

Vitamin D, a modulator of musculoskeletal health in chronic kidney disease

Pablo Molina^{1,2,3*} , Juan J. Carrero⁴, Jordi Bover^{2,5,6}, Philippe Chauveau⁷, Sandro Mazzaferro⁸ & Pablo Ureña Torres^{9,10} for the European Renal Nutrition (ERN) and Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Working Groups of the European Renal Association–European Dialysis Transplant Association (ERA-EDTA)[†]

¹Department of Nephrology, Hospital Universitario Doctor Peset, Valencia, Spain; ²REDinREN, Madrid, Spain; ³Department of Medicine, Universitat de València, Valencia, Spain; ⁴Division of Renal Medicine, CLINTEC, Karolinska Institutet, Stockholm, Sweden; ⁵Department of Nephrology, Fundació Puigvert, Barcelona, Spain; ⁶IB Sant Pau, Barcelona, Spain; ⁷Service de Néphrologie Transplantation Dialyse, Centre Hospitalier Universitaire de Bordeaux et Aurad-Aquitaine, Bordeaux, France; ⁸Department of Cardiovascular, Respiratory, Nephrologic and Geriatric Sciences, Sapienza University of Rome, Rome, Italy; ⁹Department of Nephrology and Dialysis, Clinique du Landy, Ramsay-Générale de Santé, Saint Ouen, Paris, France; ¹⁰Department of Renal Physiology, Necker Hospital, University of Paris Descartes, Paris, France

Abstract

The spectrum of activity of vitamin D goes beyond calcium and bone homeostasis, and growing evidence suggests that vitamin D contributes to maintain musculoskeletal health in healthy subjects as well as in patients with chronic kidney disease (CKD), who display the combination of bone metabolism disorder, muscle wasting, and weakness. Here, we review how vitamin D represents a pathway in which bone and muscle may interact. *In vitro* studies have confirmed that the vitamin D receptor is present on muscle, describing the mechanisms whereby vitamin D directly affects skeletal muscle. These include genomic and non-genomic (rapid) effects, regulating cellular differentiation and proliferation. Observational studies have shown that circulating 25-hydroxyvitamin D levels correlate with the clinical symptoms and muscle morphological changes observed in CKD patients. Vitamin D deficiency has been linked to low bone formation rate and bone mineral density, with an increased risk of skeletal fractures. The impact of low vitamin D status on skeletal muscle may also affect muscle metabolic pathways, including its sensitivity to insulin. Although some interventional studies have shown that vitamin D may improve physical performance and protect against the development of histological and radiological signs of hyperparathyroidism, evidence is still insufficient to draw definitive conclusions.

Keywords Bone; Chronic kidney disease; Muscle; Physical performance; Vitamin D

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*Correspondence to: Pablo Molina, Department of Nephrology, Hospital Universitario Doctor Peset, Avda. Gaspar Aguilar, 90, Valencia 46017, Spain.

Telephone: +34 96 162 24 62, Fax: +34 96 162 24 62, Email: molina_pab@gva.es

[†]Board members of the ERN and CKD-MBD working groups are listed in the Acknowledgements

Introduction

Beyond the well-described functions of vitamin D in mineral bone metabolism and calcium–phosphate homeostasis, there is growing evidence of its role on muscle health and function.^{1–3} Vitamin D deficiency is common in patients with chronic kidney disease (CKD),⁴ a population in whom muscle wasting and weakness are also highly prevalent.^{5–7} Observational studies have shown that circulating 25-hydroxyvitamin D [25(OH)D] levels are reduced in parallel to the severity of muscle symptoms.⁸ Similarly, emerging evidence suggests that vitamin D receptor (VDR) is expressed in muscle

and that VDR regulates gene expression and modulates the uptake of 25(OH)D in skeletal muscle cells, which may also act as a storage site for this vitamin D.^{9,10} There are also evidences that hypovitaminosis D affects both contractile muscle function and muscle metabolism via disturbing insulin sensitivity.¹¹ These observations collectively imply an integrated role of vitamin D for bone and muscle health. Such a role may have substantial clinical implications, especially for CKD patients, in which musculoskeletal alterations and their complications, including muscle pain and weakness, sarcopenia, fatigability, reduced exercise tolerance, fractures, and falls, adversely affect quality of life and survival.^{12–17}

In this review, we discuss the bidirectional actions of vitamin D in bone and muscle, arguing on the potential benefits of vitamin D supplementation as a strategy to tackle the musculoskeletal problems of patients with CKD.

Vitamin D physiology

Vitamin D and bone-mineral homeostasis

Natural (frequently referred as well as 'native') vitamin D is produced at the skin following sunshine exposure and is not totally required from the diet. The difference between natural vitamin D₂ and vitamin D₃ lies on their origin (vegetal or animal) and on the structure of their side chains.¹⁸ Vitamin D is absorbed through the proximal segments of the small intestine.¹⁹ As a hydrophobic molecule, vitamin D circulates in the bloodstream mostly (88–90%) bound with high affinity to the vitamin D binding protein (DBP). Less than 0.05% of calcidiol [25(OH)D or calcifediol] circulates free in plasma. To become fully active, vitamin D needs to be transformed twice.²⁰ A first hydroxylation occurs in the liver microsomes by the 25-hydroxylase (CYP2R1) enzyme to form 25(OH)D. There is a second hydroxylation in the proximal tubule by the 1 α -hydroxylase (CYP27B1) to form 1,25-dihydroxyvitamin D [1,25(OH)₂D], also called calcitriol. In contrast to liver hydroxylation, renal hydroxylation is highly regulated by several factors including calcium, phosphate, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23), which is produced by osteocytes and osteoblasts in bone.²¹

There is a feedback loop between FGF23 and vitamin D, whereby FGF23 inhibits 1 α -hydroxylase activity and stimulates 24,25-hydroxylase, and simultaneously vitamin D stimulates FGF23 production, which can still exacerbate the high circulating FGF23 levels already existing in CKD and impact bone metabolism.^{21,22} Indirect effects of FGF23 include the increase of renal excretion of phosphate, affecting the amount of phosphate available for mineralization at the bone surfaces.²³ Direct effects of FGF23 on bone metabolism include the modulation of bone mineralization via the tissue non-specific alkaline phosphatase through the fibroblast growth factor receptor 3. FGF23 inhibits tissue non-specific alkaline phosphatase, and consequently, FGF23 increases extracellular concentration of pyrophosphate, reduces the amount of inorganic phosphate, and indirectly stimulates osteopontin gene expression, a known mineralization inhibitor.²⁴

