Obesity, Inflammation and Aerobic Physical Exercise

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Abstract

The incidence of obesity and its association with co morbidities is dramatically increased worldwide, both in children and in adults. This difference in prevalence in different population groups is also related to environmental factors, especially diet and reduced physical activity. Some of these aspects related to or not with genetics, could be the key to explain the increasing rates of obesity in the world.

ABBR EVIATIONS

AT: Adipose Tissue; CVD: Cardio Vascular Disease; WTA: White Adipose Tissue; IL: Interleukin; TNF-A: Tumor Necrosis Factor-A; CRP: C – Reactive Protein; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; HIIT: High-Intensity Interval Training

INTRODUCTION

Recent studies present an alarming increase on the incidence of people with overweight or obesity in all countries. Obesity is considered a pandemic disease according to the World Health Organization [1,2] and almost two-thirds of American population is already classified with overweight or obesity [3]. The consequences of increasing Adipose Tissue (AT) on health range from high risk of metabolic disease and chronic low-inflammation to premature death. Biological events comprising natural body defenses against injury and infections play an important role in the immune system and persistent systemic markers of inflammation are prospective risk factors for chronic disease. Evidences show news relations between low-grade chronic inflammation and metabolic dysfunctions in some body systems and tissues, including circulatory (atherosclerosis, heart failure), endocrine (insulin resistance, type 2 diabetes), skeletal (sarcopenia, arthritis, osteoporosis) pulmonary (chronic obstructive pulmonary disease) and neurological system (dementia, depression) among other metabolic dysfunctions [4-9].

The role of genetics on obesity etiology has been studied; however, the high increase on this factor throughout the past 20 years cannot be justified by genetic changes that, theoretically, could happen in a short period of time [10]. Some authors emphasize that the prevalence of obesity in some groups is related to environmental factors [1,10] specially diet [11] and reduction of physical activity [1,2,12]. This review will discourse about the role of AT, adipokines, and high intense interval training in inflammation modulation.

OBESITY AND INFLAMMATION

Overweight and obesity became one of the most death-related problems in all worlds and it is due to the increase on processed food consumption and decrease on physical activity caused by urbanization. Some evidences indicate that obesity is related to some diseases like insulin resistance, type 2 diabetes, atherosclerosis, and chronic low-grade inflammation and it could lead to a life time reduction and social and economic problems [12,13]. Although obesity is considered the most common cause of many metabolic disorders, not all obese subjects develop those kind of alterations [10] and this is due to the difference in where fat is deposited (mainly visceral), gender, and physical activity. Other studies show that the abdominal fat excess is more pathogenic than subcutaneous and is responsible for initiate metabolic diseases with vascular involvement [14,15].

AT is responsible for many functions and is considered an endocrine organ that secretes some bioactive substances and is composed by many cells, when adipocytes are most abundant [9] and may be considered responsible for expression or secretion of inflammatory markers, being an important source of cytokines and [16].

Note that after obesity, AT deposits may change on its cellular composition including number, phenotype and immune, vascular and structural cells location. An imbalance on pro-
inflammatory and anti-inflammatory adipokines secretion by AT may contribute for Metabolic Dysfunctions (MD) [13], recent evidences shows that low-grade inflammation could be cause for increased cytokine secretion by adipocytes [17].

Inflammatory process is important and is a defense against noxious stimuli. The systemic inflammatory response is organized by immune function when internal and external stressors impairing homeostasis. The immune response has two separated, but related, pathways: innate and adaptive pathways. The key role of innate response is macrophages receptors increase, responsible for recognize pathogenic cells and stimulate phagocytesis and pro-inflammatory cytokines secretion (IL-6, IL-1 e TNF-α) and reactive oxygen species formation. Cytokines increase can increase local inflammation and also stimulate others pro-inflammatory cytokine secretion as CRP on liver [17,18].

Higher levels of inflammation may be associated with some pathology [19] as a result of neutrophils, monocytes, IL-1β, IL-6, TNF-α, CRP increase [20] and generic expression of TNF-α on IL-6 on AT is more evident in overweight or obese subjects [21,22] and it could be related to vascular damage [23].

