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COMPENDIUM ON CARDIOPULMONARY DISEASE AND EXERCISE: MOLECULAR TO CLINICAL MECHANISMS

Paradox of Exercise and Coronary Artery Calcification: Potential Underlying Mechanisms

Jeffrey J. Hsu¹, Yin Tintut², Linda L. Demer¹

ABSTRACT: Regular exercise is widely known to exert beneficial effects on the cardiovascular system. Despite the widely accepted and numerous benefits of exercise, whether there is an upper limit to these benefits is unclear, particularly with regard to atherosclerotic disease. Observational cohort studies over the past 2 decades have identified a consistent signal of increased coronary artery calcification in older men, who have been exposed to high volumes of endurance exercise over their lifetime. The clinical ramifications of these findings are not fully known, as outcomes studies in these athletic populations are needed, but given the strong associations of coronary artery calcification with adverse cardiovascular events, a deeper mechanistic understanding of the link between endurance exercise and coronary artery calcification is needed. In this review, we describe the possible underlying mechanisms that may explain this conundrum of the athlete calcification paradox at the molecular and cellular levels.

Key Words: atherosclerosis ■ athletes ■ biomineralization ■ cardiology ■ exercise ■ sports

Endurance exercise is recognized for its numerous cardiovascular benefits, including a reduced risk of cardiovascular disease, improved lipid profiles, enhanced endothelial function, and increased longevity.¹ With increasing participation in endurance sports,² such as long-distance running and cycling, it has become critically important to understand the nuanced cardiovascular consequences associated with prolonged and intensive exercise regimens. Coronary artery calcification (CAC), identified through computed tomography (CT), serves as a potent predictor of future cardiovascular events.³ Over the past decade, clinical studies have consistently shown an association of high volumes of endurance exercise with CAC in older men, despite their otherwise favorable cardiovascular risk profiles.^{4,5} Although this finding has been reproducible across many different cohorts of men, the underlying mechanisms are unclear. Previous excellent reviews have comprehensively summarized the clinical studies establishing this association and have briefly discussed potential contributing factors that may help explain this association,^{6–8} including the roles of

lifestyle and behavioral factors that may be enriched in the older male athlete population. In this review, we aim to probe more deeply into the fundamental as well as mechanobiological mechanisms that may help to explain this association, although current data on these specific exercise-induced mechanisms are scant, and more focused studies are required to investigate the exact signaling pathways behind this seemingly paradoxical clinical finding.

CAC: BACKGROUND AND PATHOPHYSIOLOGY

Cardiovascular calcification was once considered to be a passive process involving the chemical deposition of mineral crystals into cardiac and vascular tissue. However, after decades of research specifically investigating this process, the contemporary understanding of cardiovascular calcification identifies it as an actively regulated process. Calcification is often present within

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Nonstandard Abbreviations and Acronyms

BMP2	bone morphogenetic protein-2
CAC	coronary artery calcification
CRP	C-reactive protein
CT	computed tomography
IL	interleukin
KLF2	Krüppel-like factor 2
LDL	low-density lipoprotein
Lp(a)	lipoprotein[a]
MGP	matrix Gla protein
NaF	sodium fluoride
PET	positron emission tomography
PI3K	phosphatidylinositol-3-kinase
PTH	parathyroid hormone
ROS	reactive oxygen species
Runx2	runt-related transcription factor 2
TNF-α	tumor necrosis factor- α
VSMC	vascular smooth muscle cell

advanced atherosclerotic lesions, and as such, the presence of CAC identified on CT imaging is considered a surrogate marker for coronary atherosclerosis. CAC has emerged as one of the most robust predictors of cardiovascular morbidity and mortality, even surpassing traditional risk factors in predictive accuracy.^{3,9} The presence and extent of CAC have been consistently associated with an increased risk of future cardiovascular events, including myocardial infarction and cardiovascular death.¹⁰ Higher CAC scores generally reflect advanced atherosclerotic plaque burden and are associated with higher cardiovascular event rates,^{3,10} and recent analyses have suggested that a CAC score >300 Agatston units may portend cardiovascular risk equivalent to a patient with a history of ischemic heart disease.¹¹

The pathophysiology underlying the atherosclerotic calcification that comprises CAC involves complex mechanisms that drive osteogenic differentiation of vascular smooth muscle cells (VSMCs),^{5,6} including vascular inflammation, oxidative stress, and lipid accumulation.^{12,13} Lineage tracing experiments in mice show that VSMCs give rise to osteochondrogenic cells.¹⁴ Macrophages promote matrix calcification of VSMCs via secretion of proinflammatory cytokines, further enhancing the calcification process.^{15,16} Endothelial cells can also undergo osteogenic differentiation through endothelial-to-mesenchymal transition.^{17–19} Importantly, the factors that promote atherosclerosis, such as hyperlipidemia and chronic kidney disease, also promote calcification, and the presence of calcification in atherosclerotic plaque is considered an indicator of more advanced disease progression.

ATHLETE CALCIFICATION PARADOX

The role of physical activity in reducing the development of atherosclerotic cardiovascular disease was first established in the 1950s with the London Transport Workers study, which demonstrated that bus conductors had lower rates of coronary heart disease compared with bus drivers.^{20,21} These findings were attributed to the greater physical activity of the conductors in their daily work relative to the sedentary nature of the drivers' job duties, and the associations of regular exercise and greater physical fitness with better cardiovascular outcomes have been reproduced in contemporary studies.^{22–24} As such, exercise has been well established as a healthy behavior, included as one of the American Heart Association's Essential 8 components to promote cardiovascular health.²⁵

Accordingly, given the association of CAC with cardiovascular disease and the benefits of exercise in reducing cardiovascular disease, one might predict that individuals who engage in the highest levels of exercise have the least amount of CAC. Interestingly, however, clinical studies show the opposite findings in male masters athletes, defined as men over 35 years of age, who have engaged in high volumes of endurance exercise over their lifetime. Higher volumes of endurance exercise, such as seen in long-distance runners and cyclists, are associated with significantly higher CAC scores on CT imaging. First demonstrated in a German cohort of male marathon runners in the Heinz Nixdorf Recall study,²⁶ this finding has been reproduced in several other athlete cohorts.^{4,5,27,28} In Merghani et al,⁴ 48.1% of the male masters endurance athletes had CAC >0 Agatston units (compared with 40.7% in the control group), whereas 18.9% had CAC >100 (compared with 7.4% in the control group). Similarly, in the Measuring Athlete's Risk of Cardiovascular Events (MARC) study, 52% of these athletes had CAC >0, and 15% had CAC >100.^{5,29} Furthermore, in the Master@Heart study, 57.1% had CAC >0 (45.5% in the control group), and 23% had CAC >100 (14.8% in controls).²⁷ Thus, from data in separate cohorts, CAC is present in roughly half of these athletes, and significant CAC (>100) is present in $\approx$ 20%.

