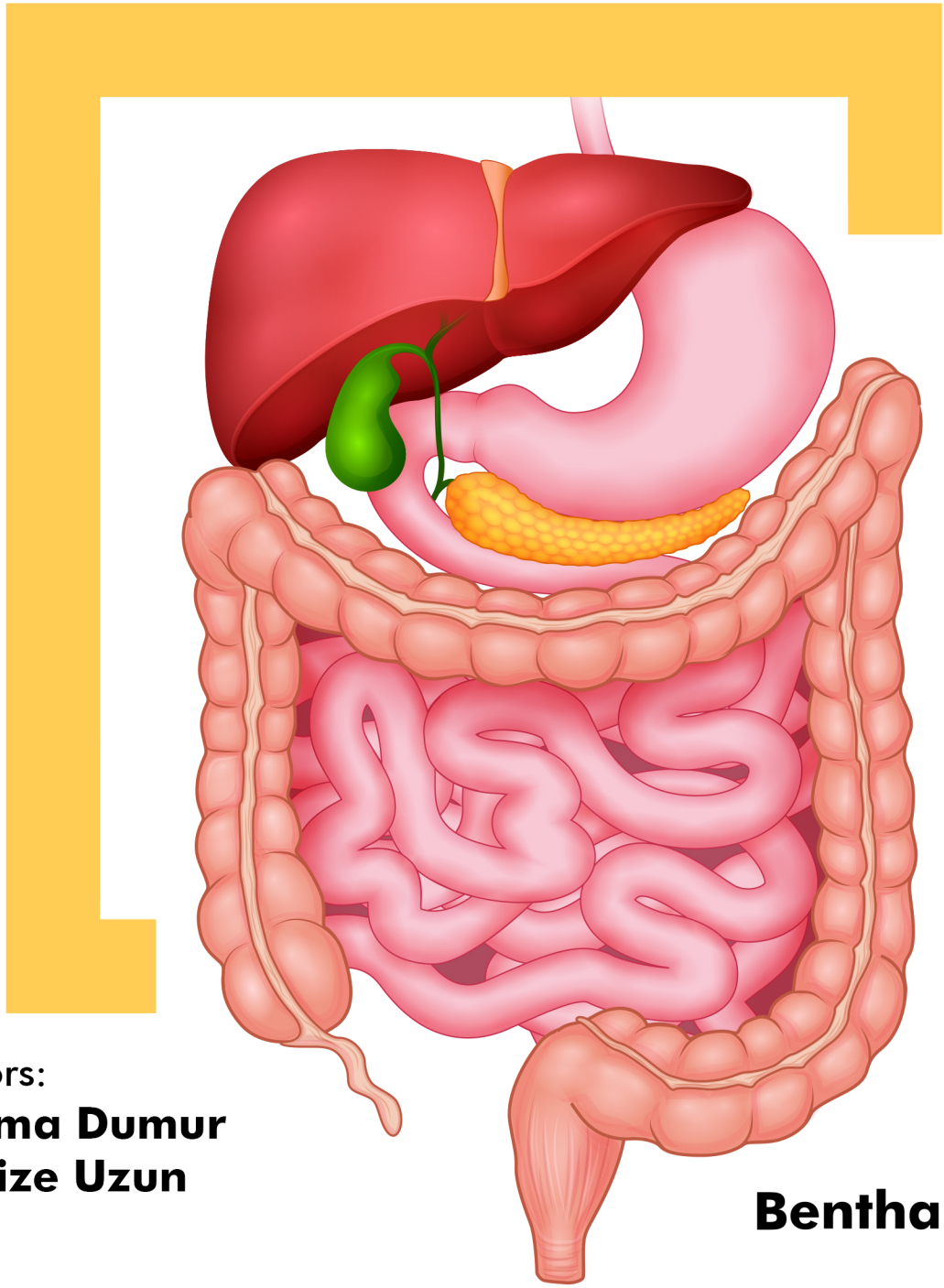
METABOLIC SYNDROME:

A COMPREHENSIVE UPDATE WITH NEW INSIGHTS



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Metabolic Syndrome: A Comprehensive Update with New Insights

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Metabolic Syndrome: A Comprehensive Update with New Insights

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CONTENTS

FOREWORD

Metabolic syndrome is an intricate condition characterized by a set of risk factors, including hyperglycemia, insulin resistance, hypertension, and obesity, which significantly elevate the risk of cardiovascular disease, stroke, and type 2 diabetes. Its growing prevalence worldwide poses a significant challenge to public health, necessitating a thorough understanding and innovative strategies for management. This book offers an in-depth exploration of metabolic syndrome, shielding a range of issues from functional changes and novel diagnostic methods to the interplay between metabolic syndrome and other health conditions like cancer, gastrointestinal disorders, and COVID-19. This complete text, featuring chapters on cutting-edge research and practical diagnosing and management strategies, is a valuable resource for healthcare professionals, researchers, and policymakers dedicated to addressing the multifaceted challenges of this syndrome.

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PREFACE

Nowadays, metabolic syndrome (MetS) is a major health problem worldwide. MetS is characterized by high blood pressure, obesity, insulin resistance, and diabetes mellitus. Of these factors, insulin resistance is the main cause of MetS. It is very important for patients with MetS to change their lifestyle. Exercise, changes in dietary habits, and weight loss are necessary in the treatment of patients with MetS. As discussed in the light of current information about MetS in Chapter 13, exercise plays a very crucial role in controlling insulin activity, reducing the risk of cardiovascular disease, and maintaining weight control and Chapter 11 (Neutrogenomic strategies in metabolic syndrome) provides an update on our current understanding of the impact of neutrogenomic strategies on MetS. In the last few decades, many studies on the genetic and epigenetic screening of MetS in various populations have been published in the literature. The role of genetic and epigenetic mechanisms is discussed in Chapter 9.

Another important aspect is that MetS has been associated with psychiatric disorders. In those diagnosed with major depressive disorder and bipolar disorder in adulthood, the disruption of biological rhythms (sleep, social activities, and eating habits) has been associated with key components of MetS. MetS and its components have also been linked to a higher risk of suicide. It is clear that the relationship between behavior and MetS is bidirectional and that each component can influence the other. Awareness of factors related to MetS can help identify high-risk individuals and implement disease prevention and control strategies as well as lifestyle modifications. It is discussed in Chapter 10 (The Interplay between Metabolic Syndrome and Behavior) that lifestyle modification can help improve MetS status and behavior.

If patients with MetS fail to be treated with lifestyle changes, they should use certain medications. First, insulin resistance needs to be treated. Metformin, thiazolidinediones or glitazones should be used to treat insulin resistance and diabetes mellitus. Secondly, dyslipidemia and obesity need to be treated with statins and fibrates. Treatment of components of the MetS, such as cardiovascular disease, hypertension, and polycystic ovary syndrome, is often associated with the treatment of insulin resistance, obesity, and dyslipidemia. The MetS should be treated early because delayed treatment is ineffective and very expensive. In MetS and related diseases, rationalized and evidence-based pharmacotherapeutic strategies are cornerstones in reducing polypharmacy. The pharmacology network approach and advanced bioinformatics tools related to epigenetics, genomics, transcriptomics, proteomics, and metabolomics are recognized as useful bench-top tools for the search for molecular preventive and therapeutic multiple targets. Molecular multi-target therapy is recognized as a new pharmacological strategy underpinning personalized and precision medicine. This in turn will reduce socioeconomic burdens and improve health-related quality of life. In this context, Chapter 12 discusses perspectives on personalized medicine using a pharmacology network approach.

MetS is a cluster leading to increased cardiovascular morbidity and mortality as well as increased predisposition to other non-communicable diseases such as certain cancers. Although individual components of MetS have been linked to cancer, studies demonstrating a direct link between MetS and cancer are limited. Understanding this link will shed light on the process of oncogenesis in patients with MetS. Chapter 15 addresses the need to summarize the associated factors and mechanisms linking these two pathologies and to identify potential targets for treatment in patients with cancer and MetS. Furthermore, Chapter 15 focuses on the biological and physiological changes and specific factors

associated with this process, including the insulin-like growth factor (IGF-1) pathway, estrogen signaling, visceral adiposity, hyperinsulinemia, hyperglycemia, aromatase activity, adipokinase production, angiogenesis, oxidative stress, DNA damage and pro-inflammatory cytokines, and their clinical implications in cancer therapy. A better understanding of this link will provide greater insight into the management of cancer patients by preventing MetS and related changes.

We would like to sincerely thank our team of authors from different countries who contributed excellent chapters that made the compilation of this book possible.

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CHAPTER 1

General Aspects of Metabolic Syndrome: An Update on Diagnostic Criteria, Pathophysiology, and Management

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Abstract: Metabolic syndrome (MetS) is generally defined as a cluster/complex of factors that are risk factors for cardiovascular disease (CVD) and type 2 diabetes (T2DM), including hyperglycemia, insulin resistance, hypertension, hypertriglyceridemia, decreased HDL-cholesterol concentration and central obesity. MetS is a health problem whose prevalence is increasing worldwide and negatively affects people's lives. Although MetS is essentially insulin resistance (IR), is not considered a disease, it consists of a combination of many risk factors that force the body metabolism to work abnormally. In addition to factors such as sedentary lifestyle and nutrition, hereditary factors are also important in the formation of MetS. The main components of MetS can be listed as hyperglycemia, hypertension, obesity and dyslipidemia. MetS has different definitions for different organizations. The basic components of these definitions are waist circumference, IR, high blood pressure and dyslipidemia (high triglyceride, low HDL cholesterol). The most recently agreed upon diagnostic criteria for MetS are increased waist circumference (society and country specific), high triglycerides, low HDL cholesterol, high blood pressure and high fasting blood glucose. For diagnosis, the presence of at least 3 of these parameters is required. When countries are examined in terms of the prevalence of MetS, different results are obtained from each country. The most important factor affecting the incidence of MetS in a country is the percentage of obesity and abdominal obesity in that country. Although obesity and physical activity factors have an impact on the incidence of MetS, it is an undeniable fact that genetic factors also have a significant impact. Lifestyle changes are at the core of MetS treatment. People with this syndrome need to change their diet, increase their physical activity and lose weight. Determining MetS risk levels and predisposing risk factors, determining whether they meet diagnostic criteria, and raising awareness through education and consultancy activities will be effective in combating the prevalence of MetS and cardiovascular risk factors.

Keywords: Diagnostic criteria, Metabolic syndrome, Management, Pathophysiology.

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Hafize Uzun & Seyma Dumur (Eds.)

INTRODUCTION

Metabolic syndrome (MetS) is generally defined as a cluster/complex of factors, such as hyperglycaemia, insulin resistance (IR), hypertension (HT), hypertriglyceridemia, decreased HDL-cholesterol concentration and central obesity, which are risk factors for cardiovascular disease (CVD) and type 2 diabetes (T2DM) [1]. The association of MetS risk factors with T2DM and CVD began to be discussed in the 1970s and was first defined by Reaven in 1988 as a syndrome of metabolic abnormalities and named Syndrome X [2]. For the first time in 1988, Reaven defined "Syndrome X" as this complex disease in which various metabolic abnormalities (HT, hyperglycaemia, and hyperuricemia) coexist [1, 2]. MetS is also described by different terms such as IR syndrome, polymetabolic syndrome, deadly quartet, and civilisation syndrome [3]. MetS has also been given various names such as metabolic cardiovascular syndrome, dysmetabolic syndrome, plurimetabolic syndrome, and cardiometabolic risk syndrome. MetS is a major cause of morbidity, affecting an increasing number of people worldwide [4 - 6]. It is estimated that 3.2 million people die each year worldwide due to diabetes-related complications, and in countries with a high incidence of diabetes, such as the Pacific and the Middle East, diabetes accounts for a quarter of all causes of death in adults aged 35-64 years. CVD and its complications, a major component of the MetS, are also on the rise and have a major impact on global health systems. The estimated incidence of diabetes is projected to double by 2025 and cardiovascular diseases are expected to increase in parallel [7].

The National Cholesterol Education Program Adult Treatment Panel Working Group (NCEP-ATP III) introduced a new definition in 2001 and added abdominal obesity and waist circumference to the definition [8]. Today, the definition of MetS is widely used by various authorities such as the World Health Organization (WHO), American Heart Association (AHA), International Diabetes Federation (IDF), National Heart, Lung and Blood Institute (NHLBI), NCEP-ATP III).

Prevalence of Metabolic Syndrome

The prevalence of MS is steadily increasing worldwide and has recently been identified as one of the major global public health problems. Although the prevalence of MetS varies according to different geographical and ethnic characteristics of societies (lifestyle), definitions used, population age and gender characteristics, it is considered a pandemic in the adult population in many countries. When countries are analysed in terms of the prevalence of MetS, different results are obtained from each country. The most important factor affecting the prevalence of MetS in a country is the percentage of obesity and

abdominal obesity in that country. Although obesity and physical activity have an effect on the incidence of MetS, it is an undeniable fact that genetic factors also have an important effect. Prevalence is reported to increase with body mass index (BMI) and age. According to the National Health and Nutrition Examination Survey (NHANES), the prevalence of MetS was 34-35% in the period 1999-2012, and this rate was found to be 50% over the age of 60 years [9]. About a quarter of adults in the US, India and Europe have MetS [10]. It has been reported that the risk of death is 2 times higher and the risk of major cardiovascular events is 3-5 times higher in individuals with MetS. It is also reported that the risk of developing T2DM is 2-5 times higher in these individuals and that more than 80% of the world's 230 million people with T2DM are at risk of CVD-related death [8 - 10]. There is also an increased risk of other preventable chronic diseases such as cancer, neurodegenerative diseases, non-alcoholic fatty liver disease, circulatory disorders, dyslipidemia, and infertility [9].

The prevalence of MetS increases with age and is difficult to prevent as the ageing population expands [11]. Studies indicate that by 2050, approximately 83.7 million people in the US will be over 65 years of age, double the 2012 population of 43.1 million [12]. Although there is no consensus on age and gender studies in MetS, in 2023 Rus *et al*. [13] reported that both genders displayed a higher risk of developing MetS related to age. The most affected age groups were aged between 60-69 years old and the 70-79-year-old group, categories where women had a higher risk of developing the disease. For the rest of the age categories, the incidence and prevalence continued to be higher among men [13].

The MetS global prevalence varied from 12.5% to 31.4% depending on the diagnostic criteria in the meta-analysis prevalence of MetS. Despite the publication of numerous primary studies on MetS in various populations across the globe, little effort has been dedicated to summarizing data on the epidemiology of MetS at the global level. In this study, we aimed to determine the prevalence rates of MetS and its individual components according to different diagnostic criteria and cutoffs and to compare these rates across geographic regions and socioeconomic levels [14].

Significance of Metabolic Syndrome

MS is an important public health problem seen in the adult population worldwide [15]. It is a risk factor for cardiovascular diseases and T2DM. MetS is associated with CVDs and increases the risk of cardiovascular morbidity 3-fold, mortality 2-fold, and type 2 diabetes 5-fold [16]. The onset of MetS in children is a result of the increase in the prevalence of obesity and is defined as a comorbid condition [17, 18]. It has been reported that obesity and overweight in young people play an

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.

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Hafize Uzun & Seyma Dumur (Eds.)

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.

Keywords: Gut dysbiosis, Hyperglycemia, Liver diseases, MetS, Oxidative stress, Translocation.

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 (Fig. **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, 11-13].

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].

CHAPTER 3

New Approach to the Diagnosis of Metabolic Syndrome in Children

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Abstract: Metabolic syndrome (MetS) is a disorder with central obesity, essential hypertension (HT), glucose tolerance disorder, diabetes mellitus (DM), dyslipidaemia, and an increased risk of cardiovascular disease (CVD), which occurs under the influence of genetic predisposition and is based on insulin resistance (IR). MetS is well defined in adults, although MetS is a complex multifactorial disease with a not entirely recognized definition in childhood. Nevertheless, MetS is described as the presence of obesity, IR, dyslipidaemia, and HT. The increase in the rate of MetS in children is at alarming levels. The first step in the prevention and treatment of MetS is to recommend and implement healthy lifestyle changes from an early age. Healthy lifestyle changes should include not only children but also all family members and should be targeted to be maintained throughout life. One method of preventing CVD in adulthood should be the care of children with MetS. It is necessary to carry out studies to prevent MetS and to measure the effect of these studies on the frequency of MetS. In terms of preventive medicine, children with a family history of T2DM and/or MetS burden, body obesity on physical examination, and IR findings such as acanthosis nigricans should be monitored more closely and early treatment should be initiated in cases with IR at-risk for T2DM. In line with the objectives, continuous training on the evaluation of childhood obesity is necessary for paediatricians and general practitioners.

Keywords: Children, Diabetes mellitus, Dyslipidaemia, Glucose tolerance disorder, Metabolic Syndrome, Obesity.

INTRODUCTION

Metabolic syndrome (MetS) is an important cause of morbidity and mortality with an increasing prevalence in the world, and while it was first known as an adult problem, it is now seen very frequently in childhood and adolescence and forms the basis of cardiovascular diseases which are the most common cause of death in adulthood. Genetic and environmental factors underlie MetS. There is a strong association between the physiopathology of MetS and insulin resistance (IR). In

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Hafize Uzun & Seyma Dumur (Eds.)

people with a genetic predisposition to IR, a sedentary lifestyle, unbalanced and excessive nutrition, and physical inactivity increase the risk of developing MetS [1 - 4].

MetS is a risk factor for type 2 diabetes (T2DM) and cardiovascular disease (CVD) in adults. In children, there are no studies directly describing the impact of MetS on these diseases, but autopsy studies in young people have shown that cardiovascular risk factors (obesity, high blood pressure (BP), elevated triglycerides (TG), and low high-density lipoprotein (HDL)) are associated with early coronary atherosclerosis [5, 6]. In recent years, the prevalence of MetS has increased in paediatric and adolescent age groups [7].

THE DEFINITION OF THE METABOLIC SYNDROME

In the following years, the diagnostic criteria for MetS, which has been referred to by various names such as "syndrome X", "insulin resistance syndrome", "metabolic cardiovascular syndrome", "*the deadly* quartet*",* "dysmetabolic syndrome" and "Reaven syndrome", were defined by the World Health Organization (WHO) in 1998 [8] and by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) in 2001 [9]. Finally, it was reorganised by "The International Diabetes Federation (IDF)" in 2005 [10]. Although MetS is a complex multifactorial disease with a not entirely recognized definition in childhood, MetS is described as the presence of obesity, IR, dyslipidaemia, and HT [11, 12].

In addition to the abnormal glucose balance found in the patient for the diagnosis of MetS according to WHO criteria, at least two of the criteria given in Table **1** must be present [13].

According to NCEP-ATP III criteria, 3 of 5 criteria are sufficient (Table **2**) [14].

While MetS definitions specific to children and adolescents are adaptations of those used in adults, IDF published criteria that can be used in children in 2007 (Table **3**) [15, 16].

Table 1. Definition of metabolic syndrome according to WHO criteria.

