Mansoura University **Training Unit** **Faculty of Pharmacy**

Metabolic Syndrome

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An Applied Research Project Submitted as partial fulfillment for the requirements of Pharmacists' Obligatory Internship Program

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2024/2025

Approval Sheet

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List of abbreviations

ASCVD	Atherosclerotic Cardiovascular Disease
BMI	Body Mass Index
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
EPA	Eicosapentaenoic Acid
FFA	Free Fatty Acids
HDL-C	High-Density Lipoprotein Cholesterol
IDF	International Diabetes Federation
LDL-C	Low-Density Lipoprotein Cholesterol
MetS	Metabolic Syndrome
NAFLD	Non-Alcoholic Fatty Liver Disease
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovary Syndrome
RAAS	Renin-Angiotensin-Aldosterone System
SBP	Systolic Blood Pressure
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
VLDL	Very Low-Density Lipoprotein
WHO	World Health Organization

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Abstract

Metabolic syndrome (MetS) is a multifaceted and progressive condition defined by a constellation of metabolic abnormalities, primarily central obesity, insulin resistance, dyslipidemia, and hypertension. These conditions act synergistically to promote chronic low-grade inflammation, endothelial dysfunction, and increased cardiometabolic risk. This review explores the individual pathophysiological roles of each component in the development and progression of MetS. Visceral adiposity initiates hormonal and inflammatory disruptions, while type 2 diabetes mellitus (T2DM) introduces persistent hyperglycemia and vascular complications. Dyslipidemia exacerbates atherogenic lipid imbalances, and hypertension contributes to vascular and renal stress. Collectively, these components form the foundation of MetS and greatly enhance the likelihood of cardiovascular disease and T2DM. Understanding their mechanisms is crucial to early identification, prevention, and treatment. This review discusses the pathogenesis and interconnectivity of these components and highlights therapeutic strategies for mitigating the global burden of MetS.

Introduction and Objectives

Introduction:

Metabolic syndrome (MetS) refers to a cluster of associated metabolic disorders, primarily central obesity, insulin resistance, hypertension, and dyslipidemia, that together considerably increase the risk of type 2 diabetes mellitus (T2DM), cardiovascular disease, and other chronic conditions. Although the definitions vary slightly across organizations, the syndrome is typically diagnosed in an individual who presents three or more risk indicators such as increased waist circumference, high triglycerides, low HDL-cholesterol, high fasting glucose, and high blood pressure [1].

The worldwide prevalence of MetS has increased exponentially over the past two decades, increasingly associated with escalating trends in obesity, sedentary lifestyle, and poor diet. An estimated one-quarter to one-third of the global adult population has MetS based on diagnostic criteria, and it has emerged as a critical public health issue [2].

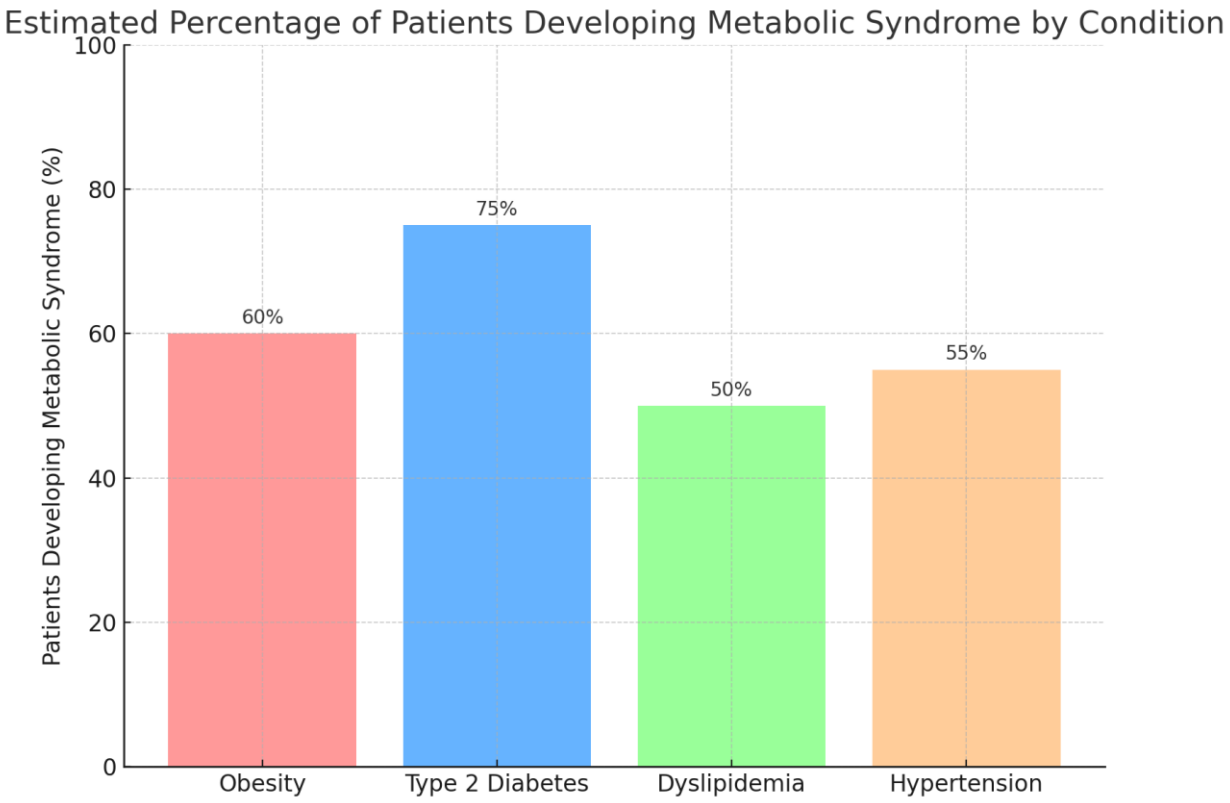

Figure 1: graph showing estimated percentages of patients with various conditions who also develop metabolic syndrome.

