Citation: BoneKEy Reports **3**, Article number: 498 (2014) | doi:10.1038/bonekey.2013.232

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REVIEW

Vitamin D and chronic kidney disease–mineral bone disease (CKD–MBD)

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Chronic kidney disease (CKD) is a modern day epidemic and has significant morbidity and mortality implications. Mineral and bone disorders are common in CKD and are now collectively referred to as CKD– mineral and bone disorder (MBD). These abnormalities begin to appear even in early stages of CKD and contribute to the pathogenesis of renal osteodystrophy. Alteration in vitamin D metabolism is one of the key features of CKD–MBD that has major clinical and research implications. This review focuses on biology, epidemiology and management aspects of these alterations in vitamin D metabolism as they relate to skeletal aspects of CKD–MBD in adult humans.

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Introduction

Chronic kidney disease (CKD) is a modern day global epidemic and it is now recognized as a public health issue.[1] Disturbance in mineral and bone metabolism accompanied by soft tissue and vascular calcification is one of the most common and important consequences of CKD development and progression. This systemic disorder is now referred to as CKD–mineral and bone disorder (CKD–MBD).[2] Renal osteodystrophy (previously also referred to as renal rickets) is a bone disease characterized by deranged bone morphology in patients with CKD. It is now considered as a component of CKD–MBD. Although renal osteodystrophy is typically seen in advanced kidney failure, other features of CKD–MBD begin to develop at earlier stages of CKD[3] and contribute to the pathogenesis of renal osteodystrophy. Alteration in vitamin D metabolism is one of the key features of CKD–MBD that has major clinical and research implications. This review focuses on biology, epidemiology and management aspects of these alterations in vitamin D metabolism as they relate to skeletal aspects of CKD–MBD in adult humans.

CKD: Definition, Classification and Epidemiology

CKD is a defined as a disease characterized by alterations in either kidney structure or function or both for a minimum of 3 months duration.[4] It can be caused by a variety of conditions and this introduces significant heterogeneity in terms of how patients with CKD may present to their clinicians. However, irrespective of the etiology of CKD, patients with mild CKD are mostly asymptomatic and symptoms are generally related to CKD complications that are observed in the late stages. The major complications related to CKD include cardiovascular disease, anemia, infectious complications, neuropathy and abnormalities related to mineral bone metabolism.[5]

According to the National Kidney Foundation criteria, CKD has been classified into five stages with stage 1 being the earliest or mildest CKD state and stage 5 being the most severe CKD stage (**Table 1**).[6] This classification takes into account both kidney function and kidney damage. Glomerular filtration rate (GFR), either directly measured by computing urinary clearance of filtration marker such as inulin or estimated by using serum marker such as creatinine) is the most commonly used parameter to assess kidney function. At least two GFR measurements or estimations must be taken no less than 90 days apart before the patient is classified into one of the stages of CKD. Although kidney damage may present with GFR impairment, many disorders that cause CKD may have preserved GFR especially in early stages but patients may have other markers of kidney damage such as albuminuria, proteinuria, hematuria or structural abnormalities in kidney. These abnormalities, especially albuminuria, have prognostic implications and thus even patients with normal GFR but with other evidence of kidney damage (such as albuminuria) are considered to have CKD.[7,8]

CKD has major prognostic implications.[9] There is abundant literature that reports increased all-cause mortality in patients with CKD compared with those without CKD. Most of the increase in mortality is attributed to increased cardiovascular events.[10] CKD is characterized by increased cardiovascular risk partly due to increased prevalence of traditional cardiovascular risk factors such as hypertension and diabetes mellitus and also due to direct increased cardiovascular risk from non-traditional

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Received 26 July 2013; accepted 4 September 2013; published online 5 February 2014

Table 1 Stages of CKD[4]

