

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

Pablo Molina<sup>1,2,3\*</sup> , Juan J. Carrero<sup>4</sup>, Jordi Bover<sup>2,5,6</sup>, Philippe Chauveau<sup>7</sup>, Sandro Mazzaferro<sup>8</sup> & Pablo Ureña Torres<sup>9,10</sup> 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)<sup>†</sup>

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

Received: 2 December 2016; Revised: 4 April 2017; Accepted: 20 April 2017

\*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

<sup>†</sup>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.<sup>1–3</sup> Vitamin D deficiency is common in patients with chronic kidney disease (CKD),<sup>4</sup> a population in whom muscle wasting and weakness are also highly prevalent.<sup>5–7</sup> Observational studies have shown that circulating 25-hydroxyvitamin D [25(OH)D] levels are reduced in parallel to the severity of muscle symptoms.<sup>8</sup> 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.<sup>9,10</sup> There are also evidences that hypovitaminosis D affects both contractile muscle function and muscle metabolism via disturbing insulin sensitivity.<sup>11</sup> 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.<sup>12–17</sup>

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 D<sub>2</sub> and vitamin D<sub>3</sub> lies on their origin (vegetal or animal) and on the structure of their side chains.<sup>18</sup> Vitamin D is absorbed through the proximal segments of the small intestine.<sup>19</sup> 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.<sup>20</sup> 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 $\alpha$ -hydroxylase (CYP27B1) to form 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D], 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.<sup>21</sup>

There is a feedback loop between FGF23 and vitamin D, whereby FGF23 inhibits 1 $\alpha$ -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.<sup>21,22</sup> Indirect effects of FGF23 include the increase of renal excretion of phosphate, affecting the amount of phosphate available for mineralization at the bone surfaces.<sup>23</sup> 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.<sup>24</sup>

1,25(OH)<sub>2</sub>D that passes into the bloodstream is also bound to DBP, binding to the VDR in several tissues, including parathyroid cells, bone, and intestine.<sup>25,26</sup> The VDR-1,25(OH)<sub>2</sub>D 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)<sub>2</sub>D 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).<sup>20,27,28</sup> As a result of these processes, 1,25(OH)<sub>2</sub>D maintains calcium and phosphate homeostasis, stimulating their intestinal absorption and bone resorption.<sup>29</sup> To accomplish this, the 1,25(OH)<sub>2</sub>D-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)<sub>2</sub>D 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.<sup>30,31</sup> 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.<sup>32,33</sup>

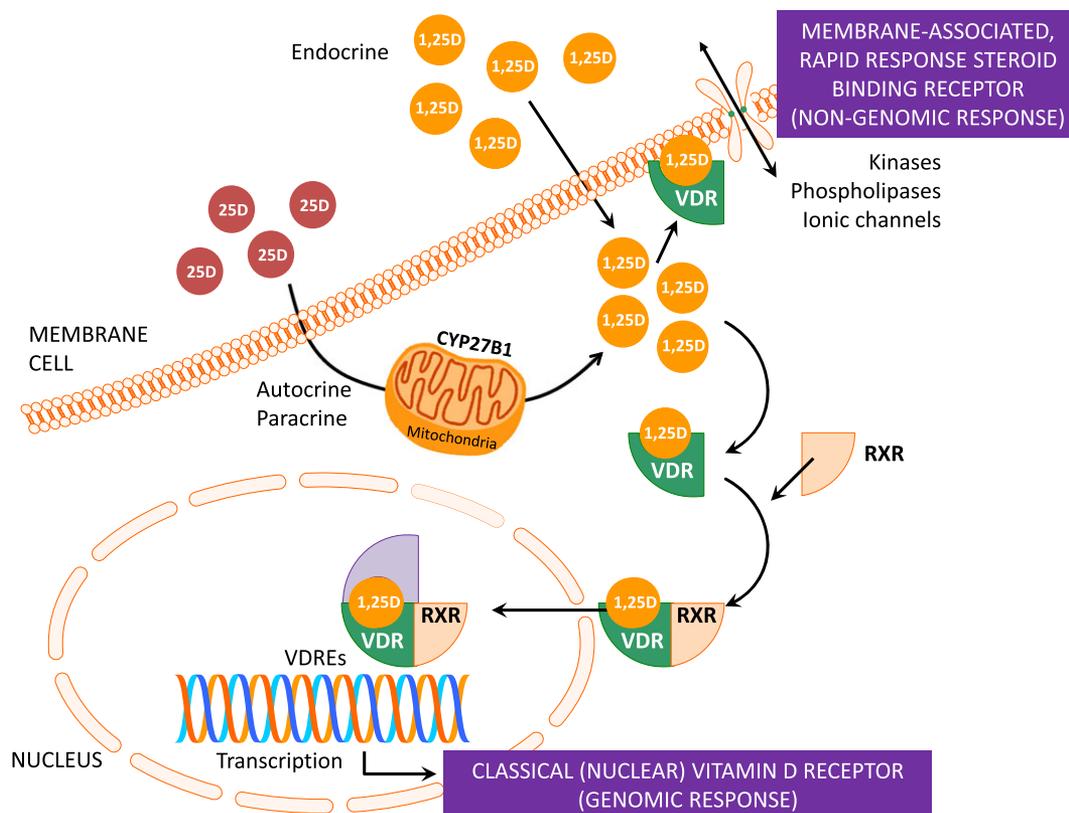
Besides this anabolic effect on bone, direct effects of vitamin D in osteoblasts may have the opposite effect, stimulating bone resorption through osteoclastogenesis to increase bone calcium mobilization.<sup>34</sup> To do this, Vitamin D interacts with the VDR in osteoblasts to induce the expression of the plasma membrane protein receptor activator of NF- $\kappa$ 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.<sup>35</sup>

The VDR is also present in other tissues (including skeletal muscle) that are not involved in mineral and bone metabolism, where 1,25(OH)<sub>2</sub>D 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.<sup>29,36</sup>

### *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.



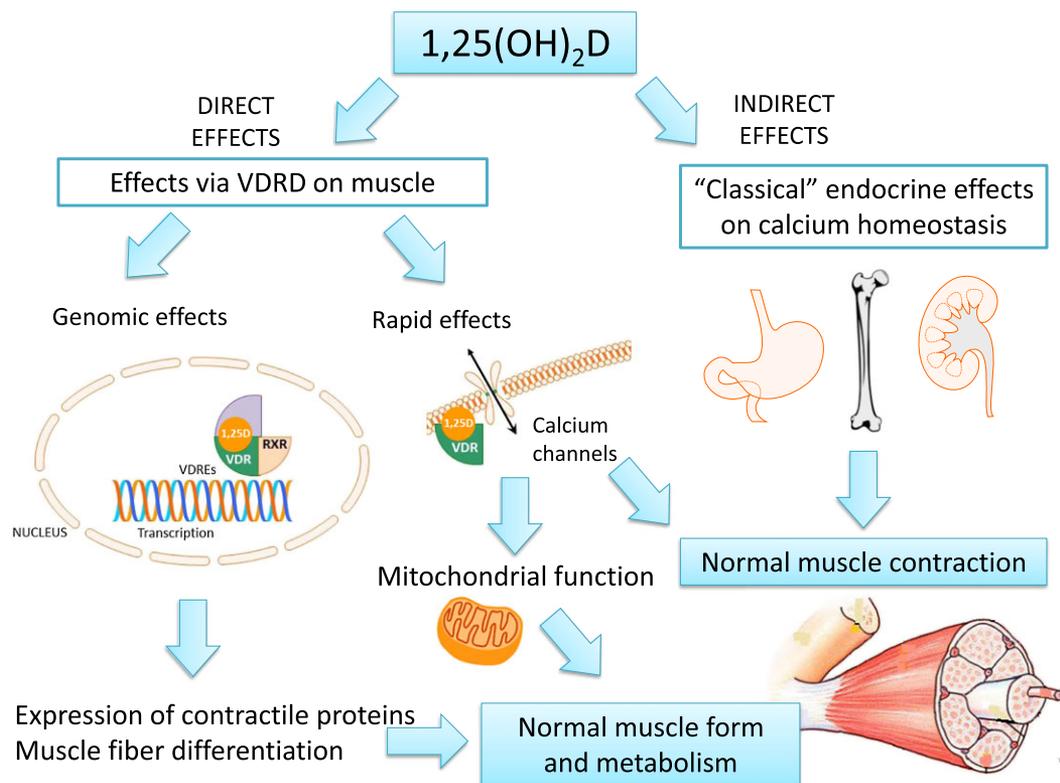
**Table 1** Effects and functions of vitamin D