Beneath all of these is visceral adiposity, which is the foundation of insulin resistance, low-grade chronic inflammation, and endothelial dysfunction. Visceral adipose tissue secretes a multitude of pro-inflammatory cytokines, adipokines, and coagulation factors that influence insulin signaling and vascular health. These pathophysiologic mechanisms are further augmented by increased free fatty acids flux and mitochondrial dysfunction, which collectively result in hyperglycemia, atherogenic lipid profiles and high blood pressure. [3]

Susceptibility to MetS is governed by genes, epigenetics, and environment. Early life exposure, such as maternal diet and intrauterine growth rate, sets the stage for elevated risk, particularly if this is reinforced later by lifestyle determinants of adverse diet and sedentary behavior. While heterogeneity of MetS and debate regarding its clinical definition are cited, its utility lies in the early detection of individuals at greater cardiometabolic risk**.**

Metabolic syndrome is a complex clinical syndrome that is characterized by the constellation of interrelated cardiometabolic risk factors, the underlying pathophysiologic substrate of which is central obesity, T2DM, dyslipidemia, and hypertension. Rather than simply co-existing, these afflictions interact synergistically and in a self-perpetuating fashion to induce global metabolic derangement. Visceral adiposity creates a pro-inflammatory and insulin-resistant milieu that underpins all of the other components of the syndrome [4]. T2DM operates via chronic hyperglycemia and secondary hyperinsulinemia, worsening endothelial dysfunction and vascular inflammation [5]. Dyslipidemia in the form of elevated triglycerides, low HDL-cholesterol, and elevated small dense LDL particles amplifies atherogenesis and cardiovascular risk [6]. At the same time, hypertension, both a consequence and a cause of insulin resistance, increases oxidative stress and arterial stiffness and adds to the metabolic and vascular injury [7]. Cumulatively, the four conditions meet the diagnostic criteria for MetS, according to leading guidelines such as the ATP III and International Diabetes Federation (IDF) and are its key pathogenic determinants [8]. Each of these components is discussed separately to demonstrate their respective mechanisms and collective roles in MetS initiation and development**.**

Because of the extent and severity of its adverse health effect, i.e., a tremendously elevated risk for the development of both diabetes and cardiovascular events, there is obviously a need to understand the multifactorial pathogenesis of MetS. The purpose of this article is to try to discuss the pathogenesis of MetS, the etiologic conditions under which it occurs, and possible preventive and therapeutic approaches.

Figure 2: primary conditions contributing to metabolic syndrome

Objectives of the Project

1- To diagnose metabolic syndrome using the most appropriate definition, symptoms, causes, risk factors.

2- To assess the relationship between metabolic syndrome and the risk of cardiovascular disease, and hypertension.

3- To assess the relationship between metabolic syndrome and the risk of type 2 diabetes mellitus.

4- To assess the role of abdominal obesity in the development and pathophysiology of metabolic syndrome.

5- To design an appropriate plan, including goals of therapy and integration of nondrug therapy, for treatment of the underlying metabolic risk factors in metabolic syndrome.

Literature Review

Obesity as a causative factor in metabolic syndrome

Obesity is a chronic, complex disorder that is caused by abnormal or excessive body fat and has the capacity to cause serious damage to health. Obesity has become one of the most worrying global public health issues, with the World Health Organization (WHO) classifying it as an epidemic globally. Global adult obesity numbers have nearly doubled since 1975, and more than 650 million adults currently live with obesity. Alarmingly, over 1.9 billion adults are overweight, and of them, an estimated 13% are obese [9]. Obesity is not the result of simple energy imbalance and is determined by genetic, behavioral, environmental, endocrine, and psychosocial etiologies.

Pathophysiological obesity, especially central (visceral) obesity, is considered to be a root and direct cause of the development of metabolic syndrome (MetS). MetS is a cluster of metabolic alterations encompassing insulin resistance, dyslipidemia, hypertension, and hyperglycemia. Central but not total obesity plays an important role in the development of this syndrome due to the unique metabolic activity of visceral adipose tissue [10].

Visceral adipose tissue is not only an energy store but also an active endocrine organ that secretes various bioactive factors known as adipokines such as Leptin which normally regulates appetite and energy expenditure, but its signaling becomes impaired in obesity (leptin resistance), Adiponectin that has anti-inflammatory and insulin-sensitizing properties; its levels decrease in obesity and Resistin which Promotes insulin resistance and inflammation. Under conditions of obesity, this tissue becomes hypertrophic and infiltrated with pro-inflammatory immune cells, namely M1 macrophages. This adaptation results in the secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and resistin [11]. These cytokines induce a low-grade systemic inflammation that is often referred to as "metaflammation" and leads to insulin receptor signaling degradation in adipose tissue, liver, and skeletal muscle by activation of stress-related signaling cascades such as JNK and NF-κB.

