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ADIPONECTIN, CARDIOVASCULAR DISEASE AND ITS RELATIONSHIP WITH PHYSICAL EXERCISE: A NARRATIVE REVIEW

ADIPONECTINA, DOENÇA CARDIOVASCULAR E SUAS RELAÇÕES COM O EXERCÍCIO FÍSICO: REVISÃO NARRATIVA

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ABSTRACT

There is a close relationship between circulating levels of adiponectin, insulin resistance and cardiovascular risk. The available evidence that evaluated the relationship between adiponectin levels and physical exercise is somewhat controversial. Recent studies have shown that aerobic training does not alter adiponectin levels without significant reduction in body weight; other studies show that modest weight loss, along with aerobic training, significantly improves the levels of this protein – even if there is no change in weight. On the other hand, it has been documented that aerobic training increases levels of adiponectin even if there is weight gain. Motivated by such inconsistencies, the purpose of this narrative review was to present and discuss the relationship between adiponectin and cardiovascular diseases, as well as the possible influence of physical exercise on blood concentrations of adiponectin and its association with improved glycemic status.

Keywords: Adiponectin; Exercise Physical; Cardiovascular Diseases.

RESUMO

Há uma estreita relação entre os níveis circulantes de adiponectina, resistência à insulina e risco cardiovascular. As evidências disponíveis que avaliaram a relação entre adiponectina e exercício físico apresentam algumas controvérsias. Estudos recentes mostraram que o treinamento aeróbico não altera os níveis de adiponectina sem que haja redução significativa no peso corporal; outros estudos mostram que uma modesta perda de peso, em conjunto com treinamento aeróbico, melhora de forma importante os níveis dessa proteína – inclusive se não houver alteração no peso. Por outro lado, foi documentado que o treinamento aeróbico aumenta níveis de adiponectina até mesmo se houver ganho de peso. Motivado por tais discordâncias, o objetivo desta revisão narrativa foi apresentar e discutir a relação entre adiponectina e doenças cardiovasculares, bem como a possível influência do exercício físico nas concentrações sanguíneas de adiponectina e a sua associação com a melhora do estado glicêmico.

Descritores: *Adiponectina; Exercício Físico; Doenças Cardiovasculares.*

INTRODUCTION

Adipose tissue is recognized for its important role in energy storage and as an organ that secretes a variety of bioactive substances with paracrine, autocrine, and endocrine functions, including leptin, tumor necrosis factor alpha (TNF-α), plasminogen activator inhibitor-1, and adiponectin, collectively referred to as adipokines.[1,2]

There has been extensive research on the association between circulating levels of adiponectin and physical exercise. A recent meta-analysis suggested that physical training, especially aerobic exercise, increases adiponectin levels.[3] This fact may be considered to be of clinical importance since adiponectin exhibits mechanisms that protect the cardiovascular system and reduce the risk of developing type 2 diabetes.[4]

ADIPONECTIN: MOLECULAR STRUCTURE

Adiponectin is a protein that consists of 244 amino acids and four domains: A variable region with 27 amino acids, a globular domain in the C-terminal end, a signal sequence in the N-terminal end, and a collagen-like domain.[5] Its plasma concentration varies between 5 and 30 μg/mL, representing 0.05% of the total plasma proteins.[6]

Adiponectin may exist as full-length proteins generated from monomers that present in three forms: low-molecular-weight trimers, middle-molecular-weight hexamers, and high-molecular-weight multimers (12–18 monomers).[7] It may also exist as small globular fragments. However, the latter is found in small amounts in circulation and results from the proteolytic cleavage of full-length adiponectin by elastase secreted by

activated monocytes and neutrophils.[8] The three multimeric forms, which are found in blood circulation and associated with various serum proteins, were recently characterized in humans.[9] As monomers are not often found in circulation, studies suggest that the biological activity of adiponectin mainly occurs through the high-molecular-weight multimers.[10]

ADIPONECTIN AND CARDIOVASCULAR DISEASE

Interest in research on adiponectin was less until 1999–2000, when obesity became associated with low circulating levels, a phenomenon known as hypoadiponectinemia that has deleterious effects on glucose metabolism and coronary artery disease.[11] Epidemiological studies conducted in humans identified hypoadiponectinemia as an independent risk factor for cardiovascular disease.[12,13] In 1999, the anti-atherosclerotic action of adiponectin was demonstrated through mechanisms that inhibit monocyte adhesion in aortic endothelial cells and suppress the transformation of macrophages into foam cells.[14]

Cardiovascular diseases develop through the interaction of numerous environmental and genetic factors and promote atherosclerosis.[15] The increased susceptibility to atherosclerosis arises from the imbalance of proatherogenic and anti-atherogenic activities.[16] Although little is known about the nature of the genetic components of this process, it is hypothesized that the variability of genes that modulate arterial wall responses to atherosclerotic damage plays a crucial role in this outcome.[17]

