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Exercise and Atherosclerotic Cardiovascular Disease

J Kelly Smith*

Departments of Academic Affairs & Biomedical Science, James H Quillen College of Medicine, East Tennessee State University, Johnson City, TN, USA

Abstract

Atherosclerotic cardiovascular disease (ACVD) is the leading cause of death in the United States and worldwide. The current pan epidemic of type 2 diabetes, a major risk factor for ACVD, suggests that the morbidity and mortality associated with ACVD will only worsen unless more effective life style modifications and therapies are developed. Encouragingly, moderate intensity physical exercise done on a regular basis has been shown to reduce all-cause mortality, particularly that due to ACVD. Physical conditioning can have a favorable impact on risk factors for ACVD, including hypertension, hyperlipidemia, obesity, diabetes, and the metabolic syndrome, and along with proper diet and drug therapy, diminish or reverse the cell-mediated inflammatory responses that are responsible for atherogenesis.

Keywords: Adipokines; Atherogenesis; Atherosclerosis; Cardiovascular disease; Cytokines; Endothelial cells; Exercise; Myokines

Introduction

According to the World Health Organization, ischemic heart disease and stroke are the top two causes of mortality worldwide, accounting for a total of 13.2 million deaths in 2011 [1]. In the United States, diseases of the heart remain the leading cause of death in both men and women, accounting for 596,339 deaths in 2011; cerebrovascular diseases rank fourth, accounting for an additional 128,931 deaths [2]. The disturbing worldwide increase in the prevalence of type 2 diabetes [3], whose co-morbidities include micro- and macro vascular disease does not bode well for future improvements in the incidence of deaths due to cardiovascular disease (CVD) unless lifestyle changes and therapeutic advances successfully address this issue [4].

A number of studies have shown that regular, moderate-intensity, physical exercise reduces mortality due to all causes, particularly deaths due to CVD [5-8]. Regular physical exercise has also been shown help prevent the onset of type 2 diabetes mellitus, and to favorably impact on the prevalence of other risk factors for CVD including hypertension, obesity, hyperlipidemia, insulin resistance, and the metabolic syndrome [9-16]. Persons with established CVD, including those with heart failure, ischemic heart disease, and peripheral vascular disease have also been shown to benefit by regular involvement in moderate-intensity exercise programs [17-19].

The evidence supporting the beneficial effects of physical exercise is sufficient to have prompted the National Institutes of Health to recommend that "children and adults alike should set a goal of accumulating at least 10 min of moderate-intensity physical activity on most, and preferably all, days of the week" [20]. A more recent policy statement issued by the American Heart Association on the value of primordial and primary prevention of CVD included physical exercise in their recommendation of lifestyle modifications [21].

This review will address what is currently understood about the impact of physical exercise on the physiological responses of muscles, endothelium, lymphocytes, monocytes, and adipose tissue as it relates to atherosclerosis. It will start with a brief review of what is currently known about atherogenesis.

Atherogenesis

The earliest manifestation of atherosclerosis is the development of subendothelial fatty streaks in large and medium sized arteries. The streaks consisting primarily of oxidized or glycated low density lipoprotein (LDL), monocytes, macrophages, and foam cells – macrophages bloated by their unrelentless ingestion of modified lipid. The deposits have been identified in young adults, and can fluctuate in extent depending on a number of variables, including plasma lipid levels. These early manifestations of atherosclerosis appear to represent an innate immune response in which monocytes respond to endothelial cell (EC) and vascular smooth muscle cell (VSMC) chemotactic signals, bind to EC adhesins, migrate into the intima, and, under the courtesy of a mixture of surface scavenger and toll-like receptors (TLR), ingest modified lipoproteins [22].

