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Review

Vascular dysfunction as a potential culprit of sarcopenia

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ABSTRACT

Aging-related changes to biological structures such as cardiovascular and musculoskeletal systems contribute to the development of comorbid conditions including cardiovascular disease and frailty, and ultimately lead to premature death. Although, frail older adults often demonstrate both cardiovascular and musculoskeletal comorbidities, the etiology of sarcopenia, and especially the contribution of cardiovascular aging is unclear. Aging-related vascular calcification is prevalent in older adults and is a known risk factor for cardiovascular disease and death. The effect vascular calcification has on function during aging is not well understood. Emerging findings suggest vascular calcification can impact skeletal muscle perfusion, negatively affecting nutrient and oxygen delivery to skeletal muscle, ultimately accelerating muscle loss and functional decline. The present review summarizes existing evidence on the biological mechanisms linking vascular calcification with sarcopenia during aging.

1. Introduction

The world's population is rapidly aging and the number of adults 65 years and older is projected to double by 2050 (Mathers et al., 2015). Given the aging society, frailty, a common geriatric syndrome of increased vulnerability to adverse outcomes including falls, dementia and physical disability (Fried et al., 2001), has become an important health issue (Ofori-Asenso et al., 2019). One of the most important factors for developing frailty is sarcopenia, a condition defined as a gradual loss of muscle mass, strength and function, assigned the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code (M62.84) (Vellas et al., 2018). Muscle mass has been reported to decline at an annual rate of 1–2% after the age of 50, with muscle strength decreasing by 1.5% per year between 50 and 60 years of age, and 3% per year thereafter (von Haehling et al., 2010; Keller and Engelhardt, 2013). There are multiple age-related factors present in sarcopenic older adults such as denervated motor units (Kung et al., 2014), hormonal changes (Kamel et al., 2002), inflammation (Schaap et al., 2006), oxidative stress (Brioche and Lemoine-Morel, 2016), decline in physical activity and malnutrition (Doherty, 2003). However, there is a lack of consensus on the pathophysiological mechanism of the development of sarcopenia (Cruz-Jentoft et al., 2019; Walston, 2012).

Older adults who demonstrate skeletal muscle loss, mostly have co-existing cardiovascular disease such as hypertension (Han et al., 2017). In some studies, vascular calcification, as one of the CVD risk factors, was negatively associated with grip strength (Rodriguez et al., 2018; Den Ouden et al., 2013), but not with muscle mass (Rodriguez et al., 2018; Everson-Rose et al., 2017). Age-related risk factors such as inflammation, oxidative stress, hypercholesterolemia, calcium deposition, hypertension, diabetes, renal disease and physical inactivity are associated with worsening vascular calcification as well as the loss of muscle function, strength and mass (Semba et al., 2007; Karwowski et al., 2012). Previous reports have shown a relationship between skeletal muscle and vascular pathology. For example, arterial stiffness was associated with limited flow volume in lower (Suzuki et al., 2001) and upper extremities (Mitchell et al., 2005), lower muscle mass (Abbatecola et al., 2012; Sampaio et al., 2014) and physical function (Rodriguez et al., 2018; Den Ouden et al., 2013; Everson-Rose et al.,

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2017; Rodríguez et al., 2016; Park and Park, 2017; Jensky et al., 2011; Alexandersen et al., 2006; Abizanda et al., 2010). Higher abdominal aortic calcification was also negatively associated with lower abdominal lean muscle (Jensky et al., 2011; Rodríguez et al., 2016) and positively associated with truncal fat mass (Alexandersen et al., 2006). In the Melbourne Collaborative Cohort Study (Rodríguez et al., 2016), lower lean muscle mass, especially in non-obese individuals, was related to the presence and severity of abdominal aortic calcification, and older women with severe abdominal aortic calcification showed a decline in handgrip strength, but not in the appendicular lean mass (Rodriguez et al., 2018). The authors assumed that aortic calcification may be related to neuromuscular factors, which represent muscle function, rather than muscle atrophy based on the data where vascular calcification was related to muscle strength, but not with muscle mass (Rodriguez et al., 2018).