General population studies have also demonstrated an association with the highest levels of cardiorespiratory fitness or physical activity volumes and increased CAC scores, exhibiting a reverse J-shaped curve.^{30–34} Given the cardioprotective benefits of regular exercise, this unexpected yet consistent association between the highest volumes of exercise with greater CAC is what we consider to be the male masters athlete calcification paradox. Notably, this same phenomenon is not identified in women,³⁵ nor has it been seen in noncoronary vascular beds,³⁶ although notably peripheral arterial calcification has not been specifically studied in endurance athlete populations.

Although this population is more likely to have significant CAC, whether CAC portends the same degree of cardiovascular risk remains an important question. Earlier studies of asymptomatic individuals with CAC supported that even in the presence of an elevated CAC score, regular exercise promotes better cardiovascular outcomes.^{30,31,37,38} However, recently published follow-up data from the Cooper Center Longitudinal Study show that while high-volume physical activity (≥ 3000 metabolic equivalents of task [MET]-min/wk) reduced mortality risk, it did not mitigate the increased cardiovascular event risk imparted by the presence of CAC.³⁹ Thus, while higher cardiorespiratory fitness and regular exercise behaviors are generally associated with improved outcomes, the presence of CAC itself remains associated with increased cardiovascular risk, even in the most physically active individuals.⁴⁰ Thus, the risks of CAC in masters athletes should not be ignored but rather actively managed, and it remains crucial to identify the factors that contribute to the more common development of CAC in this athletic population.

ROLE OF CALCIFICATION MORPHOLOGY

One possible explanation for the reduction of cardiovascular disease risk in the more athletic population even in the presence of CAC would be if exercise beneficially modified the biomechanical features of calcium deposits to a more stable form. The presence of calcification within atherosclerotic plaque is thought to impact the risk of plaque rupture, which ultimately leads to the feared clinical events of myocardial infarction and sudden cardiac death, and relevant features of calcium deposits that impact plaque stability include their size, morphology, and location within the lesion.⁴¹

Yet controversy remains over whether calcium deposits increase or decrease the risk of plaque rupture or clinical cardiovascular events. Finite element modeling analyses are often used to successfully predict mechanical responses of complex, human tissues, such as assessing rupture risk of aortic aneurysms.⁴² Finite element modeling analyses indicate that a rigid inclusion, such as a calcium deposit, embedded in a distensible material, such as vascular tissue, increases rupture (von Mises) stress at the surface of the deposit that faces the stress axis.⁴³ This phenomenon, known as compliance mismatch,^{43,44} results in rupture through a debonding process at the interface between the calcified deposit and surrounding tissue. Thus, rupture risk should correlate positively with the surface area of the calcified deposits, and accordingly, this surface area may have more prognostic potential than the total mass of calcified deposits.

In the early stages of vascular calcification, microcrystals may arise *de novo* at scattered sites. As they grow, their surface area initially increases. If the deposits are in close vicinity, the growing deposits may coalesce and

fuse with one another. Because fusion reduces surface area, the risk may theoretically level off or even decrease with progression.⁴⁵

In clinical studies of athletes, coronary CT angiography has been used to characterize whether exercise history is associated with a particular type of calcified plaque morphology. Merghani et al⁴ found that male athletes were more likely to have predominantly calcified plaques compared with sedentary controls, who were more likely to have plaques of mixed morphology. Similarly, Aengevaeren et al observed in the MARC study that the dominant plaque type in the most physically active men was significantly more likely to be calcified.⁵ In the follow-up, longitudinal MARC-2 study, very vigorous exercise intensity rather than volume was associated with the progression of predominantly calcified plaque.²⁹ However, the Masters@Heart study identified more mixed plaque in lifelong athletes than in matched healthy late-onset athletes and healthy nonathletes, in what appears to be an exercise dose-response manner.²⁷ Thus, the association of the highest volumes and most vigorous intensities of endurance exercise with improved plaque composition remains uncertain.

POSSIBLE MECHANISMS

Exploration of the mechanisms linking endurance exercise and CAC is critical to delineate the significance of this association, potentially allowing for the uncovering of novel pathways that may help to modify this process. The following sections explore various proposed biological, environmental, and lifestyle-related pathways that may contribute to this phenotype and warrant specific investigation in this setting. While direct causal evidence between exercise and CAC is lacking, the framework we apply for each potential mechanism is (1) how does this process promote calcification? (2) how does endurance exercise promote this process? and (3) what is the likelihood this process mediates the link between exercise and calcification? These findings are summarized in the Table.

Hemodynamic Stresses

Hemodynamic stresses, particularly abnormal or excessive shear and tensile forces, are recognized contributors to endothelial dysfunction and subsequent atherosclerosis.⁴⁶ Under normal physiological conditions, moderate laminar shear stress promotes endothelial health, enhancing nitric oxide production and maintaining vascular homeostasis, with an atheroprotective role for the mechanosensitive transcription factor KLF2 (Krüppel-like factor 2) in this process.^{47,48} However, excessive or disturbed flow patterns—such as oscillatory or turbulent flow—can lead to endothelial injury, activation of pro-inflammatory signaling pathways, increased oxidative

Table. Potential Mechanisms Mediating the Link Between Endurance Exercise and CAC