Endocrine effects	Non-calcaemic and non-skeletal effects
<ol style="list-style-type: none"> <li>1. Increase intestinal absorption of calcium and phosphate</li> <li>2. Down-regulate expression of PTH mRNA in the parathyroid glands</li> <li>3. Induce mature osteoclastic activity, which releases calcium and phosphate into the bloodstream</li> </ol>	<ol style="list-style-type: none"> <li>1. Maintain normal cell proliferation and differentiation.</li> <li>2. Decrease renal production of renin</li> <li>3. Stimulate pancreatic production of insulin</li> <li>4. Immunomodulation</li> </ol>
↓	↓
'Classical' functions	'Non-classical' functions
To maintain normal blood levels of calcium and phosphate in order to support: <ol style="list-style-type: none"> <li>1. Bone mineralization</li> <li>2. Metabolic functions</li> <li>3. Neuromuscular function</li> </ol>	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.

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).<sup>37,38</sup> 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.*<sup>35</sup>

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.<sup>9,39</sup> Although VDR is expressed at low levels in resting adult muscle, markedly VDR expression and 1 $\alpha$ -hydroxylase have been observed in neonatal muscle or following muscle injury, supporting the muscle capacity for local production of 1,25(OH)<sub>2</sub>D, and a developmental and regenerative role for vitamin D in this tissue.<sup>36,40,41</sup>

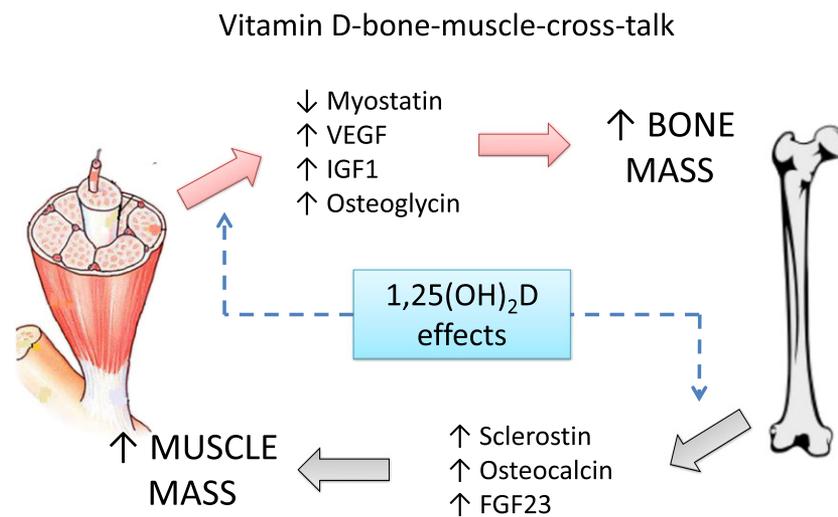
Vitamin D may also interact with the VDR in muscle cells by non-genomic effects, which are independent of the intranuclear transcription process. They involve the rapid regulation of membrane calcium channels, suggesting a role for vitamin D in the calcium-mediated muscle functions, such as muscle contraction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

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.<sup>36,47</sup> Changes in muscle morphology include derangement of the intermyofibrillar network, increases in intramuscular lipids, and atrophy of the fast-twitch white (type 2) fibres,<sup>11,44,48,49</sup> which are the first to be recruited when preventing a fall. All these changes seem to be reversible,<sup>50</sup> supporting co-ordinated effects of vitamin D in musculoskeletal physiology.<sup>51–54</sup>

### *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.<sup>37,40,55</sup> Observational data have revealed that 25(OH)D levels predict the decline in bone mineralization and physical performance when 25(OH)D falls below 8 and 20 ng/mL (20 and 50 nmol/L), respectively.<sup>8,56</sup> 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).<sup>1,37,57</sup> *In vitro* studies have reported that vitamin D

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

reduces myostatin in cultured muscle cells, a hormone released from the muscle that inhibits muscle growth.<sup>58,59</sup> A reduction in myostatin levels is also associated with increases in bone mass.<sup>60</sup> 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.<sup>61–63</sup> This may explain how the administration of vitamin D improves the recovery of skeletal muscle strength due to intense exercise.<sup>64</sup> 1,25(OH)<sub>2</sub>D also brings the expression of osteoglycin, another bone anabolic factor that is produced by muscle tissues.<sup>65</sup>

Potential bone factors that affect muscle metabolism and are regulated by vitamin D include sclerostin, osteocalcin, and FGF23.<sup>1</sup> Sclerostin is secreted by mature osteocytes, inhibiting the Wnt signalling pathway that leads to decreased bone formation and increased muscle differentiation.<sup>66</sup> Osteocalcin is a hormone produced by osteoblasts that reduces sensitivity to insulin and enhances the exercise capacity.<sup>67,68</sup> FGF23 induces hypertrophy at least on cardiac muscle, although its effects on skeletal muscle are not fully understood.<sup>69</sup> 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.<sup>70</sup>

## Vitamin D metabolism in chronic kidney disease

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

synthesis has been classically related to CKD, the circulating concentration of both metabolites, 25(OH)D and 1,25(OH)<sub>2</sub>D, begins to decrease from the earliest stages of CKD.<sup>71</sup> 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.<sup>72,73</sup> 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.<sup>74</sup> 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.<sup>75</sup>

In addition to 25(OH)D, 1,25(OH)<sub>2</sub>D levels are also reduced in CKD.<sup>4</sup> Renal 1 $\alpha$ -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)<sub>2</sub>D. 24-hydroxylase limits the amount of 1,25(OH)<sub>2</sub>D in target tissues both by producing 24,25(OH)<sub>2</sub>D (thus decreasing the availability of 25(OH)D for 1 hydroxylation) or by accelerating the catabolism of 1,25(OH)<sub>2</sub>D to 1,24,25(OH)<sub>3</sub>D resulting in calcitroic acid, which is biologically inactive.<sup>76,77</sup> CKD is also considered as a state of vitamin D resistance, because VDR expression in bone cells and in nodular parathyroid glands is reduced.<sup>78</sup> Low 1,25(OH)<sub>2</sub>D levels also impair its binding to the VDR-RXR complex.<sup>79,80</sup> The role of VDR and its interaction with

