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Case Report

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Long-term high-dose cholecalciferol in patients with heavy proteinuria

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Abstract
Four patients presenting with heavy proteinuria, vitamin D deficiency and secondary hyperparathyroidism were treated with cholecalciferol for 1.5–3 years. Doses of 7143–14286 U/day were necessary to achieve the calcidiol target of >75 nmol/L. The effect of dosing on calcidiol levels was inconsistent and there was no apparent relationship between changing calcidiol levels and intact parathyroid hormone (PTH) levels. Toxicity was not observed. This series suggests high doses of cholecalciferol over a prolonged period of time are necessary to achieve recommended calcidiol levels; however, the lack of an impact on PTH casts doubt on the suitability of the calcidiol target, in patients with heavy proteinuria.

Keywords: cholecalciferol; parathyroid hormone; proteinuria; vitamin D deficiency

Introduction

Vitamin D status is determined by the 25-hydroxy-D (calcidiol) level; however, the level that denotes deficiency is uncertain and there is no standard recommended replacement dose. The kidneys convert calcidiol to 'active' vitamin D (1,25-hydroxy-D or calcitriol), but even in severe kidney failure, calcidiol continues to exert significant metabolic (and therefore potentially toxic) effects [1]. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline suggests a target calcidiol level of >75 nmol/L for those with an estimated glomerular filtration rate (eGFR) of 15–60 mL/min but does not comment on the use of prolonged high cholecalciferol doses that may be necessary to achieve this target [2]. This report examines the safety and effect of such dosing on parathyroid hormone (PTH) and calcidiol levels in four patients with heavy proteinuria.

The cases

The cases all presented to nephrology outpatients with heavy proteinuria, vitamin D deficiency and secondary hyperparathyroidism. They were prescribed oral cholecalciferol targeting a plasma calcidiol level >75 nmol/L, as measured by the 'Liaison® 25 OH Vitamin D TOTAL Test' assay. The data sheet for this assay reports an 8% inter-assay coefficient of variation at 21 nmol/L but local results indicated poor precision at <20 nmol/L, so results below this cutoff were not quantitated. Results <20 nmol/L were assumed to be 10 nmol/L for the purposes of analysis. Dosing intervals for cholecalciferol and calcidiol level timing for the cases varied. The PTH assay used was the Abbott Diagnostics, Architect, intact-PTH assay. The quoted reference range for this assay is 1.6–7.2 pmol/L with a coefficient of variation of ~5.3%. Quoted eGFR were calculated using the four variable Modification of Diet in Renal Disease equation [3]. Cholecalciferol dose changes and attained calcidiol levels are shown in Figure 1. The relationship between calcidiol levels, eGFR and plasma PTH for the cases with preserved renal function is shown in Figure 2.

Case 1 was a 53 years old Caucasian man who presented with nephrotic syndrome from IgG-lambda amyloidosis and an eGFR of 50 mL/min/1.73m^2. His initial calcidiol level was <20 nmol/L with PTH of 12.6 pmol/L. He required a cholecalciferol dose of 7143 U/day to achieve a calcidiol level >75 nmol/L.

Case 2 was an obese diabetic 53 years old Asian woman who presented with poor energy, an eGFR of 18 mL/min/1.73m^2 and heavy proteinuria but a normal serum albumin. A renal biopsy had been performed 16 years earlier for proteinuria and had shown glomerulomegaly only. Her initial calcidiol level was 23 nmol/L with PTH of 25 pmol/L. She had a past history of metastatic breast cancer in remission on hormonal therapy and minimal trauma fractures to both hips. She required a cholecalciferol dose of 14 286 U/day to achieve calcidiol levels >75 nmol/L, and calcitriol was commenced at Day 335 due to persistent elevations in PTH (51 pmol/L). At commencement of calcitriol, her eGFR was 12 mL/min/1.73m^2.

Case 3 was a 64 years old Caucasian woman who presented with nephrotic syndrome from IgM-kappa amyloidosis and an eGFR of >60 mL/min/1.73m^2. Her initial calcidiol level was <20 nmol/L with a mildly elevated PTH of 8.5 pmol/L. She required treatment with 10 714 U/day cholecalciferol to achieve calcidiol levels >75 nmol/L.

