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Physical activity and lipid oxidation

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Abstract
Regular physical activity (PA) is associated with lower cardiovascular mortality and morbidity. Part of these benefits is related to the effects over the classic cardiovascular risk factors. These effects, however, only explain part of the protection of PA from these types of diseases. The oxidation of LDL cholesterol particles, which is the aetiopathogenic mechanism of a great part of cardiovascular diseases, plays an important role in the arteriosclerotic process. This narrative review presents current knowledge on the relationship between carrying out physical activity and lipid oxidation.

PALABRAS CLAVE
Arteriosclerosis;
Oxidación lipídica;
Patologías cardiovasculares;
Actividad física

Actividad física y estrés oxidativo

Resumen
La práctica regular de actividad física (AF) se asocia con una menor mortalidad y morbilidad cardiovascular. Parte de estos efectos beneficiosos están relacionados con los efectos favorables sobre los factores de riesgo cardiovascular clásicos. Sin embargo, estos efectos explican sólo una parte de la protección de la AF sobre este tipo de enfermedades. La oxidación de las partículas de LDL colesterol tiene un papel fundamental en el proceso de la arteriosclerosis que es el mecanismo etiopatogénico de gran parte de las enfermedades cardiovasculares. En esta revisión narrativa se presenta el conocimiento actual sobre la relación entre la práctica de AF y la oxidación lipídica.

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Introduction

Atherosclerosis is the process that explains the aetiopathogenesis of various chronic cardiovascular pathologies responsible for much morbi-mortality in most of the world. Among this group of diseases, coronary disease constitutes the highest single cause of death in the western world[1,2]. In Spain, coronary disease was responsible for 10.2% of all deaths and 3% of hospital morbidity in 2007[3,4]. Prospects for the future, according to various authors, include an increasing trend that will also reach developing countries[5].

Regular practice of physical activity (PA) reduces the risk of all-cause premature death in young and middle-aged individuals[6] and is also associated with better survival in older people[7]. Regular exercise diminishes the risk of presenting with a cerebrovascular accident[8] and cuts the risk of an acute coronary event in half[9-12]. As a consequence, sedentary lifestyle is an independent risk factor for coronary disease[13,14], and promoting the practice of PA is one of the most important elements of public health campaigns for cardiovascular prevention[15,16].

Regular practice of PA produces favourable effects on classic risk factors for cardiovascular diseases: improves the lipid profile[17], control blood pressure[18] and prevents the appearance of non-insulin-dependent diabetes[19]. Nonetheless, these effects explain only part of the protection PA offers against this type of diseases[20].

PA has beneficial effects on lipid oxidation, haemostasis and endothelial function, factors that are also directly involved in the development and progression of atherosclerosis. In this narrative review of the literature we present the current knowledge about the relationship between PA and lipid oxidation.

Lipid oxidation and atherosclerosis

Oxidative stress has been associated to the development of diverse diseases and chronic processes, including atherosclerosis. The oxidative state is controlled by the equilibrium between the formation of free radicals, which are pro-oxidants, and the action of antioxidant systems. Oxidation of the components of low-density lipoprotein (LDL) is one of the cornerstones of atherosclerosis[1,21,22]. Oxidized LDL (LDL_{ox}) participates in various processes that favour the appearance and progression of atheromatous plaque: LDL_{ox} particles a) cause lesions on endothelial cells that change the vascular tone and permeability of the endothelium[1,22]; b) induce expression of monocyte adhesion molecules on the surface of the endothelial light[23,24]; c) act as chemotactic factors to attract monocytes from the bloodstream to the subendothelial space[25]; d) enter the macrophages by way of the scavenger receptor, which are converted into foam cells and then form the fatty streak that constitutes the first atherosclerotic lesion[22]; and e) induce proliferation of smooth muscle cells and their migration from the media layer of the arterial wall to the subendothelial space[26].

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

a) Formation of free radicals (FR). FR are unstable and very reactive molecules that are produced in any process in which oxygen intervenes[27]. They can react with all of the molecules in an organism (proteins, lipids, DNA), changing their structure and function[28]. The reaction of FR with fatty acids is responsible for LDL oxidation in a process called lipid peroxidation[29,30].
b) Activity of antioxidant substances. To protect itself from the action of FR, the organism has an antioxidant defense system[31]. This system consists of endogenous substances, synthesized by the organism itself, such as superoxide dismutase (SOD), glutathione reductase (GSR) or paraoxonase (PON), and others of exogenous origin, ingested with food, such as vitamins E and C, ß-carotenes and polyphenols[31-33]. In addition, antioxidants are a heterogeneous group of substances that act synergistically, some in liquid medium (GSR, SOD, vitamin C, polyphenols) and others in the lipid environment (PON, vitamin E, ß-carotenes) (Figure 1).
c) Intrinsic properties of LDL. The larger and less dense the LDL particle, the less susceptible it is to oxidation[34]; a higher polyunsatured fatty acid content[35] and glycosylation of the particle result in greater susceptibility to oxidation[36]; on the other hand, a greater presence antioxidant substances, primarily vitamin E and to a lesser extent the ß-carotenes in the LDL particle itself protect against the action of free radicals[37].