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

The combination of vitamin D and/or 1,25(OH)<sub>2</sub>D 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 production<sup>81</sup> and the altered Wnt signalling in osteoblasts and osteocytes observed in CKD,<sup>82</sup> which is associated with bone loss and vascular calcification.<sup>83,84</sup> 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.<sup>85</sup>

## 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.<sup>86</sup>

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 post-menopausal osteoporosis where the loss is mainly due to cancellous bone from the axial skeleton.<sup>87</sup> Moreover, CKD patients show different patterns of bone loss. Whereas some patients have a minimal bone loss, others show rapid bone losses.<sup>86</sup> Additionally, the presence of aorta calcification and spinal osteoarthritis may bias BMD measurement,<sup>88</sup> 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.<sup>89</sup> Several other recent papers have shown that low BMD actually predicts fracture in dialysis and renal transplant patients.<sup>90,91</sup> 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.<sup>92</sup> Overall, although there have been uncertainties concerning the utility of BMD in CKD,<sup>93</sup> BMD measure may become useful in this population. This issue is currently under review,<sup>94</sup> 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.<sup>95,96</sup>

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.<sup>97,98</sup> 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 m<sup>2</sup> and increases concurrently with the decline in GFR, concerning to more than half of dialysis patients.<sup>99–101</sup> 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.<sup>102</sup> Whereas muscle enzymes levels and electromyographical studies are usually normal, muscle biopsies show atrophy of the fast-twitch white (type 2) fibres.<sup>103,104</sup> These morphological features are similar from those found in patients with vitamin D deficiency.<sup>11,48</sup>

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.<sup>105,106</sup> Observational studies have shown an inverse correlation between muscle mass and blood levels of IL-6 and C reactive protein in CKD patients,<sup>12,107,108</sup> 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.<sup>109–111</sup> Although the process by which inflammation produces sarcopenia has not yet been identified, several mechanisms have been described, including activation of NF- $\kappa$ B and angiotensin II

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

## 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. <sup>116</sup>	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. <sup>117</sup>	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. <sup>118</sup>	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. <sup>119</sup>	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. <sup>120</sup>	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. <sup>121</sup>	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)<sub>2</sub>D and PTH.<sup>116</sup> Other studies have shown that CKD patients with low circulating 25(OH)D have an increased risk of reduced BMD and of skeletal fractures,<sup>117–119</sup> as well as of radiologic features of secondary hyperparathyroidism.<sup>120</sup> 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.<sup>121</sup> 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.<sup>122</sup> 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.<sup>123,124</sup>

### 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,<sup>125–127</sup> only a few studies have been undertaken in CKD patients (Table 4). Gordon *et al.*<sup>128</sup> observed a relationship between 1,25(OH)<sub>2</sub>D levels, and physical performance and muscle size in non-dialysis CKD patients. Further, Zahed *et al.*<sup>129</sup> 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,<sup>130–132</sup> 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.<sup>133</sup> Table 5 summarizes studies that investigated the impact of vitamin D on skeletal health in CKD.<sup>134–142</sup> 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.<sup>133,143</sup> 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.<sup>144</sup>

**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> <sup>128</sup>	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) <sub>2</sub> D values. Variance in MCSA was best explained by a model containing 1,25(OH) <sub>2</sub> D values.
Zahed <i>et al.</i> <sup>129</sup>	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> <sup>134</sup>	1979	10	HD	Open-label interventional	6 months	Oral alfacalcidol (1–2 mcg/d) vs. oral calcifediol (50–100 mcg/d)	Bone matrix mineralization evaluated by histomorphometry	Calcifediol induced more effectively bone mineralization
<i>Memmos et al.</i> <sup>135</sup>	1981	57	HD	RCT	1–2 years	Oral 1,25(OH) <sub>2</sub> D (0.25–0.50 mcg/d) vs. placebo	Radiological signs of hyperparathyroidism	1,25(OH) <sub>2</sub> D prevented radiological signs of secondary hyperparathyroidism in patients with normal radiographs 1,25(OH) <sub>2</sub> D arrested or reversed radiological signs of secondary hyperparathyroidism in patients with abnormal radiographs No differences between groups.
<i>Morinière et al.</i> <sup>136</sup>	1985	27	HD	RCT	6 months	Oral alfacalcidol (0.3–1.0 mcg/d) + CaCO <sub>3</sub> (3 g/d) vs. CaCO <sub>3</sub> (9 ± 5 g/d)	Development of bone pain	No differences between groups.
<i>Baker et al.</i> <sup>137</sup>	1986	76	HD	RCT	5 years	Oral 1,25(OH) <sub>2</sub> D (0.25–1.00 mcg/d) vs. placebo	Bone biopsy Fracture risk	1,25(OH) <sub>2</sub> 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> <sup>138</sup>	1989	13	Stage 3–4 CKD	RCT	1 year	Oral 1,25(OH) <sub>2</sub> D (0.25–0.50 mcg/d) vs. placebo	Bone biopsy	1,25(OH) <sub>2</sub> D ameliorated histological signs of secondary hyperparathyroidism
<i>Llach et al.</i> <sup>139</sup>	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> <sup>140</sup>	1998	12	CAPD (children)	RCT	6 months	Placebo 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> <sup>141</sup>	2000	15	HD	RCT	1 year	Intravenous 1,25(OH) <sub>2</sub> D (0.5–2.0 mcg) plus CaCO <sub>3</sub> vs. CaCO <sub>3</sub> alone (control)	Fracture risk	No differences between groups.
<i>Mager et al.</i> <sup>142</sup>	2016	60	Stage 1–4 CKD	RCT	6 months	Oral cholecalciferol (2000 IU/d) vs. oral cholecalciferol (40,000 IU/month)	Bone mineral density	No differences between groups. 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,<sup>40,50,145,146</sup> there is not enough evidence to address the role of vitamin D on musculoskeletal outcomes in CKD population.<sup>147</sup> 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.<sup>148</sup> Similarly, only few small studies have addressed the effect of vitamin D on muscle metabolic pathways in renal population.<sup>149,150</sup> Whereas in general vitamin D does not seem to have any additional benefit on glucose homeostasis and insulin sensitivity,<sup>151</sup> repletion with ergocalciferol may assist in improving glycaemic control in CKD patients.<sup>150</sup>

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.<sup>152</sup> 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.<sup>153,154</sup> 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),<sup>154,155</sup> the Institute of Medicine and the World Health Organisation favour the range 20 to 40 ng/mL (50 to 100 nmol/L).<sup>156,157</sup> 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)<sub>2</sub>D and ensure optimal calcium absorption has been estimated to be >4.4 ng/mL (11 nmol/L).<sup>158</sup> However, this definition may be unsuitable for CKD patients, in whom calcium absorption and 1,25(OH)<sub>2</sub>D production are impaired.<sup>159</sup>
- *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,<sup>160</sup> KDIGO guidelines suggest to maintain serum 25(OH)D levels >30 ng/mL (75 nmol/L) in CKD patients.<sup>154</sup> Other experts, however, estimate that 25(OH)D > 20 ng/mL (50 nmol/L) are adequate to suppress PTH.<sup>157</sup> Although there is also an inverse relationship between 25(OH)D and PTH levels in CKD patients,<sup>161,162</sup> 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.<sup>163</sup>
- *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.<sup>164–166</sup> 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.<sup>153</sup> 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.<sup>167</sup> 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.<sup>133</sup> 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.<sup>117</sup>
- *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).<sup>168</sup> Similar data have been reported for non-dialysis patients in two prospective studies of small sample size.<sup>169,170</sup> 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.<sup>171</sup>

There are currently insufficient data to determine the safe upper limit of serum 25(OH)D.<sup>153</sup> 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).<sup>167,172–175</sup> 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.<sup>176</sup> 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.<sup>177</sup>

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.<sup>154–157</sup> 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.<sup>153</sup> 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.<sup>178</sup>

## 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).

## Acknowledgements

The European Renal Nutrition (ERN) and the Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) working groups are initiatives of and supported by the European Renal Association-European Dialysis Transplant Association (ERA-EDTA). The authors thank to the website <http://www.free-anatomy-quiz.com/> for sharing free images used on the figures of this article.

