



## **Physical Exercise as a Modulator of Oxidative Stress and Inflammation in Atherosclerotic Plaque**

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### **Authors' contributions**

*"This work was carried out in collaboration among all authors. Authors MRB and DTRS prepared the study design, in the literature review and participated in the writing of the manuscript. Authors DM, ECS and LNJ contributed to the literature review and the writing of the manuscript. All authors read and approved the final manuscript.*

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### **ABSTRACT**

Cardiovascular diseases are the leading cause of death and reduced quality of life worldwide. One of the main risks to the development of cardiovascular diseases is inflammatory diseases, which are related to oxidative stress, among them, atherosclerosis. Atherosclerosis consists of a process of chronic inflammation, in which the accumulation of lipids occurs in the subendothelial space of the tunica intima of large caliber vessels. This is due to the accumulation of fibrous elements and inflammatory cells. Thus, regular physical exercise contributes to improving the body's immune defenses, while modulating inflammatory processes. In addition, physical activity is responsible for increasing the production of antioxidant enzymes, increasing the synthesis of nitric oxide, decreasing oxidative stress and decreasing systemic inflammation. Thus, physical exercise directly changes the genesis of atherosclerosis.

**Keywords:** *Plaque atherosclerotic; exercise therapy; oxidative stress; inflammation.*

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## 1. INTRODUCTION

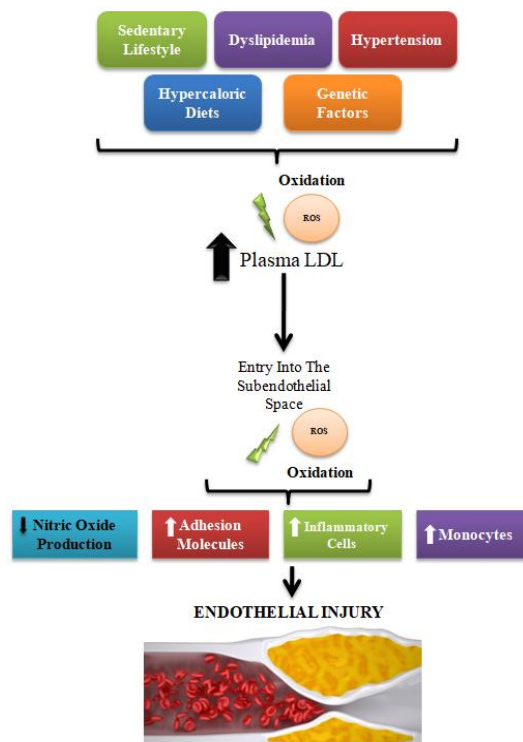
Cardiovascular diseases (CVD) represent the main causes of mortality worldwide. The atherosclerotic process is responsible for conditions such as acute myocardial infarction, unstable angina and stroke. As a result of the technological revolution experienced by modernity, the population has become less physically active, thus providing metabolic dysfunctions related to physical inactivity [1]. Thus, the regular practice of physical exercises contributes to reducing the incidence of cardiovascular events related to sedentary lifestyle, given that physical activity promotes cardiac changes beneficial to individuals. Atherosclerosis is responsible for 50% of deaths worldwide. This disease is determined by the circulation of low density lipoprotein (LDL) in the plasma, which passes into the subendothelial space of the blood vessel. Over time, the accumulation of LDL narrows the arterial lumen and decreases the blood supply to organs and tissues. It is known that the formation of atheromatous plaque is due, among other factors, to increased inflammation, increased endothelial lesions, increased production of reactive oxygen species and genetic predisposition (Fig. 1) [2]. Thus, physical exercise is responsible for reversing the visceral fat accumulation, reducing inflammation and promoting metabolic balance, in order to contribute to the reduction of cardiovascular complications [3].

Therefore, this article aims to conduct an integrative literature review relating the role of physical exercise on the immune system in the fight against atherosclerosis. For this, the bibliographic study included knowledge about cardiovascular diseases, oxidative stress, influences of physical exercise on the immune system and formation of atheroma plaque and, thus, proposed the understanding of the most recent information on the immunopathogenesis of atherosclerosis, also understanding its relationship with the physical conditions of individuals.

