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ABDOMINAL OBESITY – A CARDIOMETABOLIC RISK FACTOR

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Abstract

Background and aims: *In the modern society, obesity represents an important health issue, both because the great number of obese patients in the developed and developing countries and the complications that occur in obese patients, accompanied by an increased risk for cardio-metabolic complications, cancer and death.* ***Material and methods:*** *Among the numerous data recorded in the literature, I made reference to about 30 articles supporting certain hypotheses or truths regarding the pathogenesis of obesity and its cardio-metabolic consequences.*

key words: *Obesity, insulin resistance, metabolic syndrome, leptin, adipocyte, cardio-metabolic risk factors*

Background and aims

In the modern society, obesity represents an important health issue, both because its increasing prevalence in the last decades in the developed and developing countries, and the complications that occur in obese patients, accompanied by an increased risk for cardio-metabolic diseases, cancer and death [1]. Nowadays, the metabolic syndrome is both a public health issue due to the pandemic evolution of obesity and a major cardiovascular risk factor (the risk is two times greater compared to individuals who do not have metabolic syndrome). Metabolic syndrome represents also a risk factor for diabetes mellitus (five times greater than in individuals without metabolic syndrome) and other comorbidities [2].

Material and methods

Starting with the research studies published in the last 4 years in the Romanian and international medical literature, we reviewed the causes of obesity and the pathophysiological mechanisms involved. We analyzed about 30 references supporting some hypotheses and truths regarding the pathogenesis of obesity and its cardio-metabolic consequences.

The real cause of obesity is the disruption of the balance between the intake and the energy expenditure. Food intake is managed by the central nervous system, the neuro-endocrine system components and the products secreted by the adipose cells. At the central level, the feeding behavior is influenced by the hypothalamus, the brainstem and the prefrontal cortex. Higher nerve centers in turn are influenced by the

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incoming information from the periphery and by the hormones synthesized in the stomach, intestine, adipose tissue and endocrine glands. The nerve centers are influenced directly by the circulating blood glucose and other drug metabolites. Food intake is influenced at a psychological level by the satisfaction-reward, pleasure-displeasure mechanism [1,3-5].

The reward mechanism is influenced also by dopamine [6]. A disturbance in the dopaminergic mechanisms, in the sense of increased dopamine release during food intake, provides a feeling of pleasure [6].

The endocannabinoids release leads to inhibition of satiety signals [7]. The palatable food will be consumed even if there are signs that the energy requirement was achieved. Overstimulation of the endocannabinoid system through continuous food intake leads to an increase of body fat [8].

Leptin, a hormone secreted by the adipose cells, is closely correlated with the amount of fat; thus, most of the obese people have high concentrations of leptin [9,10]. Leptin acts as an anorectic hormone, and its increased concentration should inhibit food intake. However, this is not the case in most obese people, so that common obesity is considered rather a leptin resistance syndrome than a defect in its secretion from adipocytes [3]. The phenomenon of leptin resistance occurs also in the case of the reward system - it is assumed that leptin causes a feeling of reward for small food amounts, if access to the food is limited. However, in the presence of a heavy diet, leptin does not alter the reward mechanism [10,11].

Leptin stimulates lipolysis, increases catabolism, and can increase blood pressure [9,12]. Its effect of increasing blood pressure might explain why obesity is a cardiovascular risk factor. Leptin also stimulates the secretion of adiponectin and increases insulin sensitivity in liver and muscle. It also modifies hepatic gluconeogenesis and pancreatic cell function [3].

Insulin, an important hormone regulating the energy balance, acts on the central nervous system through its receptors, and has an anorectic effect [13]. By disrupting the central mechanisms of action that are not yet precisely defined, the phenomenon of cerebral insulin resistance develops, which, together with the leptin resistance, may be considered a risk factor for obesity, diabetes, and metabolic syndrome [8,14]. It is also known that the phenomena of insulin and leptin resistance are more common in people with increased waist circumference, independent of BMI (body mass index), due to excessive visceral fat [15,16]. Insulin resistance, a cardio-metabolic risk factor frequently associated with abdominal obesity, is considered a consequence of liver and muscular hyperproduction of lipoprotein and the inability of the adipose tissue to store the calorie excess due to high calorie diet and sedentarism [17].

The phenomenon of insulin resistance appears also in the peripheral target tissues (skeletal muscle, adipose tissue and liver), leading to a decrease of the peripheral glucose uptake, and evolving towards hyperglycemia and the development of diabetes mellitus and metabolic syndrome [13,14,17].

Increased visceral adipose tissue is also determined by the androgen and estrogen hormones and the decreased secretion of growth hormone [18]. There are differences in receptor number and structure between the adipocytes of the two types of adipose tissues [18]. There are more receptors for glucocorticoid and androgen hormones in the adipocytes of the visceral adipose tissue. As for the estrogen hormones, the receptors in the adipocytes have a higher density in the subcutaneous adipose tissue, are in greater number in women than in men, and cause gynoid obesity and visceral adipose tissue growth in postmenopausal women [18,19].

The corticoid hormones have high levels in the adipose tissue of obese individuals, increase blood sugar, blood pressure, insulin resistance and adipocyte size [19]. It was reported that the levels of ghrelin and glucagon-like peptide-1 (GLP-1) are reduced in obese individuals due to chronic hyperphagia - but this hypothesis is not supported by all the studies [4].

