Vitamin D and muscle

Giovanni Iolascon, Antimo Moretti

University of Campania "Luigi Vanvitelli", Multidisciplinary Department of Medical and Surgical Specialties and Dentistry

VITAMIN D
UpDates
2020;3(3):78-80
https://doi.org/10.30455/2611-2876-2020-4e

VITAMIN D AND MUSCLE

The last decades have seen increased scientific interest in the extra skeletal effects of the vitamin D system, including its role in muscular function. The hypothesis that this seco-steroid was involved in muscle activity derives from the observation that vitamin D-deficient children affected by rickets experience serious muscular impairment, defined as "myopathia rachitica" [1]. In the first half of the last century, to better understand the pathophysiological mechanisms of such muscular damage, a theory was formulated based on the key role of alterations of phosphoric ester concentrations in muscle tissue [2]. This theory, however, did not take into account the effects on skeletal muscle of secondary hyperparathyroidism due to hypovitaminosis D. In fact, it is known that the hyperparathyroidism leads to significant muscular damage characterized by muscle atrophy due to the loss of mainly type II fibers [3]. This damage is different from pathognomonic alterations of primary myopathy, in which there is degeneration or even necrosis of muscle fibers, together with a proliferation of the endomysial connective tissue.

The discovery of vitamin D receptors (VDRs) is a milestone in the study of vitamin D pleiotropic effects [4]. At the muscular level, VDRs have been identified not only in the myoblasts, myotubes and muscle cells of animal models, but also in human myocytes [5,6]. As a consequence, vitamin D is said to act on multiple cellular components of skeletal muscle during the different stages of an individual's life, starting from embryonic development. In particular, it is involved in tissue repair after injury in all stages of life, until regressive alterations due to aging.

The effects of vitamin D on muscle tissue occur mainly by means of two mechanisms: a long-term one, which involves genomic action, and a short-term one, which entails a non-genomic mechanism [7]. The two mechanisms act in synergy, both on muscle contraction, in response to calcium intracellular fluxes (rapid response), and on muscle strength and mass (long-term response).

Through the first mechanism, vitamin D stimulates the proliferation and differentiation of muscle cells, modulating gene transcription in the myoblasts and thereby increasing synthesis of specific muscle proteins, such as myosin and the calcium-binding protein CBP. This mechanism involves a direct bond of vitamin D activated by the nuclear VDR/retinoid-X receptor (RXR) complex with specific DNA sequences, known as vitamin D response elements (VDREs), with the resulting transcription regulation. In addition to modulating calcium absorption, vitamin D regulates phosphate metabolism at the muscle level to meet structural and energetic cellular needs. Recently, Shirvani et al. [8] have shown that the genomic mechanism activated by vitamin D is proportional to the dosage of vitamin D taken as a supplement. In fact, the expression of 162 genes (86 up-regulated and 76 down-regulated) in peripheral white blood cells were influenced in normal adults who took 600 IU/day for 6 months, while the number of these genes doubles with an intake of 4,000 IU/day and even increases eightfold if the dose reaches 10,000 IU/day.

By means of the short-term mechanism, meanwhile, vitamin D regulates the calcium-dependent action of second messengers, which come into play both in the interaction between cytosol and mitochondria in order to modulate muscle energy metabolism, and in the mechanisms at the base of muscle contraction [9]. Non-genomic mechanisms, which occur following binding between vitamin D with the nuclear VDR (nVDR) and/or the membrane VDR (mVDR) associated with caveolin-1, include the activation of intracellular signal molecules such as PKC, PI3K, MAPK, CaMKII and PLA2 [10]. In its active form, calcitriol influences muscle function by acting on the dependent voltage channels SOC/TRPC3 to regulate calcium intracellular levels and consequently the excitation-contraction coupling of skeletal muscle fibers.

More recently, a third mechanism has been suggested through which vitamin D presum-

Corrispondence
Giovanni Iolascon
giovanni.iolascon@unicampania.it

Conflict of interest
The Authors declare that they have no conflicts of interest.

