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Vitamin D: an overview of its role in skeletal muscle physiology in children and adolescents

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Many children may have insufficient serum concentrations of vitamin D, which could prevent optimal muscle development and function. Vitamin D deficiency in animal models results in negative effects on muscle fiber structure and calcium/phosphorus handling, suggesting an integral role of vitamin D in skeletal muscle function. While there is a dearth of data in humans, the available evidence demonstrates a positive association between vitamin D status and muscle function. This review focuses on the important role of vitamin D in muscle function in children and adolescents who live in North American regions where exposure to ultraviolet B radiation is limited and who are thus at increased risk for vitamin D insufficiency. The effects of vitamin D on muscle cell proliferation and differentiation, muscle fiber structure, and calcium and phosphorus handling are discussed. Moreover, the roles of vitamin D and the vitamin D receptor and their genomic and nongenomic actions in muscle function are explored in depth. Future research should aim to establish a vitamin D status consistent with optimal musculoskeletal development and function in young children.

INTRODUCTION

Childhood represents a critical period of growth and development that is highly dependent on a balanced diet. Vitamin D is essential for bone growth and mineralization because it promotes the efficient absorption of dietary calcium and phosphorus,[1,2] but recent research suggests that the benefits of vitamin D may extend to the musculoskeletal system as a whole. This observation is important, as the prevalence of vitamin D deficiency in children and adolescents has increased in recent years.[3–7] Normally, the major source of vitamin D is exposure to sunlight, which results in cutaneous synthesis of vitamin D. Fewer hours of daylight during the fall and winter months at northern latitudes makes it difficult for persons in those regions to obtain sufficient sunlight exposure to produce adequate levels of vitamin D. This is a concern, as the typical diet is incapable of providing sufficient vitamin D as a sole source (see detailed reviews[8–10]) and there are very few foods that are naturally high in vitamin D_3. Exceptions include oily fish, such as salmon and mackerel, which may contain about 500–1,000 IU per serving (approx. 135 g), depending on the origin, and some foods in North America that are fortified with vitamin D_3, such as milk, cereal, and yogurts.[8,11] Recently, national surveys of the vitamin D status of the Canadian and US populations demonstrated that many children living in northern latitudes may have less-than-desired levels of 25-hydroxyvitamin D [25(OH)D].[12,13] The present review provides a comprehensive look at vitamin D and musculoskeletal physiology in children and adolescents, with an emphasis on countries and regions with limited exposure to ultraviolet B (UVB) solar radiation.

VITAMIN D STATUS IN CHILDREN AND ADOLESCENTS

Vitamin D status of children under 12 years of age is an understudied yet important area because cutaneous

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synthesis of vitamin D is only possible for about half the year in northern locales above approximately 35° latitude.[14] The Canadian Paediatric Society has defined a 25(OH)D status of less than 75 nmol/L (30 ng/dL)[15,16] as insufficient for normal growth and development of children aged 6 to 11 years, whereas the Institute of Medicine in the United States defines 50 nmol/L (20 ng/dL) as the sufficient concentration.[17,18] Increasing evidence also suggests this 50 nmol/L cutoff level should be implemented as an optimal level for health and prevention of disease.[1,15,19,20] Several investigations of the vitamin D status of adolescents in both the United States[6,13,21–25] and Canada[12,26–30] (Table 1) demonstrate that a large portion of children have lower-than-desired 25(OH)D concentrations, regardless of whether the cutoff level is 50 nmol/L (20 ng/dL) or 75 nmol/L (30 ng/dL). Insufficient vitamin D levels could have a significant impact on the musculoskeletal development of children. This issue is not unique to North American children, as suboptimal 25(OH)D concentrations have been observed in China,[31,32] Ireland,[33–35] India,[36] the Middle East,[37–39] and several European countries.[40–46]

There are several factors that could contribute to lower-than-desired 25(OH)D concentrations in children. The ability of skin to synthesize vitamin D is complicated by many factors, such as intensity of UVB exposure (time of year and day), skin type (color and amount of melanin), and the quantity of skin exposed (anatomical region and surface area) (see detailed reviews[9,47–49]), which make it difficult to synthesize sufficient amounts of vitamin D during the fall and winter months in the northern United States and Canada.[50,51] Furthermore, children who have little or no outdoor activities, always wear sunscreen, avoid sunlight exposure, and/or spend the bulk of their time playing indoors (using computers or watching television) may have an elevated risk of vitamin D deficiency.[24] This places an increased importance on the dietary intake of vitamin D, as it is essential to maintain a 25(OH)D status above the deficiency range year-round.[8] Despite an abundance of foods available in North America, many children have inadequate nutrition practices.[12,52–54] Furthermore, obese children may be at additional risk for low vitamin D status because excess body fat is associated with low 25(OH)D concentrations[55,56] and may sequester circulating vitamin D,[57] thereby preventing its subsequent metabolism and function.[58]

CONSEQUENCES OF VITAMIN D DEFICIENCY ON MUSCLE FUNCTION

It is well known that very young children are more vulnerable to malnutrition due to the rapid development that takes place from birth to 5 years of age. In fact, not only do young children with vitamin D deficiency develop rickets, they also commonly display delayed growth and motor development/function.[59,60] Growth delay and impaired motor development/function are accompanied by weak bones and muscles,[11] which impair crawling or walking and promote instability. Vitamin D deficiency prevents efficient absorption of calcium and phosphorus, resulting in low serum concentrations of both minerals,[11] and negatively effects muscle function and development, besides causing the classic manifestations in bone. Therefore, it is unclear whether a 25(OH)D concentration higher than 50 nmol/L (20 ng/dL), as suggested by the Institute of Medicine,[17,18] or 75 nmol/L (30 ng/dL), as suggested by the Canadian Paediatric Society,[15,16] results in optimal benefits to the musculoskeletal system during childhood.