The following are the board members of the ERN working group: Denis Fouque (France); Juan J Carrero (Sweden); Daniel Teta (Switzerland); Vincenzo Bellizi (Italy); Christoph Wanner (Germany); Peter Ter Wee (Netherlands); Siren Sezer (Turkey); Lina Johansson (United Kingdom); Philippe Chauveau (France); and Pablo Molina (Spain).

The following are the board members of the CKD-MBD working group: Mario Cozzolino (Italy); Marc Vervloet (Netherlands); Vincent Brandenburg (Germany); Jordi Bover (Spain); Adrian Covic (Romania); Pieter Evenepoel (Belgium); David Goldsmith (United Kingdom); Ziad Massy (France); Sandro Mazzaferro (Italy); and Pablo Ureña-Torres (France).

The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.<sup>179</sup>

## Conflict of interest

P.M. has received speaking honoraria from Vifor-Pharma-Fresenius Medical Care and Abbott Nutrition. J.J.C. has received speaking honoraria from Abbott Nutrition and Baxter Healthcare; institutional grants from AstraZeneca and Vifor-Pharma. J.B. has received speaking honoraria from Abbvie, Amgen, and Shire; fees as a consultant for Abbvie, Amgen, Vifor/Fresenius-Pharma, Chugai, Medice,

Genzyme/Sanofi, and Sanifit. P.C. acknowledges speaker honoraria from Fresenius Kabi and Vifor Pharma. S.M. has received speaker honoraria from Abbvie and Amgen. P.U.T. has received personal fees and grants from Abbie, Amgen, Astellas, Genzyme-Sanofi, Hemotech, and Vifor-Pharma-Fresenius Medical Care.

## References

1. Gunton JE, Girgis CM, Baldock PA, Lips P. Bone muscle interactions and vitamin D. *Bone* 2015;**80**:89–94.
2. Halfon M, Phan O, Teta D. Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. *Biomed Res Int* 2015;**2015**:953241.
3. Tanner SB, Harwell SA. More than healthy bones: a review of vitamin D in muscle health. *Ther Adv Musculoskelet Dis* 2015;**7**:152–159.
4. Górriz JL, Molina P, Bover J, et al. Characteristics of bone mineral metabolism in patients with stage 3-5 chronic kidney disease not on dialysis: results of the OSERCE study. *Nefrologia* 2013;**33**:46–60.
5. Kittiskulnam P, Carrero JJ, Chertow GM, Kaysen GA, Delgado C, Johansen KL. Sarcopenia among patients receiving hemodialysis: weighing the evidence. *J Cachexia Sarcopenia Muscle* 2016. <https://doi.org/10.1002/jcsm.12130>.
6. Kalantar-Zadeh K, Rhee C, Sim JJ, Stenvinkel P, Anker SD, Kovesdy CP. Why cachexia kills: examining the causality of poor outcomes in wasting conditions. *J Cachexia Sarcopenia Muscle* 2013;**4**:89–94.
7. Mak RH, Ikizler AT, Kovesdy CP, Raj DS, Stenvinkel P, Kalantar-Zadeh K. Wasting in chronic kidney disease. *J Cachexia Sarcopenia Muscle* 2011;**2**:9–25.
8. Wicherts IS, van Schoor NM, Boeke AJ, et al. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 2007;**92**:2058–2065.
9. Girgis CM, Mokbel N, Cha KM, et al. The vitamin D receptor (VDR) is expressed in skeletal muscle of male mice and modulates 25-hydroxyvitamin D (25OHD) uptake in myofibers. *Endocrinology* 2014;**155**:3227–3237.
10. Abboud M, Puglisi DA, Davies BN, et al. Evidence for a specific uptake and retention mechanism for 25-hydroxyvitamin D (25OHD) in skeletal muscle cells. *Endocrinology* 2013;**154**:3022–3030.
11. Ceglia L. Vitamin D and its role in skeletal muscle. *Curr Opin Clin Nutr Metab Care* 2009;**12**:628–633.
12. Carrero JJ, Chmielewski M, Axelsson J, et al. Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr* 2008;**27**:557–564.
13. Ioyama N, Qureshi AR, Avesani CM, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. *Clin J Am Soc Nephrol* 2014;**9**:1720–1728.
14. Kutner NG, Zhang R, Huang Y, Painter P. Gait speed and mortality, hospitalization, and functional status change among hemodialysis patients: a US Renal Data System special study. *Am J Kidney Dis* 2015;**66**:297–304.
15. Stenvinkel P, Carrero JJ, von Walden F, Ikizler TA, Nader GA. Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. *Nephrol Dial Transplant* 2016;**31**:1070–1077.
16. Mak RH, Ikizler AT, Kovesdy CP, Raj DS, Stenvinkel P, Kalantar-Zadeh K. Wasting in chronic kidney disease. *J Cachexia Sarcopenia Muscle* 2011;**2**:9–25.
17. Carrero JJ, Stenvinkel P, Cuppari L, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr* 2013;**23**:77–90.
18. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. *Chem Biol* 2014;**21**:319–329.
19. Lo CW, Paris PW, Clemens TL, Nolan J, Holick MF. Vitamin D absorption in healthy subjects and in patients with intestinal malabsorption syndromes. *Am J Clin Nutr* 1985;**42**:644–649.
20. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;**357**:266–281.
21. Jüppner H. Phosphate and FGF-23. *Kidney Int Suppl* 2011;**121**:S24–S27.
22. Kolek OL, Hines ER, Jones MD, et al. 1 $\alpha$ ,25-Dihydroxyvitamin D<sub>3</sub> upregulates FGF23 gene expression in bone: the final link in a renal-gastrointestinal-skeletal axis that controls phosphate transport. *Am J Physiol Gastrointest Liver Physiol* 2005;**289**:G1036–G1042.
23. Prié D, Ureña Torres P, Friedlander G. Latest findings in phosphate homeostasis. *Kidney Int* 2009;**75**:882–889.
24. Murali SK, Roschger P, Zeitz U, Klaushofer K, Andrukova O, Erben RG. FGF23 regulates bone mineralization in a 1,25(OH)<sub>2</sub>D<sub>3</sub> and Klotho-independent manner. *J Bone Miner Res* 2016;**31**:129–142.
25. Bover J, Ruiz CE, DaSilva M, Diaz M, Guillen E. In Urena Torres P, Cozzolino M, Vervloet, eds. *Vitamin D receptor and interaction with DNA: from physiology to chronic kidney disease*. Vitamin D in Chronic Kidney Disease: Cham, Switzerland: Springer; 2016.
26. Haussler MR, Whitfield GK, Haussler CA, Hsieh JC, Jurutka PW. *Nuclear Vitamin D Receptor: Natural Ligands, Molecular Structure-Function, and Transcriptional Control of Vital Genes*. In David Felman JW Pike, Adams JS, eds. *Vitamin D*. San Diego, CA: Elsevier; 2011. p137–169.
27. Souberbielle JC, Body JJ, Lappe JM, et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: recommendations for clinical practice. *Autoimmun Rev* 2010;**9**:709–715.
28. Haussler MR, Jurutka PW, Mizwicki M, Norman AW. Vitamin D receptor (VDR)-mediated actions of 1 $\alpha$ ,25(OH)<sub>2</sub>vitamin D<sub>3</sub>: genomic and non-genomic mechanisms. *Best Pract Res Clin Endocrinol Metab* 2011;**25**:543–559.
29. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006;**116**:2062–2072.
30. Panda DK, Miao D, Bolivar I, et al. Inactivation of the 25-hydroxyvitamin D 1 $\alpha$ -hydroxylase and vitamin D receptor demonstrates independent and interdependent effects of calcium and vitamin D on skeletal and mineral homeostasis. *J Biol Chem* 2004;**279**:16754–16766.
31. Goltzman D. Use of genetically modified mice to examine the skeletal anabolic activity of vitamin D. *J Steroid Biochem Mol Biol* 2007;**103**:587–591.
32. He W, Kang YS, Dai C, Liu Y. Blockade of Wnt/ $\beta$ -catenin signaling by paricalcitol ameliorates proteinuria and kidney injury. *J Am Soc Nephrol* 2011;**22**:90–103.
33. Al-Aly Z. Arterial calcification: a tumor necrosis factor- $\alpha$  mediated vascular Wnt-opathy. *Transl Res* 2008;**151**:233–239.
34. Haussler MR, Whitfield GK, Kaneko I, et al. Molecular mechanisms of vitamin D action. *Calcif Tissue Int* 2013;**92**:77–98.
35. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr* 2004;**79**:362–371.
36. Kaludjerovic J, Vieth R. Relationship between vitamin D during perinatal development and health. *J Midwifery Womens Health* 2010;**55**:550–560.
37. Girgis CM, Clifton-Bligh RJ, Hamrick MW, Holick MF, Gunton JE. The roles of vitamin D in skeletal muscle: form, function, and metabolism. *Endocr Rev* 2013;**34**:33–83.
38. Hamilton B. Vitamin D and human skeletal muscle. *Scand J Med Sci Sports* 2010;**20**:182–190.
39. Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. *Calcif Tissue Int* 2013;**92**:151–162.
40. Girgis CM, Clifton-Bligh RJ, Turner N, Lau SL, Gunton JE. Effects of vitamin D in skeletal muscle: falls, strength, athletic

