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Review Article

Inflammatory Process in Obesity and the Effects of Omega-3 Supplementation and Aerobic Exercise as Adjuvant Treatment

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Abstract

Obesity is a complex disease of multifaceted etiology, with its own pathophysiology, comorbidities, and inflammatory profile. Accepting obesity as an inflammatory process is a key process to its treatment. Currently, the adipose tissue is a major focus of research in obesity due to an evolution in the understanding of the biological function of this tissue over the last decade. It is known that adipose tissue secretes multiple bioactive peptides, termed adipokines (proteins synthesized and secreted by adipose tissue) with specific actions towards inflammation. Also, many studies have shown an anti-inflammatory role for both Omega-3 supplementation and moderate aerobic exercise. Thus, the objective of this review is to approach the relationship between obesity and inflammatory adipokines, and discuss the role of Omega-3 and aerobic exercise in the treatment of this pathology. In this narrative review data collection has been performed through research articles published in the last five years through sites like PubMed and SCIELO, including some classic articles. It has been found that the Polyunsaturated Fatty Acids (PUFAs) supplementation may be an alternative, however its use targeting the decrease in inflammation caused by obesity has little scientific evidence; nevetheless, the role of aerobic exercise as an important concomitant intervention practice is well established, due to its implications both in the hypothalamic and endocrine anti-inflammatory process.

Introduction

Obesity is a disease that has emerged as a multi-factorial epidemic in developed and developing countries, which expanded during the last decades of the twentieth century as an important risk factor for the emergence, development, and worsening of other illnesses. According to the World Health Organization (WHO), obesity is characterized by an excess of body fat that can affect health outcomes, originated from a prolonged energy imbalance, in which there is an increase in body fat deposits [1].

The obesogenic process is accompanied by a chronic inflammation of the adipose tissue, which corresponds to an increase in circulating concentrations of inflammatory cytokines: Tumor Necrosis Factor (TNF), Interleukin 6 (IL-6), and C-Reactive Protein (CRP); and decreased adiponectin concentrations. This chronic inflammation associated with obesity may lead to the development of insulin resistance, coronary heart disease, cancer, hiperleptinemia, and abnormalities in systemic metabolism, also known as metabolic syndrome [2]. In this regard, nutritional interventions may feature beneficial results. E.g. it is known that diets high in saturated fatty acids are associated with increased incidence of inflammation through the activation of toll-like receptors (the innate immune receptors for Lipopolysaccharide (LPS)). However, anti-inflammatory dietary factors may assist in the treatment of obesity. The same holds true regarding the role of aerobic exercise in inflammation. This review aims to discuss the etiology of inflammation in obesity and the role in alleviating this situation through supplementation of Omega-3 and the practice of aerobic physical activity [2,3].

Development

Omega-3, inflammation and obesity

We can understand food control as a combination of several factors, one of them is the control modulated by neural structures and specific neurochemical and neuroendocrine systems. Alterations in the begginninng of this sentence that may occur in these neural systems might be associated with changes in eating behavior [4-6]. The brain plays a crucial role in regulating weight through our appetite education, motivation and physical activity, in addition to managing how energy is allocated in the body. In fact, it is known that the hypothalamus is the central portion for controlling these power-regulating activities. In animal studies, tiny lesions observed in this area can cause disorders such as obesity, for example, depending on its location. These observations led to the determination of certain parts of the hypothalamic centers as "satiety" or "hunger" [5,6].

Other than hypothalamus, adipose tissue is a major focus of obesity research as it is possible to analyze the different responses to various treatments that may be related to the cell characteristics of this tissue; thus, obesity needs to be evaluated in a multifactorial fashion. For example, weight control is determined by neural, endocrine, intestinal and psychological aspects beyond adiposity [7]. Obesity is characterized by a low-grade chronic inflammation of the adipose tissue, since fat plays the role of a secretory organ for signaling molecules; therefore obesity is considered an inflammatory process, increasing the circulation of pro-inflammatory cytokines [5]; mainly pro-inflammatory adipokines such as TNF-α, IL-6, decreasing the levels of anti-inflammatory adipokines as Interleukin 10 (IL-10) [1,2,6,7]. Adipokine is a general term adopted to describe the proteins secreted (and synthesized) by fat tissue, this protein being a cytokine or not. This inflammatory process resulting in the release of cytokines can be justified as the source of inflammatory markers in obesity; one can notice the difference and changes in adipokines in obese individuals [8] (Table 1).

