The forgotten face of regular physical exercise: a ‘natural’ anti-atherogenic activity

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ABSTRACT

Humans are not programmed to be inactive. The combination of both accelerated sedentary lifestyle and constant food availability disturbs ancient metabolic processes leading to excessive storage of energy in tissue, dyslipidaemia and insulin resistance. As a consequence, the prevalence of Type 2 diabetes, obesity and the metabolic syndrome has increased significantly over the last 30 years. A low level of physical activity and decreased daily energy expenditure contribute to the increased risk of cardiovascular morbidity and mortality following atherosclerotic vascular damage. Physical inactivity leads to the accumulation of visceral fat and consequently the activation of the oxidative stress/inflammation cascade, which promotes the development of atherosclerosis. Considering physical activity as a ‘natural’ programmed state, it is assumed that it possesses atheroprotective properties. Exercise prevents plaque development and induces the regression of coronary stenosis. Furthermore, experimental studies have revealed that exercise prevents the conversion of plaques into a vulnerable phenotype, thus preventing the appearance of fatal lesions. Exercise promotes atheroprotection possibly by reducing or preventing oxidative stress and inflammation through at least two distinct pathways. Exercise, through laminar shear stress activation, down-regulates endothelial AT1R (angiotensin II type 1 receptor) expression, leading to decreases in NADPH oxidase activity and superoxide anion production, which in turn decreases ROS (reactive oxygen species) generation, and preserves endothelial NO bioavailability and its protective anti-atherogenic effects. Contracting skeletal muscle now emerges as a new organ that releases anti-inflammatory cytokines, such as IL-6 (interleukin-6). IL-6 inhibits TNF-α (tumour necrosis factor-α) production in adipose tissue and macrophages. The down-regulation of TNF-α induced by skeletal-muscle-derived IL-6 may also participate in mediating the atheroprotective effect of physical activity.

INTRODUCTION

Cardiovascular diseases remain the leading cause of death in modern societies. The dramatic clinical events of cardiovascular diseases, such as unstable angina, myocardial infarction and stroke, are caused by an atherosclerotic process which generally starts to develop in childhood. Over the last 30 years, people in developed and developing countries have become more obese and less physically active. As a result, there is an emergence of diseases associated with metabolic and cardiovascular dysfunctions, such as obesity, Type 2 diabetes and the...
metabolic syndrome. Physical inactivity and sedentary lifestyle are believed to be independent risk factors for the occurrence of these metabolic disorders leading to atherosclerosis and cardiovascular complications [1]. In a recent paper, Pedersen [2] hypothesizes that physical inactivity leads to the accumulation of visceral fat and consequently the activation of a network of inflammatory pathways that promote the development of some pathological disorders, among them insulin resistance and atherosclerosis, and thereby the development of a cluster of diseases defined as the ‘diseasome of physical inactivity’. On the other hand, there is a body of clinical and experimental evidence showing that voluntary and imposed physical exercise prevents the progression of vascular diseases and reduces cardiovascular morbidity and mortality [3,4]. Therefore a physically active state is the appropriate and natural biological condition for humans and most animal species [5]. The purpose of the present review is to present regular exercise as a ‘natural’ anti-atherogenic activity which has been forgotten by modern societies and their new lifestyles. Biological mechanisms will be discussed to understand the atheroprotective effects of exercise.

**EXERCISE IS ‘NATURALLY’ ESSENTIAL FOR METABOLIC HEALTH**

**Humans are not programmed to be inactive**

During the late-Paleolithic era (50 000–10 000 BC), success of finding and procuring food was largely dependent on physical activity to guarantee the survival of our ancestors in hostile environments. Food supply was never consistent. It is contended that the ancient hunter-gatherers had cycles of feast and famine, punctuated with obligate periods of physical activity for food procurement [6]. In this context, it is proposed that the human genome was conceived and evolved in a cyclical manner (feast–famine) to ensure consequent metabolic adaptations with different pathways that oscillate to support and coincide with the cycles. Genes evolved in order to select adaptive thrifty mechanisms to ensure adequate storage of fuel during the feast period for the following period of famine and fast. Glycogen storage, triacylglycerol (triglyceride) synthesis and carbohydrate oxidation would predominate during the feast period, whereas glycogen conservation, gluconeogenesis and fatty acid oxidation would occur during the fast period. These metabolic adaptations, via efficient utilization of stored fuel, permitted our hunter-gatherer ancestors to continue intense physical activities to cover great distances and to hunt for food despite a prolonged fasted state [6].