1,25(OH)₂D that passes into the bloodstream is also bound to DBP, binding to the VDR in several tissues, including parathyroid cells, bone, and intestine.^{25,26} The VDR-1,25(OH)₂D complex acts as heterodimer with the retinoic X receptor (RXR) to control transcriptional activity

of target genes, after binding to special DNA sequences called vitamin D response elements. Circulating 1,25(OH)₂D also exerts non-genomic effects through the binding in some tissues to membrane proteins with subsequent modification of the intra-cellular calcium flux and stimulation of tyrosine kinases (Figure 1).^{20,27,28} As a result of these processes, 1,25(OH)₂D maintains calcium and phosphate homeostasis, stimulating their intestinal absorption and bone resorption.²⁹ To accomplish this, the 1,25(OH)₂D-VDR-RXR complex binds to the vitamin D response elements in the small intestinal cells, increasing the expression of the epithelial calcium channel. It permits more calcium to enter the cell, which is translocated into the circulation, ensuring the availability of sufficient calcium and phosphate for adequate mineralization of the newly formed bone matrix to avoid rickets/osteomalacia. 1,25(OH)₂D induces skeletal anabolism and couples the activity of osteoblasts and osteoclasts through the regulation of several genes including osteopontin, osteocalcin, and the Wnt receptor LRP5.^{30,31} Indeed, vitamin D stimulates the expression of LRP5, which, together with sclerostin, Dkk1, and frizzled, constitutes the Wnt pathway, a critical process for skeletal mineralization that is tissue specific. Unlike in bone, Vitamin D inhibits Wnt signals in the vessels and the kidney, ameliorating the effect of Wnt activation on the vascular calcification and kidney progression.^{32,33}

Besides this anabolic effect on bone, direct effects of vitamin D in osteoblasts may have the opposite effect, stimulating bone resorption through osteoclastogenesis to increase bone calcium mobilization.³⁴ To do this, Vitamin D interacts with the VDR in osteoblasts to induce the expression of the plasma membrane protein receptor activator of NF- κ B ligand (RANKL). The RANK on the plasma membrane of preosteoclasts binds RANKL, which induces the maturation of preosteoclasts to osteoclasts. The mature osteoclast releases collagenases and hydrochloric acid to dissolve bone and release its calcium and phosphate stores into the bloodstream. Therefore, the 'classical' physiologic function of vitamin D is to maintain blood levels of calcium and phosphate within the normal physiologic range to support most metabolic functions, neuromuscular transmission, and bone mineralization.³⁵

The VDR is also present in other tissues (including skeletal muscle) that are not involved in mineral and bone metabolism, where 1,25(OH)₂D can locally be produced in an auto-paracrine or paracrine way (Figure 1), what results in the so-called 'non-classical' vitamin D effects. Table 1 summarizes the main functions of vitamin D.^{29,36}

Vitamin D and skeletal muscle weakness

In addition to the endocrine effects on calcium homeostasis that are essential for muscle function, *in vitro* and *in vivo* studies, along with changes in muscle morphology and

Figure 1 Vitamin D receptor (VDR)-mediated actions of vitamin D: genomic and non-genomic (rapid response) cellular signalling. $1,25(\text{OH})_2\text{D}$ interacts with caveolae-associated VDR to activate second messengers systems, including protein kinase C, phosphatidylinositol phosphate kinase, phospholipase C, or opening of the voltage-gated chloride channels or calcium channels, to generate non-genomic responses. In the genomic pathway, $1,25(\text{OH})_2\text{D}$ associates with the retinoic acid receptor (RXR) and the trimeric complex ($1,25(\text{OH})_2\text{D}$ -VDR-RXR) binds to the DNA in special sites called 'vitamin D responsive elements' (VDRE) to stimulate or inhibit the transcription of various genes. $1,25(\text{OH})_2\text{D}$ can locally be produced in an auto-paracrine or paracrine way.

