

Original Article

## High-dose cholecalciferol to correct vitamin D deficiency in haemodialysis patients

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### Abstract

**Background.** Vitamin D has emerged as an important survival factor in patients with chronic kidney disease. Non-activated vitamin D may also have beneficial effects on bone, cardiovascular and immune functions. Cholecalciferol is the prevalent non-activated vitamin D in Europe, but there is no valid prospective data available about its use in haemodialysis patients. Thus, we initiated a prospective study to evaluate dosing, safety and tolerability of cholecalciferol supplementation in haemodialysis patients.

**Methods.** The prospective study included 64 haemodialysis patients. During replenishment phase patients received 20 000 IU cholecalciferol/week for 9 months. In the open maintenance phase (15 months), patients were randomized to a treated group (20 000 IU cholecalciferol/month) and an untreated group, which did not receive cholecalciferol.

**Results.** Calcidiol [25(OH)D] deficiency (<37.5 nmol/l; <15 µg/l) was detected in 61/64 patients (95%). During the replenishment phase, calcidiol increased significantly from 16.65 ± 9.6 to 79.48 ± 27.15 nmol/l (6.66 ± 3.84 µg/l to 31.79 ± 10.86 µg/l) ( $P < 0.001$ ). Recommended levels (>75 nmol/l; >30 µg/l; K/DOQI) were achieved in 57% of patients. Calcium increased from 2.28 ± 0.17 to 2.37 ± 0.19 mmol/l (9.1 ± 0.69 mg/dl to 9.49 ± 0.75 mg/dl) ( $P < 0.01$ ). Phosphorus, calcium-phosphorus product and parathyroid hormone showed no significant changes. Fifty-nine patients progressed to the maintenance phase. Analysis per protocol showed a significant drop of calcidiol in the treated [83.98 ± 31.73 versus 78.5 ± 38.75 nmol/l (33.59 ± 12.69 versus 31.4 ± 15.5 µg/l) ( $P < 0.001$ )] and untreated groups [86.35 ± 40.75 versus 53.4 ± 26.2 nmol/l (34.54 ± 16.3 versus

21.36 ± 10.48 µg/l) ( $P < 0.001$ )]. The comparison of the treated and the untreated groups showed no significant differences at the beginning of the maintenance phase: 83.98 ± 31.73 versus 86.35 ± 40.75 nmol/l (33.59 ± 12.69 versus 34.54 ± 16.3 µg/l). At the end they differed significantly: 78.5 ± 38.75 versus 53.4 ± 26.2 nmol/l (31.4 ± 15.5 versus 21.36 ± 10.48 µg/l) ( $P < 0.001$ ).

**Conclusion.** Vitamin D deficiency is present in a majority of haemodialysis patients. Supplementation with cholecalciferol is safe, well tolerated and reasonable to replenish vitamin D stores in haemodialysis patients. However, only 57% of patients achieved recommended calcidiol levels, thus favouring additional dose-finding studies.

**Keywords:** calcidiol; cholecalciferol; chronic kidney disease; haemodialysis; vitamin D

### Introduction

Vitamin D deficiency is a common problem in patients undergoing dialysis [6]. Only recently cross-sectional studies suggested that treatment with activated vitamin D may be associated with a better outcome in patients with end-stage renal disease [18,19]. These results propose that the effects of vitamin D must reach much further than the regulation of calcium and phosphate homeostasis. Indeed there has been gathering evidence that vitamin D influences gene expression in many tissues, mainly through its active hydroxylated form calcitriol. Local calcitriol is produced by 1- $\alpha$ -hydroxylase and serves as an important cell-differentiating factor and anti-proliferative agent in an autocrine or paracrine manner [11]. Besides the kidney, this enzyme is abundant in many tissues, such as keratinocytes, macrophages, brain and parathyroid tissue. It depends on an adequate level of circulating substrate calcidiol [12]. In contrast to calcitriol, which can be normal despite nutrient deficiency, calcidiol levels are indicative of vitamin D body

