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REVIEW

Exercise and Endothelial Function: Insights from a Redox Perspective

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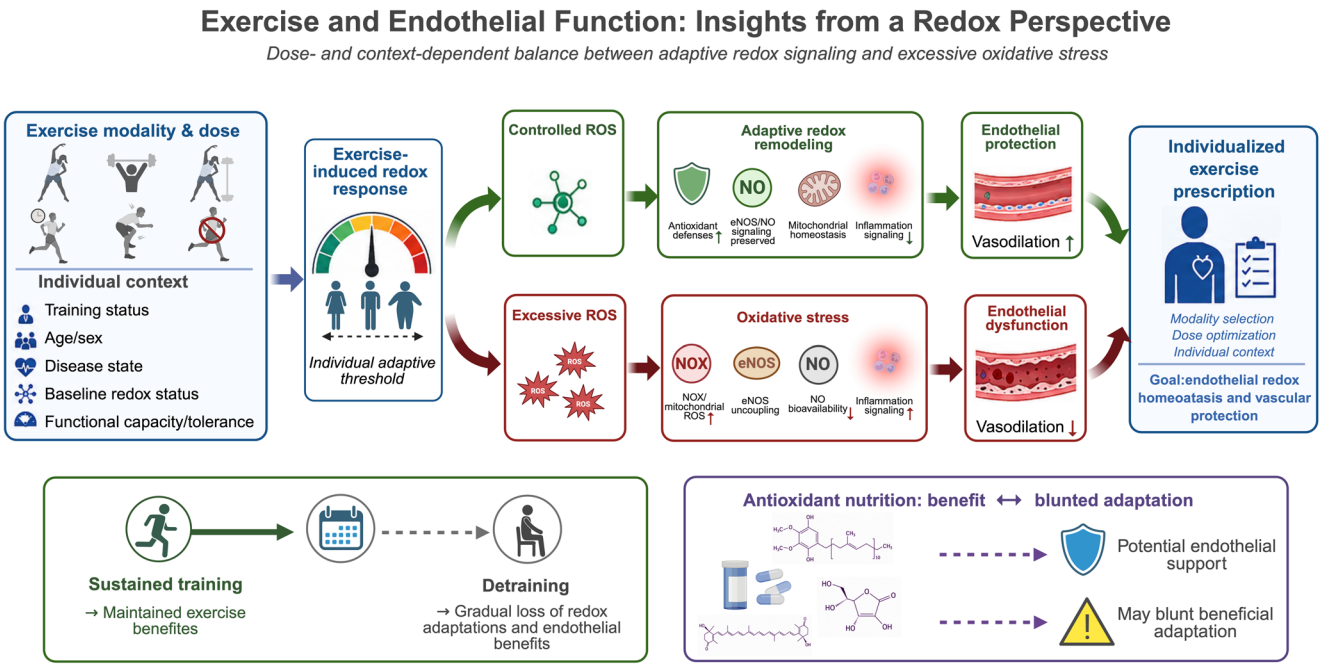
Abstract

Purpose of Review This review aims to synthesize the evidence linking exercise, redox regulation, and endothelial function. It considers the effects of different modes of regular exercise, acute exercise, and exercise combined with antioxidant interventions. The review places particular emphasis on the molecular mechanisms and signaling pathways underlying the effects of these approaches on oxidative stress and endothelial function.

Recent Findings Disrupted redox homeostasis is increasingly recognized as an important driver of endothelial dysfunction and subsequent cardiovascular disease progression. Exercise training may counteract this imbalance by strengthening endogenous antioxidant defenses, limiting oxidative stress, and restoring endothelial redox homeostasis.

Summary Current evidence indicates that exercise helps preserve and enhance endothelial function by regulating redox homeostasis. A deeper understanding of exercise–redox interactions may inform strategies for preventing and managing cardiovascular diseases associated with endothelial dysfunction.

Graphical Abstract



Keywords Exercise · Oxidative stress · Endothelial function · Redox homeostasis · Antioxidant interventions

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Introduction

Regular physical activity is a key nonpharmacological strategy for preventing and managing cardiovascular disease. Increasing evidence indicates that exercise exerts multifaceted benefits on redox homeostasis. Oxidative stimuli induced by moderate exercise can promote redox remodeling, activate endogenous antioxidant defense systems, and attenuate pathological oxidative stress, thereby conferring cardiovascular protection [1, 2]. For example, treadmill exercise has been reported to ameliorate atherogenesis and vascular inflammation [3]. However, the mechanistic links between exercise-induced oxidative stress and vascular health remain incompletely understood. Elucidating how exercise regulates redox homeostasis and endothelial function may therefore advance current understanding of cardiovascular disease pathogenesis and inform the development of precision exercise prescriptions.

Endothelial cells (ECs) form a continuous monolayer lining the entire vascular system and are aligned longitudinally with the direction of blood flow. The vascular endothelium separates blood from surrounding tissues and serves as a key metabolic and endocrine organ [4]. It synthesizes and releases various bioactive mediators, including growth factors, vasodilators, vasoconstrictors, and factors involved in coagulation and anticoagulation. Through these mediators, the endothelium regulates vascular tone and hemostasis; limits platelet and leukocyte activation and adhesion, inflammation, and smooth muscle cell proliferation; promotes fibrinolysis; and preserves vascular integrity [5]. Endothelial dysfunction is characterized by reduced nitric oxide (NO) production or bioavailability, an imbalance between vasodilatory and vasoconstrictive factors, and a shift toward an inflammatory, pro-adhesive, and pro-thrombotic endothelial phenotype [6]. This condition arises when ECs lose their ability to adapt and respond to various stressors. Dietary imbalance, pathogen exposure, alcohol consumption, smoking, and physical inactivity can drive excessive reactive oxygen species (ROS) production and oxidative stress in ECs. These processes contribute substantially to endothelial dysfunction and the development and progression of cardiovascular disease [7, 8]. In this context, long-term aerobic exercise has been shown to facilitate endothelial progenitor cell-mediated repair of endothelial injury induced by metabolic stress [9]. This evidence suggests that exercise may counteract endothelial dysfunction through redox-related molecular pathways.

This review synthesizes evidence from human studies and animal models on how exercise regulates oxidative stress, redox signaling, and endothelial function. It integrates findings on regular aerobic, resistance, combined, and high-intensity interval training, as well as acute and strenuous exercise, within a unified redox framework. It distinguishes adaptive redox signaling from excessive oxidative stress and examines how these context-dependent responses influence endothelial function. The review further considers the reversibility of exercise-induced endothelial benefits after detraining and whether antioxidant interventions enhance vascular protection or blunt beneficial exercise adaptations. Together, this synthesis provides a mechanistic framework to inform individualized exercise prescriptions for endothelial protection.

Methodology-Literature Search Strategy

For this narrative review, a structured literature search was conducted in PubMed and Web of Science from database inception through August 15, 2026, using combinations of terms related to exercise (e.g., “aerobic exercise,” “resistance exercise,” “combined training,” “high-intensity interval training,” “acute exercise,” “strenuous exercise,” and “detraining”), redox regulation (e.g., “oxidative stress,” “reactive oxygen species,” “antioxidant defense,” “redox homeostasis,” and “mitochondrial dysfunction”), endothelial function (e.g., “endothelial dysfunction,” “nitric oxide,” “endothelial nitric oxide synthase,” “flow-mediated dilation,” and “endothelium-dependent dilation”), and antioxidant interventions. Additional records were identified by manually screening reference lists of relevant original articles and reviews.

Studies were eligible if they examined exercise-related changes in redox regulation and endothelial function or investigated mechanisms linking these processes in humans or experimental models, including studies of regular or acute exercise, detraining, and exercise combined with antioxidant interventions. Studies were excluded if they focused exclusively on exercise performance or non-vascular outcomes, lacked relevant redox or endothelial endpoints, or were published as conference abstracts, editorials, protocols, or non-peer-reviewed reports.

Oxidative Stress in Endothelial Dysfunction

Endothelial dysfunction manifests at an early stage and plays a significant role in the initiation and progression of atherosclerosis and other cardiovascular disorders. Oxidative stress is a principal mechanism driving damage to the vascular endothelium [10]. At physiological levels, ROS act as signaling mediators that modulate vascular

tone, cellular proliferation and migration, and immune defense [7]. In parallel, antioxidant defenses, including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), peroxiredoxins, and thioredoxin (TRX), work in concert to neutralize excessive ROS and maintain vascular redox homeostasis. When ROS generation surpasses antioxidant capacity, a redox imbalance occurs, leading to oxidative damage to nucleic acids, proteins and lipids, thereby impairing endothelial function [10, 11]. Risk factors for cardiovascular disease, including diabetes, hyperlipidemia, hypertension, obesity, smoking, and aging, disrupt redox balance by increasing ROS production and weakening endogenous antioxidant defenses [6]. The primary sources of ROS within the vascular endothelium include leakage from the mitochondrial electron transport chain, NADPH oxidases (NOXs), xanthine oxidase, uncoupled endothelial nitric oxide synthase (eNOS), and myeloperoxidase (MPO) [12]. Notably, mitochondrial dysfunction, activation of NOXs, and increased activity of xanthine oxidase contribute to the enhanced production of superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2). In conditions characterized by tetrahydrobiopterin (BH4) deficiency, limited availability of L-arginine, or an elevated oxidative environment, eNOS transitions from a coupled to an uncoupled state, thereby converting from a NO-producing enzyme to a source of $O_2^{\bullet -}$, which exacerbates oxidative stress. NO serves as a crucial mediator of endothelium-dependent dilation (EDD) and exerts important vasoprotective effects. However, oxidative stress diminishes NO bioavailability by promoting its reaction with $O_2^{\bullet -}$ to form peroxynitrite ($ONOO^-$) and by oxidizing BH4, which leads to eNOS uncoupling and impaired EDD [13, 14]. In addition, excessive ROS activate signaling pathways that involve NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, nuclear factor-kappa B (NF-κB), and matrix metalloproteinases (MMPs). This activation results in the upregulation of intercellular adhesion molecule-1 (ICAM-1), E-selectin, vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1, thereby facilitating leukocyte adhesion and transmigration. Consequently, the endothelial phenotype shifts from an anti-inflammatory and anticoagulant state to a pro-thrombotic, pro-adhesive, and pro-inflammatory condition [15, 16]. Concurrently, the oxidative environment induces the conversion of low-density lipoprotein (LDL) into its oxidized form (ox-LDL), which further intensifies endothelial oxidative stress and inflammation, perpetuating a deleterious cycle that exacerbates endothelial dysfunction [17] (Fig. 1).

Exercise as a Regulator of Endothelial Redox Homeostasis

Exercise provides a nonpharmacological approach to enhancing vascular endothelial function. Clinical studies and experimental disease models demonstrate that regular physical activity improves flow-mediated dilation (FMD), reduces arterial stiffness, and mitigates endothelial dysfunction. These benefits have been observed in hypertension, diabetes, coronary artery disease, and heart failure [18, 19]. The underlying mechanisms of these effects include the activation of eNOS, increased bioavailability of NO, reduction of vascular inflammation, and improved endothelial repair capacity [20]. Emerging evidence indicates that the vasoprotective benefits of exercise are intricately associated with the preservation of endothelial redox homeostasis. Physical inactivity has been shown to upregulate the expression and activity of vascular NOXs, resulting in excessive ROS production and subsequent endothelial dysfunction [21]. By contrast, regular exercise alleviates age-associated oxidative stress within the vascular endothelium [22]. Moderate physical exercise serves as a controlled physiological oxidative stimulus that triggers adaptive antioxidant responses, enhances endogenous antioxidant defenses, curtails excessive accumulation of ROS, and maintains the integrity of eNOS/NO signaling [23]. The slight increase in ROS produced during exercise also functions as a signaling cue that activates the Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, thereby promoting antioxidant gene expression and enhancing endothelial antioxidant capacity [24]. In addition to redox adaptations, ECs are highly responsive to hemodynamic stimuli. Exercise-induced elevations in blood flow and laminar shear stress activate multiple vasoprotective signaling pathways [25, 26]. In particular, laminar shear stress upregulates endothelial protective transcription factors such as Krüppel-like factor 2 (KLF2), promotes eNOS phosphorylation and coupling, and augments NO-dependent vasodilatory responses [27]. Furthermore, laminar shear stress suppresses angiotensin II (Ang II) type 1 receptor (AT1R) expression, thereby reducing NOX activity and $O_2^{\bullet -}$ generation, limiting NO degradation, and preserving NO bioavailability [28]. Exercise also disrupts the self-perpetuating cycle between oxidative stress and inflammation, thereby ameliorating endothelial dysfunction and decelerating disease progression [29, 30]. It facilitates mitochondrial biogenesis and improves mitochondrial quality control, which reduces ROS leakage from dysfunctional mitochondria, further contributing to endothelial redox balance and vascular health [31]. Collectively, these findings indicate

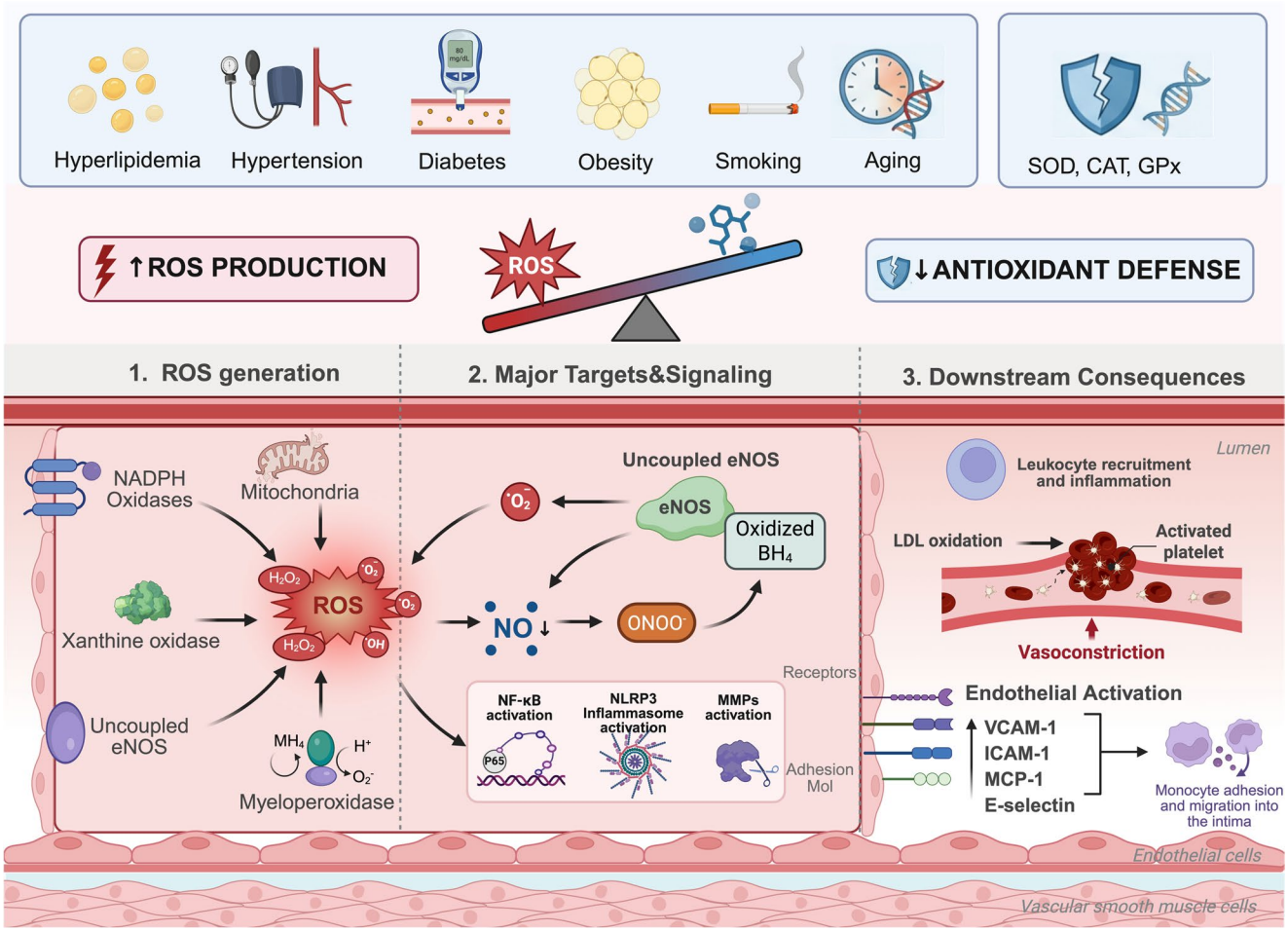

Fig. 1 Oxidative stress-mediated endothelial dysfunction. Cardiovascular risk factors increase ROS production and impair antioxidant defenses, thereby reducing NO bioavailability, promoting eNOS uncoupling, and activating inflammatory signaling. These changes lead to endothelial activation, leukocyte recruitment, platelet activation, LDL oxidation, vasoconstriction, and vascular inflammation. Figure was drawn using BioRender (https://app.biorender.com/)

that exercise preserves endothelial function and delays the progression of vascular injury by remodeling endothelial redox homeostasis through multifaceted mechanisms.

