VITAMIN D
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Vitamin D deficiency and osteosarcopenia

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INTRODUCTION

The musculoskeletal system can be considered one of the most advantageous anatomo-functional outcomes that have appeared throughout the evolutionary history of the animal world. This complex system sees the interaction of several organs and tissues, mostly of the same embryogenetic derivation, which integrate different vital functions, and which go beyond the primary purpose of locomotion, into a single "organ" that develops during the period of growth, and is modelled and remodelled throughout a person's life [1,2]. At least three fundamental tissues are involved in this anatomical-functional interaction: bone tissue, striated muscle tissue and adipose tissue.

These three tissues, which have the same embryological derivation, develop from the mesodermal germ layer, which can be divided into three basic regions: paraxial, intermediate and lateral mesoderm. Somitogenesis is a fundamental step that occurs in the paraxial mesoderm where cells divide into somites. Each somite contains specific precursors for the development of the axial skeleton (sclerotome), tendons (syndetome), skeletal muscles (myotome) and the dermis (dermatome) [3]. The sclerotome develops into pre-cartilage, then into cartilage, which finally undergoes ossification. The precursors derived from the paraxial mesoderm that turn towards myogenesis are under the control of Pax3/7 (Paired Box 3/7), followed by the activation of differentiation and fusion into multinucleated syncytium, i.e. myotubes, driven by the expression of myogenic factors, such as Myf5 (Myogenic Factor 5) and MyoD (Myogenic Differentiation).

The fusion of myotubes gives rise to muscle fibres, which then group into bundles and the bundles join together to form muscle tissue. Some of these cells, so-called "satellite cells", are Pax7+ muscle precursors that localise under the basal lamina of muscle fibres in a latent state and act as a source of myonuclei during postnatal growth and after muscle injury [4].

Bone and skeletal muscle tissue are intimately connected to each other from a biomechanical standpoint. Whilst bone plays a supportive role, muscle enables motor activity through the interaction of contractile proteins within sarcomeres and through their insertion through tendons onto skeletal structures. Both tissues also regulate energy metabolism through the production and release of several molecules, especially cytokines. Molecules produced by bone tissue and released into the circulation to carry out local or remote biological activity are called "osteokines". These include Wnt, sclerostin, RANK-L (Receptor Activator of Nuclear Kappa B Ligand), osteocalcin, FGF-23 (Fibroblast Growth Factor-23), BMP (Bone Morphogenetic Protein), PGE-2 (Prostaglandin E2), and IGF-1 (Insulin like Growth Factor-1). These molecules all have one or more roles modulating muscle's biological and functional activity. At the same time, muscle tissue produces other cytokines, known as myokines, including irisin, myostatin, various interleukins, and neurotrophic factors, which act in an autocrine, paracrine and endocrine manner. The cross-talk among the component tissues that make up the locomotor system is due precisely to the production and circulation of these different substances [5].

Deep knowledge of the function of the molecules involved in these complex interconnected tissue systems is necessary to identify useful therapeutic strategies for the management of musculoskeletal disorders, particularly osteosarcopenia.

There is speculation that vitamin D may be considered a "director" molecule of the inter-tissue cross-talk that governs the structural and functional efficiency of the musculoskeletal system [6] (Fig. 1).

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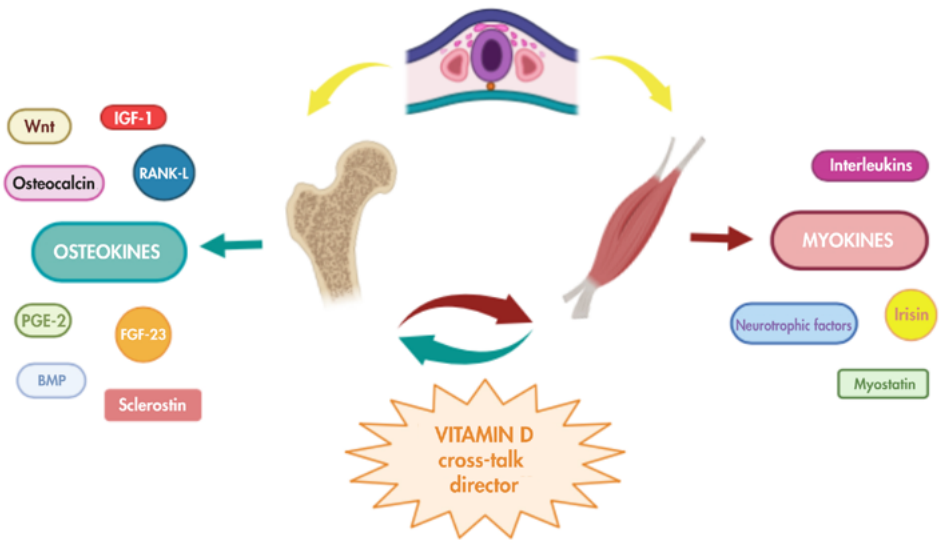


IGF-1: Insuline like Growth Factor-1; RANK-L: Receptor Activator of Nuclear Kappa B Ligand; PGE-2: Prostaglandin E2; FGF-23: Fibroblast Growth Factor-23, BMP: Bone Morphogenetic Protein.