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stores [2,8]. The widespread extra-renal expression of the 1-alpha-hydroxylase supports the notion that it is crucial to supply target tissues with active hormone in order to control local gene expression. Deficiency of calcidiol is a risk factor for the development of secondary hyperparathyroidism and osteoporosis-independent calcitriol deficiency [9]. A higher incidence of epithelial cancers, muscle weakness and infections has also been correlated with vitamin D deficiency [13]. It has been shown that vitamin D deficiency leads to impaired localized innate immunity and defects in antigen-specific cellular immunity [21]. An emerging treatment strategy for vitamin D deficiency in chronic kidney disease (CKD) is supplementation of high doses of non-activated vitamin D, which is activated by non-renal 1-alpha-hydroxylase. This exciting treatment strategy is motivated by low-cost, physiological vitamin D replacement, and few side effects; however, as yet there is little published evidence to support its use, also explaining lacking recommendations in the current K/DOQI guidelines [1]. Only in CKD stage 3 and 4 patient with elevated intact parathyroid hormone (iPTH), guidelines support the use of non-activated vitamin D. K/DOQI recommends the use of ergocalciferol, the dose adjusted to baseline levels of calcidiol [1,11]. Ergocalciferol is mainly used in the United States. However, only retrospective data are available so far [16]. Furthermore, cholecalciferol is the prevalent non-activated vitamin D used in Europe. Studies on dosing and safety of cholecalciferol supplementation in haemodialysis patients are lacking. Doses required to maintain sufficient levels are another important issue not clarified yet. We conducted a prospective study in dialysis patients of a German outpatient facility to gather information about the prevalence of vitamin D deficiency, dosing and safety of cholecalciferol supplementation needed to achieve and maintain recommended vitamin D levels.

## Methods

### *Patients and design*

The prospective study was conducted between May 2004 and June 2006. The study population consisted of 64 haemodialysis patients (26 females and 38 males) treated in a German outpatient centre. Informed and written consent was obtained from every participant. The study was approved by the local ethics committee.

Exclusion criteria were known tertiary hyperparathyroidism and treatment with cinacalcet. Treatment with calcitriol or alfacalcidol was allowed in stable doses during the study. Three patients were treated with calcitriol and 37 patients were treated with alfacalcidol. The therapy strategy of secondary hyperparathyroidism did not change during the study phase. The dialysate calcium was kept stable during the study phase. Baseline calcidiol, calcium, phosphorus and iPTH were measured predialysis at the initiation in May 2004. The study was separated into replenishment and maintenance phases. During the replenishment phase, patients were administered 20 000 IU of cholecalciferol, given as one capsule (brand name Dekristol®) once every week

after the dialysis session. The supplementation was carried on for 9 months. Final analysis was performed in February 2005. For the open maintenance phase, 59 patients were randomized in a treated group (30 patients) and an untreated group (29 patients). From March 2005 till June 2006 the treated group received 20 000 IU of cholecalciferol once every month; the untreated group did not receive cholecalciferol. In the follow-up calcidiol levels were recorded. Final analysis of 23 patients from the treated group and 19 patients from the untreated group was performed in June 2006 (Figure 1).

### *Analytical methods*

Blood samples were analysed at Labor Limbach, Heidelberg, Germany. iPTH was measured with an electrochemiluminescence immunoassay (ECLIA, Roche Diagnostics, Mannheim, Germany). Calcidiol [25(OH)D] levels were determined with Nichols Advantage™ 25(OH)D assay (Nichols Diagnostic Institute, San Clemente, CA, USA). This assay is based on vitamin D-binding protein recognition and chemiluminescence detection. According to K/DOQI guidelines, vitamin D insufficiency was defined at calcidiol levels of 37.5–75 nmol/l (15–30 µg/l) and vitamin D deficiency was defined at calcidiol levels <37.5 nmol/l (<15 µg/l) [1].

### *Statistical methods*

Descriptive statistics used include means and standard deviations. Paired *t*-test analysis was used for paired samples of two groups of continuous data, and the unpaired *t*-test for comparisons between groups. Analyses were done for two-tail significance and a *P*-value <0.05 was considered statistically significant. Computational analyses were done using SPSS version 15.0 (SPSS, Chicago, IL, USA). All levels are given in mean ± SD.