In other forms of rickets, such as vitamin-D-resistant rickets (VDRR), increasing the 25(OH)D status may not counteract the associated muscle weakness and delayed growth. Type 1 VDRR is a disorder characterized by low or undetectable concentrations of 1α,25-dihydroxyvitamin D [1,25$(OH)_2$D, an active metabolite of vitamin D] due to a mutation in the renal enzyme 25(OH)D-1-α-hydroxylase (CYP27B1).[61] This mutation prevents conversion of 25(OH)D to 1,25$(OH)_2$D, which can only be corrected with 1,25$(OH)_2$D supplementation. This provides evidence that 1,25$(OH)_2$D is the active vitamin D metabolite necessary for proper muscle function and growth. Similarly, in type II VDRR, normal concentrations of 25(OH)D and 1,25$(OH)_2$D are ineffective due to defects in the vitamin D receptor (VDR).[62] Pharmacological doses of vitamin D ranging from 125 μg/day to 1,000 μg/day 25(OH)D or from 20 μg/day to 200 μg/day 25(OH)D combined with 17 μg/day to 20 μg/day 1,25$(OH)_2$D may be effective in correcting the associated hypocalcemia[63–65] and the subsequent muscle weakness caused by the VDR defects. Children who do not respond to these super doses of vitamin D are treated with intensive calcium therapy (3–4 g/day orally or intravenously), which corrects the vitamin-D-related calcium malabsorption, thereby normalizing serum calcium concentrations.[64]

MUSCLE CONTRACTION AND FUNCTION

The basis of muscle contraction (Figure 1) and, ultimately, muscle function is the coordinated contraction of the individual muscle fibers within each skeletal muscle. Each muscle fiber is made up of thousands of myofibrils that are each composed of several smaller units known as sarcomeres.[66] The sarcomere is the fundamental functional unit of a muscle fiber and is the foundation for the contractile properties of skeletal muscle. Each sarcomere contains both thick (myosin) and thin (actin) filaments

Table 1 **Biochemical assessment of 25(OH)D status in North American studies focused on children over 2 years of age.**

Location and latitude of study (listed by decreasing degree of latitude)	No. of subjects	Age (y)	Sex	Serum/plasma 25(OH)D (nmol/L)	Range (nmol/L)	Assay used	Season
Canada							
National[a12]	903	6–11	M & F	75	70.3 – 79.7	CL	All
	945	12–19		68.1	63.8 – 72.4		
Northern Canada[26]	282	3–5	M & F	43.0	21.4 – 71.3	CL	Winter
51–70°N; Nunavut				Median			Summer
Western Canada[30]	35	2–8	M & F	51.5	23 – 89	CL	Spring
52°N; Edmonton, Alberta	33	9–16		42.6	12 – 75		
Eastern Canada[29]	48	0–14	M & F	~60.1	NA	LC-MS/MS	Winter
47°N; Newfoundland & Labrador							Summer
Eastern Canada[28]	1,753	9–16	M & F	~45.9	20 – 74.2	RIA	Winter
45–48°N; Quebec							Spring
Southeastern Canada[27]	91	2–2.5	M & F	60	20 – 126	LC-MS/MS	Winter
43°N; Toronto, Ontario				Median			Spring
United States							
National[b13c]	2,909	12–19	M & F	~78.4	NA	RIA	Summer
25–41°N							
Northeastern United States[24]	23	9–11	F	~62.9	21 – 116	CB	Winter
44°N; Bangor, Maine							Summer
Northeastern United Stated[6]	307	11–18	M & F	~59.0	12.5 – 133	CB	All
42°N; Boston, Massachusetts							
Northeastern United States[22]	339	12–18	F	55.0	NA	CB	Winter
41°N; Cleveland, Ohio							Summer
Northeastern United States[25]	382	6–21	M & F	70	13.3 – 159.1	RIA	All
40°N, Philadelphia, Pennsylvania				Median			
Southeastern United States[23]	168	4–8	F	93.8	31.1 – 181.4	RIA	All
34°N; Athens, Georgia							
Southwestern United States[21]	90	16–22	F	75.2	16.8 – 174	RIA	Summer
34°N; Los Angeles, California							Fall

[a] Excluding the northern territories of Nunavut, Yukon, and the Northwest Territories.
[b] Excluding Hawaii and Alaska.
[c] Looker et al. 2002[13]: The NHANES data measured the northern (higher) latitudes in the summer and the southern (lower) latitudes in the winter.
Abbreviations: CB, competitive binding; CL, chemiluminescence; LC-MS/MS, liquid chromatography-tandem mass spectrometry; NA, not available; RIA, radioimmunoassay.

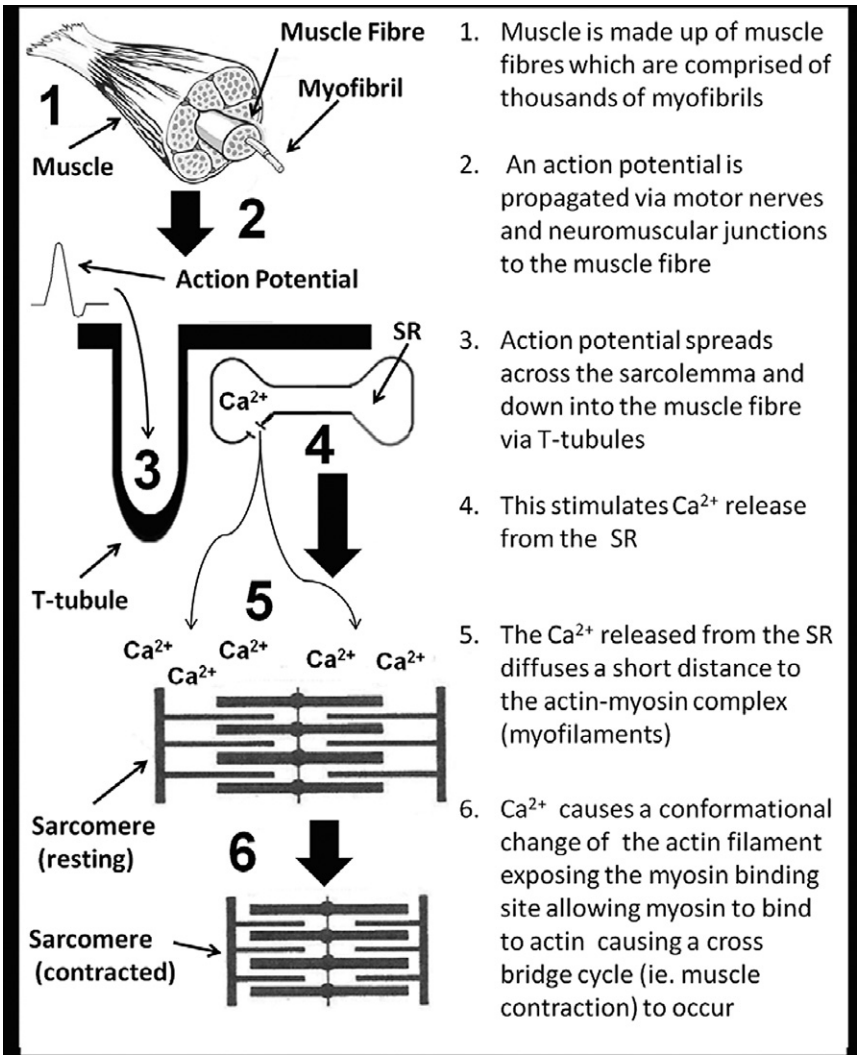

Figure 1 **Overview of skeletal muscle contraction.**
Abbreviations: Ca^{2+}, calcium; SR, sarcoplasmic reticulum.

