Pathophysiology of the Metabolic Syndrome

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Metabolic syndrome (MetS) is a disease that has a complex etiology. It is defined as the co-occurrence of several pathophysiological disorders, including obesity, hyperglycemia, hypertension, and dyslipidemia.

metabolic syndrome

1. Introduction

Metabolic syndrome (MetS), a risk factor for cardiovascular diseases (CVD) and type 2 diabetes, affects a significant part of the population worldwide, with a prevalence of 10–30%. It is a clustering of interrelated metabolic disorders, which include insulin [1][2][3][4][5][6] resistance, central obesity, hypertriglyceridemia, lowered HDL cholesterol concentration, and hypertension [1][2]. MetS has had different criteria over the years, mainly associated with distinguishable definitions of abdominal obesity, with the World Health Organization (WHO), the National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP111), the American Association of Clinical Endocrinologists (AACE), and the European Group for Study of Insulin Resistance (EGSIR) all proposing their own diagnostic criteria [3][4]. Finally, in 2005, the International Diabetes Federation (IDF) provided a standardized consensus. The proposed definition includes waist circumference as a precondition for the identification of MetS and embraces the standard features of the previous definition, such as the assessment of triglyceride (TG) level, high-density lipoprotein cholesterol (HDL), blood pressure, and fasting glucose [5][6].

Metabolic pathways comprising the pathomechanism of MetS have not yet been clearly characterized. However, this is a tedious process due to the wide range of different pathophysiological mechanisms needing to be considered. Evidence suggests that various factors may predispose one to the development of MetS, such as genetics, diet, lifestyle, and gut microbiome [7][8]. A syndrome, which is more of a clinical term than a disease entity, suggests an association with other disorders. The current research shows that MetS predisposes one to cardiovascular dysfunctions via, e.g., atherosclerotic changes [9][10][11] and type 2 diabetes [12]. The correlation with other disorders is based on oxidative stress's role in the pathomechanism. Studies have indicated that there may be an association between MetS and Parkinson's disease [13], obstructive sleep apnea [14], and the progression and development of different cancers, such as colon cancer or gastric cancer [15][16][17]. Treatment is mainly based on lifestyle changes involving increased physical activity and a balanced diet. Researchers are currently looking for new substances that could significantly mitigate the severity and progression of MetS symptoms by affecting the metabolic pathways involved in the MetS pathophysiology. Numerous studies based on animal models have demonstrated the existence of a relationship between the intake of polyphenol-rich products and the mitigation of

individual components of MetS. A beneficial effect was obtained via a reduction in body weight, blood pressure, blood glucose levels, and improved lipid metabolism.

2. Pathophysiology of the Metabolic Syndrome

The main molecular changes in MetS result from a complex interaction between genetic and environmental factors. Visceral adipose tissue endocrine mediation, insulin resistance, and hypertension have been included as pathophysiological elements. The literature also highlights the contribution of endothelial dysfunction, systemic inflammation, and oxidative stress to MetS pathogenesis. However, it is difficult to identify individual pathophysiological mechanisms due to overlapping changes, where one pathology generates the next one, which determines yet another, and so forth.

2.1. Obesity

One of the main change-inducing factors is visceral obesity. An excess of adipose tissue contributes to the disruption of the body's homeostasis and the initiation of adaptive changes [18]. The state of positive energy balance and low-grade chronic inflammation leads to increased plasma FFA levels, which result in ectopic lipid storage and lipotoxicity. It is believed that the accumulation of visceral adipose tissue precedes the development of insulin resistance, and its role in MetS is associated with the secretion of numerous inflammatory mediators. Inflammation, in turn, is inextricably linked to the pathogenesis of atherosclerosis, forming a link between obesity and increased risk of CVD [18]. Adipose tissue as a whole is an endocrine organ. Adipocytes secrete numerous bioactive substances called adipocytokines, which maintain systemic homeostasis. An altered profile of adipocytokines may stimulate the development of MetS and play a crucial role in cellular dysfunction. The cytokines that predominantly contribute to abnormalities are resistin, leptin, adiponectin, TNF-α, and IL-6. A unique role is played by resistin, whose increased secretion by adipocytes in obese individuals correlates with increased cellular insulin resistance [19].

2.2. Insulin Resistance

The core element of MetS is insulin resistance (IR). Insulin resistance decreases the ability of various organs, for example, the liver, skeletal muscle, or adipose tissue—to respond to insulin [20]. Insulin regulates a wide range of biological processes by the activation of two crucial post-receptor transduction signaling cascades, PI3K (phosphatidylinositide 3 kinase) and RAS-MAPK (mitogen-activated protein kinase) [21]. PI3K cascade activation is responsible for the insulin effect on the metabolism by adjusting the activity of transcription factors responsible for cell proliferation and apoptosis. This pathway in vascular endothelium enhances nitric oxide production, inducing vasodilatation [22][23]. The RAS-MAPK signaling cascade plays a role in cell growth and proliferation and results in vasoconstriction [24][25]. The molecular alterations caused by insulin resistance are based on the downregulation of the PI3K pathway and the upregulation of RAS-MAPK [26][27]. In MetS, the insulin resistance that seems to emerge from positive energy balance is mainly caused by the oxidative stress to which cells are exposed. An excessive intake of energy-providing substances leads to an increased synthesis of nicotinamide adenine dinucleotide

phosphate (NADP), which promotes the biosynthesis of reactive oxygen species (ROS). As a means of defense, cells block the entry of energy-providing compounds, including, for example, glucose. Therefore, it may be concluded that insulin resistance in MetS serves as an adaptive mechanism protecting cells from potential damage related to the excessive generation of free radicals, thus exacerbating pathological changes in carbohydrate metabolism [2][19][28].

