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Review Article

Metabolism of fatty acids, secondary complications and effects of physical exercise: integrative review

Metabolismo dos ácidos graxos, complicações secundárias e efeitos do exercício físico: revisão integrativa

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ABSTRACT

Introduction: Diet is a complex set of exposures that frequently interact, and whose cumulative effects influence the results of health. This includes effects on systemic inflammation markers in metabolic disturbances and cardiovascular diseases. Various studies have been presented relating the effect of physical exercise on lipids, however, the results are still controversial. **Objective:** To describe fatty acid metabolism and the effect of physical exercise on secondary complications. **Methods:** An integrative review was conducted on topics in the Medline, Pubmed, Web of Science and Scopus databases, published up to the year 2017. **Results:** Fatty acids, depending on their biochemical characteristics and spatial configuration, have differentiated effect on cardiovascular health, however, studies still present contradictory results about the therapeutic use of certain fatty acids. Physical exercise appears to benefit fatty acid metabolism and attenuate the complications secondary to the intake of certain fatty acids, and potentializes the positive effects of distinct fatty acids. **Conclusion:** However, variants of physical exercise, such as intensity, duration, time of observation of effects of the results, limit the authors to concluding, with a certain degree of certainty, about the effect of physical exercise on fatty acids and secondary complications, since the studies in the literature continue to be contradictory.

Key-words: Fatty Acids, Exercise, Inflammation, Oxidative Stress.

RESUMO

Introdução: A dieta é um conjunto complexo de exposições que interagem frequentemente e cujos efeitos cumulativos influenciam os resultados da saúde. Isso inclui efeitos nos marcadores de inflamação sistêmica em distúrbios metabólicos e doenças cardiovasculares. Vários estudos foram apresentados relacionando o efeito do exercício físico sobre lipídios, no entanto, os resultados ainda são controversos. **Objetivo:** Descrever o metabolismo dos ácidos graxos e o efeito do exercício físico nas complicações secundárias. **Métodos:** Foi realizada uma revisão integrativa dos assuntos nas bases de dados Medline, Pubmed, Web of Science e Scopus, publicadas até o ano de 2017. **Resultados:** Os ácidos graxos, dependendo

de suas características bioquímicas e configuração espacial, têm efeito diferenciado na saúde cardiovascular, no entanto, estudos ainda apresentam resultados contraditórios sobre o uso terapêutico de certos ácidos graxos. O exercício físico parece beneficiar o metabolismo dos ácidos graxos e atenuar as complicações secundárias ao consumo de certos ácidos graxos, além de potencializar os efeitos positivos de diferentes ácidos graxos. **Conclusão:** No entanto, variantes do exercício físico, como intensidade, duração, tempo de observação dos efeitos dos resultados, limitam os autores a concluir, com certo grau de certeza, sobre o efeito do exercício físico sobre ácidos graxos e complicações secundárias, uma vez que estudos na literatura continuam sendo contraditórios.

Palavras-chave: Ácidos Graxos, Exercício, Inflamação, Estresse Oxidativo.

Introduction

Cardiovascular diseases continue to be the main cause of morbidity and mortality in the world, in spite of improvements in the results [1,2]. However, risk factors such as obesity and diabetes mellitus (DM) have increased substantially and increased the inequalities among countries. Not only the prevalent risk factor cause concern about these diseases, but also the low level of implementation of preventive measures, such as low quality diet and physical inactivity [3].

A large portion of the cardiovascular disturbances have their origin in atherosclerosis, characterized by changes in the intima, represented by accumulation of lipids, components of the blood, cells, intercellular matter and carbohydrates [4].

Lipids have always been present in diets. Diet is a complex set of exposures that frequently interact, and whose cumulative effects influence the results of health. This includes effects on systemic inflammation markers in metabolic disturbances and cardiovascular diseases [5].

The fat consumed is composed of fatty acids (FA) and glycerol. The larger part of FAs in humans are of the long chain type, divided into saturated and unsaturated types that may present a cis or trans configuration [6]. The composition of FAs coming from the diet is an important factor, because they cause different metabolic changes [7].

At present, an increase in trans fat consumption by individuals has been observed. This has aroused the interest of the scientific community, because the consumption of trans fatty acids has been related to increased risk of coronary diseases [8], changes in plasma lipoproteins and triglycerides, increased risk for Diabetes Mellitus [9], elevation of serum inflammatory markers [5], oxidative stress and endothelial dysfunction markers, as well as worsened nitric oxide-mediated vasodilator response [10]. The physical-chemical characteristics of fatty acids, such a melting point, carbon chain size, presence of double bonds and geometric configurations are important aspects that may interfere in the absorption of fatty acids by tissues, especially the adipose and vascular types, and the development of health problems.

