Is Vitamin D a Key Factor in Muscle Health?

Marie-Laure Kottler

Centre Hospitalier Universitaire de Caen, Department of Genetics, Reference Center for Rare Disorders of Calcium and Phosphorus Metabolism Caen, F-14000, France; UCBN, Caen, F-14032; and Institut National de la Santé et de la Recherché Médicale, U1075, Caen, F-14032, France

Historically, vitamin D is viewed as fundamental to bone mineralization. However, it is well established that muscle strength and muscle mass are important determinants of bone density, bone geometry, and fracture risk. Vitamin D therefore plays a key role in bone metabolism not only through its direct effects on osteoblasts, calcium absorption by the intestines, but also through its effects on muscle fiber size and muscle function (1–3).

Vitamin D may influence muscle physical function in 2 ways: indirectly through calcium-related effects and directly via its role in muscle cell regulation.

On a cellular level, a variety of mechanisms by which vitamin D impacts upon the function of skeletal muscle have been elucidated. These can be broadly divided into genomic effects that arise from the binding of the nuclear receptor (NR) (vitamin D receptor [VDR]), and nongenomic effects.

In its biologically active form 1,25(OH)₂ D binds to VDR, which is a ligand-dependent nuclear transcription factor (4). VDR is heterodimerized with retinoid X receptor (RXR) and the complex activates positive vitamin D response element genes transcription. This increases synthesis of proteins related to several pathways in muscle functions, including Ca²⁺/-binding proteins, such as calmodulin and calbindin D-9K. It also results in an increase in synthesis of other muscle cytoskeletal proteins important for muscle function and trophicity, namely IGF-binding protein-3, thereby inducing muscle hypertrophy. However, in some tissues, RXR levels are greater than VDR levels (5). Therefore, changes in VDR levels are rate limiting for VDR/RXR-mediated target gene expression. Coimmunoprecipitation analyses have also demonstrated direct binding of VDR with c-src under the influence of 1,25(OH)₂ D, which mediates the stimulation of muscle growth and differentiation by its subsequent effects on MAPK-signaling pathways (6).

Cellular 1,25(OH)₂ D also elicits fast-acting responses that cannot be explained by activation of the slow nuclear VDR genomic pathway that requires hours for protein synthesis. This response is believed to be mediated by the activation of a plasma membrane-associated VDR that stimulates several interacting second-messenger pathways that transmit the signal to the cytoplasm (7). However, a cross talk between 1,25(OH)₂ D activation of the plasma-membrane-bound VDR and the nuclear VDR action can exist.

Both types affect Ca²⁺ handling and muscle cell proliferation and differentiation.

The presence of VDR in muscle has been reported on the basis of immunohistochemistry and detection of VDR mRNA by RT-PCR (7), but these results are subject to challenge due to the experimental conditions (8). Differences in the expression of VDR through the various stages of muscle differentiation may have accounted for these discrepancies.

Deletion of VDR in mice (VDR knockout [KO] mouse model) has provided valuable insights into the biologic function of the vitamin D endocrine system. VDRKO mice present with abnormal skeletal muscle development and deregulated expression of myoregulatory transcription factors (9). These mice display atrophy of type I and II muscle fibers. These changes were observed in VDRKO mice on high-calcium diet, suggesting that the absence of VDR was the predominant cause rather than systemic biochemical changes.

A positive association between vitamin D status and muscle function has been observed in rodent models or in humans.

Vitamin D deficiency impairs excitation-contraction coupling in skeletal muscle leading to impairment in muscle-force generation. In a rat model, a decrease in sarcoplasmic
The data presented in this paper suggest that vitamin D could have a function in preventing proteolysis to mobilize amino acids from dispensable muscle proteins. Thus, in addition to its role in calcium homeostasis, vitamin D could be an important factor in the balance between protein synthesis and degradation that determines whether muscles hypertrophy or atrophy.

The better understanding of mechanisms of vitamin D action in muscle highlights the significance of maintaining optimal levels of vitamin D and calcium for good muscle health.

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Address all correspondence and requests for reprints to: Marie-Laure Kottler M.D., Ph.D., Head Centre Hospitalier Universitaire de Caen Genetics, Avenue Georges Clemenceau, Caen, France F-14033. E-mail: kottler-ml@chu-caen.fr.

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**References**