The main trigger inflammation in obesity occurs as a metabolic response to tissue injury caused by excessive consumption of nutrients. Weight loss diminishes inflammation by reducing fat cells present in adipose tissue, pancreatic, liver and muscle, linking these cells to the onset of this inflammatory process [9,10]. This pro-inflammatory condition where the adipocytes and cells of the immune system (particularly macrophages and lymphocytes) are hypertrophied contributes to the associated state of chronic low grade systemic inflammation in obesity, called "metabolic inflammation", which is considered a point of prime importance in the pathogenesis of insulin resistance and type 2 diabetes in humans and in rodents; these metabolic conditions reveal molecular mechanisms involved in obesity and inflammation, which also include stress and mitochondrial dysfunction in the endoplasmic reticulum. Numerous studies indicate evidence demonstrating that the inflammatory condition also can be associated to insulin resistance and other disorders linked with obesity, such as hyperlipidemia, and the Metabolic Syndrome reviewed by itself [11].

This inflammation is characterized by the presence of macrophages in the vascular stroma- main source of inflammation induced by obesity. The number of macrophages present in this organelle is directly related to the level of adiposity and size of adipocytes. The adipocyte hypertrophy results in increased secretion of the chemokine, e.g., transforming growth factor β1, soluble Intracellular Adhesion Molecule-1 (ICAM-1) and Monocyte Chemoattractant Protein-1 (MCP-1). There is a subsequent increase in the infiltration

Table 1: Adipokines and Obesity.

Adipokines	Distribution	Function	Effects in obesity
Leptin	Predominantly secreted by white adipose tissue, to a lesser extent in the hypothalamus, gastric epithelium, placenta, and the gonads	Regulates energy consumption, costs and feeding behavior. It also regulates fat storage and insulin signaling	Increased levels in models made with obese mice. The increase in human obesity is correlated with BMI – decreased with weight loss.
Resistin	In rodents is secreted by adipocytes. In humans, secreted predominantly by circulating macrophages and monocytes, and to a lesser extent by white adipose tissue	Participates in the glucose metabolism, and regulation of gluconeogenesis and insulin resistance in rodents. In humans it is more pro-inflammatory	Increased circulating concentrations in rodent models of obesity. Increased in human obesity
TNF – α	Expressed by macrophages and adipocytes (visceral adipose tissue> subcutaneous adipose tissue)	It affects insulin and glucose metabolism, causes insulin resistance and stimulates lipolysis	Increase observed in obese mice models as well as in human obesity correlated with BMI.
IL-6	A third of all the circulating levels is expressed predominantly by adipocytes. Also expressed in macrophages, skeletal muscle, endothelial cells, and fibroblasts	Controversial role in the development of insulin resistance. It affects glucose metabolism	Increased circulating levels in humans obese and correlated with adiposity reduced by weight loss. Increased in the plasma of patients with DM2
IL-7	Secreted by the stromal and vascular endothelial cells	Participates in the regulation of body weight, adipose tissue and insulin signaling	Increase in individuals with morbid obesity
IL-8	Secreted by visceral adipocytes of White Adipose Tissue> subcutaneous adipose tissue) and macrophages	Neutrophil chemotaxis	Increased in obese subjects, increased fat mass and levels of TNF-α
Adipokine	**Distribution**	**Function**	**Effects in obesity**
IL -1	Mainly secreted by adipocytes and macrophages	Role in the chemotaxis of macrophages and thermogenesis	The increase in obese mice. Increased human and predictive obesity DM2
RBP4	Secreted by adipocytes, macrophages and hepatocytes	Affect the sensitivity to insulin, liver, the production of glucose and insulin signaling in muscle	Increased circulating levels in obese subjects
MCP-1	Secreted by adipose tissue	It affects the sensitivity to insulin increases, and the recruitment of macrophages in adipose tissue and inflammation	Increase in obese mice, and individuals with DM2
PAI -1	Expressed by white adipose tissue	Fibrinolytic pathway inhibitor	Increase in obesity and T2DM
CXCL – 5	Secreted by macrophages within stromal vascular fraction	Interferes with insulin signaling in muscle	Circulating levels are higher in obese individuals with insulin resistance
Visfatin	Expressed in liver, muscle, white adipose tissue, bone marrow and lymphocytes	Role in insulin sensitivity, insulin secretion and inflammatory properties	Increases in individuals with obesity and visceral adiposity
Chemerin	In rodents and humans, expressed in the placenta and white adipose tissue	Regulates the development of adipocytes and metabolic function	Increased circulating levels in obese and patients with DM2
Vaspin	Secreted by white adipose tissue, hypothalamus, pancreatic islets and skin	Improves insulin sensitivity	Increases in obese individuals