Various studies have been presented relating the effect of physical exercise on lipids, however, the results are still controversial [11-14]. Over the last few decades it has been possible to observe growing evidence that acute physical exercise could have an acute beneficial influence on the lipid profile [15,16].

The difficulty with analyses and interpretation of these studies lies in the use of different physical activity protocols established.

Fatty acids: definition and classification

Lipids are distinct elements among them, presenting different chemical and functional characteristics. Fatty acids, the constituent elements of lipids, are present in any lipid structure.

Fatty acids are organic components that contain carbon and hydrogen in their molecules. Depending on the type of combination among fatty acids and their constituents, they will form different types of lipids. Based on these combinations, they may be classified as simple or complex types. Simple lipids are those in which the fatty acid combines with only one other element (e.g.: triglycerides), whereas, complex lipids are those in which the fatty acid combines with more than one element (e.g.: lipoproteins) [17].

Among the characteristics that distinguish the fatty acids is the size of the carbonated chain. Fatty acids may also be classified as short and long chain types. The short chain type has between 4 and 16 carbon molecules, and when they are not supplied by the diet, they are synthesized, mainly in the cytoplasm of hepatic and adipose tissue cells. The long chain fatty acids have 16 or more carbon molecules, and when they are not supplied by the diet, they are formed by elongation of pre-existent fatty acids [18]. In addition, fatty acids may be classified based on the type of bond among their molecules, differing between saturated or unsaturated types. Unsaturated fatty acids have double bonds between their carbon molecules, while the unsaturated type does not have these bonds [19]. Unsaturated fatty acids are chemically more unstable and may be of the monounsaturated type, when they have only one double bond, or polyunsaturated when they have two or more double bonds [20].

Unsaturated fatty acids may present a cis or trans configuration. They are characterized as a cis fatty acid when the hydrogen molecules in their geometric configuration are presented in the same plane as that of the double carbon bond. They are characterized as an unsaturated fatty acid of the trans type when their hydrogen molecules are on the opposite side of the double carbon bond. The trans fatty acid is a geometric isomer of the original cis fatty acid; that is, it presents the same quantity of carbon, oxygen and hydrogen molecules but with a different spatial configuration [19].
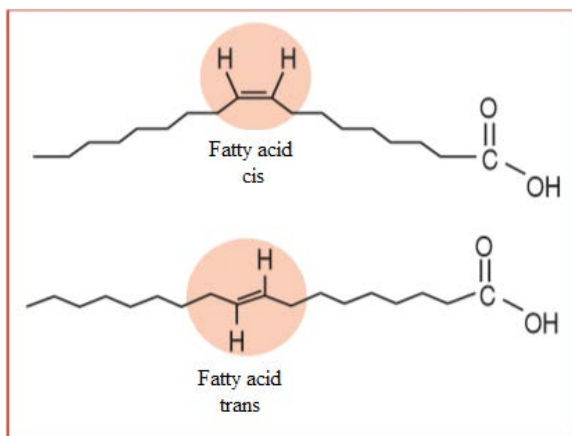

Figure 1 – Illustration of o cis-unsaturatel fatty acid and a trans-unsaturated fatty acid. Source: Lima [21].

The two types of fatty acids may be found in nature, however, the cis configuration is more common, because the enzymes that synthesize fatty acids prefer this configuration. The trans fatty acids found in nature are present, in a reduced manner, in meats and milk. More expressive incorporation of trans acids into the human diet occurred with the process of hydrogenation of vegetable oils, especially by the food industry. Heating vegetable oil also induces the formation of geometric isomers of polyunsaturated fatty acids, and so does the irradiation of foods [22].

Trans fatty acids are more stable than the cis fatty acids, and therefore less energetic. Because the cis isomers are more energetic, they would be involved in the synthesis of different cellular lipids. The change in the structure of fatty acids to the trans form modifies the melting point, increases the plasticity and oxidative stability of these fats. Elaidic acid, for example, (9trans-18:1) presents a melting point of 440C whereas, oleic acid (9cis-18:1) has a melting point of 130C [23].

Melting point is an important characteristic of fatty acids. The higher the melting point, the greater the quantity of thermal energy necessary to break down their molecular arrangements. This allows greater impregnation into the tissues such as the vascular endothelium, and particularly in the adipose tissue. As the carbonated chain length increases, the melting point also increases. However, the presence of double bonds makes the melting point fall. Due to the geometric configuration, the melting point of trans fatty acids is also higher [24].

When trans fatty acids are ingested and absorbed, they may change the composition and biochemical activity of the cell membranes, thus changing the physical properties of the membrane, and finally change its functions [20,24]. The composition of phospholipids in the plasma membrane has a crucial influence on cellular growth and metabolic activity. In the last two decades, studies have suggested that the lipid composition in the diet influences the fatty acid profile of serum and the lipid content of the plasma membrane. In fact, the length of the fatty acid chains and the degree of saturation or unsaturation have been shown to change the fluidity and activity of various proteins associated with the membrane [25].