2.3. Free Radicals

Free radicals are small, diffusible, and highly reactive molecules marked by cytotoxic and genotoxic effects. The production of reactive oxygen species (ROS) is many associated with dysfunctional homeostasis, though some of these, called bioradicals, originate from the physiological process [17][29]. The excess accumulation of free radicals leads to chronic inflammation and an imbalance in cellular apoptosis and proliferation via the altered hyper- or hypo-activation of some cellular signaling pathways [17]. In MetS, visceral obesity contributes to the overproduction of adipokines [30][31]. Abnormal adipokine levels yield a persistent increase in systemic inflammation, and the infiltration of macrophages in visceral adipose tissue has collectively been indicated as a possible factor enhancing reactive oxygen species production. ROS contribute directly to autonomic balance dysregulation and, in turn, to inadequate blood pressure control [32][33].

2.4. Renin–Angiotensin–Aldosterone System (RAA)

The cardiovascular system is also subject to alterations related to MetS. Essential roles in hemodynamic pathophysiology are played by the activation of the renin–angiotensin–aldosterone system [34]; differing levels of adipocytokine secretion—i.e., leptin, tumor necrosis factor (TNF-α), and interleukin 6 (IL-6) [35][36]; and the hyperactivity of the sympathetic nervous system [37][38]. The hyperactivity of the sympathetic nervous system alone contributes to an increase in heart rate, circulating blood volume, ventricular end-diastolic volume, and cardiac output, which can directly—or indirectly via a feedback loop with the RAA system—lead to the development of hypertension [10]. The activation of the RAA system in the insulin resistance state is closely related to sodium retention, which leads to increased intravascular volume. However, an increase in the aldosterone serum level may also occur due to the upregulation of the angiotensinogen gene in adipose tissue. Studies suggest that increased proinflammatory adipokine secretion contributes to RAA activation by stimulating angiotensinogen production in adipocytes. The local stimulation of RAA in visceral adipose tissue may be critical in the pathogenesis of hypertension in obesity and metabolic syndrome [34][39].

3. Cardiovascular Consequences

The changes that occur in the cardiovascular system are extensive and lead to cardiomyopathy, microcirculation damage, and endothelial function impairment [9][10]. Each component of MetS is an independent risk factor for cardiovascular diseases. Studies indicate an association between MetS and the elevated risk of atherosclerosis, myocardial infarction, and heart failure. Obesity-associated cardiomyopathy is characterized by concentric left ventricular hypertrophy and systolic or diastolic dysfunction. In addition, myocardial contractility, systolic velocity,

and left ventricular shortening have been proven to be impaired [40][41]. Changes in microvascular tone and density are attributable to the non-equilibrium between oxygen delivery and tissue metabolism in miscellaneous vascular beds. These alternations in MetS are mainly caused by the significant variations existing in the control of arteriolar resistance [42]. Endothelial dysfunction is associated with decreased nitric oxide bioavailability in the setting of MetS. The underlying mechanism contributing to endothelial pathology is the augmented production of vasoconstrictors, including endothelin-1 (ET-1), thromboxane A_2 (TXA_2), and prostaglandin H_2 (PGH_2) [42]. The progression of atherosclerosis occurs over the years and is strongly correlated with age. The relation between the metabolic abnormalities occurring in MetS and atherosclerotic disease is undoubted. MetS leads to accelerated and more advanced atherosclerotic disease, which is correlated with a greater incidence of myocardial infractions. The adipose-derived hormones and adipokines released from fat depots, including perivascular adipose tissue, are considered to be the core of the pathological process and thought to mediate vascular calcification [43][44].

4. Polyphenols

Polyphenols are the most widespread bioactive compounds derived from plants. The basic monomer forming these secondary metabolites is a phenolic ring. According to their diverse chemical structures, polyphenols are classified into two major groups, flavonoids and nonflavonoids, as well as many subsequent groups [45][46]. The most widely known polyphenol substances include phenolic acids, flavonoids, stilbenes, lignans, and phenolic alcohols. Fruits and beverages constitute the core sources of polyphenolic compounds. Plants contain mixtures of polyphenols. They are considered to play a crucial role in adapting plants to their environment. In addition, they represent a significant source of bioactive pharmaceuticals [47]. Their health-promoting properties are mainly attributed to their antioxidant activity. However, polyphenols also possess pronounced anti-inflammatory, antiatherosclerotic, antiallergic, anti-microbial, anti-carcinogenic, and antimutagenic activities [48]. Considering that chronic progressive inflammation is a feature of MetS, polyphenols appear to be promising dietary supplements for preventing the progression of the disease and minimizing the effects of MetS.

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