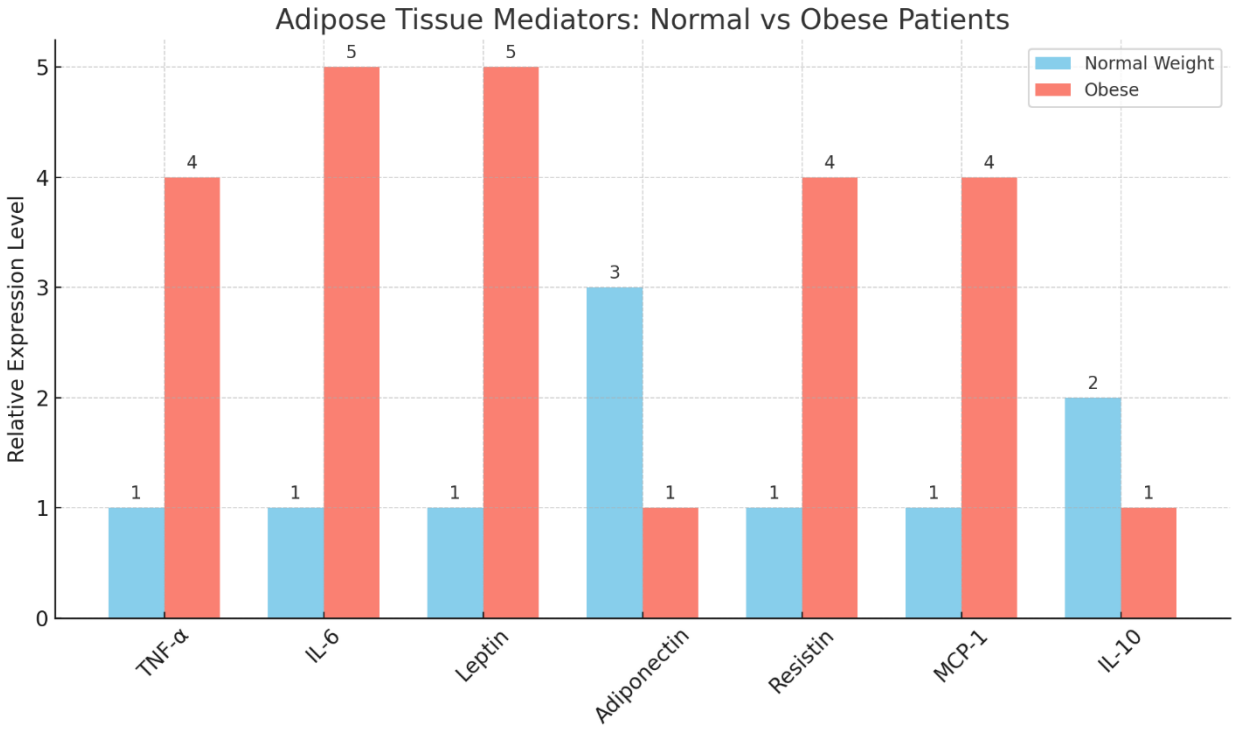

Figure 3: a bar chart comparing key inflammatory mediators, adipokines, and cytokines released from adipose tissue in normal-weight versus obese individuals.

Apart from evoking inflammation, obese adipose tissue releases an overabundance of free fatty acids (FFAs), triggering lipotoxicity in non-adipose organs like the liver and pancreas. This results in increased hepatic glucose production, beta-cell impairment, and dyslipidemia—the key components of metabolic syndrome [12]. Moreover, obesity demonstrates a close association with increased renin-angiotensin-aldosterone system (RAAS) activity, oxidative stress, and sympathetic nervous system stimulation, all of which contribute to the pathogenesis of hypertension [13].

The pathogenesis of obesity is multifactorial: Dietary Patterns: Excessive calorie-dense, nutrient-low intake of foods (e.g., processed foods, sweetened beverages) is the leading cause of excess energy intake.Physical Inactivity: Work and leisure screen time influences sedentary behavior and decreases total energy expenditure. Genetic Predisposition: Genetic influences on appetite regulation, fat distribution, and metabolic rate. Hormonal Dysregulation: Pathological conditions such as hypothyroidism or polycystic ovary syndrome (PCOS) result in retention of fat. Medication Effects: Some pharmacologic agents, including corticosteroids, antipsychotics, and antidepressants, have been reported to induce weight gain. Psychological Factors: Emotional food intake and stress are established causes of heightened caloric intake and fat accumulation.

Clinically, obesity is defined by body mass index (BMI), with ≥30 kg/m² being utilized to define obesity. However, BMI does not distinguish fat distribution, and therefore other measures such as waist circumference and waist-to-hip ratio have been employed, both of which are stronger predictors of metabolic and cardiovascular risk. Waist circumference >102 cm in men and >88 cm in women defines increased cardiometabolic risk.

