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The Vitamin D/Vitamin D receptor (VDR) axis in muscle atrophy and sarcopenia

Shelby E. Bollen [a,*], Joseph J. Bass [a], Satoshi Fujita [c], Daniel Wilkinson [a], Martin Hewison [b], Philip J. Atherton [a,*]

[a] MRC/ARUK Centre for Musculoskeletal Ageing Research and National Institute for Health Research (NIHR), Nottingham Biomedical Research Centre (BRC), School of Medicine, University of Nottingham, DE22 3DT, UK
[b] Metabolism and Systems Research, University of Birmingham, Birmingham, UK
[c] Faculty of Sport and Health Science, Ritsumeikan University, Kusatsu, Shiga, Japan

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ABSTRACT

Muscle atrophy and sarcopenia (the term given to the age-related decline in muscle mass and function), influence an individuals risk of falls, frailty, functional decline, and, ultimately, impaired quality of life. Vitamin D deficiency (low serum levels of 25-hydroxyvitamin D ($25(OH)D_3$)) has been reported to impair muscle strength and increase risk of sarcopenia. The mechanisms that underpin the link between low $25(OH)D_3$ and sarcopenia are yet to be fully understood but several lines of evidence have highlighted the importance of both genomic and non-genomic effects of active vitamin D (1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$)) and its nuclear vitamin D receptor (VDR), in skeletal muscle functioning. Studies in vitro have demonstrated a key role for the vitamin D/VDR axis in regulating biological processes central to sarcopenic muscle atrophy, such as proteolysis, mitochondrial function, cellular senescence, and adiposity. The aim of this review is to provide a mechanistic overview of the proposed mechanisms for the vitamin D/VDR axis in sarcopenic muscle atrophy.

1. Introduction

Skeletal muscle accounts for almost 40% of an individual's body weight, is fundamental for locomotion, breathing, lipid and glucose homeostasis, and is the primary protein reservoir of the human body [1]. As such, extant muscle atrophy is a clinical problem across the life-course, irrespective of the underlying aetiology, e.g. post-trauma or disease. In terms of ageing, the incipient loss of muscle mass (and sometimes increase in fat mass) and function, is termed sarcopenia [2]. Maintenance of skeletal muscle mass relies on a strictly regulated balance of muscle protein synthesis (MPS) and breakdown (MPB) - or proteostasis. Muscle atrophy occurs when the rate of MPB exceeds that of MPS, so there is understandably great interest into elucidating the mechanisms underlying atrophy and any key factors that may influence the process [3–5].

Muscle atrophy is influenced via genetic, epigenetic, and behavioural mechanisms, but environmental and nutritional factors also play a key role. Prominent among these is vitamin D, which plays a key role in regulating musculoskeletal function. Classically associated with maintaining calcium homeostasis and skeletal health, vitamin D is a fat-soluble steroid hormone obtainable via two main sources: diet and exposure to ultraviolet B rays (UVB). Cholecalciferol (vitamin D_3) is the product of subcutaneous UV irradiation of 7-dehydrocholesterol (7-DHC), while ergocalciferol (vitamin D_2) is synthesised via UV irradiation of the yeast sterol, ergosterol. Activation of these two forms of vitamin D requires two hydroxylation steps. First, in the liver, where 25-hydroxylase hydroxylates the C25 of vitamin D to form 25-hydroxyvitamin D ($25(OH)D_3$; calcidiol) - the metabolite used clinically to determine an individual's vitamin D status [6]. Subsequently, $25(OH)D_3$ is hydroxylated at its C1α site by the enzyme 1α-hydroxylase (CYP27B1) to form the biologically active hormone, 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$; calcitriol) [7]. This second hydroxylation step was initially believed to be specific to the kidney, but current evidence indicates widespread extra-renal expression of CYP27B1 [8,9]. In contrast to the kidney CYP27B1, which supports the circulating levels of $1,25(OH)_2D$ and its endocrine actions [10], extra-renal CYP27B1 functions mainly to enhance local site-specific concentrations of $1,25(OH)_2D_3$ which are then able to interact with endogenous VDR in the same tissue [11]. In

* Corresponding authors at: MRC-ARUK Centre for Musculoskeletal Ageing Research and National Institute for Health Research (NIHR), Nottingham Biomedical Research Centre (BRC), School of Medicine, University of Nottingham, UK Research Centre, School of Medicine, Derby DE22 3DT, UK.
E-mail addresses: shelby.bollen@nottingham.ac.uk (S.E. Bollen), philip.atherton@nottingham.ac.uk (P.J. Atherton).

