

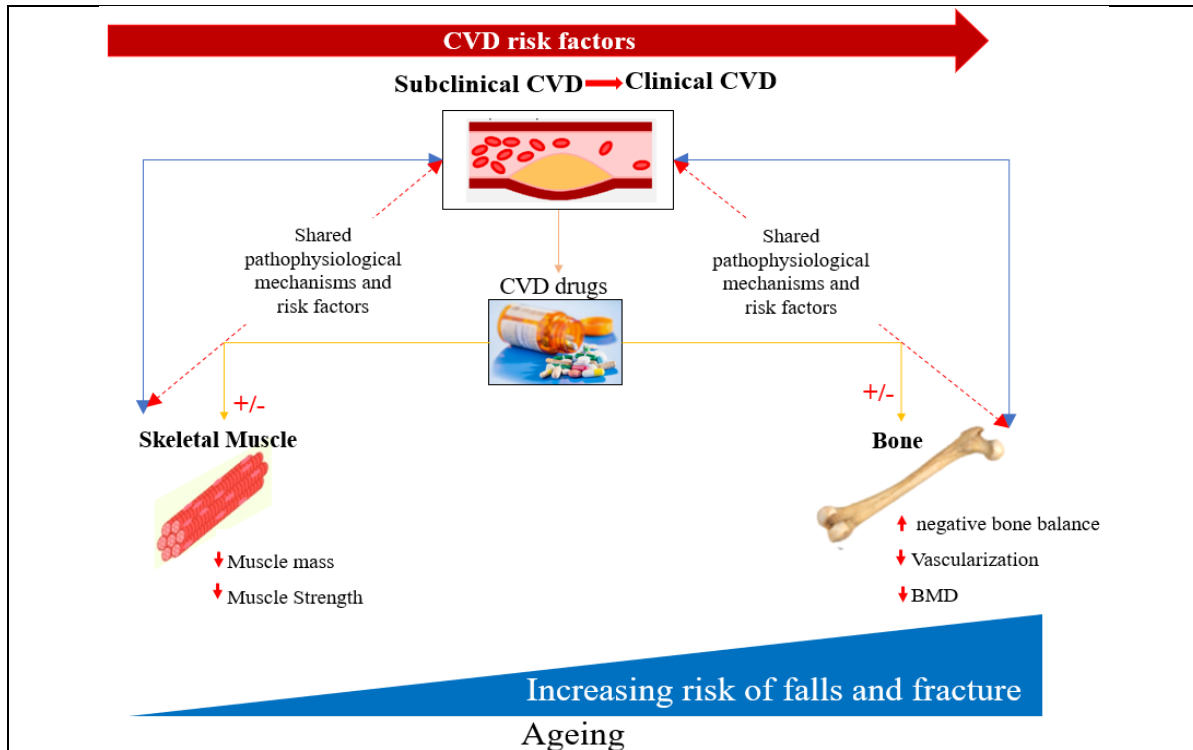
Novel atherosclerotic cardiovascular causes of falls and fracture

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GRAPHICAL ABSTRACT



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Abadi K. Gebre is a PhD student at the School of Medical and Health Sciences, Edith Cowan University, Perth, Western Australia with an MSc in Pharmacology. His research interests include unravelling the nexus between cardiovascular

and musculoskeletal diseases, skeletal safety of cardiovascular drugs and cardiovascular safety of bone active medications in older people. Specifically, his research aims to disentangle the cardiovascular causes of falls and fracture and explore the potential mechanisms and underpinning lifestyle factors to promote healthy ageing.

ABSTRACT

Transient cardiovascular events including neurally mediated syncopal syndromes, hypotension, and bradyarrhythmias are common causes of falls and subsequent fracture in older individuals with low bone mass or impaired bone structure. More recently, there is renewed interest in the role of atherosclerotic and vascular calcification processes as risk factors for falls and fractures in older individuals. Optimal function of muscle and bone is dependent on healthy vasculature for the supply of blood and nutrients and removal of metabolic waste products. Evidence supporting the importance of blood vessels health for musculoskeletal outcomes has come from many sources such as genetic twin studies, RCTs of cardiovascular or bone active medications and observational studies. Better understanding of these relationships will potentially lead to new ways to prevent falls and fractures.

Introduction

With a rapidly ageing global population, falls and fracture are becoming the major causes of functional dependence in activities of daily living leading to significant health and financial burden. The causes of falls and fracture are multifactorial and many of the risk factors are often similar with other disease of ageing (Berry and Miller, 2008).