How to cite this article: Iolascon G, Moretti A. Vitamin D and muscle. Vitamin D – Updates 2020;3(3):78-80. https://doi.org/10.30455/2611-2876-2020-4e

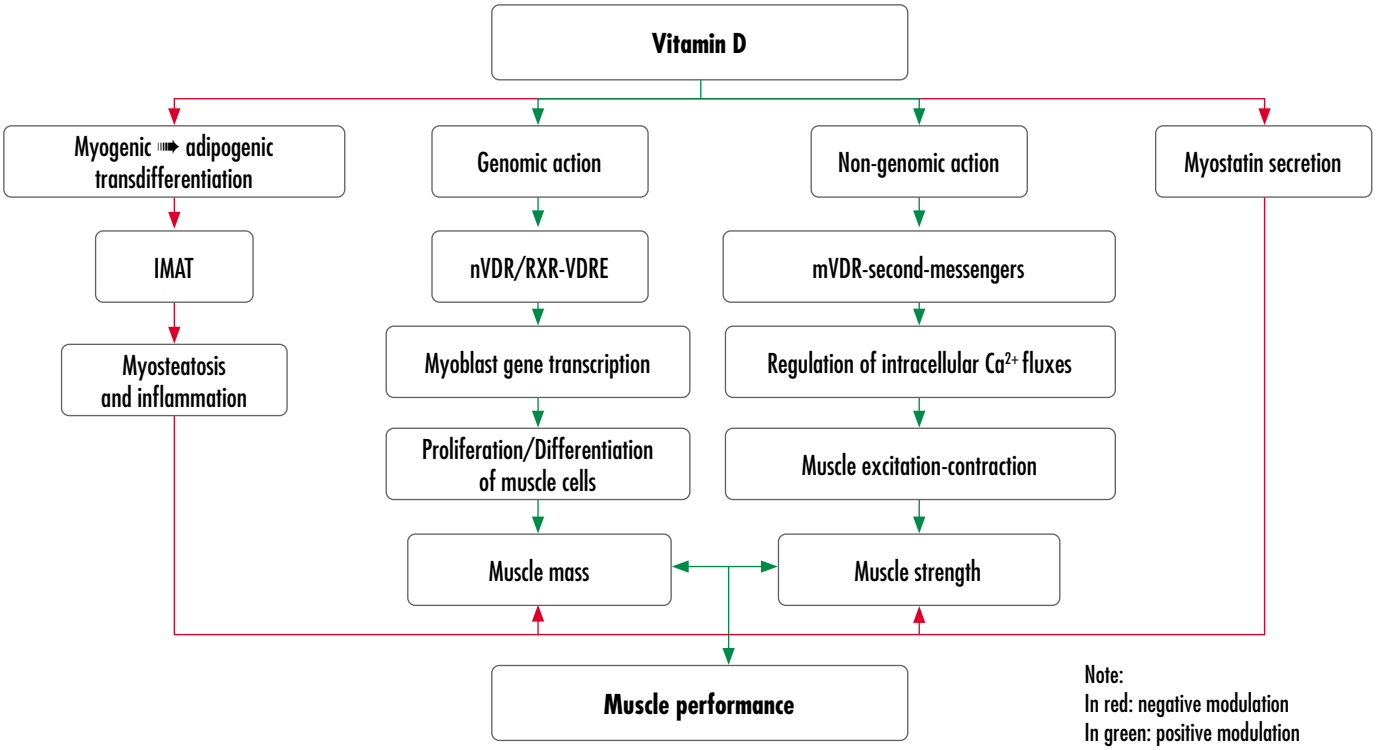

FIGURE 1.
Biological mechanisms of vitamin D effects on skeletal muscle.

ably exerts beneficial effects on muscle function, namely by inhibiting the trans-differentiation of myogenic precursors in adipocytes, thereby reducing intra- and inter-muscular adipose tissue accumulation (IMAT) [11]. *In vitro* studies on myoblasts exposed to calcitriol [12] demonstrate another of its hypothetical indirect effects: vitamin D inhibits the secretion of myostatin, a key negative regulator of muscle mass (Fig. 1).

From a clinical point of view, the evidence that vitamin D can play a key role on muscle function mainly derives from the many studies performed on the controversial association between hypovitaminosis D and risk of falls, particularly during the aging.

As it is commonly known, older people, especially when institutionalized, show reduced VDR expression in muscle and lower serum concentrations of 25(OH)D [13]. It has been suggested that vitamin D deficiency plays a key role in the age-related muscle mass loss and that muscle impairment precedes the onset of biochemical aspects of osteomalacia [14].