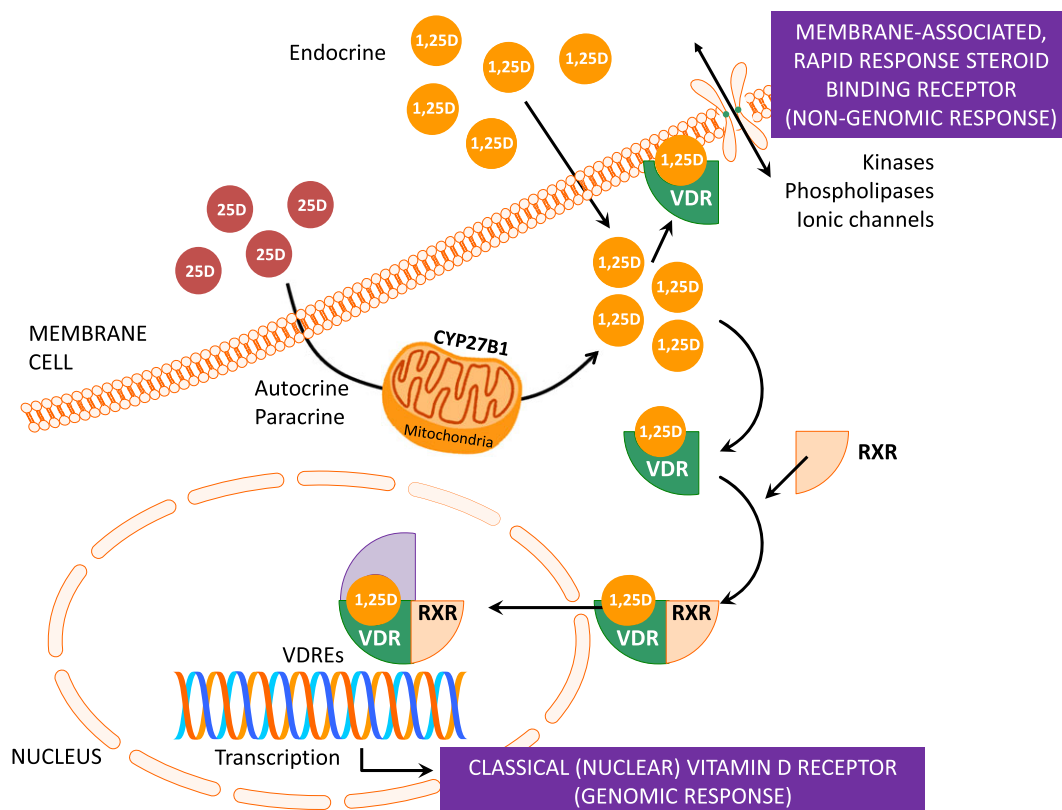


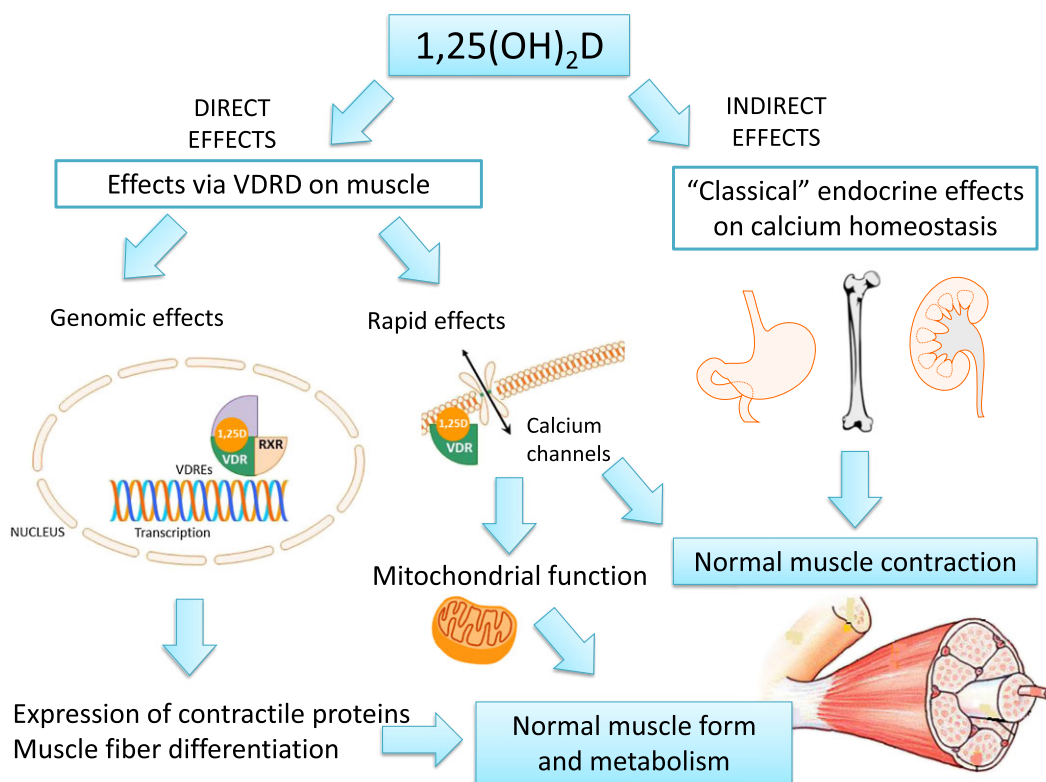
Table 1 Effects and functions of vitamin D

Endocrine effects	Non-calcaemic and non-skeletal effects
<ol style="list-style-type: none"> 1. Increase intestinal absorption of calcium and phosphate 2. Down-regulate expression of PTH mRNA in the parathyroid glands 3. Induce mature osteoclastic activity, which releases calcium and phosphate into the bloodstream 	<ol style="list-style-type: none"> 1. Maintain normal cell proliferation and differentiation. 2. Decrease renal production of renin 3. Stimulate pancreatic production of insulin 4. Immunomodulation
↓	↓
<p>'Classical' functions</p> <p>To maintain normal blood levels of calcium and phosphate in order to support:</p> <ol style="list-style-type: none"> 1. Bone mineralization 2. Metabolic functions 3. Neuromuscular function 	<p>'Non-classical' functions</p> <p>To modulate human health by metabolic imprinting during the pre-natal and neo-natal periods that may influence chronic disease susceptibility to cancer, autoimmune, and cardiovascular diseases, soon after birth as well as later in life.</p>

mRNA, messenger ribonucleic acid; PTH, parathyroid hormone.

metabolism observed in subjects with hypovitaminosis D, have allowed the elucidation of novel pathways by which vitamin D might act directly on skeletal muscle. These include

genomic and non-genomic (rapid) effects (Figure 2).^{37,38} Genomic effects are delayed and include the gene expression of contractile proteins and myogenic transcription factors

Figure 2 Plausible effects of vitamin D on muscle cells. Adapted from Girgis *et al.*³⁵

after interacting vitamin D with the VDR in skeletal muscle cells, which regulate muscle development and metabolism. Several studies confirm that VDR is expressed in muscle cells.^{9,39} Although VDR is expressed at low levels in resting adult muscle, markedly VDR expression and 1α -hydroxylase have been observed in neonatal muscle or following muscle injury, supporting the muscle capacity for local production of $1,25(\text{OH})_2\text{D}$, and a developmental and regenerative role for vitamin D in this tissue.^{36,40,41}