Transient cardiovascular events or its consequences such as neurally mediated syncopal syndromes, hypotension (post-prandial or orthostatic), dizziness, loss of balance, and bradyarrhythmia's are well-known but often underappreciated cause

of falls and subsequent fracture (Cronin and Kenny, 2010). A growing body of evidence also suggests a link between atherosclerotic processes and its sequelae with falls and fracture (Gray et al., 2019, Lewis et al., 2019). In particular, an association between atherosclerotic vascular disease and (i) bone mineral density (BMD), (ii) skeletal muscle mass and function, (iii) falls propensity, and (iv) osteoporotic fracture and fracture risk has been highlighted suggesting the impact of blood vessel disease on musculoskeletal health. These epidemiological findings are further strengthened by genetic studies (Sennerby et al., 2009) and RCTs of bone active medications that revealed the presence of shared genetic risk factors and mechanisms (Lewis et al., 2018, Cosman et al., 2016).

Alternatively, low BMD, falls and osteoporotic fracture are associated with cardiovascular morbidity and mortality suggesting shared pathophysiological mechanisms (Veronese et al., 2017). Nonetheless, the underlying mechanism(s) that explain the link between vascular and musculoskeletal disease remain unclear.

Given atherosclerotic vascular diseases are associated with poor musculoskeletal health, the plausible association between cardiovascular disease (CVD) and increased falls and fracture risk might be due to: (i) shared modifiable and non-modifiable risk factors; (ii) common pathophysiological signaling mechanisms; (iii) causal relationships in which diseased vasculature might impair musculoskeletal health leading to falls and fracture.

Vascular and musculoskeletal disease: shared mechanisms and risk factors

For some time now, chronic diseases such as CVD, osteoporosis and sarcopenia were considered age-related comorbidities. Recently, however, it has been demonstrated that their co-existence is due to active and dynamic processes which cannot be explained by age alone (Lee et al., 2020). Shared genetic, environmental, and lifestyle factors are also plausible links between vascular and musculoskeletal disease (Rodriguez et al., 2019).

For example, vascular and musculoskeletal disease share modifiable lifestyle factors such as smoking, sedentary lifestyle, unhealthy dietary choices and comorbid conditions including hypertension, dyslipidemia, vitamin D and K abnormalities, chronic inflammation, oxidative stress and estrogen deficiency (Szekanecz et al., 2019). These multifaceted lifestyle, nutritional and co-morbid factors may alter shared signaling processes and pathways linking these diseases. To date, limited studies have investigated the role of such modifiable factors on the shared burden of falls, fracture and cardiovascular events.

Atherosclerotic vascular disease, skeletal muscle and falls

A recent systematic review suggested the impact of atherosclerosis on skeletal muscle, with links between macrovascular (arterial stiffness, carotid intima-media thickness and flow-mediated dilation) and microvascular disease (capillary density or microvascular flow) with poor physical

function and muscle strength, and low muscle mass (Dvoretzkiy et al., 2020). Vascular calcification has also been linked to long-term decline in muscle strength (Rodriguez et al., 2018).

The underpinning impact of atherosclerotic disease processes on skeletal muscle may be due to its detrimental effect on, i) size of muscle fibres, ii) the ratio of muscle type II (fast twitch) versus type I (slow twitch) which is related to impairment of fast coordination of skeletal muscle contraction to counteract activities that require more intensity, iii) capillary-fibre ratio. Low capillary-fibre ratio decreases the efficiency of oxygen and nutrient delivery as well as the removal of metabolic waste products. This may cause, i) accumulation of oxidative reactive species, ii) inflammation, iii)-mitochondrial deficits, iv)-altered enzymatic activities v)-apoptosis and fibrosis. It may also affect angiogenesis and sprouting that consequently impact skeletal muscle capillarization, remodeling and healing after injury.

Unsurprisingly, given these relationships to muscle, cardiac biomarkers, subclinical atherosclerosis and clinical cardiovascular disease have all been shown to be associated with increased falls propensity (Jansen et al., 2016, Wong et al., 2014, Juraschek et al., 2019). While the underlying mechanisms for increased falls propensity is unclear, atherosclerotic vascular disease may, i) limit the tolerance to physical activity resulting poor muscle strength and postural instability, ii) increase falls risk factors such as visual and cognitive impairments, iii) impair cerebrovascular autoregulatory mechanisms affecting balance and

posture, iv) impair blood flow to skeletal muscle affecting reaction time and the capacity to counteract falls risk. However, these concepts must be carefully considered in light of the overlapping known relationship between syncope and falls, which may confound studies with falls outcomes (Jansen et al., 2015).

Atherosclerotic vascular disease, osteoporosis and fracture

Genetic studies have identified shared genetic loci between atherosclerotic vascular diseases and osteoporosis (Peng et al., 2017, Reppe et al., 2015), suggesting a bone-vascular axis. There are also substantial overlap in circulating cytokines which regulate both cardiovascular and bone health such as OPG/RANK/RANKL, PTH, Wnt signaling, BMP4, IL-6 and TNF α pathways (Thompson and Towler, 2012). Despite an abundance of cross-sectional evidence, few studies have explored the temporal nature of these relationships.