To date, besides the clinical cross-sectional and observational studies, a pathophysiological mechanism on how vascular calcification contributes to skeletal muscle atrophy and functional loss is unclear. It is an important topic to investigate because if vascular dysfunction precedes and leads to the loss of skeletal muscle, interventional studies would target modifiable features of the vasculature to improve its function and prevent the loss of skeletal muscle in older adults. Therefore, in this article, we aim to review the pathophysiological mechanisms contributing to age-related vascular and skeletal muscle dysfunction and the available biological mechanisms through which vascular calcification can contribute to sarcopenia. The novel hypothesis is that endothelial dysfunction contributes to sarcopenia by increasing arterial calcification that restricts blood flow and muscle perfusion, which attenuate substrate delivery to skeletal muscle and contributes to atrophy and loss of function.

2. Literature search

A literature search for this review was conducted via the PubMed database for English-language publications on pre-clinical and clinical studies using the terms “vascular calcification” AND “skeletal muscle” (103 articles), “vascular calcification” AND “sarcopenia” OR “muscle strength” (19 articles). Two authors independently performed the database searches, screened potential studies, and reviewed the data. Discrepancies were resolved by consensus. The main focus of this article was to find relevant research articles exploring the mechanistic link between vascular calcification and sarcopenia including changes of muscle mass and function. Due to the limited literature evidence, we did not apply an age criterion in the selection process.

3. Biological factors contributing to vascular calcification

Vascular calcification has two categories according to the location in the vessel (mostly arteries) i.e. intimal and medial calcification. Atherosclerotic intimal calcification occurs at the innermost layer (tunica intima) (Amann, 2008; Mackey et al., 2007). In response to the increasing shear stress during aging the intimal wall becomes thicker (Orlandi et al., 1993). The shear stress as a mechanical strain on the vascular wall induces an inflammatory process that leads to an atherosclerotic plaque formation and blood flow restriction with increased vulnerability to a thrombotic event (Gofman et al., 1950; Amann, 2008). The medial calcification occurs in the middle layer (tunica media), which is composed of vascular smooth muscle cells (VSMCs), elastin, and collagen (Rodriguez et al., 2019). VSMCs have two main functions such as contraction and synthesis of extracellular matrix proteins (Metz et al., 2012). Medial calcification is caused by elastic fiber mineralization, degeneration and osteogenic process in the VSMCs (Amann, 2008). Below, we specify the biological mechanisms leading to vascular calcification.

3.1. Oxidative stress

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen with oxidizing capabilities (Mittal et al., 2014). Physiological levels of ROS regulate cell growth and differentiation, but in excess as oxidative stress, well-known as an age-related factor, have detrimental effects such as senescence and apoptosis (Thannickal and Fanburg, 2000; Griffith et al., 2009).

Oxidative stress results in endothelial cell apoptosis, monocyte adhesion, and inactivation of nitric oxide (NO), which enhances endothelium-dependent vasorelaxation (Taniyama and Griendling, 2003). Apoptotic bodies, calcifying membrane bound matrix vesicles that result from apoptosis, could become a site of calcification in blood vessels (Proudfoot et al., 2000). Oxidative stress also involves disturbance of inorganic phosphate homeostasis resulting in vascular calcification through promotion of the p65 nuclear translocation (Zhao et al., 2011). Hyperphosphatemia-induced VSMCs senescence and osteochondrogenesis result in calcification of VSMCs (Takemura et al., 2011). Hyperphosphatemia and calcium-phosphate products cause a progressive increase in calcium deposition in arteries (Giachelli, 2009).

Generation of ROS is central to progression of inflammation in blood vessels (Byon et al., 2008). For example, ROS activate the nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κβ) (Gloire et al., 2006), a transcription factor, which increases proinflammatory cytokine production (Tak and Firestein, 2001).