that overlap to allow a crossbridge cycle or muscle fiber contraction to occur.[66,67] The process of excitation-contraction coupling is the physiological mechanism for skeletal muscle function. An action potential initiated in the brain (voluntary) or spinal cord (involuntary) is propagated electrically and chemically via the spinal cord, motor nerves, and neuromuscular junctions to the myocyte plasma membrane, known as the sarcolemma.[66–68] The action potential spreads across the membrane and down into the muscle fiber via invaginations in the sarcolemma known as T-tubules, where it stimulates calcium (Ca^{2+}) release from the sarcoplasmic reticulum (SR). This release of Ca^{2+} from the SR is integral to muscle contraction. The released Ca^{2+} diffuses a short distance to the actin-myosin complex, where it binds to troponin, causing a conformational change of the actin filament which exposes the myosin binding site and allows actin and myosin to interact.[66–68] With the actin-myosin interaction initiated, an adenosine triphosphate (ATP) molecule is split by an activate myosin ATPase and the energy created (released) causes a crossbridge interaction to occur (muscle fiber contraction). This crossbridge interaction is uncoupled when a second ATP molecule binds to the myosin crossbridge, thereby uncoupling actin and releasing Ca^{2+}, after which it awaits its next activation. This process is known as muscle relaxation. The free Ca^{2+} is then resequestered by the SR until the next excitation-contraction coupling cycle.[66–68]

VITAMIN D RECEPTORS AND SKELETAL MUSCLE

Early reports investigating the presence of VDRs in skeletal muscle suggested there were little or no VDRs present.[69–71] Many studies utilizing different methodologies, however, have demonstrated that VDRs are present in both the nucleus and the plasma membrane of skeletal

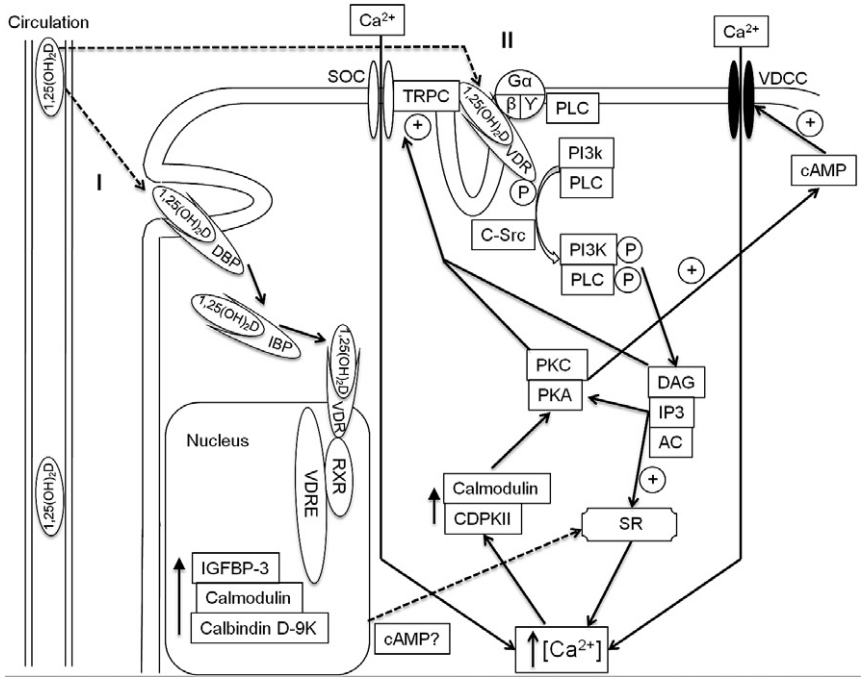

Figure 2 **Overview of genomic and nongenomic cellular signaling in skeletal muscle of the 1,25(OH)$_2$D and vitamin D receptor complex.**

[I] Genomic (slow pathway): (1) 1,25(OH)$_2$D binds to DBP in a caveola of the plasma membrane. (2) 1,25(OH)$_2$D is transported to the nucleus via IBP. (3) 1,25(OH)$_2$D binds to nuclear VDR. (4) VDR is heterodimerized with RXR. (5) RXR-VDR complex binds to VDRE, located within the 5` region of target genes. (6) Synthesis of calmodulin, calbindin, and IGFBP-3 is increased. (7) Synthesis of SR proteins, which is potentially mediated by cAMP, is increased.

[II] Nongenomic (fast pathway): (1) 1,25(OH)$_2$D binds to the VDR in a caveola of the plasma membrane. (2) PLC activity increases via coupling through a G protein. (3) VDR, PI3-K, and PLC are phosphorylated via the action of C-Src. (4) Production of second messengers DAG and IP3 increases via increased PLC and PI3-K activity. (5) PLC, PI3-K, and AC increase the activity of PKA and PKC. (6) Increased PKA and PKC increases cAMP, thus stimulating the influx of Ca^{2+} through the VDCC from the extracellular matrix. (7) Coupling of PKC and DAG stimulates the influx of Ca^{2+} via the SOC. (8) VDR phosphorylation can also stimulate Ca^{2+} influx directly from the SOC via TRPC. (9) IP3 mobilizes intracellular stores of Ca^{2+} in the SR. (10) Increased stores of intracellular Ca^{2+} induced by 1,25(OH)$_2$D activate calmodulin and CDPKII, which further stimulates PKC.