Case 4 was a 22 years old obese Caucasian woman who presented with nephrotic syndrome from tip lesion variant focal-segmental glomerulosclerosis and an eGFR >60 mL/min/1.73m^2. Her bone density *t*-scores measured at the spine and hip were +2.11 and +2.33, respectively, at

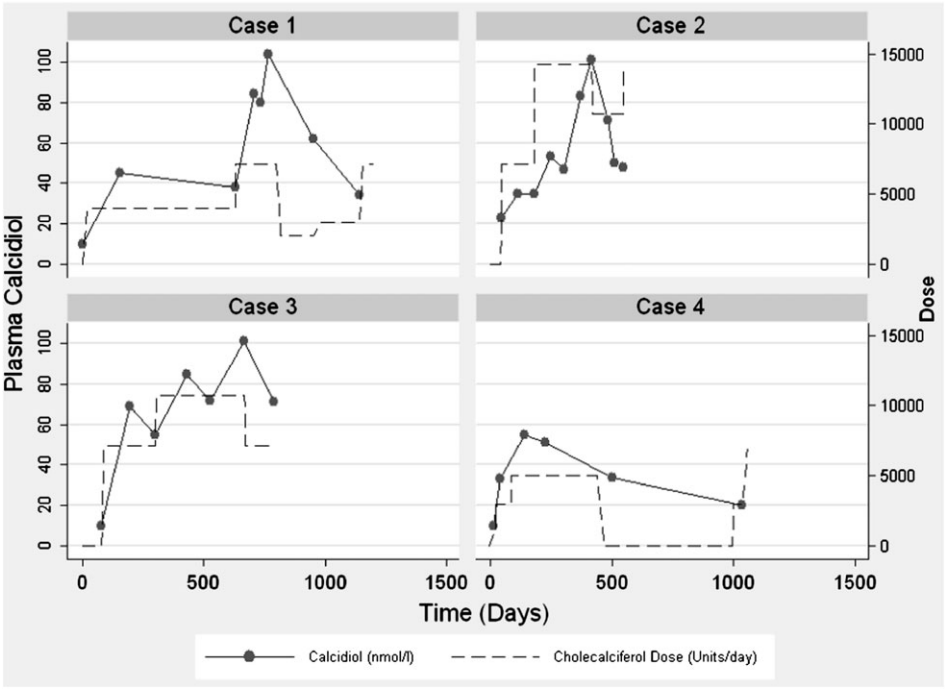

Fig. 1. Cholecalciferol dose and calcidiol level over time.

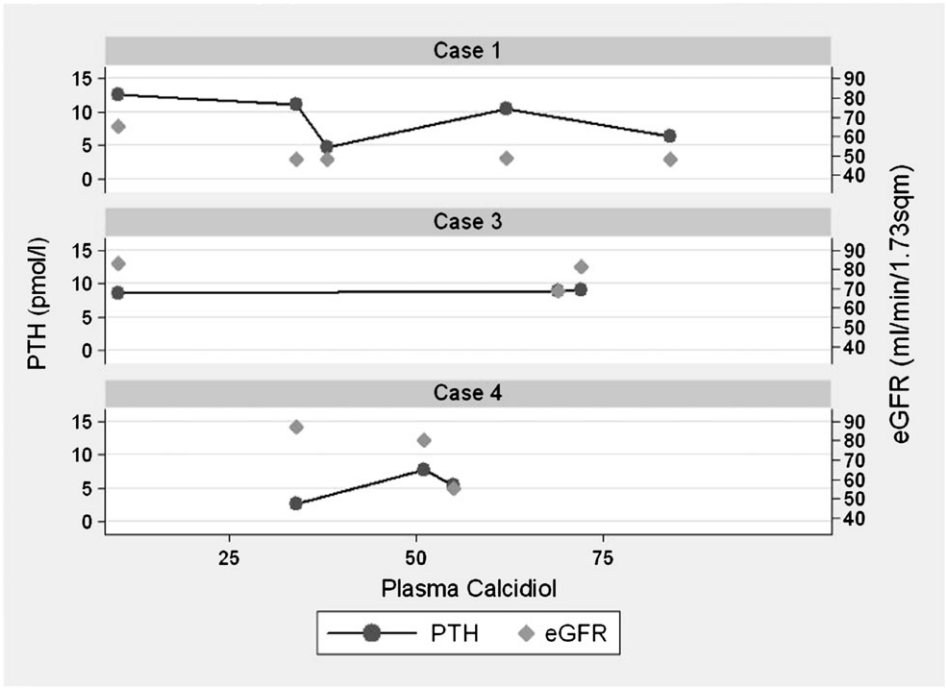

Fig. 2. Relationship of calcidiol level and eGFR to PTH.

presentation. Her initial calcidiol level was <20 nmol/L and a PTH after 4 months therapy with cholecalciferol was mildly elevated at 7.7 pmol/L. Adherence to prescribed therapy was suboptimal, although she stated that her non-adherence was predominantly with the evening dose of cyclosporine, not cholecalciferol. The patient ceased all medications ~63 weeks after presentation.

Discussion

The four patients in this report were vitamin D deficient and were prescribed high doses of cholecalciferol to achieve calcidiol levels >75 nmol/L. Despite maintenance of high doses for >1 year in all patients and frequent monitoring of serum calcium, toxicity was not observed.