The various revolutions (neolithic, industrial and telecommunication) which succeeded one another have contributed to an altered human environment and behaviour, leading to inactivity in many people. The neolithic revolution permitted our ancestors to domesticate animals and plants, and create primitive agriculture and industry. They definitively settled down in villages and cities, and created the beginning of a sedentary society. The industrial revolution (19th Century) led to sedentary humans with the invention of the combustion engine, cars, public transportation, industrialized agriculture, devices for food extraction, storage and transportation, etc. Since the latter half of the 20th Century, the last revolution has contributed to dramatically increase the sedentary lifestyle of people in modern societies. Watching television, playing video games and staying seated in front of computer screens are the main activities of young people and workers in the 21st century [7]. As a consequence, people in industrialized society move less and take fewer steps. Furthermore, food abundance and availability are constant today. These behavioural modifications (sedentary lifestyle and constant food) have arrived too fast for the genome to adapt. The human genetic constitution has probably remained relatively identical since the appearance of the ancestral Homo sapiens, approx. 40 000 years ago [8], suggesting that our genome is not selected for a sedentary existence. As it has been proposed by Chakravarthy and Booth [6], the combination of both a sedentary lifestyle and constant food availability eliminates the evolutionary metabolic processes emanating from the feast–famine cycle programmed during the Paleolithic era. Certain metabolic genes (which are evolutionarily programmed to expect a threshold of physical activity) are misrepresented, leading to a greater storage of fuel without enough stimuli for its utilization (Figure 1).

**Physical activity is crucial for metabolic balance**

The unhealthy consequences of mis-programmed fuel utilization are metabolic derangements, such as obesity, Type 2 diabetes and the metabolic syndrome, due to excessive storage of fuel in tissues. In accordance with previous authors [1], the reasons for the current epidemics of obesity and Type 2 diabetes are not solely due to eating an excess amount of energy-dense food with refined carbohydrates and high-saturated fats, but to a positive caloric balance. This is mainly attributed to an increase in sedentary lifestyles and an alarming decline in daily physical activity over the past 50 years. It is often admitted that a reduction in caloric intake may be sufficient to prevent and correct excess body weight and Type 2 diabetes. Scientific evidence, however, supports the necessity to perform adequate physical activity without necessarily modifying caloric intake to keep a metabolic balance. In other words, metabolism will be maintained in balance irrespective of caloric
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Figure 1 Schematic diagram demonstrating the possible links between human behavioural modifications induced by the three consecutive revolutions (neolithic, industrialized and telecommunication), which have contributed to genomic maladaptation, metabolic derangement and atherosclerotic cardiovascular disease development.

Consumption if the energy expenditure covers the caloric intake. For instance, a few days of bed-rest in healthy volunteers results in profound resistance to the action of insulin on whole-body glucose utilization, despite the maintenance of a normal diet [9–11]. It has been demonstrated previously that reducing the number of daily steps within a free-living environment for 2–3 weeks is associated with negative metabolic consequences (decreased insulin sensitivity and increased abdominal fat mass) [12]. Early studies have also shown that whole-body insulin sensitivity rapidly declines after cessation of aerobic training [13]. Therefore, physical activity appears to be one of the most ‘natural’ regulators to prevent the development of insulin resistance during metabolic derangement. Interestingly, there are several well-described clinical stress states, such as surgical trauma, infection and burns, where the development of insulin resistance constitutes a central feature [14].
fact, the main factors responsible for the loss of insulin sensitivity are starvation, hypocaloric nutrition and immobilization, which are often associated with surgical intervention. In healthy subjects, insulin resistance and marked alterations in substrate utilization induced by a few days of starvation or hypocaloric nutrition [15,16] are more pronounced with combined immobilization [17,18]. Such stress situations (starvation and hypocaloric nutrition) resemble those lived by our hunter-gatherer ancestors. During a famine state, regulatory biochemical processes, with insulin resistance, may develop in order to conserve and avoid a loss of skeletal muscle glycogen and fatty acid in starvation. On the other hand, these metabolic processes may be reversed by exercise in order to conserve muscle glycogen stores by oxidizing greater quantities of fatty acids. This ‘thrifty’ regulation allows skeletal muscle to consume enough energy and permitted our ancestors to continue intense physical activities to hunt for food, despite prolonged fasted states [5].