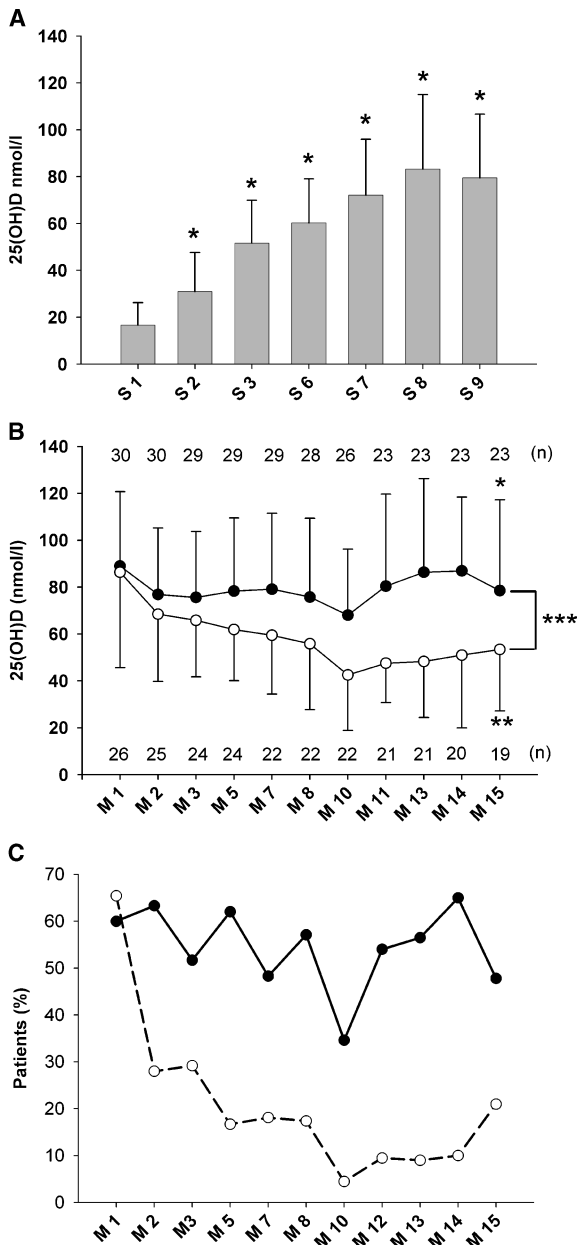
## Results

### *Frequency of calcidiol [25(OH)D] deficiency in haemodialysis patients*

At study entry 5% of patients (*n* = 3) were vitamin D insufficient with calcidiol levels between 37.5 and 75 nmol/l (15–30 µg/l) and 95% (*n* = 61) were vitamin D deficient with calcidiol levels <37.5 nmol/l (<15 µg/l).

### *Replenishment phase (June 2004–February 2005)*

From June 2004 each patient received 20 000 IU of cholecalciferol per week regardless of the baseline calcidiol level. After 9 months calcidiol levels increased significantly from  $16.65 \pm 9.6$  to  $79.48 \pm 27.15$  nmol/l ( $6.66 \pm 3.84$  µg/l in June 2004 to  $31.79 \pm 10.86$  µg/l) (*P* < 0.001) in February 2005 (Figure 1A). Thirty-four percent of patients (*n* = 20) remained calcidiol insufficient (37.5–75 nmol/l; 15–30 µg/l) and 8% (*n* = 4) remained deficient (<37.5 nmol/l; <15 µg/l). Recommended levels (>75 nmol/l; >30 µg/l)



**Fig. 1.** (A) Calcidiol [25(OH)D] levels (nmol/l) during the replenishment phase (months S1–S9). 20 000 IU cholecalciferol per week led to a significant increase in calcidiol levels in comparison to baseline level S1 (\**P* < 0.001). (B) Calcidiol levels of treated group (black) and untreated group (white) during the maintenance phase (months M1–M15). Significant decrease is observed in treated group from months M1 to M15 (\**P* < 0.001). The decrease in untreated group from months M1 to M15 is also highly significant (\*\**P* < 0.001). There is no significant difference between treated and untreated at M1. At the end (M15), they differed significantly (\*\*\**P* < 0.001, unpaired *t*-test). (C) Percentage of patients with recommended calcidiol levels (>75 nmol/l (>30 µg/l) of treated group (black) and untreated group (white) during the maintenance phase (months M1–M15). Within the treated group, the percentage of patients decreased from 60 to 48% throughout the study period. In the untreated group, 21% had recommended 25(OH)D levels at M15.

were achieved in 57% of patients (*n* = 31). Calcium increased from 2.28 ± 0.17 to 2.37 ± 0.19 mmol/l (*P* < 0.01). Phosphorus levels, calcium-phosphorus product and PTH levels did not change significantly (Table 1).