Physical activity and lipid oxidation

Both acute and regular PA practice influence FR production, antioxidant activity and LDL susceptibility to oxidation.

Acute physical activity practice and production of free radicals

The average FR life span is very short, and therefore direct quantification is impossible. For this reason, indirect markers are used. For the lipid oxidation study, the markers most often used are malondialdehyde (MDA) and substances that react with thiobarbituric acid (TBARS)[38,39].

During exercise, oxygen consumption increases, which translates into higher FR production. This increase could be so great that it surpasses the protective capacity of the antioxidant systems, resulting in increased oxidation processes, among them lipid peroxidation[40].

Various studies have observed that after acute PA there is a higher plasma level of by-products of lipid oxidation[41-48] (Tables 1 and 2). Some researchers have observed that this increase is directly related to the intensity of the PA involved[43]. In any case, this increased oxidative stress does not persistent and, at least in people accustomed to exercise, is normalized in a few hours[44,48]. Another fact that emerges from these studies is that in animals or individuals who regularly train, the observed increase is less than in sedentary subjects[45,46], suggesting the

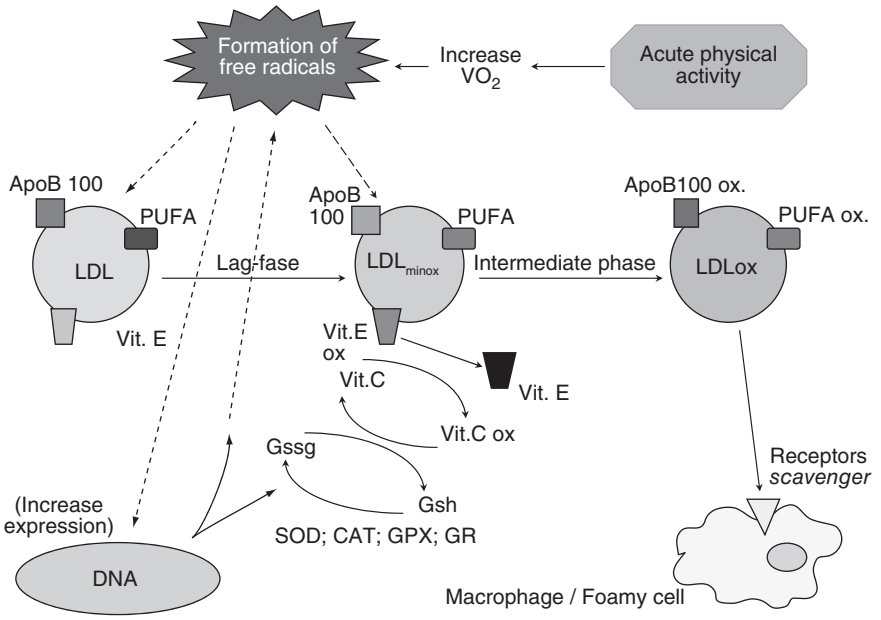

Figure 1 Simplified relationship between the practice of acute physical activity, regular physical activity practice and production of free radicals, lipid oxidation and antioxidant systems. [Adapted from Codina et al. Med Clín (Barc). 1999;112:508-15].
ApoB 100: apoprotein B-100; PUFA: polyunsaturated fatty acids; Vit. E: vitamin E; LDL: low density lipoproteins; Vit. Eox: vitamin E oxidized; LDL_{minox}: low density lipoproteins minimally oxidized; LDLox: low density lipoproteins oxidized; Apo B100ox: apoproteín B-100 oxidized; PUFAox: polyunsaturated fatty acids oxidized; Vit. C: vitamin C; Vit. Cox: vitamin C oxidized; Gssg: glutathione oxidized; Gsh: glutathione reduced.