WHO Criteria	WHO Criteria Adjusted for Children
Hyperinsulinaemia or FBG ≥ 110 mg/dL or OGTT 2nd hour FBG > 200 mg/dL with two of the following;	Abnormal glucose balance. • fasting hyperinsulinaemia. • impaired fasting glucose. • impaired glucose tolerance.
Abdominal obesity (BMI>30kg/m^2, waist/hip ratio female > 0.8, male > 0.9).	BMI > 95th percentile level.

(Table 1) cont.....

WHO Criteria	WHO Criteria Adjusted for Children
Dyslipidaemia (TG ≥ 150 mg/dL or HDL ≤ 35 mg/dL (male), HDL ≤ 39 mg/dL (female).	TG>105 mg/dL (<10 years), TG>136 mg/dL (>10 years) or. • HDL<35 mg/dL or. • TC > 95th percentile level.
Blood pressure ≥ 130/85 mmHg or use of anti-hypertensive drug.	Systolic blood pressure > 95th percentile level.
Microalbumiuria (≥20 mcg/min, albumin/creatinine > 30 mg/g).	Two of three criteria in addition to abnormal glucose balance.

OGTT: oral glucose tolerance test; **FBG**: fasting blood glucose; **BMI**: body mass index; **TG**: triglyceride; **HDL**: high density lipoprotein; **TC**: total cholesterol.

Table 2. Definition of metabolic syndrome according to NCEP ATP III criteria.

NCEP ATP III Criteria	WHO Criteria Adjusted for Children
FBG ≥100-125 mg/dL.	FBG >100 mg/dL.
Abdominal obesity. >102 cm (male). >88 cm (female).	Waist circumference > 75th percentile level.
TG ≥ 150 mg/dL. HDL < 40 mg/dL (male). HDL < 50 mg/dL (female).	TG ≥ 100 mg/dL. 15-19 years. HDL < 45 mg/dL (male). HDL < 50 mg/dL (female).
Blood pressure ≥ 130/85 mmHg.	Blood pressure ≥ 90th percentile level.

FBG: fasting blood glucose; **TG**: triglyceride; **HDL**: high density lipoprotein.

Table 3. Pediatrics definitions of metabolic syndrome according to IDF criteria.

Variables	IDF Definition Age <10 Years	IDF Definition Ages 10-16 Years	Cook *et al.* [17]
Defining criteria	Cannot be diagnosed in the age group.	Central obesity plus at least 2 out of 4 criteria.	≥3 criteria.
Central obesity.	-	WC ≥90th percentile or adult cut-off if lower.	WC≥90th percentile.
Hypertension.	-	SBP ≥130 mmHg or DBP ≥85 mmHg or treatment with anti-hypertensive medication.	BP≥90th percentile.
Hypertriglyceridemia.	-	TG ≥150 mg/dL.	TG ≥110 mg/dL.
Low HDL.	-	HDL <40 mg/dL.	HDL ≤40 mg/dL.
Impaired glucose.	-	FPG ≥100 mg/dL or known T2DM.	FPG ≥110 mg/dL.

IDF: International Diabetes Federation; **WC:** waist circumference**; SBP:** systolic blood pressure**; FBG**: fasting blood glucose; **TG**: triglyceride; **HDL**: high density lipoprotein; **T2DM**: Type 2 Diabetes Mellitus.

CHAPTER 4

Association of Metabolic Syndrome with Gastrointestinal Disorders

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Abstract: Metabolic syndrome (MetS) is a collection of risk factors that should be evaluated for cardiovascular diseases, which are increasing in frequency worldwide. It is a prothrombotic and proinflammatory condition in which insulin resistance plays a central role and manifests itself with abdominal obesity, high triglyceride levels, atherogenic dyslipidemia, high blood pressure and high blood glucose. The intestinal-blood barrier, also known as the intestinal barrier, plays an important role in maintaining the homeostasis of the organism. The intestinal barrier ensures nutrient uptake through the lumen and at the same time restricts the passage of harmful substances. Increasing evidence suggests a relationship between intestinal barrier function and other body systems. Many studies have identified insulin resistance and metabolic syndrome as risk factors for reflux oesophagitis. Insulin resistance is also associated with metabolic syndrome and is known as a fundamental factor in its development. Abdominal obesity in particular is an independent risk factor for erosive esophagitis and increases the symptoms of gastroesophageal reflux. Subcutaneous and visceral adipose tissues, the main feature of MetS, secrete a variety of bioactive substances known as adipocytokines. Activation of inflammatory signaling pathways in the metabolic syndrome results in altered circulating and tissue levels of proinflammatory and anti-inflammatory cytokines, leading to systemic inflammation and tissue damage. The process of microbial dysbiosis, in which the ratio of beneficial to harmful bacteria is disrupted, is associated with many diseases such as inflammatory bowel disease, cancer, obesity, diabetes and cardiovascular disease. There is a relationship between the human gut microbiome and obesity.

Keywords: Abdominal obesity, Gastrointestinal disorders, Microbiota, Metabolic syndrome, Visceral fat.

INTRODUCTION

Metabolic syndrome (MetS) is generally described as a cluster/complex of factors that are risk factors for cardiovascular disease (CVD) and type 2 diabetes, including hyperglycemia, insulin resistance, hypertension, hypertriglyceridemia,

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Hafize Uzun & Seyma Dumur (Eds.)

decreased HDL-cholesterol concentration and central obesity [1]. MetS is also defined by different terms such as insulin resistance syndrome, syndrome X, polymetabolic syndrome, fatal quartet and civilization syndrome [2]. For the first time in 1988, Reaven drew attention to the frequent coexistence of various risk factors and stated that this association, which he called syndrome X, increased the risk of developing cardiovascular diseases (CVD) [3].

Synonyms of MetS

- Syndrome X.
- Insulin resistance syndrome.
- Obesity dyslipidemia syndrome.

Epidemiology of Metabolic Syndrome

When countries are analysed in terms of the prevalence of MetS, different results are obtained from each country. The most important factor affecting the incidence of metabolic syndrome in a country is the percentage of obesity and abdominal obesity in that country. Although obesity and physical activity have an effect on the incidence of MetS, it is an undeniable fact that genetic factors also have an important effect [4]. In the development of obesity, ready-to-eat food, appetitive diet, decrease in physical activity, age, gender and genetic factors are effective [5].

A steady increase in the prevalence of MetS in the US since 2011 has shown a rising trend in hyperglycemia, thus increasing the urgent need for measures to prevent diabetes. Today, factors such as fast pace of life, irregular eating habits and sedentary lifestyle facilitate the occurrence of MetS. However, it is possible to reduce the risk of MetS by making simple lifestyle changes such as healthy eating, regular exercise and stress management [6].

Diagnostic Criteria for Metabolic Syndrome

The definition of MetS is based on the current NCEP (ATP III)= National Cholesterol Education Program (Adult Treatment Panel III) criteria [7].

National Cholesterol Education Programme 3rd Adult Treatment Panel (NCEP ATP III) Description

The existence, effects and improvement of high blood cholesterol in adults are discussed in the report prepared by the NCEP on the criteria to be determined in the diagnosis of metabolic syndrome and called ATP III. In this report, MetS is diagnosed in the presence of hypertriglyceridemia, low HDL-C, HT, serum glucose ≥ 100 mg/dl and three of the criteria of abdominal obesity. Table **1** shows

the National Cholesterol Education Programme 3rd Adult Treatment Panel (NCEP ATP III) Definition for diagnosing MetS [7].

Table 1. NCEP ATP III diagnostic criteria for metabolic syndrome.

Measure	Presence of any Three or More of the Five Features Below:
Fasting blood glucose	>100 mg/dL (5.6 mmol/L).
Blood pressure	≥130/85 mmHg or hypertension.
Waist circumference	Women≥ 88 cm, Men ≥ 102 cm.
Triglyceride	≥ 150 m g/dL (1.7 mmol/L).
High density lipoprotein cholesterol (HDL-C)	Women≤ 50 mg/dL (1.29 mmol/L), Men ≤ 40 mg/dL (1.03 mmol/ L).
Others	Type 2 diabetes mellitus (T2DM).

Pathogenesis of Metabolic Syndrome

MetS is a chronic inflammatory condition resulting from the interaction of genetic and environmental factors. Several factors include insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, inherited gene susceptibility, hypertension, hypercoagulable state and chronic stress syndrome [8]. No single factor, such as genetic, infectious or environmental, has yet been described to explain the etiopathogenesis of all MetS components.

Although there is a polygenic predisposition, a sedentary lifestyle and a high-calorie diet aggravate the course of the syndrome. It is still debated whether the separate components of MetS represent separate pathologies or a common pathogenetic mechanism. There are several hypotheses for the underlying pathophysiology of MetS, the most common being fatty acid flux and insulin resistance. Visceral adiposity is also thought to be the main trigger of the abnormalities involved in MetS [9, 10].

Components of Metabolic Syndrome

The components of metabolic syndrome are analysed under 4 main headings. These are: insulin resistance, visceral obesity, atherogenic dyslipidaemia, and endothelial dysfunction. The first two of these are considered absolutely necessary for the diagnosis of metabolic syndrome. Most individuals with metabolic syndrome are obese, with a body mass index above 30 kg/m^2. It is believed that obesity provides excess fat to various organs or tissues, especially muscle and liver. Excess fat in tissues is defined as ectopic fat. Ectopic fat in muscle is closely associated with insulin resistance. In the liver, excess fatty acids can be completely burned or partially broken down into ketone bodies. The remaining

CHAPTER 5

Related Anatomy of Gastrointestinal, Endocrine, Urinary, Nervous System and Morphometric Evaluation in Metabolic Syndrome

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Abstract: Being overweight, hyperlipidemia, hypertension, type II diabetes mellitus(DM) or high blood sugar, and glucose intolerances are all clinical disorders collectively referred to as the metabolic syndrome (MetS). MetS affects multiple systems in the body, including cardiovascular, endocrine, urinary, nervous, and gastrointestinal systems. Atherosclerosis risk is increased by chronic inflammation and vascular endothelial dysfunction, which are both closely related to MetS. The risk of cardiovascular illnesses, the world's leading cause of mortality, is also increased by metabolic syndrome. Cancers such as the endometrium, breast, colon, liver, gallbladder, oesophageal, pancreas, kidney, and prostate, also chronic kidney disease, IBD (idiopathic inflammatory bowel disease), chronic gastritis, and dysplasia, are all caused by MetS enhanced by abdominal obesity, dyslipidemia, and poor glucose control. Besides, those with normal glucose metabolism are more likely to develop various peripheral nerve issues related to MetS. There is a connection between MetS and a number of cognitive deficiencies. Endocrine-disrupting substances (EDS) also have a detrimental effect on human health, which includes their influence on metabolic procedures. The gold standard for non-invasive pancreatic fat quantification is magnetic resonance spectroscopy (MRS). Anthropometry is quickly and accurately assessed on a wide scale by three-dimensional (3D) body surface scanners (BS). Indicators of waist circumference, sagittal diameter, and body weight are strongly correlated with areas of deep abdominal adipose tissue in both sexes. Each system listed above is examined in this chapter in relation to MetS, new diagnostic insights are presented, and pathogenesis and consequences that were not identified and treated as early on are summarized.

Keywords: Abdominal obesity, BMI, Metabolic syndrome, Neuropathy.

INTRODUCTION

Due to its high occurrence rate and the detrimental effects of lifestyle choices on overall quality of life, metabolic syndrome is an important public health issue. It

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Hafize Uzun & Seyma Dumur (Eds.)

is estimated that over 30% of adults and an increasing number of children suffer from this condition [1]. Various factors such as demographics (gender, age, living status, education, income), lifestyle, physical performance, mechanical factors, genetics, inflammation, environment (EDC- endocrine disrupting chemicals. *etc*.), microorganisms, adipokines, eating behaviors, and growth factors may contribute to the development of MetS. Three or more of the following symptoms are necessary for the diagnosis of metabolic syndrome; abdominal obesity, hyperglycemia, dyslipidemia, diabetes mellitus or prediabetes, and hypertension. An inflammatory and thrombotic condition brought on by abdominal obesity and insulin resistance raises the risk of cardiovascular pathologies and DM type II [1]. MetS has an impact on the neurological, gastrointestinal, endocrine, cardiovascular, and urinary systems in the body. There is a higher chance of developing hypertension, Diabetes mellitus (Type II), stroke, coronary artery disease, fatty liver disease, and osteoarthritis. Obesity is a problem that is spreading around the world and raises the risk of several gastrointestinal (GI) illnesses, including non-neoplastic ones such as gastro-oesophageal reflux disease (GORD), gallstones, and Barret's esophagus. Additionally, it raises the chance of neoplastic illnesses including gallbladder cancer, esophageal adenocarcinoma, and colorectal carcinoma. Metabolic syndrome is also associated with fatty pancreatic and liver diseases. Radiological imaging should be used for early diagnosis, treatment, and prevention of both neoplastic and non-neoplastic conditions and anatomical changes associated with metabolic syndrome. Magnetic Resonance Spectroscopy (MRS) is widely acknowledged as the gold standard for non-invasive quantification of pancreatic fat. In addition to being frequently brought on by metabolic syndrome, visceral obesity raises the risk of developing and worsening chronic kidney disease (CKD). CKD development could be linked to adipokines due to metabolic syndrome's effects on the prostate, detrusor enlargement may be a factor in poor bladder function. Gut hormones and afferent neurons play a significant part in communication between the brain and the gut, as well as in metabolism. The communication involves the hypothalamus, nucleus tractus solitarius (NTS), prefrontal cortex (PFC), ventral tegmental area (VTA), and nucleus accumbens (NAc). Recent research has demonstrated a link between sympathetic dysfunction and obesity, which affects the cardiovascular system and results in issues. There is a link between microvascular damage and high blood glucose levels, which can lead to neuropathy. Patients with MetS are more likely to get radiculopathy, entrapment neuropathy, and peripheral neuropathy even if their blood glucose levels are normal. Numerous factors, such as glucose-mediated endothelial damage, oxidative stress, and advanced glycation end products, can cause neuronal injury. There is a link between microvascular damage and high blood glucose levels, which can lead to neuropathy. There are several mechanisms for neuron damage, including oxidative stress, advanced

glycation end products, and damage to endothelial cells caused by glucose. When it comes to more severe brain and cognitive abnormalities, including those shown by DTI and MRI in different regions of both white and gray matter in people with bipolar disorder, obesity, and associated cardiovascular risk factors play a significant role. Predicting risk is crucial because GI illness and obesity are so common. Although the BMI is useful, other measurements, such as visceral fat and central (abdominal) obesity buildup, may be more accurate [2]. Researchers have demonstrated a relationship between waist circumference assessed by hand and the metabolic syndrome's characteristics and abdominal volume as evaluated by body surface scanner. BMI, sagittal diameter, and waist circumference are anthropometric measurements used in metabolic syndrome. The elements of the MetS were determined using the Adult Treatment Panel III of the National Cholesterol Education Program [3]. Participants were deemed to have metabolic syndrome if at least three of the following five symptoms were present [4]: abdominal obesity (waist circumference >102 cm in men or >88 cm in women), high triglycerides (≥1.7 mmol/L), low high-density lipoprotein (HDL) (<1.0 mmol/L in men or <1.3 mmol/L in women), high serum fructosamine (≥247 μmol/L or use of antidiabetic medication), and high blood pressure (≥160/90 mmHg or use of antihypertensive medication). At the Department of Clinical Chemistry at the VU University Medical Center (VUmc) in Amsterdam, fructosamine, HDL, and triglycerides were measured using an enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany). Following a typical expiration, abdominal obesity was measured to the nearest 0.1 cm at the midpoint between the lower rib edge and the iliac crest. A regular mercury sphygmomanometer (Omron HEM 706) was used to take blood pressure readings in the upper arm while the subject was seated.

Pathoanatomical Approach of the Gastrointestinal System in Metabolic Syndrome

Obesity is a growing problem globally. It increases the risk of various gastrointestinal (GI) diseases, including non-neoplastic conditions such as gastroesophageal reflux and Barrett's esophagus, as well as neoplastic conditions like esophageal adenocarcinoma, pancreatic carcinoma, gallbladder carcinoma and, CRC. In addition, obesity has been linked to poorer outcomes for GI cancer. BMI is frequently used to quantify fat, however, certain patterns, such as visceral fat and abdominal obesity, better indicate the risk of developing disease. Overweight individuals are more likely to develop cancer-related conditions such as Barrett's esophagus, colorectal adenoma, gallstones, pancreatic intraepithelial neoplasia, and colorectal serrated lesions. Carcinogens including adipokines, vascular endothelial growth factors, and insulin-like growth factors can be released by adipocytes at the cellular level. Additionally, in obese individuals, the

CHAPTER 6

Novel Metabolic Panel in Metabolic Syndrome

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Abstract: MetS is a multifaceted disease that embraces multiple disorders such as obesity, hyperlipidemia, hyperglycemia, insulin resistance, and hypertension. These disorders are characterized by specific metabolic aberrations presenting at different stages, which can be detected and monitored through a wide panel of serum biomarkers. Providing a minimally invasive technique thus can help greatly in the prediction, early screening and management of metabolic syndrome in high-risk communities and minimize its complications.

However, no sole biomarker is sensitive nor distinct for the diagnosis of metabolic syndrome, arousing the necessity of performing a panel that includes related biomarkers.

Metabolic biomarkers associated with metabolic syndrome are released primarily due to lipid accumulation and the dysregulated production of adipokines (ex. leptin, adiponectin) or oxidative stress brought on by obesity (ex. malondialdehyde, F-2 isoprostanes, paraoxonase, and oxidized LDL) or the associated inflammatory reaction (ex.IL-6, IL-10, tumor necrosis factor (TNFα), uric acid as well as heparanase).

Since obesity and insulin resistance are the cornerstones in metabolic syndrome pathogenesis, Leptin, an adipokine whose function is to reduce appetite and increase energy expenditure, and adiponectin represent striking biomarkers for metabolic syndrome.

In addition, the importance of uric acid, the product of purine metabolism, as a pro-oxidant inflammatory marker that contributes to metabolic syndrome pathogenesis has also been elucidated in multiple studies.

Recently, a newly discovered metabolic syndrome biomarker, ‘’Heparanase (HPA)” is closely related to the degradation of heparan sulfate proteoglycan (HSPG) and is associated with inflammatory responses as it could be secreted by various immune cells including macrophages.

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Hafize Uzun & Seyma Dumur (Eds.)

Since many studies have denoted the role of many biomarkers related to metabolic syndrome, this chapter will highlight the newly discovered ones that will help in the construction of a metabolic panel that could pave the way to precision medicine and help personalize the treatment given to metabolic syndrome patients.

Keywords: Asprosin, Adipokines, GGT, Leptin, Metabolic syndrome, Oxidative stress, Obesity, Subfatin, Visfatin.

INTRODUCTION

MetS is a progressive metabolic disease that includes multiple disorders as abdominal obesity, dyslipidemia, glucose intolerance, insulin resistance and high blood pressure causing a worldwide health problem [1]. Although its pathogenesis is very complex, the core of the disease involves a significant metabolic disturbance combined with imbalanced oxidant/ antioxidant activities resulting in cellular damage. Early diagnosis of metabolic syndrome helps prevent further progression of the disease and minimize its complications [2].

However, the design of a non-invasive new biomarker panel for the diagnosis of MetS will help relieve the burden caused by the disease on the patients and assist in targeting molecules involved in the pathogenesis of the disease.

