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Vitamin D

Editorial Comment

The beneficial impact of vitamin D treatment in CKD patients: what's next?

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Patients with chronic kidney disease (CKD) have markedly higher rates of severe vitamin D deficiency and reduced ability to convert 25-(OH)vitamin D into the active form, 1,25-dihydroxyvitamin D [1]. In the setting of CKD, secondary hyperparathyroidism develops as a consequence of reduced renal production of active vitamin D and phosphate retention resulting in hypocalcaemia and hyperphosphataemia. This is a process that is dangerously linked with metabolic bone disease, arterial calcifications and cardiovascular mortality [2]. Therefore, the conventional rationale for vitamin D treatment in CKD is to slow the progression of secondary hyperparathyroidism.

In addition to the classical pathway for activation of 25-(OH)vitamin D to 1,25-$(OH)_2$ vitamin D, a peripheral autocrine pathway exists and results in calcitriol synthesis in a variety of peripheral extra-renal tissues [3]. By binding with its intracellular vitamin D receptor (VDR) in these tissues, calcitriol can regulate cellular proliferation and differentiation, inflammation, the immune system and the endocrine system, including insulin resistance, lipid metabolism and renin–angiotensin system (RAS) [4]. Interestingly, active vitamin D analogues have shown demonstrably favourable effects on proteinuria, likely through interference with RAS [5, 6]. The discovery of this non-classical pathway has brought new significance to the importance of addressing nutritional vitamin D deficiency [7].

Vitamin D deficiency has been associated with all-cause and cardiovascular mortality in patients with CKD, whereas therapies with vitamin D and analogues have been associated with reduced mortality, recently also in meta-analysis of observational studies (Table 1). However, evidence from randomized controlled trials (RCTs) supporting a survival benefit from active and/or pre-active vitamin D administration in CKD patients is still lacking. Moreover, it is not even known whether different types of active vitamin D, selective or non-selective VDR activators, or precursors have a diversified effect on mortality in the CKD population.

In the present issue of the *Clinical Kidney Journal*, Mann *et al.* [8] present a meta-analysis of RCTs to investigate the effect of oral vitamin D therapy versus placebo on mortality and cardiovascular outcomes among adults with CKD, whereas vitamin D supplementation was not found to exert any significant effect on these hard outcomes. Analysis of pooled data displayed a substantial overlap in confidence intervals and homogeneity between study results. Stratification of trials by CKD stage, weekly vitamin D dose, proportion of diabetic subjects and vitamin D compound displayed similar results. In detail, 13 trials that, overall, enrolled 1469 patients with CKD stage 1–5D were selected for analysis and none of them had mortality as a primary outcome. These studies were mainly designed to test biochemical or bone histological end points and consequently had a rather short follow-up. On the whole 41 all-cause deaths (2.8%) were recorded during a follow-up ranging from 3 to 104 weeks (mean 41 weeks). Of note, about two-thirds of the patients ($n = 1087$) had been followed for <1 year (mean 21, range 3–48 weeks), registering 17 all-cause deaths (41%), 8 cardiovascular deaths (62%) and 18 cardiovascular events (86%). Only two trials (total patient number = 233) had a follow-up time up to 2 years, but they registered only 11 deaths of which, 5 had a cardiovascular cause. Taken together, these observations could indicate that the duration of follow-up may have been insufficient to capture possible differences in mortality, as correctly stated from the authors in the limitation section and as well as suggested by the relatively low number of events displayed.

Moreover, not negligible differences are also present in patient populations (End Stage Renal Disease in 5 of 13 trials) and in interventions, above all considering the heterogeneity in administered vitamin D compounds and dosages.

In conclusion, it is not the time to say that interventions based on vitamin D may reduce mortality in patients with CKD, but the opposite cannot be said yet beyond all