With time, fatty streaks evolve into atherosclerotic plaques consisting of a variety of immune cells, including Th1 and Th2 lymphocytes, T regulatory lymphocytes (Treg), dendritic cells, B cells, and mast cells. There is a mixture of atherogenic cytokines (TNF-α, IFN-γ, IL-1β, and IL-12) produced by Th1 cells and/or activated macrophages, as well as atheroprotective cytokines (IL-10, IL-4, and TGF-β), produced by Th2 and Treg lymphocytes. Antibodies, secreted under the direction of Th2 cells, and Type V collagen, produced by infiltrating mast cells, add to the mixture. Macrophages can evolve into dendritic-like cells with advanced capabilities of binding to and activating Th1 cells, thus enhancing the atherosclerotic process. Ultimately, the plaque assumes it's most advanced form, with a fibrous cap produced by VSMC, a necrotic core containing foam cells, cellular debris, cholesterol crystals, and a mixture of partially digested lipids. Rupture of the cap exposes platelets to the underlying thrombogenic constituents, resulting in clot formation and occlusion of an already narrowed lumen. It is this event that precipitates most myocardial infarctions [22,23].

There is a Yin-Yang relationship between the atherogenic and atheroprotective elements, with the former winning out in the process of plaque formation [24]. There is now evidence that moderate levels of physical activity, done on a regular basis, can reverse this relationship.

***Corresponding author:** J Kelly Smith, Departments of Academic Affairs & Biomedical Science, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, TN, USA, Tel: 423-794-7425; E-mail: smithj@etsu.edu

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Physical activity and atherogenesis

Skeletal muscle and myokines: Myokines are contraction-related proteins secreted from skeletal muscle that act on signaling pathways within myocytes and/or other tissues. The first identified and most studied myokine is interleukin-6 (IL-6), which activates 5` adenosine monophosphate activated protein kinase (AMPK) and/or phosphatidylinositol-3-kinase (PI3K) to increase fat oxidation and glucose uptake within myocytes. The level of circulating IL-6 increases in an exponential fashion (up to 100 fold) in response to exercise and declines in the post-exercise period. The increase is related to exercise intensity, duration, the mass of muscle recruited, and one's endurance capacity. Released into the circulation, IL-6 induces lipolysis and fat oxidation in other tissues, including adipocytes, while exerting both local and systemic anti-inflammatory effects by suppressing the production of TNF-α and IL-1 and by stimulating the production of the anti-inflammatory cytokines IL-10 and IL-1ra [25,26]. Although IL-6, a pleotropic cytokine with both pro- and anti-atherogenic activities, is produced by most nucleated cells, including hepatocytes, endothelial cells, T cells and macrophages, it is likely that a significant proportion of exercise-related increases in circulating IL-6 is from contracting muscle, and that IL-6 contributes to the anti-inflammatory effects of exercise by its effects on lipid metabolism and cytokine production.

Exercise also increases the expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) in muscle. PCG-1α, a transcription coactivator, stimulates the expression of the membrane protein fibronectin type III domain containing 5 (FNDCS), which is prototypically cleaved to form the myokine irisin. Irisin drives the transformation of white fat cells into brown-in-white, or brite, cells with a phenotype similar to brown fat cells [27]. Brown adipose tissue serves as a thermogenic organ in which mitochondrial respiration is uncoupled from ATP production to dissipate energy [28]. In obese mice, elevated levels of plasma irisin are followed by a reduction in body weight and an improvement in metabolic homeostasis [27]. The importance of this muscle-fat connection in obese humans remains to be established.

Vascular endothelial cells: An early event in atherogenesis is the activation of ECs in response to the injurious effects of glycated or oxidized LDL, oscillatory or diminished levels of shear stress, infection with agents such as CMV, HIV-1, or *Chlamydia pneumoniae*, free radicals arising during oxidative stress, heat shock protein 60, hypertension, cigarette smoking and/or inactivity [10,16,29-35]. Activated ECs upregulate their production of chemokines, adhesins, VSMC growth and activation factors, and downregulate their production of TGF-β, vasodilators, antioxidants, and anticoagulants. The endothelium is dysfunctional, particularly with regard to its ability to maintain normal vascular tone, and is distinctly Proatherogenic [23,36-41] (Table 1).

