

# Effects of Physical Activity on The Inflammatory Process Related to Insulin Resistance and Obesity

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**Abstract:** Atherosclerosis, the pathophysiological substrate for cardiovascular disease (CVD), is the final stage of an inflammatory cascade. During the process, endothelial dysfunction ensues and the inflammatory state is perpetuated. A number of traditional risk factors, as obesity and insulin resistance/type 2 diabetes, are characterized by a proinflammatory state as well, with increased levels of cytokines, interleukins, vasoactive peptides and enhanced expression of specific cellular receptors. The anti-inflammatory properties of physical exercise and its positive effects as a strategy for obesity and insulin resistance have already been shown in terms of cardiovascular protection and survival.

**Keywords:** Inflammation, Endothelial dysfunction, Obesity, Insulin resistance, Exercise.

## INTRODUCTION

“Low-grade” chronic inflammation is related to chronic diseases. Cardiovascular risk factors, like hypertension, excess of adiposity (mainly visceral), physical inactivity, inadequate alimentation and hyperlipidemia can precede the inflammatory process. These behavioral and biochemical factors predispose the individual to insulin resistance and type 2 diabetes mellitus (T2DM), and, consequently, to endothelial dysfunction and atherosclerosis. Therefore, the quantification of serological markers emerged as an important tool for a better understanding of the pathological process, diagnosis and prognosis of the inflammatory status. It is also useful in evaluating and monitoring the effects of therapeutic strategies, like exercise.

## ENDOTHELIAL DYSFUNCTION AND ATHEROSCLEROSIS - THE ROLE OF INFLAMMATORY MARKERS

For many years, atherosclerosis was thought to be simply the accumulation of lipids in the arterial wall.

Although elevated plasmatic levels of cholesterol - especially its low-density lipoprotein fraction, LDL - is a well established risk factor, it is now known that the atherosclerotic process is more than that. Atherosclerosis is an inflammatory disease [1].

There is a large body of evidence sustaining the central role played by endothelial dysfunction in the pathophysiology of atherosclerosis. The endothelium is a single-cell lining covering the internal surface of blood vessels. It behaves as a receptor-effector structure, capable of sensing different stimulus (physical or chemical) that occur inside the vessel and, therefore, acts modifying the vessel shape or releasing the necessary substances to maintain homeostasis. The endothelium produces and releases both agonists and antagonists molecules (pro- and anti-inflammatory, pro- and anticoagulants, vasodilators and vasoconstrictors, fibrinolytics and antifibrinolytics, oxidizing and antioxidantizing) [1-3]. Endothelial dysfunction ensues when this balance is disrupted, as in the presence of classic cardiovascular risk factors (e.g. hypertension, diabetes, smoking, high LDL-cholesterol levels, obesity). It represents a reduction in endothelial-mediated vasodilatation and a pro-inflammatory/pro-thrombotic state of the endothelium [4].

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Once dysfunction takes place, the endothelium is no longer capable of fully preserve its homeostatic properties, and thrombosis is facilitated. There is reduction of nitric oxide (NO) synthesis and increased angiotensin II response; in addition, leukocytes (monocytes and T-lymphocytes) adhere to the endothelial cells and migrate into the intima [5]. The result is amplification and chronification of the inflammatory response [6-9].

In time, the initial stage of atherosclerotic lesion - fatty streak - appears. As the disease evolves, modified lipids and inflammatory cells and mediators accumulate further in the vessel intima as atheromatous plaques, which may reduce vascular flow by chronic stenosis (or acute thrombosis). The compensatory increase of blood flow velocity is responsible for the so-called shear stress in the vascular wall, being the main stimulus for NO release and, finally, for endothelium-mediated vasodilatation (EMD) - or flow-mediated dilation (FMD). Nevertheless, this adaptive response is inhibited in hyperadrenergic states - characteristic of conditions such as hypertension [10, 11] and sleep apnea [12-14], for example.

There is evidence of the benefits of such conditions' treatment on endothelial dysfunction [15-20]. The use of biochemical markers of inflammatory response as cardiovascular risk predictors has been extensively studied, with conflicting results so far [21-28]. On the other hand, data regarding FMD as an indicator of endothelial dysfunction and cardiovascular risk are more robust.

