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

Luigi Francesco Morrone¹ and Mario Cozzolino²

¹Renal Division, A.O. Rummo, Benevento, Italy and ²Laboratory of Experimental Nephrology, Renal Division, Department of Health Sciences, San Paolo Hospital, University of Milan, Milan, Italy

Correspondence and offprint requests to: Mario Cozzolino; E-mail: mario.cozzolino@unimi.it

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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 reasonable doubt. In fact, given the paucity of good quality data, the reliability of the pooled results is still uncertain.
| First author, year | Methodology | Number of trials/patients pooled in the analysis | Outcomes tested | Main results |
|-------------------|-------------|---------------------------------|----------------|--------------|
| Palmer, 2007      | 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     | Meta-analysis | 6 RCTs/174 CKD patients | 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      | 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      | 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       | 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        | 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     | 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 hypercalcemia and hyperphosphatemia |
| Pilz, 2011        | Meta-analysis | 10 prospective studies/6853 patients with CKD | Mortality | Higher 25(OH)D circulating levels are associated with significantly improved survival |
| Cheng, 2012       | Meta-analysis | 9 RCTs/832 patients with stage 2–5 CKD | Clinical and biochemical outcomes | Paricalcitol suppresses PTH and lowers proteinuria without an increased risk of adverse events |
| Duranton, 2013     | 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         | 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 hypercalcemia |
| Xu, 2013          | 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     | 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       | 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 | 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), hypercalcemia (7/612 NRD; 5/182 RD), hyperphosphatemia (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 hypercalcemia 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.
Editorial Comment

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