Some (Zhang and Feng, 2017, Szulc, 2016) but not all (Barzilay et al., 2018) epidemiological studies have identified a link between atherosclerotic vascular disease and low BMD. Despite these inconsistent findings, the totality of the current evidence supports a link between atherosclerotic vascular disease and low BMD. Vascular and inflammatory biomarkers are also associated with bone mineralization disorder. For example, low N-terminal pro-B-type natriuretic peptide (NT-proBNP)(Lee et al., 2014, Nordling et al., 2016), and high level of high-sensitivity C-reactive protein (hsCRP) have been associated with low BMD and fracture risk (Dahl et al., 2015). These

studies suggest CVD biomarkers may be used to predict disorder of bone mineralization and fracture risk. However, incorporating CVD biomarkers in fracture risk prediction is not well supported, and the findings should be interpreted cautiously until further well-powered studies considering the influence of bone and vascular risk factors are conducted.

Atherosclerotic vascular diseases may affect BMD and increase fracture risk via; i) impairment in absorption and supply of minerals and vitamins, ii) release of reactive molecules from the injured blood vessel that induce inflammation and oxidative stress, iii) reduced vascularization impacting delivery of essential nutrients and removal of toxic metabolites, iv) impaired kidney function affecting calcium and vitamin D metabolism, and v) decreasing muscle mass and function. The above mechanisms may ultimately lead to reduced bone quality and mass.

Alternatively, osteoporosis is related to atherosclerosis and cardiovascular disease. For example, extracellular calcium liberated during rapid bone loss is associated with vascular calcification and increased burden of atherosclerotic plaques (Ewence et al., 2008, Shanahan et al., 2011).

CVD medications, falls and fractures risk

Mechanistically, cardiovascular drugs may increase fall propensity, particularly at the beginning of new treatment regimens by affecting, i) cerebrovascular autoregulation, ii) visual acuity, ii) muscle strength, iii) reaction time and iv) balance. However, the long-term relationship

between cardiovascular drugs and falls risk/benefit remains relatively underexplored.

Cardiovascular drugs such as loop diuretics, antiarrhythmic drugs, digoxin have been shown to be associated with increased risk of fracture. In contrast, statins, β -blockers, thiazide diuretics are related to reduced risk of fracture (Takeuchi, 2014, Rejnmark et al., 2007). Loop diuretic increase urinary calcium excretion. In contrast, thiazide diuretics reduce calcium excretion by increasing tubular reabsorption (Rejnmark et al., 1998). β -blockers are somehow associated with increased bone mass (Khosla et al., 2018). The aforementioned mechanisms may partly explain the difference in fracture risk of these drugs. However, the underlying mechanism in which most of the CVD drugs affect the risk of fracture is unclear.

The current evidence focuses on the relationship between the fracture risk of classes of cardiovascular drugs not on specific cardiovascular drugs. Estimating and pooling the fracture risks of different drugs together may potentially confound the overall risk because the mechanisms and adverse effects of each cardiovascular drug is likely to differ.

The interaction of these drugs with other drugs or disease conditions may also affect musculoskeletal health. Although there are a lot of uncertainties, cardiovascular drugs may influence skeletal health by affecting, i) calcium and vitamin D metabolism, ii) falls propensity and iii) bone mineral density.

On the other hand, bone active medications such as romosozumab (Saag et al., 2017), odanacatib (McClung et al., 2019), and zoledronic acid (Black et al., 2007) are associated with increased adverse cardiovascular events .

Uncertainties in the field and future directions

While the totality of the available evidence suggests atherosclerotic vascular disease are associated with poor musculoskeletal health there are numerous uncertainties and controversies. This is primarily because only few observational studies and randomized controlled trials investigated both vascular and musculoskeletal phenotypes and outcomes. Understanding how and why vascular and musculoskeletal systems are linked will contribute for a better risk stratification, improve selection of pharmacological interventions, and development of new lifestyle or pharmacological therapies. In the future, detailed studies investigating the temporal nature of the association between subclinical and clinical atherosclerotic vascular disease and, falls and fracture in the last few decades of life are needed. Similarly, when developing and evaluating pharmacological agents the potential effects on the bone or vasculature should also be considered and tested.

Conclusion

In conclusion, atherosclerotic vascular diseases are related to compromised muscle function, lower bone mass and poorer structure and higher falls and

fracture risk in older individuals. However, the causal nature of the association and the underlying mechanisms have yet to be fully elucidated. Exploring and disentangling the nexus between atherosclerotic vascular disease and falls and fracture may pave the way for new detection as well as better primary and secondary prevention strategies for falls and fracture. This represents a shift in treatment approaches from organ centric medicine towards a more holistic view of healthy ageing.

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