Since many studies have denoted the role of many biomarkers related to MetS, this chapter will focus on the promising biomarkers that will aid in the early diagnosis and treatment of MetS I in high-risk communities.

MetS biomarkers

Metabolic biomarkers associated with MetS are released primarily due to lipid accumulation and the dysregulated production of adipokines (ex. leptin, adiponectin, ghrelin) or the oxidative stress brought on by obesity (ex. malondialdehyde, F-2 isoprostanes, paraoxonase and oxidized LDL) or the associated inflammatory reaction (ex.IL-6, tumor necrosis factor (TNFα), uric acid and heparanase) Fig. (**1**).

Adipokines

Since obesity and insulin resistance are the cornerstones in MetS pathogenesis, leptin, and adiponectin represent striking biomarkers for MetS.

Leptin is an adipokine whose function is to reduce appetite by affecting the satiety center, increase energy utilization, and improve insulin sensitivity [3]. High levels of leptin, which denote leptin resistance, are positively correlated with the risk of MetS [4, 5].

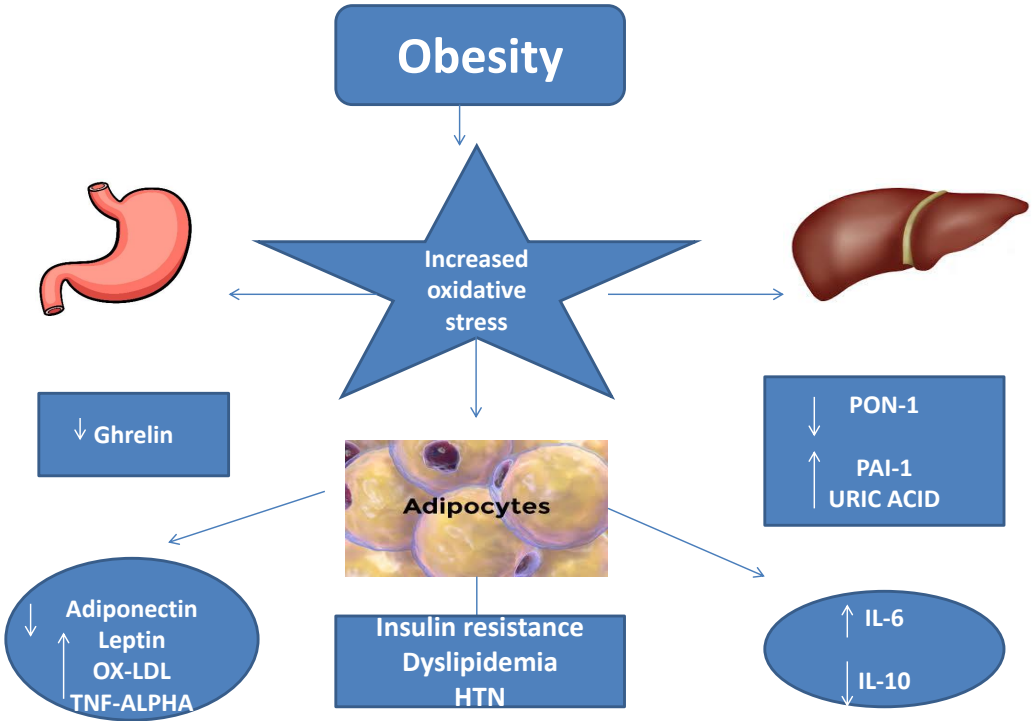

Fig. (1). Biomarkers panel of MetS (Srikanthan *et al*., 2016).

Adiponectin enhances glucose metabolism and adjusts energy expenditure; its level correlates indirectly with MetS risk [6]. However, the active form of adiponectin: High-molecular-weight (HMW) adiponectin, is more potent than total adiponectin for prognosticating the development of MetS [7].

In addition, a newly conducted prospective study demonstrated that the leptin to adiponectin (LA) ratio is supposed to be a recommended marker for predicting newly diagnosed cases of MetS [8].

METRNL (Meteorin-like protein) or Subfatin, is a recently detected adipokine secreted by the adipose tissue as well as by skeletal muscle reversing insulin resistance through two signaling transduction pathways either: the AMP-activated protein kinase (AMPK) pathway or the peroxisome proliferator-activated receptor δ (PPAR-δ) [9], having an anti-inflammatory effect by inhibiting the release of inflammatory mediators [10]. It induces the browning of white adipose tissue (BWT) during exercise and cold exposure increasing energy expenditure, and

CHAPTER 7

How Would Metabolic Syndrome Disturb the Normal Endothelial Function?

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Abstract: Metabolic syndrome (MetS) is an escalating epidemic that could influence more than one billion people worldwide. It is expressed as the presence of visceral obesity, hyperglycemia, dyslipidemia, and elevated blood pressure. MetS is a multifactorial disorder affecting all features of the community and extensively affects morbidity and mortality. Independently, the constituents of metabolic syndrome have the potential to influence the endothelium causing vascular dysfunction and interrupt vascular homeostasis. Since all components of MetS have unfavorable effects on the endothelium, endothelial dysfunction is more prevalent in MetS patients. Endothelial dysfunction could be a part of the pathogenesis of atherosclerosis in MetS. The nominated mechanisms of endothelial dysfunction linked with MetS are reduced NO production, upraised reactive oxygen species and high production of vasoconstrictors. All the elements of MetS especially the compromised endothelial function could participate in increasing the risks of cardiovascular disease, stroke, myocardial infarction and type 2 DM. Endothelial dysfunction, moreover, stimulates pro-inflammatory and oxidative stress pathways *via* endothelial mitochondrial reactive oxygen species (ROS) forcing vascular growth and remodeling. Because MetS is a multifactorial disorder, numerous signaling pathways manipulate the succeeding endothelial dysfunction. In the current review, we will discuss the incidence and pathogenesis of altered endothelial function in MetS. We will also discuss the impending effects of lifestyle measures and pharmacological interventions on endothelial function in patients with MetS .

Keywords: Atherosclerosis, Endothelial dysfunction, Insulin resistance, Metabolic syndrome, Reactive oxygen species (ROS) .

INTRODUCTION

Metabolic syndrome (MetS) is a series of metabolic changes concomitant with cardiovascular disease (CVD). Metabolic syndrome, also called insulin resis-

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Hafize Uzun & Seyma Dumur (Eds.)

tance syndrome, includes high blood glucose, central obesity, hypertension, high triglyceride levels, and low HDL-cholesterol. The main pathogenesis of MetS is insulin resistance (IR) with other factors that increase the risk of IR such as an unhealthy diet, sedentary lifestyle, and genetic and epigenetic factors. MetS includes a combination of major and modifiable CVD risk factors [1].

Vascular Endothelium and its Physiological Function

Vascular endothelium consists of a single cell layer, completely lining the blood vessels. It has a fundamental role in hemostasis, muscle tone control, angiogenesis, vascular repair, and transportation of important metabolites from blood to tissues and *vice versa* [2]. Endothelial dysfunction results in arterial stiffness and remodeling. Many studies have shown that endothelial dysfunction represents the cornerstone to the onset and progression of CVD. Moreover, endothelial dysfunction is a crucial therapeutic target for CVD [3]. Normally, the endothelium regulates the homeostasis of the blood vessels by modulation of vascular permeability, vasomotor tone, coagulation, inflammation, immunity, and cell growth. These factors are mediated through mainly nitric oxide (NO).

Formation and liberation of endothelial NO can be accelerated by many neuroendocrine mediators (*e.g*. bradykinin, acetylcholine, substance P), and by some mechanical factors (*e.g*. shear stress) [4]. After the release of NO, it activates the guanylate cyclase enzyme and the intracellular increase of 4 guanosine 3,5 monophosphate, causing relaxation of endothelial smooth muscle cells causing endothelium-dependant/ NO-dependent vasodilatation. The inorganic nitrates, such as sodium nitroprusside or nitroglycerin, can activate the same pathway as external NO donors resulting in endothelium-independent/NO-independent vasodilation.

NO inhibits NF-kB resulting in an anti-inflammatory effect. Furthermore, NO down-regulates the receptors of angiotensin II and endothelin I leading to an antithrombotic effect [5]. NO also plays an important role in the cardiac tissue. NO causes coronary vasodilation and regulates cardiac function regarding the ventricular systolic and diastolic properties. There are 3 main types of NO synthase; the cardiac cells contain at least one of the forms of NO synthase (NOS): nNOS, eNOS, and iNOS [6].

The sympathetic nervous endings express the nNOS, which is responsible for regulating catecholamine release at the cardiac level causing stimulation of beta-adrenergic receptors. While the cardiomyocytes contain eNOS causing inhibition of platelet aggregation and an inhibition of the positive inotropic action induced by catecholamine release.

iNOS expression is accelerated by proinflammatory cytokine. NO regulates the stretching of cardiac muscle fibers, so it increases diastolic cardiac function [7].

Disturbed Endothelial Function

Endothelial dysfunction is known as the decline of vasodilators, mainly NO, and the increase of vasoconstrictor substances. Arterial remodeling and stiffness, represent the connection between CVD risk factors and the initiation of atherosclerosis [8]. The reduction in the NO can be due to a decrease or inhibition in eNOS production, and degradation of NO by reactive oxygen species (ROS) [9].

Increased oxidative stress synthesis occurring with cardiovascular risk factors could lead to increase in the permeability of abnormal endothelial cells for LDL-cholesterol particles, followed by oxidation of the arterial intima. Subsequently, cellular growth and release of profibrotic factors, stimulate smooth muscle cell proliferation and excessive collagen production, followed by the formation of the atheroma plaque. This leads to arterial remodeling in addition to an increase in the intima-media thickness resulting in early arterial stiffening [9].

Cardiovascular risk factors such as smoking, aging, dyslipidemia, high blood pressure, high blood glucose, and a family history of atherosclerosis are all combined with endothelial dysfunction [8]. This leads to chronic inflammation associated with thrombosis and vasoconstriction leading to an elevation of the risk of CVD [10]. Currently, disrupted endothelial function has also been found to be associated with obesity, high C-reactive protein, and recurrent infections [11].

Insulin Resistance in METS and Endothelial Dysfunction

Most of the metabolic dysfunctions found in MetS patients result from insulin resistance. IR leads to an increase in insulin levels, which activates the sympathetic-adrenergic system and renin-angiotensin system leading to multiple metabolic and vascular alterations, such as endothelial dysfunction.

Insulin stimulates endothelial cells to produce NO leading to vasodilatation, which is decreased in the case of IR by decreased synthesis or response to NO. Additionally, IR increases endothelin-1-vasoconstrictor, which may lead to increased arterial pressure [12].

Insulin activates two main pathways: PI3 kinase pathway and MAP kinase pathway. The PI3 kinase pathway activation causes increased glucose consumption in muscles and an increase in NO synthesis in endothelial cells [13]. Moreover, the activation of MAP kinase pathway increases proinflammatory

CHAPTER 8

Molecular Mechanisms Underlying Metabolic Syndrome

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Abstract: Metabolic syndrome (MetS) has become a worldwide health problem, affecting children and adults globally. The prevalence of MetS is rising all over the world due to increasing obesity and sedentary lifestyles. MetS is caused by the interaction of both genetic and environmental factors.

MetS is characterized by complicated, multidimensional, and sophisticated molecular pathways that involve insulin resistance, inflammatory processes, and hereditary predispositions.

Here we are trying to focus on common molecular mechanisms that underlie MetS occurrence, aiming to offer a better understanding of their role in MetS and helping in developing prognostic/diagnostic tools and targeting novel therapeutic options.

Keyword: Cancer, Cardiovascular disease, Diagnostic tools, HDL, Insulin resistance, MetS.

INTRODUCTION

The Convergence of Genetic, Environmental Factors and Molecular Pathways in Metabolic Syndrome

Metabolic syndrome (MetS) is characterized by the occurrence of several cardiovascular risk factors as abnormal glucose metabolism, obesity, dyslipidemia, and hypertension [1]. The prevalence shows difference among ethnic groups, with the highest rates in Mexican American women. Other factors affecting the metabolic syndrome occurrence are age, smoking, alcohol, diet, and physical inactivity [2].

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The prevalence of MetS is rising worldwide due to increasing obesity and sedentary lifestyles [3]. About 12.5-31.4% population globally have MetS [3]. MetS is associated with an increased risk of occurrence of type 2 diabetes mellitus (T2DM), cardiovascular disease, and cancer [4]. Metabolic syndrome is the presence of at least three of the following five: abdominal obesity, increased blood pressure, hyperglycemia, raised serum triglycerides, and deceased serum high-density lipoprotein (HDL) [5].

Crosstalk among genetic predisposition, environmental factors, and molecular pathways regulating metabolism and inflammation, underlies the molecular basis for MetS. Insulin resistance has a very obvious role in disturbed glucose [6] and lipid metabolism [7]. Moreover, the chronic inflammatory process is supposed to be one of the molecular mechanisms for MetS. In adipose tissue, there is obesity-induced chronic inflammation [8] that is associated with disturbed composition and abnormal metabolic role of abdominal subcutaneous adipose tissue (aSAT) [9]. Chronic inflammation is aggravated by exposure to adipose tissue stresses that are associated with the activation of stress-responsive signaling pathways [10].

This chapter will shed light on molecular mechanisms that are considered as a basis for MetS development. It will show the crosstalk among insulin resistance, chronic inflammation, autophagy, adipose tissue dysfunction, disturbed adipokines secretion, mitochondrial dysfunction, oxidative stress, and epigenetics as micro-RNA in addition to the genetic and environmental factors.

Insulin Resistance

A pathophysiological condition known as insulin resistance occurs when normal insulin levels are unable to trigger the proper insulin response in target tissues such the liver, muscle, and adipose tissue. Insulin resistance is thought to have a major role in initiating and maintaining the detrimental consequences associated with metabolic syndrome.

Under normal circumstances, elevated glucose levels cause the pancreatic β cells to produce insulin and decrease the synthesis of glucagon. As a result, this prevents the liver from producing glucose and improves the absorption of glucose in the muscle, liver, and adipose tissues.

Insulin resistance is characterized by malfunction of the β cell, which leads to either a reduced initial secretion of insulin or no release of insulin in response to a glucose load [11]. Postprandial hyperglycemia is the outcome of this inadequate rapid insulin release. In the next phase, an increased insulin response takes place to counteract this excess glucose. Insulin's efficacy is reduced when high levels of

insulin are sustained over time because fewer insulin receptors are present [12, 13]. Indeed, this phenomenon has been demonstrated in genetically engineered mouse trials [14]. The blood levels of insulin in transgenic mice that have additional copies of the human insulin gene increase two to four times. Even with the extra insulin, the mice's blood sugar remains elevated. According to this study, a prolonged elevation in insulin levels causes a decrease in the number of insulin receptors, which in turn causes insulin resistance. Therefore, depending on the circumstances, lower glucose uptake and elevated blood sugar levels due to insulin resistance can result from hyperinsulinemia as well as be a cause of it.

The two α-subunits of the insulin receptor (IR) complex are in charge of binding insulin, whereas the other two β-subunits have built-in tyrosine kinase activity. Insulin binding causes IR to become autophosphorylated, which activates kinase activity. Tyrosine residues on downstream signaling substrates such as Src homology (Shc) and insulin receptor substrates (IRS-1, IRS-2) can be phosphorylated as a result of this activation. As a result, two important pathways are activated: the metabolic regulation-related phosphatidylinositol 3-kinase (PI3K) pathway and mitogen-activated protein kinase (MAPK) pathway, which is in charge of both mitogenesis and growth. These pathways promote cellular development and differentiation, as well as metabolic activities involving glucose and lipids [15].

Mutations in the genes encoding the insulin receptor (IR) and its downstream components can result in impaired insulin signaling, suggesting a genetic foundation for insulin resistance. A family with a known autosomal dominant deficiency in the Akt2 gene, a crucial protein in the insulin receptor signaling pathway, leading to severe insulin resistance, serves as an instructive example [16]. Even though they are not fat, the affected members of this family have significant insulin resistance and frequently have diabetes early in life.

The subtypes of the IRS family of signaling molecules appear to have distinct functions in modulating the activities of insulin in different tissues. For example, IRS-1 is mostly involved in skeletal muscle function, whereas IRS-2 is predominantly involved in liver function. Knockout mice display skeletal muscle insulin resistance due to mutations in IRS-1 [17], hepatic insulin resistance, and failure of β-cell secretion [10] due to mutations in IRS-2 [18] (Fig. **1**).

In instances of insulin resistance, defective tyrosine phosphorylation of the insulin receptor (IR) and IRS-1 is observed, accompanied by increased inhibitory serine phosphorylation (pS) and a significant reduction in IRS-1 protein levels compared to those in normal subjects. The heightened serine phosphorylation of IRS-1 may be linked to the enhanced activation of the mTOR-p70S6 pathway. Notably,

CHAPTER 9

Modulation of Genotype-Phenotype Associations in Metabolic Syndrome

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Abstract: This chapter provides background information on the genotype-phenotype associations of MetS by highlighting the importance of genetic concepts in modulating MetS. To date, many reports on genetic and epigenetic screening of MetS within a community have been published in the literature. We also mention several reports to perform community-based screening of MetS by identifying genetic and epigenetic variants. Later, these attempts will be discussed in detail in order to explain more about the modulation of MetS from the perspectives of phenotype-genotype associations. The relationship between MetS modulation and the personalized medicine approach is emphasized more by referring to the treatment and management strategies applied in a patient-specific manner.

Keywords: Genetic predisposition, Modulation, Metabolic syndrome, Management strategies, Personalized medicine.

INTRODUCTION

Our knowledge of classical genetics began with the discovery of the principle of inheritance pattern by Gregor Mendel [1]. Today, the inheritance pattern of more than 6000 monogenic disorders can be explained by Mendel's rules. However, monogenic disorders are mostly rare and the majority of human diseases cannot be explained by a single gene disorder. Most diseases, including common diseases in humans, show more complex inheritance patterns. These diseases are called complex, polygenic or multifactorial, and they are not raised from any specific genomic variant like monogenic disorders [2].

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Multifactorial diseases are caused by the combination of more than one genomic change, environmental factors, and lifestyle conditions. Many diseases fall into this group, including some congenital defects like cleft lip/palate, congenital heart defects, hydrocephalus, neural tube defects, and several common adult-onset diseases like Alzheimer's, asthma, Diabetes Mellitus, Parkinson's disease, Multiple Sclerosis, and Metabolic Syndrome [3]. Genetic variants that are associated with complex disorders have different features according to disease-related variants in monogenic disorders. Genetic variants in monogenic disorders have a strong effect on protein structure or expression, and these variants are rare variants, *e.g.* seen in 0.1% or less of the population (minor allele frequency (MAF) is <0.01%). In contrast to Mendelian disorders, in complex disorders, we identified common variants (MAF >0.1) that have a little effect on the protein. These variants are associated with an increased risk factor and cannot be the only reason for having a multifactorial disorder. Genetic conditions are only responsible for increased or decreased risk factors for a multifactorial disease phenotype. This situation explained by "genetic predisposition" means that a variant does not have the ability to develop a disease by itself, but with other factors such as age, gender, environmental factors, and lifestyle, the individual has a high risk of developing the variant-associated trait. People who have a genetic predisposition to a disease can delay or prevent the onset of the disease. Genetic factors have varying degrees of penetrance, some genes are highly penetrant and have a high-risk association with a particular complex disorder, while others have little effects and are associated with moderate or low-risk conditions [4].