With the change in the physiological processes as a consequence of the incorporation of these fatty acids into the different tissues, evidence of different adverse clinical situations has been shown in the literature. Among these, for example, increase in triglycerides, change in lipoproteins such as increase in LDL, VLDL, reduction in HDL concentration [26], increase in insulin resistance, increasing the risk of diabetes Mellitus [27], increase in the production of pro-thrombotic factors, increase in reactive oxygen species [28], increased risk for CAD, especially Acute Myocardial Infarction [29], among other pathologies [23].

Studies such as that of Chajés *et al.* [30], have suggested that high ingestion of industrial trans fatty acids could cause an increase in body weight, especially in women. Furthermore, as mechanism for the prevention of obesity, they have suggested limitation of the consumption of highly processed foods must be considered, as they are the main source of industrially produced trans fatty acids [31].

On the other hand, unsaturated fatty acids with cis configuration have been related to favorable effects on the metabolism. Evidence has been shown

of association between the consumption of unsaturated fat and aspects such as reduction in: blood viscosity and plasma triglycerides; higher level of endothelium relaxation [32]; improvement in insulin sensitivity [33], among others.

Evidence has been shown that the intermediate products of fatty acid metabolism are important for myoblast survival, proliferation, differentiation and fusion. Studies have suggested that the lipid metabolites derived from polyunsaturated fatty acids accelerated protein synthesis, and the fusion and growth of muscle cells in different animal models [34]. Fostok *et al.* [35], have demonstrated that oleic acid (cis, unsaturated fatty acid) supplementation attenuated incomplete repair actions, optimizing the regenerative capacity and contractile function of the injured muscle.

In spite of the body of evidence presented up to now, substitution of saturated fats with polyunsaturated fats in diets as a way of preventing cardiovascular diseases continues to be questionable. According to Hamley [36], in a meta-analysis published in 2017, the evidences available in the randomized clinical trials up to now suggested that the substitution of saturated fatty acids with polyunsaturated fatty acids (n-6) in diets was not sufficient to reduce the events of cardiovascular diseases, mortality due to coronary disease or total mortality. Furthermore, he suggested that his results have implications for present dietary counsel, in which the recommendations to reduce saturated fat and/or substitute saturated fatty acids with polyunsaturated fatty acids must not be emphasized, because the maintenance of these recommendations would probably not have the intended effect and could reduce the efforts towards (encouraging) persons to adopt other lifestyle changes that would most probably be more beneficial.

The chart below presents the summary of the studies cited above, on the effect of fatty acids on the cardiovascular and metabolic systems.

Frame 1 - Summary of the studies about fatty acids and effect on the cardiovascular and metabolic systems.

Authors	Year	Type of study	Population	Results
Sandres TA, Oakley FR, Crook D, Coper JA, Miller GJ [26]	2003	A Randomized Clinical Trial	29 men	Trans diet reduced HDL cholesterol, however, did not change the hemostatic risk factors
Zapolska-Downar D, Kośmider A, Naruszewicz M [28]	2005	Controlled Study	Umbilical cells	Increase in apoptosis and induction of intracellular production of Reactive Oxygen Species
Sun Q, Ma J, Campos H, Hankinson SE, Manson JE, Stampfer MJ *et al.* [29]	2007	Case Control Study	493 cases and controls	The highest total trans fatty acid content in the erythrocytes was associated with an elevated risk of Cardiovascular Disease
Chajès V, Biessy C, Ferrari P, Romieu I, Freisling H, Huybrechts I *et al.* [30]	2015	Prospective study	1949 participants	High consumption of trans fatty acids induced an increase in weight
Ford PA, Jaceldo, Siegl K, Lee JW, Tonstad S [31]	2016	Cross-sectional Cohort Study	8771 participants	Lower ingestion of dietary trans fatty acids had beneficial effects on the emotional status

Frame 1 - Continuation...

Authors	Year	Type of study	Population	Results
Abbott SK, Else PL, Hulbert AJ [33]	2010	Experimental Study	Young rats	Consumption of trans fatty acids interfered in the composition of fatty acid composition of phospholipids of the rat skeletal muscles
Fostok SF, Ezzeddine RA, Homaidan FR *et al.* [35]	2009	Experimental Study	Young rats	Monounsaturated fatty acids in the cis configuration increased the anti-inflammatory effects
Hamley S [36]	2017	Meta-analysis	Studies of the Randomized Clinical Trial Type	The evidence available in adequately controlled randomized controlled trials suggested that the replacement of saturated fatty acids with most of the polyunsaturated fatty acids n-6 would be unlikely to reduce the events of Cardiovascular Disease, mortality due to coronary disease, or total mortality

Fatty acid metabolism during exercise

Approximately 90% of the lipids consumed are in the form of triglycerides (TG). The remaining 10% are in the form of cholesterol, cholesterol esters, phospholipids and free fatty acids. Lipid digestion begins in the mouth and stomach with the action of the lingual and gastric lipases. They degrade the TGs into medium and short chain fatty acids. After the action of the lipases, they undergo the action of the biliary salts and substances produced by the pancreas such as pancreatic lipase that will degrade the TGs formed by long chain fatty acids [37].

