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ADIPOCYTOKINES INVOLVED IN THE DEVELOPMENT OF METABOLIC DISORDERS: OBESITY AND TYPE 2 DIABETES

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Abstract: *Obesity is a multifactorial, long-term disorder, which has become a global epidemic with a significant social and psychological impact and increased mortality. Adipose tissue, the excess of which defines obesity, is an important endocrine and immune organ, which produces metabolically active substances, often referred to as "adipocytokines". In humans, adipose tissue can be divided into two main subtypes, namely the brown adipose tissue that is involved in thermogenesis and the white adipose tissue which is responsible for energy storage and the secretion of several adipokines and inflammatory cytokines. Adiponectin, leptin and resistin are the most frequently studied adipokines that influences insulin sensitivity, immune response and play an important role in the development of metabolic disorders.*

INTRODUCTION

Obesity is a complex, heterogeneous disorder, characterized by an increased or abnormal fat deposition in the adipose tissue (AT), which develops when certain environmental factors—both genetic and non-genetic—interact with a genetic predisposition.(1,2) It is described as a result of an increased body weight that exceeds the requirements of the skeletal structure, usually defined in adults as a body mass index (BMI) > 30 kg/m^2.(2,3) Obesity has become a worldwide epidemic and it is considered as a major risk factor for numerous chronic disorders, including non-alcoholic fatty liver disease (NAFLD), cardiovascular diseases (CVD), atherosclerosis, insulin resistance (IR) and type 2 diabetes mellitus (T2DM), as well as several types of cancer.(4,5,6) The World Health Organization (WHO) estimated than over 650 million adults were obese in 2016 and the prevalence of obesity has nearly tripled since 1975.(7) T2DM is a complex, long-term metabolic condition, characterized by the presence of increased blood glucose levels as a result of multi-organ insulin resistance in addition to pancreatic beta-cell dysfunction and insulin deficiency.(5,8,9) The global increase in obesity prevalence is responsible for the growing prevalence of diabetes, with an estimated number of 537 million adults living with diabetes worldwide.(10) Quality of life and mental status are significantly affected in these patients, anxiety and depression being the most common diseases. Despite the fact that the connection between obesity and T2DM are still not completely understood, adipocytokines such as leptin, resistin and adiponectin could be key factors in this interaction.(11)

LITERATURE REVIEW

Adipose tissue classification and distribution

AT is a specialized type of connective tissue that is mainly composed of mature adipocytes in addition to a number of other cell types, including pre-adipocytes, fibroblasts, endothelial cells, nerve tissue and several immune cells.(12,13,14) On the contrary to the previous concept of AT as a passive energy storage reservoir, it was shown to be a multifunctional, highly active metabolic and endocrine organ, which interacts with the brain, muscles, pancreas and liver in order to maintain homeostasis.(11,14) According to morphology, location and function, AT was initially categorized into white and brown subtypes, although a third category of AT - called brite (brown-in-white) or beige adipose tissue - has recently attracted the attention of researchers, due to its possible involvement in preventing obesity and T2DM.(12,14)

Brown adipose tissue (BAT) mainly consists of polygonal adipocytes with a large number of mitochondria and multilocular lipid droplets in their cytoplasm, which are responsible for its main biological function: the capacity to generate heat through non-shivering thermogenesis.(14,15) It was previously believed that in humans BAT was only active in newborns, serving as a defense mechanism against hypothermia. During childhood this tissue undergoes an involution, however it has been demonstrated that adult humans also have small amounts of active BAT depots in specific areas, including the neck, the suprarenal, supraclavicular, axillar and paravertebral regions, the mediastinum and the main vessels surrounding the heart.(12,14,16)

Beige adipocytes are part of a recently discovered, unique type of AT that can be found in rodents and humans within the white AT depots, but it shares morphological and thermogenic characteristics with BAT and contains a large number of mitochondria.(12,16)

As opposed to BAT, white adipose tissue (WAT) is composed of large, round adipocytes with a single lipid droplet and a limited number of mitochondria.(15) According to its distribution, human WAT can be classified into further subcategories, namely: SAT or subcutaneous WAT (mainly located in the gluteofemoral region) and VAT or visceral WAT, which includes the omental, retroperitoneal, mesenteric and pericardial fat depots.(14,15) Both the physiological and anatomical variations between these two forms of AT are important, as visceral obesity (which can be measured indirectly

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by waist circumference), is strongly linked to an increased risk of CVD, whereas the expansion of SAT contributes minimally to the risk of metabolic dysfunction.(14)

Adipokines and metabolic disorders

WAT is considered the most important adipose repository and also the largest endocrine organ that secretes numerous biologically and immunologically active substances, referred to as "adipocytokines". These molecules participate in various physiological signaling cascades such as the regulation of insulin resistance, glucose absorption, fatty acid oxidation and other metabolic processes, thus changes in their concentration are thought to be a sign of AT dysfunction.(4,11,17) Leptin, resistin and adiponectin are the most investigated adipokines, as they are strongly related to the development of T2DM due to their effect on insulin sensitivity and inflammation.(11,18)