Monocyte & T cell recruitment	⇧ VCAM-1, RANTES, MCP-1
Vascular smooth muscle cell growth	⇧ PDGF-A, PDGF-B ⇩ TGF-β
Vasoconstriction	⇧ ET-1, ECE, ACE ⇩ NO, PGI_2, CNP, AM
Clotting	⇩ tPA, TM, NO
Oxidation	⇩ COX-1, COX-2, SODs

Table 1: Functional Characteristics of Proatherogenic Vascular Endothelial cells. VCAM-1: Vascular Cell Adhesion Molecule 1; RANTES: Regulated on Activation Normal T Expressed and Secreted Chemokine; MCP-1: Monocyte Chemoattractant Protein 1; PDGF: Platelet-Derived Growth Factor; TGF-β: Transforming Growth Factor β; ET-1: Endothelin 1; ECE: Endothelin-Converting Enzyme; ACE: Angiotensin-Converting Enzyme; NO: Nitric Oxide; PGI_2: Prostacyclin; CNP: C-type Natriuretic Peptide; AM: Adrenomedullin; TM: Thrombomodulin; TPA: Tissue-type Plasminogen Activator; COX: Cyclooxygenase; SODs: Superoxide Dismutases.

Exercise can normalize EC function in persons prone to atherogenesis [39]. The manner in which this occurs is incompletely understood, but hemodynamic forces, particularly shear stress, are known to exert a powerful influence on EC phenotype and function, and likely play a major role in the atheroprotective effects of exercise [30].

Shear stress mechanosensors include integrins, platelet EC adhesion molecules (PECAM)-1, cadherins, glycocalyx (whose intraluminal projections uncoil in the direction of flow), and primary cilia. Shear stress is also sensed by caveolae (small eNOS-binding membrane invaginations), G-protein-coupled receptors, and tyrosine kinase receptors. These events initiate a number of signal transduction pathways that regulate gene expression of focal adhesion kinase (FAK), Rho family GTPases, PI3 kinase, mitogen-activated protein kinases (MAPKs), protein kinase C (PKC) and nuclear factor–kB (NF-kB). The resultant change in endothelial phenotype is dependent on the type of shear stress. Laminar blood flow produces predominantly antegrade shear stress along the EC surface which favors an atheroprotective EC phenotype, whereas retrograde, oscillatory and slow shear stress of the type that occurs at bifurcations in the arterial tree predispose to an atherogenic EC phenotype [30].

Exercise and lymphocytes and monocytes: A study by Smith and associates [42] involving 45 subjects at risk of having atherosclerotic heart disease found that 6 months of moderate-intensity exercise caused a 58% reduction in blood mononuclear cell production of atherogenic cytokines (INF-γ, TNF-α and IL-1α) and a 36 % increase in the production of atheroprotective cytokines (TGF-β, IL-4, and IL-10). The total number of CD4 positive T cells did not change, suggesting that exercise had increased the proportion of atheroprotective Th2 and Treg lymphocyte populations. The systemic nature of this response is supported by their finding of a post-exercise drop in CRP levels. A subsequent study involving 28 subjects with documented coronary artery disease found that 12 weeks of aerobic exercise training resulted in a reduction in plasma levels of IL-1, IFN-γ, and CRP, and an increase in IL-10 levels [18]. Recent research involving type 2 diabetics showed that a combination of aerobic and resistance exercise was particularly effective in reducing blood levels of IL-1β and TNF-α and increasing levels of IL-4, IL-10 and adiponectin [43]. It is postulated that these changes occurred, at least in part, due to the beneficial effects of exercise training on endothelial cell function, but further study to explain the results is clearly indicated.

