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Potential mechanisms linking high-volume exercise with coronary artery calcification

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Abstract

Recent studies have found an association between high volumes of physical activity and increased levels of coronary artery calcification (CAC) among older male endurance athletes, yet the underlying mechanisms have remained largely elusive. Potential mechanisms include greater exposure to inflammatory cytokines, reactive oxygen species, and oxidized low-density lipoproteins, as acute strenuous physical activity has been found to enhance their systemic release. Other possibilities include post-exercise elevations in circulating parathyroid hormone, which can modify the amount and morphology of calcific plaque, and long-term exposure to non-laminar blood flow within the coronary arteries during vigorous physical activity, particularly in individuals with pre-existing atherosclerosis. Further, although the association has only been identified in men, the role of testosterone in this process remains unclear. This brief review discusses the association between high-volume endurance exercise and CAC in older men, elaborates on the potential mechanisms underlying the increased calcification, and provides clinical implications and recommendations for those at risk.

Introduction

Routine exercise has been demonstrated to significantly reduce cardiovascular disease (CVD) risk and increase longevity.[1,2] While physical activity improves cardiovascular

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risk profiles, high volumes of endurance exercise are associated with increased coronary artery calcification (CAC) in men.[2–6] Exercise volume captures the intensity and duration of exercise over time, often measured in metabolic equivalents (MET)-minutes/week. Elite endurance activity refers to such activities as competitive cycling, marathon running, or rowing, where maximal oxygen consumption often reaches levels of 40–85 mL/kg/min. Because CAC is considered a marker for coronary artery disease due to its relationship with atherosclerosis and cardiovascular risk,[7,8] this paradoxical association between exercise and CAC has catalyzed interest in the question of whether extreme degrees of physical activity may be associated with accentuated cardiovascular risk. In this review, we focus on the implications of CAC morphology, potential mechanisms linking exercise and CAC, and clinical implications for athletic patients.

Coronary artery calcification

CAC assessed via computed tomographic (CT) imaging correlates with both coronary plaque burden and cardiovascular events.[3,8] An elevated CAC score significantly increases cardiovascular risk in the general population. For example, a 50-year-old normotensive Caucasian male with normal total and HDL cholesterol without medications has an estimated 10-year CVD risk of 1.4% if his CAC score is 0, whereas his risk increases to 5.0% at CAC=100 and to 6.6% at CAC=300.[9] CAC score is a rough estimate of calcium content in the coronary arteries based on a formula involving the product of mineral density and volume. While high CAC is strongly associated with cardiovascular risk, calcification density may also influence risk, where higher density associates with a lower risk of events.[10] Although nascent calcium deposition within the intimal layer of the coronary vessel wall may be too small to reach the detectable threshold by CT, as these deposits grow and/or coalesce with adjacent deposits over time, they would reach the threshold for detection. The size, morphology, and location of these calcium deposits are integral determinants of plaque stability.[8]

Plaques demonstrating a “speckled” or “spotty” pattern of calcification – with small calcium deposits on the order of ~500 micrometers in diameter - are thought to confer an increased risk of plaque rupture.[8] This pattern is frequently observed in patients with acute coronary syndrome,[11–13] and it is associated with accelerated atheroma progression [14] and an increased risk for cardiac death (Supplementary Table).[15]

Conversely, whether larger calcified deposits within atherosclerotic plaque imparts lower risk of plaque rupture is not entirely clear. Based on biomechanical analyses, rupture (de-bonding) stress concentrates at the interface area between a rigid calcium deposit and the flexible surrounding tissue,[16] and the total surface area of this interface is positively related to the magnitude of concentrated stress. Many small, calcified deposits (such as in the speckled pattern) will result in higher total surface area, and, as these deposits grow and coalesce into larger calcified tissue, the interface surface area can decrease.[17] Larger calcium deposits may experience relatively less mechanical stress than the same amount of mineral in fragments. Given that calcium hydroxyapatite mineral has a known, fixed density, any calcium deposit that appears to have low density on imaging must consist of a porous deposit or a cluster of smaller deposits interspersed within soft tissue. Therefore, the

biomechanical analysis indicating that, for a given amount of mineral content, speckled calcification with high surface area confers higher risk is consistent with the clinical observation that for any degree of CAC content, a lower CAC density is associated with greater risk.[10]