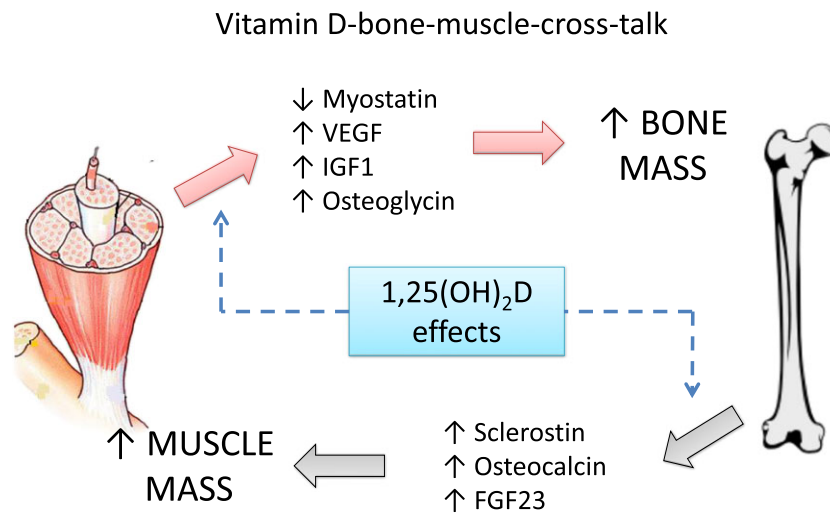
Vitamin D may also interact with the VDR in muscle cells by non-genomic effects, which are independent of the intranuclear transcription process. They involve the rapid regulation of membrane calcium channels, suggesting a role for vitamin D in the calcium-mediated muscle functions, such as muscle contraction and mitochondrial function, which leads to an adequate insulin signalling and muscle substrate metabolism.⁴² All these findings may clarify the relationship between low vitamin D status and muscle weakness,^{37,43} intramuscular fat deposition,⁴⁴ and resistance to insulin,⁴⁵ which is related to cardiovascular risk and increased skeletal muscle breakdown.⁴⁶ Of note, skeletal muscle may also act as a storage site for vitamin D, as recently described.¹⁰

In addition to changes in muscle metabolic pathways, the impact of vitamin D deficiency on skeletal muscle also concerns muscle morphology. Subjects with mutations of

the VDR or severe vitamin D deficiency show generalized muscle atrophy, even before biochemical signs of bone disease appear.^{36,47} Changes in muscle morphology include derangement of the intermyofibrillar network, increases in intramuscular lipids, and atrophy of the fast-twitch white (type 2) fibres,^{11,44,48,49} which are the first to be recruited when preventing a fall. All these changes seem to be reversible,⁵⁰ supporting co-ordinated effects of vitamin D in musculoskeletal physiology.^{51–54}

Integrated pathway of the vitamin D, bone, and muscle interplay

It is well known that sarcopenia and osteopenia occur simultaneously in vitamin D-deficient patients, whereas muscle weakness and falls have been associated to vitamin D deficiency are suggested as responsible for the high fracture rate in this population.^{37,40,55} Observational data have revealed that $25(\text{OH})\text{D}$ levels predict the decline in bone mineralization and physical performance when $25(\text{OH})\text{D}$ falls below 8 and 20 ng/mL (20 and 50 nmol/L), respectively.^{8,56} Although the underlying mechanisms remain to be elucidated, vitamin D may represent a pathway by which bone and muscle may work together, enabling cross-talk between these tissues (Figure 3).^{1,37,57} *In vitro* studies have reported that vitamin D

Figure 3 Integrative bone-muscle-cross-talk mediated by vitamin D. Adapted from Girgis *et al.*³⁸

reduces myostatin in cultured muscle cells, a hormone released from the muscle that inhibits muscle growth.^{58,59} A reduction in myostatin levels is also associated with increases in bone mass.⁶⁰ Vitamin D stimulates the muscle production of vascular endothelial growth factor and insulin-like growth factor-1 (IGF-1), which are involved in muscle regeneration after injury, as well as in bone growth and density.^{61–63} This may explain how the administration of vitamin D improves the recovery of skeletal muscle strength due to intense exercise.⁶⁴ 1,25(OH)₂D also brings the expression of osteoglycin, another bone anabolic factor that is produced by muscle tissues.⁶⁵

Potential bone factors that affect muscle metabolism and are regulated by vitamin D include sclerostin, osteocalcin, and FGF23.¹ Sclerostin is secreted by mature osteocytes, inhibiting the Wnt signalling pathway that leads to decreased bone formation and increased muscle differentiation.⁶⁶ Osteocalcin is a hormone produced by osteoblasts that reduces sensitivity to insulin and enhances the exercise capacity.^{67,68} FGF23 induces hypertrophy at least on cardiac muscle, although its effects on skeletal muscle are not fully understood.⁶⁹ In addition, the effect of vitamin D on decreasing serum levels of PTH may positively affect muscle function, given that PTH induces proteolysis and reduces creatine phosphate and inorganic phosphate in muscle cell.⁷⁰

Vitamin D metabolism in chronic kidney disease

The kidney is the main site for conversion of 25(OH)D to circulating 1,25(OH)₂D. Although decreased 1,25(OH)₂D

synthesis has been classically related to CKD, the circulating concentration of both metabolites, 25(OH)D and 1,25(OH)₂D, begins to decrease from the earliest stages of CKD.⁷¹ Several factors are associated to this phenomenon including reduced renal mass, dietary restrictions and nutritional deficiencies, reduced sunlight exposure, skin hyperpigmentation, diabetes mellitus, obesity, accumulation of uremic toxins, impaired skin synthesis of cholecalciferol, proteinuria, and increased FGF23.^{72,73} In addition, vitamin D is transported in conjugation with DBP and filtered through the glomerulus. Tubular reabsorption of vitamin D bound to DBP is facilitated by the multi-ligand receptor megalin.⁷⁴ In proteinuric CKD subjects, megalin is occupied by an extensive albumin load, and therefore fewer receptors are available to uptake 25(OH)D-DBP, which contributes to vitamin D deficiency.⁷⁵

In addition to 25(OH)D, 1,25(OH)₂D levels are also reduced in CKD.⁴ Renal 1 α -hydroxylase activity reduces as the renal mass decreases. Other down-regulating factors that are present in CKD patients include low availability of 25(OH)D, hyperphosphatemia, metabolic acidosis, and uraemia itself. Additionally, elevated FGF23 activates the enzyme 24-hydroxylase (CYP24), hydroxylating both 25(OH)D and 1,25(OH)₂D. 24-hydroxylase limits the amount of 1,25(OH)₂D in target tissues both by producing 24,25(OH)₂D (thus decreasing the availability of 25(OH)D for 1 hydroxylation) or by accelerating the catabolism of 1,25(OH)₂D to 1,24,25(OH)₃D resulting in calcitroic acid, which is biologically inactive.^{76,77} CKD is also considered as a state of vitamin D resistance, because VDR expression in bone cells and in nodular parathyroid glands is reduced.⁷⁸ Low 1,25(OH)₂D levels also impair its binding to the VDR-RXR complex.^{79,80} The role of VDR and its interaction with