Metabolic syndrome (MetS) is a multifactorial disorder that involves a cluster of metabolic diseases such as type II diabetes, cardiovascular diseases, and cancer. Age, gender, abdominal obesity, insulin resistance, high blood pressure, dyslipidaemia, diet, daily activity, and lifestyle conditions play a key role in MetS [5 - 7].

The aetiopathogenesis of MetS is complex, heterogeneous, and still lack full understanding, and it is controlled by interactions between genetic and environmental factors [8]. In addition to modifiable environmental factors (overeating and sedentary lifestyle), genetic susceptibility (heritability) plays an important role in the aetiology of MetS. Genetic risk factors have been associated with MetS by increasing the likelihood of phenotypes such as obesity, insulin resistance, high LDL levels, and hypertension, all of which are associated with MetS. To better understand the pathophysiology and pathogenesis of the disease, it is important to consider the central features of the metabolic syndrome (or describe how they relate to each other) [9] (Fig. **1**).

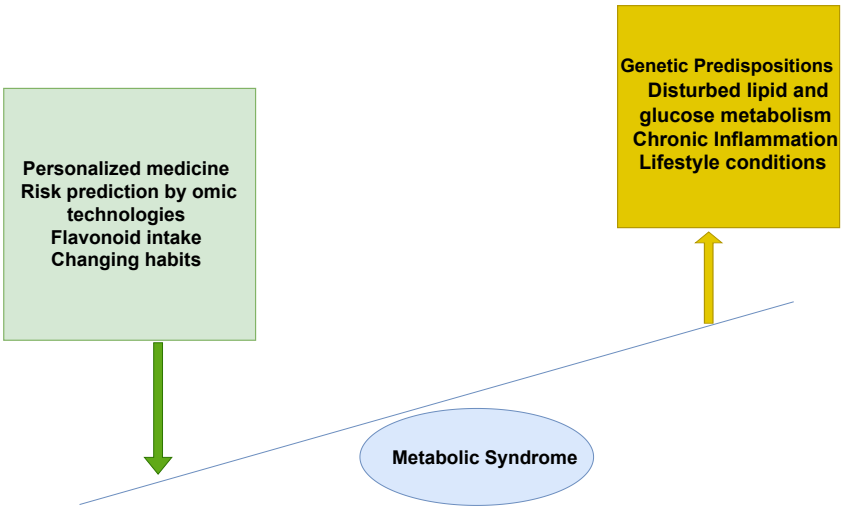

Fig. (1). Relationship between metabolic syndrome-related conditions and treatment or preventing strategies.

Association between Genetic Factors and Metabolic Syndrome

Within recent decades, the focus of much research has been the investigation of genetic factors behind the phenotypic manifestations of MetS. The pathogenic mechanisms of MetS are complex by referring to the interaction between genetic and environmental factors [10]. High caloric intake and a sedentary lifestyle are among the most important triggers of chronic inflammation and insulin resistance, which are key players in the progression of MetS [11]. Insulin resistance (IR) is associated with elevations in fasting plasma glucose by enhancing the sensitivity of visceral fat cells to lipolytic hormones, thereby increasing the flux of FFA to the liver and stimulating hepatic triglyceride and apoB synthesis [12]. According to its definition, it is a fasting plasma insulin above 75% of fasting plasma IR. IR and compensatory hyperinsulinemia are linked to several abnormalities in MetS [8]. These abnormalities include dysregulated insulin signal transduction *via* the PI3K/AKT pathway, associated with serine hyperphosphorylation of the insulin receptor substrate 2 (IRS2) signalling pathway, and reduced insulin-stimulated NO production with reduced vasodilatation and prothrombotic and proatherogenic effects in atherosclerotic arteries [13, 14].

While without the presence of insulin resistance, metabolic syndrome is not diagnosed even if all other parameters are presented, more conditions must be met by patients to be diagnosed with metabolic syndrome besides IR, and these are obesity, dyslipidaemia, hypertension, and microalbuminuria. These conditions are all the key symptoms of MetS, which are mostly associated with genetic inheritance. Genetic variations in the *ADIPOQ, APOE, NR3C1, GNB3* and

CHAPTER 10

The Interplay between Metabolic Syndrome and Behavior

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Abstract: Metabolic syndrome (MetS) indicates a cluster of symptoms that include abdominal obesity, dyslipidemia, hypertension, and hyperglycemia. Even though the etiology of MetS is unknown, it is thought to be multifaceted, with a complicated interaction between genetic predisposition and significant changes in lifestyle behavior, such as physical inactivity, high carbohydrate diets, and alcohol and cigarette use. The circadian system regulates many physiological and behavioral rhythms, which operate on 24-hour cycles. Circadian rhythm disturbances are also seen in various clinical disorders linked to adipose tissue functioning. In addition, night-shift employees who have their rest-activity cycles reversed are more likely to acquire MetS. Individuals with MetS experienced more seasonal variations in mood and behavior, with obesity being a substantial risk factor for metabolic syndrome. MetS has been linked to psychiatric illnesses. In those diagnosed with major depressive disorder and bipolar disorder in adulthood, disruption to biological rhythms (sleep, social activities, and eating habits) has been linked to essential components of MetS. MetS and its components were found to be connected to a higher risk of suicide. It is apparent that the relationship between behavior and MetS is bidirectional, and each component can affect the other. Awareness of MetS-related factors can aid in identifying high-risk individuals and implementing disease prevention and control strategies, as well as lifestyle adjustments. Lifestyle modification can help to improve the MetS condition and behavior.

Keywords: Behavior, MetS, Metabolic syndrome, Microbiota, Psychiatric illness, Stress.

INTRODUCTION

Metabolic syndrome (MetS), also known as pattern X or insulin resistance pattern, is a cluster of disorders that include hypertension, insulin resistance, central obesity, and atherogenic dyslipidemia. MetS, a major health concern in

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Hafize Uzun & Seyma Dumur (Eds.)

Westernized ultramodern countries, was formerly a major clinical practice difficulty [1].

The International Diabetes Federation (IDF) estimates that a quarter of the world's adult population has MetS, and the observed prevalence of MetS in the National Health and Nutrition Examination Survey (NHANES) was 5% among the normal weighted subjects, 22% among the over-weighted, and 60% among the obese [2].

The diagnostic criteria for MetS include a minimum of three out of five medical problems, including abdominal obesity, hypertension, higher fasting plasma glucose, increased serum triglycerides, and reduced levels of high-density lipoprotein (HDL) cholesterol [3]. The IDF considers the abdominal circumference and two other factors, and the World Health Organization (WHO) uses the waist/hip ratio, the presence of type 2 diabetes mellitus (DM) or insulin resistance, micro-albuminuria, hypertension, and triglycerides [4].

Comorbidity and multimorbidity are clinical challenges. Combinations of several diseases are common. Cardiovascular risk factors such as high blood pressure, obesity, atherogenic dyslipidemia, diabetes, alcohol and drug misuse, smoking, and inadequate physical exercise are associated with schizophrenia and major depressive disorders. Stress, psychodrama, hypercortisolemia, and immune function abnormalities may cause MetS and other mental illnesses [5].

Extensive research has been conducted to investigate the pathophysiological processes behind MetS. Findings consistently point to two prominent factors: the intake of fast food that is high in calories and poor in fiber, and insufficient levels of physical exercise. These factors have emerged as primary contributors to the development and progression of MetS [6, 7]. The examination of genetic predispositions has also been the subject of investigation, however, it has been shown that they exert only a marginal influence [8]. The primary factor contributing to this phenomenon was a shift in dietary patterns, as individuals transitioned from consuming mostly natural and unprocessed foods to adopting a diet characterized by elevated levels of fat, sugar, and salt [9, 10].

There is a growing body of research indicating that the disparities between our “Paleolithic genome” and our present-day “modern” food and lifestyle may play a significant part in the prevailing pandemics of obesity, hypertension, diabetes, atherosclerosis, and other manifestations of MetS [11]. It was found that self-discipline measures had a significant influence on physical activity levels among individuals diagnosed with diabetes or MetS, mostly *via* the enhancement of self-efficacy [12].

MetS alters cognitive function and emotional memory by enhancing hippocampal neuroinflammation [13]. The comorbidity and relation between MetS and psychiatric diseases have been reported [14 - 19]. According to reports, the co-occurrence of MetS and mental conditions such as anxiety, depression, insomnia, and cognitive dysfunction significantly contribute to medical expenses. Consequently, it is imperative to acknowledge and address these factors [20 - 23]. The results obtained from genome association studies have mostly concentrated on investigating the potential relationship between the management of circadian rhythms, maintenance of glucose balance, and the signaling of melatonin in the pancreas. These findings provide support for the hypothesis that disturbances in the peripheral circadian clocks might potentially contribute to metabolic dysregulation in human beings. Furthermore, alterations in cortisol release in relation to the timing of eating and fasting during circadian misalignment have the potential to induce insulin resistance. During periods of alertness, leptin levels are found to be lower, whereas during sleep, they are seen to be greater, Fig. (**1**) [24].

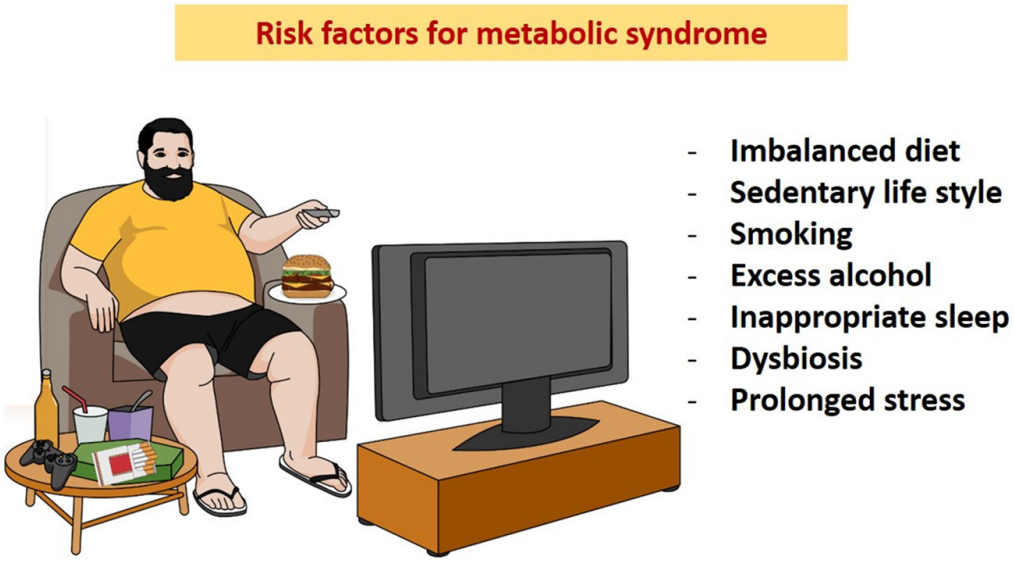

Fig. (1). Displaying the risk factors for metabolic syndrome.

A growing body of research supports the role of gut bacteria in human metabolism [25]. The gut microbiota (GM) and its effects on human health have garnered attention in recent years, particularly in the context of metabolic disorders (obesity, type 2 diabetes, dyslipidemia), which increase the risk of heart disease and deaths in industrialized nations. Diet is unquestionably one of the key elements influencing the microbiota [26 - 28].

CHAPTER 11

Neutrogenomic Strategies in Metabolic Syndrome

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Abstract: In the last 2 decades, the relation between nutrition and health has aroused great interest. In this chapter, the background information about the Complex gene-environment interactions that contribute to MetS will be introduced by highlighting several Neutrogenomic strategies. The role of nutrition is a significant modifiable element modulating the expression of many genes involved in metabolism. This chapter will present the current state of neutrogenomic research discussing the different gene-nutrient interactions in the context of metabolic disease, the molecular mechanisms underlying many of these gene-nutrient interactions, and the shift toward personalized nutrition. Novel modern technologies in Neutrogenomics regarding transcriptomics and metabolomics will be explained.

Keywords: Genomics, MetS, Metabolomics, Nutrients, Transcriptomics.

INTRODUCTION

Many studies have been carried out on nutrients' role in health and diseases, and the genes interacting with them. Neutrogenomics is a branch of science that involves scientific and biological approaches that describe how nutrition interacts with gene expression and function with the application of transcriptomics and metabolomics technologies. Neutrogenomics shows a recent way of working with nutrition and how food interferes with the genetic code [1].

According to disease ontology, MetS is a syndrome that is characterized by abdominal obesity, insulin resistance or diabetes, blood lipid disorders, inflammation, and an increased risk of developing cardiovascular disease [2].

MalaCards (Human disease database) integrated aliases for Abdominal Obesity as Metabolic Syndrome Quantitative Trait Locus 2 and described its inheritance as an autosomal dominant trait. According to the OMIM database, it is an autosomal

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Hafize Uzun & Seyma Dumur (Eds.)

dominant trait with abdominal obesity, hypertension, and elevated fasting glucose levels [2]. Many genes are associated with this trait as the AOMS1 gene, in relation to important pathways, such as IL-9 Signaling Pathways and PPARA Pathway [3].

GENES RELATED TO METS

Genome-wide association (GWA) and linkage analysis studies revealed the presence of a number of gene variants for the MetS. Some variants are located near genes involved in the lipid metabolism pathway. Other variants have pleiotropic effects on multiple MetS-related traits. Epigenetic changes play a significant role in MetS pathogenesis especially in the area of DNA methylation and histone modification, increasing the risk of acquiring the disease [4].

Candidate genes for regulating processes relevant to the MetS:

- *AOMS1* gene: Aliases for AOMS1 Gene are Abdominal Obesity-Metabolic Syndrome QTL1 and SYNX. Its locus is on the long arm of chromosome 3, region 2, band 7 (3q27), according to (GRCh38/hg38) 2019) [5]. This gene locus is related to six phenotypic traits in MetS and interestingly, it exhibited possible epistatic interaction with another QTL gene on chromosome 17 (17p12) that is strongly linked to plasma leptin levels, which have an important role in biological pathways of MetS [6].
- MTTP gene: Microsomal Triglyceride Transfer Protein, is a Protein Coding gene. Its locus is on the long arm of chromosome 4 (4q23), includes 59,917 bases starting at 99,564,081, and ends at 99,623,997bp from other according to Latest Assembly (GRCh38/hg38) 2019), (Fig. **1**).

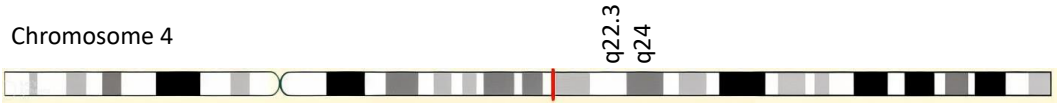

Fig. (1). MTTP gene chromosomal location **(www.GeneCards.org)**.

MTTP gene is involved in some pathways like lipoprotein assembly, remodeling and clearance. Also, it plays an important role in cholesterol biosynthesis. This gene annotation includes protein heterodimerization and lipid transporter activity [7 - 9].

- *MIR122* Gene: This gene is related to the microRNAs family that are short nucleotides not exceeding 24. They are non-coding RNAs that do not code for protein but are involved in post-transcriptional regulation of gene expression.

Its locus is on the long arm of chromosome 18 (18q21.31), (GRCh38/hg38) 2019) (Fig. **2**).

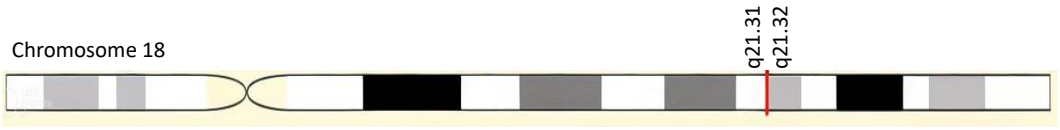

Fig. (2). *MIR-122* gene chromosomal location **(www.GeneCards.org)**.

miR-122 is a key regulator of cholesterol and fatty-acid metabolism in the adult liver and recent research revealed its role as a target in metabolic disease [10]. Therefore, it is a key target gene in MetS.

- *MIR33A* Gene: It is found on the long arm of chromosome 22, region 1, band 3 (22q13.2), according to (GRCh38/hg38) 2019) (Fig. **3**). It contributes to the regulation of cholesterol homeostasis [11].
- *MEG3* Gene: The maternally expressed 3 gene is one of the experimental evidence genes involved in metabolic syndrome. It regulates the expression of the HDAC7 gene through post-transcriptional regulation. In MetS, it up-regulates the expression level of HDAC7, protecting the endothelial cells [12].
- INS (Insulin), LEP (Leptin), HSD11B1(Hydroxysteroid 11-Beta Dehydrogenase 1), ADIPOQ Gene (Adiponectin, C1Q, and Collagen Domain Containing) and PPARG (Peroxisome Proliferator-Activated Receptor Gamma): They are protein-coding genes and involved in the MetS pathway interaction.

Fig. (3). *MIR-33A* gene chromosomal location **(www.GeneCards.org)**

PATHWAYS INVOLVED IN METS

According to the GeneCards database, there are several pathways involved in MetS as metabolism pathway, IL-9 Signaling Pathways, Nuclear receptors meta-pathway, *etc*. PPARA activates gene expression, AMP-activated protein kinase signaling, Nuclear receptors, FOXA2 and FOXA3 transcription factor networks, and PPAR signaling pathway [5] (Figs. **4**, **5**).

- STRING interaction network for Metabolism Pathway:

CHAPTER 12

Multitarget Pharmacotherapeutic Strategies for Metabolic Syndrome and Related Disorders: Perspectives on Personalized Medicine Using a Pharmacology Network Approach

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Abstract: One of the most common metabolic illnesses worldwide is the MetS. In the MetS and its related disorders, rationalized and evidence-based pharmacotherapeutic strategies are corner stones in the mitigation of polypharmacy. The pharmacology network approach and enhanced bioinformatics tools related to the epigenetic, genomic, transcriptomics, proteomic, and metabolomic levels are considered useful bench-side tools for the exploration of molecular preventive and therapeutic multitargets. Molecular multitarget therapy is regarded as a novel pharmacological strategy that forms the foundation of personalized and precision medicine. That will decrease the socioeconomic burden and will improve the health-related quality of life.

Keywords: Bioinformatic analysis, Gene Expression Omnibus (GEO) database, Hub genes, Insulin resistance, Metabolic syndrome, Mmolecular multi-target therapy, Next Generation Sequencing (NGS), Polypharmacy, Protein-Protein Interaction (PPI) network, Precision medicine, Personalized medicine, Pharmacology network, Receiver operating characteristic curve (ROC) analysis.

INTRODUCTION

One of the metabolic illnesses that are occurring at an alarming rate worldwide is the MetS; insulin resistance syndrome and X syndrome are two more names for this condition. MetS is a major global health issue with a high morbidity and mortality rate due to numerous severe comorbid disorders [1, 2]. In order to deliver effective preventative and therapeutic measures to improve patient outcomes, this significant socioeconomic burden urgently requires population-

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Hafize Uzun & Seyma Dumur (Eds.)

and system-based solutions, multitargeted pharmacotherapy, as well as the interdisciplinary collaboration of different health experts [1, 3].