	Associations with vascular calcification	Associations with endurance exercise	Likelihood of mediating exercise effects on CAC
Hemodynamic stresses	Disturbed flow/shear stress may activate calcification pathways in EC and VSMC	Intense endurance exercise may significantly increase oscillatory shear and tensile stress in the coronary arteries, although direct evidence is lacking	Low
	Oscillatory or disturbed shear stresses lead to endothelial dysfunction and vascular remodeling		
Oxidative stress	Promotes VSMC osteogenic differentiation	Exhaustive/intensive exercise increases ROS acutely	Moderate
	Activates <i>Runx2</i> transcription factor	Regular moderate exercise increases antioxidant defenses and reduces ROS	
	Induces endothelial dysfunction and vascular inflammation		
Inflammation	Drives VSMC osteogenic differentiation	Acute exhaustive exercise elevates systemic inflammation	Moderate
	Stimulates calcification via inflammatory cytokines (eg, IL-6, TNF- α)	Regular moderate exercise reduces systemic inflammation	
PTH	Altered calcium-phosphate balance promotes vascular calcification	High-intensity exercise can influence calcium homeostasis and elevate PTH transiently	Moderate
	Transiently elevated PTH associated with osteogenic differentiation of VSMCs		
Steroid hormones	Androgens promote vascular calcification via receptor-mediated mechanisms, as well as indirectly via altered lipid metabolism and endothelial function	Supplemental testosterone may be used as a performance-enhancing drug by some athletes	Low
	High cortisol promotes vascular calcification	Cortisol increases during competitive stress and high-intensity or prolonged exercise	
	High dose vitamin D induces extensive calcification in animal models	Outdoor exercise may increase vitamin D levels via prolonged sun exposure	
Environmental exposures	Air pollutants (eg, PM _{2.5}) promote VSMC osteogenic differentiation via cytokine release	Outdoor endurance exercise in polluted environments increases exposure	Unclear
Genetics	Polymorphisms in osteogenic genes (eg, <i>BMP2</i> , <i>MGP</i> , <i>RUNX2</i>) increase propensity toward vascular calcification	Endurance exercise associated with epigenetic modifications	Unclear

CAC indicates coronary artery calcification; EC, endothelial cell; IL-6, interleukin-6; PM_{2.5}, particulate matter <2.5 micrometers in diameter; PTH, parathyroid hormone; ROS, reactive oxygen species; TNF- α , tumor necrosis factor-alpha; and VSMC, vascular smooth muscle cell.

stress, and subsequent osteogenic differentiation of endothelial cells via endothelial reprogramming, including endothelial-to-mesenchymal transition.^{48–53} These changes collectively promote vascular calcification, especially at arterial bifurcations or curvatures where disturbed flow is common. Vascular regions subjected to repeated mechanical stress exhibit chronic inflammation and endothelial dysfunction, setting the stage for atherogenesis and calcification progression.^{46,54}

During strenuous exercise, physiological increases in cardiac output and sympathetic activation substantially elevate heart rate, systolic blood pressure, and pulse pressure, intensifying mechanical forces exerted on the arterial wall and exposing vessels to oscillatory shear stress and tensile stress.⁵⁵ Healthy adults commonly experience significant yet transient elevations of systolic blood pressure, frequently surpassing 180 to 200 mm Hg at peak exercise intensities without adverse long-term effects.⁵⁶ However, certain individuals exhibit exaggerated hypertensive responses during exercise, characterized by disproportionate increases in blood pressure that may reflect underlying arterial stiffness or

endothelial dysfunction. Such individuals may experience amplified vascular injury and enhanced susceptibility to endothelial dysfunction with chronic exposure to elevated hemodynamic stresses.⁵⁶ Indeed, resting hypertension is associated with higher CAC scores in the general population,⁵⁷ and although such data in athlete populations are more limited, higher resting systolic blood pressure is also independently predictive of CAC in male masters athletes.⁵⁸ Similarly, in the Coronary Artery Risk Development in Young Adults (CARDIA) study, a higher blood pressure response to submaximal exercise in young adults has been shown to associate with an increased risk of developing CAC in the next 25 years. However, a small study of male masters athletes with significant CAC (>300 Agatston units or >75th Multi-Ethnic Study of Atherosclerosis [MESA] percentile) and those without any CAC (n=20 per group) did not find differences in blood pressure response to a maximal effort endurance cycling test between the groups.⁵⁹

Endurance exercise may thus repeatedly expose the coronary arteries to episodes of exaggerated shear and tensile stress, potentially exacerbating endothelial

damage and oxidative stress, particularly in coronary segments exposed to disturbed or nonlaminar flow.⁶⁰ Such mechanical stresses may further stimulate osteogenic differentiation of VSMCs, promote inflammation, and accelerate the formation and calcification of atherosclerotic plaques.⁵⁴ Despite this compelling mechanistic hypothesis, clinical evidence directly linking repetitive hemodynamic stress during exercise to increased coronary calcification remains indirect, primarily due to challenges in accurately modeling coronary hemodynamics during prolonged endurance activities.

Although mechanistically plausible, several considerations suggest that altered hemodynamic stresses alone are unlikely to fully explain the observed increase in CAC among endurance athletes. The condition of external iliac artery endofibrosis in cyclists, thought to result from repetitive mechanical trauma and friction due to prolonged cycling, notably does not exhibit arterial calcification despite severe vascular remodeling and fibrosis.^{61–64} This observation argues against a purely mechanical explanation for the CAC observed in endurance athletes. Rather, the increased CAC seen among athletes is more likely mediated indirectly through hemodynamic-induced endothelial injury and subsequent promotion of atherosclerotic plaque development, which in turn leads to calcification. While hemodynamic stresses during endurance exercise may act as facilitators or accelerators of endothelial dysfunction and plaque progression, their direct role in calcification requires further empirical investigation through advanced modeling of coronary hemodynamics during exercise.

Oxidative Stress

Oxidative stress results from excessive exposure to reactive oxygen species (ROS), leading to cellular damage and vascular dysfunction. In the vasculature, increased ROS production contributes to endothelial dysfunction by reducing NO bioavailability, enhancing endothelial permeability to atherogenic lipoproteins, and activating inflammatory pathways—all fundamental processes in the development of atherosclerosis and subsequent calcification.^{65–67} At the cellular level, ROS directly promotes the osteogenic differentiation of VSMCs, as demonstrated by increased expression of osteogenic markers such as Runx2 (runt-related transcription factor 2). Early experiments with calcifying vascular cells showed that increasing oxidative stress using hydrogen peroxide or xanthine/xanthine oxidase treatments enhanced osteoblastic differentiation and mineralization.⁶⁸ In VSMCs specifically, ROS activate osteogenic differentiation via signaling pathways involving PI3K/Akt (phosphatidylinositol-3-kinase/protein kinase B) and subsequent Runx2 upregulation, facilitating vascular mineralization and calcification.⁶⁹