	Description	*Criteria*[a]
Stage 1	Kidney damage with normal or increased GFR	GFR $\geqslant 90$ ml min^{-1} but with abnormal urine findings (albuminuria, hematuria) or structural kidney abnormalities
Stage 2	Kidney damage with mild reduction in GFR	GFR 60–89 ml min^{-1}
Stage 3	Moderate reduction in GFR	GFR 30–59 ml min^{-1}
Stage 4	Severe reduction in GFR	GFR 15–29 ml min^{-1}
Stage 5	Kidney failure	GFR <15 ml min^{-1} or requirement of renal replacement therapy

[a]Alterations in either kidney structure or function or both must be present for a minimum of 3 months duration.

cardiovascular risk factors such as anemia, malnutrition-inflammation syndrome, retention of uremic toxins and CKD–MBD.[11,12] CKD patients are also at high risk to develop end-stage renal disease (ESRD) and risks for all-cause as well as cardiovascular mortality are even higher for ESRD compared with CKD patients.[13]

CKD–MBD: Pathogenesis and Role of Vitamin D

In addition to effects on mortality and progression to ESRD, CKD is marked by alterations in mineral bone metabolism that are collectively referred to as CKD–MBD (**Figure 1**).[2] These alterations include (1) biochemical abnormalities in calcium, phosphorous, parathyroid hormone (PTH), vitamin D and fibroblast growth factor-23 (FGF-23), (2) changes in bone morphology such as bone volume, bone turnover and bone mineralization and (3) calcification of soft tissue and blood vessels.[2] Current understanding of CKD–MBD suggests that calcium, phosphorous, PTH, FGF-23 (a phosphatonin hormone that is elevated in CKD to promote renal phosphate excretion) and vitamin D are the key players in regulating mineral and bone metabolism.[14] These factors are inter-related and their major target organs include parathyroid gland, kidneys, bone and intestinal tract. The classic biochemical abnormalities in CKD–MBD are hypocalcemia, hyperphosphatemia, hyperparathyroidism, hypovitaminosis D and elevated FGF-23; however, significant variations especially in serum calcium are not uncommon.[15] Bone abnormalities in CKD include high bone turnover disease related to secondary hyperparathyroidism (referred to as osteitis fibrosa cystica), low turnover disease (referred to as adynamic bone disease), osteomalacia (low turnover disease accompanied by undermineralized bone tissue) and mixed disease where features of both high and low bone turnover disease are present.[16,17] Patients with these bone abnormalities may be asymptomatic or may develop symptoms related to bone pain or fractures. Although association with bone fractures in earlier stages of CKD has been inconsistent across studies,[18–20] dialysis-dependent ESRD patients have over three to four times increased risk of vertebral and hip fractures compared with general population even after adjustment for age, gender and race.[21,22] Factors related to CKD–MBD including elevated PTH, vitamin D deficiency, bone remodeling, increased bone fragility and micro-structural

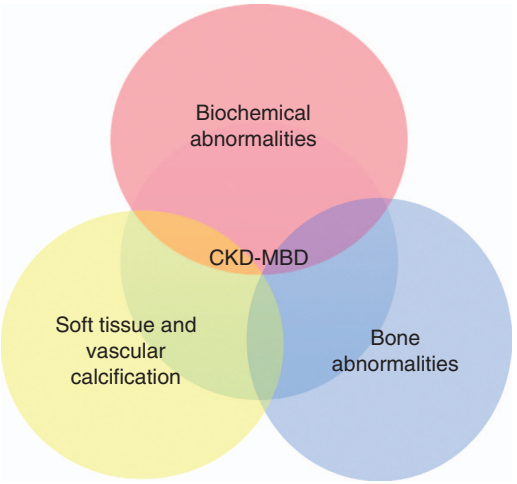

Figure 1 Chronic kidney disease–mineral and bone disorder.