In addition to the size and density of calcium deposits, their location, morphology, and other features influence lesion stability. The proximity of deposits - to one another, to the lumen, and to lipid pools - magnifies the stress.[16] The strength of the bonding between hard and soft tissue is an additional key determinant. As deposits mature and coalesce, the surrounding tissue may increase its strength, such as by collagen deposition or alignment of collagen fibers. These tissue property changes may reduce the risk of rupture at the surface of larger deposits. Importantly, non-contrast CT imaging does not capture other morphological features of calcified plaque, such as its composition. Stable calcified plaques have a smaller lipid pool, fewer inflammatory cytokines, and thicker fibrous caps. They have decreased risk for plaque rupture, subsequent thrombosis, and acute myocardial infarction.[10] For example, when coronary CT angiography was used to assess the coronary vasculature, plaques bearing a predominantly calcified morphology were associated with a lower risk of adverse events than non-calcified, soft tissue plaques.[18] Recently, use of machine-learning radiomics modeling, which extracted predictive features of CAC lesions (e.g., texture, shape) on cardiac CT scans, was found to augment risk stratification beyond the routine CAC score.[19] Thus, while CAC scores may reasonably predict cardiovascular events in the general population, use of additional imaging modalities or analyses may be useful in refining risk stratification by providing a deeper assessment of plaque composition and associated vulnerability.

Elite endurance exercise and CAC

Among the earliest studies evaluating the link between exercise and CAC, Möhlenkamp et al investigated the association between endurance exercise and atherosclerosis in middle-aged marathon runners,[4] comparing an athletic cohort against both age-matched and Framingham Risk Score (FRS)-matched control groups. Marathon runners were found to have similar degrees of CAC when compared to age-matched controls, but significantly greater CAC when compared to FRS-matched counterparts.[4] Similar associations were observed among middle-aged endurance athletes with low atherosclerotic risk. In a study that evaluated masters athletes with no appreciable cardiovascular risk factors, the male athletes were found to have higher CAC scores than their sedentary FRS-matched controls (Figure 1A).[5] A CAC score >70th percentile was positively associated with the number of years of training in these athletes.[5] Coronary plaques from the athletic cohort consisted predominantly of calcium, rather than the mixed morphology more commonly observed in sedentary males (Figure 1B). Notably, the female masters athletes did not have a higher prevalence of CAC compared to their control group.

A similar study by the Eijsvogels group found that higher lifetime volume of exercise is associated with an increased risk for CAC in men.[3] Middle-aged male recreational athletes were stratified by self-reported lifetime exercise history. Those men classified within the highest exercise-volume cohort (>2000 MET-min/week) were found to have

significantly greater prevalence and severity of CAC when compared to men from the lowest exercise-volume cohort (<1000 MET-min/week) (Figure 1C).[3] For reference, current physical activity guidelines recommend between 500–1000 MET-min/week,[1] less than half of the exercise dose performed by the highest exercise-volume cohort in this study. Additionally, the highest exercise-volume cohort were also found to have the greatest prevalence of atherosclerotic plaques (Figure 1D). Imaging analyses of these atherosclerotic lesions also revealed that this group had the greatest prevalence of calcified plaques and the lowest prevalence of mixed composition and non-calcified plaques.[3] This study suggests that while athletes with the highest level of physical activity are more likely to have atherosclerosis and CAC, when present, these plaques are more likely to have a lower risk morphology compared to those seen in more sedentary groups. Aengevaeren and colleagues recently published a follow-up study on this cohort demonstrating that very vigorous exercise intensity, rather than exercise volume, was associated with a greater CAC increase and plaque progression.[20] While the significance of changes in CAC is currently unclear, these results suggest an intensity threshold for the effect of exercise on calcification progression.