Hypovitaminosis D is closely associated with both the reduction of muscle mass and with the worsening of appendicular muscle strength – in particular with regard to antigravity muscles – and physical performance [15,16]. It is interesting to note that the same myopathic pattern present in rickets, with a prevalent reduction of type II fibers, is found in elderly people affected by long-term vitamin D deficiency. This pattern is also evident in sarcopenia, a disease characterized by a reduction of muscle mass and function. Such deficiency increases the risk of falls and fragility fractures [17], which in turn initiates a vicious circle of reduced mobility and autonomy and an exacerbation of hypovitaminosis D status because of fewer outdoor activities and less exposure to sunlight [18].

By means of its many receptors and enzymes ubiquitously present in the human body, the vitamin D system contributes to modulating muscle performance by regulating various functions related to physical performance, androgen synthesis, cognitive status and neuroprotection. Depletion of active vitamin D needed to carry out the organism's physiological functions triggers a series of pathological events which compromise muscle function (Fig. 2).

Although hypovitaminosis D and altered muscle functions are more common later in life, we should emphasize that vitamin D also plays a key role in the physical and cognitive performance of younger subjects. In fact, a recent study suggests the use of vitamin D supplementation in specific populations which require high-level physical and psycho-emotional performance, such as that demanded of soldiers in wartime situations. Wentz et al. [19] claim that vitamin D supplementation given to soldiers affected by hypovitaminosis D represents a noninvasive and low-cost measure for improving combat performance.

Among the many extra skeletal actions attributed to the vitamin D system, that which regards striated muscles undoubtedly represents an intriguing element in understanding the mechanisms at the basis of its complex biological function. Pre-clinical, clinical and observational studies appear to confirm a close relationship between serum 25(OH)D and muscle activity, in particular in improving functional performance and in reducing the risk of falls and disability.

At the moment, however, there is no agreement about the optimal serum levels of 25(OH)D to reach, the dosage to give as supplement, or the frequency of administration which would lead to the attainment of potential beneficial effects of vitamin D on muscle function.

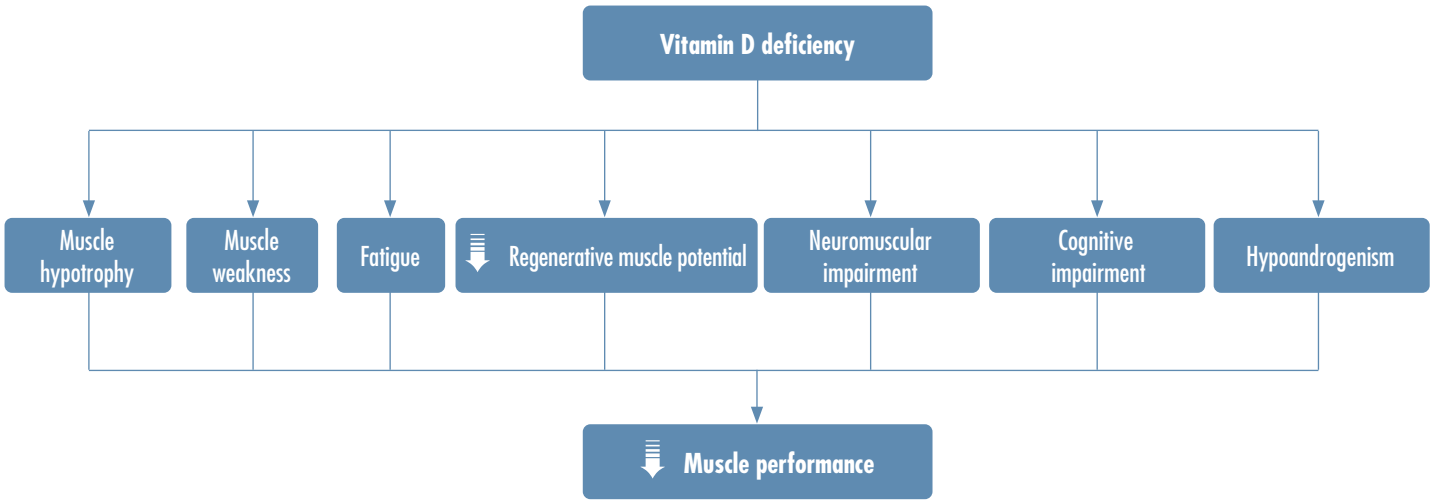

FIGURE 2.
Pathologic mechanisms of hypovitaminosis D in compromising muscle performance.