Effects of Different Exercise Modalities on Oxidative Stress and Endothelial Function

The impact of exercise on oxidative stress and endothelial function varies with exercise modality, dose, and training status. This section summarizes current evidence on how aerobic exercise (AE), resistance exercise (RE), combined aerobic and resistance training (CT), high-intensity interval training (HIIT), acute and strenuous exercise, and detraining influence endothelial redox homeostasis and function (Fig. 2). Findings from human studies are detailed in Table 1, while mechanistic evidence from experimental models is summarized in Table 2.

Regular AE Training

AE is an effective strategy for promoting vascular health. Regular engagement in AE enhances endothelial function and lowers oxidative stress. These endothelial benefits are closely associated with higher total antioxidant capacity [32]. Individuals who consistently participate in AE demonstrate elevated levels of circulating eNOS and NO, alongside reduced oxidative stress index (OSI) and ox-LDL levels, in comparison to their inactive counterparts [33, 34]. Human studies showed that 20 weeks of moderate-intensity AE reduces the markers of endothelial glycocalyx damage in healthy sedentary young men by attenuating oxidative stress and enhancing antioxidant defenses, thereby improving endothelial glycocalyx integrity at rest and during exercise [35]. Even low-intensity regular AE, which is below the minimum level recommended by current guidelines, improves arteriolar endothelial function in overweight and

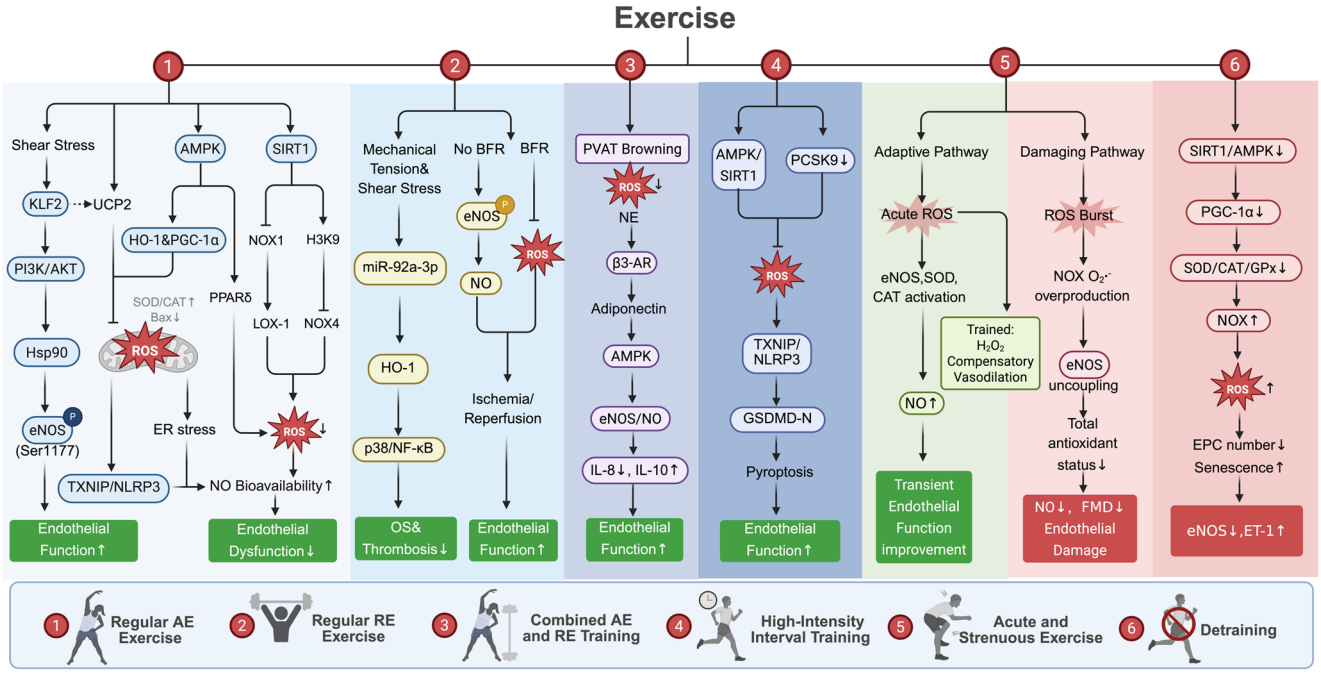

Fig. 2 Effects and potential pathways of different exercise modalities on oxidative stress and endothelial function. Abbreviations: PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; Hsp90, heat shock protein 90; HO-1, heme oxygenase-1; PPARδ, peroxisome proliferator-activated receptor-δ; H3K9, Histone H3 Lysine 9; p38, p38 mitogen-activated protein kinase; PCSK9, proprotein convertase subtilisin/kexin type 9; GSDMD-N, N-terminal fragment of gasdermin D; EPC, endothelial progenitor cells. Figure was drawn using BioRender (https://app.biorender.com/)

obese postmenopausal women by enhancing endogenous antioxidant enzyme activity [36]. In addition, a 12-week regimen of either home-based or supervised interval walking AE has been shown to decrease serum-induced apoptosis of ECs in patients with symptomatic peripheral artery disease. This exercise modality confers protective effects by enhancing antioxidant capacity, promoting angiogenesis, and reducing endothelial inflammation [37]. However, the vascular benefits of AE are significantly modulated by its intensity. High-intensity AE has been observed to lower circulating antioxidant levels and impair endothelial function in the forearm [38]. In healthy young men, a 12-week program of moderate-intensity AE enhances EDD by increasing NO production, whereas high-intensity exercise increases oxidative stress markers and fails to improve endothelial function [39]. These adverse effects may be attributed to oxidative stress-induced uncoupling of eNOS and diminished NO bioavailability [40, 41]. Consequently, regular low- to moderate-intensity AE may represent an effective exercise strategy.

Animal studies have further elucidated the molecular mechanisms through which AE ameliorates vascular oxidative stress and enhances endothelial function. AMP-activated protein kinase (AMPK) serves as a pivotal regulatory node in this process [42]. Specifically, endothelial AMPKα1 acts as a crucial molecular switch for exercise-induced vascular protection; its deletion negates the beneficial effects of AE, such as increased NO bioavailability and reduced oxidative stress, leading instead to NOX2 upregulation, eNOS uncoupling, and endothelial dysfunction [43]. Through an AMPKα1-dependent pathway, AE augments antioxidant defenses mediated by heme oxygenase-1 and peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), thereby reducing vascular ROS levels [44]. In diabetic and obese mice, AE activates AMPK/peroxisome proliferator-activated receptor-δ (PPARδ) signaling, which suppresses endothelial endoplasmic reticulum (ER) stress and oxidative stress, enhances NO bioavailability, and restores EDD [45]. Moreover, AE activates AMPKα2, upregulates eNOS expression and phosphorylation, and increases aortic mitochondrial content along with MnSOD- and CAT-mediated antioxidant capacity, thereby enhancing vasodilatory function [46]. Mitochondrial homeostasis is essential for maintaining endothelial antioxidant capacity and vascular function [47]. Chronic AE preserves aortic mitochondrial function, reduces oxidative/nitrative stress, and enhances mitochondrial antioxidant defenses, thereby improving EDD and reducing aortic stiffness in aged rats [48]. AE also maintains endothelial function by inhibiting mitochondrial ROS accumulation and the associated inflammatory response [49]. In

Table 1 Effects of different exercise modalities on oxidative stress and endothelial function in human studies

Exercise modality	Study Population	Training Protocol	Oxidative Stress-Related Effects	Endothelial Function-Related Effects	Ref
AE	Formerly pre-eclamptic women	16 weeks; 3 sessions/week; cycling at VO_2AT-based target HR	TAC↑ MDA, 8-isoprostane↓	RHI↑	[32]
AE	Previously untrained healthy young men	20 weeks; cycling; 40 min/session; 4 sessions/week; ~50% VO_2max	Isoprostanes↓ SOD2↑	Syndecan-1 and heparan sulfate at rest and after exercise↓	[35]
AE	Overweight or obese postmenopausal women	4 months; walking; 1 h/session; 2 sessions/week; low intensity	SOD, GPx↑	RHI↑	[36]
AE	Patients with symptomatic PAD	12 weeks; intermittent walking; 3 sessions/week; to mild-to-moderate claudication pain	HORAC↑	Endothelial cell apoptosis↓ VEGF-A↑ E-selectin↓	[37]
AE	Fit healthy young men	3 months; running; 1 h/session; 4 sessions/week; 70–80% VO_2max	Circulating antioxidants↓	ACh-induced EDD↓ NO-dependent basal flow↓	[38]
AE	Healthy young men	12 weeks; cycling; 30 min/session; 5–7 sessions/week; 25%, 50%, or 75% VO_2max	75% VO_2max: 8-OHdG, MDA-LDL↑	50% VO_2max: ACh-induced and NO-mediated EDD↑	[39]
RE	Obese adult men	12 weeks; 3 sessions/week; circuit RE; 60–80% HRR	TAS↑ OSI↓	NO↑ PWV↓	[64]
RE	Hypertensive elderly women	10 weeks; 2–3 sessions/week; 9 machine-based exercises; OMNI-RES 5–7	MDA↓ TAC↑	Forearm blood flow and vascular conductance↑	[65]
RE	Young healthy adults	Habitual RE ≥ 3 sessions/week for ≥ 6 months	SOD↑ hs-CRP↓	FMD↑	[66]
RE	Midlife/older adults with SBP ≥ 120 mmHg	Inspiratory muscle strength training; 6 weeks; 30 breaths/day; 6 days/week; 75% maximal inspiratory pressure	ROS↓	FMD↑ eNOS, NO↑	[67]
RE	Maintenance hemodialysis patients	Respiratory muscle training; 8 weeks; 3 sessions/week during hemodialysis	MDA↔	Syndecan-1↓ Angiopoietin-2↓ ET-1↓	[68]
RE	Maintenance hemodialysis patients	12 weeks; 3 sessions/week during hemodialysis; 50 min/session; 3 sets of 8–12 repetitions; OMNI-RES 6–8	TBARS↓ TAC↑	NO↑ ADMA↓	[69]
RE	Young African American and Caucasian men	6 weeks; 3 sessions/week; ~60 min/session; split-body RE	8-IsoP↓in African American men	MMP-9↓in African American men	[70]
RE	Competitive male powerlifters	12 weeks; 4 sessions/week; 90–120 min/session; 60–90% 1-RM	Total peroxide concentration, OSI↑ TAC↓	PWV↑	[71]
AE vs. CT	Women with abdominal obesity	3 months; 3 sessions/week; 60 min/session; AE: 50–70% HRmax; CT: RE + AE	AE: GSH, TAS↓ CT: GSH, TAS↔	No between-group difference in eNOS or PWV	[85]
AE vs. CT	Sedentary middle-aged men	12 weeks; 3 sessions/week; AE: cycling at 65% HRR; CT: cycling + RE	Both: LPO, acute GSSG/GSH response↓ CT: GSSG↓	AE: FMD↑ CT: FMD↔	[86]
AE vs. CT	Women with obesity	3 months; 3 sessions/week; AE: cycling at 60–80% HRmax; CT: RE + AE	AE: TBARS↓ CT: TBARS↔	AE: eNOS↑ CT: eNOS↔	[87]
HIIT vs. MICT	Stable CHD patients after coronary stenting	2 weeks; 3 sessions/week; HIIT: 4 × 4 min at 60–80% HRR; MICT: 29 min at 50–60% HRR	HIIT: SOD3↔ MICT: SOD3↓	HIIT: eNOS↑ FMD↑	[94]
HIIT	Young, sedentary obese adults	8 weeks; 3 sessions/week; 4 × 4-min treadmill intervals at 88–92% HRmax	H_2O_2, NOX subunits p22phox and p67phox↓	ACh-stimulated microvascular blood flow↑	[95]
HIIT	HFrEF patients	12 weeks; cycling; 30 min/day; 3 days/week; alternating 40% and 80% VO_2peak intervals	MPO↓ IL-6↓	Endothelial microparticles↓ Vascular endothelial shedding/damage↓	[96]

Table 1 (continued)

Exercise modality	Study Population	Training Protocol	Oxidative Stress-Related Effects	Endothelial Function-Related Effects	Ref
HIIT vs. MICT	Type 2 diabetic patients and sedentary older adults	12 weeks; 3 sessions/week; treadmill walking; HIIT: 80–85% VO_2peak intervals; MICT: 50–65% VO_2peak	HIIT: MDA↓ GPx↑	HIIT: NO↑ FMD↑ Cutaneous reactive hyperemia↑	[97]
HIIT	Post-acute myocardial infarction patients	16 weeks; 2 sessions/week; low- or high-volume HIIT	ox-LDL↓	FMD↑	[98]
Acute AE	Healthy young men	Single bout; cycling; 30 min; 25%, 50%, or 75% VO_2max	75% VO_2max: 8-isoprostane↑	50% VO_2max: NO bioavailability↑ Forearm blood flow↑ Forearm vascular resistance↓	[108]
Acute RE	Healthy regularly trained young men	Single bout; 300 unilateral eccentric knee-extension repetitions; NAC or placebo during 8-day recovery	NAC attenuated endothelial oxidative stress	Placebo: FMD↓ NAC: FMD↔	[111]
Detraining	Older healthy men	> 30 years of endurance exercise followed by 10 days of detraining	TAC↓	$CD34^+$ cells↓	[119]

1-RM, one-repetition maximum; 8-OHdG, 8-hydroxy-2′-deoxyguanosine, *ACh* acetylcholine, *ADMA* asymmetric dimethylarginine. *AE* aerobic exercise, *CHD* coronary heart disease, *CT* combined training, *EDD* endothelium-dependent dilation; *eNOS* endothelial nitric oxide synthase, *ET-1* endothelin-1, *FMD* flow-mediated dilation, *GPx* glutathione peroxidase, *GSH* glutathione, *GSSG* oxidized glutathione; H_2O_2, hydrogen peroxide; HFrEF, heart failure with reduced ejection fraction, *HIIT* high-intensity interval training; *HORAC*, hydroxyl radical antioxidant capacity; HR, heart rate; HRmax, maximal heart rate, *HRR* heart rate reserve, *hs-CRP* high-sensitivity C-reactive protein; IL-6, interleukin-6; IMST, inspiratory muscle strength training; *L-NMMA*, NG-monomethyl-L-arginine, LPO lipid peroxidation; *MDA*, malondialdehyde, *MDA-LDL* malondialdehyde-modified low-density lipoprotein, *MICT* moderate-intensity continuous training, *MMP-9* matrix metalloproteinase-9, *MPO* myeloperoxidase, *NAC* N-acetylcysteine; *NO*, nitric oxide, *NOX*, NADPH oxidase, *OMNI-RES* OMNI resistance exercise scale; *OSI*, oxidative stress index, ox-LDL oxidized low-density lipoprotein; *PAD*, peripheral artery disease; PWV, pulse wave velocity, RE, resistance exercise, RHI reactive hyperemia index, ROS reactive oxygen species, SBP systolic blood pressure, *SH-groups* sulfhydryl groups, *SOD* superoxide dismutase, *SOD2* superoxide dismutase 2, *SOD3* superoxide dismutase 3, *TAC* total antioxidant capacity, *TAS* total antioxidant status, TBARS, thiobarbituric acid-reactive substances, VEGF-A vascular endothelial growth factor A, *VO_2AT* oxygen uptake at anaerobic threshold, *VO_2max* maximal oxygen uptake, *VO_2peak,* peak oxygen uptake

high-fat-diet-induced obese mice, voluntary AE restores NO bioavailability by attenuating endothelial oxidative stress and inhibiting the activation of the NLRP3 inflammasome in coronary arterioles [50]. This suggests that the interruption of the reciprocal amplification between oxidative stress and inflammation may be fundamental to the endothelial protective effects of AE.

