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Review article

Vitamin D, muscle recovery, sarcopenia, cachexia, and muscle atrophy

Matheus Garcia [a,*], Marilia Seelaender PhD [b], Athanassia Sotiropoulos PhD [c], Dario Coletti PhD [d], Antonio Herbert Lancha Jr, PhD [a]

[a] Biodynamic Department Physical Education and Sport School University of São Paulo, São Paulo, Brazil
[b] Molecular Biology of the Cell Group Department of Cell and Developmental Biology Institute of Biomedical Sciences University of São Paulo, São Paulo, Brazil
[c] Institut Cochin Université Paris Descartes, Paris, France
[d] Sorbonne Université, Biological Adaptation and Ageing, Paris, France

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ABSTRACT

The relevance of vitamin D to skeletal muscle metabolism has been highlighted in recent years. The interest arises from the important findings of studies demonstrating multiple effects of vitamin D on this tissue, which can be divided into genomic (direct effects) and non-genomic effects (indirect effects). Another important aspect to be considered in the study of vitamin D and muscle fiber metabolism is related to different expression of vitamin D receptor (VDR), which varies in muscle tissue depending on age, sex, and pathology. The correlation between low circulating levels of vitamin D and muscle metabolism disorders is documented in various contexts, including muscle recovery, atrophy, sarcopenia, and cachexia. The aim of this review was to analyze recent results of both in vitro and in vivo studies to address the relationship between vitamin D and skeletal muscle biology. The words *muscle atrophy, muscle hypertrophy, sarcopenia,* and *cachexia* were crossed over with vitamin D in a Pubmed search. All original contributions, along with reviews on the topic, were included, and no publications in the past 10 y were discarded. The papers retrieved different topics such as vitamin D in skeletal muscle; vitamin D in circulation; vitamin D, sarcopenia, and muscle atrophy; vitamin D and cachexia; and vitamin D and muscle recovery.

Introduction

The main pathway for vitamin D obtention in humans is through cutaneous synthesis under the action of ultraviolet rays. Vitamin D production in the skin provides 80% to 100% of body requirements [1]. However, factors such as season of the year, regional latitude, day time of sun exposure, use of sunscreen and clothing, ethnicity, and age may influence vitamin D synthesis rate [2]. The precursor, 7-dehydrocholesterol (pro-vitamin D), synthesized by the liver from cholesterol, is converted in the skin while the individual is exposed to solar radiation [3]. Through thermal isomerization, previtamin D converts to vitamin D, and in the circulation it binds to vitamin D binding protein (DBP) and proceeds to the liver, where a hydroxyl group binds to the carbon atom 25 to generate 25-hydroxyvitamin D or 25(OH)D (calcidiol). After these steps, the 25(OH)D is released into the circulation, undergoing a new stage of activation in the kidneys, where 1-α-hydroxylase converts 25(OH)D to 1,25 dihydroxyvitamin D or 1,25(OH)D (calcitriol), thus turning it into its active form, which is distributed to different body tissues, such as the bone, muscular tissue, or intestine [2,4].

Vitamin D is found in small amounts in plants, in the form of ergocalciferol (vitamin D_2), or found in food of animal origin as cholecalciferol (vitamin D_3) [5]. Vitamin D_3 food sources are liver, fish liver oil, fish fat (salmon, tuna, sardines) and eggs, and some foods fortified by industry, such as milk, morning cereal, and juices. In addition, vitamin D_2 can be obtained by consuming some types of mushrooms (shiitake) [3]. Vitamin D obtained from dietary sources will also bind to DBP to convert the active form 1,25(OH)D in the kidneys in a similar way to the vitamin D obtained by ultraviolet B action [2].

Vitamin D in musculoskeletal tissue

In cellular models, a variety of mechanisms by which vitamin D interferes with skeletal muscle function has been elucidated. These can be divided into the following effects:

- Genomic effects arising from the interaction of the 1,25-VDR-retinoid X receptor heterodimer at specific nuclear receptors that influence gene transcription.
- Non-genomic effects, characterized by rapid activation followed by other complex pathways of intracellular signal transduction after binding of 1,25(OH)D to its non-nuclear receptor [2,6,7].

* Corresponding author.
E-mail address: Matheus_dag@usp.br (M. Garcia).

