

## REVIEWS

## ARTICOLE DE SINTEZĂ

# Adipokines, systemic inflammation and exercise

## Adipokinele, inflamația sistemică și exercițiul fizic

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### Abstract

Adipokines are metabolically active molecules involved in the development of insulin resistance, which is closely correlated with obesity, diabetes mellitus and metabolic syndrome. All these diseases are associated with an increased cardiovascular risk. Adipokines are produced by white adipose tissue and may have local or systemic pro- or anti-inflammatory activities. Inflammation in adipose tissue is considered an important factor that induces peripheral insulin resistance. Exercise may reduce both inflammation and body weight and consequently, insulin resistance and the risk of metabolic diseases and atherosclerosis. We present a short review of the literature underlining the roles of adipokines in inflammation and insulin resistance and the favorable effect of exercise that may reduce inflammation and ameliorate insulin resistance by inducing a favorable anti-inflammatory adipokine profile.

**Key words:** adipokines, inflammation, insulin resistance, exercise.

### Rezumat

Adipokinele sunt molecule active metabolice implicate în dezvoltarea insulinorezistenței, la rândul ei strâns corelată cu obezitatea, diabetul zaharat și sindromul metabolic. Toate aceste afecțiuni sunt asociate cu un risc cardiovascular crescut. Adipokinele sunt produse de țesutul adipos alb și pot avea efecte pro- sau antiinflamatoare la nivel local sau sistemic. Inflamația din țesutul adipos este considerată un factor important în dezvoltarea rezistenței periferice la insulină. Exercițiul fizic poate reduce atât inflamația, cât și greutatea corporală și în consecință, rezistența la insulină și riscul afecțiunilor metabolice și al aterosclerozei. Prezentăm o scurtă sinteză a literaturii, subliniind rolul adipokinelor în inflamație și insulinorezistență și efectul favorabil al exercițiului fizic, care poate reduce inflamația și rezistența la insulină, prin inducerea unui profil antiinflamator favorabil al adipokinelor.

**Cuvinte cheie:** adipokine, inflamație, rezistența la insulină, exercițiul fizic.

## Introduction

Low-grade chronic systemic inflammation is a state defined by a 2 to 3-fold increase in the systemic concentrations of tumor necrosis factor alpha (TNF- $\alpha$ ), interleukins (IL-1, IL-6), interleukin 1 receptor activator (IL-1ra), soluble TNF- $\alpha$  receptors and C-reactive protein (CRP). The trigger of this inflammatory reaction is not known (Coppak, 2001; Petersen & Pedersen, 2005), but systemic inflammation has been associated with aging and with many pathological conditions such as diabetes mellitus, obesity, insulin resistance or atherosclerosis (Barziley et al., 2001; Duncan et al., 2003; Han et al., 2002; Ross, 1999). Markers of systemic inflammation have been correlated with an elevated risk of acute cardiovascular events and cardiac death. Plasma IL-6 and TNF- $\alpha$  concentrations have been shown to predict the risk

of myocardial infarction (Ridker et al., 2000a; Ridker et al., 2000b). Elevated CRP levels are highly predictive of cardiovascular events (Khera et al., 2005).

Obesity has become an important health problem all over the world. It is usually associated with other metabolic diseases including type 2 diabetes mellitus, arterial hypertension, non-alcoholic fatty liver disease or polycystic ovary syndrome (Finkelstein et al., 2012). Adipose tissue is not only a passive energy storage organ for triglycerides, but also an active endocrine organ that secretes important functional molecules called adipokines. Subcutaneous and visceral adipose tissues produce adipokines involved in systemic inflammation and insulin resistance in obesity (Kwon & Pessin, 2013). The perturbation of insulin mediated mechanisms determines hyperglycemia and type 2 diabetes mellitus. Insulin resistance is also linked to hypertension and hyperlipidemia (Cornier et al., 2008).

*Received:* 2015, May 16; *Accepted for publication:* 2015, June 2;

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Diabetes, hypertension and hyperlipemia are important cardiovascular risk factors which may be influenced by non-pharmacological and pharmacological therapies.