Potential mechanisms linking high intensity exercise to CAC

Mechanical stress—Among the potential mechanisms posed connecting higher levels of exercise with CAC is the role of mechanical stress experienced by the coronary vasculature during vigorous physical activity. During intense exercise, the increase in heart rate and contractility may create adverse fluid dynamics.[21] The wall shear stresses along the coronary endothelium are increased by exercise including at the sites of non-laminar (“disturbed”) blood flow, such as arterial branch points. Disturbed and oscillatory flow patterns are associated with endothelial cell dysfunction and the formation of fatty streaks, precursors of atherosclerotic plaques.[22] (Figure 2A) Supraphysiologic wall shear stress, such as that seen during high intensity exercise, similarly leads to excessive reactive oxygen species (ROS) production in endothelial cells.[23,24] Thus, it is possible that, in certain patients, long-term exposure to the hemodynamics that result from excessively strenuous physical activity may contribute to atherosclerotic plaque formation.[22]

Importantly, however, if altered coronary hemodynamics alone were the causative factor for CAC, most masters endurance athletes would have increased CAC. Yet Merghani et al found that most athletes (~60%) have a normal CAC score.[5] One potential explanation is that exercise-induced hemodynamic changes may accelerate atherosclerosis and CAC development in athletes with pre-existing disease. In a study by the Baggish group, in which 8 runners were followed over the course of a 140-day “Race Across the USA,” the effects of this extreme level of endurance exercise on coronary plaque anatomy were evaluated by coronary CT angiography.[25] Four runners had no plaque seen on their baseline study and remained free of atherosclerotic plaque after the race. However, for the other four runners who had pre-existing coronary artery disease, plaque size increased in each runner by the end of the race. This change was predominantly driven by an increase in non-calcified plaque, but 3 of the 4 runners also had a slight increase in calcified plaque volume. Thus, it is possible that high volumes of intense exercise may not necessarily promote

the development of atherosclerotic plaque but may instead accelerate the progression of pre-existing coronary lesions.

Parathyroid hormone—Parathyroid hormone (PTH) is a principal regulator of calcium homeostasis and is thought to be associated with the pathogenesis of cardiovascular disease. Patients with primary hyperparathyroidism have a higher prevalence of cardiovascular disease, including aortic valve calcification, aortic stiffness, coronary microvascular dysfunction, endothelial dysfunction, and hypertension.[26] Patients with secondary hyperparathyroidism have an increased risk of cardiovascular mortality secondary to vascular and valvular calcifications.[26] PTH has also been strongly associated with atherosclerosis in population studies.[27]

In mice, brief treadmill exercise (30 minutes) raises serum PTH levels.[28] In hyperlipidemic mice, endurance exercise, in the form of a progressive treadmill regimen, doubles serum PTH levels compared to those in sedentary mice.[29] While mice in the control and exercised cohorts had similar progression of aortic calcification by CT, histopathology showed that exercised mice had coalescence of calcium into larger macrocalcium deposits with decreased mineral surface area (Figure 3). Daily PTH injections in mice similarly promoted coalescence of mineral deposits in the aorta.[30]

In humans, serum PTH is also raised immediately post-exercise.[31] The degree of PTH elevation depends on both exercise duration and intensity, suggesting a threshold effect. Either high-intensity and long-duration exercise, or low-intensity and extremely long-duration (5 hours) exercise, are required to raise serum PTH. This threshold effect may explain the dose-dependence of vascular calcification on exercise volume observed (Figure 2B). However, the direct effect of exercise-induced PTH elevation on the coronary vasculature remains unknown.

