EDITORIAL COMMENTARY

Hypervitaminosis D and nephrocalcinosis: too much of a good thing?

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Introduction

The worldwide interest in vitamin D appears insatiable and shows no sign of abating. Literature on vitamin D spans a wide range of clinical specialties, including endocrinology, immunology, and nephrology, among many others. In almost all fields, the same debate continues with both proponents and opponents of vitamin D supplementation, yet questions of "how much" and "for how long" remain subjects of considerable discussion but with no clear consensus among clinicians or researchers. Despite little compelling evidence of benefit on almost all of the health outcomes investigated to date [1, 2], the last two decades have witnessed a significant increase in vitamin D consumption [3–6]. This may reflect in part the increased testing for vitamin D deficiency in response to widespread public health initiatives [5, 7, 8]. On the other hand, evidence of indiscriminate use of vitamin D supplements may suggest an emerging "more is better" attitude which deserves our attention [9–11].

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Vitamin D, the "sunlight hormone"

Vitamin D is obtained by humans through cutaneous synthesis and from dietary sources, with cutaneous production contributing up to 90% of an individual's vitamin D requirement [12]. Few foods naturally contain or are fortified with vitamin D [12]. Vitamin D supplements, either as ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3), thus provide an alternative source and are particularly important for individuals with little or no sunlight exposure. To be biologically active, vitamin D, transported bound to vitamin D binding protein, is metabolized by a series of cytochrome P450-containing hydroxylases to 25-hydroxyvitamin D (25(OH)D), the major circulating metabolite of vitamin D, followed by 1α-hydroxylation which results in the formation 1α,25-dihydroxyvitamin D (1α,25(OH)$_2$D) [12]. This latter step principally occurs in the kidney, and it is 1α,25(OH)$_2$D, which acts through its nuclear receptor, that enhances calcium and phosphate absorption in the small intestine, bone demineralization to release calcium into the circulation, and renal calcium reabsorption [12].

Vitamin D in chronic kidney disease

In the chronic kidney disease (CKD) population, studies in children report a vitamin D deficiency prevalence of 50–92%, with a negative association between CKD stage and 25(OH)D concentrations [13]. Several reasons have been suggested for the high prevalence including inadequate sunlight exposure, low dietary intake, proteinuria and accompanied losses of vitamin D metabolites, increased catabolism of vitamin D metabolites due to secondary hyperparathyroidism, and the negative effect of uremia on cutaneous 25(OH)D synthesis [13, 14]. This reduction in substrate 25(OH)D is thought to be one of the contributing factors to the reduction in 1α,25(OH)$_2$D production, driving the pathogenesis of secondary hyperparathyroidism in CKD patients [13].

Benefits of vitamin D in CKD

The role of vitamin D in intestinal calcium absorption and maintaining calcium homeostasis and skeletal integrity is indisputable. Intuitively, improving the vitamin D status of those who are deficient appears sensible, although what constitutes deficiency is controversial, and evidence to show true patient level benefits, not simply the correction of biochemical abnormalities, is lacking.

Evidence on the effects of vitamin D supplementation on bone, fracture prevention, and growth in otherwise healthy children is inconclusive [15, 16], and there are even fewer studies in CKD patients [17]. While most studies in children with CKD have evaluated biochemical end-points only, randomized controlled trials (RCTs) have assessed the effects of vitamin D supplementation on clinical outcomes. In our paper on prevention of secondary hyperparathyroidism, it was shown that children on ergocalciferol who achieved 25(OH)D concentrations > 30 ng/mL had a significantly longer time to development of secondary hyperparathyroidism (hazard ratio = 0.30, 95% confidence interval = 0.09–0.93) compared with those children on placebo [18]. The study by Rianthavorn et al. also points to a possible beneficial role; they reported a significant decrease in the dose of erythrocyte-stimulating agent required in children with CKD stages 5 and 5D treated with ergocalciferol for 12 weeks; a change that was not observed in the control group [19].

While knowledge on the non-calcemic effects of vitamin D awaits prospective RCTs, there is growing and converging evidence from in vitro, clinical, and epidemiological studies suggesting potential beneficial effects of vitamin D supplementation [13, 17, 20]. Observational studies have shown an association between vitamin D deficiency in CKD patients and increased arterial calcification and stiffness [20]. Moreover, there is emerging evidence of anti-hypertensive and anti-proteinuria effects of vitamin D, suggesting that vitamin D may have a cardioprotective effect and slow down the progression of CKD [20].