**Table 1.** Parameters during the replenishment phase

Replenishment phase	Start June 2004	End February 2005	P-value
25(OH)D (nmol/l)	16.65 ± 9.6	79.48 ± 27.15	<0.001 <sup>c</sup>
Calcium (mmol/l)	2.28 ± 0.17	2.37 ± 0.19	<0.05 <sup>c</sup>
Phosphorus (mmol/l)	5.29 ± 1.64	5.19 ± 1.36	NS <sup>c</sup>
Ca × P <sup>a</sup> (mmol <sup>2</sup> /l <sup>2</sup> )	3.8 ± 1.22	4.0 ± 1.14	NS <sup>c</sup>
iPTH <sup>b</sup> (pmol/l)	22.37 ± 21.74	21.84 ± 23	NS <sup>c</sup>

All values are given in mean ± SD.

<sup>a</sup>Ca × P, calcium-phosphorus product.

<sup>b</sup>iPTH, intact parathyroid hormone.

<sup>c</sup>Paired *t*-test, *P* < 0.05 was considered significant.

#### Adverse events

Cholecalciferol (Dekristol<sup>®</sup>) was well tolerated by all patients. All subjects remained within the safe range of calcidiol (<220 nmol/l; <88 µg/l) [20]. No serious adverse event occurred throughout the duration of the study. Three patients had transient hypercalcaemic events (calcium >2.6 mmol/l; >10.5 mg/dl) during treatment with cholecalciferol. The events occurred during the replenishment phase and lasted from 2 to 4 weeks. All responded to a transient cessation of alfacalcidol. After normalization of the calcium level, alfacalcidol was restarted at a lower dose. No further hypercalcaemia was noted during the course of the study. Among these patients, no particular risk factor was found to predict the development of hypercalcaemia.

#### Maintenance phase (March 2005–June 2006)

Fifty-nine patients were randomized to treated (30 patients) or untreated group (29 patients). From March 2005 patients in the treated group received 20 000 IU of cholecalciferol once every month. Ten patients dropped out in the untreated group, and seven in the treated group. As the reasons for these dropouts were similar, an intention-to-treat analysis that includes these patients on a last observation carried forward basis might overestimate the effects. Exclusion of the dropouts from the analysis rendered the following results. In the treated group, the calcidiol level dropped to a statistically significant level during the maintenance phase: 83.98 ± 31.73 versus 78.5 ± 38.75 nmol/l (33.59 ± 12.69 versus 31.4 ± 15.5 µg/l) (*P* < 0.001). As expected, there was a statistically significant decrease of calcidiol levels in the untreated group: 86.35 ± 40.75 versus 53.4 ± 26.2 nmol/l (34.54 ± 16.3 versus 21.36 ± 10.48 µg/l) (*P* < 0.001). The comparison of the treated and untreated groups showed no significant differences at the beginning of the maintenance phase: 83.98 ± 31.73 versus 86.35 ± 40.75 nmol/l (33.59 ± 12.69 versus 34.54 ± 16.3 µg/l). At the end they differed significantly: 86.35 ± 40.75 versus 53.4 ± 26.2 nmol/l (31.40 ± 15.5 versus 21.36 ± 10.48 µg/l) (*P* < 0.001) (Figure 1B). If data are analysed on an intention-to-treat basis (last observation carried forward), calcidiol levels drop significantly in the treated group: 83.98 ± 31.73 versus 71.6 ± 37.02 nmol/l (33.59 ± 12.69 versus 28.64 ± 14.81 µg/l) (*P* < 0.001), and in the untreated group: 86.35 ± 40.75 versus 61.1 ± 34.83 nmol/l (34.54 ± 16.3 versus 24.44 ± 13.93 µg/l) (*P* < 0.001). In this model the treated and untreated groups