Oxidative stress—Oxidative stress occurs when there is an abundance of ROS and/or diminished antioxidant capacity. Excessive free radical species are known to contribute to vascular damage. ROS are intimately involved in the formation of atherosclerotic plaques through their role in producing oxidized low-density lipoproteins (LDL), triggering the pathogenesis of plaque formation.[32] The increased prevalence of atherosclerotic plaques at sites of turbulent blood flow, which boast increased ROS and diminished vasodilatory nitric oxide, supports the role of oxidative stress in atherosclerotic plaque formation. Furthermore, key risk factors for atherosclerosis, including hyperlipidemia and tobacco smoking, are associated with increased production of ROS.[32]

The effects of exercise on oxidative stress are not straightforward. Acute bouts of strenuous exercise generate ROS, thereby increasing vascular oxidative stress (Figure 2C).[33] Oxygen radicals induced by acute, intense exercise may account for the link to vascular calcification, since they promote osteogenic differentiation and calcium mineralization in vascular cells.[34] However, consistent exercise induces athero-protective effects such as downregulation of the pro-oxidant enzyme NADPH oxidase and upregulation of antioxidant enzymes such as superoxide dismutase in the endothelium.[33] Thus, while strenuous exercise generates

the release of ROS that may contribute to atherogenesis and CAC, a regular exercise regimen likely helps to counteract this effect by inducing antioxidant defenses.

Inflammatory mediators—Inflammatory mediators are closely associated with the development and destabilization of atherosclerotic plaques.[35] During the initiating step of plaque formation, LDL accumulates within the tunica intima and is subsequently converted to oxidized LDL by ROS. Chemokines are then responsible for the recruitment of immune cells, including macrophages, which consume oxidized LDL via scavenger receptors and toll-like receptors. Downstream signaling events result in the release of pro-inflammatory cytokines which are principal mediators in inflammation and plaque growth. Once plaque has formed, inflammatory mediators are also involved in the processes of plaque rupture and thrombosis.[35]

The greater extent of CAC among patients with more severe rheumatoid arthritis suggests a role for inflammatory mediators in the pathogenesis of atherosclerotic calcification.[36] Exhaustive exercise results in enhanced systemic release of proinflammatory cytokines and markers (Figure 2D).[25,37] Marathon runners demonstrated elevations in plasma IL-6 from 1.27 pg/ml at baseline to 101.4 pg/ml post-race.[37] For reference, baseline IL-6 level >2.8 pg/ml is associated with an increased risk of myocardial infarction in healthy men.[38] Similarly, elevations in C-reactive protein (CRP) were observed in the majority of athletes who completed an ultra-endurance competition, [25] with three out of six athletes transitioning from a baseline low-risk (<1.0mg/L) to an intermediate-risk CRP level (1–3 mg/L) post-race. While the role of inflammatory mediators in atherogenic processes is well-documented, how these inflammatory mechanisms affect CAC in athletes requires further elucidation.

Testosterone—The increased prevalence of CAC among male endurance athletes, but not in female athletes, raises the question of the role of sex hormones in the pathophysiology of atherosclerotic calcification. While endogenous estrogen is thought to be protective against atherosclerosis, with post-menopausal women showing a greater risk of CAC, the effect of testosterone remains unclear. Testosterone administration in experimental models has been observed to be both pro-calcific and anti-calcific. Testosterone induced calcification of vascular smooth muscle cells (VSMC) via the androgen receptor in one study,[39] while it inhibited VSMC calcification in another.[40] In hyperlipidemic mice, supplemental testosterone increased atherosclerotic calcification.[41] Epidemiological studies have demonstrated low testosterone is strongly associated with coronary artery disease and cardiovascular events.[42] However, clinical studies evaluating the cardiovascular effects of testosterone supplementation in men have had conflicting results; some have identified increased cardiovascular events with testosterone, whereas others have found a decrease or no change in these outcomes.[42] Interestingly, testosterone treatment for 1 year led to a greater increase in non-calcified coronary plaque volume, but no significant change in CAC score.[43] These findings suggest a threshold level of testosterone to maintain cardiovascular health, but more research is needed to decipher its role in atherosclerotic calcification (Figure 2E).