Wild animals do not suffer from metabolic diseases because their physically active state is maintained in the same appropriate biological condition. Caged experimental rodents will voluntarily run 3–4 h/day if they have free access to a running wheel, suggesting the existence of genetic programme which regulates spontaneous physical activity [19]. If rats have no access to voluntary running wheels for a few hours, epididymal and abdominal fat mass rapidly increases and is associated with a prolonged synthesis of triacylglycerols [20,21]. Cessation of voluntary wheel running also induces a rapid decrease in insulin sensitivity, insulin receptor activation and glucose transporter GLUT4 (glucose transporter 4) in skeletal muscle [22]. Landmark studies using rats that were artificially selected to be high- or low-capacity runners clearly demonstrate that intrinsic aerobic endurance capacity is markedly connected with metabolic derangement and risk factors for metabolic and cardiovascular diseases [23,24]. Bred rats selected as high-capacity runners have higher skeletal muscle lipid oxidation [25], higher serum NEFA (non-esterified ‘free’ fatty acid) concentrations, which may reflect enhanced lipolysis from adipose tissue, and an increased use of fatty acids for energy [24,26]. It has been shown, in a genome-wide microarray analysis, that 239 genes in skeletal muscle are differently expressed between high- and low-capacity runner rats, indicating phenotypic differences between low and high intrinsic aerobic endurance capacities [24]. Furthermore, mRNA expression of some co-regulated genes named centroids, including genes encoding for oxidative phosphorylation and fatty acid metabolism, is correlated with physical activity and disease risk phenotypes, such as body weight, insulin sensitivity and blood triacylglycerols [24]. These experimental findings are consistent with clinical data in patients with Type 2 diabetes, showing a positive correlation between total aerobic capacity and expression of skeletal muscle genes involved in oxidative phosphorylation [27]. These findings support the notion that low aerobic exercise capacity can elicit an abnormal phenotypic expression of genes, and act as a predictor of metabolic disorders and associated cardiovascular complications. In other words, a strong link exists between physical inactivity and the risk of metabolic diseases. Modern populations with sedentary lifestyle and escalating physical inactivity behaviour are thus exposed to the risk of developing hypertension, insulin resistance and elevated glucose, increased body fat and elevated triacylglycerols, which, in concert with tissue and systemic inflammation, constitute the metabolic syndrome, leading to atherosclerosis and complicated cardiovascular events.

Physical inactivity is linked to the progression of metabolic disorders, and cardiovascular morbidity and mortality

Physical inactivity is presented as a ‘silent epidemic’ of modern societies causing many chronic diseases [28]. Environmental and lifestyle changes during the past 50 years have modified the prevalence of overall and cardiovascular deaths. Low levels of physical activity and decreased daily energy expenditure are strongly associated with an increased risk of cardiovascular and all-cause mortality in apparently healthy individuals and in patients with documented cardiovascular and metabolic diseases [29–31]. According to Booth et al. [28], the number of deaths due to physical inactivity and inappropriate diet are underestimated. Sedentary lifestyles could be responsible for at least one-third of deaths due to coronary heart disease, colon cancer and Type 2 diabetes.

The occurrence of cardiovascular diseases increases in the presence of multiple risk factors established for proatherogenic chronic diseases, leading to atherosclerosis. Such chronic diseases possibly did not exist in young and old individuals from ancient and contemporary hunter-gatherer societies [28]. Type 2 diabetes, obesity and associated cardiovascular complications have appeared over the past century, and the prevalence of each has exploded over the last 30 years [32–34]. The environmental factors that have directly elicited the increase in the incidence of chronic diseases over the past century are unlikely to be identified [28]; however, they strongly coincide with decreased daily physical activity related to technological advances in engineered physical-labour-saving devices in industrialized societies since the 1980s, and then, with the appearance of sedentary behaviour related to technological advances in computing and broadcasting, leading to a modern society based on work whilst seated and on-screen entertainment. Growing evidence demonstrates direct relationships between physical inactivity and new sedentary behaviour, such as television viewing and computer screen watching,
and related metabolic and cardiovascular risk factors in both children and adults [35–37].