did not differ significantly at the beginning. At the end there was a significant difference:  $71.6 \pm 37.02$  versus  $61.1 \pm 34.83$  nmol/l ( $28.64 \pm 14.81$  versus  $24.44 \pm 13.93$   $\mu\text{g/l}$ ) ( $P < 0.001$ ). After 2 months only half of patients still had recommended calcidiol levels, and after 8 months only 25% of the untreated group were in the normal range (Figure 1C). Thirty-four percent of the patients starting with recommended calcidiol levels in the untreated group had their levels dropped below 75 nmol/l (30  $\mu\text{g/l}$ ) within 15 months of follow-up.

## Discussion

Our study shows that vitamin D deficiency is a major problem in haemodialysis patients at least in Germany. Within our collective virtually all patients suffered a severe deficiency of vitamin D. No patient had recommended levels at baseline. This alarming finding is consistent with results of other groups [16,17]. Although approximately half of patients undergoing haemodialysis receive activated forms of vitamin D, the primary reason to initiate this therapy has rested solely on the management of secondary hyperparathyroidism. Recent cross-sectional studies have shown that patients receiving activated vitamin D show a higher survival rate [18,19]. This might be due to improved cardiovascular structure and function, improved vascular compliance and reduced pro-inflammatory cytokines [3].

Treatment with non-activated vitamin D might also have beneficial effects, but no accepted treatment guidelines for patients with ESRD exist. At present the K/DOQI only supports the use of non-activated vitamin D in CKD stages 3 and 4 with elevated PTH levels [1]. It is important to note that inadequate application of non-activated vitamin D can also harm the patient. Hypercalcaemia and hyperphosphataemia are the major adverse events that lead to discontinuation of vitamin D therapy. Thus it was our goal to establish an easy-to-use regimen to achieve a safe and efficient replenishment suitable for all haemodialysis patients regardless of their baseline calcidiol levels.

Vitamin D supplementation can be achieved with cholecalciferol or ergocalciferol. The latter is mostly used in studies in the United States, because it is the only high-dose preparation available there. The two vitamin D isoforms have been considered equivalent. However, recently it has been shown that the potency of vitamin D2 seems to be less than one-third of vitamin D3 [4]. So far the only retrospective data about the use of non-activated vitamin D have been available [16]. In Europe cholecalciferol is the favoured preparation. Being aware of these problems, we conducted a prospective study using cholecalciferol. Our patients received cholecalciferol 20 000 IU once every week after the dialysis session. This regimen combines a high compliance and was well tolerated by the patients. No serious adverse event occurred throughout the study. The low cost of  $\sim 1.4$  Euro per patient and month is another advantage in days of scarce economic resources. At baseline, 95% of our study population suffered vitamin D deficiency [calcidiol  $< 37.5$  nmol/l ( $< 15$   $\mu\text{g/l}$ )]. No patient had recommended levels  $> 75$  nmol/l (30  $\mu\text{g/l}$ ). The calcidiol baseline was  $16.65 \pm$

$9.6$  nmol/l ( $6.66 \pm 3.84$   $\mu\text{g/l}$ ). The individual baseline levels reached from 12.5 to 67.5 nmol/l ( $5\text{--}27$   $\mu\text{g/l}$ ). Low sun exposure, immobility and hyperpigmentation in photo-exposed areas due to uraemia and diet may contribute to the vitamin D deficiency. Others found lower prevalences for vitamin D deficiency in patients with CKD stage 5 [16]. In American patients (St Louis, latitude  $38^\circ$ ), 52% had  $< 75$  nmol/l (30  $\mu\text{g/l}$ ) calcidiol, whilst studies in an Argentinean collective (Quilmes, latitude  $34^\circ$ ) revealed only 23% [6]. Besides differences in vitamin D assays, the geographical position of Bochum (latitude  $41^\circ$ ) in comparison to the other study locations and associated higher sun exposure there might be responsible for higher vitamin D levels in American patients. Results similar to ours were reported for aged, bedridden patients (mean GFR 64–66 ml/min) by a Finnish group. The authors found 98% to be vitamin D deficient [5]. Even in young healthy adults, one-third were found to be vitamin D deficient at the end of winter [14]. During the replenishment phase, the calcidiol baseline levels of our study population increased significantly from  $16.65 \pm 9.6$  to  $79.48 \pm 27.15$  nmol/l ( $6.66 \pm 3.84$   $\mu\text{g/l}$  to  $31.79 \pm 10.86$   $\mu\text{g/l}$ ) ( $P < 0.001$ ). That means that  $\sim 57\%$  of the patients reached recommended calcidiol levels. Apparently even high doses (80 000 IU cholecalciferol/month) seem not to be sufficient to achieve recommended vitamin D levels in all patients. It has to be pointed out that our collective started from an extremely low baseline. This important finding underlines the notion that empty vitamin D stores require extremely high doses for replenishment. In a recent American study, haemodialysis patients were supplemented with monthly doses of 50 000 IU of ergocalciferol for 6 months [16]. Although ergocalciferol was found to have a lower potency [4], a greater percentage of the patients from St Louis achieved recommended calcidiol levels. One explanation might be the higher baseline calcidiol levels of this collective [16].