DNA has been comprehensively reviewed recently from regular physiology to the systemic effects of CKD.²⁵

The combination of vitamin D and/or 1,25(OH)₂D insufficiency and end-organ resistance to vitamin D contribute to the development of CKD-MBD. Additional mechanisms include the impairment of vitamin D-dependent osteocalcin production⁸¹ and the altered Wnt signalling in osteoblasts and osteocytes observed in CKD,⁸² which is associated with bone loss and vascular calcification.^{83,84} As vitamin D inhibits the adverse TGFβ/Smad action on bone cells, a normal vitamin D status might provide protection against Wnt signalling-related bone loss in CKD.⁸⁵

Bone and musculoskeletal abnormalities in chronic kidney disease patients

Alteration of bone mass in chronic kidney disease

Patients with CKD exhibit considerable skeletal fragility, which results from the large spectrum of CKD-related bone diseases, in addition to a variety of other factors including age-related osteoporosis and a significant number of non-specific therapeutic approaches directly affecting bone metabolism such as the use of glucocorticosteroids, intestinal phosphate binders, vitamin D compounds, bisphosphonates, and calcimimetics. The measurement of bone mineral density (BMD) is the usual method to assess bone quantity in these patients. However, the assessment of bone quality is uncommon and difficult, involving others factors such as remodelling rate, bone geometry, and the extracellular matrix properties.⁸⁶

In addition, in CKD, the relation between BMD values, fragility of bone, and fracture risk is not always so clear. Bone loss is site specific, predominating at the mid-radius, with a greater loss of cortical rather than cancellous, which is related to hyperparathyroidism, as opposite to the postmenopausal osteoporosis where the loss is mainly due to cancellous bone from the axial skeleton.⁸⁷ Moreover, CKD patients show different patterns of bone loss. Whereas some patients have a minimal bone loss, others show rapid bone losses.⁸⁶ Additionally, the presence of aorta calcification and spinal osteoarthritis may bias BMD measurement,⁸⁸ being the hip and the radius better sites for the BMD assessment. Interestingly, it has been shown in a population of 2754 elderly subjects, including 587 subjects with CKD, that lower BMD was a risk factor associated with skeletal fractures.⁸⁹ Several other recent papers have shown that low BMD actually predicts fracture in dialysis and renal transplant patients.^{90,91} The use of micro-computerized tomography might also be a useful tool

for the estimation of bone loss and micro-architectural changes; however, they need further evaluation in CKD.⁹² Overall, although there have been uncertainties concerning the utility of BMD in CKD,⁹³ BMD measure may become useful in this population. This issue is currently under review,⁹⁴ and it is likely that BMD testing could be suggested in CKD patients with evidence of CKD-MBD and/or risk factors for osteoporosis, if results may affect treatment decisions.^{95,96}

Although bone histomorphometry is not routinely recommended or executed in uremic patients, it is the gold standard and the only way to evaluate the type of renal osteodystrophy in CKD-MBD.^{97,98} The bone histologic findings in CKD range from low to high bone turnover, mineralization troubles, and changes in bone volume. Each of these histological patterns can appear isolated or co-exist; and none of them can be properly discriminated by using imaging tools or circulating bone biomarkers. It must be stressed here that because the prevalence of renal osteodystrophy in CKD-MBD is high, the presence of osteoporosis is often a diagnosis of exclusion. In spite of this, the KDIGO working group recommended to use in CKD the same World Health Organisation osteoporosis definition applied to the general population. It defines osteoporosis as a bone disorder resulting in decreased bone strength and increased risk of fracture, which is a broad definition that can be appropriately used for diagnostic and management purposes at least in CKD stages 1 to 4.

Alterations of muscle in chronic kidney disease

Severity and prevalence of myopathy in CKD develops already at an eGFR <25 mL/min/1.73 m² and increases concurrently with the decline in GFR, concerning to more than half of dialysis patients.^{99–101} The diagnosis of uremic myopathy is based on clinical features, including weakness (defined as a failure to generate force) and wasting (sarcopenia), which affect predominantly the proximal lower limbs.¹⁰² Whereas muscle enzymes levels and electromyographical studies are usually normal, muscle biopsies show atrophy of the fast-twitch white (type 2) fibres.^{103,104} These morphological features are similar from those found in patients with vitamin D deficiency.^{11,48}

The aetiology of uremic myopathy is multifactorial (Table 2), including physical inactivity, reduced protein intake, vitamin D deficiency, hyperparathyroidism, metabolic acidosis, electrolyte disorder, low serum levels of testosterone, resistance to growth hormone and insulin, accumulation of uremic toxins, and carnitine deficiency, which can lead to mitochondrial dysfunction.^{105,106} Observational studies have shown an inverse correlation between muscle mass and blood levels of IL-6 and C reactive protein in CKD patients,^{12,107,108} postulating

Table 2 Causes of muscle wasting in chronic kidney disease

1. Physical inactivity
2. Reduced protein intake
3. Protein-energy wasting
4. Hormonal disorders:
 - Vitamin D deficiency
 - Low testosterone
 - Hyperparathyroidism
 - Resistance to growth hormone
 - Resistance to insulin
 - Increased Angiotensin II
5. Metabolic disorders:
 - Metabolic acidosis
 - Electrolyte disorder
 - Uremic toxins accumulation
6. Inflammation
7. Myostatin overexpression
8. Low carnitine

inflammation as an additional cause of muscle wasting in this population.^{109–111} Although the process by which inflammation produces sarcopenia has not yet been identified, several mechanisms have been described, including activation of NF- κ B and angiotensin II

pathways,^{112–114} and the ATP-dependent ubiquitin–proteasome system, which has been identified as the most important pathway for muscle wasting.¹¹⁵ Excellent reviews on muscle wasting and dysfunction in patients with CKD have been recently published.^{102,106}

