The Role of Physical Activity in the Prevention of Atherosclerosis

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Abstract. Atherosclerosis remains a leading cause of death and disability worldwide. Despite advances in pharmacotherapy and revascularization, residual risk, adherence barriers, and adverse effects persist. Physical activity (PA) offers a scalable non-pharmacological strategy to reduce this burden. Regular physical activity mitigates atherogenesis by enhancing endothelial function and nitric oxide bioavailability, lowering blood pressure, improving insulin sensitivity and glycaemic control, optimizing lipid handling, and attenuating chronic low-grade inflammation. Evidence suggests that aerobic, resistance, and isometric exercise modalities are beneficial, and combined training programs show complementary advantages. Key gaps remain regarding the optimal intensity and dose, real-world long-term adherence, and potential risks from excessive training in susceptible individuals. This review systematically synthesizes contemporary epidemiological, mechanistic, and interventional evidence on the role of PA in preventing and managing atherosclerosis, compares aerobic, resistance, and isometric modalities in their effects on endothelial function, blood pressure, glycaemic control, lipid metabolism, and inflammation, and highlights individualized prescriptions and practical strategies for precise prevention and management.

1 Introduction

Atherosclerosis is a chronic, progressive disease of the arterial wall characterized by lipid accumulation, endothelial dysfunction, inflammation, and fibrous plaque formation, ultimately causing arterial stiffening and lumen narrowing, and serving as the pathological basis for major cardiovascular diseases (CVD) such as coronary artery disease, stroke, and peripheral artery disease [1]. In 2021, the global number of incident cardiovascular disease cases reached 66.81 million and deaths 19.42 million, while age-standardized incidence and death rates declined by 10.4% and 34.3% compared with 1990. Nevertheless, the absolute burden continued to increase as a result of population growth and ageing [2]. Atherosclerosis is the dominant pathological substrate for coronary, cerebrovascular, and peripheral arterial disease and thus drives a large share of CVD-related morbidity and mortality. In industrialized countries, deaths attributable to atherosclerotic CVD approach one-half of all deaths [3]. According to the British Heart Foundation, cardiovascular disease imposes a substantial economic burden in England, with annual healthcare costs for heart and circulatory diseases estimated at £10 billion, equivalent to a significant proportion of the national health budget. Of this expenditure, hospital care constitutes the largest share, followed by pharmacological treatments, rehabilitation, and long-term follow-up. When broader societal costs are considered, including productivity losses from premature mortality, long-term care, disability, and informal caregiving, the total economic impact rises to approximately £24 billion per year, bringing the overall annual burden to more than £34 billion [4]. Consequently, given the scale of its health and economic impact, early prevention and timely treatment of atherosclerosis become imperative.

Traditional risk factors for atherosclerosis include dyslipidaemia, hypertension, diabetes mellitus, obesity, smoking, and sedentary lifestyle. Physical activity (PA), defined as any bodily movement produced by skeletal muscles that results in energy expenditure, encompasses a range of domains including occupational, transportation, household, and leisure-time activities. Much evidence support that regular PA contributes to the reduction of cardiovascular risk factors, enhancement of endothelial function, and prevention of atherosclerosis. Specifically, regular PA improves lipid profiles, lowers blood pressure, enhances insulin sensitivity, and promotes endothelial health, thereby mitigating key mechanisms in atherogenesis. In contrast, physical inactivity is a major contributor to impaired lipid metabolism, endothelial dysfunction and chronic low-grade inflammation. PA protects cardiovascular health, yet evidence on the most effective exercise types and doses for limiting atherosclerosis remains incomplete, and mechanistic links to nitric oxide bioavailability, inflammatory pathways, and vascular markers are not consistently demonstrated. This review systematically synthesizes contemporary epidemiological, mechanistic, and interventional evidence on the role of PA in the prevention of atherosclerosis, with particular emphasis on the differential effects of exercise modalities and intensities,

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as well as individualized intervention strategies. By integrating these dimensions, the review aims to establish a comprehensive framework that advances understanding of the multifaceted protective effects of PA.

2 Pathophysiology of Atherosclerosis

The pathophysiology of atherosclerosis comprises multiple interlocking and mutually amplifying pathways, including endothelial dysfunction with abnormal permeability, intimal retention and oxidative modification of lipoproteins, oxidative stress and sterile inflammatory cascades with inflammasome activation, dysregulated recruitment and polarization of immune cells, vascular smooth muscle cell phenotypic switching with extracellular matrix remodelling, hemodynamic microenvironmental changes driven by aberrant shear and wall stress, and chronic abnormalities in systemic metabolic and pressure load. Atherosclerosis often begins with endothelial dysfunction. Under cardiometabolic stress and disturbed flow, nitric oxide bioavailability declines, permeability increases, and leukocyte adhesion is induced, allowing low density lipoprotein (LDL) to traverse the endothelium and become retained in the intima while monocytes are recruited and transmigrate [5].