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many extra-renal tissues this intracrine synthesis of $1,25(OH)_2D_3$ appears to be the predominant mechanism for 1,25D-VDR mediated regulation of gene transcription and provides a potential explanation for impaired tissue function and possible disease in the setting of low serum levels of $25(OH)D_3$.

It is estimated that vitamin D deficiency affects approximately 1 billion people globally and these individuals typically present with bone pain, fatigue, muscle pain (myalgia), muscle atrophy and weakness, and an increased risk of sarcopenia [12]. While these muscle symptoms are among some of the key features of hypovitaminosis D, the relationship between vitamin D and skeletal muscle is still not fully understood. Several lines of evidence suggest roles for the vitamin D/VDR axis in myogenesis (formation of skeletal muscle), skeletal muscle regeneration and calcium homeostasis, but the link with muscle atrophy is complex due to conflicting results generated by large randomised controlled trials (RCTs) and molecular studies conducted in vitro [13]. As such, the aim of this review is to provide a more mechanistic review of vitamin D and the VDR axis in sarcopenia.

2. Evidence from human studies

As an individual ages, the need for optimal maintenance of muscle mass and strength is imperative due to the impact sarcopenia can have on functional independence and, ultimately, quality of life. Multiple human studies have indicated a relationship between vitamin D deficiency (low serum $25(OH)D_3$), reduced muscle function and an increased risk of sarcopenia [14]. In the United Kingdom, NICE guidelines state that serum $25(OH)D_3$ levels of less than 25 nmol/L should be considered as vitamin D deficiency (hypovitaminosis D), 25–50 nmol/L as insufficiency, and over 50 nmol/L as sufficient [15]. Risk of vitamin D deficiency and dysregulated vitamin D function increases with age. This may be attributed to reduced sensitivity to $1,25(OH)_2D_3$ due to a combined effect of age-related decline in VDR expression within skeletal muscle, impairment of cutaneous vitamin D synthesis, or altered expression of vitamin D metabolic enzymes [9,16–18]. In addition, poor nutrition and reduced exposure to sunlight are commonly seen in institutionalised individuals - a population at a particularly high risk of deficiency [19]. It has been well-established that low serum $25(OH)D_3$ levels are associated with reduced muscle strength [20–27] and impaired physical function [28–34]. Longitudinal studies indicate that deficiency may exacerbate the age-related decline in strength and physical performance [35–42] whilst also potentially acting as an independent risk factor for sarcopenia [40,43,44].

Vitamin D deficiency-related muscle dysfunction may be partly explained by alterations to skeletal muscle morphology, particularly type II muscle fibres (fast-twitch). Degenerative changes, such as muscle opacity, fibrosis, fibre atrophy and enlarged interfibrillar spaces have been seen in patients with osteomalacic myopathy (a condition associated with vitamin D deficiency) [45]. Sarcopenia has similar morphological manifestations in skeletal muscle to vitamin D deficiency, and its effects are, again, also more prominent in type II fibres [46]. Given that preservation of fast-twitch type II muscle fibres is crucial for maintaining posture due to their role in generating rapid forces, it is perhaps unsurprising that low 25(OH)D levels are associated with an increased risk and prevalence of falls [47–51]. Vitamin D supplementation has been shown to increase the percentage of type II muscle fibres in both males and females, but further investigations are needed to confirm these results [52,53].