Vitamin D in children with CKD

There is consensus across government organizations and professional societies in Europe and North America that serum 25(OH)D concentration should be maintained above 10 ng/mL, but beyond this, the debate continues over the optimal concentrations of 25(OH)D required for health [2, 21, 22].

In children with CKD, the European Society for Paediatric Nephrology clinical practice guideline recommends a target 25(OH)D concentration of 30 ng/mL based on an in-depth review of the available evidence, while acknowledging that the optimal target concentration of 25(OH)D in CKD patients is unclear and may need to be higher than that in the general population [17]. In addition, patients with CKD may need higher doses of vitamin D supplements in order to achieve target concentrations compared to the healthy age-matched population. An RCT by Greenbaum et al. has recently shown that a dose of 4000 IU of cholecalciferol was required to achieve and maintain vitamin D sufficiency in children with CKD stages 3–5, with a lower dose of 1000 IU daily being inadequate [23]. Similarly, an RCT by Iyengar et al. shows that an equivalent dose of 3000 IU/day of cholecalciferol provided as either daily, weekly, or monthly treatments was needed to achieve equivalent 25(OH)D concentrations [24]. There are also data indicating that children with proteinuria may require higher doses to achieve target 25(OH)D concentrations [24], presumably due to the loss of 25(OH)D bound to vitamin D binding protein.

Hypervitaminosis D

Like other therapeutic treatments, vitamin D in excess may be harmful. Early reports of hypervitaminosis D in children were attributed to overfortification of infant formula with reports of an outbreak in the United Kingdom (UK) during the 1950s when a small number of infants presented with hypercalcemia, failure to thrive, abnormal facies, learning difficulties, and nephrocalcinosis [25]. While some of these cases have now been attributed to other disorders, such as Williams syndrome or mutations in enzyme-coding genes such as *CYP24A1* responsible for vitamin D catabolism [26], case reports of hypervitaminosis D due to both intentional and inadvertent administration of large doses of vitamin D have continued to appear in the literature with increasing frequency [9, 11]. Attempts to consolidate our understanding of hypervitaminosis D have so far been slow; we have learned that the association between the amount of vitamin D administered and the resulting serum 25-hydroxyvitamin D 25(OH)D concentrations is unpredictable, and even with comparable serum 25(OH)D concentrations, variations were seen in the severity of hypercalcemia and presenting symptoms, such as nephrocalcinosis, between individuals [27–29]. Thus, an important question remains unanswered: how much is too much?

Hypervitaminosis D and nephrocalcinosis

In this issue of *Pediatric Nephrology*, Lin et al. investigate hypervitaminosis D-related nephrocalcinosis in a retrospective cohort study of 44 children exposed to an erroneously manufactured nutritional vitamin D supplement [30]. The

authors evaluated the clinical features of these children and explored risk factors associated with the development of nephrocalcinosis.

Hypervitaminosis D is a well-known cause of nephrocalcinosis. However, literature delineating the relationship between vitamin D and the development of nephrocalcinosis is scarce. The study by Lin et al. sheds light on this important issue, and furthermore, the longer-term follow-up data is useful as published reports on hypervitaminosis D have largely focused on the immediate clinical features and management only [30].

Lin et al. observed that nephrocalcinosis was present in 32% (14/44) of children [30], which is close to the 39.5% (15/38) recently reported by Çağlar and Çağlar [31]. However, the 25(OH)D concentrations at which nephrocalcinosis was observed differed in these studies as well as from previously reported cohorts. Lin et al. observed a median 25(OH)D concentration of 150 ng/mL (interquartile interval: 190; 5/14 children had 25(OH)D $\leq$ 150 ng/mL) at initial presentation, whereas Çağlar and Çağlar and Vierge et al. reported a mean of 459 ng/mL (standard deviation: 68) and a median of 66 ng/mL (range: 48–140), respectively [30–32]. However, caution in interpretation is needed given consumption of supplement had stopped for a variable period of 3 days to 5 months in the study by Lin et al. [30], whereas Çağlar and Çağlar had an inclusion 25(OH)D threshold of 150 ng/mL [31], and the study by Vierge et al. was limited to preterm neonatal referrals (corrected age at presentation ranged from 37 to 68 weeks) made to pediatric nephrology clinics [32].