The metabolic effects of obesity extend far beyond metabolic syndrome. Obesity imparts heightened risk for: Type 2 diabetes mellitus, Cardiovascular disease (e.g., coronary artery disease, stroke), Hypertension, Non-alcoholic fatty liver disease (NAFLD), Certain cancers (e.g., breast, colorectal, endometrial), Gallbladder disease and osteoarthritis, Sleep apnea and other respiratory abnormalities.

Because of the systemic nature of obesity-induced metabolic impairment, its prevention and treatment are critical to retarding the global rising tide of metabolic syndrome. Interventions include lifestyle modifications: dietary change (e.g., DASH or Mediterranean diets), more physical activity (≥150 minutes/week), and behavioral modification programs remain the cornerstone.

Pharmacotherapy: Anti-obesity medications are utilized in patients with BMI ≥30 or ≥27 with comorbidities of obesity.

Surgical Treatment: Bariatric surgery (e.g., sleeve gastrectomy, gastric bypass) achieves long-term weight loss and remission of metabolic abnormality in selected patients [13].

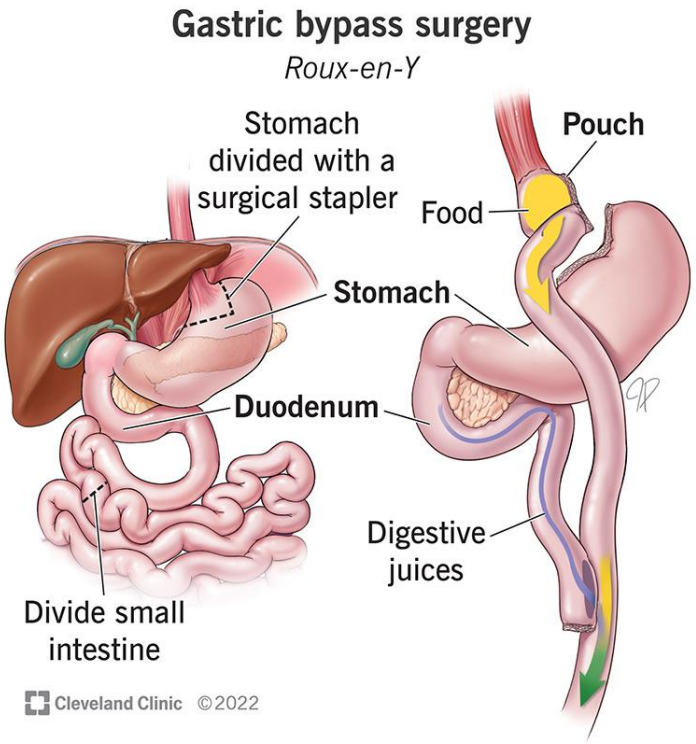

Figure 4: Gastric bypass surgery for treatment of obesity.

In conclusion, obesity is not merely a comorbidity of metabolic syndrome but a central etiological driver. The pathological changes associated with excess visceral adiposity disrupt metabolic, hormonal, and cardiovascular homeostasis. Recognizing obesity as a modifiable determinant of metabolic syndrome offers a targeted opportunity for prevention and early intervention, ultimately reducing the burden of chronic disease.

T2DM as a Causative Factor in Metabolic Syndrome

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease that is marked by insulin resistance, impaired secretion of insulin, and relative hyperglycemia. It is the most common type of diabetes globally and is both a component and a causative factor of metabolic syndrome (MetS). Metabolic syndrome is a cluster of related risk factors—central obesity, dyslipidemia, hypertension, and hyperglycemia—which collectively enhance cardiovascular risk and type 2 diabetes risk. T2DM therefore has a dual role: both as a result of metabolic derangement and as a disease which further accelerates the metabolic derangements of MetS. [14]

The pathophysiology of T2DM rests on peripheral insulin resistance, particularly in muscle and fat tissues, and impaired insulin secretion by pancreatic β-cells. This results in lifetime hyperglycemia with systemic damage to blood vessels, nerves, and organs. Insulin resistance antedates the clinical development of diabetes and is responsible for the clustering of the metabolic syndrome components. Hyperinsulinemia as a compensation for insulin resistance is involved in the pathogenesis of hypertension (through sodium retention and sympathetic nervous system activation), atherogenic dyslipidemia (hypertriglyceridemia, low HDL cholesterol), and prothrombotic conditions—major components of the metabolic syndrome phenotype [6,15].

T2DM has an insidious onset, and many patients are asymptomatic until complications develop. When symptomatic, it may present with polyuria, polydipsia, nocturia, and lethargy. Unlike type 1 diabetes, which typically occurs in lean individuals and as ketoacidosis, T2DM is commonly associated with overweight and obesity. Various risk factors predispose to T2DM and are physical inactivity, obesity (particularly central), hypertension, dyslipidemia, polycystic ovary syndrome, and gestational diabetes.