Given the volume of evidence supporting an association between vitamin D deficiency and impaired musculoskeletal function, there has been great focus on the therapeutic potential of the hormone, particularly in elderly populations. Multiple studies have demonstrated that restoration of serum $25(OH)D_3$ levels can improve measures of strength and physical function [54–62]. However, a significant number of trials have failed to show any benefits of vitamin D supplementation upon muscle strength and/or mass, therefore generating a degree of uncertainty regarding its benefits [63–70]. The potential reasons for these disparities are numerous but may include differences in the form of the supplement and its dosage, the study duration, and heterogeneity of participant demographics. Furthermore, whilst the common idealogy is that higher vitamin D levels will provide optimal physical function, this may not be correct in terms of the musculoskeletal response to vitamin D supplementation. A dose-dependent response has been proposed in the form of a U-shaped curve, as several studies have demonstrated that both those with the lowest and highest quartiles of serum $25(OH)D_3$ levels display impaired muscle strength and an increased risk of fractures and frailty [35,71]. Further research is required to fully comprehend the reasoning behind these observations, but the possibility for a potential therapeutic threshold of vitamin D in the musculoskeletal system is clear.

In view of the age-related reduction in muscle VDR expression and vitamin D synthesis and metabolism, the deficiency-associated morphological alterations of fast-twitch type II fibres and impairment of muscle strength/mass, it is of no surprise that a biological link has been hypothesised between the vitamin D system and muscle atrophy. Human studies have highlighted the phenotypical and clinical alterations that result from vitamin D deficiency, but there is a lack of understanding of the underlying molecular mechanisms.

3. The proposed mechanisms for Vitamin D function and muscle atrophy

Several in vitro studies have demonstrated a key role for the vitamin D system in myogenesis and skeletal muscle regeneration, and reviews specific to this topic are available [13], but the primary focus of the next section is to focus on the mechanistic basis of vitamin D/VDR in muscle atrophy. This includes key breakdown pathways, impaired mitochondrial function and oxidative damage, adiposity, and cellular senescence (Fig. 1).

3.1. Intracellular signalling

It has been suggested that $1,25(OH)_2D_3$/VDR play regulatory roles in protein breakdown (proteolysis) within skeletal muscle. In skeletal muscle, a bulk of intracellular proteolysis occurs via the ubiquitin-proteasome pathway (UPP) while the autophagy lysosomal pathway is also influential. The UPP is primarily composed of two subunits, 19 s and 20s, that collectively form the 26 s proteasome [72]. Conjugation of ubiquitin via a set of three families of ligases (E_1, E_2, and E_3) acts as a molecular tagging system that mark proteins for degradation. Upregulation of this pathway is a common feature of muscle atrophy, and increased expression of two key E_3 ubiquitin ligases, atrogin-1 (also known as MAFbx or FBXO32) and muscle ring finger protein (MuRF1 or TRIM63) has been suggested as a molecular marker of cachexia [73,74]. Expression of both MuRF1 and atrogin-1 is controlled by the phosphorylation state of the family of forkhead box proteins (FOXO). Basally, FOXO proteins are phosphorylated by Akt, sequestering them in the cytoplasm, and preventing their nuclear translocation and downstream transcription of MuRF1 and atrogin-1 [75]. In cellular models, treatment of fully differentiated human myotubes and C2C12 models of stress (e.g., glucocorticoid and oxidative) with $1,25(OH)_2D_3$ inhibits expression of atrogin-1 and MuRF1, but increases levels of FOXO1 [76–78]. Paraspinal muscle biopsies from patients with chronic lower back pain supplemented with vitamin D demonstrated increased Akt and reduced FOXO3a in comparison to baseline [79]. Vitamin D deficient rats display elevated levels of total protein breakdown and atrogin-1/MuRF1, and repletion of vitamin D levels also normalised atrogin-1/MuRF1 expression levels in the gastrocnemius (GA) muscle of a deficient cachexic mouse model [80,81]. MuRF1 is upregulated in the tibialis anterior (TA) muscle of mice in which the *VDR* gene has been knocked down (VDR-KD) but no significant differences are seen with control wild-type (WT) mice in the soleus muscle [82]. This reinforces the type II muscle fibre specificity observed in vitamin D deficient patients, as TA and GA are considered fast muscles whilst soleus is slow.