Physical exercise induces ROS generation primarily through increased metabolic demands, mitochondrial electron leakage, activation of xanthine oxidase, and NADPH oxidase in contracting muscles and endothelial cells.^{70,71} Although moderate-intensity exercise-induced ROS formation promotes beneficial adaptive responses—such as mitochondrial biogenesis, improved antioxidant capacity, and enhanced vascularization—high-volume, intense endurance exercise can markedly increase oxidative stress beyond beneficial levels.⁷¹ For example, circulating biomarkers of oxidative damage, including malondialdehyde and F2-isoprostanes, are significantly elevated immediately following prolonged endurance events such as marathons, reflecting substantial systemic oxidative stress.⁷² Consistent with elevated oxidative stress, marathon runners have demonstrated impaired flow-mediated dilation post-race, indicative of transient endothelial dysfunction associated with ROS-mediated vascular damage.⁷³ Chronic exposure to repeated bouts of intense exercise could therefore lead to persistent endothelial dysfunction, inflammation, and ultimately, accelerated vascular calcification.

Given robust evidence linking oxidative stress to endothelial dysfunction, vascular inflammation, and osteogenic differentiation of VSMCs, oxidative stress represents a plausible mediator connecting high-intensity endurance exercise to CAC. However, the exact threshold at which exercise-induced ROS production transitions from beneficial adaptive signaling to pathological damage remains uncertain. Importantly, regular moderate-intensity endurance training typically enhances antioxidant defenses and decreases oxidative stress levels, suggesting that oxidative stress-mediated calcification may primarily be relevant in individuals undertaking extremely high-volume or high-intensity endurance exercise without adequate recovery. Notably, an analysis of male masters athletes enrolled in the MARC-2 study did not find an association of advanced glycation end products and their precursors—which can be increased as a result of inflammation and oxidative stress—with CAC.⁷⁴ However, the study was cross-sectional, and advanced glycation endproducts are not specific markers of oxidative stress. Prospective longitudinal studies specifically examining oxidative stress biomarkers and CAC progression in endurance athletes are needed to definitively establish the extent to which oxidative stress mediates the athlete calcification paradox.

Inflammatory Mediators

Inflammatory pathways are intimately linked to the initiation and progression of atherosclerosis and subsequent calcification within plaques. Chronic inflammation promotes endothelial dysfunction, VSMC

activation, and macrophage recruitment—each critical in early plaque formation and progression. Inflammatory cytokines such as IL-6 (interleukin-6), TNF- α (tumor necrosis factor- α), and CRP (C-reactive protein) directly stimulate the activation and transition of VSMCs toward an osteogenic phenotype and accelerate matrix calcification.^{75–80} Along with other cytokines, such as IL-1 β (interleukin-1 β) and TGF- β (transforming growth factor- β), TNF- α may induce endothelial cells to undergo osteogenic differentiation via endothelial-to-mesenchymal transition.⁸¹ Inflammatory signaling can drive macrophages to ingest oxidized LDL (low-density lipoprotein), secrete cytokines, and eventually contribute to the calcific remodeling of plaques.⁸² For example, clinical studies in patients with chronic inflammatory conditions, such as severe rheumatoid arthritis, demonstrate significantly increased CAC scores, supporting inflammation's critical role in calcific vascular remodeling.⁸³

Endurance exercise acutely activates inflammatory pathways, especially after prolonged or intense physical activity. Marathon running and other forms of strenuous exercise cause pronounced transient inflammatory responses, reflected by substantial elevations in circulating cytokines such as IL-6 and CRP. Marathon runners, for instance, exhibit dramatic acute increases in plasma IL-6 levels, from baseline levels around 1 to >100 pg/mL immediately posttrace, alongside sustained elevations in CRP during subsequent recovery periods.^{84–86} Such marked inflammatory spikes represent robust immune system activation, potentially causing endothelial dysfunction and facilitating plaque progression. Over time, repetitive episodes of exhaustive exercise—particularly without adequate recovery—may lead to a persistently heightened inflammatory milieu or chronic low-grade inflammation, potentially accelerating atherosclerosis and vascular calcification in susceptible individuals.

Given the well-established, causal relationship between inflammation and vascular calcification, exercise-induced inflammation represents a plausible mediator linking high-volume endurance exercise to accelerated atherosclerosis and increased CAC scores in athletes, and the potential physiological cascades are depicted in Figure 1. However, there has not been a direct evaluation of these potential mechanisms mediating the effects of exercise on atherosclerotic calcification, and the role of inflammation in this paradox likely depends critically on the balance between acute inflammatory episodes triggered by strenuous exercise and the adaptive anti-inflammatory effects associated with regular moderate exercise. Indeed, habitual moderate-intensity training typically suppresses baseline inflammatory markers, which may offset transient postexercise inflammatory spikes. The critical question remains whether frequent, repetitive, high-intensity training, particularly without adequate recovery, shifts the inflammatory balance toward a

persistent proinflammatory state capable of enhancing vascular calcification.

Parathyroid Hormone

Parathyroid hormone (PTH) is a critical regulator of systemic calcium homeostasis, acting primarily through the PTH1 receptor on bone and kidney to maintain serum calcium concentrations. An important physiological characteristic of PTH is the duration-dependent nature of its biological effects: transient elevations of PTH have distinctly different effects compared with sustained elevations. Brief, intermittent PTH spikes—such as those occurring with daily injections of teriparatide (PTH[1–34])—promote anabolic, promineralization effects in bone and blood vessels, leading to the formation and coalescence of calcium deposits.^{87–90} In contrast, chronically elevated PTH, as seen in secondary hyperparathyroidism associated with chronic kidney disease, promotes bone resorption and pathological calcification in the medial layer of arteries.⁹¹

Preclinical studies using intermittent PTH(1–34) treatment have demonstrated the hormone's capacity to induce coalescence of mineral deposits in various tissues, including femoral bone marrow blood vessels,^{88,89} trabecular bone,⁹² and notably the aortic root.⁸⁷ This phenomenon has been further correlated with reduced uptake of radiolabeled ¹⁸F-sodium fluoride (NaF) positron emission tomography (PET) imaging, suggesting changes in mineral microarchitecture favoring larger, more consolidated calcification patterns.⁸⁷