Abbreviations: 1,25(OH)$_2$D, dihydroxyvitamin D_3 or calcitriol; AC, adenyl cyclase; Ca^{2+}, calcium; cAMP, cyclic adenosine monophosphate; CDPKII, calmodulin-dependent protein kinase II; C-Src, cellular sarcoma kinase; DAG, diacylglycerol; DBP, vitamin D binding protein; IBP, intracellular binding protein; IGFBP-3, insulin-like growth factor binding protein-3; IP3, inositol triphosphate; PI3-K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C; RXR, retinoic acid X receptor; SOC, store-operated calcium channel; SR, sarcoplasmic reticulum; TRPC, transient receptor potential channel-like proteins; VDCC, voltage-dependent calcium channel; VDR, vitamin D receptor; VDRE, vitamin D response element.

muscle cells in mammals.[72–76] From a physiological standpoint, the association between vitamin D and muscle is strengthened by these observations and the fact that 1,25(OH)$_2$D exerts its action by binding to VDRs.[72,74,75,77] Flux of Ca^{2+} in skeletal muscle is differentially affected by 25(OH)D and 1,25(OH)$_2$D. In vitro, 25(OH)D (dissolved in ethanol to yield approx. 50 nmol/L, or 30 ng/dL) results in an increase in Ca^{2+} uptake from the slow exchangeable Ca^{2+} pool, whereas 1,25(OH)$_2$D (dissolved in ethanol to yield 0.13 nmol/L, or 0.05 ng/dL) increases uptake from the fast exchangeable pool in cultured chick soleus muscle cells and myoblasts.[78] Research on skeletal muscle VDRs has identified two different types: a slow-acting nuclear (genomic) receptor and a fast-acting membrane-associated (nongenomic) receptor, which each result in different effects when interacting with vitamin D (Figure 2).[79–81] The flexible structural conformation of 1,25(OH)$_2$D[82] allows it to bind to either the plasma membrane or the nuclear receptor, as these VDRs maybe specific to only 1,25(OH)$_2$D.[83] Based on presence of mRNA, it is possible that 25(OH)D can be hydroxylated in human skeletal muscle by CYP27B1,[84] though this requires future clarification. Nevertheless, while binding to the different receptors initiates separate actions, there is a possibility of cross-talk between the activated plasma membrane VDR and the nuclear VDR.[83]

Genomic cellular signaling

When $1,25(OH)_2D$ activates the nuclear VDR, which is a ligand-dependent nuclear transcription factor,[85] several slow pathways related to muscle function are activated by gene transcription. $1,25(OH)_2D$ is transported to the nucleus by an intracellular binding protein, which then binds to the nuclear VDR, permitting heterodimerization with retinoid-X receptor (RXR) and resulting in changes in mRNA gene transcription and de novo protein synthesis for positive vitamin D response element (VDRE) genes.[86] This increases synthesis of muscle cytoskeletal proteins important for muscle function, including Ca^{2+}-binding proteins such as calmodulin[87] and calbindin D-9K[88], insulin-like growth factor binding protein-3 (IGFBP-3; binds IGF-1, thereby inducing muscle hypertrophy[89]), and other muscle cytoskeletal proteins that control muscle cell surface properties.[90] These actions help muscle cells regulate Ca^{2+} uptake by modulating the activity of the Ca^{2+} pumps and channels. Future research is necessary to elucidate whether $1,25(OH)_2D$-stimulated synthesis of these Ca^{2+}-binding proteins in muscle is dependent on activation of the VDRE gene.

The activation of the nuclear VDR also increases phosphate metabolism via increases in the uptake and accumulation of phosphate and ATP, resulting in positive effects on muscle contraction.[90] Furthermore, $1,25(OH)_2D$ plays a role in the regulation of muscle cell proliferation (growth) and differentiation via mechanisms unrelated to Ca^{2+}.[78,91] Increases in muscle cell differentiation by $1,25(OH)_2D$ (0.13 nmol/L, or 0.05 ng/dL) stimulate the synthesis of contractile and SR proteins in a process that may be mediated by cyclic AMP (cAMP).[91] In a murine model, the deletion of the VDR gene resulted in abnormal muscle growth because muscle cell differentiation and maturation is intricately controlled by myoregulatory transcription factors of the MyoD family, specifically myf5, myogenin, and E2A.[77] The absence of VDR in these mice resulted in the prolonged upregulation of these factors and may result in increased abnormal expression of muscle fiber myosin heavy chain isoforms and muscle atrophy.[77] These observations demonstrate a direct physiological role of VDR in muscle development and suggest that the absence of VDR or unbound VDR (low vitamin D status) may produce abnormal muscle growth. As age increases in adulthood, the expression of VDR decreases,[92] which may explain, at least in part, the muscle atrophy or sarcopenia associated with aging.[93]

Nongenomic cellular signaling

Cellular $1,25(OH)_2D$ also elicits fast-acting responses that cannot be explained by activation of the slow nuclear VDR genomic pathway that requires hours for protein synthesis. These rapid responses are believed to be mediated by the activation of a plasma-membrane-associated VDR. While originally believed to translocate to the plasma membrane upon activation by $1,25(OH)_2D$,[94] recent data suggest the VDR may be physically located in the plasma membrane.[95–97] The location of the VDR in the plasma membrane involves caveolae (invaginations in the membrane) that act as signaling pathway platforms for the intracellular molecules involved in the rapid responses activated by the membrane-bound VDR.[96,97] The $1,25(OH)_2D$ activation of the membrane-associated VDR stimulates secondary messenger pathways that take effect within seconds to minutes (in rat and chick skeletal and cardiac muscle cells).[98] These rapid actions are different from those involved in the genomic actions,[99] but both types affect Ca^{2+} handling and muscle cell proliferation and differentiation.