FIGURE 1.
Role of vitamin D in embryonic skeletal muscle development.

VITAMIN D AND OSTEOSARCOPENIA

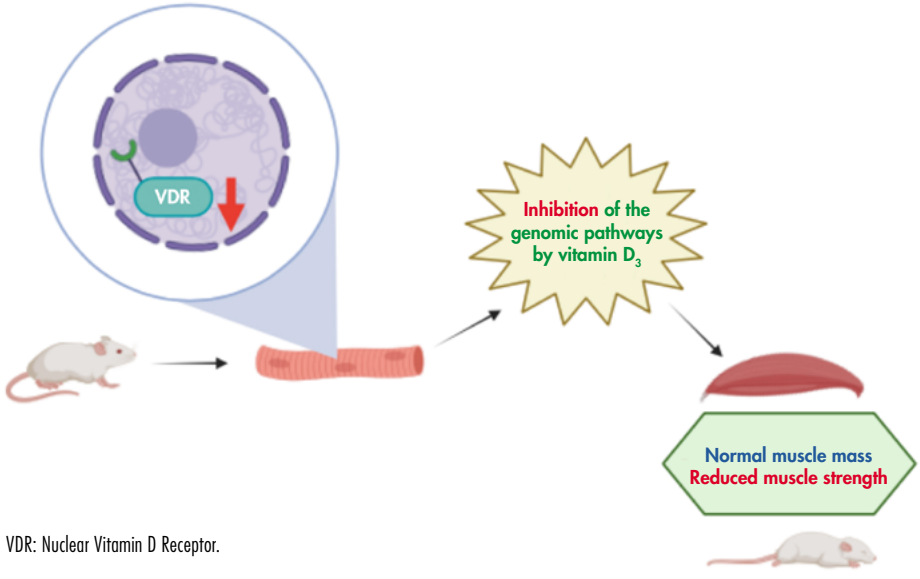
The relationship between the low concentration of vitamin D [25(OH)D_3] in the blood and age-related pathological conditions, such as osteoporosis and sarcopenia, has long been known. Equally well known is the close relationship between vitamin D deficiency and increased risk of falls, linked to consistent decrease in muscle strength, primarily due to the depletion of type 2 muscle fibres, which are principally engaged in postural changes [7-9]. For example, a decrease of type 2 muscle fibres will necessarily cause a significant increase in the risk of falling when one stands up from a seated position. After all, the replenishment of the serum level of 25(OH)D_3 of patients with established vitamin D deficiency through supplementation can induce a significant recovery of muscle strength, which can lead to an important reduction in the risk of falling among elderly patients [10].

As is well known, vitamin D primarily acts through a genomic pathway, which is mediated by binding to vitamin D nuclear receptors (VDRs). In the presence of a significant decrease in the serum level of vitamin D, which is frequent if not constant among many elderly patients, muscles are effected negatively, with histological signs of age-related muscle atrophy, characterised mainly by the depletion of type 2 fast-twitch muscle fibres. Experimental evidence has shown that inhibition of the vitamin D genomic pathway leads to muscle weakness in mature mice with muscle fibre-specific VDR deficiency, with no affect on muscle mass [11] (Fig. 2).

This finding appears to have been confirmed by a longitudinal epidemiological study of community residents, in whom serum 25(OH)D_3 levels had no significant effect on muscle mass, but were significantly correlated with muscle strength [11]. The aforementioned experimental and epidemiological data could well lead to the conclusion that vitamin D deficiency on mature muscle fibres exerts its negative effects primarily on muscle strength. As a consequence, it has therefore been hypothesised that since low serum vitamin D levels are closely related to age-related muscle weakness, 25(OH)D_3 dosage could be considered a good predictor of muscle weakness and therefore a biomarker of sarcopenia.