PHYSICAL ACTIVITY PREVENTS AND REDUCES ATHEROSCLEROTIC RISK FACTORS AND THE ATHEROSCLEROTIC PROCESS

Physical activity and atherosclerotic risk factors
It is well established that physical activity reduces all of the atherosclerotic risk factors that emerge with metabolic disorders. Physical activity corrects elevated blood pressure, insulin resistance and glucose intolerance, decreased HDL (high-density lipoprotein)-cholesterol concentrations, elevated LDL (low-density lipoprotein)-cholesterol and triacylglycerol concentrations, and obesity if combined with other lifestyle changes, such as dietary modification and weight loss [38]. Several studies, however, argue for a direct effect of physical activity. In the Amish community, which has maintained an 18th Century rural culture and physically active lifestyle, prevalence of Type 2 diabetes and obesity is lower than that of the modern population, despite a rich daily caloric intake [39–41]. In experimental studies, regular exercise corrected all of the cardiovascular and metabolic risk factors to baseline values in obese rats that were maintained on a high-fat diet [42]. In the same manner, it is generally believed that the effects of exercise on existing risk factors and cardiometabolic diseases are less than that achieved by pharmacological therapies. Several studies, however, demonstrate that lifestyle intervention (including physical activity) is more effective than insulin and metformin in preventing diabetes and risk markers [43,44]. Physical activity and exercise are thus recommended for the prevention and management of Type 2 diabetes, the metabolic syndrome and cardiovascular diseases [38,45,46]. Compelling evidence shows that physical activity and exercise are clearly effective in primary and secondary prevention of cardiometabolic and atherosclerotic cardiovascular diseases, and in attenuating the cardiovascular risk of morbidity and mortality among men and women [47,48]. Furthermore, a dose–response relationship appears to exist such that people who have the highest levels of physical activity (highest energy expenditure) are at lowest risk of premature death.

Physical activity and the atherosclerosis process
Physical activity reduces atherosclerotic plaque
Numerous clinical cross-sectional studies have focused on the progression of atherosclerosis to explain the protective effect of exercise training. Measurement of IMT (intima-media thickness) of the common carotid artery can be used to quantify cerebrovascular and generalized atherosclerosis, and is closely associated with an increased risk of ischaemic events, such as myocardial infarction and stroke [49]. Physical inactivity increases carotid IMT [50]. An inverse association exists between aerobic exercise capacity and the progression of carotid IMT, roughness and plaque height [51,52]. These findings support the notion that sedentary and physical inactivity contribute to the development of atherosclerosis and that physical activity is atheroprotective. In obese and Type 2 diabetic patients, exercise programmes, combined with other lifestyle changes (low-fat diet and lipid-lowering medication), stop the progression or induce the regression of carotid atherosclerosis [53,54]. In patients with coronary artery disease, exercise training conducted over 4–6 years regresses or stops the progression of coronary stenosis, quantified by angiography, and reduces cardiac events [55–59]. Hambrecht et al. [60] also report the necessity to expend at least 1500 kcal/week (1 kcal = 4.184 kJ) to stop the atherosclerotic process and 2200 kcal/week to induce stenosis regression.

Regression of coronary stenosis may have at least two beneficial effects for patients with coronary artery disease: (i) improvement in myocardial perfusion; and consequently (ii) a significant reduction in the incidence and severity of myocardial ischaemia [55,59]. Stenosis in the coronary artery reduces blood flow. Although exercise training can attenuate the progression of coronary atherosclerosis, it is argued that the decline in the internal diameter of the coronary artery is too small to explain the substantial increase in myocardial perfusion associated with regular exercise [61]. Several others effects may be associated such as improvement of coronary vasomotion. The endothelial function of patients with coronary artery disease is generally altered. This alteration consists of endothelial dysfunction and a paradoxical vasoconstriction of the atherosclerotic coronary artery in response to acetylcholine infusion, leading to a decrease coronary blood flow [62]. In patients with coronary artery disease, exercise training improves impaired endothelial function, attenuates the paradoxical acetylcholine-induced vasoconstriction, increases coronary blood flow and thus myocardial perfusion [62], leading to a reduced incidence of myocardial ischaemia.

Physical activity preserves atherosclerotic plaque stability
Atherosclerosis proceeds silently over time as long as lesions remain stable. However, conversion into a vulnerable phenotype renders plaques susceptible to rupture with well-known dramatic clinical events: unstable angina, acute myocardial infarction and stroke. On the basis of experimental data, it has been demonstrated that exercise slows the progression of atherosclerosis in a variety of hypercholesterolaemic animal
Atherosclerosis is a disease characterized by endothelial dysfunction, an increase in oxidant stress, an accumulation of lipids in the arterial wall, and chronic systemic and arterial wall inflammation.