Clinical implications

While CAC is associated with an increased risk of adverse cardiac events within the general population, this association may not necessarily apply to masters athletes in the same manner, and identification of CAC alone should not discourage individuals from engaging in higher levels of physical activity. Even in individuals with prevalent CAC (≥100 AU), higher levels of physical activity are not associated with increased cardiovascular or all-cause mortality.[2,44] Nevertheless, it remains critically important to identify underlying cardiovascular risks and symptoms which may go underrecognized in athletic populations. For older asymptomatic athletes, cardiovascular risk should be objectively assessed and integrated into treatment recommendations according to primary prevention guidelines.[45] Notably, conventional preparticipation risk stratification in this population (cardiovascular risk assessment, ECG, echocardiogram, exercise testing), was found to have limited sensitivity in identifying subclinical coronary artery disease,[46] and further evaluation with cardiac CT can be considered. If CAC is identified, the athlete should be treated according to guidelines,[45] with consideration of statin therapy when appropriate, and counseled on the potential risks of strenuous exercise as well as symptoms that should prompt urgent clinical re-assessment. Objective evaluation of cardiorespiratory fitness on exercise testing can further aid in risk stratification, as higher baseline fitness is associated with lower cardiovascular risk even in the presence of CAC.[47]

Nonetheless, these risks should be weighed against the wide-ranging benefits of exercise, which are speculated to extend beyond the attenuation of traditional cardiovascular risk factors. The hearts of endurance athletes undergo beneficial physiological remodeling—with improved myocardial and vascular compliance.[48,49] Endurance athletes also demonstrate marked dilation of the coronary arteries and greatly improved microvascular collateral circulation.[4,50] These features may be important factors in mitigating the increase in plaque burden in some athletes. There may also be substantial health benefits to the increased postural stability and coordination associated with physical activity.

Summary—Multiple studies have revealed the increased prevalence and severity of subclinical coronary artery plaques among a significant minority of male endurance athletes. The plaques from athlete cohorts are comprised predominantly of calcium, which are thought to confer greater protection against rupture than mixed plaques. While CAC is strongly associated with adverse outcomes in the general population, whether the same degree of increased risk is present among athletes is unclear, though an elevated risk is likely still present and warrants attention.[47] Highly active individuals have been found to have improved survival relative to sedentary controls, even in the presence of higher CAC.[2] Physical activity may indirectly contribute to increased survival due to attenuation of atherosclerotic risk factors or improved coronary collateral perfusion.

The list of potential mechanisms reviewed above is not comprehensive, and other possible contributors, such as diet and supplement use, have been excellently reviewed elsewhere [6] and should be considered. Studies characterizing the molecular changes induced by exercise in athletes via multi-omic approaches, such as the ongoing Molecular Transducers of Physical Activity Consortium (MoTrPAC), and particularly those examining the differential