## 2. VASCULAR DISEASES

Chronic non-communicable diseases (CNCDs), mainly cardiovascular diseases, cancers, chronic respiratory diseases and diabetes, are responsible for 73.4% of deaths in the world, characterizing the largest cause of global death [4]. Of these deaths, 31% are due to

cardiovascular diseases, and 90% are considered premature deaths, that is, they occurred in people under the age of 70 years. Premature deaths are potentially preventable and generally associated with modifiable risk factors such as smoking, sedentary lifestyle, unhealthy eating and dyslipidemia [5].



**Fig. 1. Formation of atheromatous plaque**  
Source: The authors, 2020

Based on this epidemiological profile, the World Health Organization (WHO) established as one of the 9 voluntary global goals, the reduction of 25% of CNCDs by the year 2025. In addition, WHO believes that 75% of the mortality related to the system cardiovascular disease can be reduced from lifestyle changes [5].

Cardiovascular complications, mainly myocardial infarction, coronary artery disease and stroke, are generally related to the presence of atherosclerotic plaques. The genesis of atherosclerosis is considered multifactorial, being associated with the processes of dyslipidemia, hypercoagulability, oxidative stress, endothelial dysfunction and inflammation [6]. Atherosclerosis mainly affects the intima of the medium and large caliber arteries, through the accumulation of lipids, inflammatory response, cell death and

fibrosis in the arterial wall [7]. Lifestyles that involve smoking, obesity and physical inactivity can be aggravating factors in the development of atheroma plaques [8].

Atherosclerosis is directly linked to high plasma levels of LDL cholesterol and low plasma concentrations of high density lipoprotein (HDL) cholesterol. Thus, it is understood that HDL cholesterol is inversely associated with the risk of atherogenesis and, consequently, with the development of coronary disease and other cardiovascular diseases. The potential increase in HDL cholesterol levels in plasma may further reduce the risk of CVD, since HDL has a cardioprotective function in the theory of reverse cholesterol transport, where excess cholesterol accumulated in peripheral tissues is removed by HDL and taken to the liver for excretion in faeces, through bile [7].

In addition, the chronic inflammation caused by atherosclerosis is the result of an endothelial aggression that allows plasma lipoproteins to increase the permeability of the intima, which allows their retention in the subendothelium [8]. The oxidation of LDL fragments is favored by this retention, making them immunogenic. This accumulation of LDL and the proliferation of cells to the lumen of the arterial vessel are related to atherogenesis, due to an exacerbated local inflammatory reaction [9]. The inflammatory lesion causes platelet adhesion and promotes the release of mediators by platelets, macrophages and vascular wall cells that, when activated, induce the recruitment of smooth muscle cells to the intima, where they synthesize extracellular matrix, mainly collagen [10]. The atheromatous plaque is covered by an endothelial membrane and a fragile fibrous tissue, which makes the atherosclerotic plaque prone to rupture, which can cause the artery to block due to the released materia [11].

Therefore, it is understood that atherogenesis and the main processes of the development of cardiovascular diseases are related to the lifestyle adopted by each individual. Modifiable risk factors can be controlled, such as physical exercise on sedentary lifestyle and other aggravating factors.

### 3. PHYSICAL EXERCISE

It is a consensus that physical exercise is important for health and for the prevention of diseases, such as hypertension, type 2 diabetes

mellitus and obesity. However, a sedentary lifestyle is present in 30% of the world population, which can lead to immune and metabolic disorders [12].

During physical exercises, there is contraction of the skeletal muscles, which causes the release of free radicals, due to aerobic cellular respiration [13]. These can be harmful to cells, causing tissue damage when they are at exacerbated levels. Therefore, excessive physical exercise is harmful, as it increases pro-inflammatory markers, causing sleep disturbances and worsening performance [14].

On the other hand, low and moderate levels of free radicals assist in the regulation of cellular functions, such as gene expression and cell signaling [13]. The impact of aerobic exercises in this respect is significant, as it increases the levels of antioxidant factors, as well as enzymes [14]. Among these, catalase is mentioned. superoxide dismutase and glutathione peroxidase [13]. Resistance training, on the other hand, causes minor tissue damage, which must be recovered and, after this period, there is also a decrease in oxidizing factors [14].