of macrophages, which in turn, secrete cytokines such as IL-6 and TNF, thereby settling chronic low-grade inflammation [7]. If on one hand obesity triggers an inflammatory process, adiponectin also produced by adipose tissue plays a protective role by decreasing insulin resistance; thus adiponectin appears to act as a sensitizing agent to insulin by reducing hepatic production of glucose and increasing insulin action in the liver. In addition to these actions, it reduces the activity of enzymes phosphoenol pyruvate carboxykinase, gluconeogenic, and glucose 6-phosphatase, responsible for the release of glucose from the liver into the blood, and decreases the oxidation of fatty acids in liver. Nevertheless, adiponectin in obese subjects is decreased, leading to an insulin resistance [10-12].

Obesity, as already shown, is a multi-factorial inflammatory process and have been studied in the neuroendocrine optical. Studies have pointed to the role of the brain as a large central controller in the development of obesity. The brain mechanisms are directly linked to this process [12-14]. The first evidence that the hypothalamus could exercise control over function in this process came in 1840, from the description of the case of a woman who had become extremely obese and whose autopsy revealed a large pituitary tumor compressing the base of the brain [15].

A study with human volunteers proved that the brains of obese individuals work differently when compared to the brains of normal individuals, and the final message of the authors relies on the role of the central nervous system and the influence of fatty acids in the functioning of the hypothalamus. It was proven by results of neuroimaging studies (functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET)) that there are significant differences in hypothalamic activity in response to the intake of fatty acids, which bind to cell membrane proteins known as TLR-4 -this receptor when activated triggers inflammation and cell endoplasmic reticulum stress that can cause the death of neurons. The consequence can be an imbalance in their number, leading to a possible reduction of neurons that trigger the desire to eat or of neurons that suppress hunger [13,14].

Studies have revealed that the relationship between the CNS and leptin in obese subjects is compromised due to the hypothalamus inflammation. This is derived from the high intake of fatty acids, primarily of animal origin. It was observed that neural activity in the hypothalamus of obese subjects, before and after bariatric surgery, is only partially recovered, suggesting that there may be irreversible damage. Accordingly, saturated fat consumption in long-term is related to apoptosis of neurons. Thus, obesity could be originated also by an error in the processing of information that reaches the brain [1,13]. These views allow relating various environmental factors triggering obesity, so that changes in the diet cause an impact in glucose levels and thereby reduce the inflammatory process. Obesity is also characterized by a process known as the release of pro-inflammatory cytokines; therefore anti-inflammatory mechanisms may come to counteract the response generated by adipose tissue [15].

Current studies are demonstrating and confirming that the hypothalamus is subjected to lipotoxicity and cellular stress, decreasing sensitivity to negative feedback signals important in appetite regulation and energy balance, ultimately contributing to the metabolic dysfunction. A study conducted with mice in 2014 sought to observe the manipulation of neuronal metabolism on hypothalamic level to reshape the metabolism and verify if it was possible to reverse the lipotoxicity induced by excess saturated fat [12]. The authors concluded that over nutrition, when specially characterized by high-fat diet consumption, as demonstrated previously, participates in TLR-4 signaling pathway activation by triggering the transcription factor NF-κB, which is responsible for conducting the processes and metabolic disorders such as leptin resistance, glucose intolerance and weight gain. In this sense, improving the type of dietary fat may offer benefits in reducing the inflammatory process, especially polyunsaturated fatty acids [16].