In sequence, the short and medium chain free fatty acids are directly absorbed by the enterocytes of the intestinal mucosa and are released into the venous blood stream. They are then transported to the liver by albumin, by the hepatic port circulation, or to the peripheral tissues in which they are directly absorbed and used as energy substrate. Whereas, the long chain free fatty acids, non-esterified cholesterol, phospholipids together with their biliary salts and the liposoluble vitamins (A, D E and K), form the mycelia, which are hydrophilic particles that facilitate lipid transport, and these liposoluble vitamins, through the membrane of the enterocytes [38].

After crossing the intestinal mucosa, the compounds of the mycelia, together with Apolipoprotein B-48, will form the primogenitor lipoprotein – Chylomicra or Chylomicrons. At this point, the fatty acids are again resynthesized into triglycerides and the free cholesterol is esterified. Therefore, the chylomicras mainly transport triglycerides and esterified cholesterol [39].

The chylomicras are then transported to the peripheral tissues, to which mainly fatty acids are released for energy production. To enable them to be released, these fatty acids must be cleaved from the glycol. Lipoprotein lipase is the enzyme that cleaves the triglycerides coming from the chylomicras and later from the VLDL. The free fatty acids are then absorbed by the adipose or muscle tissue, or then transported to other tissues by albumin [37].

Lypolysis comprises four stages: cleavage of the triglycerides in the blood; beta-oxidation of the fatty acids; the citric acid cycle, and the electron transport chain. The first stage, as previously described, occurs in the blood, where the triglycerides present in the low density lipoproteins are cleaved by lipoprotein lipase. In this process, the fatty acids are released from the glycerol and transported up to the sarcolema (plasma membrane of the muscle cell) by albumin. On entering the cell, the second stage - beta-oxidation - occurs. In this stage, the fatty acids undergo the action of enzymes, such as thiokinase, present in the external membrane of the mitochondria. The mitochondria have two membranes - internal and external - and a space between these membranes. Beta-oxidation is finalized in the external membrane of the mitochondria, the site where thiokinase is found, which will finalize this process. However, the long chain fatty acids, differently from the medium and short chain types, are not permeable to the internal membrane of the mitochondria, and requires the action of carnitine, nutrient transporter of AcetylCoA, resulting from the catabolism of the long chain fatty acids through the internal membrane of the mitochondria [40].

Oxidative metabolism allows energy to be obtained from fatty acids in an intramitochondrial localization. Thus, to enable acyl-CoA to be used by it (oxidative metabolism), it is necessary to overcome the impermeability of the external and cytoplasmic membrane of the mitochondria to attain the acyl--CoA. The enzyme responsible for this transport is Carnitine-CoA acyltransferase (Carnitine O-Palmitoyltransferase). This enzyme presents greater specificity for Palmitoyl-CoA, however, it catalyzes transport of fatty acids with a carbonated chain length between C4 and C18. Fatty acid chains longer than these are more difficult to be transported. Once inside the mitochondria, acyl-CoA may be used in the lipolytic metabolism of LYNEN [41].

Carnitine palmityl transferase was historically seen as the only regulator of fatty acid oxidation. However, other FA translocators, such as FAT/CD36 have been identified. Specifically, FAT/CD36 appears to have a differentiated mechanism of action with respect to fatty acid oxidation during exercise, influencing lipid transport through the sarcolemal membrane and to the mitochondria [42].

Differently from the striated muscles, adipose tissue allows the entry and exit pathway of fatty acids. While the fatty acids only enter the muscles with the purpose of producing energy, whereas, on entering into the adipose tissue, the fatty acids may produce energy and may also be accumulated. When necessary, the fatty acids accumulated in the form of triglycerides may be hydrolyzed and thus release fatty acids into the blood stream, and these are transported by albumin to be used in other tissues to produce energy. The main consumer of these fatty acids released by the adipose tissue are the striated cardiac and skeletal muscles [40].

Fatty acid metabolism during exercise

The process of fatty acid uptake and oxidation is important for ATP resynthesis [43]. Once the fatty acids enter the skeletal fiber, they have different destinations, depending on the metabolic state of the cells. In conditions of rest, the plasma fatty acids are conducted to triglyceride synthesis as the first destination, instead of being moved to the mitochondria for oxidation [43].

As the exercise progresses, long chain fatty acids, provided by the blood or from hydrolysis of intramuscular triacylglycerols, are metabolized to generate energy. The supply of fatty acids from the hydrolysis of intramuscular triacylglycerols is limited and during exercise; the myocytes consume approximately 90% of the free fatty acids derived from blood plasma [41].