It has been shown that aerobic exercise increases insulin sensitivity (Heath et al., 1983), induces positive effects on endothelial function (Higashi et al., 1999), and accelerates fat oxidation (Romijn et al., 1993). The beneficial effects of exercise in metabolic diseases have also been linked to its influence on adipokine activities.

Adipokines are active molecules (cytokines) secreted by the white adipose tissue. They have many important roles, regulating local metabolic processes (autocrine and paracrine functions) and systemic processes due to their endocrine functions (Gnacińska et al., 2009). Adipokines play an important role in the maintenance of the energetic balance, in lipid and glucose metabolism, in immune reactions and angiogenesis (Gnacińska et al., 2009). These metabolically active molecules are produced by adipocytes (the main source of adiponectin and leptin), macrophages (the main source of TNF- $\alpha$ ) and stromal and vascular cells (Gnacińska et al., 2009).

The involvement of adipokines in systemic inflammatory reactions plays an important role in their relationship with cardiovascular diseases that are frequently associated with insulin resistance, obesity and diabetes. Adipokines have pro- or anti-inflammatory activities. Most of them are pro-inflammatory molecules, being increased in obese persons.

We present a short review of the literature underlining the correlations between systemic inflammation and adipokines and the possible roles of exercise in reducing inflammation, insulin resistance and subsequently, cardiovascular risk.

### Adipokines and inflammation

There are many recent data regarding the involvement of adipokines in both local and systemic inflammation in obesity and insulin resistance states. Many recent data support their role as pro-inflammatory (leptin, interleukin-6, tumor necrosis factor- $\alpha$ , retinol binding protein 4, resistin, chemokines and their receptors, angiopoietin-like protein and chemerin) or anti-inflammatory mediators (adiponectin, secreted frizzled-related protein 5, visceral adipose tissue-derived serine protease inhibitor, omentin-1 and apelin).

Among *pro-inflammatory adipokines*, the most studied are *leptin*, *IL-6* and *TNF $\alpha$* .

#### *Leptin*

The main source of leptin is white adipose tissue; it is encoded by an obesity gene located on human chromosome 7q31.3 (Considine & Caro, 1997). Leptin regulates weight by decreasing appetite and food intake through a hypothalamic regulation in the central nervous system (Zhang et al., 1994). The lack of leptin due to a mutation in the obesity gene in mice induces hyperphagia, obesity and insulin resistance. Exogenous administration of leptin in these situations reduces obesity and insulin resistance (Lönnqvist et al., 1999). Interestingly, circulating leptin levels are increased in obese subjects who are not anorexic, suggesting a lack of sensitivity to leptin action. Chronic inflammation induced by obesity is an important factor that mediates leptin resistance (Kleiridders et al., 2009).

Leptin has pro-inflammatory actions. It activates monocytes and macrophages to produce pro-inflammatory IL-6, TNF- $\alpha$  and IL-12 (Gainsford et al., 1996) and it enhances the production of pro-inflammatory Th1 cytokines (Grunfeld et al., 1996). Leptin also suppresses the synthesis of anti-inflammatory Th2 cytokines such as IL-4 (Lord et al., 1996).

Hyperleptinemia in obese patients has been correlated with the development of type 2 diabetes mellitus. Insulin influences glucose concentration and stimulates leptin production. Increased leptin levels induce, as a result of a negative feed-back, a decrease of insulin secretion (Havel, 2004; Gnacińska et al., 2009).

#### *Interleukin-6*

IL-6 is produced in adipocytes in correlation with the degree of obesity, but its role in obesity and insulin resistance is still unclear. IL-6 is also produced in T cells and macrophages and is considered an inflammatory cytokine as it stimulates the production of acute phase reactants, including CRP (Gauldie et al., 1987), in various situations that stimulate inflammatory response. Increased CRP concentrations are associated with metabolic syndrome and insulin resistance (Pepys & Hirschfield, 2003).

In peripheral tissues, IL-6 decreases the production of insulin receptors (Pittas et al., 2004). In contrast, in IL-6 deficient mice that develop obesity and hepatic inflammation, central administration of IL-6 reverses insulin resistance (Wallenius et al., 2002). Because central administration was associated with energy expenditure and a reduction in body weight, it was concluded that the effects of IL-6 may depend on its site of action (Kwon & Pessin, 2013).