Table 2 Reasons for altered vitamin D metabolism in CKD[25]

Calcidiol deficiency	Reduced sun exposure, reduced skin synthesis, reduced ingestion of foods rich in vitamin D, loss of DBP with proteinuria
Calcitriol deficiency	Reduced calcidiol availability, reduced renal 1-α hydroxylase availability, down regulation of renal 1-α hydroxylase from hyperphosphatemia and FGF-23, reduced endocytotic uptake by megalin, increased degradation of calcitriol by PTH and FGF-23
Calcitriol resistance	Loss of VDR in parathyroid glands, impaired binding of active vitamin D to VDR and impaired binding of vitamin D–VDR complex to the VDR element

Adpated with permission from Nigwekar *et al.*[25]

deterioration along with increased fall risk are reported to explain this increased fracture risk in ESRD patients.[23,24]

As well described in the literature, CKD is characterized by low 25(OH) vitamin D (calcidiol), low 1,25$(OH)_2$ vitamin D (calcitriol) as well as vitamin D resistance.[25,26] Key mechanisms for these changes are summarized in **Table 2**. Alterations related to vitamin D metabolism, hyperphosphatemia and hypocalcemia lead to increased synthesis and/or secretion of PTH leading to secondary hyperparathyroidism that sets in as soon as GFR falls below 60 ml min^{-i} (**Figure 2**).[15,27] Secretion of FGF-23 from osteocytes is increased in CKD and FGF-23 has been shown to reduce PTH expression via its action through Klotho-FGFR1c receptor complex.[28,29] However, down-regulation of this complex likely explains why despite increased FGF-23, PTH levels are not reduced in CKD.[30]

As early as stage 2 of CKD, serum 25(OH) vitamin D levels begin to decline.[31] Reduced sun exposure,[32] impaired skin synthesis of cholecalciferol due to renal disease,[33] hyperpigmentation seen in late CKD stages[34] and dietary restrictions that are commonly advised to CKD patients contribute to high prevalence of vitamin D deficiency. In addition, uremia impairs intestinal absorption of dietary and supplemental vitamin D,[35] and in CKD patients with severe proteinuria there are high urinary losses of vitamin D binding protein (DBP) leading to increased renal loss of vitamin D metabolites.[36,37]

In addition to reasons for calcidiol deficiency in CKD patients described above, CKD is also marked by calcitriol deficiency. Availability of renal 1-α hydroxylase, a key enzyme involved in

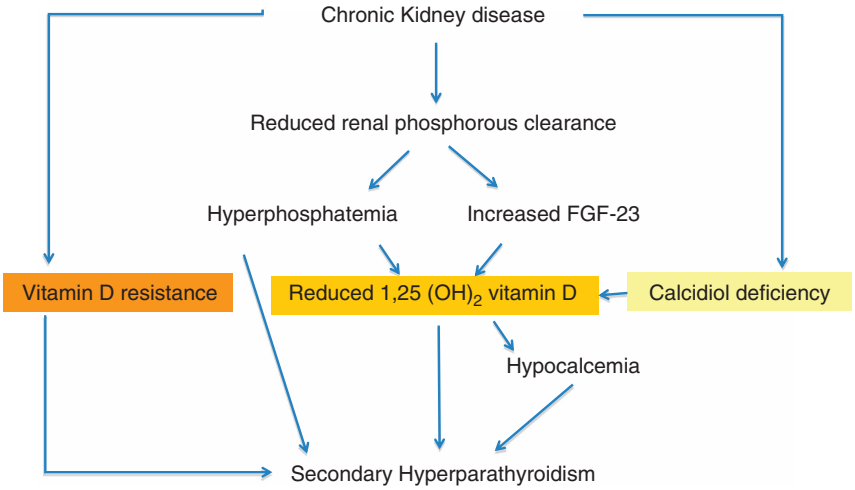

Figure 2 Role of vitamin D in the development of secondary hyperparathyroidism in CKD.