## **INFLAMMATORY MEDIATORS IN OBESITY AND INSULIN RESISTANCE**

Adipose tissue is an important endocrine organ involved in a number of metabolic, immunological and neuroendocrine reactions. It is known that obesity is related to a chronic inflammatory state. This, in turn, is deeply connected to the presence of a series of serological markers that act as mediators of obesity-related inflammation.

Firstly, the adipocyte - the cellular unit of adipose tissue - secretes adipokines, which play a central role in inciting and perpetuating the inflammatory process in obesity. Also, considerable levels of tumor necrosis factor  $\alpha$  are present on fat tissue [29]. Besides, alimentary factors can play a role in the pathophysiology of this condition, once fatty acids are capable to interact with toll-like receptors (TLRs), activating nuclear factor kappa B (NF $\kappa$ B) and promoting its translocation to the cellular core, where it

regulates the expression of a variety of genes involved in the pro-inflammatory process [30].

In fact, there is evidence that modifications on the adipocyte-signaling process and infiltration of immune system's cells present in the adipose mass may be the link between obesity and conditions as insulin resistance - and, consequently, endothelial dysfunction (Figure 1)[31].

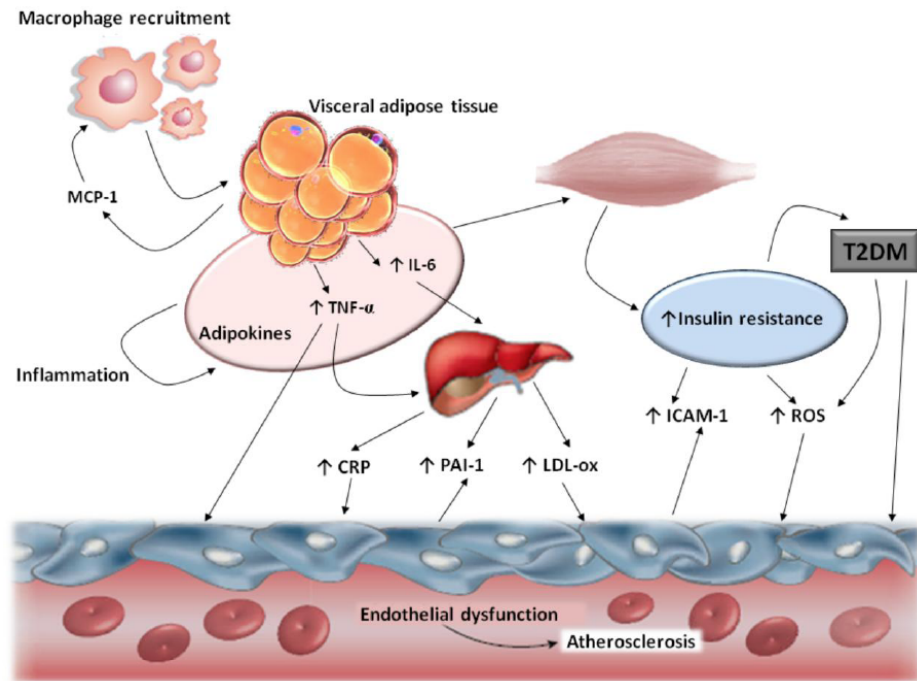
Insulin resistance is related to a pro-inflammatory state that results from release of cytokines and the consequent intra-cellular signaling modifications in key-organs for glycemic control (e.g. liver, striated muscle and adipose tissue) [32]. One of these alterations is the sequential activation of a series of kinase proteins, like nuclear factor kappa-B kinase subunit beta (IKK- $\beta$ ), protein kinase C (PKC) and c-Jun N-terminal kinase (JNK). These proteins cause the reduction of phosphatidylinositol 3-kinase (PI3-K) activity, thus, downregulating the transport of glucose. Additionally, there is the dissociation of the I $\kappa$ B/NF $\kappa$ B complex in the cytoplasm, by the IKK- $\beta$  enzyme, what allows its migration to the cellular nucleus, enhancing the negative effects on the insulin-signaling pathway [33].