3.2. Inflammation

Inflammation plays a detrimental role in the vascular calcification process (Ceneri et al., 2017; Fujio et al., 2004; Zickler et al., 2018; Wang et al., 2001; Sun et al., 2017; Yao et al., 2009; Hess et al., 2009; Lee et al., 2010). For example, inflammatory cells such as macrophages release cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNF)-α, which induce VSMCs apoptosis and osteogenic differentiation resulting in mineral deposition in arterial plaques (Nadra et al., 2005). Circulatory inflammatory cytokines contribute to increasing calcification through TNF-α and calcium phosphate (Nadra et al., 2005). In particular, internalization of calcium phosphate crystals into vacuoles of macrophages trigger secretion of inflammatory cells such as TNF-α and IL-6 (Nadra et al., 2005). In the pro-inflammatory state, TNF-α reduces the level of matrix Gla-protein (MGP), which is an inhibitor of vascular mineralization secreted by chondrocytes and VSMCs in the arterial tunica media (Proudfoot and Shanahan, 2006). TNF-α activates the bone morphogenetic protein (BMP)-2, a potent bone anabolic factor in VSMCs contributing to vascular calcification (Ikeda et al., 2012). In in vitro studies, TNF-α induced differentiation of VSMCs to osteoblast-like morphology enhancing matrix mineralization (Tintut et al., 2000), and increasing calcium deposits (Villa-Bellosta et al., 2009; Shioi et al., 2002). TNF-α also stimulates IL-6 production (Wang et al., 2001). IL-6 is also involved in inhibiting MGP (Sun et al., 2017; Yao et al., 2009), which results in activation of BMP-2, which increases osteogenesis and contributes to arterial calcification (Fujio et al., 2004; Zickler et al., 2018).

3.3. Hormonal dysregulation

Chronic inflammation associated with aging is also related to insulin resistance, defined as a decrease in tissue response to hormonal insulin stimulation (Park et al., 2014). Insulin resistance causes reduction in NO bioavailability and increases generation of ROS, which result in oxidative stress and endothelial dysfunction (Duncan et al., 2008). Insulin resistance is also associated with glucotoxicity, lypotoxicity, and inflammation that also contribute to endothelial dysfunction (Kim et al., 2006).

Dysregulation of other hormone levels during aging affects vascular walls as well. For example, estrogen enhances the production of the

transforming growth factor-β (TGF-β), which has antioxidant and anti-TNF-α effects, leading to suppression of ROS over-production as well as has anti-inflammatory effects (Ashcroft et al., 1997; Das, 2002). Estrogen was also reported to prevent oxidative stress in ovariectomized rats through an increase in NO synthesis, which mediated vasodilation (Hernández et al., 2000).

Growth hormone (GH) has been reported to increase inducible nitric oxide synthase (NOS) expression, which catalyzes the production of NO from L-arginine (Kanno et al., 2008). NO showed an inhibitory effect on calcification of VSMCs through the TGF-β signaling (Kanno et al., 2008). GH replacement therapy showed an improvement of endothelial function and reduction of oxidative stress (Evans et al., 2000) through increased NO release in endothelial cell (Thum et al., 2003). The effect of GH on improved endothelial function is mediated by the insulin like growth factor-1 (IGF-1) (Kimbrough et al., 1991; Werner et al., 2008). Chronic inflammation during aging reduced expression of IGF-1 in VSMCs in a rat model (Anwar et al., 2002), and decreased expression of IGF-1 triggers VSMCs' apoptosis resulting in atherosclerosis, plaque instability, and rupture (Okura et al., 2001).