The WHO recently reiterated that inadequate diets and physical inactivity are among the ten major mortality factors. The current outlook showed that 170 million children and young people under 18 years old are overweight, alerting to the problems to be faced in the coming decades. Several articles have shown that dietary interventions may lower or even prevent the onset of many chronic diseases. In this context, the role of diet has always been mentioned in clinical and epidemiological studies. Thus, it has been well established in the literature that the amount and type of dietary fat have a direct influence on risk factors. However it should be noted that the lipids have importance in the supply and energy storage, they are precursors of steroid hormones and bile components of the cell membrane and participate in complex intracellular signaling systems [19,20].

Fatty acid derivatives act in the synthesis of prostaglandins, leukotrienes and thromboxanes [17]. Polyunsaturated fatty acids are classified as Omega-3 and 6, and have been studied for a long time. They have known anti-inflammatory effects such as the inhibition of cyclooxigenase pathway, neutrophils adherence reduction, lower expression of inflammatory cytokines and cell signaling inhibition via TLRs receptors. These anti-inflammatory effects encounter with the need and the importance of nutrition in the prophylaxis and treatment instrument for the treatment of obesity [18-22].

The daily intake recommendations of omega-3 and omega-6 supplementation vary according to age, gender and life stage (e.g. pregnant and lactating women). Recently the ISSFAL (International Society for the Study of Fatty Acids and Lipids) published a report on the recommended intake of Polyunsaturated Fatty Acids (PUFA) for healthy adults. This recommendation notes the concern in establishing the amount of intake of essential fatty acids (linoleic and linolenic AG), Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA):

1. Adequate intake of linoleic acid (Omega-6): 2% of total energy;

2. Healthy intake of linolenic acid (Omega-3): 0.7% of total energy;

3. To maintain cardiovascular health, minimum intake of EPA and combined DHA 500 mg/day.

The comparison of the effects of the types of fat and inflammatory processes mediated by C-reactive protein can be analyzed in figure 1, which can lead us to concept that dietary fat profile is capable of generating different inflammatory stimuli [13,15,16,18].

A pioneering work rated Eskimo populations whose staple food marine products and, on the other hand, people who consume a

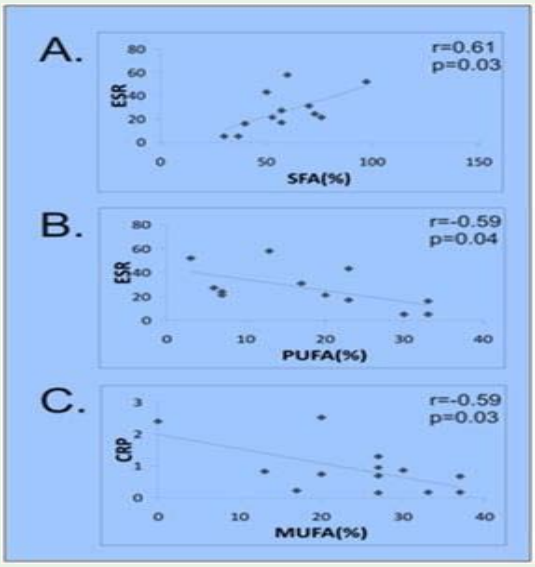

Figure 1: Representation of the correlation between Erythrocyte Sedimentation Rate (ESR) and ratio of saturated fat consumption (A), ESR and the ratio of polyunsaturated fat (PUFA) (B) and c-reactive protein ratio and monounsaturated fat (C) in patients before bariatric surgery [13].

Mediterranean diet, both showing reduced morbidity and mortality and related it to Omega-3 consumption. The authors concluded that Eskimos had low incidence of coronary heart disease, major bleeding time and lower concentration of lipids and lipoproteins. It was found that these factors were probably related to the high consumption of fish and other habits of that population [19-22].

The essential polyunsaturated fatty acids comprise one class of molecules that are necessary for the adequate functioning of the organism. The fatty acids of family n-6 (linoleic acid) and n-3 (linolenic acid) are obtained from the diet or produced by the body from linoleic and alpha-linolenic acids, by the action of desaturase and elongase enzymes. The elongase acts adding two carbon atoms to the initial part of the chain, by oxidizing desaturases and two chain carbons, yielding a double bond with the cis configuration according to figure 2, showing that Omega-3 and Omega 6 compete for the desaturation reactions and chain elongation; in this way the ratio between the intake of these nutrients make it important [23].