the production of calcitriol from calcidiol, is reduced as the renal mass reduces.[38] Renal 1-α hydroxylase is highly dependent on substrate calcidiol in patients with CKD and reduced availability of calcidiol substrate has an important role in calcitriol deficiency in CKD patients.[25,39] In addition, there are a number of factors that are responsible for downregulation of renal 1-α hydroxylase in CKD. These include hyperphosphatemia, FGF-23, acidosis, hyperuricemia and uremia.[40–43] Although, the enzyme 1-α hydroxylase is also present in extra-renal tissues, effects of CKD on this enzyme in these locations are unclear.[44] Expression of renal tubular receptor, megalin that is normally responsible for uptake of calcidiol–DBP complex from the glomerular filtrate is reduced in CKD and reduced filtration of calcidiol–DBP complex in the setting of reduced GFR further limits its delivery and uptake by renal tubular receptors.[45,46] Furthermore, secondary hyperparathyroidism and elevated FGF-23 lead to degradation of 25(OH) vitamin D by promoting the enzyme 24-hydroxylase to form 24,25-dihydroxy vitamin D.[47]

CKD is also characterized by vitamin D resistance as there is a progressive loss of vitamin D receptor (VDR) in the parathyroid gland.[48] Low levels of active vitamin D lead to impairments in the binding of active vitamin D to VDR as well as in the binding of the vitamin D–VDR complex to the vitamin D response element.[49,50]

Prevalence of Vitamin D Deficiency in CKD

There is no consensus on how to define vitamin D deficiency and this introduces significant difficulties in conducting epidemiological studies in this field.[25] The most widely accepted definition for vitamin D deficiency includes circulating serum 25 (OH) vitamin D level below 20 ng ml^{-1} and patients with 25 (OH) vitamin D levels between 20 and 30 ng ml^{-1} are referred to as vitamin D insufficient. The prevalence of vitamin D deficiency in the CKD population has been described to range between 70 and 80%.[51] In a cross-sectional analysis of 825 consecutive incident hemodialysis patients from 569 unique centers in the United States, Wolf *et al.* reported that over 3/4th of the cohort was vitamin D deficient (serum 25(OH) vitamin D <30 ng ml^{-1}) and $\sim$1/5th of the cohort was severely deficient (serum 25(OH) vitamin D <10 ng ml^{-1}).[51] LaClair *et al.* performed a cross-sectional study in stage 3 and 4 CKD patients derived from diverse geographical areas from the United States and reported that only 29 and 17% of patients with stage 3 and stage 4 CKD had adequate vitamin D status, respectively.[52] They used stricter definition of vitamin D deficiency as 25(OH) vitamin D levels <10 ng ml^{-1}, and insufficiency was defined as levels of 10–30 ng ml^{-1}. Vitamin D deficiency is also prevalent in milder CKD (stages 1 and 2),[53,54] and vitamin D deficiency has been described to begin even before other abnormalities in mineral bone metabolism such as hyperphosphatemia become detectable.[3]

Vitamin D Deficiency and Skeletal Outcomes in CKD

Vitamin D status is generally measured in CKD patients using 25 (OH) vitamin D levels as 1,25 $(OH)_2$ vitamin D levels are not a reliable measure of vitamin D status. Despite the central biological role of vitamin D in CKD–MBD, studies examining association between 25 (OH) vitamin D levels and biochemical abnormalities in calcium, phosphorous and PTH in CKD have not shown consistent association between serum 25 (OH) vitamin D levels and elevated serum PTH or lower serum calcium.[37,55] One possible explanation for this is based on free hormone hypothesis as 25 (OH) vitamin D is a highly protein bound hormone and <1% of circulating 25 (OH) vitamin D exists in free form.[56] The majority (85–90%) of 25(OH) vitamin D is tightly bound to DBP and a smaller amount (10–15%) is loosely bound to albumin.[57] Bioavailable 25 (OH) vitamin D (albumin-bound hormone combined with the free fraction) levels have been shown to have a better association with serum calcium and PTH than total 25 (OH) vitamin D in ESRD patients by Bhan *et al.*[57] Corresponding data in CKD are lacking and remain under investigation.