Small quantities of the triglycerides are stored within the lipid droplets in the skeletal muscle and may be hydrolyzed to produce fatty acids for energy production by means of β oxidation and oxidative phophorylation. Although there has been some controversy about the quantitative importance of intramyocellular (IMTG) as metabolic substrate, recent studies have demonstrated a substantial contribution by IMTG to energy production [45].

There are three lipases expressed in the skeletal muscle, which are responsible for the degradation of TG: monoacylglycerol lipase; Adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL).

ATGL is the first step of TG lipolysis in the skeletal muscle of humans and mice, resulting in the release of one fatty acid molecule. Monoacylglycerol lipase is responsible for the hydrolysis of monoacylglycerol, releasing glycerol and fatty acids. The HSL catalyzes the hydrolysis of TG to release FA in the cytoplasm [41]. The HSL is highly present in the type I oxidative fibers of skeletal muscle and is activated by adrenergic stimulation and contraction. ATGL is activated by the comparative identification of genes-58 (CGI-58), These proteins are localized on the surface of the mitochondria, and are preferentially expressed in oxidative muscle, such as the cardiac and soleus muscles [45]. Resistance training leads to increased levels of ATGL, increasing intramuscular lypolysis, particularly in Type I oxidative fibers [46]. Studies such as that of Roepstorff *et al.* [47] have demonstrated that exercise triggered the rapid activation of HSL dependent on protein kinases in human beings, promoting the release of FA.

The mechanisms that regulate exercise-induced lipolysis in the skeletal muscle have not yet been completely elucidated and may be more complex than lipolysis in adipose tissue [48].

Studies have also suggested that physical exercise performed in an acute manner promotes changes in the fatty acid transport genes, preceding increases in RNAm expression [49]. This will allow greater metabolization of fatty acids, although the latter possibility has not yet been tested [50].

According to the research of Kim *et al.* [51], physical exercise is also capable of significantly increasing the expression of components of the metabolic pathway and components related to the redox signal induced a similar increase in the FAT/CD36 content of the cell membrane of skeletal muscle in rats.

In a randomized clinical trial published in 2017, the response of post-prandial triglycerides was observed to be attenuated by low to moderate intensity periodized exercises, when measured after 24 hours [52].

The use of lipids is modulated by the availability of fatty acids in the plasma. In obese subjects, the plasma AG levels are more elevated. Glycolytic activity is altered in this population, and lipid metabolism may be a preferential route. In obese subjects, the metabolic responses of fatty acid mobilization appear to be less favored by aerobic activity, however, the responses are not yet conclusive [11].

Recent studies have reinforced the differences in the patterns of lipolysis stimulation between thin and obese subjects during physical exercise. The difference in the lipolytic rate appear to be due to differences in the quantity or

activity of the lipases present in the skeletal muscle, especially ATGL, and not the mRNA levels [53].

Frame 2 - Effect of exercise on fatty acid metabolism.

Authors	Year	Type of study	Population	Results
Turnbull PC, Longo AB, Ramos SV *et al.* [46]	2016	Randomized Experimental Study	10 male rats per Control and Experimental Groups	Resistance training increased the TGLA, increasing intramuscular lypolysis, particularly in Type I oxidative fibers
Roepstorff C, Vistisen B, Donsmark M *et al.* [47]	2004	Self-controlled Study	8 moderately trained men	Exercise triggered rapid LHS activation dependent on protein kinases, promoting AG release
Barres R, Yan J, Egan B, Treebak JT *et al.* [49]	2012	Self-controlled Study	14 sedentary and healthy participants	Acute physical exercise promoted change in fatty acid gene transporters
Kim J, Lee K-P, Lee D-W, Lim K [51]	2017	Experimental Study	18 Rats	Exercise induced significant increase in expression of components of the lipid metabolic pathway and components related to the redox signal
Homer AR, Fenemor SP, Perry TL *et al.* [52]	2017	A Randomized Clinical Trial	36 adult participants	The post-prandial triglyceride response was attenuated with physical exercise
Jabbour G, Iancu H-D, Paulin A *et al.* [11]	2015	Comparative Study	45 obese adolescents	Greater lipid mobilization in adolescents with changed weight when compared with those with normal weight
Petridou A, Chatzinikolaou A, Avloniti A *et al.* [53]	2017	Comparative Study	16 adults divided into two groups 7 thin and 9 obese subjects	No change in the mRNA levels during exercise was found, but the obese presented lower levels of mRNA, ATGL and HLS, in comparison with the adults with normal weight

Fatty acid consumption, inflammatory and endothelial dysfunction status

There are various mechanisms by means of which diet increases or diminishes the risk for cardiovascular diseases. Investigation of the mechanisms that determine atherosclerosis have suggested that an inflammatory process plays a central role in its development, progression and outcomes. This inflammatory process causes structural and functional changes in the blood vessel walls, which leads to endothelial dysfunction and the development of atherosclerotic lesions [54]. Calorie-restriction diets are known to reduce the circulating levels of C-reactive protein, which is a systemic inflammation marker that may also play its own role in the inflammatory process, and many studies have shown that it prevented cardiovascular events [55]. Diets rich in omega-3 fatty acids appear to reduce atherosclerosis by means of the process of down-regulation of intracellular mechanisms that lead to the expression of pro-atherogenic genes [5].