Hyperglycemia, the defining feature of diabetes, is the cause of microvascular injury in the guise of diabetic nephropathy, retinopathy, and neuropathy, while insulin resistance, more directly linked to visceral adiposity, is at the root of macrovascular disease. Notably, individuals with T2DM have a 2- to 4-fold risk of cardiovascular disease and stroke compared to non-diabetic individuals. This relationship is bidirectional and synergistic: metabolic syndrome increases the risk for T2DM, and chronic T2DM exacerbates other features of the syndrome, establishing a metabolic vicious circle of dysfunction. [16]

Diagnosis of T2DM is established by one of the following: fasting plasma glucose ≥126 mg/dL, 2-hour plasma glucose ≥200 mg/dL during an OGTT, HbA1c ≥6.5%, or random plasma glucose ≥200 mg/dL with symptoms [17]. Once diagnosed, early intensive therapy is required to avert both microvascular and macrovascular complications.

Lifestyle modification—including medical nutrition therapy, physical activity, and smoking cessation—is the cornerstone of management. Pharmacologic treatment, including metformin, GLP-1 receptor agonists, and SGLT2 inhibitors, is typically added to augment glycemia control

and lower cardiovascular risk [18].

In addition, T2DM indirectly contributes to the MetS burden through its systemic complications. Chronic hyperglycemia and glycation end products amplify endothelial dysfunction, oxidative stress, and low-grade inflammation. These alterations further raise the vulnerability to atherosclerosis and cardiovascular disease, incorporating strength to the significance of T2DM as a key driver in the metabolic syndrome continuum [19]. Lastly, T2DM is not just a consequence of Metabolic Syndrome but also a powerful amplifier of its pathophysiological processes. Its presence signifies advanced metabolic dysfunction and warrants vigorous control of risk factors. As obesity and sedentariness levels rise worldwide, the confluence of T2DM and MetS represents a growing menace to public health that demands concerted prevention and intervention strategies.

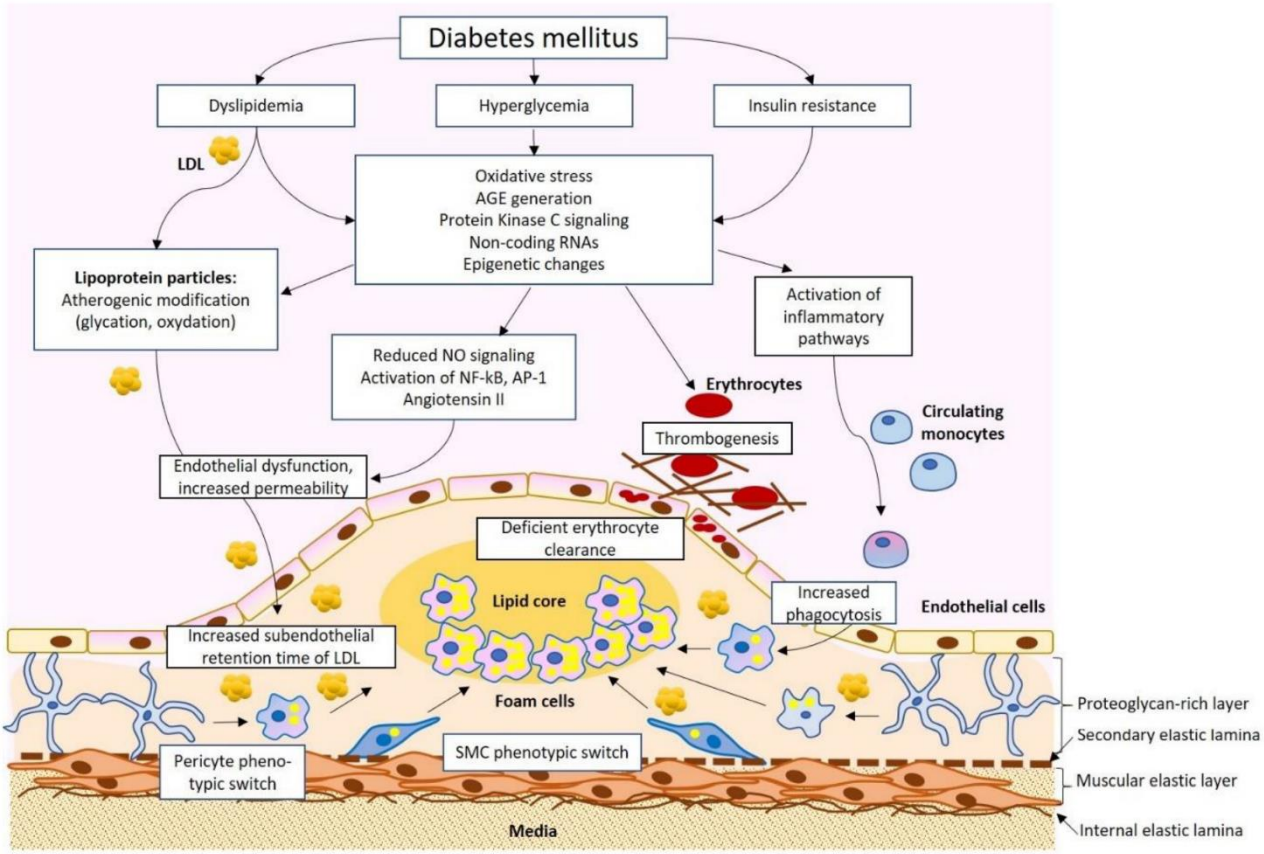

Figure 5: how type 2 diabetes (T2DM) leads to endothelial dysfunction and promotes atherosclerosis