Thus, in the long run, physical exercises decrease oxidative stress, regardless of type, volume and intensity. However, if the individual is sedentary, there may be a deregulation of free radicals, which influences cardiovascular pathologies [15].

### 4. OXIDATIVE STRESS, INFLAMMATION AND ATHEROSCLEROSIS

Reactive Oxygen Species (ROS) comprise cell metabolism and act on biogenesis, microbicidal activities, signaling, adhesion, differentiation, healing and cell repair. In addition, apoptosis can be induced due to changes in DNA by the action of ROS. Thus, appropriate concentrations of ROS are beneficial for maintaining normal cell states [16]. In situations of inflammation, for example, there is an increase in the production of ROS by leukocytes, whose objective is to increase the body's defense against pathogens. Because they are electronically unstable, ROS induces a chain activation process called lipid peroxidation (PL). PL is responsible for causing damage to cell membrane phospholipids, enzymatic cofactors, DNA nucleotides and proteins, in order to promote changes in cellular water balance, apoptosis and breaks in calcium homeostasis ( $Ca^{2+}$ ). The frequent practice of

physical exercise in a prolonged and strenuous way, is responsible for promoting PL. This is because, high intensity exercises induce oxidative stress, which is characterized by promoting an imbalance between the synthesis of ROS and the antioxidant activity of the human organism, given that these exercises are characterized by increasing the oxygen consumption of the organism and muscle fiber in isolation [17].

During physical activity, there is a process called ischemia and reperfusion, in which blood flow increases in active muscle tissue and, consequently, decreases in other cells and tissues. Thus, a situation of hypoxia or tissue ischemia is created. After the hypoxia period, the tissues that had a low oxygen supply start to receive it in large quantities, a process that is called tissue oxygen reperfusion. Due to the process of ischemia and reperfusion, the oxidative stress mechanism, triggered by the enzyme xanthine oxidase, is triggered, thus occurring the synthesis of ROS. In addition, physical activity promotes microlesions in muscle fibers and connective tissues, either through the impact of body extremities with the surface, or through the mechanism of muscle contraction and relaxation. Thus, the activation of cells of the immune system occurs, thus promoting an inflammatory condition. Muscle damage is responsible for the synthesis of chemotactic factors, including: prostaglandins, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  and interleukin-6 (IL-6), which act on the activation of inflammatory cells. Thus, events such as neutrophilia and leukocytosis are observed. First, neutrophils migrate to the injury site, then lymphocytes and monocytes are recruited, which are responsible for producing proteolytic enzymes in order to repair damaged tissue. It is worth mentioning that a picture of worsening of the injury and impaired muscle physiological functions can be identified for 24-72 hours after physical activity [17].

Oxidative stress (OE) is understood as the excessive, decompartmentalized and non-compensated production of ROS. Thus, the intense production of ROS is responsible for triggering inflammatory responses present in atherosclerosis, in all its phases. In addition, oxygen free radicals, oxygen ions and peroxides, have high reactivity, in order to participate in redox reactions, which are responsible for causing damage to the endothelium, favoring the progression of atherosclerosis. In the process of atherosclerosis, cell dysfunction and infiltration

that occurs in the subendothelial space is responsible for providing events such as OE and inflammation. Thus, LDL particles undergo oxidation in the subendothelial space due to the action of oxidizing agents present in the cells that make up the environment. Thus, LDLs that remain in the subendothelial space are precursors to atherosclerosis, so that these particles gradually acquire pro-atherogenic and pro-inflammatory properties [18].

At the baseline level, ROS act in the regulation of vascular tone, cell proliferation and growth, inflammatory response and apoptosis. However, in adverse conditions, they establish OE, through enzymatic and non-enzymatic systems, both of cellular and extracellular origin, thus causing changes in lipoproteins. Alterations in the LDL molecule are: lipolysis, oxidation and proteolysis, so that lipid oxidation is responsible for initiating subendothelial lesions. The accumulation of LDL in the arterial intima is responsible for activating smooth muscle cells, endothelial cells, macrophages and lymphocytes, thus triggering the formation of pro-inflammatory mediators. Furthermore, the activation of endothelial cells stimulates the production of superoxide, responsible for reducing circulating nitric oxide levels and, consequently, altering the vasodilation process [18].