ROLE OF ADIPOKINES ON LOW-GRAGE INFLAMMATION

The number of adipokines and other molecules linked with low-grade inflammation is growing. On this review we will focus on main IL secreted by AT and possible roles on low-grade inflammation development as obesity consequence.

IL-6 is more found on blood [24] and is synthesized by endothelial cells, monocytes and AT [14] in response to microorganisms and may be stimulated by other cytokines, predominantly by IL-1 and TNF-α and is responsible for immune and adaptive response to inflammation [23]. IL-6 can be considered an important inflammatory mediator including hepatic control of acute-phase proteins, including CRP [14,23] and is described as a pro-inflammatory cytokine because there it levels are increased after Sepsis and can stimulate other pro-inflammatory cytokine production from some sources, including liver [24].

Clinically, a plasmatic level of IL-6 has correlation with AT levels and the reduction on AT cause and reduction on IL-6 levels [13]. One-third of circulating IL-6 is from AT, principally AT visceral when compared to subcutaneous [9,13]. The increase on IL-6 expression may contribute to metabolic dysfunction, could be related to death by CVD, can cause atherosclerosis by an increase on endothelial chemokines and cell adhesion molecules (CAMs) and, also, involves in insulin resistance [13,24]. Recently, IL-6 has been shown as a potential hepatocyte insulin transduction signal [25] and also and leptin resistance mediator in obese subjects [26].

Either IL-6 or TNF-α are correlated with insulin resistance. Macrophages are the major source of TNF-α generated by AT and contribute with 30% of IL-6 production by AT [9]. TNF-α is considered an pro-inflammatory cytokine and is secreted by AT monocytes and macrophages with a role in inflammatory and autoimmune diseases and may be involved on paracrine function, with no increase on blood [13,27]. Both cytokine are linked with neurodegenerative diseases as Alzheimer and Parkinson.

Both TNF-α IL-1β as are related to a number of neurodegenerative diseases like Alzheimer’s and Parkinson’s disease. They can affect insulin sensitivity, lipid metabolism, and endothelial function [28]. TNF-α is positively correlated with insulin resistance markers associated with increased visceral adiposity, the level of TNF-α the mechanism attenuates the induction of serine phosphorylation by insulin receptors and inhibits insulin signaling in muscle and AT, may lead to insulin resistance [9,10,13,17] and IL-1α pro-inflammatory cytokine IL-1 family secreted by macrophages and TA can assist in increasing insulin resistance [14].

TNF-α may adversely affect lipid profile by increasing hepatic free fatty acid and triglyceride synthesis and through the decrease in endothelial lipoprotein lipase activity, leading to increased triglycerides and decreased levels of HDL and increased atherogenic synthesis of LDL particles [27,28]. The increase in systemic levels of TNF predisposes to endothelial dysfunction and subsequent atherosclerosis. TNF induces the expression of endothelial adhesion molecules and consequent endothelial nitric oxide synthase deletion, damaging the endothelium-dependent vasodilation [14,24,28].

In the same way TNF-α may increase the risk of developing atherosclerosis, CRP, which is an acute phase protein secreted by primary hepatocytes in response to IL-6 stimulation, also assists in the initial recruitment of inflammatory molecules into the vessel wall. Contributing to the formation of lesions and plaque ruptures and mechanisms of coronary thrombosis [4,23,24]. Concomitant with this, high levels of IL-1α (pro-inflammatory cytokine produced by TA) were also detected in atherosclerotic lesions in humans and may indicate instability of plaque [13].