IL-6 is also an anti-inflammatory cytokine through its inhibitory effects on TNF- $\alpha$  and IL-1, and activation of IL-1ra and IL-10, being involved in controlling local and systemic inflammation. Its relationship with exercise is complex because it is secreted by myocytes in response to exercise (Pedersen & Febbraio, 2008). IL-6 secreted in response to muscle contraction (as a myokine) has a strong anti-inflammatory action (Pedersen & Febbraio, 2008).

#### *Tumor necrosis factor alpha*

TNF- $\alpha$  is an anti-inflammatory cytokine produced primarily by macrophages and also by other cells including adipocytes. Its concentrations are elevated in obesity and it contributes to insulin resistance (Kwon & Pessin, 2013). Experimental studies showed that genetic deletion of TNF- $\alpha$  or its receptors in *ob/ob* and diet-induced obese mice reduced insulin resistance in muscle and adipose tissue (Uysal et al., 1997). A recent review pointed out that TNF- $\alpha$  plays a direct role in insulin resistance and metabolic syndrome (Plomgaard et al., 2008) and it also increases the release of free fatty acids from adipose tissue, which contributes indirectly to insulin resistance (Plomgaard et al., 2008). Increased circulating levels are correlated with cardiovascular risk and development of atherosclerosis (McKellar et al., 2009).

Several adipokines such as adiponectin, secreted frizzled-related protein 5, visceral adipose tissue-derived serine protease inhibitor, ometin-1 and apelin have *anti-inflammatory* properties (Kwon & Pessin, 2013). Of these, the most important and extensively studied is adiponectin.

*Adiponectin*

Adiponectin is mainly produced in adipocytes and has significant anti-inflammatory actions. It has an antiatherogenic effect by decreasing the expression of adhesion molecules, reducing proliferation of vascular smooth muscle cells and the transformation of macrophages to foam cells (Shimada et al., 2004). In contrast to pro-inflammatory adipokines, adiponectin inversely correlated with the body mass index, visceral adiposity and markers of insulin resistance (Mazaki-Tovi et al., 2005). Adiponectin has some important metabolic effects, reducing hepatic glucose production and improving glucose uptake and fatty acid oxidation in skeletal muscles (Yamauchi et al., 2002). Total adiponectin consists of three oligomers (low molecular weight, medium molecular weight and high molecular weight) (Oh et al., 2007). The most active form involved in glucose metabolism seems to be high molecular weight adiponectin, which also has the strongest association with cardiovascular disease (Rizza et al., 2010).

**Exercise and adipokines**

Exercise may reduce systemic inflammation and insulin resistance. However, the effect of exercise on adipokine levels depends on the type and duration of exercise; hence, it is difficult to compare and standardize the results reported by various studies.

*Effects of exercise on circulating leptin*

Leptin was determined before and after acute or chronic exercise. Sakurai et al. reported in a recent review that the results of previous studies indicated that short periods of exercise ( $\leq 12$  weeks) did not influence leptin concentrations (Sakurai et al., 2013). Physical training for more than 3 months reduced leptin levels only if exercise was accompanied by a reduction in body weight (Sakurai et al., 2013; Kraemer et al., 2002). Favorable effects of exercise were attributed to alterations in energy balance, improvements in insulin sensitivity and alterations in lipid metabolism (Kraemer et al., 2002). Exercise seemed to be more efficient in diabetic patients who presented a delayed response after short-term resistance and reduced leptin levels with long-term exercise (Sakurai et al., 2013; Kraemer et al., 2002).