As previously stated, the synthesis and secretion of various cytokines by adipose tissue contribute to the development of cardiovascular diseases.[18] Among these cytokines is adiponectin, which has been extensively studied due to its anti-atherogenic effect[19,20] and is related to insulin sensitivity, free fatty acid oxidation, and inhibiting inflammation.[21] Therefore, hypoadiponectinemia is present in conditions such as metabolic syndrome and aggravates cardiovascular risk.[22]

Several recent clinical studies support the idea of a direct relationship between hypoadiponectinemia and the occurrence of vascular complications in humans. For example, they reported that this condition favors endothelial dysfunction in the coronary arteries regardless of insulin resistance, body mass index, and dyslipidemia.[23]

Accordingly, animal models with adiponectin deficiency become more exposed to harm under endothelium-dependent vasodilation and systemic arterial hypertension. In rabbits, adiponectin mediated a significant attenuation of atherosclerotic plaque in the abdominal aorta and was associated with a lower expression of cell adhesion molecules (including vascular cell adhesion molecule-1, intercellular adhesion molecule-1), thus sparking tremendous enthusiasm around this protein.[24]

Aside from its recognized beneficial effects on insulin sensitivity and lipid metabolism, adiponectin generates multiple vasoprotective effects through its action on the vascular system, including endothelial cells, monocytes, macrophages, leukocytes, platelets, and outer membrane proteins; plaque formation; and thrombosis development.[25]

ADIPONECTIN SECRETION

Adiponectin secretion is regulated by substances such as insulin as evidenced in some studies based on cultures of 3T3-L1 adipocytes and human visceral fat.[26,27] Conversely, Fasshauer et al.[28] demonstrated an inverse relationship, specifically a decrease in mRNA levels for adiponectin in 3T3-L1 adipocytes and an association between hyperinsulinemia and hypoadiponectinemia. Thus, the mechanisms related to insulin-regulated adiponectin synthesis and secretion have not yet been fully clarified.[8]

TNF-α promotes a significant decrease in the synthesis of adiponectin and the secretion of 3T3-L1 adipocytes by suppressing its gene promoter.[29] Regarding catecholamines, studies have examined the effects of β-adrenergic agonists and cyclic adenosine monophosphate (cAMP) analogs on the inhibition of adiponectin expression and release.[30] Glucocorticoids, interleukin 6 (IL-6), and endothelin 1 (ET-1) also had the same effect.[31]

ADIPONECTIN'S MECHANISMS OF ACTION

Adiponectin acts on receptors called AdipoR1 and AdipoR2.[32] The former is widely expressed in hepatic stellate and skeletal muscle cells; the latter is mainly expressed in the liver but is also present in macrophages and monocytes. Finally, both are expressed in the hypothalamus and in the paraventricular nucleus.[3]

Two signaling pathways result from the action of adiponectin on its specific receptors: One is mediated by the activation of peroxisome proliferator-activated receptor-alpha (PPAR-α) receptors, while the other is due to AMP-activated protein kinase (5α-AMP-activated protein kinase [AMPK]). In hepatic stellate cells, AdipoR1 activates AMPK and consequently inhibits the expression of genes involved in gluconeogenesis and lipogenesis, whereas AdipoR2 exerts few effects on glucose production.[33] Nevertheless, by activating PPAR-α receptors, the AdipoR2 receptor induces fatty acid oxidation, while the same result is not observed in AdipoR1 stimulation.[34]

In the skeletal muscle, adiponectin binds to AdipoR1 and causes the interaction between this receptor and the APPL1 protein, a GTPase (effector of the small GTPase). This in turn promotes the translocation of glut-4, which is responsible for the facilitated diffusion of glucose and contributes to increased insulin sensitivity.[35]

In PPAR-α nuclear receptors, adiponectin acts on and promotes the expression of various genes related to lipid metabolism, consequently leading to fatty acid oxidation.[36] This improves insulin sensitivity by preventing lipid accumulation within the skeletal muscles.[37]

Subcellular activation in endothelial cells involves AMPK and protein kinase A of cyclic AMP (cAMP/protein kinase A or cAMP-dependent protein kinase), which causes nitric oxide production through phosphoinositide 3-kinase–dependent pathways, a mechanism involving endothelial nitric oxide synthase activation through AMPK phosphorylation. The activation of cAMP-dependent protein kinase also occurs, thereby inhibiting nuclear factor kappa beta activation. This process attenuates the inflammatory pathways

mediated by TNF-α and inhibits the cellular adhesion of inflammatory cells.[38]

In smooth muscle cells, adiponectin inhibits cell proliferation by directly binding to different growth factors and inducing their inhibition, mainly platelet-derived growth factor--BB, fibroblast growth factor, and heparin-binding epidermal growth factor-like growth factor.[39]