Sirtuin 1 (SIRT1) represents another key target through which AE regulates oxidative stress and endothelial function [51]. AE activates the SIRT1/AMPK signaling pathway, inhibits oxidative stress mediated by NOX1/LOX-1, suppresses inflammation driven by extracellular signal-regulated kinase (ERK)/NF-κB, and reduces mitochondria-dependent endothelial apoptosis, thereby mitigating aortic endothelial injury induced by hyperhomocysteinemia [52]. In spontaneously hypertensive rats, maternal AE during gestation downregulates NOX4 transcription via SIRT1-mediated deacetylation of histone H3 lysine 9, decreases vascular ROS production in progeny, and enhances NO-mediated EDD, suggesting a potential transgenerational protective effect of AE against vascular oxidative stress and endothelial dysfunction [53]. With long-term adaptation to AE, the role of SIRT1 in EDD diminishes, and a SOD-centered antioxidant defense mechanism becomes predominant, indicating a shift in the vasculature from stress adaptation to homeostatic remodeling [54]. As one of the earliest antioxidant enzymes to respond to intracellular ROS, SOD is particularly responsive to AE stimulation [55, 56]. Regular AE enhances the expression of various vascular SOD isoforms, including Cu/Zn-SOD (SOD1), Mn-SOD (SOD2), and extracellular SOD (EC-SOD/SOD3). Concurrently, it downregulates the expression of NOX2 and diminishes vascular sensitivity to Ang II [57].

Recent evidence further indicates that AE upregulates the shear stress-responsive transcription factor KLF2 in the vascular endothelium of diabetic mice. KLF2 subsequently promotes eNOS coupling and phosphorylation through the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway and heat shock protein 90, thereby enhancing NO bioavailability, improving EDD and FMD, and reducing arterial oxidative stress [27]. Additionally, uncoupling protein 2 (UCP2), a crucial mitochondrial antioxidant, is integral to AE-induced endothelial protection. AE increases UCP2 expression and NO production in the hearts of apolipoprotein E-deficient ($ApoE^{-/-}$) mice, suppresses ROS generation in coronary arterioles, and reduces the expression of ER stress-related

Table 2 Effects of different exercise modalities on oxidative stress and endothelial function in animal models

Exercise Modality	Animal Model	Training Protocol	Oxidative Stress-Related Effects	Endothelial Function-Related Effects	Key Pathways/Targets	Ref
AE	Endothelial-specific AMPKα1 knockout mice and WT controls	7 weeks; voluntary wheel running; ~3 km/day	WT: ROS, 3-NT, NOX2↓ Nrf2, HO-1, UCP-2↑ AMPKα1 deficiency: ROS, NOX2↑	WT: NO bioavailability and ACh-induced EDD↑ AMPKα1 deficiency: eNOS uncoupling↑	AMPKα1-mediated vascular protection	[43]
AE	db/db diabetic mice and high-fat diet-induced obese mice	5 weeks; treadmill running; 30 min/day; 6 days/week; 5–8 m/min; moderate intensity	ROS↓ ER stress↓	Aortic ACh-induced EDD and mesenteric artery FMD↑	AMPK/PPARδ axis activation	[45]
AE	AMPKα2$^{-/-}$ mice and WT controls	6 weeks; treadmill running; 90 min/day; 5 days/week; 9 m/min	WT: SOD2, CAT↑ AMPKα2 deficiency: antioxidant adaptation abolished	WT: ACh-induced EDD, eNOS, p-eNOS↑ AMPKα2 deficiency: endothelial improvement attenuated	AMPKα2-mediated endothelial and mitochondrial protection	[46]
AE	Aged Fisher 344 rats	12 weeks; treadmill running; 8–20 m/min; 30–60 min/day; 10° incline	ROS, 3-NT, MDA↓ Mitochondrial ROS↓ SOD2, ALDH-2↑	ACh-induced EDD↑ PWV↓	Mitochondrial function maintenance	[48]
AE	Aged C57BL/6 mice with normal chow or Western diet	3–27 months; voluntary wheel running	Aortic and mitochondrial ROS↓ Pro-inflammatory cytokines↓	ACh-induced and NO-mediated EDD↑ PWV↓	Suppression of mitochondrial oxidative stress and inflammation	[49]
AE	HHcy C57BL/6 mice induced by 1% L-methionine	14 weeks; treadmill running; 60 min/day; 5 days/week; 6–10 m/min; moderate intensity	NOX1, LOX-1↓ MDA↓ SOD↑	ICAM-1,VCAM-1↓ Bax/Bcl-2, activated caspase-3↓	SIRT1/AMPK axis activation	[52]
AE	Pregnant SHR rats and hypertensive offspring	GD1–GD20; swimming; 60 min/day after gradual adaptation	NOX4, ROS↓ MDA↓ GPx, SOD↑	ACh-induced and NO-mediated EDD↑ eNOS, p-eNOS↑	SIRT1-mediated H3K9 deacetylation	[53]
AE	Male C57BL/6J mice; adipose resistance arteries exposed to acute high intraluminal pressure	2 weeks; voluntary wheel running; ~6 km/day	NOX2 subunits gp91phox/p47phox↓ SOD 1/2/3↑	FMD↑ Ang II sensitivity↓	SOD/H_2O_2-dependent vasodilation	[57]
AE	db/db diabetic mice	4 weeks; treadmill running; 30 min/day; 6 days/week; 5–8 m/min	ROS↓ Nitrotyrosine↓	ACh-induced EDD↑ FMD↑ NO bioavailability↑	KLF2/eNOS/NO axis activation	[27]
AE	Obese Zucker rats	8 weeks; treadmill running; 60 min/day; 5 days/week; 60–70% maximal running speed; 5% incline	tPVAT and aortic ROS↓ NOX2↓ SOD↑ Pro-inflammatory cytokines↓	ACh-induced EDD↑ tPVAT-mediated vasodilatory effect↑ NO bioavailability↑	Suppression of tPVAT oxidative stress and inflammation	[61]
AE	db/db diabetic mice	8 weeks; treadmill running; 60 min/day; 5 days/week; 10 m/min	tPVAT and aortic ROS↓	NO↑ ICAM-1, VCAM-1↓	Suppression of tPVAT oxidative stress and inflammation	[62]
RE	Rat CRT model	8 weeks; ladder climbing; 5 days/week; 3 bouts/day; 2 min/bout; 10–70% body weight tail load	ROS↓ MDA↓ HO-1↑	Endothelial oxidative injury↓ CRT incidence↓	miR-92a-3p downregulation	[73]
RE	Male Wistar rats with sham or femoral arteriovenous BFR model	4 weeks; ladder climbing; 3 sessions/week; 6 sets × 10 repetitions; 50% maximum loaded weight	ROS↓	ACh-induced EDD↑	NO/ROS balance	[81]

Table 2 (continued)

Exercise Modality	Animal Model	Training Protocol	Oxidative Stress-Related Effects	Endothelial Function-Related Effects	Key Pathways/Targets	Ref
CT	Male Wistar rats with myocardial infarction-induced heart failure	8 weeks; 5 days/week; 1 h/day; alternating treadmill AE and ladder RE; AE: 50–60% maximal speed; RE: 40–60% maximal load	tPVAT ROS↓ Pro-inflammatory cytokines↓ IL-10↑	NO bioavailability↑ tPVAT anticontractile function↑ MCP-1↓	NE/β3-AR/adiponectin/AMPK/eNOS/NO pathway	[88]
HIIT	ApoE$^{-/-}$ mice with early atherosclerosis	12 weeks; treadmill running; 5 days/week; 60 min/session; MICT: 45–55% maximal aerobic speed, 8–12 m/min; HIIT: 70–80% maximal aerobic speed, 15–25 m/min intervals	SOD↑ GPx↑ MDA↓	eNOS↑ ACh-induced EDD↑	PCSK9/TRX/TXNIP/NLRP3/GSDMD-N pathway	[99]
HIIT	Spontaneously hypertensive rats	12 weeks; treadmill running; 5 days/week; 60 min/session; MICT: 45–55% VO_2max, 14–16 m/min; HIIT: 70–80% VO_2max, 45–55 m/min intervals	SOD, GPx, CAT↑ NOX4↓ 8-OHdG↓	p-eNOS/eNOS↑ iNOS↓ ACh-induced EDD↑	AMPKα/SIRT1 axis activation	[100]

3-NT, 3-nitrotyrosine, *8-OHdG*, 8-hydroxy-2′-deoxyguanosine, *ACh* acetylcholine, *AE* aerobic exercise, *ALDH2* aldehyde dehydrogenase 2, *AMPK*, *AMP*-activated protein kinase, Ang II, angiotensin II; ApoE, apolipoprotein E; Bcl-2, B-cell lymphoma 2; BFR, blood flow restriction, *CAT* catalase, *CRT* cerebral radiation-induced toxicity, *CT* combined training, *EDD* endothelium-dependent dilation; eNOS, endothelial nitric oxide synthase, *ER* endoplasmic reticulum, *FMD* flow-mediated dilation, *GD* gestational day, *GPx* glutathione peroxidase, *GSDMD-N* N-terminal gasdermin D, H_2O_2 hydrogen peroxide, *H3K9* histone H3 lysine 9; HFD, high-fat diet; HHcy, hyperhomocysteinemia, *HIIT* high-intensity interval training, *HO-1*, heme oxygenase-1, *ICAM-1* intercellular adhesion molecule-1, *IL-10* interleukin-10, *iNOS* inducible nitric oxide synthase; KLF2, Krüppel-like factor 2, *LOX-1* lectin-like oxidized low-density lipoprotein receptor-1; MCP-1, monocyte chemoattractant protein-1, *MDA* malondialdehyde, *MICT* moderate-intensity continuous training; miR, microRNA, *NE* norepinephrine; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3, *NO* nitric oxide, *NOX* NADPH oxidase, *Nrf2* nuclear factor erythroid 2-related factor 2, *PCSK9* proprotein convertase subtilisin/kexin type 9; p-eNOS, phosphorylated endothelial nitric oxide synthase; PPARδ, peroxisome proliferator-activated receptor δ, *PWV* pulse wave velocity, *RE* resistance exercise, *ROS* reactive oxygen species, *SHR* spontaneously hypertensive rat, *SIRT1* silent information regulator 1; SOD, superoxide dismutase, *SOD* superoxide dismutase *tPVAT* thoracic perivascular adipose tissue; TRX, thioredoxin; TXNIP, thioredoxin-interacting protein *UCP2* uncoupling protein 2 *VCAM-1* vascular cell adhesion molecule-1, *VO_2max* maximal oxygen uptake, *WT* wild-type, *β3-AR*β3-adrenergic receptor

proteins, components of the Trx-interacting protein (TXNIP)/NLRP3 inflammasome pathway, and BCL-2-associated X protein, thereby alleviating UCP2 deficiency- and ER stress-associated endothelial dysfunction [58]. The expression of endothelial UCP2 is modulated by the upstream transcription factor KLF2 [59]; however, the interplay between KLF2 and UCP2 in response to AE training remains inadequately understood. Oxidative stress and inflammation within perivascular adipose tissue (PVAT) are increasingly recognized as important contributors to endothelial dysfunction [60]. AE improves aortic endothelial function in rats with metabolic syndrome by suppressing oxidative stress and inflammation in thoracic PVAT (tPVAT), enhancing eNOS/NO signaling, and strengthening antioxidant defenses [61]. Furthermore, AE also reduces the expression of endothelial adhesion molecules, including ICAM-1 and VCAM-1, by attenuating oxidative stress and inflammation in tPVAT [62]. Collectively, these findings suggest that regular AE enhances vascular redox homeostasis and endothelial function through multiple molecular pathways, underscoring its potential as an effective vasoprotective intervention.

Regular RE Training

RE, a type of physical activity characterized by skeletal muscle contraction against external resistance, enhances antioxidant defenses and exerts favorable effects on endothelial function [63]. In a study involving obese adult men, a 12-week regimen of circuit RE training was found to increase TAS and NO levels, while simultaneously reducing OSI and arterial stiffness, thereby contributing to improved vascular health [64]. Similarly, a 10-week RE program was observed to mitigate oxidative stress in older women with hypertension, enhance forearm vasodilation, and reduce blood pressure both at rest and during static handgrip exercise [65]. Furthermore, RE has been demonstrated to prevent the decline in FMD following high-glucose or high-fat meals, with this protective effect being closely linked to a low baseline inflammatory status and elevated SOD activity in physically active individuals [66]. Beyond conventional RE, respiratory muscle strength training may also offer vascular benefits. In middle-aged and older adults with above-normal baseline systolic blood pressure, a 6-week program of high-resistance inspiratory muscle strength

training improves blood pressure and endothelial function. In vitro investigations utilizing human umbilical vein ECs have found that exposure to post-training serum enhances NO production, which is correlated with increased eNOS activity and decreased ROS levels [67]. Another study reported that respiratory muscle strength training attenuates glycocalyx damage and abnormal angiogenesis in patients undergoing maintenance hemodialysis, while also aiding in blood pressure regulation by reducing endothelin-1 (ET-1) levels; however, it does not significantly impact markers of endothelial activation or oxidative stress [68]. Conversely, a 12-week regimen of whole-body RE has been shown to improve redox status and inflammatory profiles, enhance NO bioavailability, and reduce asymmetric dimethylarginine concentrations in these patients [69]. Additionally, whole-body RE enhances muscle strength [69], which may be an important contributor to endothelial improvement. In young men, regular RE reduces oxidative stress and circulating MMP-9 levels; gains in muscle strength, assessed by one-repetition maximum, are positively associated with reductions in MMP-9, suggesting that strength gains may help maintain vascular health [70]. Although RE is generally considered safe for individuals with cardiovascular diseases, caution is advised against excessive training intensity. Evidence indicates that a 12-week regimen of high-intensity RE can elevate total peroxide levels and reduce total antioxidant capacity, thereby contributing to aortic stiffness through the exacerbation of oxidative stress [71].

Animal studies directly examining the mechanisms by which RE influences oxidative stress and endothelial function remain sparse. In hypertensive and ovariectomized rat models, RE has been shown to lower arterial blood pressure and oxidative stress by enhancing autonomic regulation and increasing GPx activity, demonstrating greater efficacy than AE in boosting GPx activity and reducing oxidized GSH levels [72]. Furthermore, RE mitigates vascular oxidative stress and thrombosis by downregulating miR-92a-3p, upregulating HO-1, and inhibiting the p38 MAPK/NF-κB pathway [73]. Studies utilizing cardiovascular disease models, particularly those focusing on myocardial infarction, have demonstrated that regular RE training modulates oxidative stress through various molecular pathways, including the TGF-β1/Smad2/3 [74], AMPK/PGC-1α [75], and AMPK/SIRT1 axes [76]. While endothelial function is not directly evaluated in these studies, the identified antioxidant pathways offer significant mechanistic insights and necessitate further validation in models of endothelial injury.