Safety is a key aspect when treating patients with vitamin supplements [15]. During the replenishment phase, 3 out of 64 patients died; during the maintenance phase, deaths were almost equally distributed among treated (6 out of 30 patients) and untreated groups (5 out of 29 patients). This is within the range of the known 1-year-mortality of European dialysis patients [10]. However, we are aware of the limitations of our study on predicting the impact of cholecalciferol on outcome. The replenishment phase holds no untreated group. Furthermore, the overall patient numbers are comparatively small. Thus, higher mortality after replenishment of vitamin D body stores cannot be excluded by the present results. All subjects in our study remained within the safe range of calcidiol  $< 200$  nmol/l ( $< 88$   $\mu\text{g/l}$ ) [20]. Calcium showed a significant increase but remained safely within the desired range. Phosphorus levels were not significantly altered during the supplementation and the calcium–phosphorus product stayed on a similar level. Notably, iPTH did not show significant changes, although a lowering effect could have been expected. The finding that iPTH levels in patients with higher stages of CKD hardly respond to non-activated vitamin D is consistent with the results of other groups. It is therefore postulated that only in early stages can increased PTH levels be attributed to

vitamin D deficiency to a certain extent. Together these findings suggest that extra-renal 1-alpha-hydroxylase activity is not sufficient to warrant sufficient systemic calcitriol levels to control PTH levels. Activated vitamin D analogues seem to be indispensable to adequately control hyperparathyroidism in late stages of CKD [7,22].

Taken together, our results suggest that supplementation with cholecalciferol 20 000 IU once a week is safe and well tolerated by haemodialysis patients. To achieve a greater percentage of patients reaching recommended levels of calcidiol, either the dosage or the duration of weekly application has to be increased. This will be a subject of additional studies. It has become clear that the replenishment of empty vitamin D stores requires high cumulative doses of cholecalciferol. The inevitable question is now which amounts would be necessary to maintain recommended levels. Thus, the second part of our study was designed to determine the dose necessary for maintaining recommended calcidiol levels without putting the patient at risk for vitamin D intoxication and associated adverse events. Furthermore, we were interested in the kinetics of vitamin D in haemodialysis patients after the withdrawal of the vitamin supplementation. Therefore, patients were randomized in a treated and an untreated group. Even the treated group showed a significant decrease after 15 months. The percentage of patients with the recommended vitamin D level fell from 60 to 48%. This shows that a monthly dose of 20 000 IU cholecalciferol may not be enough to maintain adequate serum levels of calcidiol in those patients. Withdrawal of vitamin D supplement is associated with a marked decrease in the vitamin D levels. After 2 months, only half of patients still had recommended calcidiol levels, and after 8 months only about a quarter was within the range. Thirty-four percent of the untreated group became vitamin D deficient/insufficient within 15 months of follow-up.

## Conclusion

Our study confirms the notion that vitamin D deficiency is an underestimated problem in haemodialysis patients. Supplementation of non-activated vitamin D, activated by 1-alpha-hydroxylase, promises a physiological vitamin D replacement with few side effects at low costs. As we could demonstrate, supplementation of cholecalciferol leads to a safe and well-tolerated replenishment of vitamin D stores in haemodialysis patients. However, additional studies to determine the ideal dosage to achieve and maintain vitamin D levels in the majority of patients have to be conducted.