effects of moderate- and high-intensity exercise, [51] will deepen our understanding of these mechanisms. Importantly, longitudinal assessments evaluating the prognostic significance of CAC specifically in athlete cohorts are needed to help inform clinical management. Further, as a majority of studies strictly followed middle-aged white males, more inclusive studies are required to understand how this association manifests among female athletes and athletes of different races and ethnicities. Ultimately, while the added benefit of extremely high lifetime levels of physical activity remains uncertain, physical activity at the recommended dose has been unequivocally shown to improve cardiovascular risk factors, longevity, and wellbeing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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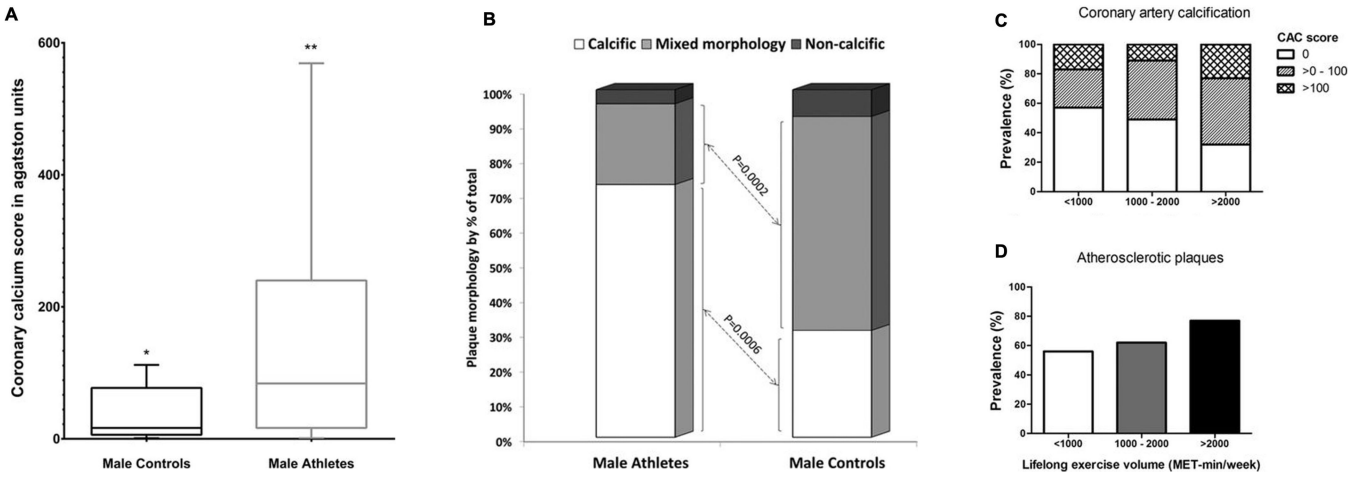

Figure 1. Higher prevalence of coronary artery calcium (CAC) in male endurance athletes.

A, Comparison of CAC score among male athletes and sedentary males with CAC ≥ 1 Agatston units. Tukey Box-and-whisker plot of CAC scores among male endurance athletes and sedentary male controls. Male athletes demonstrate a greater likelihood of having a CAC score > 300 Agatston units compared to sedentary males with a similar atherosclerotic risk profile. **B**, Morphology of atherosclerotic plaques among male athletes and sedentary male controls. 99 coronary plaques were isolated from male athletes and 26 coronary plaques were isolated from male controls. Male athletes demonstrate a predominance of calcified plaque morphology. **C**, Comparison of CAC score across three exercise-volume groups. Data was obtained from CT coronary angiography scans. Significantly higher CAC scores were observed among the highest exercise-volume group (>2000 MET-min/week). **D**, Comparison of the prevalence of atherosclerotic plaques among three exercise-volume groups. Increased prevalence of atherosclerotic plaques were observed among the highest exercise-volume group (>2000 MET-min/week). Reprinted with permission from References [3] and [5].