Table 1 Basic description of studies that have assessed the relationship between the practice of physical activity and the production of free radicals and other oxidation products in animal models

Author	Physical activity					Results
	n	Model	Level of training	Intervention	Variable	
Davies[40]	6	Rats	Sedentary	Submaximal exercise until exhaustion	MDA	↑MDA in muscles and liver
Ji[41]	6	Rats	Sedentary	Submaximal exercise until exhaustion	MDA	↑MDA in liver, without muscle changes
Alessio[58]	32	Rats	One group that trains	Submaximal exercise until exhaustion	MDA	↑MDA in sedentary subjects, not found in those who trained
Jenkins[48]		Rats	One group that trains	Submaximal exercise until exhaustion	MDA	↑urinary excretion of MDA in both those who trained and those who did not

MDA: malondialdehyde.

existence of a protective effect from the regular practice of PA.

Another of the mechanisms that explain lower free radicals production in those who train is explained by an improvement in metabolic efficiency mainly related to the metabolic substrate used to obtain energy. A person who weighs 70 kg has approximately 15 kg of fat in the form of triglycerides in the adipose tissue, which represents about 140,000 Kcal. With the availability of this great quantity of energy, the question is why triglycerides are not the organism's only source of energy, since obtaining energy while exerting physical effort at maximum intensity requires the utilization of carbohydrates. The explanation for this limitation on using adipose tissue as the metabolic substrate to derive energy during the practice of maximum intensity exercise is not entirely clear, although it could be related to different factors:

1) The speed at which fat is released from the peripheral adipose tissue. Lipolysis in the adipose tissue is regulated by the nervous and hormonal systems. It has recently been demonstrated that 70% of fatty acids released from

Table 2 Basic description of studies that have assessed the relationship between the practice of physical activity and production of free radicals other products of oxidation in humans

Author	n	Level of training	Intervention	Variables	Results
Maughan[42]	16	Sedentary	45 min with incline of 12% to 75% TMHR	MDA	↑MDA. (Gradient: 6 hours post-exercise > 24 hours > 48 hours)
Kanter[45]	20	Training, with VO_2 max >50 ml·kg^{-1}. min^{-1}	30 min running at 60% VO_2 max. + 5 min of gradual increase to 2.5 min at 90% VO_2 max.	MDA	↑MDA in serum
Viinikka[46]	10	Cyclists	10-14 min. exercise on stationary bicycles	MDA	No change, MDA in serum
Laaksonen[43]	22	Sedentary	40 min. exercise on stationary bicycles at 60% VO_2 màx.	TBARS	↑TBARS
Treuth[44]	8	Sedentary	PA (intense): 60 min bicycling at 50% VO_2 max. PA (very intense): intervals bicycling at 100% VO_2 max.		↑Oxidation, greater with higher PA intensity
Neubauer[47]	42	Triathletes	Triathlon	Various products	Increase in products of oxidation after competition, normalized by day 5 post-competition

MDA: malondialdehyde; TBARS: thiobarbituric acid reactive substances; TMHR: theoretical maximum heart rate; Vo_2 max: maximum oxygen volume.

the adipose tissue are reesterified; this value drops to 25% at the start of submaximal exercise (40% of the maximum oxygen consumption). Therefore, a mechanism that increases fat utilization could be related to a reduction in reesterification.

2) The carrying capacity of fatty acids in the fatty tissue surrounding muscles and the muscles' captation capacity. A correlation has been found between increased plasma concentration of free fatty acids (FFA) and captation of these FFA by the muscle during exercise. Increased muscle capacity for FFA captation is directly related to an increase in muscle lipoprotein lipase (LPL) activitiy[49]. Muscle captation of FFAs increases linearly with the availability of FFAs circulating in the trained muscle, while the untrained muscle reaches a maximum FFA captation capacity in time. This difference in behaviour between the trained and untrained muscle partly explains the greater utilization of fats in the trained muscle during PA and suggests that local adaptations secondary to training, as for example the increase in LPL activity, are important[50]. On the other hand, muscle captation of glucose increases during prolonged exercise, both in those who train and those who don't, although this captation is much higher in those who do not train.
3) Muscle deposits of fats. Training increases the intramyocellular deposits of fat, parallel to the muscle's capacity for oxidation of fats[51]. Circulating FFAs from the peripheral adipose tissue and intramuscular deposits are the primary sources of fats. Catecholamines are the main stimulants for lipolysis in the adipose tissue, although the low plasma concentration of insulin also has a relevant role. On the other hand, lipolysis of intramuscular fat deposits is mediated only by beta-adrenergic stimulation. Training induces a progressive increase in the utilization of the fat in intramuscular deposits and a reduction in the utilization of carbohydrates[52]. These changes have now been observed at 5 days after the start of training, even before any increase in enzymatic mitochondrial muscle activity[53].