Dyslipidemia and its role in Metabolic Syndrome

Dyslipidemia is an abnormal blood level of lipids that comprises high low-density lipoprotein cholesterol (LDL-C), high triglycerides (TG), and low high-density lipoprotein cholesterol (HDL-

C). Dyslipidemia is a key metabolic derangement in the patient with metabolic syndrome (MetS). Atherogenic dyslipidemia, the lipid triad characteristic of MetS, consists of high triglycerides, low HDL-C, and predominance of small, dense LDL particles. This constellation of lipid disorders has a direct contribution to atherosclerotic cardiovascular disease (ASCVD), which is the primary clinical manifestation associated with metabolic syndrome. [20]

The mechanistic foundations of dyslipidemia within the scenario of Metabolic Syndrome (MetS) are essentially due to insulin resistance. In the setting of insulin resistance, the adipose tissue manifests metabolic defectiveness, augmenting lipolysis and promoting the liberation of free fatty acids (FFAs) into the bloodstream. The liver, overwhelmed by the excess FFAs, escalates the production of triglyceride-enriched very low-density lipoproteins (VLDL), subsequently causing the hyperproduction of small, dense LDL particles and the lowering of HDL-C levels. [20]

This lipid profile has high pro-inflammatory and atherogenic activity, thereby promoting plaque development and vascular damage. [20]
A series of lifestyle and genetic risk factors enhance this metabolic derangement. Abdominal obesity, physical inactivity, high intake of saturated and trans fatty acids, and high-glycemic-load diets are all strongly associated with the development of dyslipidemia. In addition, monogenic disorders such as familial hypercholesterolemia or familial combined hyperlipidemia may be present in some individuals, putting them at risk for both MetS and premature ASCVD. [21]

Clinically, dyslipidemia is diagnosed with fasting lipid panels and risk-stratified based on cardiovascular risk. In patients with established ASCVD, the goal is ≥50% reduction in LDL-C and an absolute LDL-C level of <70 mg/dL. In primary prevention, risk-based algorithms (e.g., ASCVD risk score) guide the initiation of lipid-lowering therapy. In patients with triglycerides ≥500 mg/dL, there is a need for urgent intervention to prevent acute pancreatitis, in addition to reducing cardiovascular risk. [22]

Management of dyslipidemia rests on both pharmacologic and lifestyle regimens. The initial treatment is dietary change—namely, reduced saturated fat and refined carbohydrate intake—combined with regular aerobic exercise, weight reduction, and smoking cessation. At the pharmacologic level, the statins

(HMG-CoA reductase inhibitors) are the cornerstone of treatment, decreasing LDL-C levels by up to 50% and significantly lowering cardiovascular event rates in high-risk populations. [22]

For statin-intolerant or patients who are not meeting lipid targets, ezetimibe or PCSK9 inhibitors (i.e., evolocumab, alirocumab) may be used. Omega-3 fatty acids and fibrates are particularly useful in patients with severe hypertriglyceridemia. [23,24]. Novel drugs such as inclisiran (small interfering RNA targeting PCSK9 synthesis), bempedoic acid (ATP-citrate lyase inhibitor), and new formulations of icosapent ethyl (EPA) have added to the therapeutic arsenal. These medications offer additional LDL or TG lowering in high-risk individuals, particularly those with statin intolerance or familial hyperlipidemias. [25] In metabolic syndrome, dyslipidemia does not occur in isolation. It interacts synergistically with insulin resistance, obesity, and hypertension and thereby facilitates endothelial dysfunction, inflammation, and atherogenesis. Lipid abnormalities in metabolic syndrome are more than biomarkers; they are pathogenic initiators. Hence, the detection and vigorous treatment of dyslipidemia in individuals with or at risk of developing metabolic syndrome at an early stage are crucial in preventing cardiovascular events and in promoting long-term health outcomes.