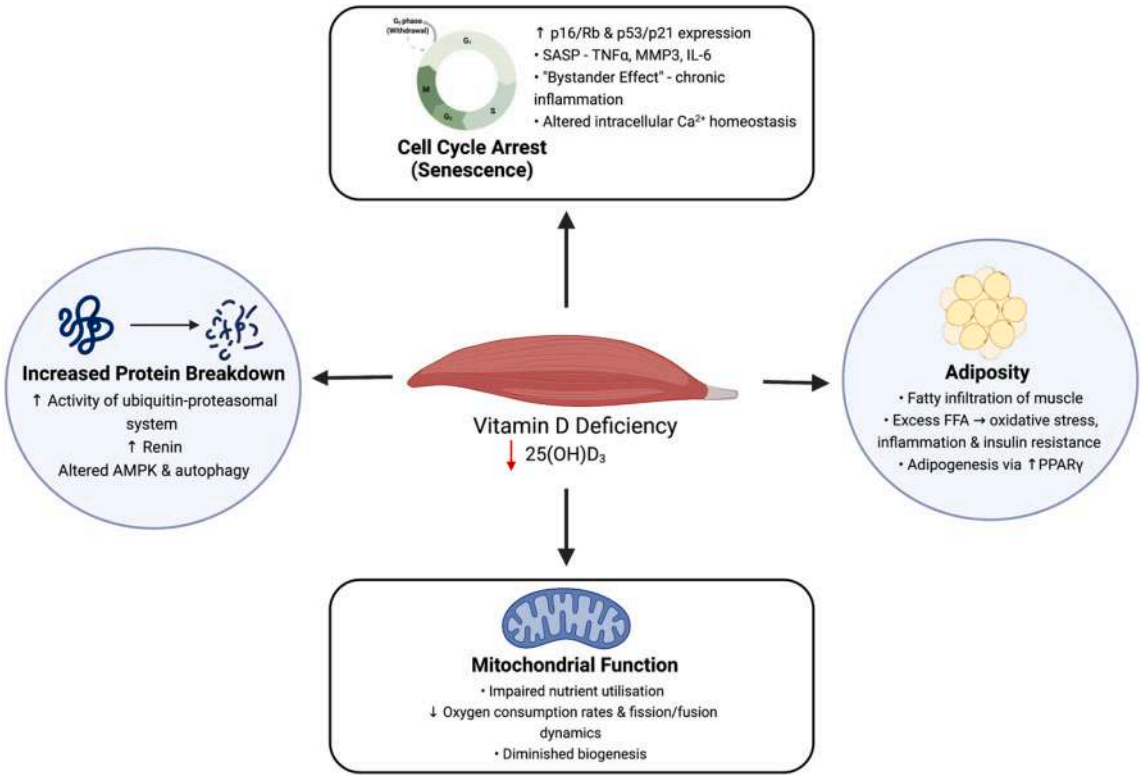

Fig. 1. The proposed mechanisms of vitamin D deficiency in skeletal muscle atrophy. Deficiency appears to lead to raised muscle protein breakdown via the ubiquitin-proteasomal pathway (UPP) and autophagy, and upregulation of AMPK and members of the renin-angiotensin system. Whilst unclear, it has been proposed that low vitamin D states leads to impaired mitochondrial function and increased adiposity in muscle. Permanent withdrawal from the cell cycle (senescence) is a key phenomenon in ageing, and the vitamin D/VDR axis has been shown to have regulatory control.
25(OH)D_3, 25-hydroxyvitamin D; *AMPK*, 5′ adenosine monophosphate-activated protein kinase; *SASP*, senescence associated-secretory phenotype; *Ca^{2+}*, calcium ion; *FFA*, free fatty acids; PPARγ, peroxisome proliferator-activated receptor gamma. Created with BioRender.com