References

1 Bing R. Myopathia rachitica. J Kinderheilk 1908;68:64.

2 Peitsara H. Tierexperimentelle Rachitisuntersuchungen mit besonderer Berticksichtigung der Muskeltatigkeit. Acta Paediatr 1944;31(Suppl III):1.

3 Patten BM, Bilezikian JP, Mallettfe LE, et al. Neuromuscular disease in primary hyperparathyroidism. Ann Intern Med 1974;80:182. https://doi.org/10.7326/0003-4819-80-2-182

4 Haussler MR, Norman AW. Chromosomal receptor for a vitamin D metabolite. Proc Natl Acad Sci USA 1969;62:155-62. https://doi.org/10.1073/pnas.62.1.155

5 Simpson R, Thomas G, Arnold A. Identification of 1,25-dihydroxyvitamin D3 receptors and activities in muscle. J Biol Chem 1985;260:8882-91.

6 Pojednic R, Ceglia L, Olsson K, et al. Effects of 1,25-dihydroxyvitamin D and vitamin D on the expression of the vitamin D receptor in human skeletal muscle cells. Calcif Tissue Int 2015;96:256-63. https://doi.org/10.1007/s00223-014-9932-x

7 Christakos S, Hewison M, Gardner DG, et al. Vitamin D: beyond bone. Ann NY Acad Sci 2013;1287:45-58. https://doi.org/10.1111/nyas.12129

8 Shirvani, A, Kalajian, TA, Song, A, et al. Disassociation of vitamin D's calcemic activity and non-calcemic genomic activity and individual responsiveness: a randomized controlled double-blind clinical trial. Sci Rep 2019;9:17685. https://doi.org/10.1038/s41598-019-53864-1

9 Dzik KP, Kaczor JJ. Mechanisms of vitamin D on skeletal muscle function: oxidative stress, energy metabolism and anabolic state. Eur J Appl Physiol 2019;119:825-39. https://doi.org/10.1007/s00421-019-04104-x

10 Hii CS, Ferrante A. The non-genomic actions of vitamin D. Forum Nutr 2016;8:135. https://doi.org/10.3390/nu8030135

11 Ryan KJ, Daniel ZC, Craggs LJ, et al. Dose dependent effects of vitamin D on transdifferentiation of skeletal muscle cells to adipose cells. J Endocrinol 2013;217:45-58. https://doi.org/10.1530/JOE-12-0234

12 Garcia LA, King KK, Ferrini MG, et al. 1,25(OH)2vitamin D3 stimulates myogenic differentiation by inhibiting cell proliferation and modulating the expression of pro myogenic growth factors and myostatin in C2C12 skeletal muscle cells. Endocrinology 2011;152:2976-86. https://doi.org/10.1210/en.2011-0159

13 Bischoff-Ferrari HA, Borchers M, Gudat F, et al. Vitamin D receptor expression in human muscle tissue decreases with age. J Bone Miner Res 2004;19:265-9. https://doi.org/10.1359/jbmr.2004.19.2.265

14 Glerup H, Mikkelsen K, Poulsen L, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcif Tissue Int 2000;66:419-24. https://doi.org/10.1007/s002230010085

15 Iolascon G, de Sire A, Calafiore D, et al. Hypovitaminosis D is associated with a reduction in upper and lower limb muscle strength and physical performance in post-menopausal women: a retrospective study. Aging Clin Exp Res 2015;27(Suppl 1):S23-30. https://doi.org/10.1007/s40520-015-0405-5

16 Iolascon G, Mauro GL, Fiore P, et al. Can vitamin D deficiency influence muscle performance in postmenopausal women? A multicenter retrospective study. Eur J Phys Rehabil Med 2018;54:676-82. https://doi.org/10.23736/S1973-9087.17.04533-6

17 Anagnostis P, Dimopoulou C, Karras S, et al. Sarcopenia in post-menopausal women: is there any role for vitamin D? Maturitas 2015;82:56-64. https://doi.org/10.1016/j.maturitas.2015.03.014

18 Artaza-Artabe I, Sáez-López P, Sánchez-Hernández N, et al. The relationship between nutrition and frailty: effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review. Maturitas 2016;93:89-99. https://doi.org/10.1016/j.maturitas.2016.04.009

19 Wentz LM, Eldred JD, Henry MD, et al. Clinical relevance of optimizing vitamin D status in soldiers to enhance physical and cognitive performance. J Spec Oper Med 2014;14:58-66.