Vitamin D status in chronic kidney disease: data from observational studies

Vitamin D status, bone mineral density, and fractures

A limited number of studies have looked at the relationship between 25(OH)D levels and bone histology, BMD, and fractures in CKD patients (Table 3). An observational study of 104 dialysis patients who underwent a trans-iliac bone biopsy showed that patients with vitamin D insufficiency [25(OH)D \leq 15 ng/mL] had lower trabecular mineralization

Table 3 Studies investigating the association between circulating 25(OH)D levels and skeletal outcomes in chronic kidney disease patients

Reference	Year	N	CKD stage	Study design	Outcome	Results
Coen et al. ¹¹⁶	2005	104	HD	Retrospective	Renal osteodystrophy assessed by transiliac bone biopsy	A mineralization defect and high bone turnover was found with serum 25(OH)D < 15–20 ng/mL. Serum 25(OH)D > 40 ng/mL were accompanied by a reduction of bone turnover. The optimal circulating level of 25(OH)D appeared to be between 20 and 40 ng/mL.
Ambrus et al. ¹¹⁷	2011	130	HD	Cross-sectional	Bone densitometry of the lumbar spine, femoral neck, and distal radius	Patients with low-trauma fractures (n = 21) had lower serum 25(OH)D levels (6.3 ng/mL vs. 12.0; p = 0.029). 25(OH)D < 8 ng/mL was independently associated with bone fractures [OR 11.2 (95% CI: 1.3–94.8); p = 0.026].
Elder et al. ¹¹⁸	2006	242	Stage 5 CKD (5D, 85%)	Cross-sectional	Prevalent spinal fracture assessed by X-ray and BMD by DXA	25(OH)D correlated positively with Z-scores of BMD at the lumbar spine (r = 0.24, p = 0.0005), femoral neck (r = 0.23, p < 0.001), and wrist (r = 0.22, p < 0.01).
Mucsi et al. ¹¹⁹	2005	69	HD	Cross-sectional	Bone densitometry and quantitative bone ultrasound	25(OH)D concentration was positively correlated with BMD measured at the radius (r = 0.424, p < 0.01) and with attenuation on quantitative bone ultrasound (beta = 0.262, P < 0.05).
Ghazali et al. ¹²⁰	1999	113	HD	Cross-sectional	X-rays of the hands and pelvis were obtained for evaluation of sub-periosteal resorption and Looser's zones	25(OH)D was significantly lower in the groups with isolated sub-periosteal resorption (17.6 vs. 22.8 ng/mL; p < 0.05) and with the combination of resorption with Looser's zones (10.4 vs. 22.8 ng/mL; p < 0.004) than in the normal X-ray group.
Brunerová et al. ¹²¹	2016	59	HD	Cross-sectional	Bone densitometry, including trabecular bone score	Similar T-scores and trabecular bone scores among patients according to their serum 25(OH)D levels

CKD, chronic kidney disease; HD, haemodialysis.

surface and bone formation rate regardless of levels of 1,25(OH)₂D and PTH.¹¹⁶ Other studies have shown that CKD patients with low circulating 25(OH)D have an increased risk of reduced BMD and of skeletal fractures,^{117–119} as well as of radiologic features of secondary hyperparathyroidism.¹²⁰ In contrast, a more recent study that included 59 dialysis patients did not show significant differences in T-scores and trabecular bone scores among patients according to their 25(OH)D levels.¹²¹ This apparent discrepancy may be explained by the currently available treatments for CKD-MBD disorders that could alter the classical pathologic findings of the bones in CKD and their relation to 25(OH)D levels. Collectively, it seems clear that low vitamin D status is associated with osteomalacia and fractures, presumably because of mineralization defects. However, the data are less robust in CKD than in the general population.¹²² In addition, the increased osteoclastic activity due to secondary hyperparathyroidism also removes matrix and minerals, exacerbating low bone mass and osteoporosis. It is the combination of mineralization defect and low bone mass that likely increases risk for fractures.^{123,124}

Vitamin D status, falls, muscle mass, and muscle function

Although several studies have described the association between low 25(OH)D levels with lower muscle strength and mass, increased body instability and falls, worse physical performance and frailty in vitamin D-deficient older adults,^{125–127} only a few studies have been undertaken in CKD patients (Table 4). Gordon *et al.*¹²⁸ observed a relationship between 1,25(OH)₂D levels, and physical performance and muscle size in non-dialysis CKD patients. Further, Zahed *et al.*¹²⁹ showed that 25(OH)D levels were positively associated with muscle strength of the lower extremities in haemodialysis patients, suggesting altogether

a plausible role of vitamin D supplementation for improving muscle health in this population.

Interventional studies on vitamin D for improving musculoskeletal health in chronic kidney disease

Effect of vitamin D supplementation on bone mineral density, renal osteodystrophy, and fractures in chronic kidney disease

Multiple randomized trials have been conducted to examine the effect of active vitamin D metabolites as well as nutritional vitamin D supplements on bone biochemical markers in CKD and end-stage renal disease. Most of these studies have been summarized in some meta-analysis,^{130–132} demonstrating the ability of vitamin D for lowering PTH, although treatment was associated with clinical elevations in serum phosphate and calcium. However, data are lacking in terms of patient-level skeletal outcomes such as fractures, BMD, bone pain, or histomorphometric analysis of bone biopsies.¹³³ Table 5 summarizes studies that investigated the impact of vitamin D on skeletal health in CKD.^{134–142} Although vitamin D appeared to protect against the development of histological evidence of osteitis fibrosa and radiological signs of hyperparathyroidism, most published studies have multiple methodological limitations including small sample size and insufficient follow-up to appropriately ascertain these outcomes. To date, no clear benefit on skeletal outcomes can be concluded from the vitamin D administration in renal populations.^{133,143} Fortunately, a new meta-analysis will conduct a systematic review of nutritional vitamin D supplementation and health-related outcomes including fracture in end-stage renal disease patients.¹⁴⁴

Table 4 Studies investigating the association between circulating 25(OH)D levels, muscle strength, and physical performance in chronic kidney disease patients

Reference	Year	N	CKD stage	Study Design	Outcome	Results
Gordon <i>et al.</i> ¹²⁸	2012	26	CKD stage 3 or 4.	Cross-sectional	Gait speed, 6 min walk, sit-to-stand time, 1-legged balance, and thigh MCSA, measured by MRI.	Serum 25(OH)D levels were associated with normal gait speed only ($r = 0.41$, $P = 0.04$). Normal and fast gait speed, the distance walked in 6 min, and sit-to-stand time were best explained by 1,25(OH) ₂ D values. Variance in MCSA was best explained by a model containing 1,25(OH) ₂ D values.
Zahed <i>et al.</i> ¹²⁹	2014	135	HD	Cross-sectional	Muscle strength estimated using a micro manual muscle tester	Lower serum 25(OH)D levels were observed in the group with less muscle strength in lower extremities

CKD, chronic kidney disease; HD, haemodialysis; MCSA, muscle cross-sectional area; MRI, magnetic resonance imaging.