Another key regulator of proteostasis is adenosine monophosphate-activated protein kinase (AMPK). Functioning as a nutrient sensor, AMPK is activated in states of metabolic stress, such as low ATP levels, and acts by activating ATP-producing pathways whilst inhibiting those that are ATP-consuming [83]. For example, activated AMPK phosphorylates mechanistic target of rapamycin (mTORC1) and uncoordinated 51-like kinase 1 (ULK1), thereby inhibiting the positive influence of mTORC1 upon MPS yet promoting autophagy via ULK1. The impact of ageing upon AMPK expression is uncertain, but a large body of evidence suggests its expression decreases with age, and this decline may be augmented by inactivity/unloading (common features of ageing) [84]. An age-related loss of AMPK would be detrimental as this impairs the ability for the cell to respond to states of metabolic dysregulation, thereby increasing oxidative stress. In cellular models of atrophy and stress, $1,25(OH)_2D_3$ treatment seems to increase AMPK activity and vitamin D deficient rats display reduced activation of sirtuin-1 (SIRT1), a key activator of AMPK [85–87]. Muscle of VDR-KD mice display higher AMPK levels, which may initially appear paradoxical due to the pro-catabolic influences of AMPK, but it is likely that this is a compensatory mechanism for the diminished ATP levels also seen in these animals [88]. Whilst there is evidently much more to be understood regarding this relationship, it is sensible to question whether age-related declines in vitamin D serum levels exercabate the effects of reduced skeletal muscle AMPK activity that have been proposed to occur with increasing age.

A novel link has recently been found between vitamin D/VDR signalling and the renin/angiotensin system (RAS) in skeletal muscle [20]. Possibly more well-known for its role in maintaining blood pressure and fluid homeostasis, hyperactivity of this system has been implicated in increased proteolysis due to the positive effects of angiotensin II on atrogin-1/MuRF1 expression [89]. It appears that $1,25(OH)_2D_3$ suppresses expression of renin and vitamin D deficiency is associated with increased renin production/activity [90], and early studies using VDR-KD rodents have demonstrated that lack of the *VDR* gene results in hypertension and elevated water intake [91]. These effects have been explored further in a VDR-KD rodent model of atrophy in which knockdown of VDR, in both the presence and absence of dexamethasone-induced atrophy, was accompanied by increased expression of angiotensinogen, renin, and angiotensin II [20]. Whilst further work is needed to confirm these results, the link between RAS and vitamin D/VDR could provide another explanation for the increased levels of proteolysis observed in states of deficiency.

Whilst the link between proteolytic signalling pathways and vitamin D has been well-documented, evidence exploring the relationship between the autophagy lysosomal pathway and the vitamin D system in skeletal muscle is notably much sparser. Expression of Cathepsin L, a lysosomal cysteine protease, was higher in VDR-KD rats versus controls and treatment with $1,25(OH)_2D_3$ suppressed glucocorticoid-induced expression of Cathepsin L in C2C12 myotubes [78,92]. As discussed previously, $1,25(OH)_2D_3$ stimulates AMPK activity, which is pivotal in activating autophagy via phosphorylation of ULK1, plus markers of autophagy (namely Beclin-1 and light chain 3B-11 (LC3B-II)) are heightened in various cell types (e.g. macrophages and neurones) treated with $1,25(OH)_2D_3$ [93,94]. Evidence from VDR-KO Recent RNA sequencing (RNAseq) data has also highlighted key autophagy-related gene sets that are upregulated in VDR-KD rats, thereby providing a solid platform for researchers to devise and plan future research upon [92].