Once trapped, LDL undergo oxidative modification, and the resulting oxidized ligands stimulate endothelial upregulation of VCAM-1, ICAM-1, E-selectin, P-selectin, and monocyte chemoattractant protein 1, which strengthens monocyte adhesion and migration. Macrophages entering the intima take up oxidized lipoproteins via scavenger receptors to form foam cells, and lipid loading together with inflammatory mediator release drives fatty-streak expansion and extracellular matrix remodelling [6].

In parallel, vascular smooth muscle cells switch phenotype, migrate, and deposit matrix to form a fibrous cap that initially stabilizes the lesion, but they may adopt foam cell like and matrix degrading phenotypes that thin the cap. Activation of the NLRP3 inflammasome generates interleukin 1 β and interleukin 18, which further aggravate endothelial injury and macrophage activation and thereby promote plaque growth and instability [7]. These events localize preferentially to regions of low or oscillatory shear, where flow dependent endothelial reprogramming induces proatherogenic transcriptional and metabolic states that intensify local progression.

From a risk-factor to phenotype perspective, dyslipidaemia and diets rich in saturated fat and refined sugars primarily increase the burden and intimal retention of oxidizable LDL, triggering fatty-streak formation and immune recruitment. Metabolic derangements with insulin resistance enhance reactive oxygen species and advanced glycation end product signalling, reducing nitric oxide bioavailability and amplifying adhesion, chemotaxis, and inflammatory transcriptional networks. Low or oscillatory shear and hypertension induced wall stress reprogram the endothelial phenotype, promote lipid uptake and procoagulant pathways, and together with vascular smooth muscle cell phenotypic switching determine fibrous cap thickness and matrix homeostasis. Exogenous stimuli such as cigarette smoke and environmental pollution provide additional oxidative and inflammatory stress that cooperatively enlarge the necrotic core and thin the cap. Ultimately, these pathways converge on a vulnerable plaque phenotype beneath a thin fibrous cap, characterized by a lipid rich necrotic core, cholesterol crystals, and macrophage rich shoulders, which is prone to stress triggered rupture with subsequent platelet activation and thrombosis, culminating in myocardial infarction or ischemic stroke.

3 Protective Effects of Physical Activity against Atherosclerosis

PA is a potent, non-pharmacological intervention that directly counteracts the mechanisms driving atherosclerosis. In addition, PA is bodily movement produced by skeletal muscle contractions that increases energy expenditure. By mode it includes aerobic training in continuous or interval formats, resistance training, and isometric training. It spans leisure, transport, household, and occupational activity, and is typically quantified by weekly MET hours, device recorded steps and minutes of moderate to vigorous activity, and cardiorespiratory fitness such as VO_2peak or exercise METs. Large meta-analyses demonstrate a steep inverse association between leisure time PA and atherosclerosis related outcomes, with cardiovascular and coronary heart disease incidence lower by about 19% and 20% and stroke lower by about 22% around 20 MET hours per week, while occupational PA does not show comparable protection [8].

At the level of risk factors and biological pathways, PA produces quantifiable effects that are concordant with improved outcomes. For blood pressure, repeated shear stress activates and phosphorylates endothelial nitric oxide synthase, increases nitric oxide bioavailability, and counteracts endothelin-1, while training enhances vagal activity, attenuates sympathetic drive, improves baroreflex sensitivity, downregulates the renin angiotensin aldosterone system, promotes natriuresis, and increases arterial compliance. At the vascular level, repeated bouts of PA restore endothelial homeostasis. Shear stress from rhythmic muscle contractions activates and phosphorylates endothelial nitric oxide synthase, increases nitric oxide bioavailability, and counteracts endothelin-1. Exercise training improves baroreflex sensitivity, enhances vagal tone, attenuates sympathetic drive, and downregulates the renin–angiotensin–aldosterone system.

In trials these adaptations yield average resting reductions near 4-6 millimetres of mercury for systolic pressure and 2-3 millimetres of mercury for diastolic pressure, with isometric training producing typical falls close to 8 over 4 millimetres of mercury and ranking highly among modalities for blood pressure control [9].