Low-load RE combined with blood flow restriction (LLRE-BFR) has recently attracted considerable attention as an alternative strategy for individuals in whom high-load RE (HLRE) is contraindicated or poorly tolerated. Current evidence indicates that LLRE-BFR induces acute increases in endogenous NO production comparable to those elicited by HLRE, while eliciting a relatively attenuated oxidative stress response [77]. However, other studies have reported that a single session of LLRE-BFR does not alter NO bioavailability nor induce redox imbalance, although SOD activity remains significantly lower than that observed following HLRE [78]. Regarding the degree of BFR, LLRE with partial BFR exerts more favorable effects on oxidative stress regulation compared to either HLRE or total BFR [79]. Consistent with this observation, partial BFR increases oxidative stress under resting conditions and amplifies the oxidative stress response to moderate-intensity RE; however, when combined with LLRE, it attenuates oxidative stress [80]. Animal studies further demonstrated that 4 weeks of LLRE, with or without the incorporation of BFR, improves aortic endothelial function. The protective effect observed with BFR appears to be primarily mediated by a reduction in ROS production, whereas the benefits associated with LLRE are largely attributed to increased NO production [81]. Taken together, available findings do not yet establish whether BFR-assisted RE is more effective at reducing oxidative stress and enhancing endothelial function, warranting further investigation.

Combined AE and RE Training

Combined training (CT), which integrates AE and RE, emerges as a promising approach for enhancing endothelial function and vascular health. Current physical activity guidelines recommend supplementing regular AE with muscle-strengthening exercises targeting all major muscle groups at least twice weekly. This combined prescription reflects the complementary contributions of AE and RE to chronic disease prevention and management [82]. In individuals with peripheral artery disease, a single session of either AE or CT yields similar improvements in lower-limb blood flow and vascular resistance; however, CT exerts a greater effect on reducing oxidative stress [83]. In obese women, an 8-week CT program proves more effective than either AE or RE alone in improving body composition and vascular elasticity, showing endothelial benefits associated with reduced interleukin-8 (IL-8) and increased IL-10 levels [84]. Among women with abdominal obesity, CT prevents the reductions in GSH and TAS observed after AE, despite its comparable effects on endothelial function and arterial stiffness [85]. This observation suggests that CT may enhance vascular health without significantly depleting antioxidant defenses. Nonetheless, the evidence remains inconsistent. In middle-aged men, AE is more effective than CT in improving FMD, although CT more strongly attenuates acute exercise-induced oxidative stress and monocyte/macrophage inflammatory activity [86]. In obese women, both

AE and CT improve lipid metabolism, yet only AE reduces thiobarbituric acid-reactive substances and increases eNOS activity [87]. Evidence from an animal study shows that 8 weeks of CT reinstates the protective anticontractile function of tPVAT in rats with myocardial infarction-induced heart failure [88]. This restoration is linked to adipocyte browning, reduced oxidative stress and inflammation, and activation of the norepinephrine (NE)/β3-adrenoceptor (β3-AR)/adiponectin/AMPK/eNOS/NO signaling pathway [88]. However, the study does not provide a direct comparison of CT with either AE or RE alone. Overall, CT may offer complementary redox and vascular advantages; nonetheless, whether it surpasses single-modality exercise in reducing oxidative stress and enhancing endothelial function remains to be conclusively determined.

High-Intensity Interval Training

HIIT involves alternating short bursts of intense exercise with recovery periods. As a form of AE, HIIT may provide a time-efficient alternative or complement to traditional moderate-intensity continuous training (MICT). Accumulating evidence suggests that HIIT exerts effects comparable to or even superior to those of MICT in improving vascular endothelial function [89–91], potentially due to its beneficial regulation of oxidative stress [92]. Acute HIIT elicits lower pro-oxidant and pro-thrombotic responses than MICT, indicating a more favorable vascular-adaptive and protective profile [93]. For those with stable coronary artery disease, a 2-week regimen of HIIT following stenting has been shown to increase eNOS expression more effectively than MICT, while preserving SOD3 activity and FMD [94]. Furthermore, long-term HIIT confers vascular benefits. In young sedentary adults with obesity, obesity-related skeletal muscle microvascular endothelial dysfunction is associated with excessive NOX-derived H_2O_2 and $O_2^{\bullet-}$ production; an 8-week HIIT program reduces ROS levels by downregulating NOX subunit expression and restores microvascular endothelial function to levels comparable to those in lean individuals [95]. In patients suffering from heart failure with reduced ejection fraction, a 12-week regimen of HIIT has been shown to decrease levels of MPO and IL-6, thereby attenuating oxidative stress, suppressing systemic inflammation, and alleviating endothelial injury [96]. Similarly, in individuals with type 2 diabetes, a 12-week HIIT program has been demonstrated to enhance FMD, reduce oxidative stress, and improve NO bioavailability more effectively than MICT [97]. In patients who have experienced an acute myocardial infarction, a 16-week HIIT intervention results in dose-dependent increases in FMD, reductions in ox-LDL levels, and decreases in carotid intima-media thickness, with improvements in FMD inversely correlated with ox-LDL levels. Notably, low-volume HIIT, involving less than 10 min of high-intensity exercise per session, is sufficient to initiate protective endothelial adaptations [98]. Mechanistic evidence from animal studies further supports these findings. In $ApoE^{-/-}$ mice with early atherosclerosis, both 12-week HIIT and MICT improve vascular endothelial function by downregulating proprotein convertase subtilisin/kexin type 9 expression, reducing oxidative stress, and suppressing the TRX/TXNIP/NLRP3/gasdermin D N-terminal inflammatory pathway. Notably, HIIT more effectively upregulates eNOS expression and enhances EDD [99]. In spontaneously hypertensive rats, both a 12-week HIIT regimen and a 12-week MICT regimen ameliorate endothelial dysfunction by inhibiting NLRP3-mediated pyroptosis, with HIIT demonstrating superior antioxidant effects through a more pronounced activation of the AMPKα/SIRT1 signaling pathway [100].

Acute and Strenuous Exercise

Acute or strenuous exercise exerts bidirectional and dose-dependent effects on oxidative stress and endothelial function. A single bout of acute exercise may transiently increase oxidative stress, as evidenced by a temporary reduction in antioxidant capacity and an increase in oxidative damage markers [101]. However, these alterations are generally short-lived and reversible, returning to baseline levels within several hours [102]. Within a physiological range, exercise-induced redox perturbations may serve as adaptive stimuli, activating endogenous antioxidant defense systems and facilitating the remodeling of redox homeostasis [103]. For instance, animal studies have demonstrated that a single bout of moderate-intensity AE improves aortic EDD by increasing NO bioavailability, accompanied by controlled ROS generation and elevated activities of SOD and CAT [104, 105]. Research on human subjects has demonstrated that sedentary individuals exhibit elevated NOX-dependent $O_2^{\bullet-}$ levels and diminished eNOS expression in $CD34^+$ circulating progenitor cells in comparison to those who engage in endurance training. Notably, a single bout of moderate-intensity AE can mitigate the abnormal elevation of $O_2^{\bullet-}$ within these cells [106]. In addition, engaging in a single bout of AE on the day prior has been shown to prevent oxidative stress induced by a high-fat meal in $CD31^+$ circulating angiogenic cells. This suggests that acute exercise may contribute to the maintenance of endothelial homeostasis by protecting endothelial repair-related circulating cells [107].

However, when the intensity of exercise surpasses an individual's adaptive capacity, oxidative stress may be exacerbated and adversely affect endothelial function. In healthy young men, acute moderate-intensity AE has been observed to enhance forearm blood flow and decrease

vascular resistance by increasing NO bioavailability. In contrast, high-intensity AE significantly increases the oxidative stress marker 8-isoprostane [108]. In healthy trained individuals, a single bout of exhaustive high-intensity AE increases the markers of endothelial glycocalyx shedding and circulating ECs. These alterations are closely associated with a post-exercise reduction in total antioxidant capacity [109]. The oxidative stress induced by acute AE appears to be primarily dependent on exercise intensity, and improvements in FMD are strongly associated with achieving a sufficient level of energy expenditure, such as the caloric equivalent of 30 min at 50% VO_2peak [110]. These findings indicate that the effects of acute AE on oxidative stress and endothelial function are jointly regulated by exercise intensity and energy expenditure. Furthermore, a single bout of high-intensity eccentric RE significantly reduces FMD within 48 h post-exercise in healthy young men. However, pretreatment with the antioxidant N-acetylcysteine partially attenuates this decline, indicating the contributory role of oxidative stress in acute RE-induced endothelial dysfunction [111]. The ability to maintain endothelial function in response to acute high-intensity exercise is strongly influenced by the training status of the individual. Subcutaneous adipose microvascular EDD is preserved after a single bout of high-intensity RE in individuals with chronic training, whereas it is significantly compromised in sedentary individuals. This protective effect may be attributed to a transition from NO-mediated to H_2O_2-mediated vasodilation [112]. A similar phenomenon is observed after AE training. An 8-week AE regimen induces a transition from NO-dependent to H_2O_2-dependent microvascular dilation in overweight and obese sedentary adults, thereby preserving endothelial function after acute high-load exercise [113]. Moreover, following a single high-intensity AE session, there is an increase in NO bioavailability and antioxidant status in both endurance-trained and sedentary healthy men. However, the NO response is more sustained in endurance-trained individuals, which is associated with a larger brachial artery diameter and higher peak blood flow [114]. Overall, these findings indicate that the adverse oxidative and endothelial responses to acute exercise intensify with increasing exercise intensity but are mitigated in better-trained individuals.

Detraining

Detraining is defined as the partial or complete loss of physiological adaptations acquired through exercise training, occurring after the cessation of regular exercise or a significant reduction in training load. Current evidence suggests that the improvements in endothelial function induced by exercise training are not permanently sustained [115]. The endothelial protective effects of AE, RE, and CT can disappear after 1 month of detraining [116]. In healthy young adults, the increase in NO and the decrease in ET-1 following 8 weeks of AE are maintained for up to 4 weeks after training cessation, but revert to baseline levels after 8 weeks of detraining [117]. In patients with atrial fibrillation, 6 months of aerobic interval training reduces circulating von Willebrand factor and IL-1β levels, thereby enhancing endothelial function. Although these benefits are maintained with continued training for up to 1 year, the thrombogenic markers return to baseline levels following detraining [118]. From a mechanistic perspective, short-term detraining may diminish the vascular protective effects of long-term exercise by reducing antioxidant capacity, disrupting redox homeostasis, and altering the abundance and senescence status of $CD34^+$/$VEGFR2^+$ endothelial progenitor cells [119].

The impact of detraining on adaptations related to oxidative stress is influenced by the type of exercise and the presence of disease. In healthy older adults, a 12-week period of detraining does not fully negate the enhancements in oxidative stress biomarkers and NO bioavailability achieved through 12 weeks of RE [120, 121]. This suggests that the antioxidant adaptations induced by RE may persist beyond the cessation of training. Conversely, in healthy older men, the protective effects against oxidative stress conferred by 16 weeks of AE are entirely lost following a similar period of detraining [122]. This indicates that the antioxidant adaptations resulting from RE may be more enduring than those from AE in healthy populations. However, exercise-induced redox adaptations appear to be highly reversible in the presence of diseases. For instance, in older patients with chronic obstructive pulmonary disease, the beneficial effects of 12 weeks of RE on systemic oxidative damage and antioxidant capacity are not maintained after detraining [123]. In individuals with coronary artery disease, an 8-month regimen of regular exercise training significantly enhances health outcomes; however, a mere 3-month period of detraining is adequate to negate these positive effects [124]. These findings collectively indicate that the antioxidant and endothelial protective benefits conferred by exercise are highly reversible, especially in the context of pathological conditions such as cardiovascular diseases, thereby underscoring the critical importance of sustained exercise adherence for maintaining vascular health. Additionally, animal studies have demonstrated that exercise-induced antioxidant adaptations are more enduring in male rats [125], suggesting that sex differences may influence detraining-related changes in redox homeostasis. This issue requires further investigation.

Combined Effects of Exercise and Antioxidant Interventions on Oxidative Stress and Endothelial Function

Regular exercise enhances vascular endothelial function by strengthening antioxidant defenses and reducing oxidative stress; specific antioxidant interventions may further influence exercise-related vascular adaptations. Research suggests that acute elevations in oxidative stress or oscillatory/retrograde shear stress induced by exercise can temporarily impair post-exercise FMD, while acute vitamin C administration can prevent this decline [126, 127]. Pre-exercise supplementation with polyphenol-rich jaboticaba berry juice has been shown to maintain GSH levels and limit excessive ROS production, thereby attenuating transient macrovascular and microvascular dysfunction within 48 h following eccentric exercise [128]. In healthy trained individuals, short-term supplementation with reduced coenzyme Q10 enhances antioxidant capacity, mitigates strenuous exercise-induced oxidative damage, and preserves NO homeostasis [129]. *Lycium barbarum* polysaccharide supplementation activates Nrf2 antioxidant signaling and upregulates its downstream targets, including GCLC, NQO1, and GCLM, while reducing serum malondialdehyde (MDA), Ang II, and tumor necrosis factor-α (TNF-α) levels, thereby attenuating oxidative stress, inflammation, and apoptosis in the thoracic aorta and myocardium of rats subjected to exhaustive exercise [130]. These results indicate that antioxidant interventions could potentially alleviate oxidative stress-mediated endothelial injury under acute or strenuous exercise conditions.

The combination of exercise with antioxidant-based nutritional strategies may offer synergistic vascular protection. In healthy postmenopausal women, an 8-week regimen of RE combined with fish oil supplementation has been found to more effectively reduce blood pressure, triglycerides, TNF-α, IL-6, and oxidative stress markers more effectively than RE alone [131]. Additionally, in women with type 2 diabetes, an 8-week program of CT with astaxanthin supplementation proves more efficacious than either intervention alone in decreasing oxidative stress, inflammation, and metabolic dysfunction. These benefits may be attributed to the upregulation of humanin and the microRNA-mediated regulation of mitochondrial function, insulin signaling, lipid metabolism, and homeostasis [132]. Animal studies have demonstrated that AE combined with polyphenol antioxidant nutrition provides vascular protection superior to that provided by either intervention alone. This is evidenced by decreased aortic MDA and protein carbonyl levels; increased activities of antioxidant enzymes, including SOD, CAT, and GPx; and enhanced eNOS/NO signaling, thereby mitigating oxidative stress and improving endothelial function [133, 134]. In aged rats with type 2 diabetes, an 8-week regimen of AE or RE combined with ursolic acid supplementation modulates the SIRT1-eNOS signaling pathway and elevates total antioxidant capacity, partially reversing increased aortic oxidative stress and diminished NO bioavailability [135]. Furthermore, in aged rats with diet-induced atherosclerosis, an 8-week program of AE combined with Korean red ginseng supplementation suppresses the NF-κB/TNF-α/IL-6/cyclooxygenase-2 inflammatory cascade, enhances eNOS/NO signaling, and reduces the expression of 4-hydroxynonenal, ICAM-1, and VCAM-1. This combined intervention appears to yield more favorable endothelial outcomes compared with either intervention alone [136].

Nonetheless, the combination of exercise and antioxidant-based nutritional interventions does not invariably yield additional benefits. In rats with metabolic disorders, a regimen of 7 weeks of AE or supplementation with 2% taurine independently enhances aortic SOD3, decreases $O_2^{\bullet-}$ production and vascular oxidative stress, and improves EDD; however, their combination fails to confer additional improvement [137]. Moderate exercise-induced oxidative stress facilitates adaptive vascular protection by upregulating CAT and eNOS expression. In contrast, vitamin E supplementation negates exercise-induced increases in antioxidant enzyme levels and eNOS expression, suggesting that excessive antioxidant supplementation may disrupt beneficial exercise-mediated redox adaptations [138, 139]. Previous studies reported that antioxidant supplementation can attenuate some health-promoting effects of exercise in humans [140]. This observation does not detract from the potential benefits of antioxidant-rich nutrition; instead, it underscores the critical importance of considering timing, dosage, and physiological context. In summary, the integration of exercise with targeted antioxidant-based nutritional interventions may offer synergistic vascular protection; however, it also poses the potential risk of disrupting beneficial exercise-induced redox adaptations. Consequently, a dietary approach rich in phytonutrients may be more suitable during exercise training than high-dose antioxidant supplementation.