The ratio of the n-6 and n-3 fatty acids can be assessed so that they can drive the formation of certain leukotriens with greater affinity for the n-3 family fatty acids; conversely, conversion of alpha-linolenic fatty acid in LC-PUFA is strongly influenced by linoleic acid levels in the diet.

The daily ingestion of foods containing fatty acids of the n-6 and n-3 family is extremely important in human nutrition, resulting in a number of recommendations that have been established by authors and health authorities in different countries [24]. The figures show the trend of convergence ratio between fatty acids of the n-6 and n-3 to the range of 4:1 to 5:1. The ratio of 2:1 to 3:1 has been recommended by some authors, by allowing a greater conversion of alpha-linolenic acid to DHA, which reaches its maximum value around 2.3:1. Thus, the ratios of 2:1 and 4:1 are most common which result in a low intake of EPA and DHA. Moreover, diets with n-6/n-3 ratios of less than 1:1 is not recommended to inhibit the conversion of linoleic acid in PUFA-CML [24].

Linolenic acid's main sources are marine plants and animals, mostly phytoplankton, algae and fish oils. The phytoplankton, which constitutes the base of the food chain of the oceans, synthesizes EPA and DHA, which are found in high concentrations in fish oils and fish of cold, deep water, especially: mackerel, sardines, salmon and trout. Essential fatty acids from n-3 series can also be found in vegetable oils from flaxseed and canola [25]. The PUFAs have mechanisms related to chronic diseases due to the suppression of inflammatory processes and are required to maintain under normal conditions, cell membranes, brain function and the transmission of nerve impulses. Omega-3 fatty acids have anti-inflammatory effect for three important mechanisms: First, they influence the composition of the phospholipid cell membrane, resulting in the synthesis of lipid mediators with lower inflammatory potential mediators derived Omega-6 of GA. Secondly, they act as PPAR (Peroxisome Proliferation Activated Receptor), whose activation exerts anti-inflammatory effects. Thirdly, the Omega-3 AG stabilizes the NFkB/IkB complex, suppressing the activation of genes involved in the inflammatory process [26].

This process, in summary, influences on the decrease of leukocyte chemotaxis and adhesion molecules *via* cytokine pathway NF-κB and inflammatory eicosanoids, e.g. the increase of anti-inflammatory mediators and resolvins also observed after Omega-3 supplementation. Regarding the anti-inflammatory benefits of Omega-3 and gene expression; in this aspect we highlight genes that are regulated by the AG C-3 which can decrease the expression of inflammatory proteins: NF-κB; IKKS; iNOS; IFNg; IL-1b, 2, 6, 8, 12; E-selectin; VCAM1; LCAM1; 1MCP; CRP; MMP9; TNF-α; COX2 [26,27].

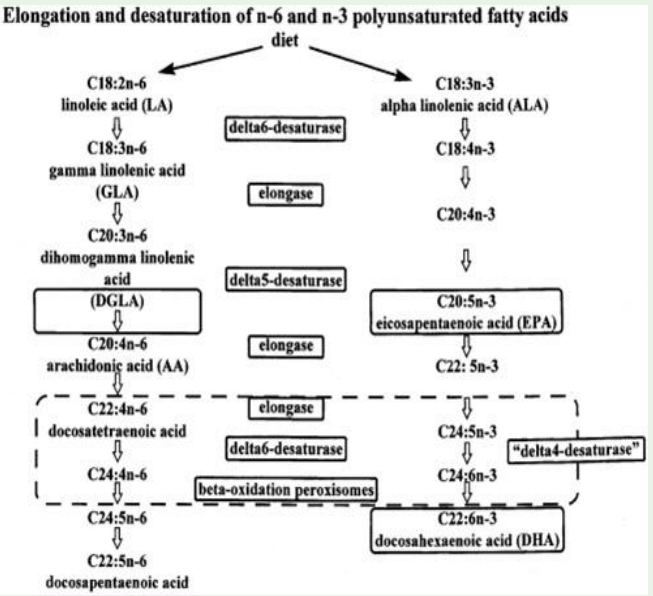

Figure 2: Competition in the metabolic formation of LCPUFAs, omega 6 and Omega-3 [21].