Calcium handling

The early effects of $1,25(OH)_2D$ on Ca^{2+} homeostasis in skeletal muscle rely on rapid mobilization of Ca^{2+} from three different stores: 1) intracellular Ca^{2+} from the SR; 2) extracellular Ca^{2+} influx across voltage-dependent Ca^{2+} channels (VDCC); and 3) store-operated Ca^{2+} channels (SOC).[100–106] Binding of $1,25(OH)_2D$ with the membrane-bound VDR allows its interaction with and activation of the ubiquitous cytoplasmic tyrosine kinase c-Src, which results in tyrosine phosphorylation of the VDR, phosphoinositide 3-kinase, and phospholipase C (PLC)-γ.[107] The increases in PLC-γ and phosphoinositide 3-kinase stimulate the production of inositol triphosphate,[101] which mobilizes Ca^{2+} from the intracellular Ca^{2+} stores in the SR. This $1,25(OH)_2D$-induced increase in Ca^{2+} release activates calmodulin and calmodulin-dependent protein kinase II, which activates protein kinase C (PKC).[103]

The activation of PKC, when coupled with the production of diacylglycerol, stimulates the influx of extracellular Ca^{2+} via SOC.[104] The $1,25(OH)_2D$-stimulated Ca^{2+} entry via SOC is mediated by an interaction between VDR and the transient receptor potential channel-like proteins, suggesting that VDR plays a direct role in the Ca^{2+} entry via SOC.[106] Tyrosine phosphorylation of the $1,25(OH)_2D$/VDR complex also causes reverse trafficking of the nuclear VDR to the SOC on the plasma membrane to further increase Ca^{2+} influx.[100] Moreover, the tyrosine phosphorylation of the $1,25(OH)_2D$/VDR complex activates PLC-γ, which mediates mobilization of intracellular Ca^{2+} stores and flux of external Ca^{2+} via its effect on SOC.[108]

The Ca^{2+} entry via the VDCC involves an indirect G-protein-stimulated activation of PLC,[109,110] generating

inositol triphosphate, diacylglycerol, and adenyl cyclase.[101,111] The generation of inositol triphosphate, diacylglycerol, and adenyl cyclase increases the activity of PKC and protein kinase A[102,105,109,112–115], which then increases cAMP,[115] stimulating the influx of Ca^{2+} via the VDCC. There are also potential roles for phospholipases D and A2 in these processes.[102,116,117] These cellular effects of $1,25(OH)_2D$ on Ca^{2+} handling likely play an integral role in skeletal muscle function.

Muscle cell proliferation and differentiation

While $1,25(OH)_2D$ typically affects muscle cell proliferation and differentiation via its slow or genomic mechanism of action, there is the potential for cross-talk when $1,25(OH)_2D$ activation of the plasma-membrane-bound VDR can modulate the nuclear VDR actions. $1,25(OH)_2D$ mediates the stimulation of muscle growth and differentiation by its interaction with c-Src and its subsequent effects on mitogen-activated protein kinase (MAPK) signaling pathways.[97,108,118] This interaction transmits signals to intracellular targets, resulting in the initiation of myogenesis, cell proliferation, differentiation, or apoptosis.[119] The effects of c-Src on MAPKs are prevented by caveolin (part of the caveolae), but the interaction between $1,25(OH)_2D$ and c-Src is disrupted by the binding of $1,25(OH)_2D$ to the plasma membrane-associated VDR, inducing the translocation of $1,25(OH)_2D$ to the plasma membrane.[97,118] The interaction between $1,25(OH)_2D$ and the VDR activates c-Src (dephosphorylates), which stimulates tyrosine phosphorylation of several subgroups of the MAPK family, especially the extracellular signal-related kinases (ERK), c-Jun N-terminal kinases (JNK), and p38.[97,112,118,120,121] The activation of ERK 1/2 is mediated by the activation of PKC-α via Raf-1, Ras, and MAPK/ERK kinase (MEK).[121–123] The ERK 1/2 isoform then translocates to the cell nucleus, which results in the phosphorylation or induction of transcription factors, such as the oncogenes c-myc, c-fos, cAMP response element binding protein, and Elk-1, which regulate gene expression leading to cell growth.[122,123] The interaction of $1,25(OH)_2D$ and MAPK also activates p38 by phosphorylating MEK 2 and MEK 6 as well as MAPK-activated protein kinase 2, potentially mediating the phosphorylation and activation of heat-shock protein 27, which plays a role in cellular proliferation and differentiation.[118] The other known interaction between $1,25(OH)_2D$ and the MAPK family is with JNK 1/2; however, the cellular actions downstream from this interaction are still unclear.[118]

The peroxisome proliferator-activated receptor pathway may also play a role, as peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) serves as a coactivator for VDR, suggesting its involvement in the regulation of genes during the development of skeletal muscle tissue.[124] Though $1,25(OH)_2D$ affects muscle cell differentiation via downregulation of specific members of the MyoD family (myf5, myogenin, and E2A),[77] it is unclear if these effects are brought about via genomic or nongenomic mechanisms.[125] These observations demonstrate that $1,25(OH)_2D$ plays a role in the regulation of muscle cell proliferation and differentiation, both of which are important for muscle growth.[100] Therefore, vitamin D metabolism appears to be involved in muscle growth and, possibly, muscle hypertrophy.

VITAMIN D AND MUSCLE FUNCTION: EVIDENCE THROUGH IN VIVO AND IN VITRO STUDIES

Historically, vitamin D is viewed as fundamental to bone mineralization. Recent research, however, also demonstrates a positive association between vitamin D status and muscle strength and function.[79,126] Early observations demonstrated that the proximal muscle weakness associated with osteomalacia improved with vitamin D supplementation.[126–130] Moreover, data on experimental vitamin D deficiency in animal models has provided greater understanding of the mechanisms by which vitamin D status affects muscle function.

Calcium handling and transport

Vitamin D deficiency impairs excitation-contraction coupling in skeletal muscle. Rodman and Baker[131] examined the force generation and relaxation of soleus muscle cells in situ from male rats (approx. 9–11 weeks) fed a vitamin-D-depleted diet for 9 days. Significantly decreased time to peak tension (9%) and slower relaxation (40%) in response to a single isometric contraction (0.1 ms pulse), as well as significantly decreased relaxation (17%) in response to a tetanus (150 Hz for 300 ms) stimulus, were observed relative to control. Pleasure et al.[132] demonstrated similar results in vivo in chicks (3 weeks of age) fed a vitamin-D-deficient diet from hatching. Repetitive stimulation of the tibial nerve (0.2 ms pulses at 100 or 200 Hz for 200 ms) reduced generation of muscle fiber tension by 55% and slowed time to relaxation by 35%.[132] These impairments in muscle-force generation could result from alterations in Ca^{2+} handling in the myocyte SR or from impaired Ca^{2+} transport across the plasma membrane or sarcolemma; both would limit Ca^{2+} signaling.