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**Conflict of interest statement.** None declared.

## References

1. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42: S1–S201
2. Adams JS, Clemens TL, Parrish JA *et al.* Vitamin-D synthesis and metabolism after ultraviolet irradiation of normal and vitamin-D-deficient subjects. *N Engl J Med* 1982; 306: 722–725
3. Andress D. Nonclassical aspects of differential vitamin D receptor activation: implications for survival in patients with chronic kidney disease. *Drugs* 2007; 67: 1999–2012
4. Armas LA, Hollis BW, Heaney RP. Vitamin D2 is much less effective than vitamin D3 in humans. *J Clin Endocrinol Metab* 2004; 89: 5387–5391
5. Bjorkman M, Sorva A, Risteli J *et al.* Vitamin D supplementation has minor effects on parathyroid hormone and bone turnover markers in vitamin D deficient bedridden older patients. *Age Ageing* 2008; 37: 6–7
6. Del Valle E, Negri AL, Aguirre C *et al.* Prevalence of 25(OH) vitamin D insufficiency and deficiency in chronic kidney disease stage 5 patients on hemodialysis. *Hemodial Int* 2007; 11: 315–321
7. DeVille J, Thorp ML, Tobin L *et al.* Effect of ergocalciferol supplementation on serum parathyroid hormone and serum 25-hydroxyvitamin D in chronic kidney disease. *Nephrology (Carlton)* 2006; 11: 555–559
8. Eastwood JB, Daly A, Carter GD *et al.* Plasma 25-hydroxy-vitamin D in normal subjects and patients with terminal renal failure, on maintenance haemodialysis and after transplantation. *Clin Sci (Lond)* 1979; 57: 473–476
9. 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
10. Goodkin DA, Young EW, Kurokawa K *et al.* Mortality among hemodialysis patients in Europe, Japan, and the United States: case-mix effects. *Am J Kidney Dis* 2004; 44: 16–21
11. Gurlek A, Pittelkow MR, Kumar R. Modulation of growth factor/cytokine synthesis and signaling by 1alpha,25-dihydroxyvitamin D(3): implications in cell growth and differentiation. *Endocr Rev* 2002; 23: 763–786
12. Hewison M, Burke F, Evans KN *et al.* Extra-renal 25-hydroxyvitamin D3-1alpha-hydroxylase in human health and disease. *J Steroid Biochem Mol Biol* 2007; 103: 316–321
13. Jones G. Expanding role for vitamin D in chronic kidney disease: importance of blood 25-OH-D levels and extra-renal 1alpha-hydroxylase in the classical and nonclassical actions of 1alpha,25-dihydroxyvitamin D(3). *Semin Dial* 2007; 20: 316–324
14. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998; 351: 805–806
15. Quack I, Zwernemann C, Weiner SM *et al.* Dihydrotachysterol therapy for hypoparathyroidism: consequences of inadequate monitoring. Five cases and a review. *Exp Clin Endocrinol Diabetes* 2005; 113: 376–380
16. Saab G, Young DO, Gincherman Y *et al.* Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. *Nephron Clin Pract* 2007; 105: c132–c138
17. Taskapan H, Wei M, Oreopoulos DG. 25(OH) vitamin D3 in patients with chronic kidney disease and those on dialysis: rediscovering its importance. *Int Urol Nephrol* 2006; 38: 323–329
18. Teng M, Wolf M, Lowrie E *et al.* Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 2003; 349: 446–456
19. Tentori F, Hunt WC, Stidley CA *et al.* Mortality risk among hemodialysis patients receiving different vitamin D analogs. *Kidney Int* 2006; 70: 1858–1865
20. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 1999; 69: 842–856
21. Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. *Ann Nutr Metab* 2007; 51: 301–323
22. Zisman AL, Hristova M, Ho LT *et al.* Impact of ergocalciferol treatment of vitamin D deficiency on serum parathyroid hormone concentrations in chronic kidney disease. *Am J Nephrol* 2007; 27: 36–43

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