The vascular endothelium is considered a dynamic tissue, an "organ" controlling important functions, such as coagulation, maintenance of blood circulation, vagal tonus, fluidification and inflammatory responses. Among these various functions, the endothelium is also responsible to produce vasodilator and vasoconstrictive substances. Nitric oxide is the main factor in dilator responses and is directly involved in endothelial dysfunction [56].

The term "endothelial dysfunction" refers to an imbalance in endothelial production of mediators that regulate vascular tonus, platelet aggregation, coagulation and fibrinolysis. Endothelial dysfunction is also frequently reported as worsening in endothelium-dependent relaxation, caused by loss of nitric acid (NO) bioavailability, although changes in other vasoactive substances have also been found [57].

Nitric oxide has diverse antiatherogenic functions, among them, inhibition of smooth muscle cell production, inhibition of platelet aggregation and antioxidant properties. Its release is stimulated by the shear force exerted on the endothelium by blood; this fact is shown by the higher level of NO released from the arteries, in comparison with veins [56].

In the post-prandial state, a longer period during which triglyceride-rich (TG) lipoprotein levels remain elevated, may lead to endothelial dysfunction. This results in increase in the inflammatory response, lower level of nitric acid availability, and increase in oxidative stress - changes involved in the genesis of atherosclerosis [58].

After a meal with a high fat content, healthy individuals present a significant increase in the concentrations of proinflammatory cytokines, TNF-α, IL-6 and adhesion molecules (intercellular adhesion molecule-1 - ICAM-1 and Vascular cellular adhesion molecule-1 - VCAM-1), when compared with a meal with a high carbohydrate content. These changes may also be prevented with the use of Vitamin E, suggesting that oxidative stress regulates the increase in cytokines and adhesion molecules. Studies have demonstrated that the post-prandial triglyceride levels, and not those coming from adipocytes in fasting are more sensitive markers of atherosclerosis [59,60].

Elevation of C Reactive Protein (CRP) begins around 6h after inflammatory stimulation; it has a half-life of approximately 19h, and its maximum value is attained in 24-72h. Its plasma concentration is constantly low, and does not present circadian variations, in contrast with some coagulation proteins and others of the acute inflammatory stage. Once stimulation has been concluded, the values return to normal after 7 days.

Exercise, inflammatory response and endothelial dysfunction

Although studies have shown evidence that the practice of physical activity prevents the genesis and progression of atherosclerotic disease, the mechanisms to explain this effect have not yet been completely elucidated. Ghisi *et al.* [56] suggested that the factor responsible for this effect is related to the change in vascular tonus and endothelial function.

Atherosclerosis development and progression partly depend on the migration of monocytes to the blood vessels, to become active and begin the release of cytokines. According to Vuorimaa *et al.* [61] the first cytokines in the cascade are the tumor necrosis factor (TNF-α) and interleukin1 (IL1) considered proinflammatory cytokines. After an acute exercise session, there is no increase

in the proinflammatory cytokines, suggesting that physical activity suppresses the entry of these cytokines into the plasma.

Paton *et al.* [62], after a study with healthy and sedentary subjects, concluded that exercise performed at 50% to 70% intensity continuously for 6 months could improve the inflammatory response, coagulation and fibrinolytic potentials, reducing the risk for cardiovascular disease.

The effects of physical exercise on endothelial function, has been demonstrated in animal and human experiments, however, the literature is still controversial relative to the intensity of effort necessary to cause protective effects. The intensity most tested in both humans and animals is the moderate level, however, there are some evidences that high intensity, acute aerobic exercise increased the chance of cardiovascular events, but when performed chronically, it was associated with decreased occurrence of these events and mortality [58].

MacEneaney *et al.* [63] in a study about the effect of post-prandial lipemia on the inflammatory markers and endothelial activation in adolescents, found that physical exercise did not change the values of C-Reactive protein, TNF-α, IL-6 and adherence molecules in circulation, showing that in spite of significant reductions in hyperlipemia, exercise did not change the inflammatory response in 6h of observation. The findings of this study corroborated those of Dekker *et al.* [64] in which physical exercise did not significantly change the IL-6 values, although a trend towards reduction was perceived when compared with the control group.