Most of clinical studies have undertaken to examine the action of the use of Omega-3 PUFA in different inflammatory diseases such as asthma, rheumatoid arthritis, inflammatory bowel disease, cardiovascular diseases [27-29]. A study published in The American Journal of Clinical Nutrition showed that supplementation with Omega-3 fatty acids favorably modulates fat, lipid profile and reduces systemic inflammation in non-diabetic patients with severe obesity. According to the authors, these effects can be beneficial in the long-term treatment of obesity. Treatment with Omega-3 fatty acids was well tolerated and featured no adverse effects. The group that received supplementation of Omega-3 fatty acids had a decrease in blood levels of interleukin-6 [IL-6]. It was the first randomized, controlled clinical study demonstrating that treatment with Omega-3 fatty acids with 36g of Omega-3 (EPA 460mg | 380mg DHA) attenuated the systemic and adipose tissue inflammation in severely obese individuals [4].

In line with this, satisfactory results were also observed by Kratz et al. (2013), in a study with patients moderately obese, despite the limitations on the dosage, the study showed an improvement in inflammatory processes, which can be restated in other studies [17]. The recommendations in small intervention studies demonstrated that diets rich in marine Omega-3 and supplementation with fish oil or DHA showed results consistent with an attenuation of the inflammatory response in individuals with diabetes and hypertriglyceridemia, however, in other experiments, the diet supplemented with Omega-3 did not cause changes significant in inflammatory parameters in patients with metabolic syndrome (1.24 g/day) and patients with previous myocardial infarction (5.2 g/day); the same occurring with supplementation with polyunsaturated fatty acids on CRP levels in healthy subjects (2.0 or 6.6 g/day) [27-30].

Ferrucci, et al. (2006) studied the relationship between circulating inflammatory markers in plasma and PUFA in 1,123 people aged 20-98 years. The total Omega-3 fatty acids were independently associated with lower levels of pro markers-inflammatory [IL-6, IL-1ra, -a Tumor Necrosis Factor (TNF-α), CRP], markers, and anti-inflammatory top [soluble IL-6R, IL-10, Transforming Growth Factor a (TGFa)]. The ratio of Omega-6/Omega-3 was a strong correlate of negative IL-10. The authors concluded that Omega-3 is beneficial in individuals affected by diseases characterized by active inflammation [31].

In the Brazilian market, the most frequent n-3 PUFA supplements are made up of fish oil and flaxseed. Formulations of chia and microalgae oil are traded internationally. The amount of EPA and DHA in fish oil capsules is variable, reaching 90% or 1000 mg in more concentrated presentations; the remainder of the capsule is composed of other polyunsaturated fatty acids, monounsaturated and saturated, besides gelatin and glycerin vehicles. More purified fish oil capsules preparations containing 85% of EPA-DHA, are marketed abroad, and semi-synthetic formulation of EPA is being evaluated in clinical studies [32]. Guidelines on the consumption of fats and cardiovascular disease have suggested that intakes more than >14g of ALA (Alpha Linolenic Acid) to reduce inflammatory markers, confirming an inverse relationship between intake of ALA and inflammatory parameters including serum CRP. Supplementation with ALA lowers levels of inflammatory markers in dyslipidemic individuals, which occurs especially when the base diet is rich in saturated fat and low in monounsaturated fats [33].

Physical activity, inflammation and obesity

It is a general conception that obesity is multi-factorial, so that physical inactivity may contribute to increased adiposity, inducing the increase of pro-inflammatory nature of adipokine secretion. Exercise can be defined as a planned, structured and repetitive physical activity that aims to improve or maintain one or more components of physical fitness. According to the American College of Sports Medicine (ACSM), the recommendations for prevention of body weight gain are 150-250 minutes per week of aerobic exercise with moderate intensity, for the weight gain prevention, and for weight loss, 250 minutes per week of moderate intensity aerobic exercise [34].