AdipoR1 and AdipoR2 receptors within cardiac muscle cells are expressed in amounts similar to those found within skeletal muscle cells. Adiponectin binds to its specific receptors and activates AMPK, a factor that decreases apoptosis. Cardiac hypertrophy is also inhibited by ET-1 and cyclooxygenase-2. Finally, TNF-α production is inhibited.[40]

ADIPONECTIN AND APPLICATIONS TO CARDIOVASCULAR ASPECTS

At the vascular level, adiponectin plays an important anti-inflammatory role due to the following mechanisms: It induces the production of anti-inflammatory cytokines such as interleukin-10 (IL-10) and the interleukin-1 receptor antagonist (IL-1RA) in monocytes and macrophages and suppresses interferon gamma production in macrophages stimulated by bacterial lipopolysaccharides. By stimulating IL-10 secretion and metalloproteinase-1 inhibitor expression, adiponectin plays a relevant role in stabilizing atherosclerotic plaques.[41]

Furthermore, adiponectin inhibits the expression of class A scavenger receptors and thereby reduces the intracellular accumulation of lipids and the action of Acyl-CoA cholesterol acyltransferase-1, whose role is to catalyze the formation of cholesteryl ester.[42]

As for regulating lipid levels, hypoadiponectinemia is related to an accumulation of lipids in the liver and an elevation in the circulating levels of very low-density lipoprotein and chylomicrons.[43] In fact, adiponectin increases the expression of apolipoprotein A and activity of lipoprotein lipase,[44] two proteins crucial to the catabolic process of triglyceride-rich lipoproteins found within adipose tissue and skeletal muscle. However, hypoadiponectinemia increases hepatic lipase activity and decreases high-density lipoprotein cholesterol levels and a consequent increase in small dense low-density lipoprotein levels.[45] The direct relationship between small, dense low-density lipoproteins and cardiovascular risk is widely accepted and documented in the literature.

ADIPONECTIN AND PHYSICAL EXERCISE

Physical exercise increases blood flow within the skeletal muscle and improves glucose uptake due to factors including higher concentrations of Glut-4 and insulin sensitivity.[46] Calories burned from physical exercise reduces body fat, especially android fat distribution (abdominal), due to the large number of ß-adrenergic receptors at the site that is more susceptible to lipolysis.[47] As a result, insulin resistance and the inflammatory process promoted by excess fat are reduced.

Along with physical exercise, adiponectin influences glucose metabolism and blood insulin concentrations.[48] There is an increased genetic expression in AdipoR1 and AdipoR2 receptors in human skeletal muscles in response to physical exercise. However, calorie restrictions do not generate changes in the expression of the receptors in adipose tissue.[34] On the other hand, studies have reported that obese individuals tend to have higher levels of AdipoR1 than eutrophic individuals to compensate for reduced serum adiponectin levels.[49]

Some studies relate the effects of physical exercise on insulin sensitivity to plasma concentrations of adiponectin and/or its receptors.[34,50] High-intensity exercise lowers serum adiponectin concentrations immediately after exercise but does not affect insulin levels.[51] Moderately intense exercise has been linked to unmodified adiponectin concentrations and lower insulin levels.[50] Nonetheless, adiponectin's response to acute exercise differs in trained and untrained individuals.[52]

ACUTE PHYSICAL EXERCISE AND PLASMA ADIPONECTIN CONCENTRATIONS

Punyadeera et al.[53] found no changes in expression levels of both AdipoR1 and AdipoR2 in the skeletal muscle of healthy volunteers after acute physical exercise. However, high- or low-intensity aerobic exercise (75% or 50% of VO2 max) boosted adiponectin levels in inactive and abdominally obese men (waist circumference ≥ 102 cm) immediately after an acute training session, which remained elevated 30 minutes afterward. To prolong this effect by 1–3 days, only three weekly exercise sessions were sufficient. It is important to note that this occurred in the absence of any changes in weight or waist circumference; thus, it strengthens the hypothesis that exercise brings undeniable benefits regardless of alterations in body composition.[54]

Consistent with these findings, Kriketos et al.[55] reported that a week of aerobic training resulted in increased adiponectin levels in obese men. However, Numao et al.[51] suggested a direct relationship between physical intensity and adiponectin levels immediately after ceasing aerobic exercise. There is a significant decrease after high-intensity exercise but no change after low-intensity exercise.

