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REVIEW ARTICLE

Adipose Tissue in Metabolic Syndrome: Onset and Progression of Atherosclerosis

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Metabolic syndrome (MetS) should be considered a clinical entity when its different symptoms share a common etiology: obesity/insulin resistance as a result of a multiorgan dysfunction. The main interest in treating MetS as a clinical entity is that the addition of its components drastically increases the risk of atherosclerosis. In MetS, the adipose tissue plays a central role along with an unbalanced gut microbiome, which has become relevant in recent years. Once visceral adipose tissue (VAT) increases, dyslipidemia and endothelial dysfunction follow as additive risk factors. However, when the nonalcoholic fatty liver is present, risk of a cardiovascular event is highly augmented. Epicardial adipose tissue (EAT) seems to increase simultaneously with the VAT. In this context, the former may play a more important role in the development of the atherosclerotic plaque than the latter. Hence, EAT may act as a paracrine tissue vis-à-vis the coronary arteries favoring the local inflammation and the atheroma calcification.

Key Words: Coronary artery disease, Dyslipidemias, Inflammation, Microbiota, Nonalcoholic fatty liver, Osteopontin, Osteoprotegerin.

Introduction

Metabolic syndrome (MetS) is characterized by a combination of interrelated cardiometabolic risk factors. Their concomitant presence confers an increased risk to produce adverse outcomes over the next 5–10 years (1) including a 5-fold risk of type 2 diabetes mellitus (T2DM), a 2-fold risk of coronary artery disease (CAD), and a 1.6-fold risk increase in total mortality (2). MetS is a major public-health challenge worldwide. In fact, the International Diabetes Federation (IDF) estimates that one-quarter of the adult population has MetS (3). It is widely accepted that the major risk factors for developing MetS are physical inactivity and consumption of an atherogenic diet (rich in saturated fats, cholesterol and refined carbohydrates). These unhealthy habits contribute to the development of abdominal obesity, insulin resistance (IR), dyslipidemia, inflammation and oxidative stress. All of these are MetS characteristics (2) and there are several reviews about their interrelationship. Interestingly, relatively recent studies have suggested other MetS etiologic factors such as a gut microbiome unbalance. There are also other abnormalities subjacent to MetS. That is, ectopic fat deposits, such as fatty liver and epicardial fat, may actively contribute to the increased risk of atherosclerosis associated with the syndrome.

In the present review, we first outline the already known characteristics and epidemiology of MetS as a condition of increased risk of atherosclerosis. We further focus on adipose tissue as an active participant of insulin resistance, inflammation, and dyslipidemia within the context of the MetS. Epicardial adipose tissue is highlighted as a potential paracrine organ that contributes to the inflammation and calcification of the atheroma, particularly important during the MetS. We also discuss fatty liver as an indicator of adipose tissue dysfunction, which leads to inflammation and dyslipidemia, increasing the atherosclerosis risk.

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Finally, we considered the gut microbiota as a potential participant of MetS.

Overview of MetS

In 1988, at the Banting Lecture organized by the American Diabetes Association, Reaven described "The Syndrome X", as a cluster of risk factors, related through insulin resistance, to diabetes and cardiovascular disease (4). However, he omitted obesity in his definition, which was then added as a crucial component by Kaplan (5) in 1989. The syndrome was further known as insulin-resistance syndrome (6) or hypertriglyceridemic waist phenotype (7). In the cardiovascular field, the term metabolic syndrome (MetS) is the most commonly used.