In the pro-inflammatory condition, there is an increase in the expression of vascular adhesion molecules, namely: intracellular adhesion molecules (ICAM-1), E-selectin, P-selectin, vascular cell adhesion molecule (VCAM-1) and platelet adhesion-activating molecules and endothelial cells (PECAM-1), which stimulate the recruitment, binding and infiltration of monocytes into the blood vessels. In addition, adhesion molecules are also expressed in monocytes, in order to contribute to the progression of atherosclerotic lesions, among these molecules,  $\beta$ 2 integrin can be highlighted. In atherosclerotic events, the presence of the LDL molecule induces an inflammatory response and, therefore, establishes the endothelial lesion [18].

Both the acute and the chronic form of physical activity alter the immune system. Thus, the modulation of the immune response is related to factors such as intensity, regularity, type of effort and duration. Moderate exercise stimulates cellular immunity, since high intensity exercise, that is, after 90 minutes of strenuous physical activity, predisposes the body to diseases, since it causes deleterious changes to the immune

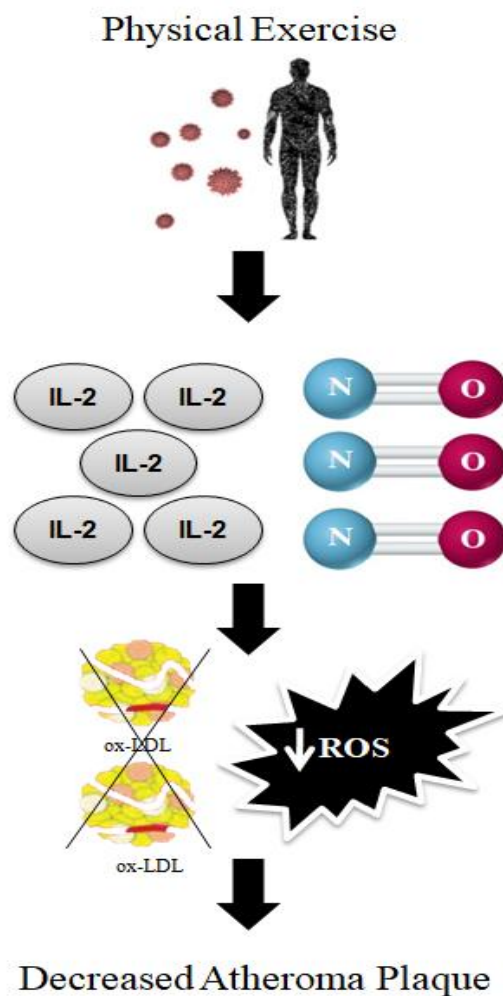
system. Thus, moderate physical activity provides a framework for immunological surveillance, where there is an increase in the antipathogenic activity of macrophages, as well as an increase in the circulation of immune cells, anti-inflammatory cytokines and immunoglobulins. Thus, there is a reduction in the systemic inflammatory process, as well as an improvement in immunity [19].

Physical activity helps to improve the systemic inflammation process and oxidative load, since it acts through the action of nitric oxide (NO). NO is related to the oxidation process of LDL cholesterol. As a result of the inflammatory process and the formation of atheromatous plaque, the expression of endothelial NO is reduced, since the ROS contribute to the suppression of NO activity. Thus, physical exercise contributes to the maintenance of a balance between NO production and inactivation. Thus, physical activity increases the expression of nitric oxide endothelial synthase, increases the antioxidant expression, decreases the activity of NADPH, responsible for the production of ROS and, therefore, promotes the reduction of ROS [3].

Therefore, physical exercise is essential in maintaining vascular homeostasis, since it acts in maintaining vascular tone, regulating the recruitment of leukocytes and maintaining blood flow. Furthermore, exercise provides an increase in the concentration of skeletal muscle endothelial NO (Fig. 2) [3].

## 5. INFLUENCE OF PHYSICAL EXERCISE ON VASCULAR CONDITIONS

Atherosclerosis is a chronic pathological process, which involves factors such as oxidative reaction, macrophage activity, endothelial injury and inflammatory components in its appearance, growth and maintenance [3]. The general benefits of physical exercise for the organism have long been known, and one field of interest is precisely its effects on atherosclerotic pathophysiology. In this regard, studies have shown that physical exercises are beneficial in the treatment of atherosclerosis and other cardiovascular diseases [20]. Regarding the profile of the exercise that benefits most, the studies are still controversial; however, improvements in risk factors are seen through several different exercise modalities [3].