4. Contribution of vascular calcification to the development of sarcopenia

A common cause of vascular calcification is endothelial dysfunction induced by chronic inflammation and oxidative stress (Incalza et al., 2018), which leads to endothelial cell apoptosis, monocyte adhesion, and decreased production of NO (Taniyama and Griendling, 2003). NO is reported to regulate blood flow to skeletal muscle at both rest and during dynamic exercise, thus inactivation of NO could impair the blood flow to the muscle (Hickner et al., 1997). Inflammation and oxidative stress-induced microcalcification and hormonal dysregulation such as insulin resistance may be mechanistically contributing factors to skeletal muscle atrophy by reduced capillary microcirculation, reduced nutrient and oxygen delivery, and thus impaired muscle protein synthesis (Toth et al., 2005), increased protein breakdown (McClung et al., 2010), mitochondrial dysfunction and apoptosis (Jaiswal et al., 2015).

Skeletal muscle is a major site that absorbs glucose through the insulin-responsive glucose transporter type 4 (GLUT4), and decreased expression of GLUT4 in insulin resistance reduces glucose uptake from the blood stream (Gaster et al., 2001; Mueckler, 2001). Therefore, sufficient available capillary surface area of trans-endothelial transport of insulin is needed (Vincent et al., 2005). Insulin is delivered into the capillaries and crosses the endothelial barrier (Vincent et al., 2005). In support of this, obese male mice treated with high-fat diet had a 15% reduction in endothelial insulin transport, which was associated with a 45% reduction in the density of endothelial vesicles (putative vehicles for the endothelial insulin transport) in skeletal muscle capillaries that increased systemic hyperinsulinemia, which is a cardiometabolic risk factor (Williams et al., 2020).

A well-functioning endothelium is essential for insulin-induced endothelial nitric oxide synthase (eNOS) phosphorylation to increase NO bioavailability, and thus capillary perfusion (Vincent et al., 2005; Kubota et al., 2011). In mice, reduction of eNOS phosphorylation reduced insulin-induced glucose uptake by skeletal muscle, and restored phosphorylation of eNOS in the endothelial cells improved capillary recruitment and perfusion (Kubota et al., 2011). Endothelial dysfunction with intimal calcification could disturb this process through attenuation of capillary recruitment and reduced insulin delivery (Muniyappa et al., 2008). Insulin resistance lowered suppression of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling leading to activation of caspase-3 and the ubiquitin-proteasome proteolytic pathway causing muscle protein degradation (Wang et al., 2006). Decreased uptake of glucose from the capillaries decreases the energy production by lower adenosine triphosphate (ATP) production, lipid oxidation (Cleasby et al., 2016), and protein synthesis in skeletal muscle (Cleasby et al., 2016; Stump et al., 2003). Additionally, capillary rarefaction and lower angiogenesis with endothelial dysfunction and microcalcification impair the capillary diffusion capacity of oxygen, nutrients and hormones to skeletal muscle during contractions (Barnouin et al., 2017). Lower angiogenesis during aging is due to reduced expression of the vascular endothelial growth factor (VEGF) and lower sensitivity of the endothelial cells to VEGF due to the dysregulated nicotinamide adenine nucleotide (NAD) metabolome (Tang et al., 2004; Das et al., 2018). Due to vascular inflammation, one of the causes of endothelial dysfunction and vascular calcification, cytokines stimulate lymph production (lymphangiogenesis) for the removal of tissue fluid and inflammatory cells (Csanyi and Singla, 2019). However, aging-related lymphatic dysfunction due to low NO in the lymphatic vessels leads to poor drainage, which causes fluid retention (edema) and accumulation of inflammatory cells, and thus a persisting pro-inflammatory process (Bridenbaugh et al., 2013; Shang et al., 2019).

Dysregulation of other hormones, diminished during aging, may be detrimental for muscle metabolism and contractile performance by modulating blood flow to and within the skeletal muscle (Clark et al., 2003). For example, in older mice with restricted blood supply, IGF-1 expression was reduced in skeletal muscle (Hammers et al., 2011), which could diminish a protective effect of IGF-1 against age-related loss of muscle mass (Ascenzi et al., 2019). In particular, binding of IGF-1 on its receptor in skeletal muscle (Pandini et al., 2002) activates the PI3K/Akt pathway (Nadler et al., 2001). Akt stimulates protein synthesis through the mammalian target of rapamycin (mTOR) (Nadler et al., 2001). Akt inactivates phosphorylation of the forkhead box transcription factor (FoxO) resulting in a decrease of proteolysis (Bois and Grosveld, 2003). Through these mechanisms, GH and IGF-1 stimulate protein synthesis and attenuate muscle breakdown, and decreased GH and IGF-1 levels during aging have negative impact on muscle mass (Lamberts et al., 1997).

