Control of Secondary Hyperparathyroidism (SPHT) by Older and Newer Vitamin D Compounds

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True deficiency, or relative insufficiency, of 25-hydroxyvitamin D (25-OHD)—and consequentially, deficiency of 1,25 di-OH vitamin D—are highly prevalent among patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) and these are critical components, together with chronic hyperphosphataemia, in the pathogenesis of SHPT. Accordingly, current guidelines have chosen to recommend the correction of hypovitaminosis D through nutritional vitamin D replacement [1, 2], though this is decidedly NOT evidenced based, more an expression of optimism that the many "pleiotropic" claimed effects of vitamin D repletion—reduction in cardiovascular disease, infection and cancer—would somehow apply to renal patients as well. A crunching, crushing hammer blow to the concept of "the sunshine vitamin" somehow protecting general health if only repleted/replaced has been dealt by the final publication of the very-long awaited study, VITAL: in this huge US-based study, a total of 25,871 participants, including 5106 black participants, underwent randomisation. Supplementation with vitamin D was not associated with a lower risk of either of the cardiovascular or cancer primary end points. During a median follow-up of 5.3 years, cancer was diagnosed in 1617 participants (793 in the vitamin D group and 824 in the placebo group; hazard ratio, 0.96; 95% confidence interval [CI], 0.88–1.06; P = 0.47). A major cardiovascular event occurred in 805 participants (396 in the vitamin D group and 409 in the placebo group; hazard ratio, 0.97; 95% CI, 0.85–1.12; P = 0.69). In the analyses of secondary end points, the hazard ratios were as follows: for death from cancer (341 deaths), 0.83 (95% CI, 0.67–1.02); for breast cancer, 1.02 (95% CI, 0.79–1.31); for prostate cancer, 0.88 (95% CI, 0.72–1.07); for colorectal cancer, 1.09 (95% CI, 0.73–1.62); for the expanded composite end point of major cardiovascular events plus coronary revascularization, 0.96 (95% CI, 0.86–1.08); for myocardial infarction, 0.96 (95% CI, 0.78–1.19); for stroke, 0.95 (95% CI, 0.76–1.20); and for death from cardiovascular causes, 1.11 (95% CI, 0.88–1.40). In the

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analysis of death from any cause (978 deaths), the hazard ratio was 0.99 (95% CI, 0.87–1.12). No excess risks of hypercalcaemia or other adverse events were identified [3].

As deficiency of 25-hydroxyvitamin D (25[OH]D) is common in patients with CKD stages 3 and 4 and is consistently associated with poor outcomes, it may seem surprising that a "controversies conference" on vitamin D in chronic kidney disease was sponsored by the National Kidney Foundation in 2017, reporting in 2018 [4]. The reason for this is that there is controversy and a lack of standardisation with respect to definition of vitamin D concentrations to be considered, optimal, adequate, insufficient or deficient in CKD. The report outlines the deliberations of the 3 work groups that participated in the conference. Until newer measurement methods are widely used, the panel agreed that clinicians should classify 25(OH)D "adequacy" as concentrations >20 ng/mL without evidence of counter-regulatory hormone activity (i.e., elevated PTH). The panel also agreed that 25(OH)D concentrations <15 ng/mL should be treated irrespective of PTH concentrations. Patients with 25(OH)D concentrations between 15 and 20 ng/mL may not require treatment if there is no evidence of counter-regulatory hormone activity (no elevation in PTH). The panel agreed that nutritional vitamin D (cholecalciferol, ergocalciferol, or calcifediol) should be supplemented before giving activated vitamin D compounds. The compounds need further study evaluating important outcomes that observational studies have linked to low 25(OH)D levels, such as progression to end-stage kidney disease, infections, fracture rates, hospitalizations, and all-cause mortality [5].

Sadly, implicit in these learned deliberations is a touching naivety that the sporadic measurement of serum/plasma PTH is reliable way to inform clinicians about skeletal health and integrity. This has been repeatedly shown not to be the case; algorithms must adapt to include the use of other biomarkers, including bone specific alkaline phosphatase [6–9].