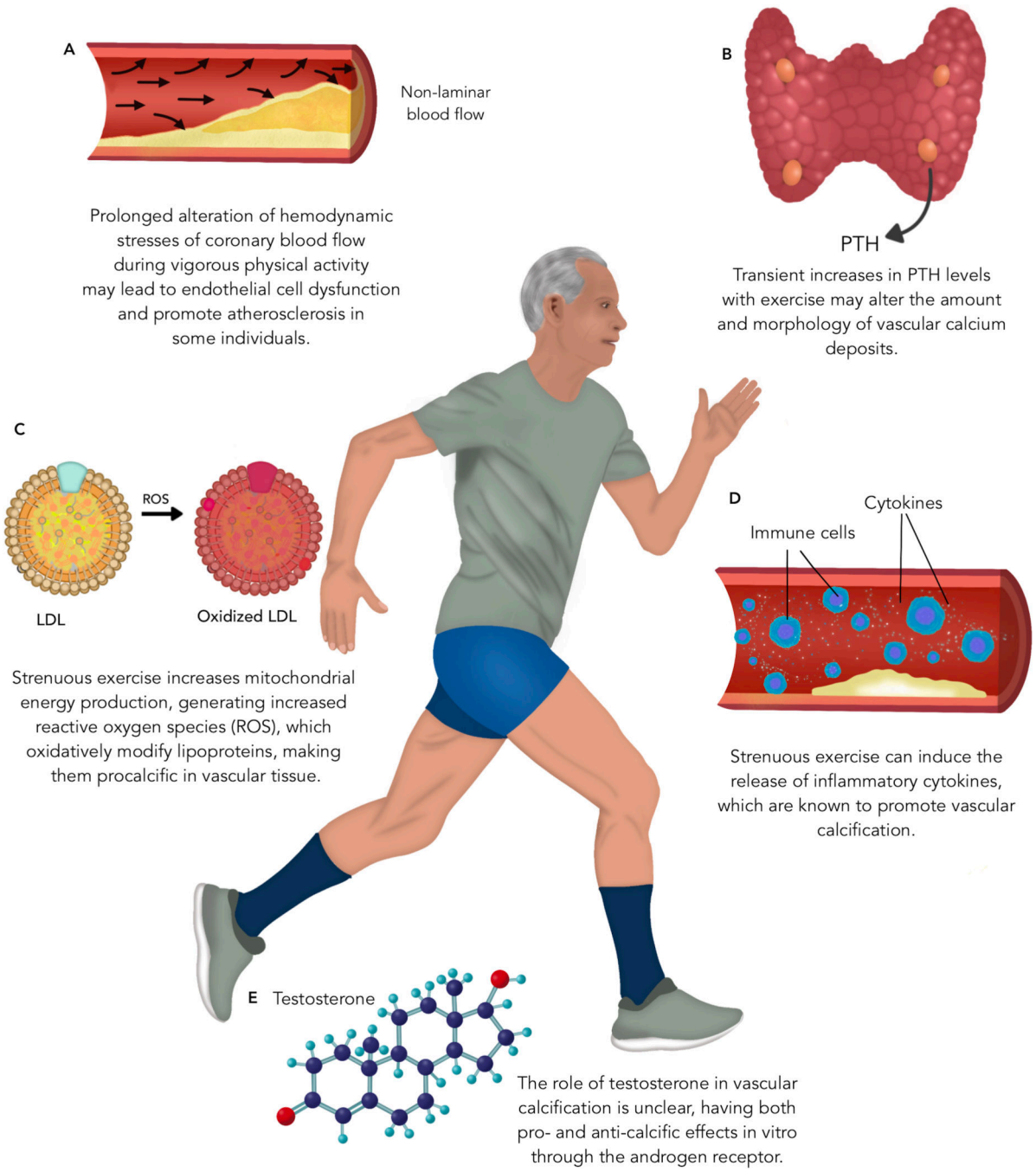

Figure 2. Potential mechanisms linking endurance exercise to coronary artery calcification.

While there are no definitive mechanisms identified for the association of high-volumes of endurance exercise with coronary artery calcification in older male athletes, potential mechanisms include: (A) alterations in coronary hemodynamics, (B) transient increases in circulating parathyroid hormone (PTH) levels, (C) increased generation of reactive oxygen species (ROS) leading to oxidative modification of low-density lipoprotein (LDL), (D) inflammatory cytokine release, and (E) testosterone effects.