PA also improves glucose and lipid metabolism, thereby targeting metabolic drivers of atherogenesis. Acute contractions activate AMPK and CaMK to drive

GLUT4 translocation and glucose uptake in muscle, while chronic training increases GLUT4 content and PGC-1 α driven mitochondrial biogenesis, reduces lipotoxic intermediates, restores IRS1 to Akt insulin signalling. These adaptations enhance muscle capillarisation and microvascular recruitment, and improve hepatic insulin sensitivity, translating into average HbA1c reductions of 0.5 to 0.7 percentage points in type 2 diabetes, with additional benefits from resistance training [10].

Sustained shear stress during repeated exercise bouts enhances vascular function. It improves coupling of endothelial nitric oxide synthase and the availability of tetrahydrobiopterin, upregulates antioxidant defences such as superoxide dismutase and catalase, reduces superoxide scavenging of NO, and lowers arterial stiffness. Smooth muscle shifts toward a contractile phenotype, matrix remodelling rebalances metalloproteinases and their inhibitors, intimal thickening slows, high-density lipoprotein (HDL) mediated cholesterol efflux improves, and endothelial progenitor cell mobilisation increases. Consistent with these mechanisms, clinical trials report increases in brachial artery flow mediated dilation and prospective cohorts indicate that each 1% higher flow mediated dilation associates with about a 10% lower risk of future cardiovascular events, supporting biological plausibility for event reduction via endothelial improvement [11].

Exercise also exerts systemic anti-inflammatory effects that further restrain atherogenesis. Myokine release increases interleukin-10 and the interleukin-1 receptor antagonist while suppressing NF- κ B signalling. With training over time C reactive protein, interleukin-6, and tumour necrosis factor α decline, AMPK and SIRT1 activity constrains NLRP3 inflammasome activation, macrophage polarisation shifts toward an M2 profile with higher regulatory T cell proportions, adipokine balance favours adiponectin, and increased short chain fatty acids from the gut support immune homeostasis, together easing endothelial dysfunction and foam cell formation. These intermediate effects translate into better clinical outcomes in patients with established coronary heart disease, where exercise based cardiac rehabilitation on top of contemporary pharmacotherapy reduces cardiovascular mortality, rehospitalisation, and myocardial infarction and improves health related quality of life [12].

In conclusion, PA lowers systolic and diastolic blood pressure, reduces HbA1c and improves insulin sensitivity, optimizes lipid profiles and systemic inflammation, enhances flow mediated dilation and induces small regressions in carotid intima media thickness, thereby directly alleviating the two core pathological pathways of endothelial dysfunction and lipid deposition, slowing plaque formation and destabilization, and ultimately reducing the risk of incident and recurrent atherosclerosis.

4 Optimizing Physical Activity for Atherosclerosis Prevention

Current WHO public health guidelines recommend that most adults perform 150-300 minutes of moderate intensity aerobic activity or 75-150 minutes of vigorous intensity aerobic activity each week, plus muscle strengthening exercise on at least two days. Doing more than this still confers benefits, though with diminishing returns, and there is no longer a requirement that each bout last at least 10 minutes. A large body of research likewise shows that moving from inactivity to roughly 500-1000 MET minutes per week, which is approximately equivalent to the time ranges above, yields the steepest risk reductions. Moreover, individuals who are habitually sedentary can achieve the greatest absolute health gains by even modest increases in activity, highlighting that the transition from inactivity to moderate activity is more critical than striving for very high volumes. Therefore, this range is best treated as a population reference target rather than a hard upper limit.

For patients with atherosclerotic cardiovascular disease, even if their PA level is lower than the aforementioned values, significant improvements in prognosis and risk factors can be achieved as long as the exercise intensity is individually adjusted and sedentary time is reduced. Organized cardiac rehabilitation programs also contribute to enhancing survival rates. In contrast, consistently exceeding the recommended physical activity levels in the guidelines yields limited benefits for preventing atherosclerosis and may even increase risks unrelated to atherosclerosis, such as atrial fibrillation, to which this group of individuals is more susceptible. Mechanistic studies suggest that extremely high training loads may lead to atrial remodelling through long-term volume overload and autonomic nervous system imbalance, indicating that exercise is not always beneficial and must be tailored according to individual susceptibility. Overall, a prudent approach is to gradually work towards the aforementioned goals, regularly interrupt prolonged sitting, such as standing up and taking a short walk every 30 to 60 minutes, and incorporate resistance training into routine activities at least twice a week. For those who prefer to track their steps, a daily step count of approximately 7000 to 10000 is a practical and achievable target, which is also associated with a lower risk of mortality.