Excess adipose tissue and high intake of fats are a major factor for the activation of inflammatory biochemical pathways as described; and thus they cause damages in intracellular signaling of insulin. The uptake of glucose into tissues consists of several stages where adipokines secreted by adipose tissue, mainly the TNF-α and free fatty acids, from the high consumption of fats, are able to activate inflammatory proteins such as c-Jun N-terminal Kinase (JNK), IKappa Kinase (IKK), transcription factor kB (NF-κB), thus altering the insulin signaling and decreasing glucose uptake into the cells. Scientific evidence shows that physical exercise increases glucose uptake by distinct method: the insulin being dependent of protein kinase activation enabled by AMP (AMPK) and the expression of this angiograms inflammatory proteins [34,35].

In a recent study conducted in rats, the authors tried to observe the anti-inflammatory action of the practice of exercises ahead to a high-fat diet. The conclusion was that the practice of moderate physical activity in the presence of a high-fat diet resulted in protection with respect to expression of inflammatory genes: gene expression of MCP-1, F4/80, and the marker bias M1 macrophage, CD11c; in white adipose tissue after 4 weeks [36,37]. Another study in 15 obese and non-diabetic women demonstrated that an intervention consisting of 30 min aerobic activity 3x/ week for three months improved anthropometric, biochemical and hormonal measures, showing how aerobic activity in obese individuals decreased inflammation and insulin resistance; and featured an smaller influence on the endocrine function in adipose tissue [38]. The benefits of greater physical fitness have been reported widely in the literature. Aerobic activities generate direct and indirect effects on the circulatory system, quality of life, tolerance to stress, muscle strength, flexibility and living habits. Regular physical activity integrates with the secretion of various substances such as neurotransmitters, leptin, beta-endorphins, nitric oxide and other, generating benefits of great significance in the welfare state and increases motivation, regulating satiety and appetite [7,9].

It is plausible to associate the hyperleptinemia observed during obesity as stimulating energy consumption, but some studies suggest that the physical activity practice promote greater energy expenditure and influence appetite control (*i.e.*, the physiological and psychological processes underlying regulatory to food) and energy consumption. This dynamic interaction means that exercise will have a negative impact (decrease) on the biological mechanisms that control appetite,

and is therefore a positive factor in reducing one aspect triggered by the inflammatory process of obesity [35,39].

Chronic responses to aerobic exercise resulted in lower concentrations of CRP, IL-6 and TNF-α, as evidenced in adults and children studies. The anti-inflammatory role of regular exercise in obesity has received significant focus on endocrine and metabolic functions of adipocytes. Physically active obese subjects release more adiponectin, resulting in increased activation of protein kinase AMPK, increased beta-oxidation rates and improves glucose transport in active muscles [36,40]. Physical exercise seems to attenuate the basal levels of TNF. A cross-sectional study using self-reported level of physical activity, showed that people with higher physical activity levels had lower circulating levels of TNF and other inflammatory markers (such as IL-6 and C-reactive protein) than those self-reportedly sedentary, regardless of gender, age, smoking, body mass index, the total cholesterol and blood glucose levels and blood pressure. It has been suggested that the high level of physical activity decreases the levels of peripheral mediators of the inflammatory response, including TNF, at a rate of 20-60% compared to sedentary lifestyle. Another observed point was the stimulus the muscle fibers and the appearance of anti-inflammatory cytokines such as IL-10 in the circulation, which inhibits the production of inflammatory cytokine TNF-α, TNF-α receptor pathway, TNF-R and IL-6. Also, it promoted greater turnover of lipids, increasing lipolysis and fat oxidation rates [37,41].

Weight loss is associated with a decreased degree of inflammation in adults. Nevertheless, a study with obese children aerobically trained by just eight weeks demonstrated that although the increase of VO2 max ($p < 0.05$) was significantly correlated with weight loss, no improvement in the profile of adipokines was seen [37,38]. A recent study showed that physical activity evaluated through physical exercise protocols improved physical, clinical and metabolic diseases in obese individuals, and found that physical exercise decreases the expression of CCR5 (Chemokine Receptor Type 5) of RANTES (Regulated upon Activation, Normal T-cell Expressed) in adipose tissue [42]. RANTES is a proinflammatory chemokine that controls traffic of immune inflammatory cells such as monocytes, macrophages, T cells and dendritic cells from the circulation in various tissues, including adipose tissue.