3.2. Senescence

Cellular senescence is the term given to the age-related irreversible arrest of cellular growth. This phenomenon can be activated by a broad range of stressors (e.g., DNA damage or mitochondrial dysfunction) and is primarily regulated by two main anti-apoptotic pathways - p16/Rb and p53-p21. Senescence acts as a control measure for cell proliferation and is therefore beneficial in the suppression of malignant cells; however, as senescent cells accumulate over time, they remain metabolically active and secrete a repertoire of pro-inflammatory cytokines, matrix metalloproteinases (MMPs), chemokines and growth factors. This pro-inflammatory environment is known collectively as the senescence-associated secretory phenotype (SASP) and can induce a state of chronic low-grade inflammation upon surrounding cells that is termed the bystander effect [95,96]. It has been demonstrated that vitamin D deficient mice have increased muscular levels of p16, p21, p53 and p19, induction of cellular senescence and heightened expression of SASP factors (i.e. TNFα, MMP3 and IL-6) [97,98]. p16 and p21 upregulation is also seen in muscles of older humans and rats, and transplantation of senescent cells into rat muscle induced a rise in senescent markers with sarcopenia-associated muscle thinning [96,99].

Recent evidence has found that increasing age and senescence are both associated with chronically elevated intracellular calcium ion $[Ca^{2+}]_i$ levels in murine skeletal muscle fibres [100]. Normal healthy muscle cells have low $[Ca^{2+}]_i$ levels (100–120 nM) that are strictly controlled as perturbations of calcium homeostasis can result in activation of proteases, impaired energy production and muscular contraction, and even cellular death [101]. In the presence of vitamin D, Ca^{2+} is rapidly mobilised into the intracellular space for utilisation in contraction and cellular metabolism, and it is notable that low grip strength in mice with hypovitaminosis D was related to expression changes of sarcoendoplasmic reticulum calcium transport ATPase (Serca) [13,102]. Future research should endeavour to investigate the influence of deficiency upon $[Ca^{2+}]_i$, as this could further our mechanistic understanding of not only vitamin D in skeletal muscle, but potentially other tissues also.

3.3. Mitochondrial function

Whilst direct vitamin D supplementation studies upon deficient individuals is lacking, there is growing evidence of a link between vitamin D status and mitochondrial function in skeletal muscle. [103,104]. Indeed, in vitro models of primary human skeletal muscle cells demonstrate improved mitochondrial bioenergetics in response to active $1,25(OH)_2D_3$ [105,106], increasing oxygen consumption rates and fission/fusion dynamics [107]. Interestingly, while CYP27B1-mediated intracrine synthesis of $1,25(OH)2D_3$ appears to be a feature of skeletal muscle, vitamin D3 metabolites lacking the 1α-hydroxyl group (i.e. $25(OH)D_3$, $24R,25(OH)_2D_3$ and $1α(OH)D_3$) do not elicit the same muscle bioenergetic response as 1,25(OH)2D [107]. Thus, the muscle CYP27B1-VDR intracrine pathway may have a selective impact on muscle function. Conversely, diet-induced $25(OH)D_3$ deficiency in mice elicits reduced mitochondrial function, whilst these changes were not mediated through alterations in mitochondrial protein content including electron transport chain (ETC) expression or citrate synthase activity [108].

Separate from mediating $1,25(OH)_2D_3$ induced effects in muscle, the VDR seems to have an independent role upon mitochondrial function. Knockdown of the VDR in vitro impairs mitochondrial function, through as yet undefined mechanisms, however dysregulation of membrane permeability or calcium handling, and raised levels of reactive oxygen species (ROS) may offer a potential means [109,110]. Further, in response to VDR knockdown in vivo, multiple mitochondrial related genesets are downregulated [92], suggesting the VDR may necessary for mitochondrial bioenergetic function though the regulation of key mitochondrial genesets. However, recent investigations have determined $VDR^{-/-}$ mice display decreased intramuscular ATP despite showing no reductions in ETC protein expression [88]. It is postulated this may be due to changes in nutrient utilisation and efficiency rather than impaired mitochondrial function, however these aspects and the surrounding role of the vitamin D/VDR upon mitochondrial function require further investigation.