Lipolitic capacity in response to exercise diminishes with higher adiposity. The slightest increase in lipolysis capacity in overweight or obese individuals limits the availability of FFA as a metabolic substrate for energy production, compared with individuals of normal weight[54]. This is important for the treatment of obesity; it has been demonstrated that training improves fat catabolism in people who have been sedentary and obese, while diet alone does not[55]. Some authors have suggested that decreased fatty mass and not age or maximum oxygen volume is the best individual predictor of a decline in fat oxidation capacity at rest. These results support the theory that a reduced fat oxidation capacity that occurs with age is associated with higher adiposity and fewer FFAs. Interventions that increase the quantity of FFAs, such as physical training, might increase oxidation capacity using fats as a metabolic substrate and limit the increase in peripheral adiposity that occurs with aging[56]. Finally, children are better adapted to aerobic metabolism because their energy expenditure depends fundamentally on oxidative metabolism using fat as a metabolic substrate[57].

The currently available data support the hypothesis that one of the protective effects of training for PA could be based on the production of fewer FRs due to higher metabolic efficiency, since less oxygen is consumed to obtain the same amount of energy.

Acute and regular physical activity practice and antioxidant systems

With the greater FR production secondary to PA practice, the organism can adapt itself by increasing endogenous antioxidant capacity. Experimental animal studies (Table 3) have demonstrated that regular practice of PA increases the activity of endogenous antioxidant enzymes[58-62]. In many of these studies, a direct relationship has been observed between the intensity of the PA during the training programme[63-66] and increased capacity of the antioxidants systems.

In cross-sectional studies (Table 4), greater antioxidant enzyme activity has been observed in trained human subjects compared to those inactive[65,66]. The few experimental studies present conflicting results: in one study, no changes were observed in antioxidant enzyme activity after a training period[67]; in other findings, activity increased[68,69]. These differences could be explained by differences in the duration and intensity of the training programme.

FRs can directly influence the expression of DNA, producing higher expression of the genes that codify these enzymes[70-72] and explain the antioxidant enzyme activity increase observed after a training period.

Physical activity and susceptibility of LDL to oxidation

Another mechanism by which PA might protect LDL from oxidation could be the reduction of LDL susceptibility to the oxidation process.

The experimental studies that have analyzed the effect of acute PA on LDL susceptibility obtained inconclusive results. Sanchez-Quesada et al[73] observed, in trained

Table 3 Basic description of studies that have assessed the relationship between regular practice of physical activity and the antioxidants system in animal models

Author	Sample		Physical activity		Results
	Animal	Tissue	Intervention	Variables	
Powers[61]	Rats	Diaphragm	Training (continuous running) in diverse groups, by intensity (high, moderate, light) and duration (30, 60, 90 min/day) 4 days/week for 10 weeks	GRS, SOD, CS	↑OD, GRX, CS at all intensities and durations of activity. SOD increase was greater at higher and moderate intensities and at 60 min/day or more
Powers[62]	Rats	Myocardium	Training (continuous running) in diverse groups, by intensity (high, moderate, light) and duration (30, 60, 90 min/day) 4 days/week for 10 weeks	SOD, GRS, CAT	↑SOD activity at high intensity, all durations, and at moderate intensity at 90 min. No changes found in other enzymes
Criswell[63]	Rats	Muscle	Two types of training (12 weeks): intervals (6 series of 5 min al 80-90% VO_2 max) and continuous (45 min at 70% VO_2 max)	SOD,GRS	↑GRS activity in interval training group. ↑SOD activity in both groups
Sen[59]	Dogs	Liver, muscle	Training (continuous running): 40 km/day at 5.5-6.8 km/hour with 15% incline, 5 days/week for 55 weeks	GRS	↑GRS (quantity)
Sen[59]	Rats	Liver, muscle	Training (continuous running): 2 hours/day at 2.1 km/hour, 5 days/week for 8 weeks	GRS	↑GRS (quantity)
Marin[60]	Dogs	Muscle, liver	Training (continuous running): 5 days/week with 15% incline for 30 weeks	GRS	↑GRS activity in muscles exercised. No changes fund in liver
Vani[64]	Rats	Liver	Training (continuous running): 3 groups at same intensity, different duration: 1 day, 10 days and 60 days.	MDA, SOD, GRS, XO	↑SOD, XO activity as training period increased. No changes found in GRS

GRS: glutathione reductase; SOD: superoxide dismutase; CS: citrate synthase; CAT: catalase; XO: xanthine oxidase; VO_2 max: maximum oxygen volume.