Table 1. Systematic literature reviews on vitamin D in patients with CKD

First author, year	Methodology	Number of trials/patients pooled in the analysis	Outcomes tested	Main results
Palmer, 2007 [9]	Meta-analysis	76 studies/3667 CKD patients	Biochemical markers of mineral metabolism, CV and mortality outcomes	Vitamin D compounds did not reduce the risk for death, bone pain, vascular calcification or parathyroidectomy
Haiyang, 2009 [10]	Meta-analysis	6 RCTs/174 CKD patients with sHPT	Suppression of circulating PTH and serum ALP	No significant differences between intermittent intravenous and oral calcitriol in the treatment of secondary hyperparathyroidism for efficacy
Palmer, 2009 [11]	Meta-analysis	60 studies/2773 CKD RD patients	Clinical, biochemical and bone outcomes	Vitamin D compounds lowered serum PTH at the expense of increasing serum calcium and phosphorus
Palmer, 2009 [12]	Meta-analysis	16 studies/894 CKD NRD patients	Biochemical, bone, CV, and mortality outcomes	Vitamin D compounds lowered serum PTH at the expense of increasing serum calcium and phosphorus
Geary, 2010 [13]	Meta-analysis	15 RCTs/369 children with CKD stages 2–5D	Clinical, biochemical and bone outcomes	Vitamin D therapy significantly reduced PTH levels without consistent differences between routes of administration, frequencies of dosing or vitamin D preparations
Wang, 2010 [14]	Meta-analysis	17 studies (8 RCTs and 9 observational studies, among which 5 were prospective studies of CKD RD patients)/315 860 patients	CV disease outcomes	The five studies of patients who received dialysis showed consistent reductions in CV mortality in those who received vitamin D supplements
Kandula, 2011 [15]	Meta-analysis	22 studies (17 observational and 5 RCTs)/1593 patients with CKD NRD, CKD RD and renal transplant recipients	Biochemical outcomes	Vitamin D supplementation (ergocalciferol or cholecalciferol) appears to improve 25(OH)D and $1,25(OH)_2D$ levels while reducing PTH levels without increasing the risk for hypercalcaemia and hyperphosphataemia
Pilz, 2011 [16]	Meta-analysis	10 prospective studies/6853 patients with CKD	Mortality	Higher 25(OH)D circulating levels are associated with significantly improved survival
Cheng, 2012 [6]	Meta-analysis	9 RCTs/832 patients with stage 2–5 CKD	Clinical and biochemical outcomes	Paricalcitol suppresses iPTH and lowers proteinuria without an increased risk of adverse events
Duranton, 2013 [17]	Meta-analysis	14 observational studies/194 932 patients with CKD NRD and CKD RD	Mortality	Therapies with 1,25-dihydroxyvitamin D and analogues are associated with reduced mortality in CKD patients
Han, 2013 [18]	Meta-analysis	9 RCTs/1113 patients with CKD NRD	Clinical and biochemical outcomes	Paricalcitol is effective in lowering PTH in CKD patients and is also effective in lowering proteinuria in diabetic CKD patients with a trend towards hypercalcaemia
Xu, 2013 [19]	Meta-analysis	18 RCTs/1836 patients with CKD at stage 3–5	Reduction in proteinuria, renal function and risk of death	Vitamin D therapy lowered proteinuria without any negative influence on renal function. No superiority for newer versus established vitamin D analogues. No differences regarding the risk of death
de Borst, 2013 [20]	Meta-analysis	6 RCTs/688 patients with proteinuria (84% treated with ACEi or ARB)	Reduction in proteinuria	Paricalcitol and calcitriol both reduced proteinuria
Zheng, 2013 [21]	Meta-analysis	20 observational studies/491 857 CKD patients (CKD RD in 17 of 20 studies)	All-cause and CV mortality	Participants receiving vitamin D had lower all-cause and CV mortality. Patients receiving paricalcitol had a survival advantage over those that received calcitriol
Theodoratou, 2014 [22]	Umbrella review	107 systematic literature reviews, 74 meta-analyses of observational studies of plasma vitamin D concentrations and 87 meta-analyses of RCTs of vitamin D supplementation	Limited to CKD (RCTs/participants): bone pain (4/109), bone fractures (4/181 RD), mortality (4/477 NRD; 5/233 RD), PTX (2/133 RD), hypercalcaemia (7/612 NRD; 5/182 RD), hyperphosphataemia (2/245 NRD; 2/59 RD), risk of requiring dialysis (4/301 NRD)	A clear role of vitamin D does not exist for any outcome, except for hypercalcaemia in CKD NRD

RCT, randomized clinical trial; CKD, chronic kidney disease; CV, cardiovascular; sHPT, secondary hyperparathyroidism; PTH, parathyroid hormone; ALP, alkaline phosphatase; RD, requiring dialysis; NRD, not requiring dialysis; ACEi, angiotensin-converting enzyme inhibitor.

reasonable doubt. In fact, given the paucity of good quality data, the reliability of the pooled results is still uncertain.

Conflict of interest statement. L.F.M. and M.C. received in the past honoraria for talk by Abbvie, Amgen, Shire.

(See related article by Mann *et al.* Effect of oral vitamin D analogs on mortality and cardiovascular outcomes among adults with chronic kidney disease: a meta-analysis. *Clin Kidney J* (2015) 8: 41–48.)

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