Endurance exercise consistently results in transient increases in circulating PTH levels. Clinical studies in healthy physically active individuals have shown that a single, moderate-duration exercise bout ($\approx$ 40 minutes) induces a transient rise ($\approx$ 1.8-fold) in serum PTH levels.^{93–95} Animal studies confirm this pattern: in mice, both acute exercise (a single 30-minute treadmill session) and chronic exercise (a progressive treadmill regimen spanning several weeks) elicited similar transient elevations ($\approx$ 2-fold increases) in serum PTH.^{96,97} These transient, repetitive increases in PTH are similar in magnitude and duration to those induced experimentally with intermittent PTH injections known to promote the coalescence of calcific deposits. Interestingly, preclinical studies demonstrated that blocking PTH signaling with a receptor antagonist inhibits the osteoanabolic effects of exercise, confirming that the PTH response is functionally relevant during exercise-induced skeletal adaptations.⁹⁶

The intermittent, exercise-induced rises in PTH represent a biologically plausible mediator linking endurance exercise to increased CAC. In vitro, PTH has been shown to induce chondrogenic differentiation of aortic endothelial cells via endothelial-to-mesenchymal transition,⁹⁸ and in mice, intermittent PTH treatment induces osteoblastic

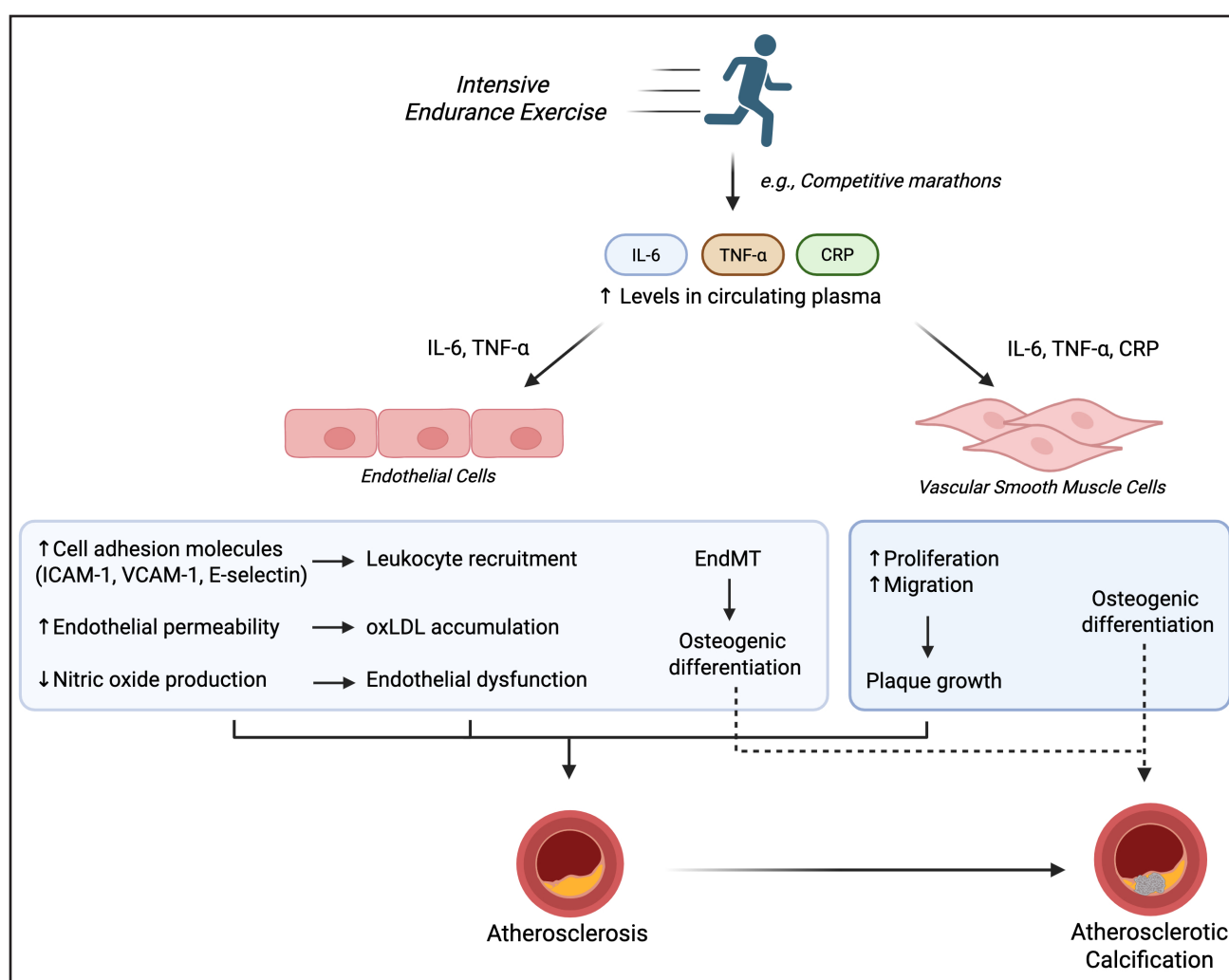


Figure 1. Potential effects of exercise-induced inflammation on the vasculature in calcific atherosclerosis.

Intensive endurance exercise, such as competitive marathons, increases circulating levels of inflammatory cytokines (IL [interleukin]-6, TNF- α [tumor necrosis factor- α]) and proteins (CRP [C-reactive protein]). These inflammatory cytokines have dramatic effects on vascular endothelial cells, such as increasing the expression of cell adhesion molecules that recruit inflammatory cells, increasing endothelial permeability which helps to facilitate the accumulation of ox-LDL (oxidized low-density lipoprotein) particles, reducing nitric oxide production, and inducing osteogenic differentiation via endothelial-to-mesenchymal transition (EndMT). In vascular smooth muscle cells, these inflammatory proteins promote cell activation, resulting in increased cellular proliferation and migration, and osteogenic differentiation via phenotype switching. Collectively, these physiological sequelae can contribute toward the accelerated development of atherosclerotic plaque and calcification. Importantly, the direct involvement of these pathways as the mechanistic link between intensive endurance exercise and atherosclerosis has not been explicitly shown. ICAM-1 indicates intercellular adhesion molecule-1; and VCAM-1, vascular cell adhesion molecule-1.

differentiation of dedifferentiated smooth muscle cells.⁹⁹ Given the established pro-mineralization and calcification-promoting effects of transient PTH spikes observed in experimental studies, repeated exercise-induced transient elevations could similarly promote the coalescence of mineral deposits in coronary plaques (Figure 2). Indeed, our preclinical imaging studies indicate that intermittent PTH treatment and exercise-induced transient PTH elevations result in similar patterns of mineral coalescence within vascular tissues, suggesting a mechanistic link.^{87,97} However, this mechanism has not been definitely shown to mediate these effects of exercise, and further studies specifically exploring PTH signaling pathways are needed.