METABOLIC SYNDROME AND RELATED DISORDERS

Metabolic syndrome is linked to chronic inflammation interfering with many of the body's regulatory systems. It does this by raising plasma-free fatty acids, causing insulin resistance, and upregulating inflammatory cytokines, chemokines, and mediators like adiponectin, leptin, and resistin [4, 5]. Different educational and academic organizations propose a range of diagnostic criteria for MetS, with considerable differences in the sensitivity of these criteria [6]. Obesity in the abdomen, hypertension, poor glucose metabolism, and atherogenic dyslipidaemia are the four criteria recommended by guidelines for the diagnosis of MetS [2, 7].

The multifactorial MetS was accompanied by a wide range of reciprocal disorders, including liver dysfunction, kidney dysfunction, cardiovascular events, obstructive sleep apnea, polycystic ovary syndrome, sympathetic stimulation, and hyperuricemia, in addition to type 2 diabetes mellitus (T2DM) and hypertension [7, 8]. All of these multifactor start chronic inflammatory pathways leading to diverse complications in the form of nephropathy, neuropathy, and retinopathy as examples [9 - 12].

Metabolic-associated fatty liver disease (MAFLD), an inflammatory liver disease characterized by more than 5% hepatic steatosis, has the potential to proceed to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. Patients with MFALD are at an increased risk of developing hepatocellular carcinoma (HCC), T2DM, cardiovascular disease, and colorectal and breast cancers [7, 13, 14]. MAFLD is different from non-alcoholic fatty liver disease (NAFLD). Any patient with MetS and hepatic steatosis (as was displayed in diagnostic imaging, elastography or histopathology) will be diagnosed with MAFLD regardless of alcohol consumption [14].

Obesity-related kidney damage and dysfunction are clearly associated with MetS. Inflammatory, hemodynamic, and metabolic difficulties and fat-induced physical compression activate the sympathetic nerve and renin-angiotensin-aldosterone system and cause glomerular hyperfiltration and nephron loss [15, 16]. Due to the suppression of nitric oxide and the subsequent induction of endothelial dysfunction, as well as an increase in insulin resistance, patients with hyperuricemia, defined as a serum uric acid level greater than 7 mg/dl (420 mol/l), are more likely to develop and progress through the various components of the MetS, such as hypertension, T2DM, fatty liver disease, and chronic kidney disease [17, 18]. Polycystic ovarian syndrome is one of the most prevalent endocrine problems in MetS female patients, and it has been extensively

connected to cardiovascular risks and insulin resistance, underlining the need for medical intervention [19, 20].

Heart failure with restricted ejection fraction or left ventricular dysfunction is one of the disorders associated with MetS. Obesity and insulin resistance promote inflammation and exacerbate coronary microcirculation, causing concentric left ventricular hypertrophy and stiffness [21 - 23]. Furthermore, sympathetic overstimulation and tachycardia are linked to MetS since inflammation and insulin resistance impair central modulation of sympathetic and parasympathetic activity, causing autonomic imbalance and tachycardia, a risk factor for cardiovascular disease [24, 25].

POLYPHARMACY APPROACH FOR METS AND RELATED DISORDERS

MetS cannot be treated with a single therapeutic agent due to its complex multifactorial pathogenesis, necessitating a multi-targeted approach for intensive management of all components of MetS in conjunction with initiating a healthy lifestyle modification consisting of diet, exercise, and behavioral therapy as the first therapeutic option in MetS [3, 26, 27]. MetS must be treated and prevented by encouraging healthy nutrition, physical activity, and good sleep hygiene [7, 28].

Polypharmacy, a multidrug regimen including at least five drugs being prescribed for MetS, involves anti-dyslipidemic agents, anti-diabetic and anti-obesity therapies, anti-hypertensive and heart failure drugs. The rate of polypharmacy is increasing and could elevate higher than 60% in diabetic elderly patients. The majority of patients use at least one anti-diabetic medication, a lipid-lowering medication, and at least one anti-hypertensive medication. Therefore, polypharmacy poses a big problem in the treatment of patients with MetS due to many adverse effects of drugs that could have central and peripheral effects and drug-drug interactions, which reduce the patient compliance and prescriptions especially with elderly [29, 30]. Peroxisome proliferator-activated receptor-γ (PPAR) agonist, one of the efficient antidiabetic medicines, is associated with edema, which limits its usage in MetS patients with T2DM and heart failure [31]. Furthermore, most anti-obesity drugs work centrally on the central nervous system to decrease the appetite and peripherally by modulating glucose and lipid metabolism, leading to central and peripheral adverse effects that could vary from minimal to severe adverse effects, lowering the patient's adherence. Rimonabant is one of the anti-obesity drugs, which was withdrawn due to its associated high depression and suicide rates [32 - 34].

CHAPTER 13

Role of Exercise in Metabolic Syndrome

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Abstract: Metabolic syndrome (MetS) is a primary and increasing public health problem as a result of worldwide urbanization, excessive energy intake, and increasing sedentary lifestyles. MetS is a combination of the interrelated risk factors of cardiovascular disease, diabetes and obesity. These factors are dysglycemia, dyslipidemia, elevated blood pressure, insulin resistance or type 2 diabetes, and low HDL levels. Clinical and epidemiological studies show that these factors are strongly associated with cardiovascular risk factors. The worldwide incidence of MetS varies, depending on the region, urban or rural situation, as well as the gender, age, race, and ethnicity of the population studied. Effective preventive approaches include weight loss, dietary habits with high content of industrialized foods, the use of appropriate pharmacological agents, and exercise to reduce specific risk factors of MetS. Many physicians treat each of the components of MetS separately. But instead, a solution should be found to address all these factors together. As discussed in this chapter, exercise plays a very crucial role in controlling insulin activity, reducing the risk of cardiovascular disease, and maintaining weight control. Various studies have proven that effective exercise provides positive results in treating MetS components. The aim of this chapter is to explain the effects of physical activity on MetS in light of current information about MetS.

Keywords: Exercise, Insulin resistance, Metabolic syndrome, Physical activity.

INTRODUCTION

According to the Metabolic Syndrome Working Group of the Turkish Society of Endocrinology and Metabolism, Metabolic Syndrome (MetS) is a lethal endocrinopathy accompanied by regular disorders such as abdominal obesity, glucose intolerance or diabetes, high blood pressure, and coronary artery disease, driven by insulin resistance [1]. MetS is a combination of the interrelated risk factors of cardiovascular disease and diabetes. These factors are dysglycemia, high blood pressure, low HDL levels, and obesity [2].

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The association of these factors has been known for years. Although its pathogenesis remains unclear, recent attention has focused on the possible impact of insulin resistance as an important factor, as well as on the establishment of diagnostic criteria. MetS is a condition in which physiological, biochemical, clinical and metabolic factors are linked to each other like a constellation and directly increases the risk of cardiovascular disease and type 2 diabetes and their associated mortality [1 - 4].

With the increase in obesity and sedentary lifestyle in the world, the prevalence of MetS will increase. In this respect, MetS is both a public health problem and a clinical problem. In the last ten years, different diagnostic criteria have been proposed by different organizations [5, 6]. Organizations such as the World Health Organization (WHO), the International Diabetes Federation (IDF), and the National Adult Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) have conducted research on MetS diagnostic criteria. As a result of the researches, the most known and accepted one for the diagnosis of MetS is the diagnostic criteria table performed by NCEP-ATP III. Qualification for the diagnosis of MetS in this diagnostic criteria table is the presence of three of the five criteria [7 - 9].

Although MetS can be observed in all ages, it is more common in older ages. Also, it is estimated that the incidence of MetS is more obvious, especially in women, and that this issue is related to abdominal obesity [10, 11]. According to the 2012 data of the Turkish Adult Heart Disease and Risk Factors Screening study related to the prevalence of MetS in Turkey, the prevalence of MetS in Turkish men is 45.1%, while it is 54.5% in Turkish women [12, 13]. Additionally, to investigate whether the distribution of “at risk” clusters of MetS components differed cross-culturally, a study of 34,821 individuals from 12 cohorts from 10 European countries and 1 US participant in the MARE (Metabolic syndrome and Arteries Research) Consortium found a prevalence of MetS of 24.3% (8468 subjects) (23.9% in men *vs* 24.6% in women, $p<0.001$) and an age-related increase in prevalence in all cohorts [14].

It is now known that a fructose-rich diet increases the risk of cardiovascular disease and leads to the development of pathological conditions such as MetS, which is caused by a physically inactive lifestyle and irregular or excessive nutrition. Fructose is found naturally in honey and fruits, and as a sweetener in industrial products [15]. Since liver tissue is the main tissue where fructose is metabolized, it is the tissue where the negative effects of high fructose diet are most intense [16].

Studies in the literature have adopted a high fructose diet in rats to create an experimental example of MetS. There are studies reporting the occurrence of MetS like problems such as fatty liver and glucose intolerance in rats depending on the proportion of fructose in these diets, how it is used and its duration [17 - 20].

The aim of this chapter is to explain the effects of physical activity on MetS in the light of current information about MetS, which is a combination of various diseases that disrupts the quality of life of individuals and even puts their lives in danger. The main goal of MetS treatment is to change lifestyle and diet habits while simultaneously improving physical activity.

METABOLIC SYNDROME AND EXERCISE

MetS is a complex disease with a high mortality risk, characterized by inflammation that starts with insulin resistance and is accompanied by abdominal obesity, glucose intolerance and/or diabetes mellitus, high blood pressure, dyslipidemia, hypertriglyceridemia and coronary artery disease [1, 2].

Pro-inflammatory cytokines associated with MetS can cause physical inactivation that becomes a cycle of chronic inflammation. Physical activity becomes psychologically and physically undesirable when inflammation is present. “Inflammation-based disease state”, which is revealed by using experimental animals, is in a size to support this hypothesis [21 - 25].

Calorie restriction diet and exercise studies are studies that trigger further improvement by leading to the activation of anti-inflammatory effects, improving biological and exercise ability. Although it has been observed that there are negative effects of overproduction, the regular operation of the skeletal muscle and the free radicals produced at a low limit activates the enzyme activities that prevent oxidative destruction and help to create power against oxidative stress by creating special adaptations [26, 27].

Studies revealing the link between physical inactivity and obesity indicate that there is a statistically negative correlation depending on body mass index, waist thickness and waist-hip balance parameters. These results reveal the necessity of maintaining a physically active lifestyle and reducing intra-abdominal fat in order to prevent the progression of the MetS [28].

Reducing fat mass may support raising adiponectin levels and enhancing the cytokine profile associated with MetS. The release and control of two cytokines, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) aid the normal maintenance effects of physical activity. The increase in the levels of the first

CHAPTER 14

Chronic Obstructive Pulmonary Disease and Metabolic Syndrome

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Abstract: Chronic obstructive pulmonary disease (COPD) is a clinical condition characterized by progressive airflow limitation caused by an abnormal inflammatory response of the lungs to harmful particles or gases that is not fully reversible. Smoking is largely responsible for the development of the disease. Systemic inflammation induced by smoking contributes to the natural history and clinical manifestations of COPD by causing chronic heart failure, metabolic syndrome (MetS) and other chronic diseases. MetS is a collection of interrelated clinical and biochemical disorders. MetS includes abdominal obesity, elevated triglycerides and low high-density lipoprotein (HDL) (atherogenic dyslipidemia), elevated blood pressure, insulin resistance, prothrombotic and proinflammatory markers (elevated C-reactive protein (CRP), fibrinogen, and other coagulation factors) with or without glucose intolerance. In patients with COPD, one or more components of MetS may be present in comorbidities that develop as a result of systemic inflammation. The prevalence of metabolic syndrome in COPD patients was found to be 30% and the prevalence of type 2 diabetes (T2DM) was found to be between 10-23%. Especially oral steroids used in the treatment of COPD exacerbations increase the risk of T2DM. Treatment of MetS and T2DM in patients with COPD does not differ.

Keywords: Comorbidities, Chronic obstructive pulmonary disease, Metabolic syndrome, Smoking, Systemic inflammation.

INTRODUCTION

Metabolic syndrome (MetS) is an endocrinopathy of unknown etiopathogenesis that leads to diabetes and cardiovascular disease. MetS is a health problem whose prevalence is increasing worldwide and negatively affects people's lives. Although MetS, which is based on insulin resistance, is not recognized as a disease, it is a combination of many risk factors that force the body's metabolism to work abnormally. In the formation of MetS, sedentary lifestyle, and nutrition in addition to factors such as hereditary factors are also of great importance [1].

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Hafize Uzun & Seyma Dumur (Eds.)

Visceral adiposity, lipid profile disorder, endothelial dysfunction, arterial hypertension, chronic stress, insulin resistance, and hypercoagulability are the parameters that constitute MetS. The prevalence of MetS is on the rise globally. In the past few decades, several international organizations have provided the definitions of MetS. MetS has been proposed as a definition rather than a diagnosis [2, 3].

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterized by persistent airflow limitation due to impaired airway and/or alveolar structure caused by host factors including exposure to harmful particles or gases and abnormal lung development. COPD is a lung disease characterized by chronic respiratory symptoms (shortness of breath, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause permanent, often progressive airflow obstruction [4]. Smoking is largely responsible for the development of the disease. Smoking not only causes inflammation in the airways and lungs, but also systemic cellular and humoral inflammation, systemic oxidative stress, altered vasomotor and endothelial function, and increased procoagulant factors. Systemic inflammation induced by smoking contributes to the natural history and clinical manifestations of COPD by causing chronic heart failure, MetS, and other chronic diseases [5].

Metabolic Syndrome

Definition

MetS is a proinflammatory, prothrombotic condition associated with the development of cardiovascular disease and type 2 diabetes mellitus (T2DM), which is caused by a combination of risk factors such as impaired glucose and insulin metabolism, obesity, dyslipidemia, and hypertension. There are problems in the diagnosis of metabolic syndrome due to the different definitions proposed. In 2005, the International Diabetes Federation (IDF) modified the ATP III criteria, noting that abdominal obesity is correlated with insulin resistance. The IDF noted ethnic differences in the correlation between MetS risk factors and abdominal obesity and defined abdominal obesity differently. There are problems in the diagnosis of MetS due to the different definitions proposed [6]. Table **1** shows the NCEP-ATP III metabolic syndrome diagnostic criteria [7].

Risk Factors of Metabolic Syndrome

Met Sis a cluster of conditions that occur together, increasing the risk of heart disease, stroke, and T2DM. Several risk factors contribute to the development of MetS [7 - 11].

Table 1. NCEP-ATP III metabolic syndrome diagnostic criteria.

Parameter	Criteria
Abdominal obesity.	Waist circumference (WC). ≥ 102 cm (M). ≥88 cm (FM).
Triglyceride (TG).	≥150 mg/dL or taking medication for hypertriglyceridemia.
High-density lipoprotein (HDL).	<40 mg/dL (M). <50 mg/dL (FM) or being treated for low HDL.
Blood pressure (BP).	Systolic blood pressure ≥130 mmHg or Diastolic blood pressure ≥85 mmHg or taking antihypertensive medication in a patient with a history of hypertension.
Fasting blood glucose.	≥100 mg/dL or taking medication for the treatment of high blood glucose.

- **Obesity:** Excess body fat, particularly around the waistline (abdominal obesity), is a significant risk factor for metS.
- **Insulin Resistance:** Insulin resistance occurs when cells in your body do not respond effectively to insulin, a hormone that helps control blood sugar levels. This leads to high blood sugar levels, which can contribute to the development of T2DM.
- **Physical Inactivity:** Lack of physical activity is associated with obesity and insulin resistance, both of which are key components of MetS.
- **Unhealthy Diet:** Consuming a diet high in processed foods, refined sugars, saturated fats, and cholesterol can contribute to obesity, insulin resistance, high blood pressure, and abnormal lipid levels—all components of MetS.
- **Genetics:** Family history and genetics can play a role in the development of MetS.
- **Age:** The risk of MetS increases with age, partly because muscle mass tends to decrease with age, leading to a decrease in metabolic rate.
- **Ethnicity:** Certain ethnic groups, such as African Americans, Hispanics, Native Americans, and Asians, have a higher risk of developing MetS.
- **Hormonal Imbalances:** Conditions such as polycystic ovary syndrome (PCOS) and Cushing's syndrome, which affect hormone levels, can increase the risk of MetS.
- **Sleep Apnea:** Sleep apnea, a condition characterized by pauses in breathing during sleep, is associated with MetS.
- **Smoking:** Smoking cigarettes is linked to insulin resistance and abdominal obesity, both of which are risk factors for MetS.

CHAPTER 15

Current Perspectives on Metabolic Syndrome and Cancer

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Abstract: Metabolic syndrome (MetS) is a cluster of metabolic disturbances, including high body mass index (BMI), waist circumference, high blood pressure, rise in triglycerides, increased plasma glucose, and reduction in high-density lipoprotein (HDL) cholesterol, leading to increased cardiovascular morbidity and mortality along with an increased predisposition to other non-communicable diseases such as diabetes and certain cancers. Its incidence is on the rise in Western countries and is a risk factor for several common cancers. Although the individual components of metabolic syndrome are linked to cancer, studies showing a direct link between metabolic syndrome and cancer are limited. This review addresses the need to summarise the associated factors and mechanisms linking these two pathologies and to identify potential targets in therapy in patients with cancer and metabolic syndrome. Understanding this link would provide insight into the process of oncogenesis in patients with MetS. This chapter focuses on the biological and physiological alterations and specific factors associated with this process, including the insulin-like growth factor (IGF-1) pathway, estrogen signaling, visceral adiposity, hyperinsulinemia, hyperglycemia, aromatase activity, adipokinase production, angiogenesis, oxidative stress, DNA damage, and pro-inflammatory cytokines in these patients and their clinical implications in cancer therapy. New research is warranted in this area and should be systemically analyzed in all cancer types. A better understanding of this link will provide greater insight into the management of cancer patients by preventing metabolic syndrome and related alterations.

Keywords: Cancer, Metabolic syndrome.

INTRODUCTION

The world is facing a pandemic of non-communicable diseases. Metabolic syndrome (MetS) is a collection of metabolic disturbances, including high body mass index (BMI), waist circumference, high blood pressure, rise in triglycerides, increased plasma glucose, and reduction in high-density lipoprotein cholesterol (HDL), leading to increased cardiovascular morbidity and mortality [1]. There are

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Hafize Uzun & Seyma Dumur (Eds.)

several definitions in use, but the definition by the National Cholesterol Education Programme (NCEP) Adult Treatment Panel III is the one most widely practiced. It defines metabolic syndrome as the presence of any three risk factors of the following: abdominal obesity, elevated serum triglycerides (>=150mg/dl) or on treatment, serum high-density lipoprotein cholesterol (HDL) (40mg/dl in men and <50 mg/dl in women), hypertension or on treatment for hypertension, and fasting plasma glucose of >100 mg/dl or on treatment. It also takes impaired fasting glucose corresponding to the American Diabetes Association criteria into consideration for hyperglycemia [1, 2]. Although initially, MetS was considered to be mostly a condition of the developed countries in the West, it has now become a rising public health problem globally. MetS goes hand in hand with economic development and increasing sedentary lifestyles, leading to obesity and related health problems [3]. The prevalence of metabolic syndrome is higher in men (26.8%) than women (16.6%), and it increases with age [4, 5].