Whereas nutritional vitamin D replacement may well easily restore 25-OHD concentration to near, or even above the "normal" range in health, the real target of treating vitamin D insufficiency **is and will always remain** the successful treatment of SHPT, which is thought to be immune to modulation (if solely defined by PTH concentrations, a poor substitute of course for proper holistic clinical care) by nutritional vitamin D [10]. Thus, while it is also the subject of a tacit recommendation by guidelines groups, it has also been stridently asserted that, there is little, if any, clinical utility or benefit of nutritional vitamin D replacement in CKD.

Ranged against that is softer evidence for the usefulness of using vitamin D to treat 'renal bone disease' which has been clinical custom and practice now for nearly six decades. In regular clinical practice, however, it is more like three decades, at most, that we have routinely been using vitamin D to try to prevent, or reverse, the impact of SHPT on the skeleton of patients with CKD. The practice has been in the main to use high doses of synthetic vitamin D compounds, not naturally occurring ones. However, the pharmacological impacts of the different

vitamin D species and of their different modes, and styles of administration cannot be assumed to be uniform across the spectrum. It is disappointingly true to say that even in 2020 there is a remarkable, unacceptable and distressing paucity of evidence concerning the clinical benefits of vitamin D supplementation to treat vitamin D insufficiency in patients with stage 3b–5 CKD.

While there are a number of studies that report the impact of vitamin D supplementation on serum vitamin D concentrations (unsurprisingly, usually reporting a robust increase), and some variable evidence of serum PTH concentration suppression, there has been much less focus on hard or semi-rigid clinical end point analysis (e.g. fractures, hospitalizations and overall mortality). Now, in 2020, with the practice pattern changes of first widespread clinical use of vitamin D and second widespread supplementation of cholecalciferol or ergocalciferol by patients (alone, or as multivitamins), it is now, in my view, next to impossible to run a placebo-controlled trial over a decent period of time, especially one which involved clinically meaningful end-points, such as fractures, hospitalization, parathyroidectomy, and death. In this challenging situation, we need to ask what it is we are trying to achieve here, and how best to balance potential benefits with potential harm.

A recent and interesting development has occurred which has served to blur the false dichotomy between opponents and proponents of the use of nutritional vitamin D in CKD. Extended-release calcifediol (ERC) 30 μg capsules were recently approved by the United States Food and Drug Administration (FDA) for the treatment of SHPT in adults with stage 3–4 (not 5) CKD and vitamin D insufficiency (serum total 25OHD <75 nmol/L) [12]. Calcifediol is 25-hydroxyvitamin D3, a prohormone of the active calcitriol (1,25-dihydroxyvitamin D3). ERC capsules have a lipophilic fill, which gradually releases calcifediol, corrects vitamin D insufficiency, and increases serum calcitriol and thereby suppresses production of PTH in CKD patients without seeming to perturb normal vitamin D and mineral metabolism. Randomized clinical trials (RCTs) have demonstrated that non-modified nutritional vitamin D is ineffective for treating SHPT (when used in conventional doses, up to the equivalent of around 4000 IU/day) whereas vitamin D receptor activators (VDRA) can very easily and significantly correct elevated PTH concentrations, but with a marked increased risk of hypercalcaemia and hyperphosphataemia [11, 12], which has led KDIGO to suggest these VDRA drugs should not be used in CKD stages 3,4,5ND.

ERC might seem to offer healthcare professionals a new treatment option that has been demonstrated in RCTs to be safe and effective for controlling SHPT without clinically meaningfully increasing serum concentrations of calcium or phosphorus (at least in tested dosing, in clinical trial subjects, with up to 12 months follow-up). This development might therefore quite literally bridge the two positions. The stricture of the need to demonstrate with hard end-points (fractures, survival, patient-reported outcome measures) that there is any demonstrable benefit from so doing remains as compelling and urgent as ever [11, 12].

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