Steroid Hormones

Steroid hormones, including testosterone, cortisol, and vitamin D, have significant effects on cardiovascular health, potentially affecting vascular calcification through several mechanisms. As indicated in prior reviews,^{100,101} most evidence indicates that supplemental testosterone beyond physiological levels in humans, as in athletes using steroids for enhanced performance, is associated with increased coronary plaque and that hypogonadal men have a higher risk of cardiovascular events. Elevated androgen levels, particularly supraphysiological doses of anabolic-androgenic steroids, have been associated with increased coronary plaque burden and accelerated

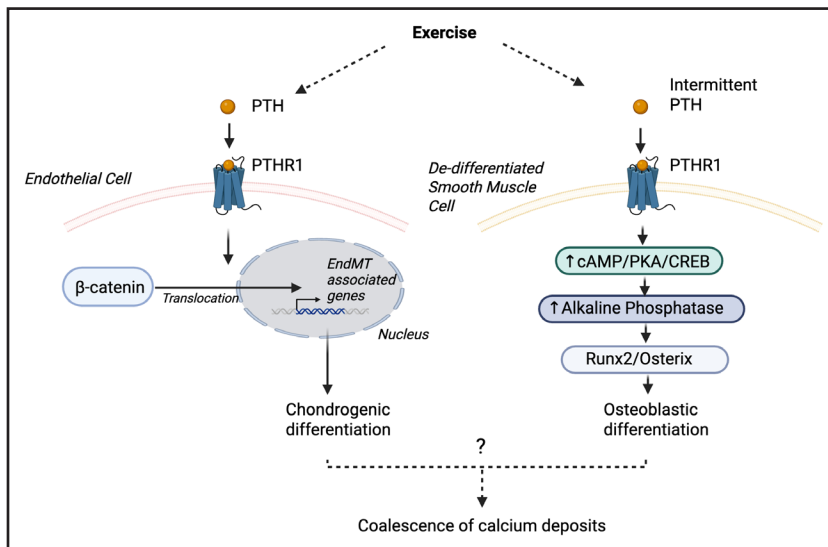


Figure 2. Potential mechanisms of exercise-induced parathyroid hormone (PTH) effects on vascular calcification.

Exercise-induced increases in circulating PTH levels may impact vascular calcification via receptor-mediated actions on endothelial cells and vascular mesenchymal cells, such as dedifferentiated smooth muscle cells. The chondrogenic and osteoblastic differentiation seen in response to PTH treatment in these cell types can potentially contribute to the effects of PTH on the coalescence of atherosclerotic calcium deposits seen in animal studies, although these precise mechanisms have not been definitively shown. CREB indicates cAMP response element binding protein; EndMT, endothelial-to-mesenchymal transition; PKA, protein kinase A; PTHR1, parathyroid hormone receptor 1; and Runx2, runt-related transcription factor 2.

atherosclerosis. For instance, studies in bodybuilders consistently demonstrate greater CAC prevalence and severity than expected based on age and traditional risk profiles, suggesting a direct procalcific effect of anabolic-androgenic steroids.^{102,103} Mechanistic animal studies have confirmed that androgen treatment directly increases calcification in vascular tissues independent of lipid alterations, involving upregulation of androgen receptor expression and downregulation of estrogen receptor alpha, highlighting receptor-mediated mechanisms in steroid-induced vascular calcification.¹⁰⁴

Exercise at high intensities or for prolonged duration increases circulating blood levels of cortisol,¹⁰⁵ although notably these increases may be blunted in trained athletes. Hair cortisol concentrations are increased in endurance athletes, suggesting elevated cortisol exposure over time.¹⁰⁶

High cortisol concentrations can promote vascular calcification via synergistic activation of mineralocorticoid receptors alongside aldosterone.¹⁰⁷ Beyond the cortisol response to exercise itself, the mental stress that may accompany training for athletic competition may also increase cortisol levels, and cortisol elevations related to psychosocial stress has been associated with a higher risk of CAC presence and progression.^{108,109} However, to our knowledge, cortisol levels (baseline or exercise-associated) in masters athletes with CAC have not been specifically studied, although notably psychosocial stress scores did not seem to be predictive of CAC of predominantly recreational masters athletes in the MARC-2 study.⁵⁸

Another steroid hormone with a potential link to calcification is a secosteroid, which, like sex steroid hormones, is derived from cholesterol. This steroid hormone, 1,25-dihydroxyD, is widely, although erroneously, considered a vitamin, vitamin D. Levels of the storage form, 25-hydroxyD, are associated with exercise, especially

endurance exercise. A meta-analysis of studies intervening with exercise and testing for effects on 25-hydroxyD levels showed no direct relationship, and the authors concluded that the association with endurance exercise may be due to its association with time outdoors and ultraviolet light-induced increases in 25-hydroxyD.¹¹⁰ In any case, the elevated level of 25-hydroxyD may contribute to coronary calcification in this manner, given that animal studies over many decades have consistently shown that high-dose vitamin D treatment causes extensive vascular calcification.¹¹¹

Ultimately, steroid hormone alterations may partially contribute to the athlete calcification paradox, although given limited data, their collective contributory weight to this association is likely to be low. Further longitudinal studies examining hormone profiles alongside CAC progression are necessary to clarify their precise roles.