Table 5 Studies investigating the effects of vitamin D supplementation on skeletal health in chronic kidney disease

Reference	Year	N	CKD stage	Study design	Duration of study	Vitamin D regimen	Endpoint	Results
<i>Fournier et al.</i> ¹³⁴	1979	10	HD	Open-label interventional	6 months	Oral alfacalcidol (1–2 mcg/d)	Bone matrix mineralization evaluated by histomorphometry	Calcifediol induced more effectively bone mineralization
<i>Memmos et al.</i> ¹³⁵	1981	57	HD	RCT	1–2 years	oral calcifediol (50–100 mcg/d) Oral 1,25(OH) ₂ D (0.25–0.50 mcg/d) vs. placebo	Radiological signs of hyperparathyroidism	1,25(OH) ₂ D prevented radiological signs of secondary hyperparathyroidism in patients with normal radiographs 1,25(OH) ₂ D arrested or reversed radiological signs of secondary hyperparathyroidism in patients with abnormal radiographs No differences between groups.
<i>Morinière et al.</i> ¹³⁶	1985	27	HD	RCT	6 months	Oral alfacalcidol (0.3–1.0 mcg/d) + CaCO ₃ (3 g/d) vs. CaCO ₃ (9 ± 5 g/d)	Development of bone pain	
<i>Baker et al.</i> ¹³⁷	1986	76	HD	RCT	5 years	Oral 1,25(OH) ₂ D (0.25–1.00 mcg/d) vs. placebo	Bone biopsy Fracture risk	1,25(OH) ₂ D appeared to protect against the development of histological evidence of osteitis fibrosa but not of osteomalacia, but accumulation of aluminium in bone occurred during the study No differences on fracture risk between groups
<i>Baker et al.</i> ¹³⁸	1989	13	Stage 3–4 CKD	RCT	1 year	Oral 1,25(OH) ₂ D (0.25–0.50 mcg/d) vs. placebo	Bone biopsy	1,25(OH) ₂ D ameliorated histological signs of secondary hyperparathyroidism
<i>Llach et al.</i> ¹³⁹	1998	35	HD	RCT	4 weeks	Intravenous paricalcitol (0.04–0.24 mcg/kg three times weekly) vs. Placebo	Development of bone pain	No differences between groups.
<i>Watson et al.</i> ¹⁴⁰	1998	12	CAPD (children)	RCT	6 months	Oral alfacalcidol (10–20 ng/kg/d) vs. no treatment	Bone biopsy Radiological signs of secondary hyperparathyroidism	Significant reduction in osteoid index and seam in alfacalcidol group. More patients developed sub-periosteal erosions on radiography in the no treatment group. No differences between groups.
<i>Delmez et al.</i> ¹⁴¹	2000	15	HD	RCT	1 year	Intravenous 1,25(OH) ₂ D (0.5–2.0 mcg) plus CaCO ₃ vs. CaCO ₃ alone (control)	Fracture risk	No differences between groups.
<i>Mager et al.</i> ¹⁴²	2016	60	Stage 1–4 CKD	RCT	6 months	Oral cholecalciferol (2000 IU/d) vs. oral cholecalciferol (40,000 IU/month)	Bone mineral density	Patients with 25(OH)D ≥ 30 ng/ml was associated with significant improved physical functioning (secondary outcome).

CAPD, continuous ambulatory peritoneal dialysis; CKD, chronic kidney disease; HD, haemodialysis; RCT, randomized controlled trial.

Effect of vitamin D supplementation on risk of falls, muscle mass and strength, and physical performance in chronic kidney disease

Although extensive literature has shown that supplementation with vitamin D in the general population has a positive effect on skeletal muscle dysfunction including falls, strength, and athletic performance,^{40,50,145,146} there is not enough evidence to address the role of vitamin D on musculoskeletal outcomes in CKD population.¹⁴⁷ Musculoskeletal outcomes have not usually been considered in most of existing trials. Although it may be argued that intervention time was too short, in a recent randomized trial providing oral cholecalciferol vs. placebo to haemodialysis patients, no difference in the frequency of falls was noted after 6 months.¹⁴⁸ Similarly, only few small studies have addressed the effect of vitamin D on muscle metabolic pathways in renal population.^{149,150} Whereas in general vitamin D does not seem to have any additional benefit on glucose homeostasis and insulin sensitivity,¹⁵¹ repletion with ergocalciferol may assist in improving glycaemic control in CKD patients.¹⁵⁰

Any vitamin D benefit on muscle strength is likely to occur in patients with severe vitamin D deficiency. In an interventional study that included both non-dialysis CKD stage 3–4 and peritoneal dialysis patients with severe vitamin D deficiency [mean 25(OH)D < 7 ng/mL (17.5 nmol/L)], vitamin D supplementation was found to improve physical performance significantly, evaluated by the time to up and go test, gait speed test, the timed chair stand test, and the stair climb test.¹⁵² However, no definite conclusions can be yet drawn from this emerging evidence and the question of whether vitamin D supplementation is effective for muscle outcomes remains unanswered.