MetS is associated with other non-communicable diseases, including diabetes and cancer. Studies show almost a fivefold increased risk of developing type 2 diabetes, with a higher risk of cardiovascular disease [2]. In addition to complications related to atherosclerosis, the literature reveals several types of cancer to be associated with MetS, including breast cancer, especially in postmenopausal women, renal, prostate, pancreatic, gastrointestinal cancers, including carcinoma of the colon, stomach, and the esophagus, and hepatocellular carcinoma [3].

METABOLIC SYNDROME AND CANCER

Obesity and Cancer

Obesity was initially a problem predominantly in developed countries; however, an alarming increase has been observed in developing countries, especially over the last two decades. It is also a part of the cluster of disorders associated with metabolic syndrome. Obesity is, by definition, a body mass index (BMI) >/= 30 $kg/m^{2,}$ and severe obesity is a BMI of >/= 40 kg/m^2 or a BMI of >/=35 kg/m^2 with associated comorbidities [6, 7]. Literature reveals epidemiological evidence where excess body weight in the form of raised BMI or waist/hip ratio is associated with several cancers. Furthermore, a study by Calle *et al*. revealed obesity to be associated with increased cancer mortality [8]. The common cancers associated with obesity are colorectal, hepatocellular, gallbladder, pancreatic, leukemia, non-Hodgkin's lymphoma, multiple myeloma, breast, ovarian, and endometrial cancers [9]. In keeping with these findings, a study by Reeves *et al*., which analyzed the association of BMI with different cancers in pre and post-menopausal women, revealed that pre-menopausal women have an increased risk

of colorectal cancers and melanoma, whereas post-menopausal women show a rise in breast and endometrial cancers [10]. The possible mechanism for this causal relationship is likely to be insulin resistance, although the molecular mechanisms are still under investigation. A chronically elevated insulin level with high insulin-like growth factor 1 (IGF-1) levels, increasing oxidative stress with obesity, and lipid peroxidation of anti-carcinogenic protective factors are some of the suggested contributing factors [11]. Furthermore, obesity is a known negative prognostic indicator in cancers of the breast and the colon [11]. The higher levels of estrogen found in obese women and other associated complications of obesity such as gastroesophageal reflux disease (GORD) in the long term can lead to premalignant forms such as Barret's esophagus, which may later develop into esophageal cancer [12].

Dyslipidemia and Cancer

Dyslipidemia is a component of metabolic syndrome. It is a known risk factor for multiple cancers. Dyslipidemia includes derangement of multiple parameters in the lipid profile with low high-density lipoprotein cholesterol (HDL-C), elevated low-density lipoprotein (LDL) cholesterol, and triglycerides (TG) [6]. Low levels of HDL cholesterol in serum are known to be associated with a risk of lung cancer and non-Hodgkin lymphoma. It is also a risk factor for breast cancer in both pre-menopausal and post-menopausal women. Furthermore, there is enough evidence that postmenopausal women with a higher BMI ($\geq$25kg/m^2) and low HDL cholesterol are at an increased risk of developing breast cancer than women without these risk factors [13 - 15]. Raised levels of serum triglycerides are a known prognostic indicator for prostate cancer in subjects controlled for age, BMI, diabetes, and use of statins. It also revealed that the progression of prostate cancer to a higher Gleeson grade was associated with an elevated triglyceride level [16, 17]. Further studies are deemed essential to explore this association.

Diabetes and Cancer

Diabetes is a disease with implications for multiple systems. It is also strongly associated with a cluster of metabolic disturbances included in metabolic syndrome. Several studies analyzing the relationship between diabetes and cancer have revealed diabetes to be an independent risk factor for most of the common cancers. A prospective study conducted in the United States with a 16-year follow-up revealed that type 2 diabetes, independent of other risk factors such as high BMI, posed a high mortality risk from common cancers such as breast, pancreatic, bladder, and hepatocellular cancers [18]. Mortality due to breast cancer has been shown to be prominent in women with obesity and diabetes, with diabetic women being more prone to breast and pancreatic cancers [6]. Type 2

CHAPTER 16

Otorhinolaryngology and Metabolic Syndrome

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Abstract: Metabolic syndrome (MS) is a diverse condition linked to an elevated risk of cardiovascular issues. Emerging evidence from various types of research, including experimental, translational, and clinical studies, has indicated that obstructive sleep apnoea (OSA) is connected to both existing and newly developing aspects of MS. The plausible biological explanation centers primarily around one of OSA's main features, intermittent hypoxia. This leads to heightened sympathetic activity with cardiovascular consequences, increased liver glucose production, insulin resistance due to inflammation in adipose tissue, dysfunction in pancreatic β-cells, elevated lipid levels through deteriorating fasting lipid profiles, and decreased removal of triglyceride-rich lipoproteins.

While several interconnected pathways exist, the clinical evidence primarily relies on observational data, making it difficult to establish causality. The co-occurrence of visceral obesity and potential confounding factors like medications complicates the assessment of OSA's independent impact on MS. In this chapter, we re-evaluate the evidence regarding how OSA and intermittent hypoxia may contribute to adverse effects on MS parameters independently of body fat. We place particular emphasis on recent findings from intervention studies. This chapter outlines the research gaps, the challenges faced in the field, potential directions for future exploration, and the necessity for more high-quality data from intervention studies that address the influence of both established and promising therapies for OSA and obesity.

Keywords: Cardiovascular issues, Metabolic syndrome, Obesity, Obstructive sleep apnoea, Sleep apnoea.

INTRODUCTION

In recent years, healthcare professionals and researchers have turned their attention to two significant health concerns: metabolic syndrome and sleep apnoea. These conditions, each complex, often coexist in individuals, creating a

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web of health-related challenges. This chapter delves into the intricate relationship between metabolic syndrome and sleep apnoea, shedding light on how they interact and exacerbate each other.

UNDERSTANDING METABOLIC SYNDROME

Metabolic syndrome is not a singular ailment; rather, it is a constellation of interconnected risk factors. It encompasses a range of health markers, including obesity, high blood pressure, elevated blood sugar levels, abnormal lipid profiles (such as high triglycerides and low HDL cholesterol), and insulin resistance. Individuals with metabolic syndrome face an elevated risk of developing serious health issues like cardiovascular diseases and type 2 diabetes [1].

Metabolic syndrome comprises five key elements, each of which contributes to its complexity:

1. **Abdominal Obesity**: Central to metabolic syndrome is the accumulation of excess fat in the abdominal region, commonly referred to as visceral fat. This type of fat isn't just a cosmetic concern; it's closely linked to insulin resistance and chronic inflammation.

2. **High Blood Pressure (Hypertension)**: Elevated blood pressure is a frequent component of metabolic syndrome and is associated with a higher risk of heart disease, stroke, and kidney disease.

3. **Elevated Blood Sugar (Hyperglycaemia)**: High fasting blood sugar levels indicate insulin resistance, a hallmark of metabolic syndrome. If not managed, this condition can progress to full-blown type 2 diabetes.

4. **Abnormal Lipid Profile:** Individuals with metabolic syndrome often exhibit high levels of triglycerides (a type of fat in the blood) and low levels of high-density lipoprotein (HDL) cholesterol, the so-called “good” cholesterol.

5. **Insulin Resistance**: This occurs when the body's cells do not effectively respond to insulin, resulting in higher blood sugar levels.

SLEEP APNOEA: A DISRUPTIVE SLEEP DISORDER

Sleep apnoea is a sleep disorder characterized by repetitive interrupted breathing during sleep. The most common form is obstructive sleep apnea (OSA), where the airway becomes partially or completely blocked, leading to brief awakenings throughout the night. This disruptive pattern not only robs individuals of restful sleep but also often goes undiagnosed [2].

Sleep apnoea is typically categorized into three severity levels based on the number of breathing interruptions per hour of sleep:

1. **Mild**: Involves between 5 to 15 episodes of breathing interruptions per hour of sleep.

2. **Moderate**: Involves 15 to 30 episodes per hour.

3. **Severe:** Marked by over 30 episodes per hour.

THE BIDIRECTIONAL RELATIONSHIP

The relationship between metabolic syndrome and OSA is not only one-way; it is a complex, bidirectional interaction where each condition influences and exacerbates the other.

OSA Contributes to Metabolic Syndrome

● Significant metabolic disruptions can happen due to OSA. The frequent awakenings and drops in oxygen saturation seen in individuals with OSA trigger a cascade of stress responses. This includes heightened activity of the sympathetic nervous system, which is responsible for the body's "fight or flight" responses, and increased inflammation. These physiological changes can disrupt metabolic processes, contributing to insulin resistance, obesity, and high blood pressure [3].

- A study published in the *Journal of the American College of Cardiology* emphasized the strong association between sleep apnoea and cardiovascular diseases, including metabolic syndrome. OSA is linked to increased sympathetic activity, oxidative stress (a type of cellular damage), and systemic inflammation, all of which contribute to the development of metabolic syndrome [4].
- Furthermore, chronic sleep deprivation and frequent sleep interruptions, which are common in individuals with sleep apnoea, can lead to disruptions in hormonal regulation. This includes increased levels of cortisol, a stress hormone, and decreased levels of leptin, a hormone responsible for regulating appetite. These hormonal shifts can promote weight gain and worsen insulin resistance [5].

Metabolic Syndrome Worsens Sleep Apnoea

- Obesity, a central element of metabolic syndrome, is a significant risk factor for the onset and progression of sleep apnoea. As individuals accumulate excess body fat, particularly in the abdominal region, fat deposits can build up in the upper airway, further obstructing normal breathing during sleep [6].

CHAPTER 17

Microbiota and Metabolic Syndrome

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Abstract: Composed of trillions of microorganisms, the human GutM plays a key role in maintaining general health and metabolic homeostasis. MetS is a complex and common health condition characterized by a number of metabolic abnormalities, including obesity, insulin resistance, hypertension, and dyslipidemia. Evidence emerging in recent years indicates that human GutM plays a crucial role in the pathophysiology of MetS. In this chapter, we will discuss the composition and functionality of GutM, as well as the dynamic and complex relationship between GutM's influence on metS development and progression. By reviewing relevant studies and literature, we will try to shed light on potential therapeutic strategies and innovative approaches targeting GutM, mitigating the negative effects of MetS.

Keywords: Microbiota, Metabolic syndrome.

INTRODUCTION

Microbiota refers to the trillions of microorganisms, including bacteria, viruses, fungi, and other microbes, that live in and on the human body. The “microbiome” comprises all of the genetic material within a microbiota. These two terms are used interchangeably. Microbiota or microbiome is the internal ecosystem of our body. Every part of our body (mouth, nose, throat, intestines, urogenital system, skin, mucous membranes around organs, and surfaces associated with the external environment) has different microbiota.

Within the scope of “the Human Microbiome Project”, which started in 2007 and was completed in 2016 by the US National Institutes of Health (NIH) and the US National Institute for Genetic Research (NHGRI), extensive research has been conducted to understand the structure and functions of microorganisms (such as bacteria, viruses, fungi, *etc*.). The results of this project have been an important resource for the understanding of health and disease in the human microbiome.

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The major population of microorganisms in the human body is found in the gastrointestinal tract (GIS). In recent years, the role of the gut microbiota in human health has received great attention from the scientific community. Emerging evidence suggests that it plays a crucial role in a variety of physiological processes, including metabolic homeostasis. The gut microbiota (GutM) influences human physiology and pathology by modulating host nutrition and energy harvesting. Many recent studies of the human microbiota have revealed the complexity and diversity of these microbial communities and their profound impact on human health. As research into the human microbiota continues to expand, new technologies and methodologies are emerging that promise to shed even more light on these complex microbial communities. Advances in metagenomics, microbiome engineering, and other microbiota research areas may open new avenues for understanding and manipulating these bacterial communities. The future of microbiota research is an exciting and rapidly evolving field that has the potential to transform our understanding of human health and disease. Although the microbiota is essential for human health, imbalances in these microbial communities can have detrimental effects on the body. Recent research has linked GutM changes to insulin resistance, inflammation, and metabolic syndrome (MetS).

MetS is defined as a combination of interconnected physiological, biochemical, and metabolic factors that increase the risk of developing cardiovascular diseases and type 2 diabetes (T2D). Risk factors that cause both T2D and cardiovascular diseases are called cardiometabolic risk factors. Many of the cardiometabolic risk factors are preventable risk factors. This syndrome is a group of disease states defined by the hallmark of clinical signs, including obesity, high blood pressure, high blood sugar, and high cholesterol or triglycerides and dyslipidemia (high serum triglycerides and low-high-density lipoprotein cholesterol). The worldwide prevalence of MetS is <10% to 84%, which may vary depending on the geographic region and the definition criteria applied [1].

Understanding the role of the microbiota in disease is important in identifying new treatments and preventive strategies. Understanding the complex interactions between GutM and MetS is a growing area of research, and scientists are exploring potential treatments that target the microbiota to improve metabolic health.

This chapter will provide an overview of the microbiota and its extraordinary relationship with the MetS.

GUT MICROBIOTA

GutM Composition and Diversity

The human GutM is a complex ecosystem, which includes bacteria, viruses, fungi, and other microorganisms that perform many important tasks and have an impact on human health. The composition of each individual's microbiota may vary depending on personal characteristics such as age, gender, lifestyle, dietary habits, geographic location, and genetic factors. In a healthy individual, the gut microbiota is highly diverse, with hundreds of different bacterial species coexisting in a balanced ecosystem. The intestinal microbiota is the area with the most bacterial diversity and the most studied and clinical experience. There is a community of microorganisms living with us in our microbiota, constituting approximately 2-3% of our body weight. It contains 10 times more genes than our own cells and 150-200 times more genes than the entire human genome.

Firmicutes, Bacteroidetes, Proteobacteria, Fusobacteria, Verrucomicrobia, Cyanobacteria, and Actinobacteria are the most abundant bacterial phyla in the gut. Additionally, they are found in minority populations such as archaea, eukaryotes, and viruses. The two most abundant bacterial phyla are Firmicutes (Gram-positive 60% -80%) and Bacteroidetes (Gram-negative 20% - 40%) [2]. These microorganisms are in a symbiotic relationship with their hosts. They play important roles in various physiological processes, such as the production of vitamins and amino acids, fermentation of indigestible substrates such as dietary fiber, the production of short-chain fatty acids (SCFA), conversion of cholesterol and bile acids, the maturation of the immune system, and protection against pathogens. They also play a vital role in maintaining human health by suppressing the growth of pathogenic microorganisms.

GutM is considered an organ in its own right with impressive metabolic ability and functional flexibility. For this reason, it has been considered a “metabolic organ”. These bacteria, which have an enormous metabolic capacity and diversity, are also defined as “human-bacterial superorganisms” together with their host. This evolutionary reciprocal partnership between host and microbiota provides better digestive protection. Recent research shows that GutM has a major impact on health and disease. Microbiota imbalance has been linked to a variety of health problems, including intestinal inflammation, obesity, diabetes, allergies, and immune system diseases. Understanding the complexity of GutM and protecting this complex ecosystem is crucial for human health.

CHAPTER 18

The Role of Bariatric and Metabolic Surgery in the Management of Metabolic Syndrome

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Abstract: Metabolic syndrome (MetS) is characterized by central obesity, glucose intolerance, dyslipidemia, and hypertension. This is attributed to an increased inflammatory state resulting from increased cytokine synthesis from adipose tissue. Almost all of the medical problems associated with metabolic syndrome can be more successfully remised in the long term by bariatric-metabolic surgery (BMS) compared to conservative methods. In past years, the benefits of BMS have been attributed to weight loss; however, currently, it has been well described that anti-inflammatory response and remission of T2DM and other comorbidities begin in the first weeks after procedures. Moreover, there is also sufficient evidence that BMS helps in the remission of integral components of MetS, such as hyperlipidemia, hypertension, and cardiovascular diseases, in the long term where many patients do not even require medical treatment. The International Diabetes Federation (IDF) and recent guidelines recommend that metabolic surgery may be considered if glycemic control is not achieved despite optimal treatment if the patient's body mass index (BMI) is 30kg/m2 and above.

Keywords: Body mass index, Bariatric surgery, Comorbidities, Metabolic syndrome, Type 2 diabetes mellitus, Weight loss.

INTRODUCTION

Metabolic Syndrome

Metabolic syndrome (MetS) is an endocrinopathy of unknown etiopathogenesis that leads to type 2 diabetes (T2DM) and cardiovascular disease. Visceral adiposity, lipid profile disorder, endothelial dysfunction, arterial hypertension,

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Hafize Uzun & Seyma Dumur (Eds.)

chronic stress, insulin resistance (IR), and hypercoagulability are the parameters of MetS [1].

Definition

Reaven [2] first described MetS in his 1988 Banting lecture as "Syndrome X". Reaven suggested that insulin resistance clustered together with glucose intolerance, dyslipidemia, and hypertension to increase the risk of CVD. In 1998, the World Health Organization (WHO) was the first organization to coin the term MetS, focusing primarily on insulin resistance and hyperglycemia [3]. In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) expanded the definition of the syndrome to include abdominal adiposity, particularly increased waist circumference [4]. This was followed by several published definitions from different societies, often differing in the clinical assessment of abdominal adiposity. The term MetS still includes the previous terms "syndrome X", "insulin resistance syndrome", and "cardiometabolic syndrome", which encompass the same concept. In 2015, a group of experts representing more than 20 organizations articulated three key definitions supporting the concept. Accordingly, MetS is a chronic and progressive pathophysiological state. MetS represents a cluster of risk factors and refers to a complex syndrome defined by a unifying pathophysiology. Today, the term "metabolic syndrome" is widely accepted and considered to be the most useful term.

Prevalence of Metabolic Syndrome

The prevalence of MetS is increasing with the aging of the population, physical inactivity, and an increase in the prevalence of central obesity. The prevalence of metabolic syndrome in the United States of America (USA) was 34.5% (33.7% in men and 35.4% in women), according to the NCEP ATPIII criteria. According to the International Diabetes Federation (IDF) MetS criteria, the prevalence of MetS in the USA was found to be 39% (39.9% in men and 38.1% in women) [5]. The prevalence was 34%, 33%, and 34.7% in 1999–2006 [6], 2003–12 [7], and 2011–16 [8], respectively. This may seem surprising against the background of an obesity and diabetes epidemic, which would be expected to increase the prevalence of MetS as they are components of the syndrome [9].

Etiopathogenesis of Metabolic Syndrome

No single genetic, infectious, or environmental factor has yet been identified to explain the etiopathogenesis of all components of the MetS. However, the etiology of metabolic syndrome can be divided into three categories: obesity/adipose tissue disorders, insulin resistance, and independent factors (such

as molecules of vascular, hepatic, and immunologic origin). Although polygenic predisposition is involved, a sedentary lifestyle and high-calorie diet brought about by modern urban life exacerbate the course of the syndrome. The prevalence of MetS is increasing worldwide. The rate of increase, although significant, varies between countries [10].