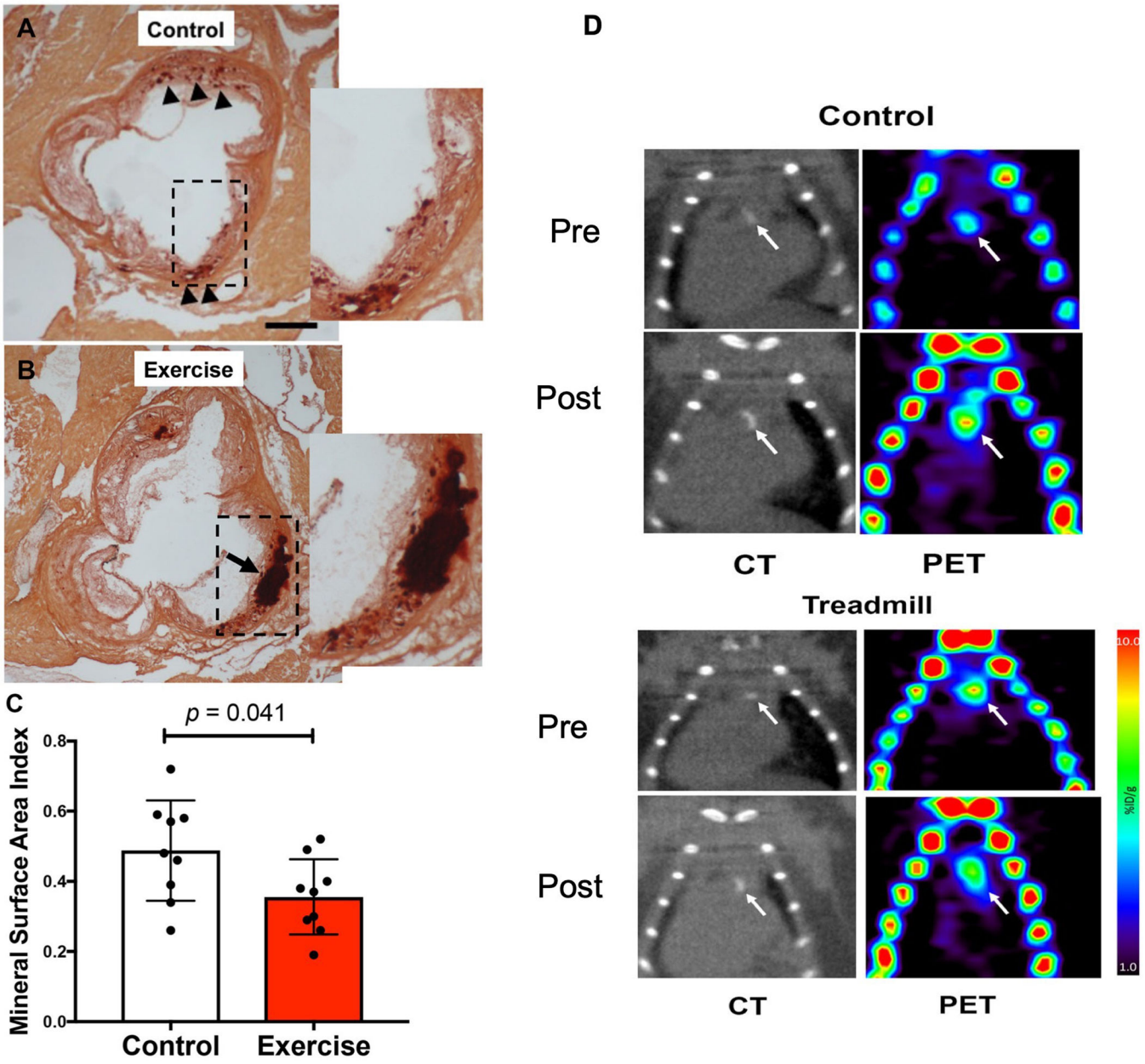

Figure 3. Imaging of aortic calcium deposition in treadmill and control mice.

A-B.Histochemical analysis with Alizarin red staining through aortic root sections of hyperlipidemic mice subjected to a progressive exercise regimen demonstrates the effect of exercise on plaque morphology. **A**, Arrows indicate the small "spotty" calcium deposition observed in the control group. **B**, The singular arrow indicates a much larger, coalesced calcified plaque in the exercise mice. **C**, Measurement of the mineral surface area index revealed a lower total mineral surface area index in the exercised mice. **D,** In vivo microCT and ^{18}F-NaF microPET images of the control (sedentary) and treadmill (exercised) mice revealed a decrease in tracer uptake in the treadmill group post-intervention, suggesting that

exercise resulted in a reduced surface area of aortic calcification lesions. Reprinted with permission from Reference [29].