Environmental Exposures

Environmental air pollutants, particularly fine particulate matter <2.5 μm in diameter, nitrogen dioxide (NO₂), and ozone, are recognized contributors to the initiation and progression of coronary artery disease and calcification. Exposure to air pollutants leads to endothelial dysfunction, increased oxidative stress, and heightened systemic inflammation—pathways intimately linked to vascular calcification.^{112,113} Exposure to particulate matter <2.5 μm in diameter specifically promotes calcification by directly stimulating inflammatory cytokine release, including IL-6 and TNF-α, activating oxidative stress pathways, and driving osteogenic differentiation of VSMCs.^{114–116} Epidemiological studies consistently demonstrate robust associations between long-term exposure to particulate matter <2.5 μm in diameter and increased prevalence and severity of CAC in general populations, underscoring its potent atherogenic potential.¹¹⁷

Endurance athletes typically spend substantial amounts of time exercising outdoors, increasing their exposure to ambient pollutants. The vigorous respiratory demands associated with endurance exercise significantly enhance pulmonary ventilation rates, resulting in deeper inhalation and greater deposition of airborne pollutants within the lungs.¹¹⁸ Acute exposure during exercise facilitates enhanced absorption and systemic dissemination of pollutants compared with resting conditions, theoretically amplifying their cardiovascular impact. Consequently, frequent outdoor exercise in environments with elevated pollutant levels—such as urban areas with dense traffic or industrial emissions—may repeatedly expose athletes to pollutant-driven vascular injury and inflammation, potentially promoting calcification processes.

Populations of athletes studied for CAC prevalence, including marathon runners from urban regions in Germany and recreational endurance athletes from cities in the Netherlands, indeed reside in areas where pollutant exposure is generally moderate to high.^{5,26} Thus, prolonged outdoor training sessions in urban environments may indirectly facilitate coronary calcification in these athletes through heightened exposure and susceptibility to pollutant-induced vascular damage, although this hypothesis remains speculative and not directly studied. Explicit data directly correlating pollution exposure levels to calcification outcomes specifically in endurance athletes does not exist to our knowledge.

Genetics

Genetic factors contribute significantly to the variability in CAC scores among the general population, with heritability estimates ranging from $\approx 40\%$ to 60% .¹¹⁹ Numerous genetic loci, associated with coronary artery disease and calcification, have been identified through genome-wide association studies, highlighting the polygenic nature of these traits.¹²⁰ Among key genetic determinants, variations within genes related to lipid metabolism, inflammation, and mineral metabolism pathways have consistently emerged. For example, polymorphisms in the 9p21 locus, as well as genes involved in lipid metabolism, VSMC differentiation, and inflammation, are strongly associated with coronary calcification and cardiovascular events.^{119,121} Additionally, polymorphisms in genes encoding osteogenic signaling molecules—such as BMP2 (bone morphogenetic protein-2), MGP (matrix Gla protein), and Runx2 transcription factor—are specifically implicated in the propensity toward vascular calcification, further suggesting a genetic predisposition to calcium deposition in arterial tissue.¹²²

In the context of endurance athletes, genetics may influence susceptibility to exercise-induced CAC. Individual genetic variations could modulate how vascular cells respond to repeated mechanical stress, oxidative

stress, inflammation, and hormonal fluctuations associated with endurance training. Genetic susceptibility to oxidative damage, impaired calcium-phosphate metabolism, and heightened inflammatory responses could predispose certain athletes to accelerated calcification processes despite similar training loads and cardiovascular risk profiles.⁶ Indeed, individual variability observed in the CAC responses of endurance athletes suggests that genetic predisposition plays an influential role. Thus, an understanding of genetic determinants could help identify athletes at greater risk and allow for individualized preventive strategies or monitoring approaches in this population. Lastly, as the Molecular Transducers of Physical Activity Consortium (MoTrPAC) study has recently demonstrated, endurance exercise training induces a vast array of transcriptional and epigenetic modifications across tissues in rats;^{123,124} the multiomic data from the human participants enrolled in the study will help to bridge the clinical relevance of these findings to highlight candidate mechanistic pathways to target in athlete studies.¹²⁵ Further investigations employing integrative genomic and epigenomic analyses, particularly among cohorts of endurance athletes, are essential to fully elucidate these genetic influences and identify individuals who may be uniquely susceptible to exercise-associated vascular calcification. Although the role of genetic factors in linking endurance exercise and CAC is currently unclear, such studies may uncover a strong influence, as was seen for the role of polygenic risk scores in identifying athletes who develop reduced myocardial function in the Pro@Heart study.¹²⁶

FUTURE DIRECTIONS

Although substantial evidence supports the athlete calcification paradox seen in older males, several critical knowledge gaps remain. Addressing these gaps may refine clinical risk stratification and provide deeper insights into underlying pathophysiology. Given the established association of the highest volumes of endurance exercise with CAC, contemporary American Heart Association and American College of Cardiology guidelines do not recommend routine assessment of CAC scores as part of risk stratification for asymptomatic masters athletes deemed to have low atherosclerotic cardiovascular disease risk.¹²⁷ Rather, CAC testing or coronary CT angiography can be considered in those at intermediate to high atherosclerotic cardiovascular disease risk.

Future investigations should explore biomarkers longitudinally at earlier time points before the development of CAC that help identify which athletes are at increased risk for CAC. Cross-sectional analyses of candidate biomarkers once CAC is already present may not capture the most relevant window, both mechanistically and clinically. Traditional risk factors, such as elevated LDL cholesterol, have been assessed in many of the studies

