

Mini Review

Effects of Exercise in Obesity-Induced Low-Grade Inflammation

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Summary

Adipose tissue was for a long time seen as just a way of storing excess of energy. However, in the second half of the past century many studies began to show that adipose tissue is in fact an endocrine organ with autocrine and paracrine functions due to the secretion of biologically active molecules, collectively called adipokines. The fast mass expansion caused by hypertrophy in obesity makes some regions of the adipocytes distant to the blood vasculature, thus leading to low PO₂. Hypoxia underpins the initiation and progression of the inflammatory response that includes increase in the production of tumor necrosis factor alpha (TNF- α), Interleukin-6 (IL-6) and leptin and reduction in the production of adiponectin. Exercise effects had been seen as indirect but new evidence suggests that exercise has somatoly effects to diet and is more effective when weight loss is the same. No specific type of exercise shows to be superior in improving inflammatory profile in obesity.

ABBREVIATIONS

IL-6: Interleukin-6; TNF- α : Tumor necrosis factor alpha

INTRODUCTION

Adipose tissue was for a long time seen as just a way of storing excess of energy. However, in the second half of the past century, many studies began to show that adipose tissue is in fact an endocrine organ with autocrine and paracrine functions due to the secretion of biologically active molecules, collectively called adipokines [1]. Changes in adipokines release due to obesity and ensuing metabolic complications are major concerns for public health and these disturbances are the major causes of life expectancy reduction in modern history [2,3].

To clarify how obesity is related to metabolic disorders and the potential benefits of exercise, this review is structured in three topics: first, we show how adipocyte hypertrophy leads to tissue hypoxia; in the second, we describe the effects of the obesity-induced adipose tissue hypoxia changes adipokines profile and; last we discuss the effects of exercise on adipokines release by adipose tissue.

Changes in adipose tissue with obesity - tissue hypoxia

Obesity leads to enlargement of adipose tissue as a response to the excess energy intake to be stored. As it is well known there is a bulk of literature on adipose tissue growth in normal and

abnormal development, characterizing the state of the tissue in terms of the mean cell size (hypertrophy) and cell number (hyperplasia) [4]. The classic work of Salans, Cushman [5] compared the size and number of adipocytes of obese and non-obese individuals. They showed that obese individuals had an average of 60kg of body fat, compared to 14kg of the non-obese and that mean cellular volume of obese individuals was twice the size of the normal population, thus obese individuals had a much larger number of adipose cells. Their work also showed that those who became obese at ages up to 25 years had hyperplastic obesity and those who became obese after the age of 25 had hypertrophic obesity.

Another ground-breaking work was made by Hirsch and Batchelor [6]. They classified individuals using ideal body weight as normal (up to 110% of ideal body weight), class I obese (115-170% of ideal body weight), class II obese (170-240% of ideal body weight) and class III obese (over 240% of ideal body weight). Results showed that individuals classified as class I had a normal number of cells, but they were hypertrophic. Adipocytes of class II individuals were slightly bigger and more numerous and class III individuals had adipocytes as big as class II individuals, but a much higher number.

The combined works of Salans, Cushman [5] and Hirsch and Batchelor [6] show that early-developed obesity tends to be hyperplastic and once individuals are adult, the first response of

the adipose tissue is hypertrophy. This increase in adipocyte cell size from 0.4-0.6 μ g in normal individuals to 1.0-1.2 μ g in obese individuals is the "tipping point" for obesity-related problems. The obesogenic environmental and genetic factors disturb homeostatic crosstalk between tissues and promote excessive fat deposition and ultimately alter cellular functions [2].

The fail of an adaptive mechanism in adipose tissue may occur because the fast mass expansion caused by hypertrophy makes some regions of the adipocytes distant to the blood vasculature, thus leading to low PO₂ [7]. Hypoxia underpins the initiation and progression of the inflammatory response in adipose tissue and it can underpin the high oxidative stress, providing dysfunction of adipose tissue due to the low level of O₂ and consequently low capillary density [7,8]. A study of Pasarica, Sereda [9] has shown that capillary density is lower in adipose tissue of obese humans compared with lean subjects and corroborate with the data of Spencer, Unal [10] that demonstrate reduced capillary density in adipose tissue of the obese is accompanied by 70% of the larger vessels. Under these conditions it is possible to identify the infiltration of macrophages once there is a great association of low PO₂ and the accumulation of immune cells [11].

It is noteworthy that the recruitment of macrophages may not necessarily reflect inflammation process but the need to remove dead adipocytes [12]. In this case, chemical signals emitted by dead microorganisms, mainly macrophages, attract leukocytes to this region. Therefore large amount of leukocytes accumulated produces an inflammatory response and induce the expression of inflammatory cytokines initiating a chronic low-grade inflammation condition and metabolic diseases [13].