**Fig. 2. Effect of exercise on oxidative stress and atherosclerosis**

Source: The authors, 2020

Among the risk factors for atherosclerosis, the involvement of factors of high prevalence in the population, such as diabetes, hypertension, hyperlipidemia, has long been noted [21]. Since the 1950s, results have been obtained on the relationship between physical activity and the reduction of coronary artery diseases, which has atherosclerosis as the main pathology involved. The association is of such relevance that since 1992 the American Heart Association started to consider physical inactivity as an independent risk factor for cardiovascular diseases [22].

Endothelial injury is one of the initial steps in the process of forming atherosclerotic plaque. One of the potential factors for endothelial damage is high blood pressure. In addition to hypertension,

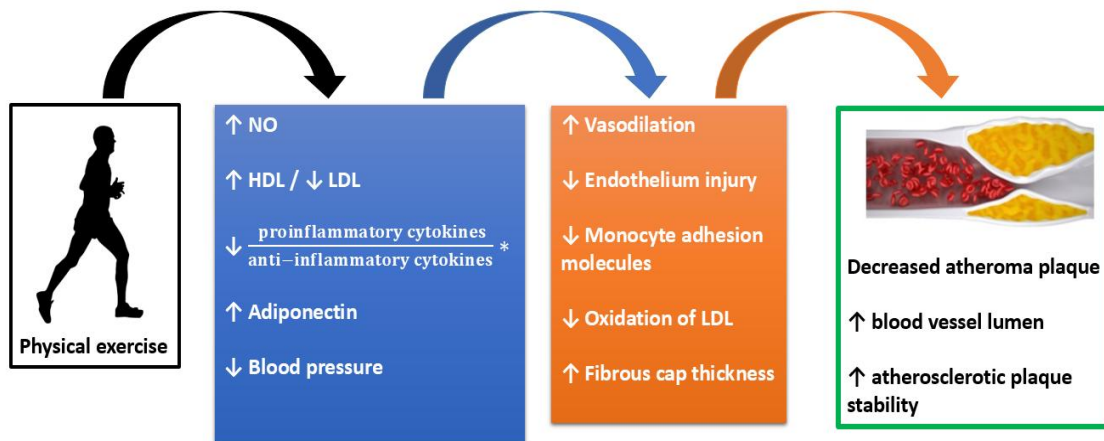
the difficulty in vasodilation is a concomitant factor of injury involved in the hypertensive process. Physical exercise reduces blood pressure at rest and is widely recommended by guidelines for hypertension, such as American and European guidelines [23]. One of the factors involved in this process is the production of endothelial NO which, as a vasodilator, acts in the regulation of blood pressure (BP) after exercise, reducing the likelihood of endothelial injury. Another protective factor of NO for atherosclerosis is its inhibitory effect on LDL oxidation [24]. Several studies prove the increase in the basal NO synthesis in physical exercise practitioners. From prevention to pre-diagnosed hypertension, several audiences benefit in this regard, having relevant findings proven, for example, in stage 1 hypertensive individuals who perform moderate intensity aerobic exercise [25]. Thus, even though during physical exercise there is a transient increase in BP, the increase in NO causes a greater period of reduced BP during rest, minimizing the chances of endothelial injury derived from BP [23,26].