Additionally, testosterone and estrogen induce relaxation of vessels through increased NO production through the PI3K/Akt pathway (Goglia et al., 2010) and improved endothelial function (Miller and Mulvagh, 2007), thus this effect is impaired with aging-related decline of these hormones. In systematic reviews and meta-analyses, testosterone showed strong effects on maintaining muscle mass and a modest to minimal effects on muscle strength and physical performance, especially with low serum levels (De Spiegeleer et al., 2018). For example, diminished endogenous production of testosterone in mice by orchidectomy induced suppression of the IGF-1/Akt pathway resulting in a reduction of muscle mass and function (Ibebunjo et al., 2011). When treated with testosterone, IGF-1/Akt pathway was activated and restored muscle mass and function (Ibebunjo et al., 2011). Loss of estrogen in female mice lead to a decrease in skeletal muscle satellite cells and lower muscle regeneration (Collins et al., 2019). Others reported that reduction of estrogen might cause a reduction of skeletal muscle IGF-1 in ovariectomized rats and it was reversed by an estrogen treatment (W-JA et al., 2007). Estrogen replacement therapy reversed ovariectomy-induced muscle contractile and myosin dysfunction in mice (Moran et al., 2007; Tanideh et al., 2014; Brown et al., 2009). Although, testosterone and estrogen have an effect on both vascular and skeletal muscle function, they have not been studied together to investigate a mediating role of the vascular dysfunction inducing skeletal muscle dysfunction.

Taken together, based on this growing body of evidence, vascular impairments due to age-related inflammation, oxidative stress and dysregulated hormonal system impair endothelial function leading to arterial calcification in the peripheral and skeletal muscle capillaries that restrict the delivery of substrates needed for muscle regeneration and hypertrophy. Fig. 1 demonstrates a simplified conceptual model of vascular calcification contributing to sarcopenia.