In the study of Tyldum *et al.* [65] when they studied vasodilation mediated by flow after lipid overload, with and without physical exercise, showed evidence that with high intensity, periodized physical activity, the vessel diameter increased when compared with that of the control, demonstrating vasodilation secondary to physical activity.

Physical exercise has been associated with an increase in the nitric oxide synthase enzyme, with an influence on the increase in nitric oxide, providing a protective effect against endothelial dysfunction through physical exercise. Physical exercise also induces the release of extracellular superoxide dismutase which, according to Vuorimaa [61], is an enzyme that acts in the antioxidant process.

Studies have shown evidence that dietary supplementation with polyunsaturated fatty acids acted on reducing inflammatory response [66]. The beneficial effects of dietary supplementation with polyunsaturated fatty acids on exercise performance and on oxidative balance of physical activity have also been shown in other studies [67] although the effects associated with intense physical activity on the immune response are still contradictory [68].

According to Capó *et al.* [69], exercise increased the activated levels of the anti-inflammatory response, increasing anti-inflammatory gene expression after the exercise, particularly in the group of young individuals. Recent studies have reinforced the idea that physical exercise attenuates the inflammatory response [70].

Fatty acids and oxidative stress

Oxidative stress formation, according to Ghisi [56] would be one of the main factors responsible for triggering atherogenesis, and that the superoxide

anion (O2-) and oxidized LDL would be the main free radicals involved in this process. In addition to this, Reactive Oxygen Species (ROS) could interact with NO and form the peroxynitrite anion (ONOO-) and nitrogen dioxide (NO2), which would be responsible for potentializing the inflammatory lesion, favoring the progression of atherosclerosis [61].

Lipid overload induces an increase in triglyceride-rich lipoprotein - TRLp, reduction in HDL and hyperinsulinemia. This metabolic condition leads to the formation of free radicals, which are reduced, according to the antioxidant capacity (endogenous and/or exogenous) present, determining oxidative stress. The free radicals stimulate tissues to secrete cytokines (TNF-α, IL-1 and IL-6), probably through the macrophages, thus stimulating the formation of adhesion molecules. The generation of reactive oxygen species diminishes the bioavailability of free NO, resulting in a lower level of endothelium-dependent vasodilation, and also in the formation of peroxynitrite (ONOO-), a potent and long lasting oxidant. These processes are associated with the genesis and progression of atherosclerotic lesions [71].

In the human body, there are lines of defense against the atherosclerotic process, among them the antioxidant enzymes nitric oxide (NO) and endothelial nitric oxide synthetase (eNOS); superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX). NO is an important factor responsible for the relaxation of arterial vessels: depending on the medium in which this may function as an oxidant or reducer, its oxidation produces nitrites and nitrates. Its anti-atherosclerotic functions includes: inhibition of adhesion and migration of leukocytes, impeding platelet aggregation; reduction in endothelial permeability to lipoprotein macromolecules; impeding the sub-endothelial accumulation of LDLc and its oxidation, among others. These factors, among others, are related to modulation of the inflammatory response [72].

According to the data from the study of Tyldum [65] the effects of a diet rich in fats on reducing the antioxidant capacity appear, on an average, 30 minutes after ingestion.

Exercise and oxidative stress

Light to moderate physical exercise performed regularly is recommended for the maintenance of health and prevention of innumerable diseases It also reduces the production of oxidants and occurrence of oxidative damage; improves the antioxidant defense system; increases the resistance of organs and tissues against the harmful action of the ROS, and diminishes systemic inflammation [69]. However, there is a body of evidence suggesting that physical exercise, particularly the more intense types, are associated with both muscular damage and elevated ROS production [68].

In the study of Jong-Shyan *et al.* [73], when they tested different intensities of physical exercise in sedentary individuals with 40% VO2max, with 60% VO2max and with 80% VO2max for 40 min, they verified that in the acute form, the highest intensity resulted in higher production of oxidized LDL. This caused an increase in the reactive oxygen species in the monocytes, when compared with the light and moderate intensities. They concluded that in their study, acute, high intensity physical exercise caused greater oxidative stress in sedentary individuals.

The study of Tyldum *et al.* [65] about the effect of acute exercise of different intensities on the antioxidant capacity, showed that both moderate and high intensity exercises interfered positively in the reduction of antioxidant capacity influenced by diet, however, the results were more expressive for the high intensity exercises.

According to Tyldum *et al.* [65] exercise and antioxidant function revealed an interesting paradox; in the acute form, an increase occurs in the levels of free radicals in the blood and muscle, which may be responsible for the inactivity of large quantities of nitric oxide and negatively change the endothelial impact mediated by vasodilation. However, the results of the study revealed an increase in the antioxidant capacity in the acute stage of exercise. The authors suggested that during the acute stage of the exercise, a transfer of antioxidants occurs between the muscle and vasculature, favoring the balance towards an inclination to favor the antioxidant effect, providing a similar effect to that offered by a diet containing antioxidants.