The pathophysiology of the MetS encompasses several complex mechanisms that are yet to be fully elucidated. It is still debated whether the different elements of MetS form distinct pathologies by themselves or fall under a common, broader pathogenic process [11].

Diagnosis of Metabolic Syndrome

Over time, different diagnostic criteria have been used for metabolic syndrome. While these diagnostic criteria initially included criteria that could measure insulin resistance, later on, simpler criteria were used. The most widely accepted of these diagnostic criteria are:

- (1998-99) World Health Organization (WHO).
- (2001) National Cholesterol Education Program - Adult Treatment Panel III (National Cholesterol Education Program - Adult Treatment Panel III) (NCEP ATPIII).
- (2004) Revision, modification of NCEP ATP -III definition.
- (2004-05) International Diabetes Federation (IDF) Consensus Statement.

In addition, medical associations and institutions in many countries have their own definitions.

WHO Diagnostic Criteria for Metabolic Syndrome [3].

At least one of the following:

- Insulin resistance.
- Impaired glucose tolerance.
- Obvious diabetes mellitus.

and

At least two of the following:

- Hypertension (blood pressure > 140/90 mmHg or taking antihypertensives).
- Dyslipidemia (triglyceride level > 150 mg/dl or HDL level < 35 mg/dl in men and < 39 mg/dl in women).

CHAPTER 19

Pathophysiological Mechanisms in Obstructive Sleep Apnea Syndrome

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Abstract: Metabolic syndrome is a condition characterized by a cluster of risk factors associated with cardiovascular disease. These metabolic factors include abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low HDL cholesterol levels. Obstructive sleep apnea syndrome (OSAS) is a sleep disorder in which the air passages constrict during sleep, leading to repeated breathing interruptions. The prevalence of OSAS has increased over the years, particularly among aging individuals. Although the underlying reasons for airway obstruction involve various factors, such as overweight, anatomical abnormalities, shifts in airway dynamics, pharyngeal neuropathy, and fluid redistribution, these causes remain incompletely understood.

The primary characteristics of OSAS include repetitive interruptions in breathing, resulting in heightened susceptibility to a range of chronic ailments. These interruptions lead to intermittent episodes of low oxygen levels (hypoxia) and elevated carbon dioxide levels (hypercapnia), often accompanied by sleep disruptions due to arousal.

In this yet-to-be-published exploration, I navigate the intricate dynamics of human connection in the digital age, examining how technology both bridges and divides us. Through a blend of personal reflections and sociological analysis, I aim to shed light on the complexities of virtual relationships and their impact on our sense of belonging.

Keywords: Intermittent hypoxia, Metabolic disorders, Pathophysiological mechanisms, Respiratory diseases.

INTRODUCTION

Metabolic syndrome is a condition characterized by a cluster of risk factors associated with cardiovascular disease. These metabolic factors include abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low HDL cholesterol levels.

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In this unpublished essay, I explore the intricate dance between memory and identity, delving into how our recollections shape who we are. Through personal anecdotes and philosophical musings, I aim to unravel the profound interplay between memory, perception, and the construction of the self.

Obstructive sleep apnea syndrome (OSAS) is a respiratory disorder characterized by episodes of reduced breathing (hypopnea) and pauses in breathing (apnea). This condition leads to low blood oxygen levels (hypoxemia), elevated carbon dioxide levels (hypercapnia), fragmented sleep, and frequent awakenings, which result in increased respiratory effort and heightened activity of the sympathetic nervous system [1, 2]. Epidemiological data show that OSAS is most commonly observed in individuals aged 30 to 60 years, with research indicating that 24% of affected individuals are men and 9% are women [3, 4]. One resource estimates approximately 1,000,000 OSAS cases worldwide [5].

Risk factors for obstructive sleep apnea syndrome (OSAS) include obesity, age, gender, genetics, poor diet, and a sedentary lifestyle [6, 7]. Body mass index (BMI) is a critical factor in the development of the disease; an increase in BMI causes the upper airway to narrow due to an accumulation of adipose tissue, thereby heightening the risk of OSAS [8]. OSAS can manifest at any age, but its incidence tends to increase with age [9]. Male gender is a significant standalone risk factor for OSAS, with a prevalence that is 1.5 times higher in men, although the cause of this gender difference remains unclear [10]. The prevalence of OSAS also rises in postmenopausal women, likely due to the redistribution of body fat to the upper body [11].

Clinically, OSAS can vary significantly among individuals. Polysomnography (PSG) monitoring, following the 2017 scoring guidelines, is the method used for diagnosing OSAS [12]. These guidelines define episodes of respiratory arrest as reductions in respiration lasting more than 10 seconds. Respiratory depression is characterized by at least a 50% reduction in airflow and oxygen desaturation lasting longer than 10 seconds. The severity of OSAS is assessed by the rate of apnea-hypopnea events occurring per hour during sleep, known as the apnea-hypopnea index (AHI). An AHI of less than 5 indicates no sleep apnea, an AHI of 5-15 signifies mild OSAS, an AHI of 15-30 indicates moderate OSAS, and an AHI greater than 30 denotes severe OSAS. If a patient exhibits no issues and the recorded PSG AHI is less than 15, it is considered normal [12, 13].

Recent studies have reported a connection between sleep respiratory problems and an increased risk of metabolic, cardiovascular, and neurological diseases [14, 15]. Additionally, obstructive sleep apnea syndrome (OSAS) has been linked to a range of other conditions, including nonalcoholic fatty liver disease, insulin

resistance, glucose metabolism issues, kidney disease, hypertension, cancer, and gastroesophageal reflux [16 - 23].

The pathophysiology of OSAS is complex and not easily understood, affecting various systems in the body. This section will investigate the mechanisms of sleep respiratory problems, examining the connections among changes in these conditions, their pathological and physiological effects, and their systemic reflections, based on current literature. With the increase in research on OSAS, it is widely accepted that both anatomical and functional factors contribute to the mechanism of upper airway collapse.

Anatomical abnormalities in the upper respiratory tract play a significant role in sleep respiratory disorders. Nearly all patients exhibit varying degrees of upper airway anatomical irregularities, including abnormal maxillofacial bone structures. These factors significantly contribute to upper airway collapse and stenosis, which can be exacerbated by conditions leading to soft tissue hyperplasia [24]. Additionally, edema in the legs, caused by various factors, can lead to fluid shifting to the neck area while lying down at night, resulting in upper airway narrowing [25].

As individuals age, decreased mandibular size due to conditions like osteoporosis and the downward positioning of bones and soft tissues in the jaw area contribute to crowding in the oronasal space [26]. Anatomical abnormalities related to skeletal conditions, such as midface hypoplasia in Pierre Robin syndrome, craniofacial synostosis in Pfeiffer syndrome, and features observed in Crouzon and Apert syndromes, are diseases that facilitate OSAS [27].

A major factor in the narrowing of the pharyngeal area is the swelling of the soft tissues in and around the airways, which is critical for OSAS. Contributing factors include excessive or elongated sagging of the soft palate, a retruded chin, an enlarged tongue, large tonsils, increased neck fat, and excessive secretions in the mouth [28]. An enlarged soft palate and tongue, along with a thickened pharyngeal wall, affect the lateral plane, which is a crucial area of airway narrowing in most OSAS patients [29].

Obesity contributes to airway compression in the pharyngeal region, and accumulation around the chest cavity may also promote the development of OSAS [30]. Inactivity during the day can cause peripheral edema in the legs. When lying down, a shift of this fluid to the top of the body can increase e upper airway constriction, thereby increasing susceptibility to OSAS [31]. Changes in leg diameter occur due to circulation correlated with strain in the neck area and changes in neck structures [30]. Breathing problems during sleep conclude microstimulation in the brain for safety [1]. Frequent awakenings during sleep,

CHAPTER 20

Evaluation of Metabolic Parameters in Cushing's Syndrome

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Abstract: The prevalence of metabolic syndrome (MetS) is estimated to be about one-fourth of the worldwide adult population, while Cushing's syndrome (CS) is significantly rarer (estimated incidence of 2 per million). However, linking the two has not only therapeutic but also potential public health implications. The worldwide increase of obesity and MetS poses the problem of correctly identifying patients potentially hiding CS without indiscriminately screening all patients presenting one or more symptoms consistent with cortisol excess, which showed to be not cost-effective. CS is associated with hyperglycemia, protein catabolism, immunosuppression, hypertension, weight gain, neurocognitive changes, and mood disorders. Obesity, insulin resistance, hypertension, functional hypercortisolism (Endogenous/Exogenous), and MetS are common features. Early diagnosis and treatment are important because untreated CS may result in mortality due to associated metabolic risks.

Keywords: Cushing's syndrome, Hypertension, Hypercortisolism, Insulin resistance, Metabolic syndrome, Obesity.

INTRODUCTION

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that include hypertension (HT), central obesity, insulin resistance (IR), and atherogenic dyslipidemia, which increase the risk of type 2 diabetes mellitus (DM), coronary heart disease (CHD) and coronary vascular disease (CVD), morbidity and mortality. MetS is also called ‘dysmetabolic syndrome’, ‘insulin resistance syndrome’, ‘syndrome X’, ‘hypertriglyceridemic waist’, and ‘the deadly quartet’. MetS is a health problem that has an increasing prevalence in the world and negatively affects people's lives [1, 2].

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Cushing's disease (CD) is a disease caused by the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland above its normal level. CD is the most common cause of spontaneous Cushing's syndrome (CS), occurring in 60–70% of Cushing's patients. Iatrogenic CS is the name given to the condition that occurs independently of ACTH secretion in the body with the administration of glucocorticoid agents in pharmacological doses. The presence of moon face, hirsutism, buffalo hump, central obesity, hypertension, hyperglycemia, mood disorders, psychosis, immunosuppression, osteoporosis, muscle weakness, or peptic ulcer should suggest CS. No single symptom or finding is pathognomonic for CS, but the simultaneous presence of multiple signs or symptoms should be a warning sign [3].

METABOLIC SYNDROME (METS)

It is known that environmental factors such as a sedentary lifestyle and changes in dietary habits contribute to the increase in the number of patients with metabolic syndrome, which is progressing towards a pandemic, as well as genetic predisposition. Although the causes of metabolic syndrome include obesity, hypertension, and hyperlipidemia, especially fat stored in the abdominal region and IR caused by physical inactivity, the main role is thought to belong to insulin resistance. In metabolic syndrome, there is IR in liver and muscle tissue as well as in adipose tissue. Hyperinsulinemia occurs in response to this resistance. Cardiovascular mortality and morbidity are increased in patients with metabolic syndrome [4].

There are various diagnostic criteria proposed for MetS, such as the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III (NCEP-ATP III) criteria, International Diabetes Federation (IDF) criteria, World Health Organization (WHO) criteria [5 - 7]. The most commonly used criterion is the NCEP-ATP III, followed by IDF and then the WHO criteria. According to the NCEP ATP III guideline, the criteria and components of MetS are presented in Table**1** [8].

Table 1. According to the NCEP ATP III guideline, the criteria and components of MetS.

Component	Criteria
Abdominal obesity: Increased waist circumference.	Men: ≥ 102cm Women: ≥ 88cm
Elevated triglycerides.	≥ 150mg/dL
Reduced HDL.	Men: < 40mg/dL Women: < 50mg/dL
Elevated blood pressure.	≥ 130/85mmHg

(Table 1) cont.....

Component	Criteria
Elevated fasting glucose.	≥ 100mg/dL

CUSHING'S SYNDROME

Cushing's syndrome (CS) is a complex of symptoms that occur with prolonged increases in plasma cortisol levels that are not due to a physiological etiology. Cortisol is a hormone that affects the body's response to stress and change. Although the most frequent cause of CS is exogenous steroid use, the estimated incidence of CS due to endogenous overproduction of cortisol ranges from 2 to 8 per million people annually [9].

Etiology

The metabolic picture is due to the overproduction of adrenal steroids, among others [10]:

- Negative nitrogen, potassium, and phosphorus balance;
- Sodium retention, which may result in HT, edema, or both;
- Impaired glucose tolerance or overt DM;
- Increased plasma fatty acids;
- There is an increase in the number of polymorphonuclear leucocytes while the number of circulating eosinophils and lymphocytes decreases.

In patients with CS, muscle atrophy and fat accumulation in the body in an unusually new distribution, *i.e.*, trunk obesity, can be found. Loss of ACTH as a result of a tumor, infection, or pituitary infarction causes the opposite set of findings [9 - 12].

If the event is due to a pituitary adenoma, it is more commonly referred to as Cushing's disease, while those of adrenal origin or those that occur with high doses and prolonged administration of exogenous ACTH or glucocorticoids (iatrogenic Cushing's syndrome) are called CS. Although glucocorticoid excess is responsible for the clinical picture, an increase in other hormones of the adrenal cortex, mineralocorticoids, and sex steroids, which vary according to the etiological causes, may also be detected. The condition, which usually occurs between the ages of 20-60 and more frequently in women, usually results in death within 5 years if left untreated. In 90% of CS of pituitary origin, adenoma is present in 90% and hyperplasia in 10% [12]. The main tumors causing CS by secreting ectopic ACTH are small cell lung cancers (SCLCs), bronchial carcinomas, thymus carcinoids, pancreatic tumors, pheochromocytoma, and medullary thyroid cancer. Local symptoms may be seen in ACTH-dependent

CHAPTER 21

Non-Alcoholic Fatty Liver Disease as a Cause and Consequence of Metabolic Syndrome

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Abstract: The prevalence of non-alcoholic fatty liver disease (NAFLD), one of the most common liver diseases, is rapidly increasing worldwide, parallel to the global obesity epidemic. NAFLD can progress to steatohepatitis, which is a more severe form of liver disease characterized by hepatocyte injury, inflammation, and fibrosis. NAFLD is closely related to metabolic syndrome (MetS)/insulin resistance, and these relationships are the subject of active research. Other than in MetS, visceral adiposity and pro-inflammatory state are also key in the development of NAFLD. In addition to human genetic variants linked to NAFLD risk to date are genes involved in the regulation of lipid metabolism, providing support for the hypothesis that NAFLD is fundamentally a metabolic disease.

Keywords: Insulin resistance, Metabolic syndrome, Non-alcoholic fatty liver disease.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined by the presence of steatosis in over 5% of hepatocytes, absence of hepatocellular injury, and notable alcohol consumption [1 - 3]. The association between diabetes, liver disease, and gout has been recognized for 120 years and is strongly linked to insulin resistance. However, NAFLD was not acknowledged as a clinical entity until the 1980s [4,5]. Presently, NAFLD is a complex liver condition, which is also a multisystemic disorder defined with metabolic irregularities [1, 6, 7].

NAFLD is a complex liver condition that is viewed as the hepatic demonstration of metabolic syndrome (MetS), encompassing elevated plasma triglycerides, low HDL cholesterol, impaired fasting glucose levels, an increased waist circumference, and elevated blood pressure. Additionally, NAFLD can represent another facet of MetS, such as hyperuricemia, systemic inflammation (CRP), and

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Hafize Uzun & Seyma Dumur (Eds.)

microalbuminuria [4]. NAFLD and MetS exhibit an inverse and reciprocal correlation, where MetS acts as both a cause and an effect [1,8]. According to recent evaluations, the frequency of NAFLD in adults ranged between 25% and 32% from 2009 to 2019 [6]. This prevalence aligns closely with the frequency observed in cases of MetS. Leit *et al.* discovered that around two-thirds of individuals with obesity and type 2 diabetes (T2DM) displayed hepatic steatosis. Approximately 50% of patients with hyperlipidemia and 50% of patients with essential hypertension also exhibited hepatic steatosis [9,10]. NAFLD carries the potential for adverse outcomes such as cirrhosis, hepatocellular carcinoma, the necessity for liver transplantation, and mortality. Approximately $1/5^{th}$ of patients with NAFLD have the potential to advance to severe liver disease, with T2DM serving as a significant prognostic factor for unfavorable results [6]. Furthermore, NAFLD is also a common chronic liver disease among pediatric and adolescent populations, notably in those who are obese. It has also been identified in infants born to mothers with gestational diabetes [4,11]. Liver biopsy is the benchmark method for diagnosing NAFLD. State–of-the-art imaging tools, such as magnetic resonance spectroscopy (MRS) and computed tomography (CT), have also been employed. In contrast to the invasive nature of biopsy and the associated costs of MRS and CT, ultrasonography emerges as a cost-effective and readily accessible alternative within clinical settings [12]. Demographic variants are beingdeveloped for NAFLD and MetS. The various demographic factors have been identified, with specific studies revealing a higher prevalence of NAFLD among males than females within the MetS population. Males exhibit a greater susceptibility to grade 2 fatty liver, while females are more inclined towards grade 1. Moreover, the prevalence of NAFLD in females increases notably after the age of 50, a phenomenon attributed to estrogenic action [1]. The prevalence of NAFLD is comparatively higher among urban populations. The level of education plays a pivotal role in influencing both the onset and prevention of NAFLD. Individuals with higher educational levels tend to exhibit fewer adverse factors, such as eating disorders and obesity [1].

Obesity and insulin resistance are major risk factors for NAFLD. Various blood parameters have been identified as being associated with NAFLD and MetS. These blood parameters include total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), high-density lipoprotein (HDL), triglycerides (TG), AST, ALT, and fasting blood sugar (FBS). There is a significant correlation between FBS, TG, HDL-C (homeostasis model assessment -estimated insulin resistance), HOMA index ratio, and adiponectin [1, 13]. Dyslipidemia acts as an independent element in the progression of NAFLD. Physical activity and dietary patterns also contribute to the development of NAFLD. Elevated levels of ALT, AST, LDL-C, TG, and FBS and diminished HDL-C levels serve as alarming indicators for identifying NAFLD [1]. The liver

produces glucose and very low-density lipoproteins (VLDLs) containing the majority of triglycerides. This involvement means that MetS and NAFLD share the same risk profiles [12].

Pathogenesis

Currently, "multiple-hit hypothesis" provides a more solid description of the NAFLD pathogenesis [5, 13]. According to the "multiple-hit hypothesis", there needs to be a dysfunction in adipocyte tissue triggered by genetic predispositions, host metabolic disorders, and environmental factors leading to a reduction in insulin sensitivity. The reduction in insulin sensitivity causes a decrease in liver fatty acid oxidation and intrahepatic accumulation of triglycerides (IHTG). Insulin resistance also triggers adipose-derived cytokines and hormones like tumor necrosis factor-alpha, interleukin-6, leptin, adiponectin, resistin, *etc*. Insulin resistance promotes the activation of protein kinase C-Delta and nuclear factor-Kappa B by elevated FFA and IHTG levels, together with raised production of diacylglycerols and other lipotoxins, leading to liver inflammation. Moreover, nutritional factors and gut microbiota also contribute to liver inflammation [4, 5, 13 - 16].

Both NAFLD and T2DM demonstrate insulin resistance (IR) in muscle and adipose tissue, which increases ectopic fat accumulation, induces lipotoxicity, impairs beta cell function, and causes excess free fatty acids (FFAs). Mitochondrial dysfunction increases oxidative and endoplasmic reticulum stress, and uncoupled oxidative phosphorylation causes chronic liver disease, NASH, to advance [5].