Sunlight can catalyse the production of 10 000–20 000 U calcidiol per day such that persons with normal renal function and a high degree of sun exposure achieve calcidiol levels of up to 250 nmol/L without toxicity [4, 5]; however, there is limited safety data for long-term oral supplementation at similar doses [6]. It is known that urinary calcidiol losses are large, proportional to the degree of proteinuria in nephrotics [7] and that cholecalciferol absorption (in animals) is not affected by proteinuria [8]. Accordingly, large oral cholecalciferol doses proportional to the degree of proteinuria should be effective in raising serum calcidiol levels. However, animal data also indicates that very high oral doses of cholecalciferol overwhelm liver 25-hydroxylation, resulting in accumulation of slowly metabolized cholecalciferol [9]. This could cause delayed vitamin D toxicity due to rising calcidiol levels, not responsive to cessation of cholecalciferol dosing. Such toxicity was not observed in this case series, with calcidiol levels falling promptly after cholecalciferol doses were reduced. Case 4 did, however, fail to achieve target calcidiol levels because she ceased therapy before the titration phase was completed.

There was a strong correlation for individual cases (Spearman rho 0.68, $P = 0.0003$) between the prescribed cholecalciferol dose and calcidiol levels obtained 3 months after the last dose change, but an inconsistent dose–response relationship across the group. The inconsistency in dose–response between cases did not appear to be explained by varying levels of proteinuria, serum albumin, eGFR, body weight or differences in baseline calcidiol levels; however, formal statistical analysis was not possible because regression models did not provide a good fit for the data.

Despite relatively stable and well-preserved kidney function in three cases, no association was found between calcidiol levels and plasma PTH, as shown in Figure 2. Calcidiol is highly (88%) protein bound [10] and the free fraction of calcidiol would likely be increased by the fall in vitamin D-binding protein that occurs in heavy proteinuria [11]. This would make the free fraction of calcidiol higher than expected, based on the total calcidiol level and therefore alter the relationship between total levels (as measured by the assay) and PTH, in patients with proteinuria. Total calcidiol levels may therefore be an inappropriate guide to cholecalciferol therapy in the setting of extreme protein losses. However, it is unlikely that a change in protein binding alone is sufficient to account for the lack of a PTH response in Cases 1 and 3. In those patients, where total calcidiol levels were very low at baseline, free levels would also have been low, regardless of the bound fraction. A substantial rise in total calcidiol from a severely deficient baseline would be expected to increase free levels, and thereby improve secondary hyperparathyroidism. However, in this series, substantial increases in total calcidiol levels did not result in significant PTH reductions (Figure 2).

The lack of a calcidiol–PTH response relationship in this series casts doubt on the benefit of supplementing cholecalciferol based on a low total plasma calcidiol level in proteinuric patients; however, if given, such supplementation is safe.

Conflict of interest statement. None declared.

References

1. Kandula P, Dobre M, Schold JD *et al.* Vitamin D supplementation in chronic kidney disease: a systematic review and meta-analysis of observational studies and randomized controlled trials. *Clin J Am Soc Nephrol* 2011; 6: 50
2. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42: S1–S202
3. Levey A, Bosch J, Lewis JB *et al.* Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; 130: 461–470
4. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr* 2005; 135: 317
5. Haddock L, Corcino J, Vazquez M. 25 (OH) D serum levels in the normal Puerto Rican population and in subjects with tropical sprue and parathyroid disease. *Puerto Rico Health Sci J* 1982; 1: 85–91
6. Heaney RP DK, Chen TC, Horlick MF *et al.* Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 2003; 77: 204–210
7. Sato KA, Gray RW, Lemann J Jr. Urinary excretion of 25-hydroxyvitamin D in health and the nephrotic syndrome. *J Lab Clin Med* 1982; 99: 325–330
8. Khamiseh G, Vaziri ND, Oveisi F *et al.* Vitamin D absorption, plasma concentration and urinary excretion of 25-hydroxyvitamin D in nephrotic syndrome. *Proc Soc Exp Biol Med* 1991; 196: 210–213
9. Shepard RM, Deluca HF. Plasma concentrations of vitamin D3 and its metabolites in the rat as influenced by vitamin D3 or 25-hydroxyvitamin D3 intakes. *Arch Biochem Biophys* 1980; 202: 43–53
10. Haddad J. The vitamin D binding protein and its clinical significance. In: Horlick M, (ed). *Vitamin D: Molecular Biology, Physiology and Clinical Applications*. Totowa, NJ: Humana Press Inc, 1999, p. 102.
11. Grymonprez A, Proesmans W, Van Dyck M *et al.* Vitamin D metabolites in childhood nephrotic syndrome. *Pediatr Nephrol* 1994; 9: 278–281

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