Physical activity corrects and prevents endothelial dysfunction

Endothelial dysfunction is the term used to refer to an impairment of endothelium-dependent vasorelaxation caused by a loss of NO bioactivity in the vessel wall. Impaired endothelium-dependent vasodilatation, which appears as an early event in the pathogenesis of atherosclerosis, has profound prognostic implications for adverse cardiovascular events and clinical outcomes [82]. Patients with atherosclerotic risk factors have blunted endothelial function, characterized by impaired acetylcholine-induced local and regional vasodilatation, and decreased blood flow [83–85]. Clinical and experimental findings clearly demonstrate that exercise training corrects and prevents endothelial dysfunction. In humans with coronary artery disease, exercise training reversed endothelial dysfunction and improved blood flow of coronary artery [86, 87]. Interestingly, improvement in endothelial function is closely linked to the amount of energy expenditure [86]. In patients with Type 2 diabetes and obesity, similar observations are made, revealing a greater improvement with high-intensity training [88, 89] and without concomitant changes in traditional risk factors [90–94], suggesting that the beneficial effects of exercise may result from a direct effect of exercise on endothelial cells. The stimulating effect of exercise on endothelium-dependent vasodilation in healthy subjects and animals has been reviewed extensively [95–97]. Numerous experimental findings confirm that exercise may have a beneficial effect on the development of cardiovascular disease through preserving endothelial function [98–100]. Less is clear in experimental mice models of atherosclerosis (Ldlr<sup>−/−</sup> and ApoE<sup>−/−</sup>). Some studies reveal a protective and stimulating effect on NO-dependent vasorelaxation of isolated arteries by exercise [75]. Other studies have failed to find this benefit [74, 101], despite a reduction in plaque extension and preservation of plaque stability, suggesting that preservation of the endothelium- and NO-dependent vasodilatation is not a prerequisite for exercise-induced atheroprotection.

If sedentary and physical inactivity are considered as independent risk factors for atherosclerosis, there is little available evidence showing that they themselves induce endothelial dysfunction. Several cross-sectional studies have revealed an impaired endothelial function in sedentary healthy subjects in comparison with physically
active subjects [102,103]. If we consider that voluntary wheel running is a natural behaviour in rodents [28], physical inactivity in mice impairs acetylcholine- and endothelium-dependent vasorelaxation [72]. To test the impact of physical inactivity itself in humans, specific methods are needed, such as bed rest or dry immersion. In these conditions, endothelial function is reduced, even with short-term duration (5 days) [104–106]. Furthermore, physical inactivity increases circulating microparticles originating from injured endothelial cells, new cellular markers of endothelial dysfunction and atherosclerotic vascular diseases [106]. Interestingly, endothelial injury is accompanied by increased blood pressure, insulin resistance and dyslipidaemia, suggesting that the concurrent appearance of all of these risk factors induced by physical inactivity might share a common mechanism [105] and that physical inactivity itself is capable of creating a pathological environment convenient to the development of atherosclerosis.

**Physical activity exerts antioxidant effects**

Decreased endothelial NO bioavailability may be one of the earliest signs of atherosclerosis. NO is considered as having a pivotal role in cardiovascular health and its deficiency is involved in the oxidation of LDL-cholesterol, as well as the initiation, progression and associated complications of atherosclerosis [82]. Several factors may explain the loss of NO bioavailability: among them, decreased expression of eNOS (endothelial NO synthase) and loss of eNOS activity, and accelerated NO degradation by ROS (reactive oxygen species). Inactivation of NO by excessive ROS production has been reported in patients with cardiovascular risk factors (Type 2 diabetes and obesity) as well as in patients with atherosclerosis and coronary artery disease [107–110]. Among many enzymatic systems that are capable of producing ROS, NADPH oxidase appears to play an important pathological role. O$_2^-$ (superoxide anions), whose production by NADPH oxidase is increased in the coronary arteries of patients with coronary artery disease, are known to rapidly inactivate NO, thereby causing endothelial dysfunction [110].

The impact of exercise training on oxidative stress has been studied extensively in relation to cardiovascular risk and disease. Exercise training is frequently presented as an effective antioxidant and anti-atherogenic therapy [111–115]. Briefly, it is postulated that exercise training readjusts the balance between NO generation and NO inactivation [97]. Most clinical and experimental studies have reported beneficial effects of regular physical activity in increasing NO bioavailability and reducing oxidative stress: physical activity increases eNOS expression and/or eNOS Ser1177 phosphorylation [mediated by an increase in Akt (also known as protein kinase B) expression and/or phosphorylation], increases antioxidant SOD (superoxide dismutase) expression, and decreases in NADPH oxidase activity and expression of its subunits (gp91phox, p22phox and nox4), leading to reduced ROS generation [98,116,117]. In healthy conditions, although intensive aerobic exercise is known to increase oxidative stress, moderate exercise induces an up-regulation of SOD and, consequently, decreases oxidative stress [118,119].

