Physical Activity and Cardiovascular Health: Effects on Lipid Oxidation and Inflammatory Biomarkers. New Fuel for an Old Fire?

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Lipid oxidation and inflammation play a fundamental role in the development of atherosclerosis, the process that causes most of cardiovascular diseases [1,2], among them cerebrovascular disease and coronary heart disease (CHD).

On the other hand, regular physical activity (PA) reduces the risk of cerebrovascular [3] and coronary events [4]. In recent years, sedentary lifestyle has been recognized as an independent risk factor for CHD [5,6] and some recommendations have been published promoting regular physical activity for both primary and secondary prevention of CHD [5,7].

Regular PA yields favorable effects on the classic risk factors for cardiovascular disease: improved lipid profile [8], lower blood pressure [9], and reduced incidence of non-insulin dependent diabetes [10]. Nonetheless, these effects represent only part of the protection PA affords against this type of disease [11].

Some of the beneficial effects of PA also may be related to lower lipid oxidation and reduced inflammation. The objective of this presentation is to review the available information about the relationship between PA and these two factors: lipid oxidation and inflammation.

1- Lipid Oxidation.
1.1. Lipid oxidation and atherosclerosis.
Oxidation of low density lipoproteins (LDL) is a fundamental factor in the etiopathology of atherosclerotic lesions [1,2]. Oxidized LDL (LDL$_{ox}$) particles may directly cause lesions in the endothelium and alterations in vascular tone, increase the synthesis and expression of chemotactic and adhesion molecules in endothelial cells, and induce the proliferation of smooth muscle cells. LDL$_{ox}$ can also attach to the scavenger receptor of the macrophages, enter in these cells and transform them to foam cells.

LDL oxidation is a complex process that depends primarily on three factors:

a) Formation of free radicals (FR): Free radicals are unstable molecules (and, as a result, very reactive) that are produced in reactions involving oxygen [12]. The reaction of FR with fatty acids and apo B is responsible for the oxidation of LDL.

b) Antioxidants: To protect against the actions of FR, the organism has an antioxidant defense system [13]. This system consists of endogenous substances, synthesized by the organism itself, such as superoxide dismutase (SOD), glutathione reductase and peroxidase (GR-GPX), or paraoxonase (PON), and exogenous substances derived from dietary intake, such as vitamins E and C, betacarotenes, and polyphenols.

c) Characteristics of the LDL particle: Greater size and lower density [14] characterize the particles most resistant to oxidation; increased susceptibility is associated with higher content of polyunsaturated fatty acids [14], along with glycation of the particle [15]. On the other hand, the presence of greater quantities of antioxidant substances, primarily vitamin E and to a lesser extent betacarotenes, protects LDL particle against the actions of free radicals [16].

1.2. PA and lipid oxidation.
Both acute and regular PA practice influence the production of free radicals, the activity of antioxidant systems, and LDL resistance to oxidation.

a) PA and FR production: Oxygen consumption increases during PA; this translates into increases in FR
formation. The increase can be so significant that it exceeds the capacity of the antioxidant systems, producing an increase in oxidation processes, including lipid oxidation [17].

Various studies have demonstrated that plasma levels of products derived from lipid oxidation increase after PA [18-21]. This increase is directly related to PA intensity [22]. Another finding that results from these studies is that the observed increase is greater in sedentary than in trained participants [23-26], suggesting that regular PA is a protective factor.

Currently available data sustain the hypothesis that one of the protective factors of PA training can be attributed to lower FR production due to greater metabolic efficiency [27], since a lower amount of oxygen is consumed to produce the same amount of energy.

b) PA and antioxidant activity: In the face of increased FR production as a secondary effect of PA, the organism can adapt by increasing endogenous antioxidant capacity.

Cross-sectional studies of human subjects have observed greater antioxidant enzyme activity in the most trained subjects [28]. The few experimental studies in this area report conflicting results. In some studies, no change in antioxidant activity is observed following a training period [29]; in others, increased activity was observed [30,31]. However, this discrepancy might be explained by differences in duration and intensity of the training program.

The increased activity of endogenous antioxidant systems could be related to increased expression of the genes that codify these enzymes, since it has been shown that FR can directly influence DNA expression [32,33].

c) PA and LDL resistance to oxidation: Another mechanism by which PA might protect LDL from oxidation is by increasing LDL resistance. Transversal studies [34,35] and the only extant experimental study [31] have observed that regular PA is associated with greater LDL resistance to oxidation.

2- Inflammation.
2.1. Inflammation and atherosclerosis.
Inflammation is another fundamental element in the atherosclerotic process [1,2]. As mentioned above, oxidation of LDL particles stimulates the expression of adhesion and chemotactic molecules in the endothelial cells. Both effects will facilitate the transport of macrophages into the subendothelial space, where they are converted to foam cells rich in LDLox particles. These foam cells present antigens to lymphocytes T, initiating the immune response and secreting pro-inflammatory cytokines and acute phase reactants that accelerate the progression of arteriosclerosis [1,2]. Between these cytokines and acute phase reactants are interleukin 6, TNFα, fibrinogen and C-reactive protein (CRP). These substances are markers and predictors of acute cardiovascular events [36].

2.2. PA and inflammation.
Many studies have analyzed the relationship between PA and fibrinogen levels, with the majority observing a beneficial effect [37].
In recent years, the relationship between PA and other inflammation markers, such as PCR, albumin, and erythrocyte sedimentation rate, has been studied. Several cross-sectional studies have found an inverse association between regular PA and PCR levels and the erythrocyte sedimentation rate [38-41] and a direct association with albumin [39]. Also experimental studies have found that diet and regular physical exercise produce a decrease in inflammatory biomarkers, in particular PCR [42].

The mechanism that explains this beneficial effect is not well established, but could be related to the following:

a) less oxidation of LDL particles will produce less inflammation [31].
b) decrease in the expression of adhesion molecules in endothelial cells, which is translated into lesser capacity for macrophage transport into the subendothelial space, and a reduced inflammatory response [43].
c) regular PA produces changes in the arteriogenic activity of the monocytes, decreasing their capacity to produce pro-atherogenic cytokines and increasing their capacity to produce anti-atherogenic cytokines [44].

3- Conclusions
Years ago, Roberts identified PA as "an agent with lipid-lowering, antihypertensive, positive inotropic, negative chronotropic, vasodilating, diuretic, anorexigen, weight reducing, cathartic, hypoglycemic, tranquilizing,
Regular PA seems to increase the activity of endogenous antioxidant systems and the resistance of LDL particles to oxidation and decrease the concentration of oxidized LDL particles and of inflammatory biomarkers.

In contrast, the performance of intense acute PA may produce other effects that are potentially harmful to cardiovascular health: increased FR production, reduced LDL resistance to oxidation, and increased lipid oxidation and inflammation. In addition to being directly related to the duration and intensity of PA, these effects are dependent upon training - whether PA is practiced regularly or not - and therefore the potentially negative effects are attenuated in persons who exercise regularly.

The overall balance of results is clearly in favor of regular PA, to the degree that public health officials have recommended it \[5\] both for primary and secondary prevention of cardiovascular disease.

Bibliografía


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