The resultant hyperglycemia has acute and chronic effects on the production of pro-inflammatory cytokines. Previous studies demonstrated that subjects with glucose intolerance have high baseline values of TNF- $\alpha$  and interleukin-6, as compared to their respective controls. Moreover, these subjects present a high and sustained release of cytokines in response to hyperglycemic peaks [34], contributing to this vicious cycle of more inflammation/more insulin resistance. Another mechanism linking these two conditions is that acute inflammatory stress can affect the non-insulin-dependent glucose availability regulation pathways, as the activation of 5' adenosine monophosphate-activated protein kinase (AMPK)[35].

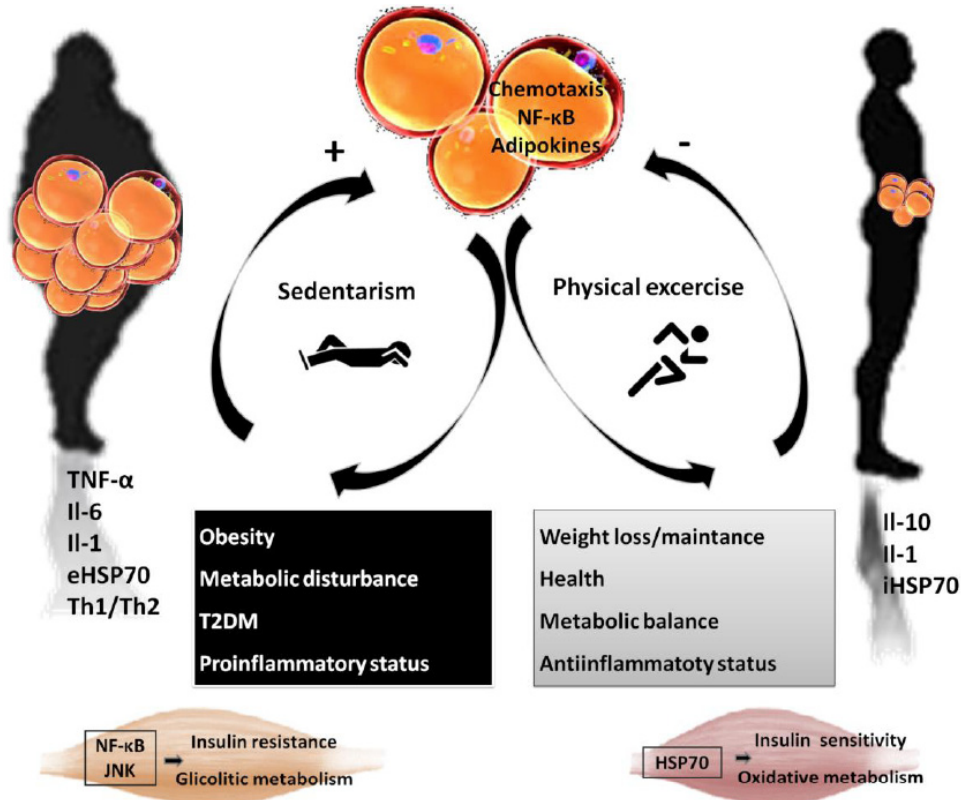
Nevertheless, inflammation and insulin resistance are not only connected by cytokines and kinase proteins. It is suggested that a special group, the heat shock proteins (HSP) have also an important role in the insulin resistance process mediated by inflammation, once diabetic obese individuals have higher circulating levels of HPS. [36].

## **PHYSICAL EXERCISE AND ENDOTHELIAL DYSFUNCTION: THE ROLE OF HEAT SHOCK PROTEINS (HPS)**

Exercise represents a physiological stress condition to the cardiovascular system. It induces acute and



**Figure 1:** Interaction between adipose tissue, insulin resistance and endothelial dysfunction. Monocyte chemotactic protein 1 (MCP-1) are released from full visceral adipocytes, which increases the macrophage recruitment into the adipose tissue establishing an inflammatory process. Higher levels of TNF-  $\alpha$  and IL-6 stimulate the production of CRP by the liver and these adipokines promote insulin resistance and endothelial dysfunction directly or indirectly. Endothelium releases biomarkers as PAI-1 and ICAM-1 in response to other injuries as LDL-ox and ROS, contributing to the vicious circle. (Adapted from Van Gaal LF et al.)[31].



**Figure 2:** Effects of the sedentary behavior and physical exercise (mediated by inflammatory status) over adipose tissue and glycemic control.

chronic modifications on endothelial cell morphology and biochemistry. This adaptive process is affected by each exercise session and by physical conditioning levels [37].