*Effects of exercise on IL-6 and TNF- $\alpha$* 

In obesity and/or hyperinsulinemic states, there is an increased adipocyte production of inflammatory molecules including IL-6 and TNF- $\alpha$ . During exercise, the response of these two adipokines is different. IL-6 is the first cytokine that increases in circulation with exercise, while TNF- $\alpha$ , a classical pro-inflammatory cytokine, is reduced (Ostrowski et al., 1999). The production of IL-6 is accompanied by the augmentation of anti-inflammatory cytokines causing an anti-inflammatory environment associated with physical exercise, as reviewed by (Brandt & Pedersen, 2010). The explanation for these apparently contradictory effects of IL-6 is based on possible different signaling pathways for IL-6 in macrophages and myocytes. It has been hypothesized that IL-6 signaling in macrophages induces a pro-inflammatory response, while activated IL-6 in muscles (as a myokine) has anti-inflammatory properties (Brandt & Pedersen, 2010). Exercise may also induce weight loss, with a decrease in the volume and number of

adipocytes and macrophages located in adipose tissue that produce pro-inflammatory cytokines. Weight loss reduces the number of circulating mononuclear cells, another source of inflammatory mediators (Brandt & Pedersen, 2010).

*Effects of exercise on adiponectin levels*

As an anti-inflammatory and cardiometabolic protective adipokine, adiponectin has been intensively studied in relation to exercise. The results must be interpreted in correlation with the type and duration of physical effort. There may also be differences regarding the form of adiponectin tested (total adiponectin or its oligomers).

Aerobic exercise increases insulin sensitivity, enhances vascular endothelial function, and accelerates fat oxidation as reviewed by Numao (Numao, 2012). Because adiponectin has similar effects to those determined by exercise (Shimada et al., 2004; Mazaki-Tovi et al., 2005; Yamauchi et al., 2002), clinical and experimental studies have investigated the hypothesis that exercise-induced changes in adiponectin may explain the beneficial consequences of physical exercise.

Acute aerobic exercise does not influence circulating levels of total adiponectin in healthy, lean subjects as reviewed by Golbidi and Laher (Golbidi & Laher, 2014). However, in inactive, abdominally obese men, both acute and short-term exercise (one week) increased plasma adiponectin levels (Saunders et al., 2012). An increase in interstitial adiponectin levels and a decrease in adiponectin mRNA in subcutaneous abdominal adipose tissue have been reported after acute aerobic exercise in both lean and obese subjects (Højbjerg et al., 2007).

Oligomers were determined after acute exercise in middle aged abdominally obese men and the results indicated that high intensity exercise decreased total adiponectin by reducing low and medium molecular adiponectin levels, while HMW adiponectin remained unchanged (Numao et al., 2011).

Chronic aerobic exercise seems to influence adiponectin levels only indirectly by reducing weight. Physical exercise accompanied by a substantial weight loss determined an increase in circulating total adiponectin (Numao, 2012). However, high intensity aerobic exercise in patients with type 2 diabetes increased total adiponectin levels despite weight remaining unchanged (Balducci et al., 2010).

In a recent study, 12 weeks of combined aerobic and resistance exercise training induced an increase in adiponectin and ghrelin levels, associated with a reduction of leptin levels and inflammatory CD14+CD16+ monocytes, without any modification of body weight, in older healthy subjects (Markofski et al., 2014). This study suggests that high intensity exercise reduces inflammation and has a favorable effect on adipokine profile independent of body weight.

**Conclusions**

1. Physical exercise may reduce systemic inflammation and insulin resistance by modifying the balance between pro- and anti-inflammatory cytokines.
2. The effects of exercise depend on the duration and on the intensity of exercise.
3. Leptin levels are influenced only by intense exercise



that reduces body weight, diabetic patients being more responsive.

4. Exercise reduces TNF- $\alpha$  and insulin resistance related to this adipokine.

5. Muscle-derived IL-6 (which acts as a myokine) is increased by exercise and exerts anti-inflammatory effects, whereas the chronic elevation of IL-6 as an adipokine proves pro-inflammatory actions.

6. Acute exercise, if mild or moderate, has no significant effects on circulating adiponectin levels, but it may increase interstitial adiponectin in adipose tissue. However, acute or chronic high-intensity exercise may increase circulating adiponectin, particularly in overweight persons. The effect of exercise on adiponectin oligomers is still unclear.

7. Further studies are necessary to establish the duration and intensity of exercise that may influence adipokine levels, as well as to determine clinical therapeutic benefits.

### Conflict of interest

The authors confirm that this article content has no conflict of interest.

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