Table 4 Basic description of studies that have assessed the relationship between regular practice of physical activity and the antioxidants system in animal models

Author	Sample				Physical activity		Results
	n	Groups	Tissue	Design	Intervention	Variables	
Mena[65]		Sedentary	Erythrocytes	Transversal		SOD, CAT, GPX	Basal: SOD activity in cyclists (professionals and amateurs) higher than in sedentary subjects.
		Cyclist (amateur) Cyclist (professional)					CAT and GPX activity higher in professionals than in amateurs and sedentary subjects
Covas[66]	488	Women		Transversal		SOD, GPX	Practice of physical activity directly associates with SOD and GPX activity
Tiidus[67]	7 6	Men Women	Muscle	Experimental	Training (cycling) 35 min 3 days/week for 8 weeks	SOD, CAT, GPX	No changes in SOD, GPX and CAT activity after training period
Elosua[68]	7 10	Men Women		Experimental	Training (aerobic), 45-60 min 3-5 days/ week, for 16 weeks	SOD,GPX, GR	↑GPX , ↑GR activity after the training period
Evelo[69]	23 18	Men Women	Erythro-cytes	Experimental	Training in two 20 weeks periods. Running 15 km after 20 weeks, half-marathon after 40 weeks	GPX	↑GPX after 20 wks of training. Levels maintained in succeeding 20 weeks. After the two races (15 km after 20 weeks of training; 21 km after 40 weeks of training) GPX activity decreased sharply, with full normalization at 5 days post-race

GPX: glutathione peroxidase; SOD: superoxide dismutase; CAT: catalase; GR: glutation reductase.

individuals, an increase in LDL susceptibility to oxidation immediately after completing a 4-hour run. Other studies that have analysed changes more than 8 hours after PA did not observe an increase[74-75]. From these studies we could hypothesize that trained individuals have increased susceptibility to LDL oxidation during a short period of time after engaging in intense, prolonged, acute PA.

No studies have addressed the effect of acute PA on oxidation susceptibility in sedentary subjects, although it would be reasonable to expect an increase of greater magnitude and duration than in the athletes studied.

Another key point is the effect of a training period on LDL susceptibility to oxidation. The crossectional studies that compared physically active and sedentary subjects have established that those actives have less LDL susceptibility to oxidation[76,77]. It has been reported that after a training period LDL susceptibility to oxidation decreases, reducing the oxidized LDL in circulation[68]. The reason for this greater resistance to oxidation is not entirely clear, although some evidence suggests that it is related to a qualitative change in LDL subclasses with a reduction of the dense fractions and an increase in the mean diameter of the LDL particles[78-80].

The global effect of all these mechanisms that adapt to training is reduced levels of lipid oxidation that has been reported in healthy individuals[68,81] and also in patients with previous ischemic heart disease[82].

Physical activity and inflammation

One of the most important consequences of this decrease in lipid oxidation is the simultaneous reduction in systemic markers of inflammation. Various transversal studies have described an inverse association between the regular practice of physical activity and diverse inflammation markers, especially high sensitivity C-reactive protein (CRPhs)[83-91]. Although a recent meta-analysis of experimental studies that considered this association concluded that aerobic exercise does not reduce CRPhs levels in adults[92], that meta-analysis included only 5 studies with a total of 323 participants. Therefore, the findings should be interpreted with caution.

A decrease in levels of interleukin 6 (IL-6) have been observed in some studies[91,93] but not in others[94]. In this context, we must take into account the role of myokines in muscle function. During contractile activity, the muscle produces a series of myokines, among them IL-6, that can exert beneficial effects at the systemic level. Some studies have observed that muscle IL-6 induces systemic expression of anti-inflammatory molecules, such as IL-10 and the IL-1 receptor antagonist, and reduces the presence of pro-inflammatory molecules such as tumour necrosis factor-alpha. In addition, muscle IL-6 induces lipolysis, which stimulates the utilization of fatty acids as a metabolic substrate to obtain energy.

Conclusions

Regular practice of PA produces a series of beneficial effects on oxidative metabolism that translate into less oxidative stress. The mechanisms involved are related to an increase in energy efficiency and the utilization of fatty acids as a metabolic substrate for energy production, a greater capacity to defend against oxidative stimulants due to an increase in endogenous antioxidant enzymes activity, and an increase in LDL resistance to oxidation. All of this translates into a reduction in the levels of oxidized LDL and systemic markers of inflammation.

Conflict of interest

The authors declare no conflict and no financial interests.

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