Use (or misuse) of vitamin D treatment in CKD and dialysis patients

A recent meta-analysis on vitamin D compounds in chronic kidney disease [1] and an editorial comment [2] accompanying this meta-analysis have already been published. We believe that these papers deserve some comments in the interest of the NDT readership.

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1,25-Dihydroxy vitamin D (vitamin D) is a hormone with a number of pharmacological and physiological effects, first demonstrated as the effect to cure osteomalacia and later as a hormone with effects related to mineral homeostasis, cell differentiation, immunology, vascular calcification and ageing [3–5]. The hormone, 1,25-dihydroxy vitamin D, is formed from cholecalciferol, that is 25-hydroxylated in the liver and 1-α-hydroxylated in the kidney. In addition 1-α-hydroxylase activity has been demonstrated in a number of cells outside the kidney. The activity of the extrarenal 1-α-hydroxylase is, however, not enough to keep physiological plasma levels of 1,25-dihydroxy vitamin D, and the renal 1-α-hydroxylase activity is therefore of utmost importance for maintaining a normal physiological homeostasis.

In patients with chronic uraemia, reduced kidney mass and low kidney function, the renal 1-α-hydroxylase activity is clearly reduced, as demonstrated by the very low levels of plasma 1,25-dihydroxy vitamin D found in a number of studies on patients with chronic kidney disease (CKD).

When dealing with administration of vitamin D compounds in patients with CKD on or not yet on dialysis, one clearly has to distinguish between the goal of providing the patients with substitution of the missing hormone or providing the patients a pharmacological effect of vitamin D.

Concerning the substitution of physiological levels of 1,25-dihydroxy vitamin D in patients with CKD, it is obvious that not many studies in a randomized controlled way have compared the effect of substitution to the effect of severe hormone depletion in patients with CKD. That is similar to the situation in other endocrine and severe hormone-depleted diseases. As such, one will not be able to find good randomized controlled studies that are comparing untreated Addison with cortisone-treated patients, or patients with severe type 1 DM treated with or without insulin.

Therefore, when looking at the physiological effects of hormones, we do accept that such effects exist, despite the absence of randomized controlled trials, the only function of which would be to confirm the knowledge that would already have been obtained from more classical, clinical and experimental studies that had shown an effect when repleting severe depleted levels of the hormone in question. There still is a need for studies, not necessarily showing an effect of the hormone in hormone-depleted organisms, but examining what substitution dosages of 1,25-dihydroxy vitamin D are essential in advanced CKD.

The other aspect of vitamin D treatment is dealing with the pharmacological effects of vitamin D. Active vitamin D is an essential part of the treatment of renal osteodystrophy with important physiological and pharmacological effects on parathyroid cell proliferation and cell function [6]. The mechanism is well characterized with 1,25-dihydroxy vitamin D having an inhibitory effect on PTH gene, an upregulatory effect on the expression of calcium-sensing receptor and an autologous, upregulatory effect on the vitamin D receptor, all effects that affect PTH biosynthesis and PTH secretion. Besides these well-known direct effects on the parathyroid glands, the hormone has a calcemic and phosphataemic effect, also of importance for the regulation and suppression of PTH levels, besides its effect on the skeleton and numerous cell functions depending upon calcium in their homeostatic regulation.

Treatment strategies have been adjusted during the years, and radical changes in the treatment of hyperparathyroidism occurred. The importance of PTH for the regulation of the bone turnover has been realized and it is today common knowledge that oversuppression of PTH might result in the induction of adynamic bone disease. All these gradually induced adjustments of the treatment strategy have been introduced on the basis of good experimental and clinical studies. In general such studies have been relatively small, with the dosages of vitamin D variable and the treatment goals varying. For example, in the initial studies, a much higher plasma level of calcium was accepted, than what would be the case today.

A recent meta-analysis by S.C. Palmer et al. from the Renal Cochrane Group, in Annals of Internal Medicine in...
The authors of this meta-analysis further stated that: chronic kidney disease remains uncertain and beneficial effects on patient outcomes are unproven. The main conclusion was ‘that vitamin D compounds do not consistently reduce PTH levels and that beneficial effects on patient outcomes are unproven and that the value of vitamin D treatment for people with chronic kidney disease remains uncertain’ [1].

In more details, in this meta-analysis it was found that:

(a) ‘Vitamin D compounds did not reduce the risk for death, bone pain, vascular calcification, or parathyroidectomy’, (b) ‘did not show a consistent reduction in parathyroid hormone (PTH) levels’, (c) ‘that established vitamin D compounds were not associated with a statistically significant reduction in PTH levels, but that should be interpreted with caution, because relevant data for this outcome were heterogeneous’, (d) ‘that newer vitamin D compounds also have a mixed effect on surrogate end points; overall, they significantly reduce PTH levels’; (e) ‘that for suppression of PTH, intravenous administration was superior to oral vitamin D, but higher intravenous doses were used’ and finally (f) ‘that trials directly comparing newer vitamin D analogues with established compounds were rare and small and did not demonstrate important differences in any outcome, and there is insufficient evidence to recommend the use of newer vitamin D analogues over calcitriol’ and (g) ‘that vitamin D is of unproven efficacy in CKD.’