- performance and insulin sensitivity. *Clin Endocrinol (Oxf)* 2014;**80**:169–181.
41. Srikuera R, Zhang X, Park-Sarge OK, Esser KA. VDR and CYP27B1 are expressed in C2C12 cells and regenerating skeletal muscle: potential role in suppression of myoblast proliferation. *Am J Physiol Cell Physiol* 2012;**303**:C396–C405.
  42. Sinha A, Hollingsworth KG, Ball S, Cheetham T. Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. *J Clin Endocrinol Metab* 2013;**98**:E509–E513.
  43. Floyd M, Ayyar DR, Barwick DD, Hudgson P, Weightman D. Myopathy in chronic renal failure. *Q J Med* 1974;**43**:509–524.
  44. Gilsanz V, Kremer A, Mo AO, Wren TA, Kremer R. Vitamin D status and its relation to muscle mass and muscle fat in young women. *J Clin Endocrinol Metab* 2010;**95**:1595–1601.
  45. Gagnon C, Lu ZX, Magliano DJ, et al. Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 years: results from a national, population-based prospective study (the Australian Diabetes, Obesity and Lifestyle study). *Diabetes Care* 2011;**34**:1133–1138.
  46. Siew ED, Pupim LB, Majchrzak KM, Shintani A, Flakoll PJ, Ikizler TA. Insulin resistance is associated with skeletal muscle protein breakdown in non-diabetic chronic hemodialysis patients. *Kidney Int* 2007;**71**:146–152.
  47. Glerup H, Mikkelsen K, Poulsen L, et al. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. *Calcif Tissue Int* 2000;**66**:419–424.
  48. Yoshikawa S, Nakamura T, Tanabe H, Imamura T. Osteomalacic myopathy. *Endocrinol Jpn* 1979;**26**:65–72.
  49. Tagliafico AS, Ameri P, Bovio M, et al. Relationship between fatty degeneration of thigh muscles and vitamin D status in the elderly: a preliminary MRI study. *AJR Am J Roentgenol* 2010;**194**:728–734.
  50. Ceglia L, Niramitmahapanya S, da Silva MM, et al. A randomized study on the effect of vitamin D<sub>3</sub> supplementation on skeletal muscle morphology and vitamin D receptor concentration in older women. *J Clin Endocrinol Metab* 2013;**98**:E1927–E1935.
  51. Sørensen OH, Lund B, Saltin B, et al. Myopathy in bone loss of ageing: improvement by treatment with 1 alpha-hydroxycholecalciferol and calcium. *Clin Sci (Lond)* 1979;**56**:157–161.
  52. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. *Cerebrovasc Dis* 2005;**20**:187–192.
  53. Cipriani C, Pepe J, Piemonte S, Colangelo L, Cilli M, Minisola S. Vitamin D and its relationship with obesity and muscle. *Int J Endocrinol* 2014;**2014**:841248.
  54. Wagatsuma A, Sakuma K. Vitamin D signaling in myogenesis: potential for treatment of sarcopenia. *Biomed Res Int* 2014;**2014**:121254.
  55. Visser M, Deeg DJ, Lips P. Longitudinal Aging Study Amsterdam. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab* 2003;**88**:5766–5772.
  56. Need AG, O'Loughlin PD, Morris HA, Coates PS, Horowitz M, Nordin BE. Vitamin D metabolites and calcium absorption in severe vitamin D deficiency. *J Bone Miner Res* 2008;**23**:1859–1863.
  57. Kawao N, Kaji H. Interactions between muscle tissues and bone metabolism. *J Cell Biochem* 2015;**116**:687–695.
  58. Garcia LA, King KK, Ferrini MG, Norris KC, Artaza JN. 1,25(OH)<sub>2</sub>vitamin D<sub>3</sub> stimulates myogenic differentiation by inhibiting cell proliferation and modulating the expression of promyogenic growth factors and myostatin in C2C12 skeletal muscle cells. *Endocrinology* 2011;**152**:2976–2986.
  59. White TA, LeBrasseur NK. Myostatin and sarcopenia: opportunities and challenges - a mini-review. *Gerontology* 2014;**60**:289–293.
  60. Elkasrawy MN, Hamrick MW. Myostatin (GDF-8) as a key factor linking muscle mass and bone structure. *J Musculoskeletal Neuronal Interact* 2010;**10**:56–63.
  61. Garcia LA, Ferrini MG, Norris KC, Artaza JN. 1,25(OH)<sub>2</sub>vitamin D<sub>3</sub> enhances myogenic differentiation by modulating the expression of key angiogenic growth factors and angiogenic inhibitors in C(2)C(12) skeletal muscle cells. *J Steroid Biochem Mol Biol* 2013;**133**:1–11.
  62. Yakar S, Rosen CJ, Beamer WG, et al. Circulating levels of IGF-1 directly regulate bone growth and density. *J Clin Invest* 2002;**110**:771–781.
  63. Street J, Bao M, deGuzman L, et al. Vascular endothelial growth factor stimulates bone repair by promoting angiogenesis and bone turnover. *Proc Natl Acad Sci U S A* 2002;**99**(15):9656–61.
  64. Barker T, Schneider ED, Dixon BM, Henriksen VT, Weaver LK. Supplemental vitamin D enhances the recovery in peak isometric force shortly after intense exercise. *Nutr Metab (Lond)* 2013;**10**:69.
  65. Tanaka K, Kanazawa I, Yamaguchi T, Yano S, Kaji H, Sugimoto T. Active vitamin D possesses beneficial effects on the interaction between muscle and bone. *Biochem Biophys Res Commun* 2014;**450**:482–487.
  66. Kaji H. Interaction between muscle and bone. *J Bone Metab* 2014;**21**:29–40.
  67. Ferron M, McKee MD, Levine RL, Ducy P, Karsenty G. Intermittent injections of osteocalcin improve glucose metabolism and prevent type 2 diabetes in mice. *Bone* 2012;**50**:568–575.
  68. Mera P, Laue K, Ferron M, et al. Osteocalcin signaling in myofibers is necessary and sufficient for optimum adaptation to exercise. *Cell Metab* 2016;**23**:1078–1092.
  69. Faul C, Amaral AP, Oskoue B, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011;**121**:4393–4408.
  70. Haroon M, FitzGerald O. Vitamin D deficiency: subclinical and clinical consequences on musculoskeletal health. *Curr Rheumatol Rep* 2012;**14**:286–293.
  71. Moranne O, Froissart M, Rossert J, et al. Timing of onset of CKD-related metabolic complications. *J Am Soc Nephrol* 2009;**20**:164–171.
  72. Jacob AI, Sallman A, Santiz Z, Hollis BW. Defective photoproduction of cholecalciferol in normal and uremic humans. *J Nutr* 1984;**114**:1313–1319.
  73. Ureña-Torres P, Metzger M, Haymann JP, et al. Association of kidney function, vitamin D deficiency, and circulating markers of mineral and bone disorders in CKD. *Am J Kidney Dis* 2011;**58**:544–553.
  74. Christensen EI, Willnow TE. Essential role of megalin in renal proximal tubule for vitamin homeostasis. *J Am Soc Nephrol* 1999;**10**:2224–2236.
  75. Sato KA, Gray RW, Lemann J Jr. Urinary excretion of 25-hydroxyvitamin D in health and the nephrotic syndrome. *J Lab Clin Med* 1982;**99**:325–330.
  76. Christakos S, Ajibade DV, Dhawan P, Fechner AJ, Mady LJ. Vitamin D: metabolism. *Endocrinol Metab Clin North Am* 2010;**39**:243–253.
  77. Shimada T, Kakitani M, Yamazaki Y, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. *J Clin Invest* 2004;**113**:561–568.
  78. Fukuda N, Tanaka H, Tominaga Y, Fukagawa M, Kurokawa K, Seino Y. Decreased 1,25-dihydroxyvitamin D<sub>3</sub> receptor density is associated with a more severe form of parathyroid hyperplasia in chronic uremic patients. *J Clin Invest* 1993;**92**:1436–1443.
  79. Hsu CH, Patel SR. Altered vitamin D metabolism and receptor interaction with the target genes in renal failure: calcitriol receptor interaction with its target gene in renal failure. *Curr Opin Nephrol Hypertens* 1995;**4**:302–306.
  80. Patel SR, Ke HQ, Vanholder R, Koenig RJ, Hsu CH. Inhibition of calcitriol receptor binding to vitamin D response elements by uremic toxins. *J Clin Invest* 1995;**96**:50–59.
  81. Oury F, Sumara G, Sumara O, et al. Endocrine regulation of male fertility by the skeleton. *Cell* 2011;**144**:796–809.
  82. Cejka D, Herberth J, Branscum AJ, et al. Sclerostin and Dickkopf-1 in renal osteodystrophy. *Clin J Am Soc Nephrol* 2011;**6**:877–882.
  83. Sabbagh Y, Gracioli FG, O'Brien S, et al. Repression of osteocyte Wnt/β-catenin signaling is an early event in the progression of renal osteodystrophy. *J Bone Miner Res* 2012;**27**:1757–1772.
  84. Evenepoel P, D'Haese P, Brandenburg V. Sclerostin and DKK1: new players in renal bone and vascular disease. *Kidney Int* 2015;**88**:235–240.