Although it could also be supposed that vitamin D deficiency does not act primarily through a depletion of muscle mass, it is probable, instead, that it acts to a greater extent through a reduced contractile function of individual muscle fibres, an impairment in motor unit activity due to decreased motor neuron discharge frequency, reduced nerve conduction velocity, and even excitation-contraction uncoupling. A non-secondary role in the genesis of the strength deficit could also be played by an increase in fat and fibrous tissue inside the muscle.

A recent animal study has revealed that the genomic pathway regulates muscle strength by modulating the expression of



VDR: Nuclear Vitamin D Receptor.

FIGURE 2.
Role of vitamin D on muscle mass and strength.

the calcium-dependent ATPase [12]. SERCA, which is a calcium pump in the sarcoplasmic reticulum membrane, concentrates calcium in the lumen of the sarcoplasmic reticulum (SR). Three distinct genes encode SERCA 1, 2 and 3, which are known to produce more than 10 isoforms. Typical isoforms are the following: SERCA1 is the fast twitch muscle isoform, SERCA2a is the slow twitch muscle isoform. VDR deficiency reduces SR Ca^2+ ATPase activity in mature myofibres, which is hypothesised to be induced by reduced SERCA gene expression. Therefore, it seems that Vitamin D alters muscle contraction dynamics by decreasing Ca^2+ reuptake in the SR, thus prolonging the relaxation phase of muscle contraction. In conclusion, reduced serum vitamin D levels lead to diminished VDR signalling in myofibres and causes an excitation-contraction uncoupling.

The non-genomic pathway by which vitamin D enters directly through the caveolae on cell membranes is modulated by a molecule interaction with a separate VDR (mVDR) pool or with a different membrane-bound or intracellular receptor. One candidate that has been proposed for such a membrane-bound protein that mediates the rapid non-genomic effects of vitamin D is PDIA3 (protein disulphide isomerase) also called $1\alpha,25D_3$-MARRS. This protein, which is associated with several cell membranes, including the plasma membrane and endoplasmic reticulum, is also known for its important role in protein folding. It has been reported that some of the new non-classical vitamin D hydroxy-metabolites, formed by CYP11A1, interact with both the nuclear VDR and membrane-bound $1\alpha,25D_3$-MARRS [13].

The interactions between vitamin D and the aforementioned membrane receptors realise the activation of a plethora of intracellular signal transduction pathways. It has been hypothesised that the non-genomic action of vitamin D activates a cascade of mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK) 1 and 2 through several intermediate effectors, which are activated when vitamin D binds to the VDR. Activated VDR stimulates calcium influx, which, in turn, activates calcium-driven intracellular pathways such as protein kinase C (PKC). Furthermore, vitamin D could activate G-protein-coupled receptors (GPCRs), which, in turn, would stimulate several downstream pathways, including phosphoinositide 3-kinase (PI3K), adenylate cyclase (AC), Ras and phospholipase C gamma (PLCγ). Through different signals, each of these pathways could converge on the activation of ERK-MAPK 1/2, which would then interact with the classical VDR-driven genomic pathway to modulate gene expression.

NEW VITAMIN D TARGETS IN MUSCLE FIBRE

The contractile function of skeletal muscle is regulated by cytosolic calcium, which is provided by transport from the sarcoplasmic reticulum and supplied by ATP hydrolysis produced by SERCA. Vitamin D causes an upregulation of SERCA expression by supplying ionised calcium in the cytosol and thus contributing to the maintenance of muscle strength. Clearly, therefore, vitamin D acts in muscle cells by promoting ATP consumption. It has further been hypothesised that vitamin D upregulates LIN-43 expression in a dose-dependent manner, promoting the release of inorganic phosphates, such as pyrophosphate, into cell surface niches where they play an important role in ATP metabolism [14].

Indeed, extra-skeletal pyrophosphates suppress ectopic calcification in muscle tissue. Ectopic calcification in skeletal muscle has been observed in mouse models showing impaired muscle function, such as Duchenne muscular dystrophy or focal skeletal muscle injury [15]. Vitamin D should have a controlling activity on skeletal muscle calcification, which is essential for maintaining proper locomotor activity.

CONCLUSION

Among vitamin D's extra-skeletal actions, what happens on striated muscle certainly impacts people's health considerably. Abundant scientific evidence has been found that confirms the activity of vitamin D in promoting muscle structure development during embryonic and foetal life as well as skeletal muscle regeneration and repair during adult life.

Furthermore, vitamin D plays a key role in the functional capacity of muscle fibre by promoting maximal efficiency of excitation/contraction coupling and in counteracting age-related structural and functional impairment of muscle and other sarcopenia conditions.

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