Clinical Implications

Exercise-induced changes in endothelial function reflect a dose- and context-dependent balance between adaptive redox signaling and excessive oxidative stress. The evidence synthesized in this review supports regular, appropriately dosed exercise as a core strategy for improving endothelial function. Low-to-moderate-intensity AE has the most consistent support from clinical studies, whereas HIIT may offer an alternative aerobic strategy to MICT for

selected individuals [37, 94, 97]. RE and CT may also be considered according to individual needs; however, available trials have not established their superiority over AE or identified a single optimal exercise dose across populations [64, 85]. Exercise modality and dose should therefore be individualized according to training status, disease burden, functional capacity, and tolerance. Exercise progression should be carefully managed to prevent workloads from exceeding individual adaptive capacity. Acute exhaustive exercise and prolonged strenuous exercise warrant particular caution, especially in untrained or clinically vulnerable individuals [38, 111, 112]. Sustained training is important because endothelial benefits may diminish after detraining [116]. Routine antioxidant supplementation solely to enhance exercise-induced endothelial adaptations is not supported by consistent evidence, and some regimens may attenuate beneficial redox adaptations [126, 140]. The characteristics and principal findings of the randomized controlled trials informing these clinical implications are summarized in Table 3.

Limitations

Although we used a structured search, prespecified eligibility criteria, and manual reference screening, the synthesis remained narrative. It lacked formal risk-of-bias and evidence-certainty assessments and meta-analysis, precluding pooled effect estimates. Subjectivity in study selection and interpretation, as well as selection and publication bias, cannot be excluded. Substantial heterogeneity in participant characteristics, baseline training status, exercise protocols, follow-up duration, sampling time points, and redox and endothelial assessments limits cross-study comparisons, generalizability, and dose–response inference. Evidence is uneven, with fewer studies of RE (with or without BFR), CT, detraining, and exercise combined with antioxidant interventions than of AE. Direct modality comparisons are limited, and some studies lack endothelial function measures. Mechanistic evidence derives mainly from animal models, whereas human studies generally have small samples and short intervention and follow-up periods. They also rely largely on circulating biomarkers and vascular function measures as surrogate endpoints and rarely assess major cardiovascular events. Consequently, causal links between endothelial cell-specific redox changes and long-term cardiovascular benefits remain uncertain. Findings on detraining and antioxidant interventions also vary with exercise protocols and individual characteristics. Accordingly, our conclusions should be interpreted cautiously when extrapolated to specific populations or used to inform precision exercise prescriptions.

Knowledge Gaps

A key remaining knowledge gap concerns the exercise dose at which redox responses shift from adaptive signaling to excessive oxidative stress in different populations. How exercise modality and dose determine this transition, and how age, sex, disease status, baseline redox status, and baseline training status modify this threshold, remain unclear. The relative effects of different exercise modalities also remain uncertain. Direct comparative evidence is currently insufficient to determine which single exercise modality or combination of modalities most effectively improves redox homeostasis and endothelial function. A further uncertainty is whether circulating redox biomarkers accurately reflect local endothelial redox status and whether the observed molecular changes causally mediate exercise-induced endothelial adaptation or merely accompany it. The persistence of exercise-induced redox adaptations and endothelial benefits after detraining, its variation across modalities, and the minimum exercise dose required to sustain these effects remain poorly characterized. For antioxidant-based nutritional interventions, the populations most likely to benefit and the optimal nutrient type, dose, and supplementation timing have not been established. The conditions under which these interventions may blunt beneficial exercise adaptations also remain uncertain. More importantly, long-term evidence remains insufficient to determine whether short-term improvements in endothelial redox homeostasis and function translate into a reduced risk of major cardiovascular events.

Future Directions

Future research should advance across three interconnected domains: mechanistic validation, study design, and clinical translation. Mechanistically, endothelial cell-specific models should be integrated with multi-omics approaches, including single-cell transcriptomics, spatial transcriptomics, and redox proteomics, to define the exercise dose threshold at which adaptive redox signaling shifts to excessive oxidative stress. Targeted perturbation studies within these models should then identify the redox pathways that drive endothelial adaptation. Studies should also determine how exercise-induced redox responses influence endothelial glycocalyx integrity, endothelial progenitor cell function, microcirculatory responses, and perivascular adipose tissue homeostasis, and whether these early changes can serve as sensitive indicators of the endothelial protective effects of exercise.

With respect to study design, adequately powered multicenter randomized controlled trials with standardized

Table 3 Characteristics and principal findings of randomized controlled trials on exercise, redox status, and endothelial function

Exercise intervention	Population and randomized sample	RCT design	Intervention, comparator, and duration	Outcomes assessed	Principal findings
Exercise-only trials					
Regular AE (walking) [37]	Symptomatic PAD; *N* = 114 randomized (38/group); 100 completed	Parallel-group RCT	Home-based or supervised intermittent walking vs. attention control; 12 weeks; ≥3 sessions/week; walking to mild-to-moderate claudication pain	**Redox**: H_2O_2, HORAC, ox-LDL; **Endothelial**: Serum-induced endothelial-cell apoptosis; NF-κB; E-selectin; VEGF-A	Both walking programs reduced endothelial-cell apoptosis vs. control and prevented the control-group increase in NF-κB activity. Pooled exercise improved HORAC, VEGF-A, and E-selectin, whereas H_2O_2 and ox-LDL were unchanged.
Regular RE (circuit training) [64]	Men with obesity, *N* = 25	Parallel-group RCT	Circuit RE vs. no exercise; 12 weeks	Redox: TAS, TOS, OSI; Endothelial/vascular: NO, baPWV	RE increased NO and improved redox status, with a reduction in baPWV.
Regular RE [65]	Older women with hypertension, *N* = 25	Parallel-group RCT	Machine-based RE vs. usual activity; 10 weeks	Redox: MDA, TAC; Endothelial/vascular: FBF, vascular conductance	RE reduced MDA and increased TAC, accompanied by improved FBF and vascular conductance.
Inspiratory muscle strength training [67]	Adults with elevated SBP, *N* = 38; 36 analyzed	Parallel-group RCT	High-resistance inspiratory muscle strength training vs. sham; 6 weeks	Redox: ROS; Endothelial: FMD; serum-treated endothelial-cell NO and eNOS	Training improved FMD and increased endothelial-cell NO/eNOS while reducing ROS.
Respiratory-muscle training [68]	Maintenance hemodialysis patients, *N* = 56; 41 analyzed	Parallel-group RCT	Intradialytic respiratory-muscle training vs. usual care; 8 weeks	Redox: MDA; Endothelial: Syndecan-1, angiopoietin-2, ET-1, and other endothelial biomarkers	Syndecan-1, angiopoietin-2, and ET-1 decreased, whereas MDA was unchanged.
Whole-body RE [69]	Men receiving maintenance hemodialysis, *N* = 55	Parallel-group RCT	Intradialytic whole-body RE vs. control; 12 weeks	Redox: TBARS, TAC; Endothelial: Nitrite, ADMA	RE increased nitrite and TAC and reduced ADMA and TBARS, supporting favorable redox and vascular effects.
Acute RE with or without BFR [78]	Physically active healthy young men, *N* = 11	Randomized crossover RCT	Low-load RE (30% 1-RM) with BFR, low-load RE without BFR, and high-load RE (80% 1-RM); randomized order; 72-hour separation	Redox: SOD, catalase; Endothelial: Plasma NOx (surrogate); no direct functional endothelial endpoint	NOx did not change within conditions and was lower after high-load RE than after BFR-assisted RE. Antioxidant-enzyme responses differed across conditions, precluding a consistent endothelial benefit.
Acute CT vs. AE (walking) [83]	Symptomatic PAD, *N* = 13 (4 men/9 women)	Randomized crossover RCT	Approximately 50-min walking session vs. combined session comprising eight RE exercises plus walking; randomized order; ≥2-day separation	Redox: MDA; Endothelial/vascular: Plasma nitrite; lower-limb blood flow; vascular resistance; reactive hyperemia	Both sessions similarly increased blood flow and reduced vascular resistance; reactive hyperemia was unchanged. CT produced a greater reduction in MDA and uniquely increased nitrite.
Regular CT vs. AE [85]	Postmenopausal women with abdominal obesity, *N* = 101; 85 analyzed	Parallel-group RCT	Supervised AE vs. CT (RE + AE); 3 sessions/week for approximately 12 weeks; no nonexercise control	Redox: GSH, SOD, TAS; Endothelial/vascular: Endothelial biomarkers; PWA/PWV	No significant between-modality difference in endothelial outcomes was detected. GSH and TAS decreased after AE.
Regular CT vs. AE [86]	Untrained sedentary middle-aged men, *N* = 20 (CT 10; AE 10)	Parallel-group RCT	Periodized CT (cycling plus eight RE exercises) vs. moderate-intensity cycling AE; 12 weeks; 3 sessions/week	Redox: GSH, GSSG, GSSG/GSH, LPO; Endothelial: Brachial FMD	FMD increased within the AE group but was unchanged after CT; a direct between-group comparison of FMD change was not clearly reported. Both regimens reduced basal LPO and attenuated the acute GSSG/GSH response; CT also reduced GSSG.
Regular CT vs. AE [87]	Women with obesity, *N* = 44; 39 analyzed	Parallel-group RCT	Supervised AE vs. CT (RE + AE); 3 sessions/week for approximately 12 weeks; no nonexercise control	Redox: TBARS, TAC; Endothelial: eNOS, VEGF	No significant between-modality difference in endothelial outcomes was detected. Within-group eNOS and TBARS changes in AE did not establish superiority over CT.

Table 3 (continued)

Exercise intervention	Population and randomized sample	RCT design	Intervention, comparator, and duration	Outcomes assessed	Principal findings
HIIT vs. MICT [94]	Stable CHD after coronary stenting, *N* = 11	Randomized crossover RCT	Energy-matched HIIT vs. MICT; 2 weeks per condition, separated by a 2-week washout	Redox: Extracellular SOD; Endothelial: FMD, eNOS	HIIT maintained FMD and extracellular SOD and increased eNOS, with more favorable post-intervention values than MICT.
Interval AE vs. continuous AE [97]	Type 2 diabetes; *N* = 45, 43 analyzed	Parallel-group RCT	Interval treadmill AE vs. continuous treadmill AE and sedentary control; 12 weeks	Redox: MDA, GPx, SOD; Endothelial/vascular: FMD; cutaneous reactive hyperemia; NO; von Willebrand factor	Both interval and continuous AE improved FMD and reactive hyperemia, with larger improvements and a more favorable redox profile after interval AE.
Low- vs. high-volume HIIT [98]	Post-acute myocardial infarction, *N* = 80; FMD/ox-LDL assessed in *n* = 78	Parallel-group RCT	Low-volume vs. high-volume HIIT and active-control advice; 16 weeks	Redox: ox-LDL; Endothelial/vascular: FMD, carotid intima–media thickness	Both HIIT volumes improved FMD and ox-LDL vs. active control, with larger changes after high-volume HIIT.
Acute AE at different intensities [108]	Healthy untrained young men, *N* = 8	Randomized within-subject crossover RCT	30-min cycling at 25%, 50%, and 75% VO_2max in randomized order; 1-week separation; L-NMMA testing during the moderate-intensity condition	Redox: 8-isoprostane; Endothelial/vascular: FBF, forearm vascular resistance	Moderate-intensity exercise increased NO-dependent forearm vasodilation without increasing 8-isoprostane. High-intensity exercise increased 8-isoprostane; FBF could not be measured during that condition, limiting direct vascular comparison.
Exercise combined with antioxidant interventions					
Acute eccentric RE with NAC redox modulation [111]	Trained healthy young men, *N* = 10	Randomized crossover RCT	Eccentric RE followed by oral NAC or placebo during an 8-day recovery period	Redox: Oxidative-stress-related responses; Endothelial/vascular: FMD, PWV	NAC preserved postexercise FMD, whereas PWV was unchanged; a direct treatment-by-time comparison for FMD was not reported.
Maximal walking + vitamin C [126]	Intermittent claudication, *N* = 31; vitamin C/saline comparison in maximal-exercise subgroup, *n* = 16	Parallel-group RCT	Intravenous vitamin C vs. saline before maximal walking	Redox: TBARS; Endothelial: FMD, sICAM-1	The postexercise reduction in FMD and increases in TBARS and sICAM-1 observed with saline were not observed with vitamin C; however, a direct between-group interaction was not reported.
Cycling/shear challenge + vitamin C [127]	Aerobically active healthy men, *N* = 12	Randomized crossover RCT	Oral vitamin C vs. placebo before cycling with forearm cuff compression	Redox: Not directly assessed; Endothelial/vascular: FMD; shear indices	Vitamin C prevented the reduction in FMD associated with the experimentally augmented adverse shear pattern.
Eccentric exercise + jaboticaba juice [128]	Healthy young adults, *N* = 24	Parallel-group RCT	Jaboticaba juice vs. placebo for 6 days surrounding eccentric exercise	Redox: GSH; Endothelial/vascular: FMD; hyperemic blood flow; tissue-oxygen reperfusion	Jaboticaba juice preserved GSH and attenuated postexercise impairments in FMD and microvascular responses.

Notes: Sample sizes refer to randomized or allocated participants; parent-study, analyzed, or outcome-specific samples are specified where applicable. Between-group or between-condition comparisons were prioritized when available; otherwise, within-group findings are reported. Some studies assessed endothelial effects using surrogate biomarkers or indirect endothelial assays rather than direct functional endpoints

1-RM, one-repetition maximum, *ADMA* asymmetric dimethylarginine, *AE* aerobic exercise, *AMI* acute myocardial infarction; baPWV, brachial-ankle pulse-wave velocity, *BFR* blood flow restriction, *CHD* coronary heart disease, *CT* combined training; eNOS, endothelial nitric oxide synthase, *ET-1* endothelin-1; FBF, forearm blood flow, FMD flow-mediated dilation, *GPx* glutathione peroxidase, *GSH* glutathione, GSSG oxidized glutathione, *HIIT* high-intensity interval training; *HORAC*, hydroxyl radical antioxidant capacity, L-NMMA, NG-monomethyl-L-arginine, *LPO,* lipid peroxidation, *MDA* malondialdehyde; MICT, moderate-intensity continuous training, *NAC* N-acetylcysteine, *NF-κB* nuclear factor-kappa B, *NO* nitric oxide, *NOx* nitrate plus nitrite, *OSI* oxidative stress index, *ox-LDL* oxidized low-density lipoprotein, *PAD* peripheral artery disease, *PWA* pulse-wave analysis, *PWV* pulse wave velocity; RE, resistance exercise, ROS reactive oxygen species, SBP systolic blood pressure, *sICAM-1* soluble intercellular adhesion molecule 1, *SOD* superoxide dismutase; TAC, total antioxidant capacity, *TAS* total antioxidant status, *TBARS* thiobarbituric acid-reactive substances, *TOS* total oxidant status, *VEGF-A* vascular endothelial growth factor A, *VO_2max* maximal oxygen uptake

reporting of exercise prescriptions, harmonized sampling time points, and consistent assessments of redox status and endothelial function are needed. Direct comparisons of exercise modalities and dose–response studies are needed to determine the relative effects of different modalities and identify safe and effective exercise dose ranges across populations. Evaluations of detraining and maintenance phases should clarify the durability of modality-specific adaptations and determine the minimum exercise dose required to sustain endothelial protection.