In atherosclerosis and cardiometabolic diseases, one of the principal sources of ROS is NADPH oxidase [120,121]. Strong correlations exist among NADPH oxidase activity, atherosclerotic risk factors and endothelial dysfunction [122]. Inactivity in mice increases the activity of NADPH oxidase, expression of the subunits nox1, p47phox and p67phox, and enhances O$_2^-$ and ROS production. These effects are accompanied by endothelial dysfunction and atherosclerotic lesion formation [72]. The findings of that study are consistent with the hypothesis that physical inactivity directly exerts deleterious biological effects, via excessive ROS production and decreased NO availability, contributing to endothelial dysfunction and atherosclerosis development.

**Physical activity exerts anti-inflammatory effects**

Chronic inflammation is a pathogenic feature of atherosclerosis [123]. Initiation of inflammation is multifactorial. However, increased vascular production of ROS and decreased NO bioactivity appear to be implicated in the ROS-mediated occurrence and development of atherosclerosis. ROS modify lipoproteins to their oxidized form such as ox-LDL (oxidized LDL) particles, one of the principal risk factors for atherosclerosis. ROS and ox-LDL activate NF-$\kappa$B (nuclear factor $\kappa$B), a key transcription factor that is involved in the regulation of many of the pro-inflammatory genes linked to atherosclerosis, including TNF-$\alpha$ (tumour necrosis factor-$\alpha$), IL (interleukin)-6, MCP-1 (monocyte chemoattractant protein-1) and adhesion molecules [e.g. VCAM-1 (vascular cell adhesion molecular-1)] [124]. Furthermore, it is important to note that elevated levels of NEFAs associated with insulin resistance, obesity, Type 2 diabetes and the metabolic syndrome activate innate immune inflammatory pathways upstream of NF-$\kappa$B [124]. Chronic systemic inflammation is also believed to contribute to the development of atherosclerosis and endothelial dysfunction [125,126]. Decreased NO production and/or bioavailability, illustrated by the endothelial dysfunction observed in most cardiovascular and cardiometabolic diseases, is known to promote inflammation, stimulate platelet aggregation, increase the synthesis and release of pro-inflammatory cytokines, and the release of growth factors in the arterial wall. For example, decreased NO bioavailability plays an important role in the initiation and progression of atherosclerosis.
of atherosclerosis [82]. Therefore it is expected that inactivity is a pro-inflammatory risk factor and physical activity thus provides anti-inflammatory effects [127–131].

Control of the release and activity of at least two cytokines (TNF-α and IL-6) may contribute to the natural protective effect of physical activity. Plasma TNF-α levels are elevated in patients with atherosclerosis, and TNF-α is implicated in the occurrence of metabolic disorders. It is likely that adipose tissue is the main source of circulating TNF-α in chronic low-grade systemic inflammation [132]. TNF-α initiates and accelerates atherogenesis, thrombosis, vascular remodelling, vascular inflammation, endothelium apoptosis, oxidative stress and impaired NO bioavailability, which contribute to the reduction of vascular function [133]. In skeletal muscle cells, TNF-α impairs insulin signalling and induces insulin resistance [134]. In adipose tissue, TNF-α induces increased lipolysis with a concomitant increase in the release of NEFAs [135]. Furthermore, TNF-α contributes to the development of insulin resistance by increasing fatty acid incorporation into diacylglycerol in skeletal muscle [136]. Therefore these findings strongly support a direct role of TNF-α in the progression of metabolic diseases. Although several studies have indicated that plasma TNF-α levels may be reduced with weight-loss interventions, others have not always demonstrated a decrease in the levels following exercise training despite a reduction in body weight [137–141]. Interestingly, in conditions of low-grade inflammation after injection of bacterial endotoxin in healthy volunteers, exercise totally prevents the increase in circulating TNF-α [142]. Progression and development of atherosclerosis depend, in part, on monocyte-derived macrophages which accumulate in plaques and release cytokines. Overexpression of TNF-α derived from macrophages is implicated in inflammatory damage in the arterial wall and plaque instability [143]. One study in healthy subjects revealed that exercise training reduces TNF-α release by LPS (lipopolysaccharide)-stimulated monocytes in whole blood [144]. Thereby exercise appears to oppose the noxious effects of TNF-α by preventing TNF-α-mediated insulin resistance and metabolic disorders and TNF-α-mediated vascular damage and plaque instability.