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The mechanism of action of vitamin D in muscle cells started to be elucidated after the discovery of VDR, which was initially detected in intestinal cells [8]. By 2004, researchers observed that when VDR is inhibited by using anti-VDR, it is possible to inhibit 1,25(OH)D-dependent mechanisms by which the rapid intracellular entry of calcium can be downregulated, implying a direct nongenomic role for VDR in manipulating calcium in both bone and muscle tissue [9,10]. The expression of VDR throughout the stages of life also appears to change, as demonstrated by the work with humans by Bischoff-ferrari et al. [11] and in a study with mice [12], in which VDR messenger RNA (mRNA) expression was found to be higher in animals at 3 wk of age than in those at 8 wk of age. Based on these findings, the authors suggested a primary role of VDR in early-stage muscle development.

VDR is expressed in the nucleus of human muscle cells, and its deficiency has been shown to affect muscle cell contractility [11].

A study exploiting another animal model (bird myoblasts) showed that after radiation exposure, 1,25(OH)D VDR appears to translocate back to the nucleus to assume its role in transcriptional regulation. This displacement of the VDR between cytoplasm and nucleus indicates its ability to induce rapid transcriptional actions [13]. In addition to the transcriptional effects in an in vitro model [7], an improvement in cell migration in injured muscle cells was reported when these cells were stimulated with 1,25(OH)D. In particular, vitamin D has the ability to improve the speed of progenitors of skeletal muscle to reach a site of damage, as to allow repair and remodeling of the area.

Another study reported that mRNA and VDR expression appear in larger numbers in satellite cells than in mature muscle fibers, suggesting a more prominent role in muscle progenitors [14].

The number of VDRs decreases with age, which is supposed to be a contributing factor to reducing muscle strength with aging [11,15].

Vitamin D in the circulation

Providing optimal dose or concentration of vitamin D to benefit muscle metabolism and regeneration has constantly proven to be a challenge owing to varying and controversial results of recent literature.

It is recognized that maintenance of good bone mass and modulation of the immune system require different vitamin D serum levels [16].

When assays are performed with muscle tissue, vitamin D deficiency seems to influence the migration and proliferation responses of satellite cells. However, this same study showed that higher doses of vitamin D also appear to disrupt the recovery of this tissue [7].

Bone-centered guidelines recommend a target 25(OH)D concentration of 20 ng/mL (50 nmol/L) and daily doses of vitamin D, depending on age, ranging from 400 to 800 IU. The guidelines focused on the pleiotropic effects of vitamin D recommend a target concentration of 25 ng/mL (75 nmol/L) of circulating 25(OH)D and doses of vitamin D depending on age, body weight, presence of disease, and ethnicity, ranging between 400 and 2000 IU/d [17].

Vitamin D, sarcopenia, and muscle atrophy

The classical view of sarcopenia, from the Greek *sarx* (flesh) and *penia* (poverty), envisages the condition as a component of the fragility syndrome and refers to the degenerative loss of mass, quality, and strength of skeletal muscle associated with aging [18,19].

This loss in the fourth decade of life is around 0.8%/y. This process can be so accelerated that from the sixth decade of life muscular degradation can reach 15% per decade [20].

With advancing age, there is also a strong incidence of vitamin D deficiency, perhaps because there is a decrease in sun exposure, concomitant with the reduction of food sources of vitamin D, and a decreased ability of the skin to synthesize vitamin D [19].

Randomized controlled trials and meta-analyses support the role of vitamin D in improving age-related declines in muscle function [19]. However, the precise effect of the mechanism of the influence of vitamin D on the development and differentiation of muscle cells remains non-conclusive [19,21].

A functional vitamin D system was proposed in C2 C12 cells, thus implying a possible direct role in muscle regulation [21]. In this scenario, silencing VDRs in C2 C12 myoblasts suppressed p38 MAPK phosphorylation and decreased ERK1 activation induced by 1,25(OH)D [22]. Another study demonstrated that the silencing of VDR expression resulted in negative regulation of MyHC mRNA in the differentiation of C2 C12 myoblasts when treated with 1,25(OH)D [23]. It seems plausible that the decrease in VDR expression observed in the elderly may reduce the functional response of muscle fibers to 1,25(OH)D [19].

The muscle fiber diameter of null VDR mice was ~20% lower and the fiber size was more variable than those of the 3-wk-old wild type mice (preweaning). By 8 wk of age, these morphologic changes were more prominent in null mice VDR compared with wild-type mice, suggesting a progressive nature of the abnormalities caused by the absence of VDR [12].

With direct regulation of cell cycle gene expression (*ATM, Myc, Rb,* and *cyclin D1*) and posttransduction hypophosphorylation of *Rb*, at 1,25(OH)D promotes cyclic arrest and quiescence in C2 C12 cells, and protection against senescence replication of human mesenchymal stem cells as exhibited in flow cytometry analysis. This may be particularly important in the muscle, where age-related dysfunction of stem cells is directly related to the negative regulation of its quiescent capacity for self-renewal [21].