For clinical translation, long-term follow-up should determine whether exercise-induced redox adaptations and improvements in endothelial function persist and translate into long-term cardiovascular benefits. Accordingly, study endpoints should extend beyond short-term circulating biomarkers to include macrovascular and microvascular endothelial function, vascular structural changes, and major cardiovascular events. Studies combining exercise with antioxidant-based nutritional interventions should use stratified or factorial designs to identify populations most likely to benefit, determine the optimal nutrient type, dose, and supplementation timing, and define the conditions under which these interventions enhance endothelial protection or blunt beneficial exercise adaptations. Such evidence will support the development of individualized exercise prescriptions.

Conclusions

Overall, current evidence indicates that regular, appropriately dosed exercise improves endothelial function through adaptive redox remodeling. This remodeling involves enhancement of endogenous antioxidant defenses, preservation of eNOS/NO signaling, improvement of mitochondrial homeostasis, and attenuation of crosstalk between oxidative stress and inflammation. The direction and persistence of exercise-induced redox and endothelial responses vary with exercise modality and dose, training status, disease state, nutritional context, and whether training is sustained. By contrast, exercise loads that exceed individual adaptive capacity may provoke excessive oxidative stress and endothelial dysfunction. Taken together, these findings support sustained, individualized exercise as a strategy to promote endothelial redox homeostasis and function. Further research is needed to define safe and effective exercise regimens across populations and determine whether these benefits translate into a reduced risk of major cardiovascular events.

Key References

- Mavraganis G, Sakelliou A, Georgiopoulos G, Delialis D, Papaioannou M, Maneta E, et al. Evidence of a redox-dependent control of vascular function after muscle-damaging exercise in young adults: a randomized placebo-controlled trial. Hellenic J Cardiol. 2025;S1109-9666(25)00182-4. https://doi.org/10.1016/j.hjc.2025.07.007.

  ○ This randomized placebo-controlled trial showed that eccentric resistance exercise transiently reduced FMD, whereas N-acetylcysteine attenuated this impairment. The findings support redox-dependent regulation of endothelial function after acute muscle-damaging exercise in humans.

  Luo JY, Cheng CK, Gou L, He L, Zhao L, Zhang Y, et al. Induction of KLF2 by Exercise Activates eNOS to Improve Vasodilatation in Diabetic Mice. Diabetes. 2023;72:1330–42. https://doi.org/10.2337/db23-0070○ This study demonstrated that exercise-induced KLF2 restores eNOS activity, increases NO bioavailability, and attenuates oxidative stress in diabetic arteries. It provides direct mechanistic evidence linking exercise-mediated shear-stress signaling to endothelial redox protection.

  Liu G, Zhao B, Chen Q, Li X, Zhu X, Duan M, et al. HIIT and MICT mitigate endothelial dysfunction in early atherosclerotic mice via PCSK9 inhibition. Sci Rep. 2025;15:30411. https://doi.org/10.1038/s41598-025-05206-7○ This study showed that both HIIT and MICT improved endothelial function in early atherosclerotic mice, with HIIT producing greater effects. The findings emphasize the role of exercise modality and intensity in vascular redox protection.

- Craige SM, Kaur G, Bond JM, Caliz AD, Kant S, Keaney JF. Endothelial Reactive Oxygen Species: Key Players in Cardiovascular Health and Disease. Antioxid Redox Signal. 2025;42:905–32. https://doi.org/10.1089/ars.2024.0706.

  ○ This review summarizes the context-dependent role of endothelial ROS in vascular signaling and endothelial dysfunction. It provides an important framework for interpreting exercise-induced ROS as adaptive signals when properly regulated but harmful when excessive or uncontrolled.

- Wang J, Zhang J, Zhang H, Yu F, Tian Z, Jia D. Exercise modulates redox homeostasis in cardiovascular and metabolic diseases: from bench to clinic. Cardiovasc Diabetol. 2026;25:127. https://doi.org/10.1186/s12933-026-03131-1.

    ○ This review integrates preclinical and clinical evidence showing that regular exercise improves cardiometabolic health by enhancing antioxidant defenses, reducing oxidative stress and inflammation, and regulating exercise-derived exerkines. It supports the broader concept that exercise preserves vascular function through redox homeostasis.

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Declarations

Competing interests The authors declare no competing interests.

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References

1. Wang J, Zhang J, Zhang H, Yu F, Tian Z, Jia D. Exercise modulates redox homeostasis in cardiovascular and metabolic diseases: from bench to clinic. Cardiovasc Diabetol. 2026;25:127. https://doi.org/10.1186/s12933-026-03131-1.
2. El Assar M, Álvarez-Bustos A, Sosa P, Angulo J, Rodríguez-Mañas L. Effect of Physical Activity/Exercise on Oxidative Stress and Inflammation in Muscle and Vascular Aging. Int J Mol Sci. 2022;23:8713. https://doi.org/10.3390/ijms23158713.
3. Guo W, Wang J, Chang Z, Lin S, Sha G, Wang S, et al. Treadmill exercise ameliorates atherogenesis and vascular inflammation in ApoE-/- mice via circulating exosome-derived let-7c-5p. Sci Rep. 2026;16:585. https://doi.org/10.1038/s41598-025-30174-3.
4. Citrin KM, Chaube B, Fernández-Hernando C, Suárez Y. Intracellular Endothelial Cell Metabolism in Vascular Function and Dysfunction. Trends Endocrinol Metab. 2025;36:744–55. https://doi.org/10.1016/j.tem.2024.11.004.
5. Gao J, Pan X, Li G, Chatterjee E, Xiao J. Physical Exercise Protects Against Endothelial Dysfunction in Cardiovascular and Metabolic Diseases. J Cardiovasc Transl Res. 2022;15:604–20. https://doi.org/10.1007/s12265-021-10171-3.
6. Scioli MG, Storti G, D'Amico F, Rodríguez Guzmán R, Centofanti F, Doldo E, et al. Oxidative Stress and New Pathogenetic Mechanisms in Endothelial Dysfunction: Potential Diagnostic Biomarkers and Therapeutic Targets. J Clin Med. 2020;9:1995. https://doi.org/10.3390/jcm9061995.
7. Craige SM, Kaur G, Bond JM, Caliz AD, Kant S, Keaney JF. Endothelial Reactive Oxygen Species: Key Players in Cardiovascular Health and Disease. Antioxid Redox Signal. 2025;42:905–32. https://doi.org/10.1089/ars.2024.0706.
8. Li X, Zou J, Lin A, Chi J, Hao H, Chen H, et al. Oxidative Stress, Endothelial Dysfunction, and N-Acetylcysteine in Type 2 Diabetes Mellitus. Antioxid Redox Signal. 2024;40:968–89. https://doi.org/10.1089/ars.2023.0524.
9. Huang J, Li P, Shen B, Gao H, Wang S, Wang P, et al. Long-term aerobic exercise enhances circulating exosomal miR-214-3p to promote endothelial progenitor cell-mediated repair of endothelial damage induced by obesity. J Sport Health Sci. 2026;15:101094. https://doi.org/10.1016/j.jshs.2025.101094.
10. Yan R, Zhang X, Xu W, Li J, Sun Y, Cui S, et al. ROS-Induced Endothelial Dysfunction in the Pathogenesis of Atherosclerosis. Aging Dis. 2025;16:250–68. https://doi.org/10.14336/AD.2024.0309.
11. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res. 2000;87:840–4. https://doi.org/10.1161/01.res.87.10.840.
12. Jin S, Kang PM. A Systematic Review on Advances in Management of Oxidative Stress-Associated Cardiovascular Diseases. Antioxid (Basel). 2024;13:923. https://doi.org/10.3390/antiox13080923.
13. Förstermann U, Xia N, Li H. Roles of Vascular Oxidative Stress and Nitric Oxide in the Pathogenesis of Atherosclerosis. Circ Res. 2017;120:713–35. https://doi.org/10.1161/CIRCRESAHA.116.309326.
14. Li H, Förstermann U. Uncoupling of endothelial NO synthase in atherosclerosis and vascular disease. Curr Opin Pharmacol. 2013;13:161–7. https://doi.org/10.1016/j.coph.2013.01.006.
15. Batty M, Bennett MR, Yu E. The Role of Oxidative Stress in Atherosclerosis. Cells. 2022;11:3843. https://doi.org/10.3390/cells11233843.
16. Młynarska E, Kowalik A, Krajewska A, Krupińska N, Marcinkowska W, Motor J, et al. Inflammaging and Senescence-Driven Extracellular Matrix Remodeling in Age-Associated Cardiovascular Disease. Biomolecules. 2025;15:1452. https://doi.org/10.3390/biom15101452.
17. Munno M, Mallia A, Greco A, Modafferi G, Banfi C, Eligini S. Radical Oxygen Species, Oxidized Low-Density Lipoproteins, and Lectin-like Oxidized Low-Density Lipoprotein Receptor 1: A Vicious Circle in Atherosclerotic Process. Antioxid (Basel). 2024;13:583. https://doi.org/10.3390/antiox13050583.
18. Isath A, Koziol KJ, Martinez MW, Garber CE, Martinez MN, Emery MS, et al. Exercise and cardiovascular health: A state-of-the-art review. Prog Cardiovasc Dis. 2023;79:44–52. https://doi.org/10.1016/j.pcad.2023.04.008.
19. Green DJ, Smith KJ. Effects of Exercise on Vascular Function, Structure, and Health in Humans. Cold Spring Harb Perspect Med. 2018;8:a029819. https://doi.org/10.1101/cshperspect.a029819.
20. Man AWC, Li H, Xia N. Impact of Lifestyles (Diet and Exercise) on Vascular Health: Oxidative Stress and Endothelial Function.

Oxid Med Cell Longev. 2020;2020:1496462. https://doi.org/10.1155/2020/1496462.
21. Laufs U, Wassmann S, Czech T, Münzel T, Eisenhauer M, Böhm M, et al. Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis. Arterioscler Thromb Vasc Biol. 2005;25:809–14. https://doi.org/10.1161/01.ATV.0000158311.24443.af.
22. Pierce GL, Donato AJ, LaRocca TJ, Eskurza I, Silver AE, Seals DR. Habitually exercising older men do not demonstrate age-associated vascular endothelial oxidative stress. Aging Cell. 2011;10:1032–7. https://doi.org/10.1111/j.1474-9726.2011.00748.x.
23. Li Q-Q, Qin K-R, Zhang W, Guan X-M, Cheng M, Wang Y-X. Advancements in the Regulation of Different-Intensity Exercise Interventions on Arterial Endothelial Function. Rev Cardiovasc Med. 2023;24:306. https://doi.org/10.31083/j.rcm2411306.
24. Fasipe B, Li S, Laher I. Exercise and vascular function in sedentary lifestyles in humans. Pflugers Arch. 2023;475:845–56. https://doi.org/10.1007/s00424-023-02828-6.
25. Zhang J, Friedman MH. Adaptive response of vascular endothelial cells to an acute increase in shear stress frequency. Am J Physiol Heart Circ Physiol. 2013;305:H894–902. https://doi.org/10.1152/ajpheart.00174.2013.
26. Hejazi P, Mury P, Thorin É, Lettre G. Single-cell transcriptomic analyses of skin vascular endothelial cells in sedentary and voluntary wheel running young mice. Physiol Rep. 2025;13:e70537. https://doi.org/10.14814/phy2.70537.
27. Luo J-Y, Cheng CK, Gou L, He L, Zhao L, Zhang Y, et al. Induction of KLF2 by Exercise Activates eNOS to Improve Vasodilatation in Diabetic Mice. Diabetes. 2023;72:1330–42. https://doi.org/10.2337/db23-0070.
28. Szostak J, Laurant P. The forgotten face of regular physical exercise: a natural anti-atherogenic activity. Clin Sci (Lond). 2011;121:91–106. https://doi.org/10.1042/CS20100520.
29. Mury P, Chirico EN, Mura M, Millon A, Canet-Soulas E, Pialoux V. Oxidative Stress and Inflammation, Key Targets of Atherosclerotic Plaque Progression and Vulnerability: Potential Impact of Physical Activity. Sports Med. 2018;48:2725–41. https://doi.org/10.1007/s40279-018-0996-z.
30. Wadley AJ, van Veldhuijzen JJCS, Aldred S. The interactions of oxidative stress and inflammation with vascular dysfunction in ageing: the vascular health triad. Age (Dordr). 2013;35:705–18. https://doi.org/10.1007/s11357-012-9402-1.
31. Zhang X, Gao F. Exercise improves vascular health: Role of mitochondria. Free Radic Biol Med. 2021;177:347–59. https://doi.org/10.1016/j.freeradbiomed.2021.11.002.
32. Sun W, Liu B, Zheng H. Response of endothelial function and oxidative stress after supervised aerobic exercise training in formerly preeclamptic women. Health Care Women Int. 2023;44:703–17. https://doi.org/10.1080/07399332.2021.2002331.
33. Yol Y, Turgay F, Yigittürk O, Aşıkovalı S, Durmaz B. The effects of regular aerobic exercise training on blood nitric oxide levels and oxidized LDL and the role of eNOS intron 4a/b polymorphism. Biochim Biophys Acta Mol Basis Dis. 2020;1866:165913. https://doi.org/10.1016/j.bbadis.2020.165913.
34. Teixeira M, Gouveia M, Duarte A, Ferreira M, Simões MI, Conceição M, et al. Regular Exercise Participation Contributes to Better Proteostasis, Inflammatory Profile, and Vasoactive Profile in Patients With Hypertension. Am J Hypertens. 2020;33:119–23. https://doi.org/10.1093/ajh/hpz160.
35. Majerczak J, Grandys M, Duda K, Zakrzewska A, Balcerczyk A, Kolodziejski L, et al. Moderate-intensity endurance training improves endothelial glycocalyx layer integrity in healthy young men. Exp Physiol. 2017;102:70–85. https://doi.org/10.1113/EP085887.
36. Merino J, Ferré R, Girona J, Aguas D, Cabré A, Plana N, et al. Even low physical activity levels improve vascular function in overweight and obese postmenopausal women. Menopause. 2013;20:1036–42. https://doi.org/10.1097/GME.0b013e31828501c9.
37. Gardner AW, Parker DE, Montgomery PS. Changes in vascular and inflammatory biomarkers following exercise rehabilitation in patients with symptomatic peripheral artery disease. J Vasc Surg. 2019;70:1280–90. https://doi.org/10.1016/j.jvs.2018.12.056.
38. Bergholm R, Mäkimattila S, Valkonen M, Liu ML, Lahdenperä S, Taskinen MR, et al. Intense physical training decreases circulating antioxidants and endothelium-dependent vasodilatation in vivo. Atherosclerosis. 1999;145:341–9. https://doi.org/10.1016/s0021-9150(99)00089-1.
39. Goto C, Higashi Y, Kimura M, Noma K, Hara K, Nakagawa K, et al. Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: role of endothelium-dependent nitric oxide and oxidative stress. Circulation. 2003;108:530–5. https://doi.org/10.1161/01.CIR.0000080893.55729.28.
40. Battault S, Singh F, Gayrard S, Zoll J, Reboul C, Meyer G. Endothelial function does not improve with high-intensity continuous exercise training in SHR: implications of eNOS uncoupling. Hypertens Res. 2016;39:70–8. https://doi.org/10.1038/hr.2015.114.
41. Fang Y, Ying W, Yu C, Daliao X, Lijun S. Impact of moderate- and high-intensity exercise on the endothelial ultrastructure and function in mesenteric arteries from hypertensive rats. Life Sci. 2019;222:36–45. https://doi.org/10.1016/j.lfs.2019.01.058.
42. Kvandová M, Rajlic S, Stamm P, Schmal I, Mihaliková D, Kuntic M, et al. Mitigation of aircraft noise-induced vascular dysfunction and oxidative stress by exercise, fasting, and pharmacological α1AMPK activation: molecular proof of a protective key role of endothelial α1AMPK against environmental noise exposure. Eur J Prev Cardiol. 2023;30:1554–68. https://doi.org/10.1093/eurjpc/zwad075.
43. Jansen T, Kvandová M, Schmal I, Kalinovic S, Stamm P, Kuntic M, et al. Lack of Endothelial α1AMPK Reverses the Vascular Protective Effects of Exercise by Causing eNOS Uncoupling. Antioxid (Basel). 2021;10:1974. https://doi.org/10.3390/antiox10121974.
44. Kröller-Schön S, Jansen T, Hauptmann F, Schüler A, Heeren T, Hausding M, et al. α1AMP activated protein kinase mediates the vascular protective effects of exercise. Arterioscler Thromb Vasc Biol. 2012;32:1632–41. https://doi.org/10.1161/ATVBAHA.111.243980.
45. Cheang WS, Wong WT, Zhao L, Xu J, Wang L, Lau CW, et al. PPARδ Is Required for Exercise to Attenuate Endoplasmic Reticulum Stress and Endothelial Dysfunction in Diabetic Mice. Diabetes. 2017;66:519–28. https://doi.org/10.2337/db15-1657.
46. Chen X, An X, Chen D, Ye M, Shen W, Han W, et al. Chronic Exercise Training Improved Aortic Endothelial and Mitochondrial Function via an AMPKα2-Dependent Manner. Front Physiol. 2016;7:631. https://doi.org/10.3389/fphys.2016.00631.
47. Gioscia-Ryan RA, Battson ML, Cuevas LM, Zigler MC, Sindler AL, Seals DR. Voluntary aerobic exercise increases arterial resilience and mitochondrial health with aging in mice. Aging. 2016;8:2897–914. https://doi.org/10.18632/aging.101099.
48. Gu Q, Wang B, Zhang XF, Ma YP, Liu JD, Wang XZ. Chronic aerobic exercise training attenuates aortic stiffening and endothelial dysfunction through preserving aortic mitochondrial function in aged rats. Exp Gerontol. 2014;56:37–44. https://doi.org/10.1016/j.exger.2014.02.014.
49. Gioscia-Ryan RA, Clayton ZS, Zigler MC, Richey JJ, Cuevas LM, Rossman MJ, et al. Lifelong voluntary aerobic exercise prevents age- and Western diet- induced vascular dysfunction,