Regarding inflammatory markers, there was always discussion about the increase in levels in the acute phase of exercise and its impacts. More recent studies attribute the role of skeletal muscle as an endocrine organ of the organism, and in this role they highlight the important production of interleukins 6 (IL-6) in muscle contraction. Considered a pro-inflammatory factor, IL-6 can have its baseline levels reduced during the rest period between physical exercise sessions, reducing several potential IL-6 stimuli [27]. However, unlike the IL-6 producing mechanism in adipose tissue, which triggers a cascade of predominantly inflammatory factors, such as TNF- $\alpha$  and interleukin-1 (IL-1 $\alpha$  and IL-1 $\beta$ ), the release of IL-6 from skeletal muscle in physical exercise it does not stimulate an increase in pro-inflammatory factors in the same proportion (TNF- $\alpha$ , IL-1  $\alpha$  and IL-1 $\beta$ ), on the other hand, there was a concomitant increase in the levels of anti-inflammatory factors, such as interleukin-10 (IL-10) [28]. Even when there was no increase in IL-10, there was still a reduction in the TNF- $\alpha$  / IL-10 ratio [29]. IL-6 also proves to be a key regulator between exercise and fat metabolism, since the induced blockage of IL-6 signaling reduces the effects of exercise on body fat mass [30]. Thus, recent studies seek to better elucidate the role of IL-6 promoted during physical exercise.

The lipid factors widely studied in the pathophysiology of atherosclerosis are, in particular, high-density lipoproteins (HDL) and LDL. Both the reduction in plasma HDL and the increase in LDL are considered risk factors for atherosclerosis, because while HDL removes lipids from the periphery to be metabolized in the liver, LDL binds to endothelial cells and oxidizes in the subendothelial space, being this LDL phagocytosis by monocytes, transforming them into foam cells [31,32]. Physical exercises of different modalities, with emphasis on aerobics, analyzed for a short or long time, tend to increase the plasma HDL concentration [33]. It is also visible the reduction in LDL levels under physical exercise programs performed at varying intensity rates, with a greater reduction in moderate intensity exercise [34].

Since the adipose tissue came to be seen as an endocrine organ and not just as a tissue that stores energy, the eyes for the signaling molecules secreted have intensified. Among these molecules, adiponectin, a hormone with anti-inflammatory and cardioprotective functions, has been highlighted [35]. These properties are mainly due to the inhibition of the expression of adhesion molecules, thus reducing the adhesion of monocytes to endothelial cells. In addition, adiponectin reduces the formation of atheromatous plaque and increases the stability of the plaque and the production of the NO vasodilator [36]. There was an increase in adiponectin levels in individuals who exercise, with a more significant increase for aerobic exercise [35].

In addition to the benefits of physical exercise in reducing risk factors for the development of atherosclerosis, physical exercise also demonstrates beneficial effects on already established atheroma plaques (Fig. 3). In studies involving animals, there was an increase in morphological characteristics that make the plaques more stable, such as the thickness of the fibrous cap, the content of elastin and collagen, as well as a reduction in macrophages and ruptures in the plaque structure [37]. In humans, the increase in the proportion of morphologically stable plaques in individuals practicing physical exercises was confirmed, as well as the regression of these plaques, allowing a better perfusion of the target tissues, which is also due to the greater vasodilator capacity mediated by NO [38,39].



**Fig. 3. Effects of physical exercise on the atherosclerotic process**

Source: The authors, 2020

Physical exercise promotes changes in factors directly involved in the genesis and maintenance of atherosclerotic plaque. The end result is that physical exercise tends to reduce the appearance of atheromas, as well as to modify existing plaques for a more benign morphological characteristic.

\*It represents both the reduction of pro-inflammatory factors associated with the maintenance of anti-inflammatory factors, as well as the maintenance of pro-inflammatory factors associated with the increase of anti-inflammatory factors.

## 6. FINAL CONSIDERATIONS

Thus, the regular practice of moderate intensity physical exercise is highly favorable in terms of the reduction of risk factors related to the development of atheromatous plaque, since it acts to decrease pro-inflammatory cytokines, improves endothelial function, decreases production of ROS, regulates the activity of macrophages, decreases LDL levels, as well as triglycerides and, thus, keeps the atherosclerotic condition stable. In addition, physical activity is beneficial in terms of regression of already established plaques, as it allows greater tissue perfusion and greater vasodilator effect. Therefore, exercise should be practiced for a long time, since a single session is unable to promote any long-term adaptations. It is important to note that strenuous exercise leads to an increase in primary coronary risk, as well as increases inflammation and oxidative stress. It is suggested that more research be carried out

involving this theme, given that few studies correlate the regular practice of physical activity as a non-pharmacological measure to maintain the inflammatory/anti-inflammatory balance and, consequently, stabilize and/or reduce the atherosclerotic process, thus providing a better quality of life for this population.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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