Vitamin D and cachexia

Cachexia is a multiple organ syndrome associated with diseases such as cancer, chronic infection, chronic obstructive pulmonary disease, and chronic heart failure. Major feature of cachexia are body weight loss (≥5%), loss of muscle and adipose tissue, inflammation, and often anorexia. Also, alterations in the metabolism of carbohydrates, lipids, and proteins are reported to be associated with this syndrome [18]. The consensus definition of cachexia states that it is “a complex metabolic syndrome associated with the underlying disease and characterized by loss of muscle mass with or without loss of fat mass. The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or failure of growth in children (excluding endocrine disorders). Anorexia, inflammation, insulin resistance, and increased muscle protein degradation are often associated with cachexia” [24]. Decreased circulating vitamin D levels, as observed in 47% of ambulatory cancer patients [25], have been associated with impairment of glucose metabolism and insulin sensitivity [26].

Interestingly, reduction in mortality was reported in patients with colorectal cancer who presented adequate levels of vitamin D, suggesting the importance of maintaining vitamin D [27].

There are still few studies on the efficacy of adequate levels of vitamin D in cachectic cancer patients. In a pioneer study performed with 16 patients with advanced metastatic prostate cancer, the daily administration of 2000 IU of vitamin D_2, concomitant with a 500 mg calcium supplement for 12 wk, resulted in improved muscle strength and a reduced pain score [28]; body composition was not assessed.

In another study, data from 308 patients who underwent chemotherapy for breast cancer between 2006 and 2012 were divided

into two groups—those receiving or not receiving vitamin D supplementation. The authors found greater disease-free survival in those individuals who were supplemented with vitamin D [29].

A more recent study in rodents with hepatoma AH 130 showed a decrease in circulating vitamin D compared with control rats, whereas muscle VDR mRNA was upregulated. Both blood levels and muscle VDR expression increased after the administration of vitamin D_3, without exerting significant effects on body weight and muscle mass. In this same study, the effects of vitamin D on C2 C12 myocytes were studied. Vitamin D-treated myoblasts did not adequately differentiate, only partially fusing and forming multinucleated, deformed, and low myosin heavy-chain structures. This treatment with vitamin D resulted in the overexpression of VDR and in the negative regulation of myogenesis. However, the silencing of VDR expression in C2 C12 cultures negated the inhibition of the differentiation exerted by the treatment with vitamin D. The results from this study suggest that the superexpression of VDR in tumor-bearing animals contributed to the muscular loss, damaging the regenerative process muscle [30]].

In another recent study, Ryan et al. [31] showed that treatment with 1α,25-dihydroxyvitamin D_3 [1α,25(OH)D] prevented the changes in myoblasts induced by Lung Lewis carcinoma (mitochondrial oxygen utilization and proteasome activity), thereby suggesting that the treatment may be effective in counteracting muscle weakness in cachexia.

Nevertheless, Penna et al. [32] argue that vitamin D supplementation, in addition to not eliciting any palpable beneficial effect, may actually impair muscle regeneration in cachexia, probably by inducing increased levels of VDR. However, the authors suggest that although 1,25(OH)D would not be adequate for treatment of cancer cachexia, 25(OH)D and also 24,25(OH)D may be adequate because they found (unpublished results) these to display protective action against the reduction in size and molecular alterations in C2 C12 myotube cultures, as induced by inflammatory cytokines.

Vitamin D and muscle recovery

The recovery of athletes during the season involves a systematic approach, aimed to maintain the physical and mental readiness to hold the next competition. Multiple variables, such as nutrition, sleep, and travel, can influence recovery. In addition to these issues, competitive training presents significant mechanical loads and metabolic demands that cause fatigue and represent challenges to the recovery process. Upon completion of training or competition, the athlete enters a recovery phase in which the body restores fuel levels (metabolic recovery) and repairs damage to the musculoskeletal system (mechanical recovery) [33].

One aspect of recovery after intense exercise is the repair of damaged musculoskeletal tissue via activation of satellite cells. Although other factors influence this repair process, current data suggest a role for vitamin D in this issue [34].

Research on rodents reports that treatment with vitamin D did not influence the morphologic characteristics of the injured muscle, leukocyte infiltration, or VDR expression. However, the administration of vitamin D accelerated the functional restoration of the injured muscle, improving cellular turnover, mainly improvement in cellular proliferation and decrease of apoptosis after muscle injury (crushing). Vitamin D treatment was correlated with a significant increase in P4 HB protein, which is associated with collagen production, which may influence muscle function. In conclusion, this study demonstrated that vitamin D has a positive influence on muscle repair regardless of satellite cell expansion or infiltration of Caprine Arthritic Encephalitis–positive leukocytes into injured muscle tissue [35].