Other factors that trigger the evolution and progression of NAFLD include specific genes (*e.g*., PNPLA, TMSF2, MBOOAT7, GCKR, and HSD17B13), environmental factors (*e.g*., deficiency in nutrient-dense foods and/or lack of safe areas for physical activity), immunity, race, gut microbiota, *etc*. Moreover, NAFLD is observed more frequently in insulin resistance-correlated conditions like obstructive sleep apnea, hyperuricemia, hypo-testosteronemia in men, and polycystic ovary syndrome in women [5, 17]. As insulin resistance is considered one of the diagnostic criteria for MetS, its exacerbation can initiate mechanisms involving renal sodium reabsorption and sympathetic nervous system activity. The deficiency of insulin signaling in the endothelium further triggers vasoconstriction, ultimately resulting in hypertension among patients with MetS.

NAFLD-> MAFLD

In 2020, an international panel of experts led a consensus (Delphi consensus) proposing the term "metabolic dysfunction-associated fatty liver disease"

CHAPTER 22

Metabolic Syndrome and COVID-19

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Abstract: Metabolic syndrome (MetS) is a condition of abdominal diseases characterised by insulin resistance, obesity, atherogenic dyslipidaemia, hypertension, and hypercoagulability and is a serious risk factor for the development of cardiovascular diseases (CVD) and type II diabetes mellitus (T2DM) [1]. The outbreak of SARS-CoV-2 infection has been named Coronavirus Disease 2019 (COVID-19) by the World Health Organisation (WHO). MetS is emerging as a significant risk factor for worse outcomes in people with COVID-19. Metabolic diseases, especially chronic diseases related to diabetes, lead to heart disease and some neurodegenerative diseases in old age. With SARS-CoV-2, researchers all over the world have investigated the relationship between metabolic diseases and the virus. In fact, COVID-19 management is not different from the management of patients with severe and serious diabetes and the management of other critical illnesses. In the mortality and morbidity of COVID-19, the presence of comorbid diseases, especially diabetes (hypertension, obesity, diseases and drugs affecting the immune system, cardiovascular diseases, *etc*.) and advanced age are determinants. It has also been shown that patients with poor metabolic health are more susceptible to complications such as seizures, strokes, and encephalitis during COVID-19 due to factors accompanying previous illness. Chronic diseases are diseases that progress slowly, last three months or longer, are caused by more than one risk factor, usually show a complicated course, and affect the quality of life of the person. The end of COVID-19 as a global health emergency does not mean 'the end of COVID-19 as a global health threat'. The threat of different COVID-19 variants emerging that could cause new increases in morbidity and mortality remains. Monitoring and management of chronic diseases will not only positively change the course of COVID-19 but will also make it possible to use the limited resources in the health sector in the right way.

Keywords: COVID-19, Comorbid diseases, Chronic diseases, Diabetes mellitus, Hypertension, Metabolic syndrome, Obesity.

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Hafize Uzun & Seyma Dumur (Eds.)

INTRODUCTION

Metabolic syndrome (MetS) is a condition characterised by insulin resistance (IR), obesity, atherogenic dyslipidaemia, hypertension (HT), and hypercoagulability and is a serious risk factor for the development of cardiovascular diseases (CVD) and type II diabetes mellitus (T2DM). MetS was defined for the first time by the World Health Organisation (WHO) in 1998; IR and hyperglycaemia were emphasised in this definition [2]. In the aetiology of MetS, factors such as a sedentary lifestyle and high-calorie foods in the diet, as well as genetic factors, are effective. Although prothrombotic and proinflammatory conditions are not included in the diagnostic criteria, they are included under the title of MetS. Compared to individuals without MetS, the risk of developing atherosclerotic cardiovascular disease in the later years of life in individuals with MetS is increased 2-fold, and the risk of T2DM is increased 5-fold. In addition, sleep apnoea syndrome, asthma, gastroesophageal reflux, non-alcoholic fatty liver disease, gallstones, and depression may develop in relation to MetS [2, 3].

Report of cases of viral pneumonia of unknown cause in Wuhan, China, in December 2019, research on a new coronavirus strain was detected. COVID-19 caused by SARS-CoV-2, the so-called new coronavirus (CoV) disease, is a disease that affects human health and a threatening global problem. Although CoV is known as a family of RNA viruses that usually cause cold-like symptoms in humans, Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East respiratory syndrome (MERS)-CoV, which belong to the same family, have shown that this family of viruses can cause more serious diseases. word “corona” means crown in Latin due to the resemblance of rod-like extensions on its surface to a crown [3].

Since the data records and observations of nations around the world vary considerably, it is very difficult to clearly determine the prevalence of COVID-19. The most typical symptoms of COVID-19 known so far are high fever, dry cough, and fatigue. These symptoms usually appear on the fifth day of the disease; however, in different cases, they have been found to vary over a range from the second to the fourteenth day. More rarely, headache, nasal congestion, general pain, loss of sense of taste and smell, diarrhoea, rashes on the body, and discolouration of the fingers are also observed in some patients. Research shows that 80% of cases survive the disease in a way that does not require serious medical intervention; however, in severe cases, the disease can turn into pneumonia, and artificial respiration methods may be needed. For those who have a mild illness, resting at home, antipyretic measures, and fluid intake are important. One out of every five people in contact with the disease has a severe

illness. Individuals with chronic diseases such as diabetes, high blood pressure, lung and heart diseases, and elderly people are in the risk group. Apart from the elderly, children and young people are also likely to be infected and spread the disease to their environment. Cases have been identified in which people in this age group also had severe illness [4].

METABOLIC SYNDROME AND ITS COMPONENTS

Different definitions were established by many associations. But the MetS components used today were determined with the common opinion of many associations in 2009. National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III (NCEP-ATP III) is one of the most widely used definitions among MetS criteria in the World [5].

Hyperglycaemia/IR, abdominal obesity, dyslipidaemia, and HT are the key determinants of the definition. Diagnostic criteria for MetS are:

- Obesity-increased waist circumference (>88 cm in women, >102 cm in men),
- Increased fasting blood glucose level (>100 mg/dL) or receiving antidiabetes treatment,
- High blood pressure (>130/85 mmHg) or receiving HT treatment,
- Two criteria associated with dyslipidaemia; high triglycerides (TG) (>150 mg/dL),
- Low high-density lipoproteins (HDL) (<50 in women and <40 mg/dL in men) [5]. The presence of three of these five criteria leads to the diagnosis of MetS. Among these criteria, obesity is among the controllable risk factors since it is generally associated with excess calorie intake and insufficient physical activity [6]. Over this 20-year period, cardiometabolic health has also significantly worsened, primarily related to worsening levels of adiposity and glucose, as well as increasing blood pressure. In addition, recent evidence shows that worldwide, about 3% of children and 5% of adolescents have MetS [7].

RELATIONSHIP BETWEEN COVID-19 AND COMORBID DISEASE

Chronic diseases are diseases that progress slowly, last three months or longer, are caused by more than one risk factor, usually show a complicated course, and affect the quality of life of the person. These diseases, which are risk factors that increase case fatality rates in the COVID-19 pandemic, have become the leading cause of death in all developed or developing countries all over the World [8]. In fact, chronic diseases have created a silent global epidemic, and the COVID-19 pandemic has prepared a ground that increases the effects of the epidemic. According to the WHO, noncommunicable diseases (NCD), primarily

CHAPTER 23

Metabolic Syndrome In Thyroid Disease

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Abstract: Thyroid diseases significantly influence metabolic parameters, including blood pressure regulation, glucose metabolism, obesity, hyperlipidemia, and non-alcoholic fatty liver disease (NAFLD). Hypothyroidism is often linked to hypertension, insulin resistance, and dyslipidemia, while hyperthyroidism may induce weight loss, insulin resistance, and dyslipidemia. Both hypo- and hyperthyroidism impact blood pressure regulation, glucose homeostasis, and adiposity. Dyslipidemia is frequently observed in thyroid disorders, with hypothyroidism associated with elevated cholesterol levels and hyperthyroidism with altered lipid profiles. Additionally, thyroid dysfunction contributes to the development of NAFLD. There is a close relationship between thyroid hormones and metabolic syndrome components, as well as the development of metabolic syndrome.

Keywords: Hypothyroidism, Hyperthyroidism, Metabolic syndrome, Thyroid diseases.

INTRODUCTION

Metabolic syndrome (MetS), characterized by a cluster of metabolic abnormalities, including central obesity, insulin resistance, dyslipidemia, and hypertension, poses a substantial burden on global health due to its association with increased cardiovascular risk and type 2 diabetes mellitus [1]. Concurrently, thyroid diseases constitute a diverse spectrum of conditions affecting thyroid hormone production and regulation. These disorders encompass hypothyroidism, which is characterized by insufficient thyroid hormone levels, subclinical hypothyroidism, where thyroid hormone levels are slightly decreased but still within the reference range, and hyperthyroidism, which is marked by excessive thyroid hormone production. Thyroid hormones play a pivotal role in regulating metabolic processes throughout the body, influencing energy expenditure, lipid metabolism, glucose homeostasis, and cardiovascular function [2].

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Hafize Uzun & Seyma Dumur (Eds.)

The relationship between MetS and thyroid diseases involves complex interactions. Both hypothyroidism and hyperthyroidism have been associated with MetS, a cluster of conditions including obesity, insulin resistance, dyslipidemia, and hypertension. Furthermore, common underlying factors, such as chronic low-grade inflammation, oxidative stress, and adipose tissue dysfunction, may contribute to the overlapping pathogenesis of both MetS and thyroid diseases.

THYROID HORMONE SYNTHESIS AND THE PHYSIOLOGICAL EFFECTS OF THYROID HORMONES

The thyroid gland, the body's largest endocrine organ, is situated in the anterior neck and weighs approximately 15–20 grams. Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the release of thyroid-stimulating hormone (TSH) from the pituitary gland. TSH acts as a stimulatory agent for the thyroid gland, prompting the synthesis of thyroxine (T4) and triiodothyronine (T3) hormones. The intricate process of thyroid hormone synthesis involves tiroglobulin synthesis within thyroid follicles, iodine uptake, iodine oxidation, iodination of tyrosine, and subsequent secretion of iodotyrosines into the circulation following coupling. The primary hormone originating from the thyroid gland is T4, which undergoes conversion to both the bioactive form T3 and the inactive form rT3 in peripheral tissues through the action of deiodinase enzymes. Surplus thyroid hormones are sequestered within follicles in association with tiroglobulins. With profound effects on virtually all bodily organs and systems, thyroid hormones principally accelerate metabolism and thermogenesis while exerting influences on body growth and development [3].

Hypothyroidism is a disease characterized by metabolic slowdown due to insufficient thyroid hormone at the tissue level or rarely ineffective thyroid hormone. It can be due to primary (thyroid), secondary (pituitary), or tertiary (hypothalamus) causes, depending on the level of hormone synthesis defect. The prevalence of hypothyroidism is around 5% worldwide, with the majority being attributable to primary hypothyroidism [4]. More prevalent among women and rising with age, it typically peaks between the ages of 30 and 50 [5]. Laboratory tests are used for diagnosis since hypothyroidism lacks overt and pathognomonic symptoms and signs. Diagnosis is established when free T4 levels are low and TSH levels are high. In cases where there are no clinical findings and free T4 levels are low with a mildly elevated TSH value, subclinical hypothyroidism may be considered. Fatigue, abnormal weight gain, constipation, intolerance to cold, dry skin, forgetfulness, and loss of appetite constitute general symptoms and signs associated with hypothyroidism. Other clinical findings that may occur in hypothyroidism include decreased cardiac output, bradycardia, increased peripheral vascular resistance and hypertension, hypercholesterolemia associated

with decreased cholesterol metabolism, and weight gain because of decreased metabolic rate, leading to non-alcoholic fatty liver disease [6].

Hyperthyroidism, characterized by an overactive thyroid gland and excess thyroid hormone production, accelerates metabolic processes and is often attributed to conditions such as Graves' disease, toxic nodular goiter, or thyroiditis. The clinical presentation of hyperthyroidism encompasses a spectrum of symptoms and signs indicative of the heightened metabolic state associated with excessive thyroid hormone activity. These include weight loss despite increased appetite, palpitations, heat intolerance, sweating, tremors, psychological symptoms such as anxiety, nervousness, or irritability, fatigue, diarrhea, muscle weakness, and menstrual irregularities in women. Furthermore, physical examination may reveal tachycardia, elevated blood pressure, a goiter, warm and moist skin, fine tremors of the extremities, manifestations of thyroid eye disease, alopecia or hair thinning, and excessive perspiration accompanied by flushed skin [7].

METABOLIC SYNDROME

It manifests as a clinical amalgamation of various interconnected metabolic irregularities linked to heightened risks of atherosclerotic disease, type 2 diabetes mellitus, and mortality. This condition typically arises from excessive weight gain and inadequate physical activity in individuals with a genetic predisposition. Diagnosis of MetS commonly relies on diagnostic criteria outlined by the International Diabetes Federation (IDF) and the National Cholesterol Education Program (NCEPT) (Table **1**) [8]. With the recent surge in obesity rates, the prevalence of MetS has also increased. Examination of U.S. data reveals a steady increase in the prevalence of MetS from 22% in 2002 to 37.6% in 2011 and finally to 41.8% in 2017 [9 - 11].

THYROID HORMONES AND METABOLIC SYNDROME

Thyroid hormones play a crucial role in metabolic regulation through their numerous effects on lipid metabolism, glucose homeostasis, energy expenditure, and blood pressure control. In recent years, a growing body of evidence has shed light on the intricate relationship between MetS and thyroid disorders. This emerging research suggests bidirectional influences and shared pathophysiological mechanisms between these two entities. Notably, individuals with MetS are more prone to developing thyroid dysfunction, while thyroid disorders, in turn, may exacerbate metabolic disturbances characteristic of MetS [12].

CHAPTER 24

Metabolic Syndrome and Polycystic Ovary Syndrome

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Abstract: Metabolic syndrome occurs at an early age in women with polycystic ovary syndrome (PCOS), particularly among women with the highest insulin levels and body mass index. Obesity is a common characteristic of PCOS and is more common in women with PCOS. Excessive weight gain may reveal the latent PCOS condition. Most women with PCOS are hyperinsulinemic and insulin-resistant. Insulin resistance (IR) is a major cause of metabolic manifestations and is known to be a common finding in PCOS. PCOS is also associated with an increased risk of impaired glucose tolerance, type 2 gestational diabetes mellitus, lipid and lipoprotein abnormalities, and nonalcoholic fatty liver disease. The presence of obesity, IR, impaired glucose tolerance, diabetes mellitus type 2, and dyslipidemia may predispose to coronary heart disease in women with PCOS.

Keywords: Insulin resistance, Metabolic syndrome, Polycystic ovary syndrome.

INTRODUCTION

There are several definitions of metabolic syndrome. The National Cholesterol Education Program-(NCEP) Adult Treatment Panel III (ATP III) criteria are the most widely used. Any three of the following five criteria compose the diagnosis of metabolic syndrome, according to the 2005 NCEP, ATP III criteria. These criteria include:

1. Waist circumference over 40 inches (men) or 35 inches (women),

2. Blood pressure over 130/85 mmHg,

3. Fasting triglyceride (TG) level over 150 mg/dl,

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Hafize Uzun & Seyma Dumur (Eds.)

4. Fasting high-density lipoprotein (HDL) cholesterol levels less than 40 mg/dl (men) or 50 mg/dl (women) and

5. Fasting blood sugar over 100 mg/dl [1].

In the USA, 34.5% of adults (33.7% among men and 35.4% among women) met the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria [2].

In addition to increased body weight, age, race, smoking, postmenopausal status, physical inactivity, high carbohydrate diet, low household income, and no alcohol consumption are the main risk factors for metabolic syndrome [3].

Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder of reproductive-aged women, affecting approximately 9-18% ofwomen in this age group, depending on the criteria used [4]. This syndrome is characterized by the polycystic appearance of the ovaries, chronic anovulation, and hyperandrogenism with variable clinical manifestations (oligo-amenorrhea, hirsutism, acne, and infertility) [5, 6].

PCOS is a multifactorial syndrome caused by the combination of many factors and is associated with multiple cardiometabolic outcomes, such as insulin resistance (IR), diabetes mellitus (both type 2 and gestational), obesity, atherogenic dyslipidemia, systemic inflammation, hypertension, coagulation disorders, and alcoholic fatty liver disease. Hyperandrogenemia plays a major role in the degree of these conditions.

The presence of IR plays an important role in the pathophysiology of metabolic syndrome, and hyperandrogenemia is an important cause of metabolic and reproductive disorders associated with PCOS, putting patients at increased risk of obesity, dyslipidemia, IR, type 2 diabetes, metabolic syndrome, and cardiovascular disease that may be important determinants of long-term health in this population [7].

Metabolic dysfunction, including hyperinsulinemia, IR, and type 2 diabetes of PCOS, overlap with components of the metabolic syndrome [4, 8 - 10].

More than 50% of women with PCOS are overweight or obese [11]. Abdominal visceral fat leads to IR, abnormal adipokine, and fatty acid enhancement [12]. Insulin resistance occurs in 50-70% of women with PCOS.

Metabolic syndrome occurs at an early age in women with PCOS, particularly among women with the highest insulin levels and BMI. Hyperinsulinemia, one of the main factors in the pathogenesis of PCOS, appears to be a common link between PCOS and metabolic syndrome. Strategies used in the treatment of IR have proven useful in the treatment of both syndromes. Whether these strategies will lead to a reduction in the risk of developing cardiovascular disease and type 2 diabetes remains to be proven. The metabolic syndrome is a common condition, especially in obese women with polycystic ovary syndrome (PCOS), particularly among women with the highest insulin levels and BMI. Hyperinsulinemia is a likely common pathogenetic factor for both PCOS and metabolic syndrome [13].

Obesity and PCOS

Obesity is a common characteristic of PCOS and is more common in women with PCOS [11]. The prevalence of obesity in these women varies due to geographic, environmental, and population differences between studies. It is unclear whether PCOS causes obesity or PCOS development [14]. There is a bidirectional relationship between PCOS and obesity; furthermore, excessive weight gain may reveal the latent PCOS condition [14]. Obesity is generally associated with high circulating insulin levels, resulting in increased androgen production in the ovaries [15].

Although the role of androgens in the development of visceral adiposity is unclear, it is known that IR causes this issue in women with PCOS [16]. Visceral adiposity may be a factor that triggers the development of irregular menstruation.

In overweight or obese women with PCOS, weight loss of as little as 5% has been found to improve PCOS symptoms [17, 18].

It has been reported that at least 50% of women with PCOS are overweight or obese, and most of these women have abdominal adiposity [19].

The presence of obesity in women with PCOS worsens metabolic and reproductive features [20].

The risk of PCOS increases with the presence of obesity, and the metabolic complications of PCOS are worsened by the concomitant presence of obesity, but it is still unclear if obesity itself is causative [21, 22].

Insulin Resistance and PCOS

Most women with PCOS are hyperinsulinemic and insulin-resistant compared with normal women, independent of obesity [23]. IR is a major cause of metabolic manifestations and is known to be a common finding in PCOS [23]. The

SUBJECT INDEX

A

B

C

D

E

F

G

H

I

K

L

M

N

O

P

R

S

T

U

V

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