Insufficient 25(OH)D in a rat model has demonstrated decreases in SR volume[133] that impair the rate of Ca^{2+} uptake as well as the amount of Ca^{2+} released in response to an action potential.[132,134] Vitamin D deficiency also impairs Ca^{2+} transport across the sarcolemma by decreasing the activity of the membranous Ca^{2+} pump in vitro[132] and increases the phospholipid content of the

SR.[135] Bauman et al.[136] demonstrated that vitamin-D-deficient chicks have increased intracellular Ca^{2+} in tibial muscle, suggesting Ca^{2+} accumulates in skeletal muscle in vitamin D deficiency. However, with the decreased functionality of the SR, this Ca^{2+} is unable to be utilized because the accumulation is likely a reflection of inadequate Ca^{2+} efflux as a result of impaired muscle contraction. Injection of both 25(OH)D (0.5 µg) and $1,25(OH)_2D$ (0.1 mL dissolved in propylene glycol) were both effective in stimulating Ca^{2+} efflux, though $1,25(OH)_2D$ more so,[136] as the VDRs in skeletal muscle are the cognate ligand specific to $1,25(OH)_2D$.

In cultured myoblasts and myocytes, $1,25(OH)_2D$ (0.13–0.24 nmol/L, or 0.05–0.1 ng/dL) increased cellular Ca^{2+} reuptake through both mitochondrial and plasma membranes within minutes,[78,137,138] specifically by increasing the activation of cell membrane voltage-gated Ca^{2+} channels. Flux of Ca^{2+} in skeletal muscle is differentially affected by 25(OH)D and $1,25(OH)_2D$. In vitro, 25(OH)D (0.5 µg) results in an increase in Ca^{2+} uptake from the slow exchangeable Ca^{2+} pool, whereas $1,25(OH)_2D$ (0.1 mL dissolved in propylene glycol) increases uptake from the fast exchangeable pool in cultured chick soleus muscle cells and myoblasts.[78] This lack of Ca^{2+} transport and utilization due to decreased SR function may impair the motor function of vitamin-D-deficient animals. Indeed, vitamin-D-deficient chicks appeared weaker than controls, were unable to stand for long periods of time, and tended to rest their bodies on the floor of the cages.[132] Perhaps ensuring vitamin D adequacy may promote normal muscle function.

In contrast to experimental vitamin D deficiency, in which both 25(OH)D and $1,25(OH)_2D$ concentrations become undetectable, vitamin D deficiency in humans can occur with high $1,25(OH)_2D$ concentrations despite low levels of 25(OH)D.[139] This may not occur in all animals, as a guinea pig model with no dietary or UVB sources of vitamin D demonstrated that deficiency is marked by very low concentrations of 25(OH)D (approx. 22.2 nmol/L, or 8.9 ng/dL) and undetectable concentrations of $1,25(OH)_2D$ (approx. 0.08 nmol/L, or 0.03 ng/dL) as a result of limited 25(OH)D.[140] Therefore, it has been speculated that low 25(OH)D impairs the absorption of Ca^{2+}, which in turn increases the secretion of parathyroid hormone (PTH), which stimulates CYP27B1 in the proximal tubule of the kidneys to produce $1,25(OH)_2D$ as long as enough 25(OH)D is available.[11] It is still unclear why Ca^{2+} absorption is impaired when PTH is increased and a higher concentration of $1,25(OH)_2D$ results. Perhaps the issue is not only low 25(OH)D status but also low Ca^{2+} as well.

In VDR knockout (VDR-KO) mice, hypocalcemia does not occur until after weaning and can be managed by a high-calcium diet. The normocalcemia observed in early life may be caused by a nonsaturable $1,25(OH)_2D$-independent mechanism, which is gradually replaced by a $1,25(OH)_2D$-dependent saturable component that results in increased $1,25(OH)_2D$ in the blood.[141] Recently, Song and Fleet[142] found that duodenal Ca^{2+} absorption and the calbindin D-9K response to $1,25(OH)_2D$ was inhibited by 40% in heterozygous VDR-KO mice. These authors suggest that impaired Ca^{2+} absorption could result from a lack of calbindin D-9K protein transcription due to resistance to $1,25(OH)_2D$, which would impair Ca^{2+} absorption. Similar progressive metabolic abnormalities were observed in muscle of 3-week-old preweaned VDR-KO mice: a 20% reduction in skeletal muscle diameter in both type I and type II muscle fibers was observed, and these abnormalities became more noticeable as the animals aged.[77] Perhaps incorporation of Ca^{2+} in myocytes is impaired via a mechanism similar to the one involved in Ca^{2+} absorption in enterocytes; at present, however, little is known about the mechanisms of Ca^{2+} handling in either type of cell in vitamin-D-deficient and VDR-KO models.

Muscle fiber structure

While there are little data on the relationship between vitamin D deficiency and muscle fiber structure in humans, ultrastructural changes in white muscle fibers (slow twitch) of fish occur with vitamin D deficiency, as evidenced by less-defined Z lines and M bands, increased mean sarcomere length, and atrophy of T-tubules, resulting in an impairment of muscle contraction.[143] Vitamin-D-deficient rats and rabbits have reduced actin-myosin content[144] and troponin C,[145] respectively, though repletion of vitamin-D-deficient chicks with vitamin D_3 (2 µg orally) increased actin and troponin C,[135] the latter of which binds Ca^{2+}, allowing the crossbridge cycle to occur. Unfortunately, the serum 25(OH)D concentrations in the vitamin-D-repleted chicks were not reported. Vitamin-D-deficient rats demonstrated decreased growth of red type C fibers (similar to human type IIb fibers),[126] which contributed significantly to impaired muscle function, as type II fibers (nonoxidative glycolytic) are characterized by fast contraction speeds and high power outputs.[146] Therefore, vitamin D deficiency may limit muscle structure and function, whereas less is known about whether a dose response exists beyond deficiency states.