Leptin is a non-glycosylated peptide hormone that is primarily produced by mature adipocytes of the WAT. Circulating leptin levels are good indicators of the body's metabolic status, since they are directly correlated with body fat mass.(17,18) Hyperleptinaemia and the development of hypothalamic leptin resistance have been reported in patients with obesity, as well as in case of individuals with coronary artery disease.(17,19) Leptin also controls lipid metabolism, pancreatic beta cell function and it has an impact on the development of insulin resistance, however the association between elevated leptin levels and T2DM is still unclear. In addition to its function in maintaining energy balance leptin regulates inflammatory responses and acts like a pro-inflammatory adipokine.(17,18,19)

Another important adipokine is adiponectin, which is a protein that shares structural similarities with TNF-alpha, and is mainly produced by SAT.(18,20) As opposed to leptin, individuals with obesity and cardio-metabolic diseases have lower blood levels of adiponectin, whilst weight loss and the use of anti-diabetic medications may increase the serum concentration of adiponectin. This adipokine has been shown to be able to reduce foam cell production and the migration of monocytes and macrophages to the arterial wall, hence avoiding atherosclerosis.(18) Adiponectin plays an important role in the control of glucose and lipid metabolism, and by promoting anti-inflammatory reactions and improving lipid oxidation it acts like an insulin sensitizer and antidiabetic adipokine. It also stimulates the glucose absorption in skeletal muscle, while suppressing gluconeogenesis in the liver.(17,21)

The name of the molecule, resistin, refers to the role of this adipocytokine in the development of insulin resistance. Since resistin levels are positively connected with insulin resistance in several in vitro and in vivo studies, resistin is thought to play a key role in the relationship between obesity and T2DM.(20,22,23) Additionally, clinical research has shown that plasma resistin levels correlate with inflammation-related biomarkers and may be a predictor of coronary atherosclerosis.(18,19) Moreover, it has been discovered that in abdominal adipose tissues the expression of resistin mRNA was significantly higher when compared to tissues in the thigh. These results suggest a connection between central or abdominal obesity and a person's increased risk of developing diabetes, as well as they support the validity of the waist-hip ratio as a quantitative indicator of the risk of T2DM.(21)

A retrospective, 8-year follow up study has been conducted in order to evaluate the metabolic differences among obese individuals that will develop and those that will not develop diabetes. According to this trial, there is a strong correlation between adiponectin and resistin levels and the onset of T2DM. Particularly, adiponectin levels were lower and resistin levels were higher in obese individuals who have developed diabetes, and these markers can be seen many years before the onset of diabetes. Taken together, these findings suggest that the above-mentioned adipocytokines can be helpful to improve preventive measures in individuals at a higher risk of developing metabolic diseases, since they are early predictors of T2DM.(24)

Obesity-related cytokines and chronic inflammation

Obesity and AT expansion has been linked to a particular type of inflammation also known as meta-inflammation (inflammatory condition in metabolic tissues) or low-grade inflammation. It is defined by only a moderate increase of pro-inflammatory cytokine levels, without clinical signs of inflammation, which induces oxidative stress and may play a key role in the development of comorbidities such as insulin resistance and T2DM.(25,26,27) Increased plasma levels of C-reactive protein (CRP), interleukine-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and other cytokines are characteristics of this low-grade inflammatory state.(3,19)

Numerous studies have demonstrated a connection between the elevated circulating CRP levels and a higher prevalence of T2DM and cardiovascular events.(28) CRP is an acute phase protein synthetized in the liver as a reaction to the IL-6 stimulus produced by adipocytes. In overweight and obese patients, CRP accelerates the atherosclerotic process by improving the expression of adhesion molecules in the endothelium, and it also influences the transcription of several genes linked to the inflammatory process.(20,29,30)

In addition to this, several authors focused on the prediction of cardiovascular events, studying the levels of other pro-inflammatory cytokines, such as IL-6, which were significantly higher in subjects with obesity and diabetes, and seemed to be useful predictor of cardiovascular events and mortality.(19,31,32) Chronically higher TNF-α levels were reported in patients with obesity and they were associated with insulin resistance, as well as with elevated plasma glucose, and insulin levels. TNF-α also encourages atherosclerosis by stimulating and activating vascular adhesion molecules and its plasma concentration is correlated with early coronary artery disease. Additionally, TNF-α increases the cytotoxicity of neutrophils and monocytes similarly to macrophages by acting as a chemoattractant for them.(19,20)

CONCLUSIONS

The complex molecular mechanisms behind metabolic disorders such as obesity and diabetes are not yet fully understood. Adipose tissue, especially adipocytokines, play an important role in metabolic regulation, immune response, thermogenesis and many other functions, for this reason, recognizing the molecular changes leading to adipose tissue dysfunction could be essential for better understanding the pathophysiology of obesity-related diseases. Abdominal obesity and the accumulation of visceral adipose tissue represent a major risk factor of developing insulin resistance and diabetes. The accumulation of white adipose tissue alters the regulation of adipocytokines in conditions including obesity, T2DM, and metabolic syndrome. Elevated plasma leptin and resistin levels on one hand, and decreased concentrations of adiponectin on the other hand, have been associated with higher risk of T2DM and cardiovascular diseases. Further research is needed to completely understand the immunological and endocrine function of AT in order to discover successful therapeutic approaches, which can improve metabolic consequences of obesity.

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