lead to systemic inflammation.
The blue arrow shows established links, the pink arrow shows possible links, and the white arrow shows indeterminate links.

Recent animal studies have revealed biologically plausible mechanisms by which experimental periodontitis can modify gut microbiota and impair gut tight junction integrity and insulin resistance[48, 49]. Periodontal pathogens impair glucose tolerance and insulin resistance in mice fed a standard or high-fat diet, leading to a significant accumulation of lipids in the liver. This is accompanied by elevated

gene expression of acetyl-CoA carboxylase, a key enzyme in hepatic lipid metabolism, and glucokinase, a pivotal glucose sensor governing the regulation of insulin secretion. This body of evidence collectively supports a consensus between clinical and experimental research, indicating a distinct involvement of specific periodontal pathogens in modulating the oral-gut-liver axis. These observations have brought forward the hypothesis of an oral-gut-liver axis, justifying longitudinal studies to influence liver-related outcomes through periodontal interventions[50]. To date, periodontal treatment seems to alter the composition of the intestinal microbiota of liver diseases, modulate their systemic immune response, and potentially benefit liver health; clear evidence demonstrating that periodontitis treatment can arrest or reverse liver disease progression and improve outcomes is still lacking[51]. Given the existing evidence, offering education and guidance on oral examinations and self-care to all patients with liver disease is advisable. Employing an integrated care approach and fostering close collaboration between hepatologists and dentists is strongly recommended for managing patients dealing with liver disease and periodontitis.

Conclusion

In conclusion, MetS's complex etiology necessitates a multifaceted approach to its prevention and treatment. Future research should focus on elucidating individual factors' precise roles and interactions to develop more targeted and effective interventions. A comprehensive understanding of these mechanisms is crucial for addressing the growing prevalence of MetS and associated complications.

As our knowledge of MetS continue to evolve, it becomes increasingly clear that effective management strategies must simultaneously address multiple aspects of the syndrome. This may involve lifestyle modifications, pharmacological interventions, and potentially novel approaches targeting specific pathways such as the oral-gut-liver axis.

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