One of the main characteristics of macrophages infiltrate in adipose tissue is the heterogeneity of their phenotype and their state of polarization; they may be pro-inflammatory (M1-phenotype) secreting various inflammatory mediators such as TNF-α, IL-6, macrophages or anti-inflammatory (M2-phenotype) to secrete anti-inflammatory cytokines such as IL-10 [43]. In obesity, we can see a differentiation of these two types of macrophages: M1, M2 is considered an important event and supports chronic inflammation. Indeed, studies in rats indicate that obesity induces a shift in the balance of macrophages M1-phenotype, which further perpetuate the inflammatory response and insulin resistance [37]. This recent study emphasizes the importance of non-pharmacological tools acting in inflammatory responses and improvements on the aspect of signaling: RANTES/CCR5 in adipose tissue.

As previously described, obesity can be triggered by numerous factors, including hypothalamic aspects, a factor possibly arising from a diet high in saturated fat, which has been evidenced as a promoter of inflammation and subsequent resistance to regulating hormones of satiety and appetite. Physical activity also was shown to have an important role in this phenomenon. In a study conducted in rats, it was observed that acute physical activity practice generates the suppression of hypothalamic PTP1B (Protein Tyrosine Phosphatase 1B) which would have a key role in resistance to leptin and insulin. The study demonstrated that prolonged acute exercise response induced an anti-inflammatory profile in the obese rodents, reducing PTP1B protein levels, insulin and leptin sensitivity improved in an IL-6-dependent manner [15,44]. Ropelle, et al. (2010) studied obese mice; in this study they gave a high saturated fat diet, and then submitted the animals to swim and run on a treadmill, while others remained sedentary. The mice that were intensively exercised produced anti-inflammatory interleukins (in this case, two types of IL-6 and IL-10). These interleukins reduced the inflammation in the hypothalamus neurons and insulin again functioned normally. The animals in this group started to eat less and lose weight. "Physical activity restored the molecular and cellular balance of the hypothalamus" concluded Ropelle. To check whether these two proteins had the same effect, IL-6 and IL-10 were found in the brains of obese animals that did not exercise and they lost weight [45,46]. This paper raises the possibility of controlling obesity by interfering with the inflammatory processes in the central nervous system by stimulating physical activity, demonstrating their importance in the treatment.

Conclusion

The adipose tissue actively secretes a variety of pro-inflammatory cytokines, the degree of inflammation caused by obesity predisposes to an increase in circulating concentrations of inflammatory cytokines TNF, IL-6, C-reactive protein (CRP) and hypothalamic inflammation, arising from the consumption of saturated fat, and decreased adiponectin concentrations. It is a complex process in which the biochemical markers play different roles and follow diverse metabolic pathways, however, more research is needed in order to identify new inflammatory markers, benchmarks, risk and cutoffs of inflammation caused by obesity; it is still necessary to conduct investigations in order to monitor a marker separately or in combination that can predict risk and the proportion of inflammation in obesity. Although several studies conducted involving the use of n3-PUFA related to the treatment and prevention of obesity, there remains a lack of evidence associating supplementation of polyunsaturated fatty acids and their influence on the modulation of inflammation in obesity. The benefit of poly-unsaturated fats in the diet can be improving the conditions of this overconsumption of saturated fats and this may reflect in anti-inflammatory benefits, yet there are not enough studies to establish degrees of recommendation and level of evidence for different strategies and dietary patterns that relate to the risk of inflammation in obesity.

Aerobic activity have a positive control of energy balance, decreases insulin resistance, contributes increasing IL-6 and IL-10 in muscle and hypothalamus, reducing hypothalamic inflammation, and basal TNF-α, however, there seems to be a new and exciting biological plausibility on the literature regarding aerobic exercise in experimental models of obesity and its possible hypothalamic benefits. Nevertheless, few studies explore the effects of both interventions in this disease in human subjects. The possible additive or synergic effects of Omega-3 supplementation with aerobic exercise in obesity merits further investigation.

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