Adiponectin, an adipocytokine, is involved in the pathogenesis of the metabolic syndrome, steatosis and T2DM (type 2 diabetes mellitus). It is anorectic, it stimulates insulin secretion and was reported to exhibit low levels in people who are insulin resistant. The adiponectin level is also low in metabolic syndrome patients. The relationship between the decrease in adiponectin in obese individuals with metabolic syndrome and increased production of pro-inflammatory proteins is still unclear [16].

Resistin is another adipocytokine with elevated levels in obesity and diabetes. It was reported to increase the hepatic synthesis of triglycerides and decrease insulin sensitivity [18].

Adipocytes increase the apelin secretion in obesity and insulin resistance. Visceral fat also produces visfatin, omentin and vaspin in a greater amount than the subcutaneous fat. Vaspin inhibits the secretion of leptin, resistin and TNF-α (tumor necrosis factor -α) and stimulates the secretion of adiponectin [20,21]. Other adipokines (chemerin and retinol binding protein 4) are involved in the metabolism of carbohydrates and lipids [21].

Studies also evidenced an association between android (visceral) obesity and cardiovascular disease, including coronary heart disease, and decreased cardiovascular risk in the case of gynoid obesity [1,15], due to the differences in the structure and function of the adipocytes. Other studies have shown that the decrease in waist circumference may lower the insulinemia, the triglycerides level and blood pressure in women [15]. In women over 45 years, increased visceral fat lowers high-density lipoprotein (HDL) cholesterol and increases the triglycerides and low-density lipoprotein (LDL)-cholesterol levels and also the degree of insulin resistance [22,23].

Abdominal obesity is also correlated with changes of the lipid levels, i.e. increased triglycerides, LDL-cholesterol and decreased HDL-cholesterol [23,24]. Excessive carbohydrate intake stimulates the hepatic production of very low density protein (VLDL) and LDL in some obese people, increasing the risk of atherosclerosis and coronary heart disease [24,25]. A carbohydrates rich diet causes hypertriglyceridemia by increasing blood sugar due to excessive food intake and reduced physical effort. The synthesis of triglycerides is affected by insulinemia, being a marker of the insulin resistance [25,26].

Hypertriglyceridemia in subjects with excessive visceral adipose tissue is due to increased flow of FFA (free fatty acids) released from the adipocytes. It was also shown that the hypertrophied visceral adipocytes are hyper-lipolytic and resistant at the anti-lipolytic action of insulin and that mitochondrial dysfunction induced by lipotoxicity contributes to the production and maintenance of high levels of FFA. Thus, adipocytes, by increasing the flow of FFA, cause an increase of liver gluconeogenesis [23,27].

FFA increase the hepatic synthesis of triglycerides and the lipid content in organs, causing, besides hypertriglyceridemia, triglyceride accumulation in ectopic deposits (liver, muscles, pancreas, myocardium) [22]. FFA also increase the oxidative stress involved in the pathogenesis of metabolic syndrome, atherosclerosis, diabetes mellitus and their complications [28].

Pro-inflammatory cytokines [C-reactive protein, TNF-α, interleukin-6 (IL-6)] are increased in obesity, as demonstrated by numerous studies [23]. Their pro-inflammatory effects represent a risk factor for atherosclerosis [23,29]. The secretion of IL-6 and TNF-α is stimulated by leptin, adiponectin, resistin and visfatin. TNF-α induces the production of cytokines which are responsible for the development of insulin resistance, inhibit the insulin receptors, modify the lipolysis process, leading to FFA release, and thus insulin resistance [20]. All these proinflammatory cytokines are released in large amounts in obese subjects and quantify the cardiovascular risk. They are part of the pathogenetic mechanism of the cardio-metabolic consequences of obesity, atherosclerosis, diabetes mellitus and metabolic syndrome [15].

Other cytokines [interleukin-8 (IL-8), monocyte chemoattractant protein-L, colony-stimulating factor (CSF)] contribute to the maintenance of chronic inflammation in the adipose tissue [25,30]. IL-6 is released by the macrophages present in the adipose tissue. The activation of the macrophages is achieved by the adipocyte necrosis, higher in obesity than in normal weight, which attracts macrophages around the necrotic adipocytes [30].

The adipose tissue contains, besides adipocytes, connective, vascular and nervous tissue, also macrophages, T lymphocytes, fibroblasts and pre-adipocytes. Recent studies on obese mice have shown that their fat contains more T lymphocytes than the normal weight mice and the T lymphocytes are the first to contribute to altered metabolism [30,31].

Other molecules released by adipocytes [cathepsin S, plasminogen activator inhibitor (PAI-1), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF)] have prothrombotic effects, being involved in the development of atherosclerosis [18].

Endothelial dysfunction, oxidative stress and vascular inflammation are associated with the development of high blood pressure and systemic atherosclerosis [23,32,33]. Nitric oxide is the most powerful endogenous vasodilator and it is produced by the endothelial cells [33]. Nitric oxide release is stimulated by insulin. Oxidative stress and lipotoxicity lead to the inhibition of nitric oxide synthesis, the activation of thromboxane and angiotensin II receptors and endothelin-I release, thus resulting in vasoconstriction, increased blood pressure and development of the systemic atherosclerosis [32].

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