The reasons for these discrepancies are not perfectly clear. However, one hypothesis that cannot be discarded concerns the ethnic diversity among studies. The participants of the study by Saunders et al.[54] were almost exclusively white, while those of the study by Numao et al.[51] were Japanese. The relevance of these data relies on the fact that adiponectin circulates in isoforms of different molecular weights and that the relative proportions of these isoforms differ among ethnicities.[56]

A study of overweight men revealed that a 45-minute submaximal aerobic exercise session (65% of VO_2 max) did not result in significant changes in adiponectin in up to 48 hours post exercise.[50]

Finally, there is evidence that acute exercise results in rapid changes in the transcription of peroxisome proliferator-activated receptor-gamma coactivator 1-alpha (co-activator of peroxisome proliferator-activated receptor-gamma) in the skeletal muscle. This pathway establishes a connection between acute exercise and adiponectin production at the myocyte level.[54]

CHRONIC PHYSICAL EXERCISE AND PLASMA ADIPONECTIN CONCENTRATIONS

Researchers have demonstrated that chronic physical exercise (for 2 months) changes adiponectin receptor levels

in KK-Ay rats. The mRNA expression of AdipoR1 in the skeletal muscle and liver increased, while that of AdipoR2 was lower in the livers of the exercise group than the control group. Moreover, in the intervention group, the mRNA expression of acyl-CoA oxidase and carnitine palmitoyltransferase 1 mRNA was greater in the liver than in the skeletal muscle.[57]

A recent study suggested that moderate aerobic exercise (3 months) modulates the mRNA expression of AdipoR1 and AdipoR2 in peripheral blood mononuclear cells. In fact, a significant increase in mRNA levels of AdipoR1 and AdipoR2 was found in these cells along with increased insulin sensitivity and high-molecular-weight adiponectin.[34]

Given the popularization that mediates high-intensity interval training (HIIT), researchers evaluated the responses to 2 months of HIIT in obese rats. HIIT increased obesity-induced insulin sensitivity, thus preventing hypoadiponectinemia. Other studies found that this type of training reversed a downward trend – arising from a diet rich in fat – of AdipoR1 and AMPK/SIRT1 proteins.[58] Based on these premises, HIIT seems to be an efficient strategy for combating metabolic complications.

To corroborate these results, when comparing 3 months of moderate-intensity interval training to HIIT in obese adolescents, adiponectin levels increased and fat percentage decreased in both groups. However, the most significant changes were observed in the HIIT group.[59] Thus, the intensity of physical exercise seems to directly influence serum adiponectin concentrations.

Although several studies reported that aerobic training does not alter adiponectin levels without significantly reducing body weight,[60-62] one study showed that small weight loss along with aerobic exercise considerably improved adiponectin levels even if there was no change in weight.[63] Other authors reported that aerobic exercise increased adiponectin levels in spite of weight gain.[64] The discrepancies in these results may be due to genetic variations among different populations.

The literature also evidenced that aerobic training leads to decreased levels of C-reactive protein (CRP), IL-6, and leptin.[65] Accordingly, regular aerobic exercise reduces the risk of heart disease by improving anti-inflammatory mechanisms. Kishida et al.[66] detailed an inversely proportional correlation between visceral fat and adiponectin in obese individuals. Another study showed that the visceral fat levels of obese and insulin-resistant individuals decreased after a few months of dietary and aerobic changes. Changes in adipose tissue distribution are related to alterations in adipokine secretion and increases in adiponectin levels.[67]

As for the role of diet, studies evaluated the effects of the association between aerobic exercise and caloric diets of low- or high-glycemic content. The results suggested that physical training, regardless of dietary reduction, favorably alters the secretion of adiponectin and leptin, possibly due to a decrease in adipocyte cell size.[67]

Evidence suggests that the accumulation of intra-abdominal visceral fat may lead to dysfunctional adipocytes and result in metabolic disease. Conversely, a recent meta-analysis of 14 randomized clinical trials and 824 patients with type 2 diabetes found no association between aerobic exercise and increased adiponectin levels.[68] To understand these results, differences in age, sex, training protocol, intensity, and exercise duration must be considered.

The amount of training may be an important factor for outcomes concerning plasma adiponectin levels and inflammatory markers (CRP, IL-6, and TNF-α). Regular long-term aerobic physical training led to significant improvements in these parameters.[69] These results were corroborated by Yoshida et al.,[70] who revealed a 51% increase in adiponectin in dyslipidemic and eutrophic patients after 4 months of moderate exercise.

The effects of exercise alone on adiponectin concentrations remain inconsistent. Numerous studies found no changes in adiponectin levels with physical training. Among them, some described the measurement time for adiponectin as being 24 hours after the last exercise session, while others did not specify it. Therefore, we cannot discard the possibility that this fact contributed to the inconsistent results.

CONCLUSION

Based on the studies we analyzed, consensus is lacking on the best type of physical training, body weight reductions, and circulating adiponectin levels. Therefore, more robust studies are necessary to obtain more reliable answers. Nevertheless, overweight or obese individuals are more susceptible to developing chronic and inflammatory diseases, and physical exercise is the best non-pharmacological treatment and preventive measure against these diseases.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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