Phosphorus handling and transport

There is also evidence that vitamin D deficiency results in impaired phosphate handling (Figure 3) in skeletal muscle membranes, and this may be even more important than the effects on Ca^{2+} handling. Normal phosphorus flux across the sarcolemma may be impaired in states of vitamin D deficiency.[135] Recently, the hypophos-

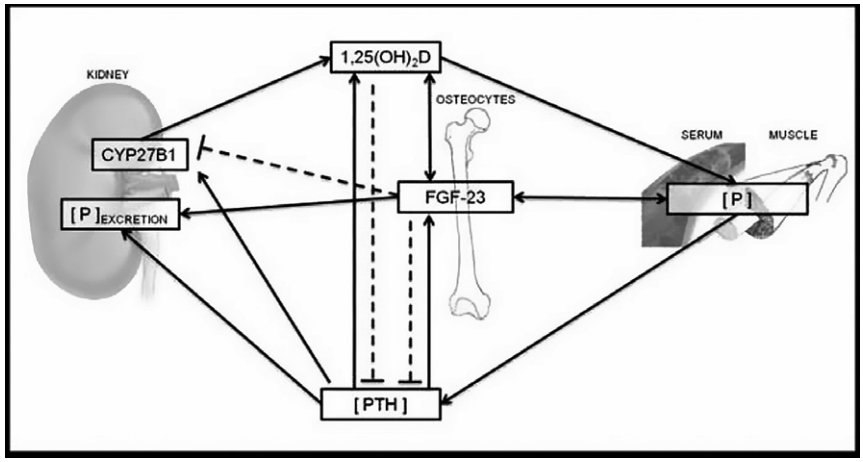

Figure 3 **Overview of phosphorus handling and its indirect interaction with 1,25(OH)$_2$D and muscle.** (1) 1,25(OH)$_2$D increases [P]. (2) FGF-23 regulates [P] and 1,25(OH)$_2$D. (3) PTH stimulates FGF-23, which increases [P], which in turn increases FGF-23 and PTH and stimulates [P] excretion in the kidneys. (4) PTH also stimulates CYP27B1 activity, resulting in increased 1,25(OH)$_2$D. (5) Increased 1,25(OH)$_2$D inhibits PTH release and, in turn, FGF-23 inhibits CYP27B1, thus decreasing 1,25(OH)$_2$D. *Abbreviations*: 1,25(OH)$_2$D, dihydroxyvitamin D$_3$ or calcitriol; CYP27B1, 25(OH)D-1α-hydroxylase isoform CYP27B1; FGF-23, fibroblast growth factor 23; [P], serum free phosphate concentration; PTH, parathyroid hormone.

phatemia associated with vitamin D deficiency was demonstrated to be the primary determinant of impaired muscle function.[147] Phosphorus in the form of free phosphate and ATP is essential for both Ca^{2+} uptake and Ca^{2+} release by the SR and the sarcolemma as well as for muscle fiber crossbridge cycling. While the research on these effects is unclear, vitamin D increases the serum phosphate concentration[147] and positively affects phosphorus metabolism in tissues other than muscle, such as the kidney and intestine.[148–150] This may be through its genomic regulation of FGF-23, which is a phosphaturic peptide secreted by osteocytes and osteoblasts and may be the most important regulator of serum phosphate and 1,25(OH)$_2$D concentrations.[151,152]

There is some evidence that PTH increases FGF-23 levels, which results in an intricate feedback loop because increased serum phosphate concentrations increase the circulating concentrations of FGF-23 and PTH, both of which stimulate phosphate excretion. In VDR-null mice, elevated PTH increases the production of 1,25(OH)$_2$D, resulting in increased FGF-23 levels and a subsequent suppression of PTH.[153] The increase in PTH increases the activity of CYP27B1 activity in the kidney, stimulating 1,25(OH)$_2$D production. Any increase in 1,25(OH)$_2$D will cause a decrease in PTH synthesis, while the increased FGF-23 inhibits CYP27B1 activity, decreasing the synthesis of 1,25(OH)$_2$D.[152] Some believe that vitamin D, specifically 1,25(OH)$_2$D, is involved in the regulation of FGF-23 synthesis.[151] Thus, low serum 1,25(OH)$_2$D could cause low circulating levels of FGF-23, resulting in impaired phosphate metabolism.[154,155] However, increasing 1,25(OH)$_2$D concentration occurs rapidly with increases in 25(OH)D above severe deficiency. This suggests that the negative effects of low 1,25(OH)$_2$D could be quickly reversed with vitamin D treatment.

VITAMIN D AND SKELETAL MUSCLE IN CHILDREN

Recently, providing vitamin D supplementation to vitamin-D-deficient children (< 3 years) who had already demonstrated impaired growth resulted in an improvement in growth, as demonstrated by increases in overall height (absolute length) and by increases in the rate of height growth (standard deviation scores of length and growth velocity).[60] Furthermore, whether the sun exposure during the summer months is adequate to provide year-long sufficient vitamin D concentrations is not well understood. The cutoff level for a vitamin D status that optimizes health and development in young children, as well as how such a level is to be achieved in the general population, is still under debate.

While the current state of knowledge on vitamin D and muscle function has been the result of vitamin D deficiency in animal studies, the majority of human research has focused on vitamin D supplementation and muscle function in healthy states more so than in severe deficiency states. To date, the preponderance of data originates from older adults, as previously reviewed.[156,157] Less data exist on the relationship between vitamin D status and muscle function in young children. It is therefore unclear whether adequate vitamin D status is associated with ideal development of muscle mass and function during growth.

The few studies (Table 2) on the impact of vitamin D on muscle function were conducted in older children (10