Adipokine release in obese adipose tissue

The obesity-induced adipocyte hypoxia promotes deregulation in the gene expression and secretion of adipokines resulting in metabolic dysfunctions associated with obesity, such as hypertension, diabetes and dyslipidemia [14]. Given the scope of this review, we will present the effects of adipose tissue hypoxia on leptin, interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α) and adiponectin.

Leptin was one of the first adipokines shown to be released by adipose tissue. It acts on the central nervous system to reduce energy intake, and increase energy expenditure [1]. Normal blood leptin values range between 6-8 ng/mL [15] and obese individuals may have values as high as 33 ng/mL [16]. This may seem a paradox, given that higher leptin expression should lead to reduced energy intake. However, obese individuals are resistant to leptin and it does not yield its expected physiological effects. High leptin concentration is associated to insulin resistance and cancer [17].

IL-6 and TNF- α are secreted predominantly by visceral adipose tissue. IL-6 is involved in hematopoiesis, immune and inflammatory responses [15]. Obese individuals have higher IL-6 and TNF- α concentration compared to individuals who are non-obese and have higher insulin sensitivity [1,18]. Both these adipokines play an important role in insulin resistance and increased TNF- α concentration is also associated to vascular inflammation and atherogenesis [19].

Among the adipokines described on this review, adiponectin is the only one with anti-inflammatory effects and has also effects against obesity, atherogenesis and diabetes [1]. Obesity leads to reduced adiponectin expression and release, which also seems to be diminished by increased TNF- α concentration [20].

The collective of data show that the obesity-induced hypoxia in adipose tissue changes adipokines release into an inflammatory profile that leads to insulin resistance, atherogenesis and even cancer. This is the link between the low-grade inflammation in obesity and metabolic disorders.

Effects of exercise on low-grade inflammation

For quite some time it was believed that the main factor in improving adipokine profile is weight loss, and despite only a few references that said otherwise, exercise would only have an indirect effect, as it would only lead to reduction in TNF- α , IL-6, leptin and other inflammatory adipokines and increase in adiponectin if it actually led to weight loss [15]. This association was made because the majority of studies showed a close relationship between inflammatory markers and weight loss. The improvement in inflammatory profile was reported, on most cases, in studies where anthropometric markers also had significant changes. For example, Kondo, Kobayashi [21] and Polak, Klimcakova [22] have shown that reductions in leptin levels were closely associated to reduction in body fat.

Some new evidence is now showing that exercise may play a more important role. Wang, You [23] compared a group that was submitted only to diet and a group that was submitted to diet and treadmill walking. The two groups had similar energy deficit and weight loss, but the exercise group was the only that had increased concentration of adiponectin after the period. In a similar manner, Weiss, Reeds [24] compared groups of caloric restriction, exercise and their combination and despite a similar weight loss of approximately 7% in all groups the combined group had a larger reduction in leptin concentration.

Two other studies were made where exercise was used compared to diet Khoo, Dhamodaran [25]. Compared the effects of 24 weeks of diet and exercise with the same energy deficit that lead to the same weight loss. However, the exercise group had a larger reduction in body fat percentage and was the only group to have elevated adiponectin concentration. van Gemert, May [26] yielded similar energy deficit and weight loss of obese individuals and found that only the exercise group had a reduction in leptin concentration.

Those studies show that the same energy deficit is actually more effective when exercise is a part of the intervention and that exercise alone is more effective than diet alone which leads to an important question: what type of exercise is more effective?

Moradi [27] reported increase in adiponectin levels of obese men after 12 weeks of resistance exercise without changes in body mass but with a reduction in body fat percentage. Gerosa-Neto, Antunes [28] submitted overweight and obese men to 16 weeks of continuous or interval training. All interventions led to increased adiponectin, continuous group had reduction in TNF- α and interval groups had reduced IL-6 and increased TNF- α . Lopes, Leite [29] verified the effects of 12 weeks of combined

(endurance and resistance) training in overweight girls and reported reduction in body and fat mass, increase in lean mass that was accompanied by reduction in leptin concentration. Chagas, Bonfim [30] submitted obese women to 20 weeks of combined training and reported reduction in body mass, body fat percentage, waist circumference and TNF- α .

This collective of studies show that there is not actually a form of exercise that is more effective, as endurance, resistance and combined training have shown to be effective. A recent meta-analysis by Clark [31] has shown that exercise is effective in improving inflammatory profile in periods of at least 8 weeks and that these modes of training lead to the same results in up to 32 weeks.

CONCLUSION

The hypertrophy in adipose cells caused by obesity leads to local tissue hypoxia, which in turn changes the profile of adipokines release and results in low-grade inflammation. Exercise plays an important role as it has effects that can be combined to diet and exercise alone is capable of reducing inflammation. Research shows that there is no preferable type of exercise, as endurance, resistance and combined training are effective in periods of at least 8 weeks.

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