The authors of this meta-analysis further stated that: Comparing the results of our systematic review of randomized trials with observational data is difficult because existing RCTs are underpowered for detection of vitamin D treatment effects on cardiovascular, bone, and mortality end points and because of the inherent problem of residual confounding in observational studies. Our meta-analysis emphasizes the paucity of well-conducted trial data to determine the effect of established and newer vitamin D compounds on cardiovascular and mortality end points in people with CKD. Such analyses do not take account of the potential pleiotropic effects of vitamin D.

This meta-analysis, which included a search that went back to 1966, did however miss many of the important effects of the hormone, vitamin D, e.g. the curable effect on Rickets. This is not because the meta-analysis was incorrectly performed, but because good randomized controlled studies do not exist and as such the basic material was not fitted for a meta-analysis. We wonder why the search in this meta-analysis focusing upon treatment with active vitamin D was started in 1966, when 1,25-dihydroxy vitamin D was not characterized before 1970 and not ready for clinical trials years later [7,8].

The main conclusion of this meta-analysis was that vitamin D compounds do not consistently reduce PTH levels. What a surprising conclusion! Especially in 2007 when all nephrologists carefully tried not to oversuppress PTH with active vitamin D. Most of the clinical studies used in this meta-analysis had some patients included with very severe hyperparathyroidism (HPT), having severe nodular hyperplasia of the parathyroid glands with very low expression of VDR and as such well-proven resistance to treatment with vitamin D. Most patients with less severe HPT will respond to treatment with vitamin D with a suppression of the secretion of PTH, but it is not correct just to group these different patient categories together and it is not clinically correct or relevant to draw conclusions from such an analysis. The authors themselves even assessed the quality of the trials included in their meta-analysis and found that the quality was difficult to assess due to the lack of many details. The authors underlined several weaknesses; just to mention a few: (a) ‘one of the weaknesses of our review was heterogeneity in PTH levels achieved by established vitamin D compounds compared with placebo’, (b) ‘trial quality varied and was difficult to assess because many details were not reported or were difficult to ascertain’, (c) ‘few relevant data were reported in available published randomized trials’ and (d) ‘the lack of direct head-to-head trials’.

Despite all these limitations, the present meta-analysis was completed and very important conclusions were made, as mentioned above, conclusions that potentially might have serious consequences for the prescribing patterns and reimbursement policies to CKD patients, besides very serious consequences of not substituting the lack of hormone to hormone-deficient patients.

In the same paper, there is a short Editorial Note from the editors of Annals of Internal Medicine stating: ‘Clinicians often treat patients with kidney disease with vitamin D compounds to prevent secondary hyperparathyroidism.’ We believe that this is not a correct statement as nephrologists today use vitamin D compounds for treatment, but not for prevention of secondary HPT. Indications for treatment are clearly described in the K/DOQI guidelines [9] that are widely used in Europe as well as in the USA.

The Editors Note further states: ‘Implication: Though commonly used, vitamin D compounds for chronic kidney disease have unclear benefits and potential harms.’ We agree that these compounds might have potential harms, but most nephrologists should today be aware of the narrow therapeutical window of active vitamin D compounds, aware of the risk of inducing hypercalcaemia and hyperphosphataemia and of oversuppression of PTH levels. There are, however, clearly and well-documented benefits, such as control of secondary HPT, cure of osteomalacia and osteitis fibrosa cystica, as proven in studies using bone biopsies [6,10]. Many nephrologists still remember the ureamic children with severe bone deformities from the time before treatment with active vitamin D as shown in Figure 1. Hopefully the Nephrological Community will not have to return to the pre-vitamin D era, just in order to fulfil the need for better randomized controlled trials, that potentially could create the background for different meta-analyses.

In the same issue of Annals of Internal Medicine, there is not just the mentioned Editorial Note, but also an Editorial by Dr Tonelli from the Institute of Health Economics, University of Alberta, Canada [2]. This editorial states:

How should the nephrology community interpret the findings of this systematic review? Skeptics will point out that, first, optimally performed meta-analyses disagree with individual large, randomized trials approximately one third of
the time. Second, many of the trials included in the systematic review were small and of short duration, and they were not intended to evaluate clinically relevant outcomes, such as mortality or hospitalization. Third, the results of some comparisons of vitamin D with placebo differed across studies; Fourth, a compelling body of experimental and observational data supports the hypothesis that vitamin D supplementation generally (and administration of injectable, activated vitamin D analogues, specifically) may improve outcomes in patients with chronic kidney disease by mechanisms that are independent of their effects on markers of metabolic bone disease, such as serum phosphate.

Although these concerns are all reasonable, the nephrology community must pay attention to the results of Palmer and colleagues’ meta-analysis. Like vitamin D supplementation today, previously recommended treatments for patients with chronic kidney disease (such as higher haemoglobin targets and more intensive dialysis) had strong support from seemingly unassailable biological and epidemiologic evidence, suggesting that they would improve clinically relevant outcomes. However, subsequent randomized trials demonstrated that these interventions were not beneficial or actually caused harm. It is hoped that we have learned that we cannot use the great clinical need of patients with chronic kidney disease to justify guidelines that recommend unproven therapies.