IL-6 has received increasing attention as an explanation for the anti-inflammatory effect of regular exercise in patients with cardiovascular diseases and cardiometabolic disorders [131,145,146]. Contracting skeletal muscles ‘naturally’ increase the production and release of IL-6 in an exponential fashion during exercise [131]. IL-6 is proposed to play a fundamental anti-inflammatory role, despite its classification as a pro-inflammatory cytokine, for at least two reasons. First, IL-6 inhibits the endotoxin-induced increase in circulating levels of TNF-α in healthy humans [142], suggesting a regulatory role of IL-6 on TNF-α release. Secondly, the release of IL-6 during exercise induces an increased production and release of two other circulating cytokines with anti-inflammatory properties: IL-1Ra (IL-1 receptor antagonist) and IL-10 [147]. Furthermore, IL-6 induces several metabolic effects. IL-6 enhances lipolysis and fat oxidation in adipose tissue, increases glucose production in the liver during exercise, and increases insulin sensitivity as observed in patients with Type 2 diabetes [131,146].

It is possible that the effects observed in endothelial cells, skeletal muscle cells and adipocytes may also exist in other cells. For instance, new findings have linked the effects of physical inactivity and activity to the phenotype of circulating immunity cells, such as monocyte-derived macrophages, whose importance in atherosclerosis is widely recognized. Monocytes can be differentiated into various macrophage subtypes upon contact with specific stimuli, such as Th1 cytokines [IFN-γ (interferon-γ)] and IL-1β] or Th2 cytokines (IL-10 and IL-4). Th1 cytokines induce differentiation into an M1 macrophage phenotype. M1 macrophages produce pro-inflammatory cytokines such as TNF-α and IL-6. Th2 cytokines induce differentiation into an alternative anti-inflammatory M2 macrophage phenotype. M2 macrophages dampen the inflammatory and adaptive Th1 responses by producing anti-inflammatory mediators such as IL-10, IL-1Ra and TGF-β (transforming growth factor-β) [148]. Moreover, macrophages demonstrate functional plasticity because they have the ability to switch between the M1 and M2 states of activation [149]. Inflammatory diseases, such as atherosclerosis, may be caused not only by a sustained M1 pro-inflammatory reaction, but also by a failure of the M2 anti-inflammatory control mechanism. Recently, it was shown that low-intensity exercise, consisting of walking 10 000 steps three times/week, up-regulated markers of M2 macrophages and down-regulated M1 markers [150]. That study clearly supports the notion that exercise can modify the phenotype of subpopulations of macrophages by a biological mechanism which remains to be determined. In summary, it is postulated that the up-regulation of M1 macrophages and the release of their respective pro-inflammatory M1 cytokines participates in the pro-atherogenic effects of sedentary lifestyles. Macrophages may be considered as a new cell target for physical activity and inactivity. Physical activity positively influences the inflammatory system as well as the atherosclerotic process.

PROPOSED MOLECULAR AND CELLULAR MECHANISMS FOR A ‘NATURAL’ ATEROPROTECTION OF PHYSICAL ACTIVITY

Physical activity may exert its beneficial effect against atherosclerosis by at least two distinct mechanisms. First,
it is well recognized that exercise-induced increases in shear stress contribute to enhanced endothelial NO availability by increasing eNOS activity and decreasing ROS production [95]. Secondly, since the landmark work of Pedersen [2], a new molecular mechanism appears to be emerging, suggesting that the contracting skeletal muscle can be seen as a new endocrine organ, which releases hormones called ‘myokines’ with anti-inflammatory effects. Although the first mechanism only implies heart and arteries for increased shear-stress-induced NO bioavailability with exercise, the second implies at least two other organs: contracting skeletal muscle and visceral fat mass [2].

**The shear stress signal**

Strong evidence supports the importance of haemodynamic forces (shear stress), as the primary signal produced by exercise, to sustain a natural anti-atherogenic phenotype of endothelial cells and prevent atherosclerosis development. During exercise, increased cardiac output and blood movements produce a longitudinal stress on the endothelial cell surface along the arterial wall in order to induce endothelium-dependent vasodilation and increase blood flow to skeletal muscle. Shear-stress-induced vasodilation is mainly attributed to NO stimulation, via mechanoreceptor stimulation on the endothelial-cell membrane. Increased shear stress is known to augment the endothelial expression of eNOS, Akt and SOD, and to decrease the expression of NADPH oxidase, VCAM-1, ET-1 (endothelin-1) and AT₁Rs (AngII type 1 receptors) [151]. Therefore increased shear stress during exercise induces intracellular signals that contribute to the anti-atherogenic phenotype of endothelial cells. The eNOS/NO pathway plays a pivotal role in the anti-atherogenic effects of exercise-induced shear stress, contributing to sustain and preserve NO bioavailability (Figure 2).