Definition and epidemiology of MetS. MetS is defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increase the risk of CAD and T2DM, and all-cause mortality (1). This cluster of cardiometabolic factors includes abdominal obesity and insulin resistance, atherogenic dyslipidemia [elevated serum triglycerides (Tg) and apolipoprotein (apo) B, increased small low-density lipoprotein particles (sdLDL) and reduced level of high-density lipoprotein cholesterol (HDL-C)], and a prothrombotic and proinflammatory state (8). In an effort to include MetS into clinical practice, several organizations have attempted to formulate simple criteria for its diagnosis (Table 1). Although the different definitions share common features, there are some factors such as variability and applicability that are not as predictive as for the rest. The World Health Organization (WHO) and the European Group for the Study of Insulin Resistance (EGIR) definitions (9,10) focus mainly on insulin resistance. In order to facilitate the clinical and epidemiological application of MetS, the National Cholesterol Education Program (NCEP) (11) proposed in 2001 a definition based on five measurements and laboratory results widely available to physicians: waist circumference, Tg, HDL-C, blood pressure, and glucose. The IDF further proposed a definition highlighting abdominal obesity as a key factor for MetS development and considering its presence as mandatory (12). The definition of thresholds for abdominal obesity is complicated because of differences in its relationship with other metabolic risk factors. Another reason is that CAD and T2DM predictive values are different among ethnic groups. Finally, in 2009, the IDF and the American Heart Association agreed that abdominal obesity should not be considered for MetS diagnosis (1). They defined MetS as the presence of any three of the five factors proposed by the NCEP but recommended different threshold values for abdominal obesity among different populations (1) (Table 2). Although this consensus gave clinicians the certainty of how to define MetS, it should be considered that abdominal obesity is the most prevalent component of this syndrome. Further studies exploring the relation of waist circumference thresholds to metabolic risk and cardiovascular outcomes in different populations are still needed.

Regardless of a specific definition, it is generally accepted that the worldwide prevalence of MetS may reach up to 84%, depending on the ethnicity, urban or rural environment, sex, and age. In the same vein, higher socioeconomic status, sedentary lifestyle, and body mass index (BMI) are directly associated with MetS prevalence. Diet, genetic background, and family history of diabetes also influence the prevalence of MetS and its components (13). The National Health and Nutrition Examination Survey (NHANES) reported a MetS prevalence of 5, 22 and 60% for normal weight, overweight, and obese subjects (14). According to age, 10% of individuals aged between 20 and 29 years developed MetS. The prevalence increased to 20% in those aged between 40 and 49 years and to 45% in those who were 40−49 years old. According to ethnicity, the NHANES survey reported that 25% of non-Hispanic black males carried MetS compared to 37% of non-Hispanic white males. In the case of females, non-Hispanic black and Mexican-Americans were 1.5 times more likely to have MetS than the non-Hispanic whites (15). Prospectively, the Framingham Heart Study reported that a weight gain of 2.25 kg over 16 years was associated with a 45% increased risk of MetS (16). Interestingly, each 11-cm increase in waist circumference is associated with an adjusted 80% increased risk for developing the syndrome (17).

Inflammasome activation in obesity and atherosclerosis. Inflammation is one of the most important mechanisms that links obesity to atherosclerosis. Inflammasomes are specialized multiprotein oligomers consisting of at least the caspase 1 apoptosis-associated speck-like protein containing a caspase-recruitment domains and nucleotide-binding oligomerization domain-like receptors (NALD or NLR), which are critical for the regulation of innate immune and inflammatory responses (18). Saturated fatty acid high-fat diets lead to obesity and enhance interleukin (IL)-1β-mediated adipose inflammation and insulin resistance. During obesity, NLRs respond to cytosolic agonists such as ceramides and palmitate. These molecules activate the NLRP3 receptor and promote the eventual conversion of pro-IL-1β into the potent pro-inflammatory cytokine IL-1β (18). The NLRP3 inflammasome is an important mechanism in obesity that participates in the development of insulin resistance through the direct inhibition on insulin signaling via IL-1β or by an increased production of tumor necrosis factor alpha (TNF-α), a known inducer of insulin resistance (19,20). Interestingly, weight loss in obese diabetic patients is associated with a decrease in NLRP3 and IL-1β expression in subcutaneous adipose tissue (SAT) (21,22). *In vitro* experiments have shown that primed macrophages secrete