85. Ding N, Yu RT, Subramaniam N, et al. A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response. *Cell* 2013;**153**:601–613.
86. Ureña P, Bernard-Poenaru O, Ostertag A, et al. Bone mineral density, biochemical markers and skeletal fractures in haemodialysis patients. *Nephrol Dial Transplant* 2003;**18**:2325–2331.
87. Riggs BL, Wahner HW, Seeman E, et al. Changes in bone mineral density of the proximal femur and spine with aging. Differences between the postmenopausal and senile osteoporosis syndromes. *J Clin Invest* 1982;**70**:716–723.
88. Ott SM. Review article: bone density in patients with chronic kidney disease stages 4–5. *Nephrology (Carlton)* 2009;**14**:395–403.
89. Yencheck RH, Ix JH, Shlipak MG, et al. Health, aging, and body composition study. Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* 2012;**7**:1130–1136.
90. Limori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study. *Nephrol Dial Transplant* 2012;**27**:345–351.
91. Naylor KL, Leslie WD, Hodsman AB, Rush DN, Garg AX. FRAX predicts fracture risk in kidney transplant recipients. *Transplantation* 2014;**97**:940–945.
92. Nickolas TL. The utility of circulating markers to predict bone loss across the CKD spectrum. *Clin J Am Soc Nephrol* 2014;**9**:1160–1162.
93. Miller PD. Bone disease in CKD: a focus on osteoporosis diagnosis and management. *Am J Kidney Dis* 2014;**64**:290–304.
94. www.kdigo.org
95. Ketteler M, Elder GJ, Evenepoel P, et al. Revisiting KDIGO clinical practice guideline on chronic kidney disease-mineral and bone disorder: a commentary from a Kidney Disease: Improving Global Outcomes controversies conference. *Kidney Int* 2015;**87**:502–528.
96. Goldenstein PT, Jamal SA, Moysés RM. Fractures in chronic kidney disease: pursuing the best screening and management. *Curr Opin Nephrol Hypertens* 2015;**24**:317–323.
97. Moe S, Drüeke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006;**69**:1945–1953.
98. Torres PU, Bover J, Mazzaferro S, de Vernejoul MC, Cohen-Solal M. When, how, and why a bone biopsy should be performed in patients with chronic kidney disease. *Semin Nephrol* 2014;**34**:612–625.
99. Campistol JM. Uremic myopathy. *Kidney Int* 2002;**62**:1901–1913.
100. Krishnan AV, Kiernan MC. Neurological complications of chronic kidney disease. *Nat Rev Neurol* 2009;**5**:542–551.
101. Patel SS, Molnar MZ, Tayek JA, et al. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. *J Cachexia Sarcopenia Muscle* 2013;**4**:19–29.
102. Fahal IH. Uraemic sarcopenia: aetiology and implications. *Nephrology Dialysis Transplantation* 2014;**29**:1655–1665.
103. Diesel W, Emms M, Knight BK, et al. Morphologic features of the myopathy associated with chronic renal failure. *Am J Kidney Dis* 1993;**22**:677–684.
104. Fahal IH, Bell GM, Bone JM, Edwards RH. Physiological abnormalities of skeletal muscle in dialysis patients. *Nephrol Dial Transplant* 1997;**12**:119–127.
105. Souza VA, Dd O, Mansur HN, Fernandes NM, Bastos MG. Sarcopenia in chronic kidney disease. *J Bras Nefrol* 2015;**37**:98–105.
106. Carrero JJ, Johansen KL, Lindholm B, et al. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. *Kidney Int* 2016;**90**:53–66.
107. Kaizu Y, Ohkawa S, Odamakami M, et al. Association between inflammatory mediators and muscle mass in long-term hemodialysis patients. *Am J Kidney Dis* 2003;**42**:295–302.
108. Isovayna N, Qureshi AR, Avesani CM, et al. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients. *Clin J Am Soc Nephrol* 2014;**9**:1720–1728.
109. Stenvinkel P, Alvestrand A. Inflammation in end-stage renal disease: sources, consequences, and therapy. *Semin Dial* 2002;**15**:329–337.
110. Guttridge DC, Mayo MW, Madrid LV, Wang CY, Baldwin AS Jr. NF-kappaB-induced loss of MyoD messenger RNA: possible role in muscle decay and cachexia. *Science* 2000;**289**:2363–2366.
111. Carrero JJ, Stenvinkel P, Cuppari L, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr* 2013;**23**:77–90.
112. Langen RC, Schols AM, Kelders MC, Wouters EF, Janssen-Heininger YM. Inflammatory cytokines inhibit myogenic differentiation through activation of nuclear factor-kappaB. *FASEB J* 2001;**15**:1169–1180.
113. Mitch WE, Du J, Bailey JL, Price SR. Mechanisms causing muscle proteolysis in uremia: the influence of insulin and cytokines. *Miner Electrolyte Metab* 1999;**25**:216–219.
114. Zhang L, Du J, Hu Z, et al. IL-6 and serum amyloid A synergy mediates angiotensin II-induced muscle wasting. *J Am Soc Nephrol* 2009;**20**:604–612.
115. Mitch WE, Goldberg AL. Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. *N Engl J Med* 1996;**335**:1897–1905.
116. Coen G, Mantella D, Manni M, et al. 25-hydroxyvitamin D levels and bone histomorphometry in hemodialysis renal osteodystrophy. *Kidney Int* 2005;**68**:1840–1848.
117. Ambrus C, Almási C, Berta K, et al. Vitamin D insufficiency and bone fractures in patients on maintenance hemodialysis. *Int Urol Nephrol* 2011;**43**:475–482.
118. Elder GJ, Mackun K. 25-Hydroxyvitamin D deficiency and diabetes predict reduced BMD in patients with chronic kidney disease. *J Bone Miner Res* 2006;**21**:1778–1784.
119. Muci I, Almási C, Deák G, et al. Serum 25 (OH)-vitamin D levels and bone metabolism in patients on maintenance hemodialysis. *Clin Nephrol* 2005;**64**:288–294.
120. Ghazali A, Fardellone P, Pruna A, et al. Is low plasma 25-(OH)vitamin D a major risk factor for hyperparathyroidism and Looser's zones independent of calcitriol? *Kidney Int* 1999;**55**:2169–2177.
121. Brunerová L, Ronová P, Verešová J, et al. Osteoporosis and impaired trabecular bone score in hemodialysis patients. *Kidney Blood Press Res* 2016;**41**:345–354.
122. Moorthi RN, Moe SM. Recent advances in the noninvasive diagnosis of renal osteodystrophy. *Kidney Int* 2013;**84**:886–894.
123. Leonard MB. A structural approach to skeletal fragility in chronic kidney disease. *Semin Nephrol* 2009;**29**:133–143.
124. Malluche HH, Porter DS, Pienkowski D. Evaluating bone quality in patients with chronic kidney disease. *Nat Rev Nephrol* 2013;**9**:671–680.
125. Dhesi JK, Bearne LM, Moniz C, et al. Neuromuscular and psychomotor function in elderly subjects who fall and the relationship with vitamin D status. *J Bone Miner Res* 2002;**17**:891–897.
126. Janssen HC, Samson MM, Verhaar HJ. Vitamin D deficiency, muscle function, and falls in elderly people. *Am J Clin Nutr* 2002;**75**:611–615.
127. Ensrud KE, Blackwell TL, Cauley JA, et al. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. *J Am Geriatr Soc* 2011;**59**:101–106.
128. Gordon PL, Doyle JW, Johansen KL. Association of 1,25-dihydroxyvitamin D levels with physical performance and thigh muscle cross-sectional area in chronic kidney disease stage 3 and 4. *J Ren Nutr* 2012;**22**:423–433.
129. Zahed N, Chehrizi S, Falaknasi K. The evaluation of relationship between vitamin D and muscle power by micro manual muscle tester in end-stage renal disease patients. *Saudi J Kidney Dis Transpl* 2014;**25**:998–1003.
130. Palmer SC, McGregor DO, Macaskill P, Craig JC, Elder GJ, Strippoli GF. Meta-analysis: vitamin D compounds in chronic kidney disease. *Ann Intern Med* 2007;**147**:840–853.
131. Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic

- kidney disease requiring dialysis. *Cochrane Database Syst Rev* 2009;**4**: CD005633.
132. Kandula P, Dobre M, Schold JD, Schreiber MJ Jr, Mehrotra R, Navaneethan SD. Vitamin D supplementation in chronic kidney disease: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Clin J Am Soc Nephrol* 2011;**6**:50–62.
  133. Nigwekar SU, Tamez H, Thadhani RI. Vitamin D and chronic kidney disease-mineral bone disease (CKD-MBD). *Bonekey Rep* 2014;**3**:498.
  134. Fournier A, Bordier P, Guerin J, et al. Comparison of 1 alpha-hydroxycholecalciferol and 25-hydroxycholecalciferol in the treatment of renal osteodystrophy: greater effect of 25-hydroxycholecalciferol on bone mineralization. *Kidney Int* 1979;**15**:196–204.
  135. Memmos DE, Eastwood JB, Talner LB, et al. Double-blind trial of oral 1,25-dihydroxy vitamin D3 versus placebo in asymptomatic hyperparathyroidism in patients receiving maintenance haemodialysis. *Br Med J (Clin Res Ed)* 1981;**282**:1919–1924.
  136. Morinière P, Fournier A, Leflon A, et al. Comparison of 1 alpha-OH-vitamin D3 and high doses of calcium carbonate for the control of hyperparathyroidism and hyperaluminemia in patients on maintenance dialysis. *Nephron* 1985;**39**:309–315.
  137. Baker LR, Muir JW, Sharman VL, et al. Controlled trial of calcitriol in hemodialysis patients. *Clin Nephrol* 1986;**26**:185–191.
  138. Baker LR, Abrams L, Roe CJ, et al. 1,25 (OH)2D3 administration in moderate renal failure: a prospective double-blind trial. *Kidney Int* 1989;**35**:661–669.
  139. Llach F, Keshav G, Goldblat MV, et al. Suppression of parathyroid hormone secretion in hemodialysis patients by a novel vitamin D analogue: 19-nor-1,25-dihydroxyvitamin D2. *Am J Kidney Dis* 1998;**32**:S48–S54.
  140. Watson AR, Kooh SW, Tam CS, Reilly BJ, Balfe JW, Vieth R. Renal osteodystrophy in children on CAPD: a prospective trial of 1-alpha-hydroxycholecalciferol therapy. *Child Nephrol Urol* 1988-1989;**9**:220–227.
  141. Delmez JA, Kelber J, Norwood KY, Giles KS, Slatopolsky E. A controlled trial of the early treatment of secondary hyperparathyroidism with calcitriol in hemodialysis patients. *Clin Nephrol* 2000;**54**:301–308.
  142. Mager DR, Jackson ST, Hoffmann MR, Jindal K, Senior PA. Vitamin D3 supplementation, bone health and quality of life in adults with diabetes and chronic kidney disease: Results of an open label randomized clinical trial. *Clin Nutr* 2016; pii: S0261-5614(16)30108-X.
  143. Theodoratou E, Tzoulaki I, Zgaga L, Ioannidis JP. Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials. *BMJ* 2014;**348**:g2035.
  144. Mehrotra A, Leung WY, Joson T. Nutritional vitamin D supplementation and health-related outcomes in hemodialysis patients: a protocol for a systematic review and meta-analysis. *Syst Rev* 2015;**4**:13.
  145. Murad MH, Elamin KB, Abu Elnour NO, et al. Clinical review: the effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;**96**:2997–3006.
  146. Morley JE, Argiles JM, Evans WJ, et al. Nutritional recommendations for the management of sarcopenia. *J Am Med Dir Assoc* 2010;**11**:391–396.
  147. Kalantar-Zadeh K, Kovesdy CP. Clinical outcomes with active versus nutritional vitamin D compounds in chronic kidney disease. *Clin J Am Soc Nephrol* 2009;**4**:1529–1539.
  148. Miskulin DC, Majchrzak K, Tighiouart H, et al. Ergocalciferol supplementation in hemodialysis patients with vitamin D deficiency: a randomized clinical trial. *J Am Soc Nephrol* 2016;**27**:1801–1810.
  149. de Boer IH, Sachs M, Hoofnagle AN, et al. Paricalcitol does not improve glucose metabolism in patients with stage 3-4 chronic kidney disease. *Kidney Int* 2013;**83**:323–330.
  150. Blair D, Byham-Gray L, Lewis E, McCaffrey S. Prevalence of vitamin D [25(OH)D] deficiency and effects of supplementation with ergocalciferol (vitamin D2) in stage 5 chronic kidney disease patients. *J Ren Nutr* 2008;**18**:375–382.
  151. Seida JC, Mitri J, Colmers IN, et al. Clinical review: effect of vitamin D3 supplementation on improving glucose homeostasis and preventing diabetes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2014;**99**:3551–3560.
  152. Taskapan H, Baysal O, Karahan D, Durmus B, Altay Z, Ulutas O. Vitamin D and muscle strength, functional ability and balance in peritoneal dialysis patients with vitamin D deficiency. *Clin Nephrol* 2011;**76**:110–116.
  153. Bouillon R, Van Schoor NM, Gielen E, et al. Optimal vitamin D status: a critical analysis on the basis of evidence-based medicine. *J Clin Endocrinol Metab* 2013;**98**:E1283–E1304.
  154. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2009; S1–130.
  155. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;**96**:1911–1930.
  156. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. *Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium: Dietary Reference Intakes for Calcium and Vitamin D*. Washington (DC): National Academies Press (US); 2011. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK56070/>.
  157. WHO Scientific Group on the Prevention and Management of Osteoporosis 2003. Prevention and management of osteoporosis: report of a WHO scientific group. Geneva: World Health Organization. [http://apps.who.int/iris/bitstream/10665/42841/1/WHO\\_TRS\\_921.pdf](http://apps.who.int/iris/bitstream/10665/42841/1/WHO_TRS_921.pdf) (last accessed on 26th March 2017).
  158. Need AG, O'Loughlin PD, Morris HA, Coates PS, Horowitz M, Nordin BE. Vitamin D metabolites and calcium absorption in severe vitamin D deficiency. *J Bone Miner Res* 2008;**23**:1859–1863.
  159. Spiegel DM, Brady K. Calcium balance in normal individuals and in patients with chronic kidney disease on low and high calcium diets. *Kidney Int* 2012;**81**:1116–1122.
  160. Vieth R, Ladak Y, Walfish PG. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *J Clin Endocrinol Metab* 2003;**88**:185–191.
  161. González EA, Sachdeva A, Oliver DA, Martin KJ. Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. *Am J Nephrol* 2004;**24**:503–510.
  162. Molina P, Górriz JL, Molina MD, et al. The effect of cholecalciferol for lowering albuminuria in chronic kidney disease: a prospective controlled study. *Nephrol Dial Transplant* 2014;**29**:97–109.
  163. Metzger M, Houillier P, Gauci C, et al. Relation between circulating levels of 25 (OH) vitamin D and parathyroid hormone in chronic kidney disease: quest for a threshold. *J Clin Endocrinol Metab* 2013;**98**:2922–2928.
  164. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997;**337**:670–676.
  165. Chapuy MC, Pampfili R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalys II study. *Osteoporos Int* 2002;**13**:257–264.
  166. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003;**326**:469.
  167. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA* 2010;**303**:1815–1822.