Sureda *et al.* [72] showed evidence that acute physical exercise performed at high intensities, induced oxidative damage in the blood cells such as erythrocytes and lymphocytes, but not in the neutrophils.

Habitual low to moderate intensity exercise is responsible for an increased cellular antioxidant defense system; reduction in lipid peroxidation, and protective effect against diseases associated with chronic inflammation [69].

Some studies have pointed out that intense exercises are associated with an increase in free radical formation. In other studies, acute and intense exercises presented significant and rapid responses in endothelial function. However, the intensity of exercise necessary to cause antioxidant responses is still controversial in the literature.

Below, please find four summaries showing the articles presented in this section, with reference to the effect of physical exercise on the inflammatory response, endothelial dysfunction and oxidative stress.

Frame 3 - Effect of physical exercise on inflammatory response, endothelial dysfunction and oxidative stress.

Authors	Year	Type of study	Population	Results
Paton CM *et al.* [62]	2006	Prospective study	Healthy participants	Improved inflammatory response, coagulation and fibrinolytic potentials, reduced risk of cardiovascular disease
MacEaneaney JO *et al.* [63]	2009	Comparative study	18 adolescents divided into: 10 normal weight and 8 obese subjects	Moderate exercise before a meal with high fat content effectively reduced the post-prandial TG concentrations in adolescents with normal weight and changed weight, but did not reduce the concomitant post-prandial increase in white globules or IL-6
Dekker MJ *et al.* [64]	2010	Self-controlled study	9 obese men	Physical exercise did the significantly change the IL-6 values

Frame 3. Continuation...

Authors	Year	Type of study	Population	Results
Tyldum GA *et al.* [65]	2006	Self-controlled study	8 healthy men	Acute exercise promoted a clinically protective effect on the vasculature that is dependent on the intensity of the exercise and strongly related to the antioxidant capacity induced by the exercise
Vuorimaa, Ahotupa M, Irjala K, Vasankari T [61]	2005	Self-controlled study	10 healthy, trained men	Light intensity and long duration physical exercise acutely suppressed the oxidative stress loads, and was inversely related to the atherogenic process
Garcia JJ, Bote E, Hinchado MD, Ortega E [68]	2011	Systematic review	10 articles	Although the responses to CRP were inconsistent, a single attack of exercise could increase both the activity and count of circulating IL-6, and the neutrophil count in non-trained adults
Capó X *et al.* [69]	2016	Comparative study	5 young adult athletes and 5 elderly athletes	Exercise increased the activated levels of the anti-inflammatory response, increasing anti-inflammatory gene expression after the exercise, particularly in the group of young individuals.
Rocha-Rodrigues S *et al.* [70]	2017	Controlled experimental study	Rats divided into control, free physical activity and resistance exercise groups	Exercise induced specific changes in fatty acids, irrespective of the composition of these in the diet, but only resistance exercise attenuated the inflammatory response
Sureda A *et al.* [72]	2005	Self-controlled Study	9 athletes	Exercise induced oxidative damage in the blood cells, such as erythrocytes and lymphocytes, but no in the neutrophils
Jong-Shyan W, Lee T, Chow S [73]	2006	Self-controlled study	25 healthy, sedentary men	High intensity exercise increased the ROS production of monocytes induced by LD, however, light and moderate exercise protected the individuals against the suppression of anti-oxidative capacity of the monocyte by LDL

Conclusion

Fatty acids, depending on their biochemical characteristics and spatial configuration, have a different effect on cardiovascular health, however, studies still show contradictory results on the therapeutic use of certain fatty acids. Physical exercise seems to benefit the metabolism of fatty acids and mitigate complications secondary to the consumption of certain fatty acids, in addition to enhancing the positive effects of different fatty acids. However, variants of physical exercise, such as intensity, duration, time of observation of the effects of the results, limit the authors to conclude, with a certain degree of certainty, the effect of physical exercise on fatty acids and secondary complications, since studies in the literature remain contradictory.

Authoral contribution
Conception and research design: Wagmacker DS, Ladeia AMT. Data collection: Wagmacker DS, Oliveira AM, Oliveira EC, Santos ACN. Data analysis and interpretation: Wagmacker DS, Oliveira AM, Santos ACN, Rodrigues LEA. Writing of the manuscript: Wagmacker DS, Oliveira AM, Oliveira EC, Rodrigues LEA. Critical revision of the manuscript for important intellectual content: Ladeia AMT.

Academic link
This article represents honest work and the validity of its results can be certified. Furthermore, this article is part of Djeyne Silveira Wagmacker M.Sc Thesis for the Bahian School of Medicine and Public Health Post Graduate Course. And all authors declare no competing interest. This work was supported by National Council for Scientific and Technological Development (CNPQ).

Potential conflict of interest
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