Table 2 **Vitamin D and muscle function in children and adolescents.**

Study	No. of subjects	Age (years)	Sex	Outcome
Cross-sectional				
Foo et al. (2009)[158]	301	10–15	F	Serum 25(OH)D > 50 nmol/L associated with greater grip strength (approx. 8%; $P = 0.014$) than 25(OH)D < 50 nmol/L
Ward et al. (2009)[40]	99	12–14	F	Serum 25(OH)D positively associated with: – Two-legged jump performance Power ($r = 0.22$; $P < 0.05$) Height ($r = 0.28$; $P < 0.01$) Velocity ($r = 0.31$; $P < 0.01$) – One-legged jump performance Normalized force ($r = 0.25$; $P < 0.05$) – Esslinger Fitness Index ($r = 0.32$; $P < 0.01$)
Randomized controlled trial				
El-Hajj Fuleihan et al. (2006)[38] (Weekly doses of 35 µg vitamin D_3[a] 350 µg vitamin D_3, or placebo for 1 year)	179	10–17	F	High-dose group Serum 25(OH)D increased from 35 to 95 nmol/L – Significantly greater increase than both low-dose and placebo groups Increase in lean mass, 4.2 kg (9.0%) from baseline – Significantly greater than the change in the placebo group but not the low-dose group Low-dose group Serum 25(OH)D increased from 35 to 43 nmol/L – No significant change Increase in lean mass, 4.1 kg (8.7%) from baseline – Significantly greater than the change in the placebo group but not the high-dose group Placebo group Serum 25(OH)D (small increase from 35 to 40 nmol/L) – Did not change significantly Lean mass did not change (small 1.8 kg increase [5.7%])
Ward et al. (2010)[159] (Four doses of 3,750 µg vitamin D_2[b] versus placebo over 1 year)	69	12–13	F	Supplemented group Serum 25(OH)D increased from 18 to 56 nmol/L – Increased movement efficiency (5.4%, $P = 0.02$) – No change in jump performance Maximum force ($P = 0.58$) Velocity ($P = 0.09$) Power ($P = 0.79$) Height ($P = 0.07$) – No change in Esslinger Fitness Index ($P = 0.077$) Placebo group Serum 25(OH)D from 17.9 to 15.7 nmol/L – No change in muscle function measurement

[a] Cholecalciferol.
[b] Ergocalciferol.
Abbreviations: 25(OH)D, 25, hydroxyvitamin D or calcidiol.

to 15 years), but a positive association between vitamin D status and muscle function was observed. In Chinese females (15 years), higher vitamin D status [25(OH)D >50 nmol/L, or 20 ng/dL] was positively associated with proximal forearm muscle strength (grip), even when adjusted for body size, pubertal stage, dietary calcium and vitamin D intake, organized sport status, and total physical activity.[158] Similarly, in the United Kingdom, girls (12 to 14 years) demonstrated a positive relationship between vitamin D status and jump height, velocity, power, movement efficiency (as assessed by the Esslinger Fitness Index, which compares maximum power relative to body weight to an age- and gender-matched reference population), and maximal voluntary force.[40]

In the Middle East, 1 year of vitamin D supplementation demonstrated positive effects in girls (10 to 17 years) with either low (35 µg or approx. 5 µg/day) or high (350 µg or approx. 50 µg/day) weekly doses of vitamin D_3. This supplementation significantly increased vitamin D status in the high-dose supplement group (from 35

nmol/L to 95 nmol/L, or 14 ng/dL to 38 ng/dL), whereas the low-dose supplement group did not show increased 25(OH)D status. Both groups, however, had significantly increased lean mass (approx. 4 kg or 9%, as measured by dual-energy X-ray absortiometry).[38] While the authors concluded that vitamin D supplementation resulted in a substantial increase in lean mass, it was unclear why the low-dose group demonstrated a similar increase in lean mass compared with the high-dose group despite the lack of a significant change in 25(OH)D status. Perhaps there is a potential threshold effect of vitamin D status for muscle mass, or perhaps the measurement of muscle mass was not sensitive enough to detect further benefits with higher 25(OH)D concentrations.

A randomized clinical trial in girls (12 to 13 years) given four doses of 3,750 μg vitamin D_2 over 12 months increased vitamin D status from 18 nmol/L to 56 nmol/L (range, 7.2–22.4 ng/dL),[159] but positive effects on muscle strength or power (countermovement jump) were not observed. Nonetheless, vitamin D supplementation increased movement efficiency, and there was a trend towards increases in jump height and jump velocity, which depend predominately on the fast-twitch fibers of the quadriceps muscle. This data may suggest that higher 25(OH)D concentrations are necessary to result in improvements in muscle function, as the postsupplemented 25(OH)D status was only 56 nmol/L (22.4 ng/dL) where almost half of the sample was below the 50 nmol/L (20 ng/dL) cutoff suggested by the Institute of Medicine and well below the 75 nmol/L (30 ng/dL) cutoff suggested by the Canadian Paediatric Society. These four studies focused on adolescent girls, and thus future research on young children is necessary to establish whether vitamin D status has a stronger relationship to muscle mass development and function early in life. Positive associations between vitamin D status and muscle mass and function in older adults underscore the importance of a sufficient vitamin D status across the lifespan.

FUTURE DIRECTIONS

Clearly, there is much work to be done to investigate the effects of vitamin D on skeletal muscle physiology, with several key areas for future investigation highlighted here. One such area of study would be to clarify whether there is a threshold concentration of 25(OH)D above which no further benefit is observed in skeletal muscle. A further topic of study is to determine whether the VDR content of tissues (particularly skeletal muscle) is decreased in vitamin-D-deficient states, especially during childhood development. Additional research is also required to further elucidate the effects of $1,25(OH)_2D$ on muscle cell proliferation and differentiation. Finally, while the alterations in phosphorus metabolism in muscle appear to contribute to the decreases in skeletal muscle function and strength that occur with vitamin D deficiency, it is essential to determine specifically how vitamin D deficiency and phosphate metabolism interact and synergistically impair muscle function.

CONCLUSION

It is widely recognized that living in high-latitude countries such as Canada and the northern United States increases the risk of vitamin D deficiency, which in turn increases the risk of rickets, osteoporosis, myasthenia, and ostealgia. However, there is also strong evidence to support the important role of vitamin D in muscle cells, and there is a positive association between vitamin D status and muscle strength/function.[79,126] Evidence from animal models suggests that vitamin D deficiency adversely affects muscle function by altering calcium and phosphorus handling as well as muscle fiber structure. Recent evidence in humans also suggests that low circulating concentrations of 25(OH)D negatively affect muscle function and strength. Furthermore, $1,25(OH)_2D$ binding to the nuclear and membrane-associated VDR-RXR of myocytes triggers genomic and nongenomic effects shown to positively affect muscle. To date, there is a paucity of data evaluating the association between vitamin D status in young children and muscle function, but there are several reports suggesting that status is frequently lower than desired for optimal development. Decreased outdoor activity, which contributes to increased body mass and decreased sun exposure, combined with inadequate nutrition can lead to a low vitamin D status, which negatively affects musculoskeletal strength and function, both directly and indirectly. Additional research in this area is warranted in order to establish a concentration of 25(OH)D consistent with musculoskeletal health in young children and to reinforce the importance of maintaining vitamin D status during childhood to optimize musculoskeletal development and prevent potential negative health effects later in life.

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