5. Conclusion

Vascular calcification induced by age-related biological processes

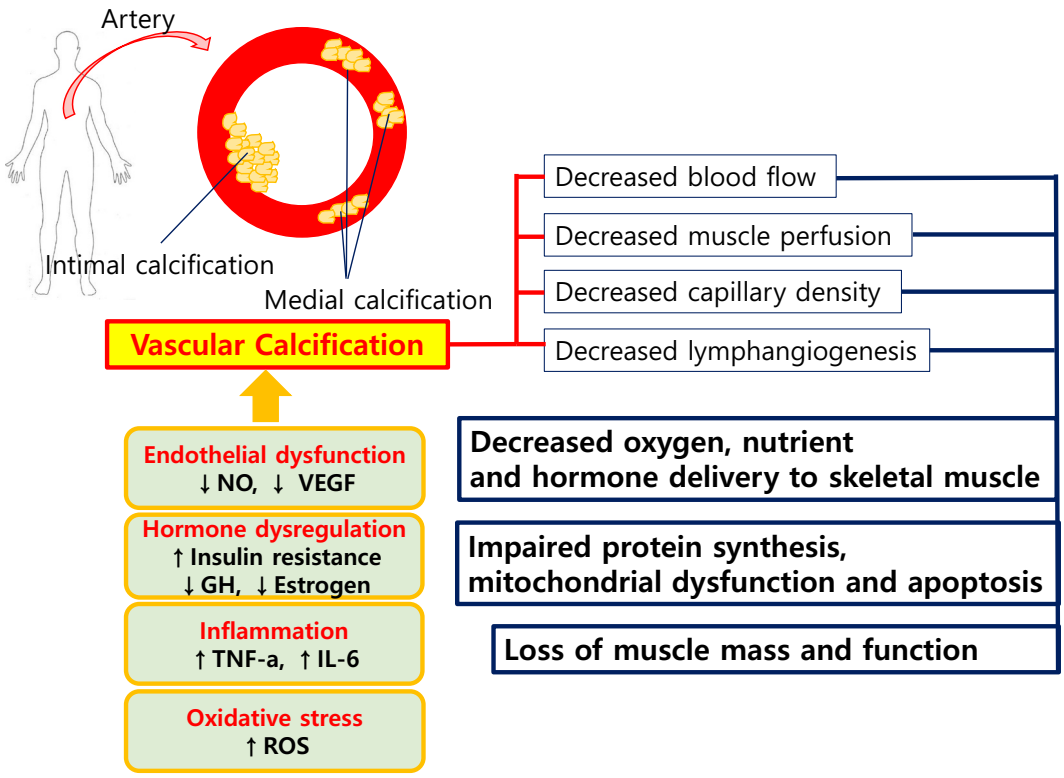

Fig. 1. Schematic interaction between vascular calcification and muscular atrophy.
NO: nitric oxide, VEGF: vascular endothelial growth factor, ROS: reactive oxygen species, TNF-α: Tumor necrosis factor, IL-6: interleukin-6; GH: growth hormone.

such as oxidative stress, inflammation and hormonal dysregulation impair endothelial function. Based on the literature evidence, we hypothesize that endothelial dysfunction increases arterial calcification that restricts blood flow and muscle perfusion, which attenuate substrate delivery to skeletal muscle and contribute to atrophy and loss of function. Human studies are warranted to experimentally investigate the causal relationship between vascular function and sarcopenia and identify interventions targeting diminished vascular function to prevent the development of sarcopenia. Studying various exercise modalities will be among these research areas to better understand how exercise can overcome the vascular limitations to improve skeletal muscle function and prevent sarcopenia.

5.1. Clinical implications

Clinically, assessments of vascular calcification can be performed frequently as Standard-of-Care. Currently, when vascular calcification is detected, risk stratification for atherosclerotic CVD (ASCVD) is needed. Assessment of CV risk factors such as serum lipids, presence of diabetes, blood pressure and smoking history becomes essential for considering long-term risk of ASCVD (Arnett et al., 2019). Clinicians often pursue additional testing such as coronary artery calcium testing for further risk stratification and often will be more aggressive with adding statin therapy in these patients. With the current emerging evidence that vascular dysfunction may precede and be a culprit of sarcopenia, future clinical studies may confirm that vascular calcification is not only a predictor of vascular disease, but may also be an important predictor of muscle loss and increased risk of mobility disability.

5.2. Potential interventions

If prospective studies support this proposed mechanistic hypothesis, then future interventions targeting sarcopenia and/or functional decline should focus on improving vascular function in parallel to physical function. For example, interventions such as high-intensity exercise training and resistance training with blood flow restriction may be appropriate interventions to improve endothelial function, muscle capillary perfusion, and thus more efficiently improve muscle function and strength (Scott et al., 2019; Lopes et al., 2019; Cook et al., 2017; Fry et al., 2010).

However, vascular dysfunction may also be a limiting factor in an effective adaptation to exercise (Yasuda et al., 2015). In particular, preclinical evidence has shown that muscle capillary perfusion and angiogenesis are diminished during aging and are the limiting factor in supplying muscle with nutrients and oxygen to induce an adaptive process of muscle strength and function. For example, age-related dysregulation of the NAD metabolome may be a reason of a diminished vascular remodeling response to exercise (Das et al., 2018; Custodero et al., 2020). Reversed vascular function and improved angiogenesis by the restored NAD metabolome, improved exercise performance and skeletal muscle function (Das et al., 2018). Therefore, future pharmacological and lifestyle interventions, and its combinations are warranted to target not only improvements of endothelial function, but also angiogenesis to maintain skeletal muscle function and strength.

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