We completely agree with all the sceptical remarks in the first part. It does, however, seems curious that the editor does not take the chance to discuss these sceptical points (limitations of the study), but instead continues directly with ‘clinical examples of higher haemoglobin targets and more intensive dialysis’, examples also mentioned by the authors of the meta-analysis. The studies on the optimal haemoglobin targets focused however on the dosage levels of EPO and did not at all question the use or no use of EPO to CKD patients; therefore the comparison with the meta-analysis on the use of vitamin D is not very relevant.

Similarly, the question of more intensive dialysis is difficult to evaluate with the available knowledge. Therefore, the consequence should not be to stop dialysis or reduce current practice.

Finally, the same Editorial states: ‘In the meantime, it is hard to argue strongly for the use of vitamin D in patients receiving dialysis or those with less-severe forms of chronic kidney disease. Current practices are costly but provide no proven benefit despite their theoretical appeal, and they have the potential to harm.’ We believe that this is a very dangerous statement that might be of appeal to some hospital administrators, but might return the treatment of renal osteodystrophy back to the past. It is clear that one should not accept overtreatment neither with EPO nor with vitamin D; this does not, however, mean that CKD patients should not be treated with these important renal hormones. The calcium, phosphate, PTH, vitamin D, skeleton and vascular interactions are extremely complex, and it is very questionable whether a meta-analysis ever will be able to provide relevant answers. We can still learn more from good experimental studies, such as the Klotho mice models and from good clinical studies.

The editor further states: ‘The large sums spent on vitamin D, its ubiquitous use in advanced renal disease argue in favor of performing well-designed, adequately powered, randomized trials of this therapy in patients with chronic kidney disease’, and finally, the editor states: ‘We need a phased sequence of trials, first to establish whether the addition of activated vitamin D to standard care improves relevant outcomes compared with placebo’. While we agree with the statement on the need for more well-designed RCTs, we strongly disagree with the latter statement: It is absolutely not advisable to withhold the hormone, vitamin D, from dialysis patients, who are severely depleted of vitamin D. This recommendation is potentially dangerous!

**Conclusion**

The important conclusion to be drawn from the present meta-analysis and Editorials in *Annals of Internal Medicine*, therefore, is that there is a need for good randomized controlled trials that are evaluating the pharmacological, but not necessarily the physiological effects of vitamin D in patients with CKD.

It is, however, equally important to stress that the present lack of such well-performed studies should not lead to immediate radical changes (withdrawal of vitamin D) in the current way patients with CKD are treated.
A vast amount of evidence, not directly included in randomized controlled studies, points towards a number of important physiological and pharmacological effects of vitamin D, although the minimal physiological substitution dosage needs to be determined.

No doubt that the balance of treating patients with vitamin D is difficult and that overtreatment might lead to negative responses such as extraskeletal vascular calcifications, etc., but that risk is today well known to most nephrologists and does not outdo the beneficial potential.

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References

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Reply

Vitamin D compounds in chronic kidney disease: change may be needed for good!

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Sir,

Over the last half a century, we have come to appreciate the importance of vitamin D prescription for people with renal disease. Vitamin D and its analogues have profoundly altered the natural history of deforming ‘renal rickets’. Observational studies have found significant associations between use of vitamin D compounds and improved survival [1,2]. We have now become convinced by clinical and experimental evidence that the abnormalities of calcium, phosphorus and parathyroid hormone observed in chronic kidney disease are associated with increased mortality [3–5]. Some of these abnormalities may be affected by treatment with vitamin D compounds. Our guidelines [6] have therefore reflected the need to target improvement of biochemical targets, including parathyroid hormone, phosphorus and calcium, which implies use of both pharmacological (vitamin D and its analogues, calcimimetics and phosphate binders) and non-pharmacological strategies (long-hours dialysis and dietary restriction). The management of bone disease/secondary hyperparathyroidism by targeting tight near-to-normal levels of these biochemical markers is now standard practice and well reflected by policy in clinical nephrology [7,8] and primary care [9]. Prescriptions of vitamin D compounds, as well as other agents for management of renal bone disease, have escalated and our annual outpatient vitamin D expenditure alone has risen from $5 million in 1992 to $400 million in 2005 for Medicare in the USA [10]. Are we done with this matter? Is progress an issue of finding additional effective agents, or is it refining performances of existing agents for improving biochemical targets of bone disease in chronic kidney disease (which is the main focus of ongoing clinical research in this area)? Or do we still need to prove that existing and newer agents are effective for improving survival of our patients?

That vitamin D compounds suppress circulating parathyroid hormone levels has been identified in clinical studies, but evidence also demonstrates that these compounds may increase serum calcium and phosphorus. Such elevations of calcium and phosphorus are identified, again in observational studies, as correlates and predictors of increased all-cause and cardiovascular mortality/morbidity, possibly through upregulation of vascular calcification [11]. This means that although there is a broad acceptance of vitamin D compounds and other therapies for bone disease in chronic kidney disease, considerable uncertainty...