The RAS (renin–angiotensin system) has vasoconstrictor properties, participating in arterial remodelling, and has pro-atherogenic effects via the direct inflammatory action of AngII on endothelial cells via AT₁Rs [152]. AT₁R signalling appears to play a key role in insulin-resistant states, the progression of atherosclerosis and the mediation of plaque vulnerability [79,153]. The main mechanism involved in the effect of AngII appears to be by the generation of ROS. Once the AT₁R is activated by AngII, it increases the generation of O₂⁻ in the vasculature, primarily through the activation of membrane-bound NADPH oxidase, and thus generates ROS after it reacts with bioavailable NO [154]. Recently, it has been shown that exercise down-regulates vascular AT₁Rs in atherosclerotic ApoE⁻/⁻ mice [74]. In addition, no change in the expression of eNOS/Akt occurred, despite prevention of plaque extension [74]. These findings propose the existence of a distinct signal derived from endothelial cells. Exercise, through laminar shear stress activation, down-regulates endothelial AT₁R expression [155], leading to a decrease in NADPH oxidase activity and O₂⁻ production, which in turn decreases ROS generation and preserves endothelial NO bioavailability with its protective anti-atherogenic effects.

**The contracting skeletal muscle signal**

Physical inactivity leads to an accumulation of visceral fat and consequently to macrophage infiltration via the activation of a network of inflammatory pathways, which promote the development of insulin resistance via the increased release of cytokines such as TNF-α. These findings support the notion that accumulation of visceral fat by inactivity precedes chronic systemic inflammation and that inflammation is responsible for insulin resistance [131]. It has been recently hypothesized that the contraction of skeletal muscle fibres induces the expression, production and release of myokines, which exert endocrine and paracrine effects, and thus explain the anti-inflammatory properties of exercise (Figure 3).

In fact, contracting skeletal muscles may be considered as a new endocrine organ that plays a central role in orchestrating glucose and lipid metabolism. A number of myokines have been listed [2]. Among them, IL-6 appears to play a central role. Once released, IL-6 exerts a specific endocrine effect on visceral fat, macrophages and other specific organs, such as liver, in order to oppose the deleterious effects of inflammation. IL-6 exerts beneficial metabolic effects such as fat oxidation and lipolysis in adipose tissue and contributes to ameliorate insulin sensitivity in skeletal muscle. IL-6 causes the anti-inflammatory environment by inducing the production and release of anti-inflammatory cytokines, including IL-10 and IL-1Ra, and by inhibiting TNF-α production in adipose tissue and infiltrated macrophages. The down-regulation of TNF-α participates in the amelioration of insulin sensitivity. The anti-inflammatory environment contributes to protect arteries against atherosclerosis and stenosis progression, and to preserve the stable phenotype of pre-existing plaques. If TNF-α derived from adipose tissue is considered as the ‘driver’ behind cardiometabolic disorders [131], strong evidence also supports the notion that the down-regulation of TNF-α by exercise-induced release of circulating IL-6 participates in mediating the atheroprotective effect of physical activity.

**CONCLUSIONS**

The scientific community is convinced that a sedentary lifestyle is a high-risk behaviour and participates in the development of atherosclerosis. However, numerous arguments claim physical activity acts as a ‘natural’ anti-atherogenic behaviour. The modern evolution of
Western societies seemingly steers populations towards a profound sedentary lifestyle and it is becoming difficult to reverse. Understanding of the mechanisms that explain the fatal effects of physical inactivity and the beneficial effects of physical activity remains largely unexplored. This understanding may contribute to an enhanced awareness of potential risks by sedentary populations and public authorities. Further research is needed to elucidate the effects of exercise on inflammatory pathways and the oxidative stress cascade. Finally, new emerging concepts reveal that exercise is a systemic activity, whose beneficial anti-atherogenic effects are not limited to one particular cell, such as the endothelial cell, but to a variety of cells and tissues involved in the pathogenesis of metabolic disorders and atherosclerosis, such as macrophages and adipose tissue.
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The contractile skeletal muscle signal

Metabolic derangements induced by inactivity and loss of energy expenditure lead to fat tissue accumulation with infiltrated macrophages producing TNF-α. Circulating TNF-α may induce several direct effects on the organism, such as insulin resistance, oxidative stress, endothelial dysfunction, vascular damage and plaque vulnerability. During exercise, contracting skeletal muscles release anti-inflammatory myokines (IL-6, IL-10 and IL-1Ra) with anti-atherogenic properties. Among them, several of these cytokines may increase insulin sensitivity and fat oxidation, and inhibit TNF-α production by fat tissue and macrophages.

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