There is evidence that the activation of HSP induced by exercise may play important roles in vascular functioning [38]. These are highly conserved proteins categorized in families according to their molecular sizes and include HSP110, HSP100, HSP90, HSP70, HSP60 HSP30 and HSP10 subclasses.

HSP facilitates intracellular protein transport, prevent protein aggregation during folding, and protect newly synthesized polypeptide chains against misfolding and protein denaturation. The expression of HSP in different parts of the cardiovascular system (e.g. cardiac muscle, arterial wall) is crucial for its role in cardiovascular protection [39].

Regular exercise promotes acute increase of blood flow. This leads to augmented shear stress and, consequently, higher NO bioavailability, increasing the endothelium-dependent vasodilatation. This occurs in parallel to the decrease in pro-inflammatory markers after exercise training. This increase in NO and decrease in pro-inflammatory markers could represent one of the most important mechanisms of cardio protection induced by regular exercise [37].

Higher levels of inflammatory markers - as IL-6 and C-reactive protein (CRP) are related to reductions in NO concentrations caused by reduced eNOS activity [40]. This, in turn, is associated to cardiovascular disease progression. This extracellular pro-inflammatory signaling pathway is enhanced in obesity and T2DM. HSP70 levels are also associated with biomarkers of acute-phase reaction, inflammation and endothelial-cell activation, suggesting an interaction between HSP70 and receptors in the surface of immune cells. Free radicals, ox-LDL and other factors can stimulate the expression of HPS in the arterial wall and/or other tissues, which are protected by high levels of HPS against apoptosis [39].

Low levels of intracellular and high levels of circulating HSP70 promote a proinflammatory state and increase the vulnerability of the arterial wall-the first stage of the development of the atherosclerotic process. Serum HSP70 (eHSP70) rises the expression of adhesion molecules in smooth muscle cells and in macrophages, inducing cellular proliferation and the release of proinflammatory cytokines [39].

Levels of plasma anti-HSP70 are significantly increased in atherosclerotic rats. These antibodies could react with endothelial surface membrane HSP70 and could mediate endothelial cytotoxicity, demonstrating a possible involvement of humoral immune reaction to Hsp70 with the pathogenesis of atherosclerosis [41].

In this way, it can be said that intracellular and extracellular HSP70 have different roles in the regulation of cardiovascular homeostasis. Also, while exercise can induce both intracellular and extracellular HSP70, and then promotes equilibrium in HSP signaling to cardiovascular system, the process of immune-metabolic disease such as atherosclerosis can promote a higher extracellular proinflammatory signaling and decrease cytoprotection HSP function in many cells and tissues, as the endothelial cells.

#### **EXERCISE AS ANTI-INFLAMMATORY STRATEGY IN OBESITY AND INSULIN RESISTANCE**

Physical inactivity promotes accumulation of visceral fat and, consequently, activates a series of pro-inflammatory signaling cascades that participate in the development process of insulin resistance, atherosclerosis and CVD. The best demonstration that physical exercise, when regularly adopted, may be a therapeutic strategy against chronic disease such as obesity and T2DM is its capacity to prolong life [42]: meta-analyses of randomized controlled trials with mortality outcomes comparing the effectiveness of exercise and drug interventions with each other or with control (placebo or usual care) shows that exercise and many drug interventions are often potentially similar in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of T2DM [43].

The decrease in levels of inflammatory markers related to exercise seems to be independent of weight loss. After six weeks of regular physical training (60% of maximum heart rate) in overweight subjects (body mass index - BMI -  $\geq 30\text{kg/m}^2$ ), a 57%-increase of natural killer (NK) cells cytolytic activity was observed, independently of weight loss [44]. On the other hand, weight loss (~8kg) in persons with grade 1 obesity (BMI ~33kg/m<sup>2</sup>) submitted to caloric restriction (12 weeks, ~1200kcal/day) led to impaired mitogen-stimulated lymphocytary proliferation, with no effects on monocytes, NK cells or neutrophils. Noteworthy is the fact that a more severe caloric restriction (950kcal/day), even for

a shorter period (8 weeks), in subjects with grade 2 obesity (BMI~36kg/m<sup>2</sup>), not only resulted in an 11% weight loss (~10kg) but also reduced the activity of NK cells in 50% [45].