3.4. Adiposity

Adiposity may also exert important effects on the $1,25(OH)_2D_3$/VDR axis in muscle. Ectopic fat deposition and infiltration of adipose tissue within muscle is known as myosteatosis; obesity is also common in sarcopenic patients due to reduced activity (sarcopenic obesity). The true pathological consequence of adipose tissue accumulation within skeletal muscle is not wholly understood, but it is believed that when adipocytes reach their maximal capacity for absorption of free fatty acids (FFA), excess lipids will spill into the surrounding non-adipose tissue (e.g., muscle), subsequently altering metabolic homeostasis [111]. Potential metabolic and physiological consequences of excess FFA include increased oxidative stress, inflammation, insulin resistance, and impaired quality of surrounding muscle fibres [112]. In both older and obese mice and humans, accumulation of fat is seen to be positively associated with muscle atrophy and transplantation of white adipose tissue (WAT) around skeletal muscle accelerated denervated-induced atrophy via induction of cellular senescence and elevated proteolysis [113,114]. A large volume of evidence exists demonstrating a negative relationship between $25(OH)D_3$ levels and fat mass, and those who are overweight and also deficient have an increased risk of deficits in muscle mass and function [115–117]. $1,25(OH)_2D_3$ suppresses differentiation of pre-adipocytes into mature adipocytes (adipogenesis) via a VDR-dependent inhibition of peroxisome proliferator-activated receptor gamma (PPAR-γ), which is the leading regulator of adipogenesis [118]. Additionally, downregulation of sterol regulatory binding protein 1 (SREBP1) by $1,25(OH)_2D_3$ has a dose-dependent negative influence upon lipid accumulation [118]. SREBP1 induces expression of genes involved in adipogenesis, fatty acid production, and glucose metabolism, which may explain why these metabolic processes are all heightened in vitamin D deficient mice [119,120]. These mice displayed notably higher levels of muscle lipid deposition, disorganisation of skeletal muscle fibres, elevated PPAR-γ expression, and an altered muscular phospholipid profile [119]. Whilst the majority of data in this field has been generated from cell or animal models, it is still possible to hypothesise that vitamin D deficiency in humans may be a driving factor for invasion of adipose tissue into muscle, and the subsequent development of sarcopenic obesity. Like the bystander effect observed in senescent cells, it is likely that invading adipose cells/tissue negatively affect physiology and metabolic environment of surrounding muscle tissue by a paracrine/endocrine mechanism of FFA production. This process that will also be exacerbated by low vitamin D levels and could explain the pathological changes seen in skeletal muscle of those who are both overweight and deficient.

Given the sheer breadth of research within the vitamin D field, we can now appreciate that there is much more to this pathway than just the vitamin D metabolites $25(OH)D_3$ or $1,25(OH)_2D_3$. For example, the vitamin D binding protein (DBP; also known as group-specific component of serum, Gc-globulin) is the primary transport protein for all vitamin D metabolites. DBP physiology represents a hugely under-researched facet of vitamin D biology, particularly in relation to skeletal muscle, but evidence suggests two roles in skeletal muscle. Firstly, DBP plays a pivotal role in the storage and transport of vitamin D metabolites, particularly $25(OH)D_3$ which is the most abundant vitamin D metabolite and which binds DBP with the highest affinity [121,122], Binding to DBP limits the biovailability of $25(OH)D_3$ to some tissues but, conversely, facilitates $25(OH)D_3$ uptake by other tissues via megalin-mediated endocytosis [121,122]. Studies have shown that C2C12 myotubes and primary rat fibres express the megalin machinery

required for uptake and its 25(OH)D_3 cargo [123], suggesting that specific uptake of DBP is essential for targeted delivery and effects of vitamin D metabolites in muscle. In addition to its vitamin D binding function, DBP is also known to play a key role in the scavenging of actin [124]. Until recently, the actin-binding capacity of DBP was thought to be restricted to the circulation. However, recent studies in several tissues have shown that DBP also acts as an intracellular actin-binder [125]. It is therefore possible that after it has delivered vitamin D metabolites to muscle, DBP may fulfil a further function as an actin-binder. Indeed, one of the earliest studies on tissue function of DBP identified its ability to interact with actin in muscle [126]. In addition, the enzymes that are pivotal to the activation and catabolism of 1,25$(OH)_2D_3$, CYP27B1 and CYP24A1, are also known to be expressed in skeletal muscle, implying a capacity for intracrine synthesis of active vitamin D, and CYP27B1 expression is altered in atrophic states [9,127]. Whilst there is still a lack of knowledge surrounding the mechanistic relationships between different components of the vitamin D pathway and muscle function, this clearly represents a promising area for future research, particularly in relation to the impact of ageing.