Studies of the association between 25(OH) vitamin D levels, bone morphology, bone mineral density and bone fractures in CKD and/or ESRD are limited in number but very informative. Coen *et al.* conducted a retrospective study of 104 patients on maintenance hemodialysis. Patients (61 males, 43 females; mean age 52.9 $\pm$ 11.7 years) were not on any vitamin D supplements and underwent transiliac bone biopsy for histologic, histomorphometric and histodynamic evaluation.[58] Patients

with serum 25-OHD levels $\leqslant 15\,ng\,ml^{-1}$ had lower bone formation rate and trabecular mineralization surface independent of PTH and calcitriol levels indicating an important role that 25 (OH) vitamin D has in bone health in ESRD patients. Ambrus *et al.* retrospectively examined the association between fracture and vitamin D status in 130 patients on maintenance hemodialysis.[24] Patients with fractures had significantly lower 25(OH) vitamin D levels compared with patients without fractures and lower vitamin D levels were independently associated with increased fracture risk in a multivariable analysis (OR 11.22, 95% confidence interval 1.33–94.82). The same investigators also described low 25 (OH) vitamin D levels associated with reduced bone mineral bone density in maintenance hemodialysis patients. In another cross-sectional study by Mucsi *et al.*[59], 25 (OH) vitamin D levels were positively associated with radial bone mineral density in maintenance hemodialysis patients ($r = 0.424$, $p < 0.01$) and with significant attenuation on quantitative bone ultrasound (beta = 0.262, $P < 0.05$). Lower 25 (OH) vitamin D levels have been shown to be associated with increased subperiosteal resorption and also with reduced bone mineral density at wrist and lumbar spine in ESRD patients.[60,61]

Vitamin D Treatment and Skeletal Outcomes in CKD

Vitamin D compounds in the setting of renal disease have been reported as early as the 1950s.[62] One of the earliest reports on the role of 25(OH) vitamin D in ESRD patients was published by Fournier *et al.* over three decades ago.[63] In this study, bone matrix mineralization evaluated by histomorphometry, increased in patients receiving 25(OH) vitamin D, whereas it did not change significantly in patients receiving calcitriol. However, this study was not a randomized trial and thus had limitations on its internal validity. The field has moved forward since then and multiple randomized trials have been conducted to examine the role of active vitamin D compounds as well as nutritional vitamin D supplements in CKD and ESRD. Many of these trials were not specifically designed to evaluate patient centered skeletal outcomes and had multiple methodological limitations including small sample size and short duration of follow-up.[64]

Palmer *et al.*[64] examined the evidence from randomized controlled trials regarding the efficacy of vitamin D compounds in CKD and ESRD patients. These investigators conducted a comprehensive literature search and included trials that investigated different vitamin D compounds including calcitriol, alfacalcidol, doxerecalciferol, maxacalcitol, paricalcitol and falecalcitriol. They noted significant variation in PTH lowering effects of vitamin D compounds with newer vitamin D compounds (doxerecalciferol, maxacalcitol, paricalcitol and falecalcitriol) significantly lowering PTH (mean reduction $98\,pg\,ml^{-1}$) compared with placebo (3 studies, 163 patients)[65–67] but no significant PTH reduction was noted with established vitamin D compounds such as calcitriol, alfacalcidol (6 studies, 187 patients).[68–73] In this meta-analysis, established vitamin D compounds were associated with increased serum calcium (mean increase $0.2\,mg\,dl^{-1}$) and serum phosphorous (mean increase $0.46\,mg\,dl^{-1}$). Several studies incorporated in this meta-analysis, however, in fact intended to raise serum calcium,[74] therefore suggesting certain therapies adversely affected serum calcium when in fact the intention was to raise serum calcium seems counterintuitive. In terms of patient-level skeletal outcomes such as fractures, bone pain, requirement of surgical parathyroidectomy, no benefit was noted from the administration of vitamin D compounds (**Table 3**).[68,71,75–77] However, most studies had inadequate power and insufficient follow-up to appropriately ascertain these outcomes. A more recent meta-analysis focused on paricalcitol in stage 2–5 CKD patients, confirmed that paricalcitol can effectively suppress PTH but did not address any patient-level outcomes.[78]