mitochondrial oxidative stress, and inflammation in mice. J Physiol. 2021;599:911–25. https://doi.org/10.1113/JP280607.
50. Lee J, Lee Y, LaVoy EC, Umetani M, Hong J, Park Y. Physical activity protects NLRP3 inflammasome-associated coronary vascular dysfunction in obese mice. Physiol Rep. 2018;6:e13738. https://doi.org/10.14814/phy2.13738.
51. Conti V, Corbi G, Russomanno G, Simeon V, Ferrara N, Filippelli W, et al. Oxidative stress effects on endothelial cells treated with different athletes' sera. Med Sci Sports Exerc. 2012;44:39–49. https://doi.org/10.1249/MSS.0b013e318227f69c.
52. Chan S-H, Hung C-H, Shih J-Y, Chu P-M, Cheng Y-H, Lin H-C, et al. Exercise intervention attenuates hyperhomocysteinemia-induced aortic endothelial oxidative injury by regulating SIRT1 through mitigating NADPH oxidase/LOX-1 signaling. Redox Biol. 2017;14:116–25. https://doi.org/10.1016/j.redox.2017.08.016.
53. Zhang Y, Shan M, Ding X, Sun H, Qiu F, Shi L. Maternal exercise represses Nox4 via SIRT1 to prevent vascular oxidative stress and endothelial dysfunction in SHR offspring. Front Endocrinol (Lausanne). 2023;14:1219194. https://doi.org/10.3389/fendo.2023.1219194.
54. Harris MB, Hoffman RM, Olesiak M. Chronic Exercise Mitigates the Effects of Sirtuin Inhibition by Salermide on Endothelium-Dependent Vasodilation. Cardiovasc Toxicol. 2021;21:790–9. https://doi.org/10.1007/s12012-021-09669-8.
55. Moien-Afshari F, Ghosh S, Elmi S, Rahman MM, Sallam N, Khazaei M, et al. Exercise restores endothelial function independently of weight loss or hyperglycaemic status in db/db mice. Diabetologia. 2008;51:1327–37. https://doi.org/10.1007/s00125-008-0996-x.
56. Guers JJ, Kasecky-Lardner L, Farquhar WB, Edwards DG, Lennon SL. Voluntary wheel running prevents salt-induced endothelial dysfunction: role of oxidative stress. J Appl Physiol (1985). 2019;126:502–10. https://doi.org/10.1152/japplphysiol.00421.2018.
57. Robinson AT, Fancher IS, Sudhahar V, Bian JT, Cook MD, Mahmoud AM, et al. Short-term regular aerobic exercise reduces oxidative stress produced by acute high intraluminal pressure in the adipose microvasculature. Am J Physiol Heart Circ Physiol. 2017;312:H896–906. https://doi.org/10.1152/ajpheart.00684.2016.
58. Hong J, Park E, Lee J, Lee Y, Rooney BV, Park Y. Exercise training mitigates ER stress and UCP2 deficiency-associated coronary vascular dysfunction in atherosclerosis. Sci Rep. 2021;11:15449. https://doi.org/10.1038/s41598-021-94944-5.
59. Luo J-Y, Cheng CK, He L, Pu Y, Zhang Y, Lin X, et al. Endothelial UCP2 Is a Mechanosensitive Suppressor of Atherosclerosis. Circ Res. 2022;131:424–41. https://doi.org/10.1161/CIRCRESAHA.122.321187.
60. Sousa AS, Sponton ACS, Trifone CB, Delbin MA. Aerobic Exercise Training Prevents Perivascular Adipose Tissue-Induced Endothelial Dysfunction in Thoracic Aorta of Obese Mice. Front Physiol. 2019;10:1009. https://doi.org/10.3389/fphys.2019.01009.
61. DeVallance E, Branyan KW, Lemaster KC, Anderson R, Marshall KL, Olfert IM, et al. Exercise training prevents the perivascular adipose tissue-induced aortic dysfunction with metabolic syndrome. Redox Biol. 2019;26:101285. https://doi.org/10.1016/j.redox.2019.101285.
62. Wang J, Polaki V, Chen S, Bihl JC. Exercise Improves Endothelial Function Associated with Alleviated Inflammation and Oxidative Stress of Perivascular Adipose Tissue in Type 2 Diabetic Mice. Oxid Med Cell Longev. 2020;2020:8830537. https://doi.org/10.1155/2020/8830537.
63. Tofas T, Draganidis D, Deli CK, Georgakouli K, Fatouros IG, Jamurtas AZ. Exercise-Induced Regulation of Redox Status in Cardiovascular Diseases: The Role of Exercise Training and Detraining. Antioxid (Basel). 2019;9:13. https://doi.org/10.3390/antiox9010013.
64. Son W-H, Kwak Y-S, Ha M-S. Circuit training on oxidative stress and arterial health: a health promotion perspective for obese adult men. Front Public Health. 2025;13:1562193. https://doi.org/10.3389/fpubh.2025.1562193.
65. Dantas FFO, Brasileiro-Santos M, do S, Batista RMF, do Nascimento LS, Castellano LRC, Ritti-Dias RM, et al. Effect of Strength Training on Oxidative Stress and the Correlation of the Same with Forearm Vasodilatation and Blood Pressure of Hypertensive Elderly Women: A Randomized Clinical Trial. PLoS ONE. 2016;11:e0161178. https://doi.org/10.1371/journal.pone.0161178.
66. Das EK, Lai PY, Robinson AT, Pleuss J, Ali MM, Haus JM, et al. Regular Aerobic, Resistance, and Cross-Training Exercise Prevents Reduced Vascular Function Following a High Sugar or High Fat Mixed Meal in Young Healthy Adults. Front Physiol. 2018;9:183. https://doi.org/10.3389/fphys.2018.00183.
67. Craighead DH, Heinbockel TC, Freeberg KA, Rossman MJ, Jackman RA, Jankowski LR, et al. Time-Efficient Inspiratory Muscle Strength Training Lowers Blood Pressure and Improves Endothelial Function, NO Bioavailability, and Oxidative Stress in Midlife/Older Adults With Above-Normal Blood Pressure. J Am Heart Assoc. 2021;10:e020980. https://doi.org/10.1161/JAHA.121.020980.
68. Campos NG, Marizeiro DF, Florêncio ACL, Silva ÍC, Meneses GC, Bezerra GF, et al. Effects of respiratory muscle training on endothelium and oxidative stress biomarkers in hemodialysis patients: A randomized clinical trial. Respir Med. 2018;134:103–9. https://doi.org/10.1016/j.rmed.2017.12.005.
69. Corrêa HL, Moura SRG, Neves RVP, Tzanno-Martins C, Souza MK, Haro AS, et al. Resistance training improves sleep quality, redox balance and inflammatory profile in maintenance hemodialysis patients: a randomized controlled trial. Sci Rep. 2020;10:11708. https://doi.org/10.1038/s41598-020-68602-1.
70. Cook MD, Heffernan KS, Ranadive S, Woods JA, Fernhall B. Effect of Resistance Training on Biomarkers of Vascular Function and Oxidative Stress in Young African American and Caucasian men. J Hum Hypertens. 2013;27:388–92. https://doi.org/10.1038/jhh.2012.48.
71. Jürgenson J, Serg M, Kampus P, Kals J, Zagura M, Viru M, et al. Oxidative Stress Parameters and Its Associations With Arterial Stiffness in Competitive Powerlifting Athletes After 12-Week Supervised Strength Training. J Strength Cond Res. 2019;33:1816–22. https://doi.org/10.1519/JSC.0000000000003067.
72. da Palma RK, Moraes-Silva IC, da Silva Dias D, Shimojo GL, Conti FF, Bernardes N, et al. Resistance or aerobic training decreases blood pressure and improves cardiovascular autonomic control and oxidative stress in hypertensive menopausal rats. J Appl Physiol (1985). 2016;121:1032–8. https://doi.org/10.1152/japplphysiol.00130.2016.
73. Wen C, Ying Y, Zhao H, Jiang Q, Gan X, Wei Y, et al. Resistance exercise affects catheter-related thrombosis in rats through miR-92a-3p, oxidative stress and the MAPK/NF-κB pathway. BMC Cardiovasc Disord. 2021;21:440. https://doi.org/10.1186/s12872-021-02233-w.
74. Ma Y, Kuang Y, Bo W, Liang Q, Zhu W, Cai M, et al. Exercise Training Alleviates Cardiac Fibrosis through Increasing Fibroblast Growth Factor 21 and Regulating TGF-β1-Smad2/3-MMP2/9 Signaling in Mice with Myocardial Infarction. Int J Mol Sci. 2021;22:12341. https://doi.org/10.3390/ijms222212341.
75. Feng L, Li B, Cai M, Zhang Z, Zhao Y, Yong SS, et al. Resistance exercise alleviates the prefrontal lobe injury and dysfunction by activating SESN2/AMPK/PGC-1α signaling pathway and inhibiting oxidative stress and inflammation in mice with myocardial

infarction. Exp Neurol. 2023;370:114559. https://doi.org/10.1016/j.expneurol.2023.114559.
76. Li H, Qin S, Tang J, Wang T, Ren W, Di L, et al. Resistance exercise upregulates Irisin expression and suppresses myocardial fibrosis following myocardial infarction via activating AMPK-Sirt1 and inactivating TGFβ1-Smad2/3. Acta Physiol (Oxf). 2024;240:e14163. https://doi.org/10.1111/apha.14163.
77. Hjortshoej MH, Aagaard P, Storgaard CD, Juneja H, Lundbye-Jensen J, Magnusson SP, et al. Hormonal, immune, and oxidative stress responses to blood flow-restricted exercise. Acta Physiol (Oxf). 2023;239:e14030. https://doi.org/10.1111/apha.14030.
78. Boeno FP, Ramis TR, Farinha JB, de Lemos LS, Medeiros NdaS, Ribeiro JL. Acute effects of strength exercise with blood flow restriction on vascular function of young healthy males. J Vasc Bras. 2018;17:122–7. https://doi.org/10.1590/1677-5449.011017.
79. de Lima FR, Marin DP, Ferreira LT, Sousa Filho CPB, Astorino TA, Prestes J, et al. Effect of Resistance Training With Total and Partial Blood Flow Restriction on Biomarkers of Oxidative Stress and Apoptosis in Untrained Men. Front Physiol. 2021;12:720773. https://doi.org/10.3389/fphys.2021.720773.
80. Garten RS, Goldfarb A, Crabb B, Waller J. The Impact of Partial Vascular Occlusion on Oxidative Stress Markers during Resistance Exercise. Int J Sports Med. 2015;36:542–9. https://doi.org/10.1055/s-0034-1396827.
81. Garcia NF, de Moraes C, Rebelo MA, de Castro FMP, Peters SMGR, Pernomian L, et al. Low load strength training, associated with or without blood flow restriction increased NO production and decreased production of reactive oxygen species in rats aorta. Life Sci. 2022;294:120350. https://doi.org/10.1016/j.lfs.2022.120350.
82. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54:1451–62. https://doi.org/10.1136/bjsports-2020-102955.
83. Lima AHRA, Correia MA, Soares AHG, Farah BQ, Forjaz CLM, Silva AS, et al. Acute effects of walking and combined exercise on oxidative stress and vascular function in peripheral artery disease. Clin Physiol Funct Imaging. 2018;38:69–75. https://doi.org/10.1111/cpf.12384.
84. Zhou H, Wang T, Fan Z, Cheng S, Wang Y, He H. Inflammatory mediation of aerobic, resistance, and combined exercise effects on the vascular elasticity of obese women. iScience. 2026;29:114297. https://doi.org/10.1016/j.isci.2025.114297.
85. Jamka M, Bogdański P, Krzyżanowska-Jankowska P, Miśkiewicz-Chotnicka A, Karolkiewicz J, Duś-Żuchowska M, et al. Endurance Training Depletes Antioxidant System but Does Not Affect Endothelial Functions in Women with Abdominal Obesity: A Randomized Trial with a Comparison to Endurance-Strength Training. J Clin Med. 2021;10:1639. https://doi.org/10.3390/jcm10081639.
86. Schaun MI, Dipp T, Rossato JdaS, Wilhelm EN, Pinto R, Rech A, et al. The effects of periodized concurrent and aerobic training on oxidative stress parameters, endothelial function and immune response in sedentary male individuals of middle age. Cell Biochem Funct. 2011;29:534–42. https://doi.org/10.1002/cbf.1781.
87. Ratajczak M, Skrypnik D, Bogdański P, Mądry E, Walkowiak J, Szulińska M, et al. Effects of Endurance and Endurance–Strength Training on Endothelial Function in Women with Obesity: A Randomized Trial. Int J Environ Res Public Health. 2019;16:4291. https://doi.org/10.3390/ijerph16214291.
88. Fontes MT, dos Reis Costa DEF, Dardi P, Paula SM, Couto GK, de Castro É, et al. Combined aerobic and resistance exercise training restores perivascular adipose tissue function in the thoracic aorta of rats with heart failure. Clin Sci (Lond). 2025;139:1355–71. https://doi.org/10.1042/CS20256965.
89. Tang S, Huang W, Wang S, Wu Y, Guo L, Huang J, et al. Effects of aquatic high-intensity interval training and moderate-intensity continuous training on central hemodynamic parameters, endothelial function and aerobic fitness in inactive adults. J Exerc Sci Fit. 2022;20:256–62. https://doi.org/10.1016/j.jesf.2022.04.004.
90. Sabouri M, Amirshaghaghi F, Hesari MM. High-intensity interval training improves the vascular endothelial function comparing moderate-intensity interval training in overweight or obese adults: A meta-analysis. Clin Nutr ESPEN. 2023;53:100–6. https://doi.org/10.1016/j.clnesp.2022.11.023.
91. O'Brien MW, Johns JA, Robinson SA, Bungay A, Mekary S, Kimmerly DS. Impact of High-Intensity Interval Training, Moderate-Intensity Continuous Training, and Resistance Training on Endothelial Function in Older Adults. Med Sci Sports Exerc. 2020;52:1057–67. https://doi.org/10.1249/MSS.0000000000002226.
92. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. Sports Med. 2015;45:679–92. https://doi.org/10.1007/s40279-015-0321-z.
93. Fall L, Stacey BS, Calverley T, Owens T, Thyer K, Griffiths R, et al. Acute high-intensity interval exercise is less pro-oxidative/thrombotic compared to isovolumic moderate-intensity steady-state exercise. J Physiol Biochem. 2023;79:35–46. https://doi.org/10.1007/s13105-022-00918-0.
94. Sarvasti D, Lalenoh I, Oepangat E, Purwowiyoto BS, Santoso A, Romdoni R. Cardiovascular Protection Variables Based on Exercise Intensity in Stable Coronary Heart Disease Patients After Coronary Stenting: A Comparative Study. Vasc Health Risk Manag. 2020;16:257–70. https://doi.org/10.2147/VHRM.S259190.
95. La Favor JD, Dubis GS, Yan H, White JD, Nelson MAM, Anderson EJ, et al. Microvascular Endothelial Dysfunction in Sedentary, Obese Humans is mediated by NADPH Oxidase; Influence of Exercise Training. Arterioscler Thromb Vasc Biol. 2016;36:2412–20. https://doi.org/10.1161/ATVBAHA.116.308339.
96. Hsu C-C, Fu T-C, Huang S-C, Wang J-S. High-intensity interval training recuperates capacity of endogenous thrombin generation in heart failure patients with reduced ejection fraction. Thromb Res. 2020;187:159–65. https://doi.org/10.1016/j.thromres.2020.01.013.
97. Mitranun W, Deerochanawong C, Tanaka H, Suksom D. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. Scand J Med Sci Sports. 2014;24:e69–76. https://doi.org/10.1111/sms.12112.
98. Aispuru-Lanche R, Jayo-Montoya JA, Maldonado-Martín S. Vascular-endothelial adaptations following low and high volumes of high-intensity interval training in patients after myocardial infarction. Ther Adv Cardiovasc Dis. 2024;18:17539447241286036. https://doi.org/10.1177/17539447241286036.
99. Liu G, Zhao B, Chen Q, Li X, Zhu X, Duan M, et al. HIIT and MICT mitigate endothelial dysfunction in early atherosclerotic mice via PCSK9 inhibition. Sci Rep. 2025;15:30411. https://doi.org/10.1038/s41598-025-05206-7.
100. Li Y, Luo M, Chang Q, Cao S, Wang Y, Chen Z, et al. High-intensity interval training and moderate-intensity continuous training alleviate vascular dysfunction in spontaneously hypertensive rats through the inhibition of pyroptosis. Heliyon. 2024;10:e39505. https://doi.org/10.1016/j.heliyon.2024.e39505.
101. Bloomer RJ, Goldfarb AH, Wideman L, McKenzie MJ, Consitt LA. Effects of acute aerobic and anaerobic exercise on blood markers of oxidative stress. J Strength Cond Res. 2005;19:276–85. https://doi.org/10.1519/14823.1.
102. Elosua R, Molina L, Fito M, Arquer A, Sanchez-Quesada JL, Covas MI, et al. Response of oxidative stress biomarkers to a