It has been long accepted that there is a significant interplay between our genetics and our physiology, and mutations of certain genes (e.g., myostatin (*MSTN)* and α-actinin3 (*ACTN3*)) have been linked with altered muscle function and performance [128,129]. The impact of genetic variation within key genes of the vitamin D system upon skeletal muscle has only been investigated in relation to the *VDR* gene, and existing data is primarily generalisable to older white populations due to the presence of racial bias. *Bsm*I (rs1544410), TaqI (rs731236), Cdx2 (rs11568820), and *Fok*I (rs2228570) are among the most frequently investigated single nucleotide polymorphisms (SNPs) of the *VDR* gene yet, due to variable methodologies and different demographics among study populations, there is large variability in results which makes definitive conclusions difficult [130]. Additionally, no evidence exists proposing a molecular basis for the differences seen between those who carry *VDR* SNPs and those who don't; clarification of the mechanisms underlying the functional consequences of these SNPs would provide further information into the role of the vitamin D/VDR axis and, also, the extent to which its genetic component contributes to our normal physiology.

4. Future directions and conclusions

Moving forward, efforts should be made to optimise future study design. Genetic association studies and supplementation trials should be conducted in populations that are more racially diverse and a better representation of the current population demographics globally. Black individuals and people of colour are among those with the highest risk of vitamin D deficiency, yet they account for a very small proportion of people included in human studies [131]. Until changes are made, their absence from scientific research will contribute further to ungeneralisable results and exacerbation of health inequalities. Additionally, considerations should be given to optimising future study methodologies. Currently, 25(OH)D_3 is the most commonly studied vitamin D metabolite and is used clinically when investigating vitamin D levels. However, data has been generated that poses an important question – should we be measuring 1,25$(OH)_2D_3$ as well? Whilst rarely measured in human studies of sarcopenia and muscle atrophy, results from work in which it is included suggest that 1,25$(OH)_2D_3$ may be a better correlate of muscle function and a potential predictor for age-related muscle loss [132–134]. Also, as research evolves, potential new mechanisms come to light which require broadening of research scope. As previously discussed, research into the role of the vitamin D/VDR axis in calcium homeostasis has been largely restricted to myogenesis and differentiation, which leaves the question of how does deficiency affect intracellular calcium in human skeletal muscle? Despite being a central protein of interest in ageing research, Klotho has barely been investigated in relation to vitamin D and skeletal muscle. Given that Klotho null mice have significantly fewer muscle stem cells and display severe muscle wasting, and vitamin D metabolism appears to be controlled by Klotho [135,136], it's sensible to wonder how these two systems interlink mechanistically in skeletal muscle in particular, and what impact ageing could have.

There is a growing body of evidence to support a role for the vitamin D/VDR axis in skeletal muscle. A great number of human studies have demonstrated that low serum levels of 25(OH)D_3 are associated with impaired muscle function and strength and can put older individuals at risk of sarcopenia. However, in vitro research sadly isn't as vast, making definitive conclusions surrounding the underlying mechanisms difficult. It is clear that the relationship between the vitamin D/VDR axis and muscle atrophy is complex and multifactorial, reliant on the involvement of multiple molecular processes (e.g., protein breakdown, cellular senescence and signalling) and even contributions from other cell/tissue types (e.g., adipose). Future research should aim to confirm existing hypotheses regarding these mechanisms but also explore avenues that remain under researched in comparison.

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