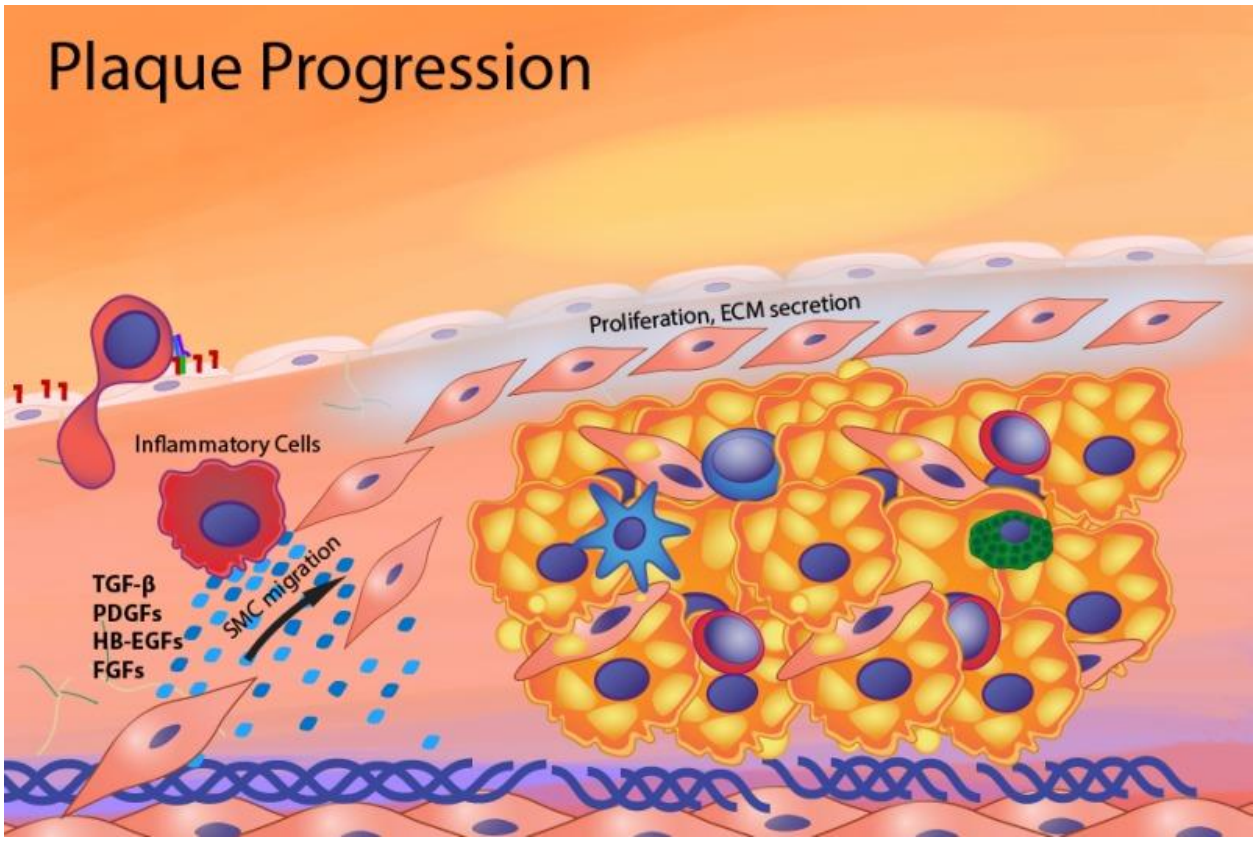

Figure 6: Plaque progression

Hypertentions and its role in Metabolic Syndrome

Hypertension (HTN), defined as persistent elevated systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥80 mmHg, is a serious and common manifestation of metabolic syndrome (MetS). It affects over one billion individuals globally and is a primary cause of cardiovascular disease (CVD), stroke, renal failure, and mortality. As a component of MetS, hypertension is both a diagnostic criterion and a promoter of pathophysiologic metabolic and vascular dysfunction. [26]