16-week aerobic physical activity program, and to acute physical activity, in healthy young men and women. Atherosclerosis. 2003;167:327–34. https://doi.org/10.1016/s0021-9150(03)00018-2.
103. Pingitore A, Lima GPP, Mastorci F, Quinones A, Iervasi G, Vassalle C. Exercise and oxidative stress: potential effects of antioxidant dietary strategies in sports. Nutrition. 2015;31:916–22. https://doi.org/10.1016/j.nut.2015.02.005.
104. Tanaka LY, Bechara LRG, dos Santos AM, Jordão CP, de Sousa LGO, Bartholomeu T, et al. Exercise improves endothelial function: a local analysis of production of nitric oxide and reactive oxygen species. Nitric Oxide. 2015;45:7–14. https://doi.org/10.1016/j.niox.2015.01.003.
105. Cheng T-L, Lin Y-Y, Su C-T, Hu C-C, Yang A-L. Improvement of Acetylcholine-Induced Vasodilation by Acute Exercise in Ovariectomized Hypertensive Rats. Chin J Physiol. 2016;59:165–72. https://doi.org/10.4077/CJP.2016.BAE387.
106. Jenkins NT, Landers RQ, Prior SJ, Soni N, Spangenburg EE, Hagberg JM. Effects of acute and chronic endurance exercise on intracellular nitric oxide and superoxide in circulating CD34+and CD34−cells. J Appl Physiol (1985). 2011;111:929–37. https://doi.org/10.1152/japplphysiol.00541.2011.
107. Jenkins NT, Landers RQ, Thakkar SR, Fan X, Brown MD, Prior SJ, et al. Prior endurance exercise prevents postprandial lipaemia-induced increases in reactive oxygen species in circulating CD31+cells. J Physiol. 2011;589:5539–53. https://doi.org/10.1113/jphysiol.2011.215277.
108. Goto C, Nishioka K, Umemura T, Jitsuiki D, Sakagutchi A, Kawamura M, et al. Acute moderate-intensity exercise induces vasodilation through an increase in nitric oxide bioavailiability in humans. Am J Hypertens. 2007;20:825–30. https://doi.org/10.1016/j.amjhyper.2007.02.014.
109. Kröpfl JM, Beltrami FG, Rehm M, Gruber H-J, Stelzer I, Spengler CM. Acute exercise-induced glycocalyx shedding does not differ between exercise modalities, but is associated with total antioxidative capacity. J Sci Med Sport. 2021;24:689–95. https://doi.org/10.1016/j.jsams.2021.01.010.
110. Johnson BD, Padilla J, Wallace JP. The exercise dose affects oxidative stress and brachial artery flow-mediated dilation in trained men. Eur J Appl Physiol. 2012;112:33–42. https://doi.org/10.1007/s00421-011-1946-8.
111. Mavraganis G, Sakelliou A, Georgiopoulos G, Delialis D, Papaioannou M, Maneta E, et al. Evidence of a redox-dependent control of vascular function after muscle-damaging exercise in young adults: a randomized placebo-controlled trial. Hellenic J Cardiol. 2025;S1109. https://doi.org/10.1016/j.hjc.2025.07.007.-9666(25)00182-4.
112. Durand MJ, Dharmashankar K, Bian J-T, Das E, Vidovich M, Gutterman DD, et al. Acute Exertion Elicits a H_2O_2–Dependent Vasodilator Mechanism in The Microvasculature of Exercise Trained But Not Sedentary Adults. Hypertension. 2015;65:140–5. https://doi.org/10.1161/HYPERTENSIONAHA.114.04540.
113. Robinson AT, Franklin NC, Norkeviciute E, Bian JT, Babana JC, Szczurek MR, et al. Improved arterial flow-mediated dilation after exertion involves hydrogen peroxide in overweight and obese adults following aerobic exercise training. J Hypertens. 2016;34:1309–16. https://doi.org/10.1097/HJH.0000000000000946.
114. Rognmo O, Bjørnstad TH, Kahrs C, Tjønna AE, Bye A, Haram PM, et al. Endothelial function in highly endurance-trained men: effects of acute exercise. J Strength Cond Res. 2008;22:535–42. https://doi.org/10.1519/JSC.0b013e31816354b1.
115. Harden JE, David Branch J, Reynolds LJ. Impacts of Physical Inactivity Models on Endothelial Function: A Systematic Review. Sports Med. 2025;55:1937–52. https://doi.org/10.1007/s40279-025-02238-x.
116. Vona M, Codeluppi GM, Iannino T, Ferrari E, Bogousslavsky J, von Segesser LK. Effects of different types of exercise training followed by detraining on endothelium-dependent dilation in patients with recent myocardial infarction. Circulation. 2009;119:1601–8. https://doi.org/10.1161/CIRCULATIONAHA.108.821736.
117. Maeda S, Miyauchi T, Kakiyama T, Sugawara J, Iemitsu M, Irukayama-Tomobe Y, et al. Effects of exercise training of 8 weeks and detraining on plasma levels of endothelium-derived factors, endothelin-1 and nitric oxide, in healthy young humans. Life Sci. 2001;69:1005–16. https://doi.org/10.1016/s0024-3205(01)01192-4.
118. Kim S, Lee S, Han D, Jeong I, Lee H-H, Koh Y, et al. One-year Aerobic Interval Training Improves Endothelial Dysfunction in Patients with Atrial Fibrillation: A Randomized Trial. Intern Med. 2023;62:2465–74. https://doi.org/10.2169/internalmedicine.0947-22.
119. Witkowski S, Lockard MM, Jenkins NT, Obisesan TO, Spangenburg EE, Hagberg JM. Relationship between circulating progenitor cells, vascular function and oxidative stress with long-term training and short-term detraining in older men. Clin Sci (Lond). 2010;118:303–11. https://doi.org/10.1042/CS20090253.
120. Padilha CS, Ribeiro AS, Fleck SJ, Nascimento MA, Pina FLC, Okino AM, et al. Effect of resistance training with different frequencies and detraining on muscular strength and oxidative stress biomarkers in older women. Age (Dordr). 2015;37:104. https://doi.org/10.1007/s11357-015-9841-6.
121. Araújo EM, Coelho-Júnior HJ, Sousa CV, Rosa TDS, Sousa Neto IV, Marzetti E, et al. Improving serum redox balance, inflammatory status, physical function, and cognitive ability through dual-task resistance training and detraining in nursing home residents. Exp Gerontol. 2025;200:112662. https://doi.org/10.1016/j.exger.2024.112662.
122. Fatouros IG, Jamurtas AZ, Villiotou V, Pouliopoulou S, Fotinakis P, Taxildaris K, et al. Oxidative stress responses in older men during endurance training and detraining. Med Sci Sports Exerc. 2004;36:2065–72. https://doi.org/10.1249/01.mss.0000147632.17450.ff.
123. Baltasar-Fernandez I, Losa-Reyna J, Carretero A, Rodriguez-Lopez C, Alfaro-Acha A, Guadalupe-Grau A, et al. Residual effects of 12 weeks of power-oriented resistance training plus high-intensity interval training on muscle dysfunction, systemic oxidative damage, and antioxidant capacity after 10 months of training cessation in older people with COPD. Scand J Med Sci Sports. 2023;33:1661–76. https://doi.org/10.1111/sms.14428.
124. Tofas T, Fatouros IG, Draganidis D, Deli CK, Chatzinikolaou A, Tziortzis C, et al. Effects of Cardiovascular, Resistance and Combined Exercise Training on Cardiovascular, Performance and Blood Redox Parameters in Coronary Artery Disease Patients: An 8-Month Training-Detraining Randomized Intervention. Antioxid (Basel). 2021;10:409. https://doi.org/10.3390/antiox10030409.
125. Bradic J, Dragojlovic Ruzicic R, Jeremic J, Petkovic A, Stojic I, Nikolic T, et al. Comparison of training and detraining on redox state of rats: gender specific differences. Gen Physiol Biophys. 2018;37:285–97. https://doi.org/10.4149/gpb_2017053.
126. Silvestro A, Scopacasa F, Oliva G, de Cristofaro T, Iuliano L, Brevetti G. Vitamin C prevents endothelial dysfunction induced by acute exercise in patients with intermittent claudication. Atherosclerosis. 2002;165:277–83. https://doi.org/10.1016/s0021-9150(02)00235-6.
127. Johnson BD, Mather KJ, Newcomer SC, Mickleborough TD, Wallace JP. Brachial Artery Flow-mediated Dilation Following Exercise with Augmented Oscillatory and Retrograde Shear Rate. Cardiovasc Ultrasound. 2012;10:34. https://doi.org/10.1186/1476-7120-10-34.
128. Ramos Junior OJF, Tavares IRG, Lima RC, Conte-Junior CA, Alvares TS. Jaboticaba berry (Myrciaria jaboticaba) supplementation protects against micro- and macrovascular dysfunction

induced by eccentric exercise: a randomized clinical trial. Food Funct. 2024;15:7148–60. https://doi.org/10.1039/d4fo01907e.
129. Sarmiento A, Diaz-Castro J, Pulido-Moran M, Moreno-Fernandez J, Kajarabille N, Chirosa I, et al. Short-term ubiquinol supplementation reduces oxidative stress associated with strenuous exercise in healthy adults: A randomized trial. BioFactors. 2016;42:612–22. https://doi.org/10.1002/biof.1297.
130. Hu X, Mu L, Zhu L, Chang X, Nie L, Wang L, et al. Lycium barbarum polysaccharides attenuate cardiovascular oxidative stress injury by enhancing the Keap1/Nrf2 signaling pathway in exhaustive exercise rats. Mol Med Rep. 2021;24:643. https://doi.org/10.3892/mmr.2021.12282.
131. Lee S-R, Directo D. Fish Oil Supplementation with Resistance Exercise Training Enhances Physical Function and Cardiometabolic Health in Postmenopausal Women. Nutrients. 2023;15:4516. https://doi.org/10.3390/nu15214516.
132. Basereh A, Khoramipour K, Hosseini N, HajHosseini M, Khodabakhshi A, Amirkhosravi L, et al. Redox-sensitive miRNAs and Humanin could mediate effects of exercise and astaxanthin on oxidative stress and inflammation in type 2 diabetes. Sci Rep. 2025;15:40113. https://doi.org/10.1038/s41598-025-23914-y.
133. de Oliveira BC, de Andrade Soares R, de Menezes MP, Cavalheira MA, da Silva DLB, de Bem GF, et al. Protective Effect of Açai Seed Extract (Euterpe oleracea Mart.) Combined with Exercise Training on Cardiovascular Alterations, Oxidative Stress, and Loss of Physical Performance in Spontaneously Hypertensive Rats. J Med Food. 2025;28:974–82. https://doi.org/10.1177/1096620X251361429.
134. Chis IC, Coseriu A, Simedrea R, Oros A, Nagy AL, Clichici S. In Vivo Effects of Quercetin in Association with Moderate Exercise Training in Improving Streptozotocin-Induced Aortic Tissue Injuries. Molecules. 2015;20:21770–86. https://doi.org/10.3390/molecules201219802.
135. Kazemi Pordanjani M, Banitalebi E, Roghani M, Hemmati R. Ursolic acid enhances the effect of exercise training on vascular aging by reducing oxidative stress in aged type 2 diabetic rats. Food Sci Nutr. 2023;11:696–708. https://doi.org/10.1002/fsn3.3105.
136. Lee J, Cho J-Y, Kim W-K. Anti-inflammation effect of Exercise and Korean red ginseng in aging model rats with diet-induced atherosclerosis. Nutr Res Pract. 2014;8:284–91. https://doi.org/10.4162/nrp.2014.8.3.284.
137. Oharomari LK, Garcia NF, de Freitas EC, Jordão Júnior AA, Ovídio PP, Maia AR, et al. Exercise training and taurine supplementation reduce oxidative stress and prevent endothelium dysfunction in rats fed a highly palatable diet. Life Sci. 2015;139:91–6. https://doi.org/10.1016/j.lfs.2015.08.015.
138. Meilhac O, Ramachandran S, Chiang K, Santanam N, Parthasarathy S. Role of arterial wall antioxidant defense in beneficial effects of exercise on atherosclerosis in mice. Arterioscler Thromb Vasc Biol. 2001;21:1681–8. https://doi.org/10.1161/hq1001.097106.
139. Garelnabi M, Veledar E, White-Welkley J, Santanam N, Abramson J, Weintraub W, et al. Vitamin E differentially affects the short term exercise induced changes in oxidative stress, lipids, and inflammatory markers. Nutr Metab Cardiovasc Dis. 2012;22:907–13. https://doi.org/10.1016/j.numecd.2011.03.002.
140. Ristow M, Zarse K, Oberbach A, Klöting N, Birringer M, Kiehntopf M, et al. Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci U S A. 2009;106:8665–70. https://doi.org/10.1073/pnas.0903485106.

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