Nevertheless, even when accompanied by physical exercise (60-80% of peak HR) for 2 months, more pronounced weight loss (5.4-8.4 kg) does not promote a significant reduction in CRP levels; on the contrary, a moderate loss (2.3-5.4 kg) is associated with a more effective decrease in the concentration of this inflammatory marker [46]. Although BMI is a predictor of IL-1 $\beta$  and IL-6 levels in subjects from the eutrophic to obesity range, increased aerobic capacity is related to lower levels of both markers and to a better response of monocytes to adrenergic stimulus, indicating the importance of physical conditioning in the immunological status in overweight and obese individuals [47]. Also, physical training may be beneficial by reducing TNF- $\alpha$  expression in macrophages.

In T2DM, from the more incipient stages of disease to its complications, the pro-/anti-inflammatory and the redox status are involved, and the Th1-lymphocytes are stimulated to express inducible nitric oxide synthase (iNOS). This happens in response to NF $\kappa$ B over activation, what imposes an enhanced flow of L-arginine through the iNOS pathway, the only form of NOS expressed in pancreatic  $\beta$  cells. Consequently, the massive production of NO has devastating effects on these cells, which rely, mainly, on glutathione (GSH) for antioxidant protection. Glutamine is used for GSH synthesis, and its stores are compromised during inflammation. It is known that physical exercise increases the influx of glutamine, thus playing a role in preventing pancreatic  $\beta$  cells death [48]. Additionally, exercise decreases the levels of circulating TNF- $\alpha$  as well as iNOS activity in persons with diabetes.

The acute response to exercise is characterized by neutrophil degranulation, phagocytosis and increased production of reactive oxygen species (ROS) by the innate immune system. It can also reduce the expression of TLR-1, 2 and 4 in CD4 monocytes, thus diminishing the probability of interactions with IL-6, IL-1- $\alpha$  and TNF- $\alpha$ . In one section of physical exercise it is observed a biphasic immune response, with an initial lymphocytosis and a later decrease in lymphocytes count. Consequently, there is a relative decrement in Th1 lymphocytes - which activates cellular proliferation by releasing IFN- $\gamma$  and IL-2 - in comparison to Th2 cells - responsible for IL- 4, 5, 6 and 13 release, acting in the

humoral immunity. Thus, both exercise intensity and duration have influence on immune response [37, 49].

The release of TNF- $\alpha$  causes inactivation of the intracellular signaling pathway of insulin on peripheral tissue receptors and consequently lowers the expression of HSP in the muscle cells. Physical exercise inhibits NF $\kappa$ B and rise HSP levels [50], reinforcing the anti-inflammatory effect and benefits of the exercise over insulin resistance mediated by inflammation. Besides, HPS released during exercise acts reducing the expression of TNF- $\alpha$ , IL-1, IL-12, IL-10 and IL-18 genes [51]. On the other hand, immunologic system can synthesize and export HPS in stress situation, so called eHPS. During exercise eHSP70 is released proportionally to the intensity of the physical activity. Some functions of the extracellular eHSP70 are immunologic system activation, recruitment of NK cells, to stimulate cytokines release and NF $\kappa$ B activation [52]. Thus, HPS intra and extracellular levels promote a balance between Th1 (proinflammatory) and Th2 (anti-inflammatory) cells in response to physical activity. HPS levels could also contribute to glycemic control, since its release occurs in hypoglycemic situations in response to a homeostatic stress [53].

## CONCLUSION

The relationship between CVD, obesity and insulin resistance/T2DM is well determined, and the available evidence about the role of inflammation as the underlying connection between such conditions is getting not only more numerous but also more robust.

Physical exercise was already prescribed as a strategy for a healthier lifestyle. In the last years, more concrete evidence of its benefits in terms of altering the pathophysiological process of CVD has emerged, signaling that exercise has anti-inflammatory properties capable of counteract the hostile environment of endothelial dysfunction.

Although more research is still needed, the present data support the use of exercise as a therapeutic strategy in persons with obesity and insulin resistance with the purpose of attenuate the inflammatory state characteristic of these entities and, thus, act on the pathological substrate of atherosclerosis.

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