To date, four studies have been published related to the specific role of vitamin D in muscle recovery in humans. Muscle weakness (measured as peak isometric force or peak torque) was chosen as a measure of recovery because it reflects both degeneration and regeneration, remains suppressed until the repair is complete, and is a functional outcome for the athlete [36].

A study using eccentric elbow flexor exercise did not show an association between baseline vitamin D status [measured as blood level of 25(OH)D] and muscle pain or peak isometric strength up to 4 d after the insult [37]. In contrast, using a resistance exercise for lower limbs, researchers found that the pre-exercise vitamin D status of recreational individuals was significantly correlated with immediate and long-term muscle weakness (48 and 72 h) after intense exercise in leg-exercised versus leg control groups [36].

Although correlating vitamin D status to functional results points out a possible relationship, intervention studies are needed to determine whether improving status may result in improved recovery [33]. In another study, researchers supplemented healthy, moderately active, adult men with 4000 IU/d or placebo for 35 d. After 28 d of supplementation, participants completed an eccentric one-leg protocol to induce muscle damage. The recovery of peak isometric strength, but not muscle pain, was significantly improved in the supplemented group 24 h after exercise, but not at any other time (48, 72, or 168 h) [38].

The results of these studies imply that adequate exposure to vitamin D may optimize the acute adaptive response to muscle damage caused by physical exercise but do not support the idea that vitamin D may be important during a long period of training [34].

In the study with the longest period of observation and intervention found, the authors supplemented 40 men, 20 elderly and 20 young, untrained with vitamin D_3 1920 UI (48 mg), concomitantly with 800 mg/d of calcium from December to April or calcium alone (placebo group) at a latitude of 56°N (very little sun exposure). During the final 12 wk of the supplementation period, participants underwent a resistance training program for the quadriceps muscles. There were no observable differences between the groups in strength gain or hypertrophy, but a large change in fiber type (plus IIA-type fibers) and a reduction in myostatin messenger RNA expression (mRNA) were observed in the young men receiving vitamin D. In addition, the elderly men who received vitamin D and calcium supplementation showed an improvement in muscle quality greater than the placebo group [39].

A study of 179 girls supplemented with vitamin D for 1 y resulted in improvement in musculoskeletal parameters, such as lean mass and bone mass gain, especially during the premenarcheal period, when compared with a control group [40].

By a carefully controlled intervention protocol, British researchers found positive results with vitamin D supplementation in improving recovery rates. Moderately active adults with deficiency in circulating levels of vitamin D at the start of the study were supplemented with 4000 IU/d or placebo for 6 wk. Before and after supplementation, participants performed eccentric exercise to induce muscle damage of knee extensor muscles, followed by peak torque during 7 d of recovery. Peak torque was improved in the group supplemented with vitamin D at 48 h and 7 d post-exercise compared with the placebo group. Although the authors believe that these data are promising, more studies are needed with a larger sample size and other exercise protocols to generate muscle damage [7].

Conclusions

Evidence is increasingly strong regarding the potent effects of circulating levels of vitamin D on its VDR receptor in muscle tissue. However, more studies need to focus on the challenge of

deciphering the main targets of muscle remodeling from VDR actions. It is also necessary to study these effects in the different age groups as expression of VDR is modified with aging.

A broad question will be to determine appropriate levels of vitamin D for different populations, taking into account the pleiotropic effects of this vitamin.

Of all the factors that lead to sarcopenia, vitamin D deficiency in the elderly has a supporting role, not least because it causes decreased amounts of VDR, usually less sun exposure, and difficulties in eating foods containing vitamin D; therefore supplementation is an important point to be considered in the prevention and treatment of sarcopenia.

The parameters found in the studies do not allow us to affirm that vitamin D is effective in the treatment of muscular remodeling in this cachexia. The factors attributed to the worsening of muscle tissue in this pathology are complex and appear to interact in ways not yet elucidated. Therefore, more studies to establish this interaction are necessary.

In athletes and those who exercise, maintaining adequate levels of vitamin D is recommended as an aid in muscle recovery, and this was evidenced in the works cited. At the same time, the molecular pathways recruited for this purpose remain inconclusive. More studies are needed with more controlled and standardized trials and with a larger number of participants in different sports genres so that the understanding becomes clearer.

Assessing people's levels of vitamin D deficiency and insufficiency seems to be one way to minimize physiological and functional changes in skeletal muscles.

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