168. Wolf M, Shah A, Gutierrez O, et al. Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney Int* 2007;**72**:1004–1013.
169. Barreto DV, Barreto FC, Liabeuf S, et al. Vitamin D affects survival independently of vascular calcification in chronic kidney disease. *Clin J Am Soc Nephrol* 2009;**4**:1128–1135.
170. Ravani P, Malberti F, Tripepi G, Pecchini P, Cutrupi S, Pizzini P, Mallamaci F, Zoccali C. Vitamin D levels and patient outcome in chronic kidney disease. *Kidney Int* 2009;**75**:88–95.
171. Molina P, Górriz JL, Molina MD, et al. What is the optimal level of vitamin D in non-dialysis chronic kidney disease population? *World J Nephrol* 2016;**5**:471–481.
172. Dror Y, Giveon SM, Hoshen M, Feldhamer I, Balicer RD, Feldman BS. Vitamin D levels for preventing acute coronary syndrome and mortality: evidence of a nonlinear association. *J Clin Endocrinol Metab* 2013;**98**:2160–2167.
173. Stolzenberg-Solomon RZ, Vieth R, Azad A, et al. A prospective nested case-control study of vitamin D status and pancreatic cancer risk in male smokers. *Cancer Res* 2006;**66**:10213–10219.
174. Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, et al. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol* 2010;**172**:81–93.
175. Ahn J, Peters U, Albanes D, et al. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J Natl Cancer Inst* 2008;**100**:796.
176. Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D deficiency - is there really a pandemic? *N Engl J Med* 2016;**375**:1817–1820.
177. Drüeke TB, Massy ZA. Role of vitamin D in vascular calcification: bad guy or good guy? *Nephrol Dial Transplant* 2012;**27**:1704–1707.
178. Cheng S, Coyne D. Vitamin D and outcomes in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2007;**16**:77–82.
179. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle *J Cachexia Sarcopenia Muscle*. 2015;**4**:315–316.