Atheroprotective cytokines are produced by Th2 lymphocytes (IL-4 and IL-10) and Treg lymphocytes (TGF-β). They inhibit cell-mediated immune reactions of the type seen in atherosclerotic lesions, primarily by suppressing macrophage and Th1 lymphocyte function. IL-4, IL-10 and TGF-β downregulate the production of IL-1, TNF-α, and IL-12 by monocytes and macrophages, and IL-10 and TGF-β inhibit IFN-γ production by Th1 lymphocytes. IL-4 also inhibits the development of Th1 cells while promoting the development of Th2 cells from Th0 progenitors. Furthermore, TGF-β helps to prevent exposure of the necrotic core of atherosclerotic plaques by stimulating VSMCs to produce a fibrous cap. This cytokine also inhibits the proliferation and migration of VSMCs into the intima, another atheroprotective activity [42,44].

Exercise and adipocytes: It is only recently that we have recognized the critical role of adipose tissue in maintaining metabolic homeostasis. Adipocytes are not simply storage depots for free fatty acids (FFA); they

are critical endocrine organs, that, by the production of adipokines, serve to regulate a variety of metabolic processes and to modulate total body mass. Although over 50 adipokines have been identified with diverse functional roles, adiponectin and leptin have been most closely studied [45].

Adiponectin enhances insulin sensitivity in muscle and liver and increases FFA oxidation in several tissues, including myocytes. It also decreases serum levels of FFA, glucose, and triacylglycerol. This hormone is a potent inhibitor of TNF-α-induced monocyte expression of adhesion molecules; it also inhibits the transformation of macrophages into foam cells, and thus displays several atheroprotective properties. In mice deficient in apolipoprotein E, adiponectin reduces plaque formation in aortic sinuses by 30% as compared to controls. Plasma concentrations of adiponectin fall with increasing obesity, contributing to insulin resistance and hyperinsulinemia in overweight individuals and, possibly, enhancing the atherogenic process [45].

Leptin is produced in adipocytes and serves to downregulate appetite by binding to leptin receptors in the hypothalamus. Animals and humans deficient in the leptin gene develop morbid obesity and diabetes, both risk factors for atherosclerosis. Unfortunately, although plasma levels of leptin increase with increasing body weight, the rise is accompanied by an increased expression of suppressor-of-cytokine-signaling (SOCS-3) which blocks the central effects of leptin, nullifying the intended feedback control of obesity [45].

Compared with lean individuals, adipose tissue of obese persons contains higher concentrations of pro-inflammatory elements (TNF-α, MCP-1, and various procoagulant proteins) produced primarily by infiltrating macrophages whose purpose is to scavenge increasing numbers of moribundly "obese" adipocytes. It would appear that adipocytes are unable to process excess amounts of FFA and, much like macrophage foam cells, are destined to die. Adipose tissue from obese individuals also contains abnormally high levels of collagen V, produced in response to mast cell protease 6 (MCP-6) secreted by infiltrating mast cells. Thus, adipose tissue from obese individuals serves as a source of chronic inflammation that may have systemic consequences, perhaps contributing to the development of atherosclerosis [45].

Lee et al. found that ten weeks of forced exercise restored acetylcholine-induced endothelial-dependent vasodilatation in the aortas of type 2 diabetic mice [46]. This effect was blunted in adiponectin knockout mice, suggesting that some of the beneficial effects of exercise on EC function may have been mediated by adiponectin. Another study demonstrated that two years of weekly T'ai Chi exercises performed by individuals with cardiovascular risk factors resulted in significant increases in circulating levels of adiponectin [47]. However, in contrast, Sjogren and associates found that 6 months of prescribed physical exercise in 30 sedentary, overweight and abdominally obese subjects failed to alter circulating levels of adiponectin; in addition, pre- and post-exercise biopsies of subcutaneous fat failed to show changes in the expression of adiponectin and a cadre of inflammatory cytokine mRNAs when compared to controls [48]. Since the exercising group only lost 1.5 kg (1.0 kg more that the control group), the study suggests that weight reduction is the single most important factor in normalizing adipose tissue in overweight individuals.

Conclusion

In persons prone to developing ACVD, regularly performed moderate intensity physical exercise protects against atherosclerosis by reducing the impact of risk factors while normalizing EC function and upregulating the proportion of circulating Th2 and Treg lymphocytes and their atheroprotective cytokines. The mechanisms by which these changes occur deserve further study.

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