An important point to note from both the Lin et al. and Çağlar and Çağlar studies is the age of children who developed nephrocalcinosis [30, 31]. Lin et al. show that younger age is associated with an increased risk of the development of nephrocalcinosis [30]. While Çağlar and Çağlar found no significant difference in age, all patients in their cohort were less than 4 years old [31], a trend which seems consistent with other published reports in children [8, 33, 34].

Although not the primary focus of their analysis, Lin et al.'s work also provides interesting insights into the long-term consequences of hypervitaminosis D on the kidney [30]. Their findings that nephrocalcinosis persisted in all patients during the 5-year follow-up period raise concerns of irreversible kidney damage, albeit the lack of more granular follow-up data precluded further analysis [30]. Indeed, concerns for long-term sequelae of nephrocalcinosis are particularly relevant for a developing kidney in the setting of neonates and infants, especially preterm neonates [32, 35]. Nonetheless, taking steps to safeguard against the avoidable risk of hypervitaminosis D and thus nephrocalcinosis should be a key consideration in the use of vitamin D supplements in all children.

Lin et al. acknowledge that the retrospective nature of their study, selection bias due to self-referral, and the variable amount of vitamin D consumed limit the ability to identify a causal relationship between vitamin D supplementation and nephrocalcinosis, and potentially undermine the validity of the identified risk factors for nephrocalcinosis [30]. Regardless, vitamin D-mediated hypercalcemia is consistent with the pharmacology of vitamin D, and calcium is central to the development of nephrocalcinosis. It is also noteworthy to recognize that a reasonable cohort size is difficult to achieve in this area of research due to the small number of cases, and therefore, the ability to analyze the confounding effects of covariates is often challenging.

Patients at risk of hypervitaminosis D

Younger children appear to be more susceptible to hypervitaminosis D [31, 36, 37], but pathophysiological mechanisms for this are not clear. The higher prevalence of hypervitaminosis D may reflect, in part, a greater use of vitamin D supplements in infants and toddlers. It may also point to a need to consider a more optimized dosing strategy in younger children. Lin et al. did not explore the association between 25(OH)D concentrations and dose [30], but other studies have suggested the need for body size-based dosing for vitamin D [38–40]. In CKD patients, our population pharmacokinetic model lends support for weight-based dosing, with model-based simulation showing improvement in attainment of target 25(OH)D concentrations while minimizing the risk of overdosing [40].

More importantly, those with reduced renal reserve, such as infants and children with CKD, would be most susceptible to hypercalciuria induced by hypervitaminosis D, and thus may be at a higher risk of nephrocalcinosis.

Unlicensed vitamin D preparations: a cautionary tale

Lin et al.'s study also highlights the public health risks of unregulated manufacture of dietary vitamin D supplements [30], as previously reported from the UK [6], New Zealand [41], USA [42], Canada [43], and India [44], all demonstrating a lack of quality control of these products. These studies all report wide variations between measured and declared vitamin D content; in our study of UK marketed vitamin D supplements, the 11 products tested showed vitamin D content ranging from $41.2 \pm 10.6\%$ to $165.3 \pm 17.8\%$ of the labelled claim [6, 41–44]. It would thus be prudent for clinicians to ensure that only quality assured products are supplied when prescribing pharmacological doses of vitamin D, as well as reinforcing the message that vitamin D is important for health, but more is not necessarily better.

Conclusion

Hypervitaminosis D is rarely reported, but the widely prevalent and overzealous use of vitamin D supplementation is likely to result in more cases of this avoidable complication. Based on the report by Lin et al. [30], we cannot be certain of the relationship between the amount of vitamin D consumed, 25(OH)D concentration, and the development of nephrocalcinosis. However, it does suggest that nephrocalcinosis can occur at a 25(OH)D concentration lower than what is generally considered to be toxic (i.e., 150 ng/mL). Of note, large epidemiological studies have suggested a reverse J-shaped association between 25(OH)D concentrations and increased all-cause mortality, with an increased risk at 25(OH)D concentrations > 48 ng/mL [45, 46]. In this regard, avoiding a 25(OH)D concentration above 50 ng/mL in children would seem reasonable, especially in the absence of compelling data demonstrating a beneficial effect of higher 25(OH)D concentrations [17, 22]. A further cautionary argument is that CKD patients may have reduced urinary calcium excretion and be more prone to nephrocalcinosis and kidney impairment [17]. Therefore, clinicians and parents should be aware of the potential adverse effects of using unlicensed vitamin D preparations, as well as inadequate monitoring of vitamin D supplementation and the possibility of unintentional vitamin D overdose.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

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Conflict of interest The authors declare no competing interests.

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