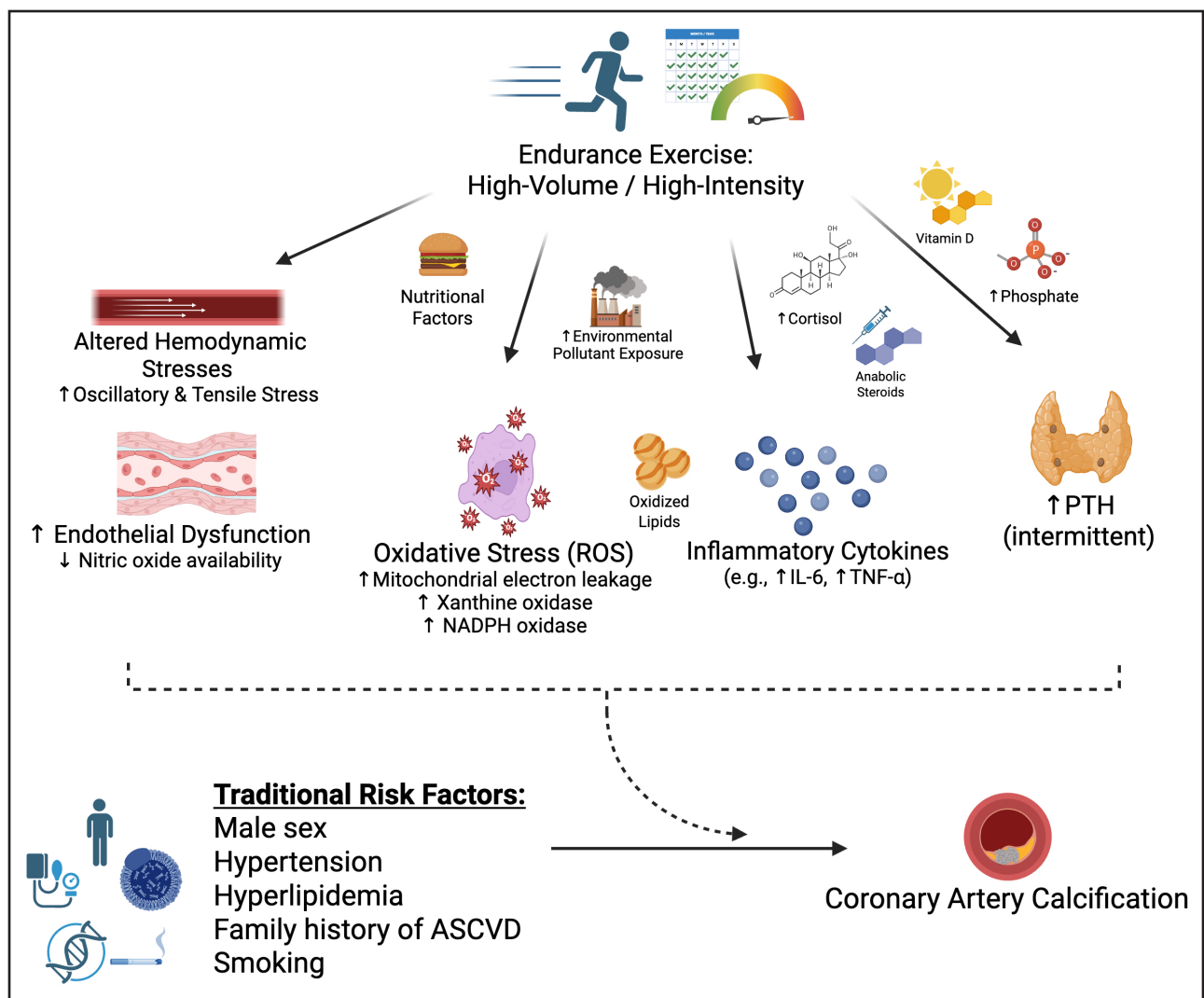


Figure 3. Potential mechanisms linking endurance exercise with coronary artery calcification.

Schematic diagram depicting the potential mechanisms for the athlete calcification paradox. ASCVD indicates atherosclerotic cardiovascular disease; IL, interleukin; NADPH, nicotinamide adenine dinucleotide phosphate; PTH, parathyroid hormone; ROS, reactive oxygen species; and TNF- α , tumor necrosis factor- α .

described above, with similar or lower levels unsurprisingly seen in those with higher exercise volume. Lp(a) (lipoprotein[a]) has emerged as a strong predictor of atherosclerotic cardiovascular disease risk even in the presence of normal LDL cholesterol levels.¹²⁸ Whether an elevated Lp(a) increases the likelihood an athlete will develop CAC remains to be determined. Examining the predictive value of Lp(a) and other biomarkers specifically among endurance athletes may facilitate the identification of individuals at greater risk for exercise-associated CAC development.

Advanced imaging modalities, including PET/CT, present exciting avenues for research. PET/CT imaging can assess active calcification processes at the molecular level, allowing evaluation of osteogenic activity within plaques through uptake of tracers such as ¹⁸F-NaF. Recent studies have demonstrated the feasibility of detecting mineral surface area of aortic calcified deposits using ¹⁸F-NaF

PET imaging in animal models,^{97,129} because fluoride is incorporated into calcium deposits by exchanging with the hydroxyl group of hydroxyapatite. Thus, fused calcium deposits may appear in serial images as a decrease in ¹⁸F-NaF uptake by PET despite an increase in mineral content by CT imaging.^{87,97} Clinical findings support this theory. ¹⁸F-NaF PET imaging of fluoride uptake associates with vulnerable plaque in patients.¹³⁰ This relationship is so strong that the presence of a spotty pattern of calcium deposits is now considered a major feature for identifying high-risk plaque.^{131–133} This approach could potentially be translated into human athlete populations to better characterize dynamic calcification changes during endurance training, potentially helping to clarify the question of whether the CAC seen in the masters athlete population is a more stable plaque phenotype.

Another crucial future research priority involves addressing the notable sex-based differences observed

in the relationship between exercise and CAC. Recent findings indicate that female endurance athletes do not exhibit increased CAC scores, unlike their male counterparts.³⁵ Investigating hormonal and genetic mechanisms underlying these sex differences will enhance our understanding of CAC pathophysiology in athletes, such as identifying protective factors, and refine risk stratification in female populations.

Lastly, longitudinal observational and outcome studies specifically evaluating cardiovascular event rates among endurance athletes are essential. For robust outcome assessment, accurate quantification of physical activity is essential. Emerging wearable technologies now enable precise, real-time quantification of exercise intensity and volume, surpassing traditional self-report measures that may underestimate or overestimate exercise volume and intensity. Leveraging wearable technology and precise activity tracking (including wearables, accelerometers, and global positioning system tracking) could provide highly accurate dose-response relationships between exercise and CAC progression. These data would inform appropriate exercise recommendations to minimize potential adverse cardiovascular outcomes.

CONCLUSIONS

The athlete calcification paradox presents a complex clinical scenario, wherein older male endurance athletes paradoxically exhibit increased CAC despite favorable cardiovascular health profiles. Although elevated CAC scores traditionally indicate increased cardiovascular risk, the generally better cardiovascular outcomes seen in this population suggest that they may have a less harmful plaque phenotype, although more recent imaging studies suggest this may not be the case. Regardless, a deeper understanding of the cellular, molecular, and tissue-level mechanisms—including oxidative stress, mechanical factors, hormonal and inflammatory responses, and genetic predisposition (Figure 3)—is essential for elucidating this paradox and guiding more precise counseling on the risk and benefit balance of exercise at the upper end of the physical activity spectrum.

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Disclosures

None.

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