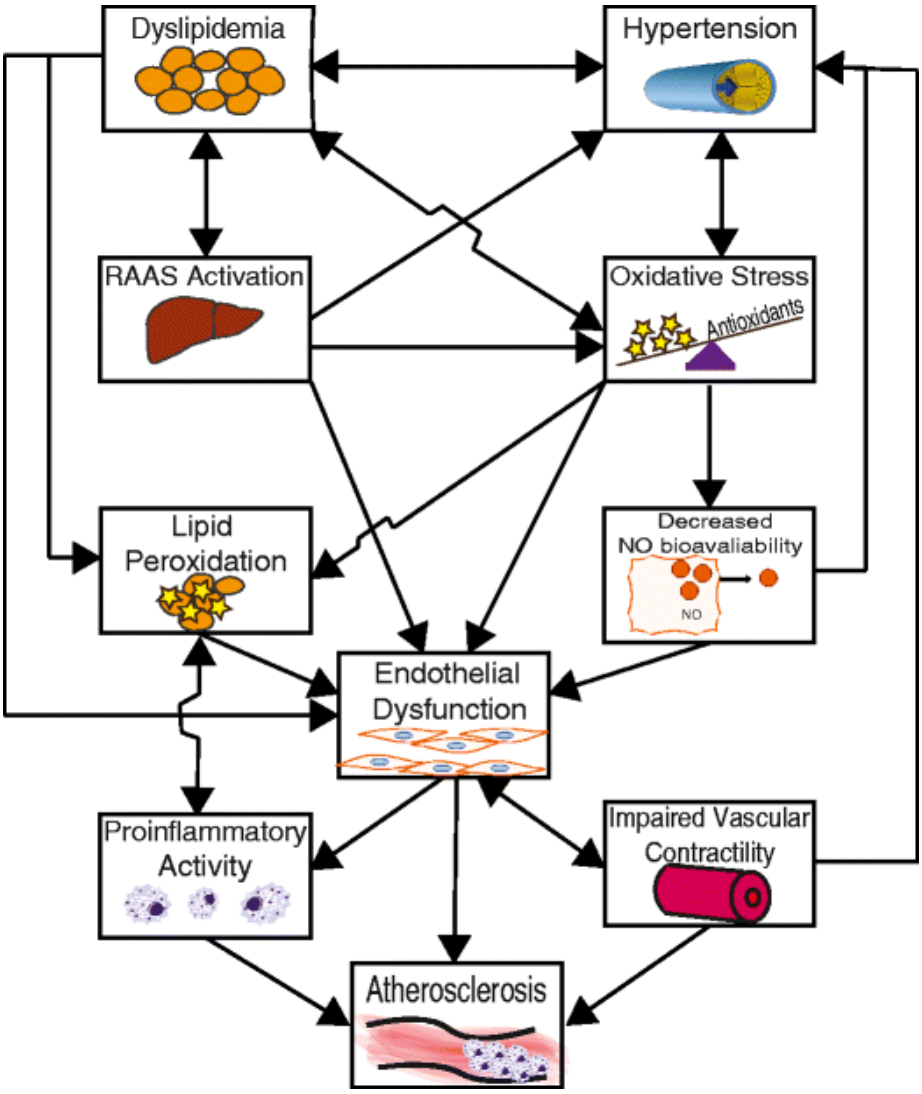

Figure 7: atherogenic effect of both hypertension and dyslipidemia

Pathophysiological Associations with Metabolic Syndrome

Pathophysiological mechanisms of hypertension are multifaceted, entail numerous factors, and are inextricably interconnected with insulin resistance, central obesity, inflammatory response, and neurohormonal mechanism dysregulation. Essential

hypertension, as the most prevalent form of cases, typically develops through a amalgamation of genetic predisposition and environmental factors, including high dietary salt consumption, obesity, and physical inactivity. One of the fundamental mechanisms is the stimulation of the renin–angiotensin–aldosterone system (RAAS), resulting in sodium retention, heightened vascular tone, and systemic arterial pressure elevation. [27].

In MetS, endothelial dysfunction and vascular stiffness compromise the delivery of insulin to skeletal muscle, promoting insulin resistance. Increased sympathetic nervous system activity also increases circulating free fatty acid levels, dyslipidemia, and central obesity. Chronic RAAS activation and systemic inflammation, in the meantime, increase oxidative stress, furthering vascular damage and insulin resistance. [8]

Abnormal adipose tissue blood flow, which leads to the release of pro-inflammatory adipokines (e.g., TNF-α, IL-6), also contributes to metabolic dysregulation. Conversely, the metabolic derangements of MetS exacerbate hypertension. Insulin resistance promotes renal sodium absorption, which expands plasma volume and elevates blood pressure. Central obesity is responsible for chronic inflammation, reduced nitric oxide availability, and increased vascular resistance. The overactivation of RAAS and sympathetic mechanisms, seen in obese and insulin-resistant conditions, sustains the hypertensive state. [28]

Hypertension as a MetS Prognostic and Diagnostic Marker ≥130/85 mmHg blood pressure or use of antihypertensive medication is one of five ATP III and IDF definitions for MetS. Its presence heightens the risk for target organ damage, i.e., left ventricular hypertrophy, vascular remodeling, and glomerular damage, all of which increase cardiovascular and renal complications of metabolic syndrome. [4] The prevalence of hypertension in MetS ranges from 50% to over 70%, differing by the population being studied. This association is strongest in obese patients, type 2 diabetics, and dyslipidemics—conditions that are often associated with elevated blood pressure and, together, synergistically heighten the risk for myocardial infarction, stroke, and heart failure. [26,29]

Management Strategies Ideal blood pressure management strategies are a

cornerstone in the management of the total cardiovascular risk in MetS patients. Both non-pharmacologic and pharmacologic approaches are recommended by guidelines:

Lifestyle Modifications: Reduction in weight (5–10% of body weight), reduced sodium intake, regular aerobic exercise (≥150 min/week), alcohol consumption in moderation, smoking cessation, and management of sleep apnea have all been shown to lower SBP by 5–20 mmHg and cardiovascular risk by up to 15%. [30]

Pharmacotherapy: Initial drugs of choice for hypertension include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), thiazide diuretics, and calcium channel blockers (CCBs). In Black patients or those with diabetic or chronic kidney disease, treatment is personalized to include drugs that are renal and cardiovascular protective. Combination therapy is usually needed to reach goal BP <130/80 mmHg in those with more than one risk factor. [31]

Hypertension must be realized not just as a result of metabolic syndrome but as an integral component that actively participates in its development and associated complications. It has a bidirectional relationship with insulin resistance, obesity, and dyslipidemia, leading to a proinflammatory and proatherogenic state. Early detection and aggressive treatment of elevated blood pressure in the context of metabolic syndrome are critical to reducing long-term cardiovascular and renal morbidity and mortality. As such, hypertension continues to be considered a significant clinical indicator and a target in the overall management of metabolic syndrome.

Conclusion

Conclusion

Metabolic syndrome is a multifactorial and progressive condition that arises from the synergistic interplay of four principal pathophysiological entities: central obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension. Each of these conditions independently promotes metabolic dysfunction, yet their convergence amplifies systemic inflammation, insulin resistance, vascular dysfunction, and cardiometabolic risk. Central obesity initiates a cascade of pro-inflammatory signaling and hormonal dysregulation; T2DM contributes chronic hyperglycemia and endothelial injury; dyslipidemia aggravates atherogenesis and lipid imbalance; and hypertension exerts mechanical and biochemical stress on the vasculature. Together, these conditions form the foundation of the metabolic syndrome phenotype and its clinical consequences. Understanding their interconnected roles is essential for the early identification, prevention, and management of metabolic syndrome to reduce long-term morbidity and mortality.

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2024/2025