Regular PA for preventing atherosclerosis should primarily consist of aerobic training, with resistance exercise serving as an essential complement and isometric training as an auxiliary means for blood pressure control. Sustained moderate-intensity aerobic training is the fundamental exercise mode for most adults, which can be carried out through activities such as brisk walking, cycling, jogging, or swimming. In cardiac rehabilitation patients or experienced individuals, high-intensity interval training can lead to greater improvements in cardiopulmonary function and endothelial function, provided that the training is initially supervised and the training process is gradually advanced to minimize the risk of arrhythmia. Resistance exercise should be performed at least two days a week. Each session should target the major muscle groups and involve eight to ten exercises, with 8 to 12 repetitions per set, using approximately 40% to 60% of the one-

repetition maximum (1RM). Individuals who are frail or elderly can start at an intensity of 30% to 40%, emphasizing the quality of movements and joint protection. Isometric training can be performed 3 to 5 days per week as four bouts of two minutes with one to two minutes of rest, a regimen that has been shown to augment antihypertensive effects when incorporated into multimodal programs. The intensity should be correlated with physiological and perceived indicators. For aerobic training, moderate intensity corresponds to a heart rate reserve (HRR) or oxygen uptake reserve (VO_2R) of approximately 40%-59%, while higher intensity ranges from 60%-89%. Resistance training should allow for some technical leeway, but the last two to three repetitions should approach the limit, with the perceived exertion level between 15 and 17 to maximize strength and insulin sensitivity. The prescription for isometric training can start at 30% of the maximum voluntary contraction force and be adjusted according to blood pressure response and tolerance. This personalized adjustment indicates that PA is more than just a general lifestyle recommendation; it is an adjustable intervention that has measurable effects on endothelial function, vascular compliance, and plaque stability in atherosclerosis.

5 Conclusion

Atherosclerosis remains the leading cause of disease and death globally, continuously imposing a substantial clinical and economic burden. Evidence from epidemiology, mechanistic research, and intervention measures indicates that regular PA can improve endothelial function and the bioavailability of nitric oxide, lower blood pressure, enhance insulin sensitivity, reduce glycated hemoglobin levels, optimize lipid processing and high-density lipoprotein function, and alleviate chronic low-grade inflammation and oxidative stress. These intermediate improvements are consistent with a moderate reduction in carotid intima-media thickness and an improvement in vascular function. In a clinical setting, physical activity is associated with a lower incidence of adverse cardiovascular events, a lower all-cause mortality rate, and can also enhance functional capacity and health-related quality of life. In secondary prevention, structured and prescription-based exercise delivered within comprehensive cardiac rehabilitation reduces rehospitalization and recurrent events and should be regarded as a standard element of long-term care.

However, some important uncertainties still remain. Substantial heterogeneity persists in the quantification of PA exposure, in intensity classification, and in the choice of mechanistic endpoints, which reduces comparability across trials. Regarding diverse patient types and various treatment stages, the optimal configurations of treatment modalities, treatment intensity levels, and total dosages remain incompletely elucidated. In actual clinical practice, patients frequently exhibit poor long-term compliance. This suboptimal compliance attenuates the potential impact on the overall patient population. Excessively high training loads can introduce certain risks unrelated to arteriosclerosis, including arrhythmias and musculoskeletal injuries. This situation underscores the crucial importance of meticulous safety monitoring and the need for a gradual approach to dose adjustment.

Future research should focus on developing precise exercise prescriptions through multi-dimensional analysis. Key factors such as age, comorbidities, physiological reserves, metabolic and inflammatory phenotypes, as well as genetic and epigenetic profiles, should be integrated into adaptive dosing strategies. By integrating wearable monitoring data, including heart rate and rhythm, activity levels, and dynamic blood pressure, with clinical indicators such as maximal oxygen uptake and flow-mediated dilation, closed-loop adjustments, early risk identification, and enhanced patient adherence can be achieved. A multidisciplinary rehabilitation approach that combines exercise with nutritional counselling, smoking cessation programs, sleep and psychological support, and medication optimization should be scientifically implemented to enable automated referrals, improve cardiac rehabilitation completion rates, and ensure equitable access as standard practice. Standardized reporting of physical activity doses using metrics such as metabolic equivalent minutes, step counts, and heart rate reserve ranges, in conjunction with unified mechanistic endpoints, will support cross-study comparisons and help clarify dose-response relationships. In conclusion, physical exercise should be recognized as a complementary therapeutic strategy and established as a fundamental component in the prevention of atherosclerosis, disease management, and long-term cardiovascular health maintenance.

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