Kandula *et al.*[79] recently in their systematic review and meta-analysis of identified five randomized trials evaluating nutritional vitamin D supplements (ergocalciferol or cholecalciferol) in CKD and ESRD. In the pooled analyses of randomized trials, there was a significant increase in serum 25(OH) vitamin D levels (mean difference $14\,ng\,ml^{-1}$) and an associated decline in PTH levels (mean decrease $31.5\,pg\,ml^{-1}$) with nutritional vitamin D supplements compared with placebo. A low incidence of mild and reversible hypercalcemia (up to 3%) and hyperphosphatemia (up to 7%) were reported with nutritional vitamin D supplements. However, none of the studies reported patient-centered outcomes related to bone fractures, bone pain or parathyroidectomy and most trials were of low to moderate quality.

Finally, in the recently published EVOLVE study, the placebo arm (standard of care, namely vitamin D analogs) achieved higher levels of serum calcium compared with the calcimimetics

Table 3 Summary of vitamin D randomized trials reporting patient level skeletal outcomes in CKD

Study	*Population*	*Number of patients*	*Intervention*	*Results*
Memmos *et al.*[68]	Maintenance hemodialysis	57	Oral calcitriol 0.25–0.5 μg per day for 1–2 years	Improvement in radiological changes of hyperparathyroidism but no change in parathyroidectomy rate
Moriniere *et al.*[71]	Maintenance hemodialysis	27	Oral 1 alpha-OH-vitamin D3 at 0.3–1.0 ug per day for 6 months	No difference in bone pain
Llach *et al.*[76]	Maintenance hemodialysis with mild to moderate secondary hyperparathyroidism	35	Intravenous paricalcitol 0.04 to $0.24\,\mu g\,kg^{-1}$ three times weekly for 4 weeks	No difference in bone pain
Baker *et al.*[75]	Stage 3–4 CKD	16	Oral calcitriol 0.25–5.0 ug per day for one year	No difference in fracture risk
Delmez *et al.*[77]	Maintenance hemodialysis with mild to moderate secondary hyperparathyroidism	15	Intravenous calcitriol 0.5–2.0 ug three times weekly for 1 year	No difference in fracture or parathyroidectomy rates

agent (cinacalcet) arm (median level 9.8 mg dl^{-1} vs 9.2 mg dl^{-1} at 4 months).[80] In this context, however, there were no differences between the two arms for fractures (13% vs 12%). As expected with calcimimetic mechanism of action, incidence of parathyroidectomy was significantly lower in cinacalcet arm compared with placebo arm (7% vs 14%, relative hazard 0.44, 95% confidence interval 0.36–0.54).

Conclusions

As discussed in this review focused on skeletal aspects of CKD–MBD, there is ample biological and observational data to support the importance of vitamin D. Accordingly, randomized controlled trials especially with newer vitamin D analogs and nutritional vitamin D compounds, have demonstrated serum PTH reductions but with a possible increased risk of hypercalcemia and/or hyperphosphatemia. The size and quality issues of the existing trials limits conclusions that can be drawn regarding their effects on patient-level skeletal outcomes and larger higher quality randomized trials focused on skeletal outcomes are needed. Furthermore, future studies to further delineate role of bioavailable vitamin D in CKD are also needed.

Acknowledgements

SUN is supported by the Clinical Scientist in Nephrology (CSN) Fellowship Award from the American Kidney Fund. RT is a consultant to Fresenius Medical Care North America and has received a research grant from Abbott Laboratories. RIT is supported by National Institute of Health grants DK094872 and DK094486.

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