POTENTIAL ADAPTATIONS OF HIGH-INTENSITY INTERVAL TRAINING CONTRIBUTING TO THE IMPROVEMENT IN INFLAMMATION

Physical exercise may be able to induce adaptations in various systems (cardio respiratory, muscular, metabolic, and neural), but the reasons why such adaptations happen are still not fully understood [29-31]. Skeletal muscle becomes the main target of physical training, and the changes that happen as a result of exercise cause improvement in endurance and metabolic efficiency. The aerobic exercise induce increases in mitochondrial biogenesis, the changes in the distribution of the fibers (for the oxidative glycolytic), increased fatty acid oxidation, increasing aerobic capacity and as a consequence the delay diseases such as obesity, type II diabetes and CVD [31] and reduction of abdominal adiposity, improved lipid profile (decrease in the levels of triglycerides and LDL and increase HDL levels), improves glucose metabolism, insulin sensitivity, lowers blood pressure, improves endothelial function, and inhibit vicious cycle of chronic inflammation [28,31].

The responses of cytokines regarding exercise are different to the various infections. When skeletal muscle contracts, it produces, expresses, and releases cytokines and other proteins, some of which have endocrine function, paracrine and autocrine,
making us realize a possible muscle communication with other organs. These mediators can be classified as myokines. A major myokine secreted is IL-6, although identified as a pro-inflammatory cytokine; IL-6 derived from the muscle contraction has anti-inflammatory function. This difference is possibly the signaling mechanism. In a state of chronic inflammation, IL-6 is responsible for the activation of monocytes and macrophages, whereas the muscular contraction induced IL-6 activation (and it occurs in the muscle cells) regardless the previous response to TNF [28].

The skeletal muscle during contraction is only able to produce IL-6 independent TNF, suggesting that IL-6 plays a role in the metabolism instead of inflammation [28,32,33]. It is suggested that IL-6 is the central mediation of acute effects caused by exercise, being succeeded by the increase in circulating levels of IL-1 receptor antagonist (IL-1ra) and IL-10, as having anti-inflammatory effect [20,28,34,35]. IL-1ra is secreted by proinflammatory action and inhibited by IL-1β, being IL-10 also secreted by monocytes and macrophages, among other sources but independent of the source, IL-10 seems to be strictly related to the process of mimetization of the induced inflammation by tissue damage. It is a potent anti-inflammatory condition promoter [20,32,35].

Many exercise protocols are designed in order to minimize the risk factors associated to chronic inflammation; the most common are regular low to moderate intensity exercise [36]. Studies have demonstrated the effectiveness of training programs with HIIT in the improvement of pro-inflammatory conditions, as well as an increase in plasma levels of anti-inflammatory molecules [32,37,38]. The High-Intensity Interval Training (HIIT) describes the physical exercise that is characterized by short burst (vigorous activity), interspersed with periods of rest or low intensity exercise. HIIT is infinitely variable with the specific physiological adaptations induced by this type of training determined by a myriad of factors including the precise nature of the exercise stimulus (i.e. intensity, duration, and number of intervals performed as well as patterns duration and activity during recovery) [39].

According to Gleeson (2011), increases in IL-6 levels did not occur substantially in the short or moderate exercise duration or low intensity, despite the many benefits that these exercises bring to health. HIIT may be associated with reductions in pro-inflammatory cytokines expression and increased anti-inflammatory cytokine, with greater efficiency when compared to moderate exercise on the reduction of risk factors of CVD and metabolic diseases [20]. Another study demonstrated that aerobic exercise of high intensity added to resistance exercise was effective in increasing the significant anti-inflammatory effects in patients with type II diabetes [40]. The HIIT can also significantly influence the production of myokines, leading to the improvement in anti-inflammatory profile [32].

The power of HIIT to induce a rapid remodeling in skeletal muscle is undoubtedly for its ability to recruit high levels of muscle fibers, mainly type II. This increase in muscle oxidative capacity is associated with optimizing the ability to oxidize fat, leading to a reduction in the risk of metabolic diseases with insulin resistance [30].

In conclusion, regular HIIT produces significant increases in aerobic e anaerobic capacity. HIIT appears to be effective in improving the inflammatory profile, indicating a decrease in risk factors for CVD and the high intensity exercise may be related to increased release of anti-inflammatory molecules. In addition, can to be involved in the improvement of insulin sensitivity.

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