Controversies in the definition of vitamin D insufficiency in chronic kidney disease

The optimal levels of 25(OH)D and the definition of vitamin D insufficiency remain controversial both for the general population and for patients with CKD.^{153,154} Whereas KDIGO and the US Society of Endocrinology favour maintaining 25(OH)D levels between 30 to 50 ng/mL (75 to 125 nmol/L),^{154,155} the Institute of Medicine and the World Health Organisation favour the range 20 to 40 ng/mL (50 to 100 nmol/L).^{156,157} Differences in these recommended target ranges are attributed to controversies regarding 25(OH)D intestinal calcium absorption, maximal suppression of PTH, or optimal levels to prevent a clinical end-point such as fracture or death:

- *Adequate intestinal calcium absorption.* The adequate 25(OH)D levels to guarantee sufficient substrate for its conversion to 1,25(OH)₂D and ensure optimal calcium absorption has been estimated to be >4.4 ng/mL (11 nmol/L).¹⁵⁸ However, this definition may be unsuitable for CKD patients, in whom calcium absorption and 1,25(OH)₂D production are impaired.¹⁵⁹
- *Maximal suppression of PTH.* Based on the inflexion point at which PTH secretion is suppressed to a minimum in its relation to 25(OH)D levels in the general population,¹⁶⁰ KDIGO guidelines suggest to maintain serum 25(OH)D levels >30 ng/mL (75 nmol/L) in CKD patients.¹⁵⁴ Other experts, however, estimate that 25(OH)D > 20 ng/mL (50 nmol/L) are adequate to suppress PTH.¹⁵⁷ Although there is also an inverse relationship between 25(OH)D and PTH levels in CKD patients,^{161,162} this pathophysiological definition is possibly inappropriate in these patients, given that PTH secretion is influenced by several factors related to the uremic state (such as hypocalcaemia or hyperphosphatemia), independently of 25(OH)D levels.¹⁶³
- *Fracture prevention.* In non-CKD population, vitamin D supplementation to achieve the 25(OH)D target concentration of 28 to 40 ng/mL (70 to 100 nmol/L) lowered fracture risk.^{164–166} However, cross-sectional studies do not agree on the 25(OH)D threshold level needed to maximize BMD and even suggest that BMD may not improve with vitamin D supplementation once baseline levels of 25(OH)D are >20 ng/mL.¹⁵³ Moreover, chronic 25(OH)D levels >40 ng/mL (100 nmol/L) after a single annual dose of 500 000 IU of cholecalciferol increased the risk of fractures.¹⁶⁷ Interventional data are lacking in CKD patients, and the optimal 25(OH)D concentration for fracture risk reduction may only be inferred from observational studies.¹³³ In a small cross-sectional study including 130 patients on haemodialysis, 25(OH)D < 8 ng/mL (20 nmol/L) was independently associated with increased risk for bone fractures.¹¹⁷
- *Death prevention.* Observational studies in both dialysis and non-dialysis patients have examined the prognostic value of 25(OH)D levels. Wolf *et al.* showed that among incident haemodialysis patients, those with 25(OH)D levels < 10 ng/mL (25 nmol/L) were at increased risk of 90 day mortality, compared with subjects with 25(OH)D > 30 ng/mL (75 nmol/L). The risk for cardiovascular-related mortality was also higher for patients with 25(OH)D between 10 to 30 ng/mL (25 to 75 nmol/L).¹⁶⁸ Similar data have been reported for non-dialysis patients in two prospective studies of small sample size.^{169,170} We have recently examined the prognostic value of 25(OH)D levels among 470 non-dialysis 3–5 stage CKD patients, and observed consistent associations between 25(OH)D levels and the risk of death, kidney progression, and

hospitalization, with the respective concentrations of 17.4 ng/mL (43.4 nmol/L), 18.6 ng/mL (46.4 nmol/L), and 19.0 ng/mL (47.4 nmol/L), denoting the highest risk prediction sensitivity and specificity.¹⁷¹

There are currently insufficient data to determine the safe upper limit of serum 25(OH)D.¹⁵³ Although the safety margin to minimize the risk of hypercalcaemia as 25(OH)D equal to 100 ng/mL (250 nmol/L), there are some concerns at serum 25(OH)D levels above 50 ng/mL (125 nmol/L). These concerns are based upon conflicting observational studies describing an increased risk for fractures, ischaemic cardiopathy, and some cancers, with levels above 30 to 48 ng/mL (75 to 120 nmol/L).^{167,172–175} Based on a recent analysis from the 2007–2010 National Health and Nutrition Examination Survey, proposals for lowering the cut-off for vitamin D deficiency to 12.5 ng/mL (31.2 nmol/L) have emerged.¹⁷⁶ CKD patients may be at special risk of overscreening and overtreatment of vitamin D, and vitamin D excess may be also a risk contributor for vascular calcifications.¹⁷⁷

Using randomized clinical trials from the general population as the main guideline, we conclude that levels below 20 ng/mL (50 nmol/L) are likely suboptimal for skeletal health, which is in agreement with current experts' recommendations.^{154–157} The recommendation of targeting 25(OH)D levels of 30 ng/mL (75 nmol/L) may be beneficial for skeletal and extraskeletal health in CKD patients, but we acknowledge that this statement is based on observational studies and warrants consensus and confirmation.¹⁵³ Although future trials will guide us to determine the optimal 25(OH) levels for dialysis patients, currently available data suggest that vitamin D administration may confer a survival benefit.¹⁷⁸

Conclusion

In addition to control bone metabolism and calcium homeostasis, growing evidence suggests that vitamin D plays a key role for muscle function and metabolism in health and CKD. Mechanistically, vitamin D exerts both genomic and rapid effects on bone and muscle metabolism. Furthermore, vitamin D may represent a pathway by which bone and muscle may work together, enabling cross-talk between these tissues. Observational studies have shown that CKD patients with vitamin D deficiency have an increased risk of reduced BMD and of skeletal fractures, presumably due to mineralization defects, although the evidence is less strong in CKD than in the general population. Likewise, the clinical symptoms and muscle morphological changes observed in CKD patients correlate with 25(OH)D levels, similarly to that

observed in subjects with hypovitaminosis D of other origin. Lastly, although some interventional studies have shown that vitamin D supplementation may improve physical performance and bone health in CKD patients, the limited evidence does not allow a certain conclusion about the definitive role of vitamin D supplementation on musculoskeletal outcomes in this population. However, this lack of evidence does not necessarily indicate that vitamin D supplementation has no effect on musculoskeletal health. Moreover, given that vitamin D supplementations is safe and cost-effective, it can be considered to improve muscle strength and physical performance in CKD patients, especially those who have 25(OH)D levels below 20 ng/mL (50 nmol/L).

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