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Vitamin D and Kidney Stone Disease

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Abstract and Introduction

Abstract

Purpose of review Vitamin D is important in maintaining calcium homeostasis, but its role in kidney stone disease and its effect on stone formation are still not clear.

Recent findings Kidney stone formers tend to experience enhanced intestinal calcium absorption, increased urinary calcium excretion, and excessive bone mineral loss. Although direct actions of active vitamin D have been implicated in all these processes, the effect of nutritional vitamin D (vitamin D_2 or vitamin D_3) use on calcium balance among stone formers is still not clear. In addition, the safety of nutritional vitamin D use in the stone forming population is also not established, considering the potential effect of its use on raising urinary calcium. However, most of the observational studies do not support a significant association between higher nutritional vitamin D store and increased risk of stone formation. Short-term nutritional vitamin D repletion in stone formers with vitamin D deficiency also does not appear to increase urinary calcium excretion.

Summary The effect of nutritional vitamin D use in stone formers is still not clear. As vitamin D deficiency is highly prevalent among stone formers, future prospective studies are needed to establish the biological effect, as well as the safety and efficacy of nutritional vitamin D therapy in this unique patient population.

Introduction

Vitamin D is a fat-soluble vitamin that also acts as a pleiotropic hormone. There are two major forms of nutritional vitamin D, vitamin D_2 and D_3. Vitamin D undergoes sequential hydroxylations, and reaches its final active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. $1,25(OH)_2D$ interacts with its nuclear receptor to modulate gene expression and biological actions. The vitamin D receptor (VDR) is present in a wide variety of cells including enterocytes, osteoblasts, and renal tubular cells. Vitamin D is crucial for proper functions of a wide variety of organ systems, and its deficiency is highly prevalent in the general population and also among kidney stone formers.

Elkoushy *et al*.[1] showed that more than 80% of stone formers that were evaluated in their stone clinic from August 2009 to January 2010 had vitamin D deficiency or insufficiency defined as serum 25-hydroxyvitamin D [25(OH)D] concentration less than 30 ng/ml. Eisner *et al*.[2] also found that 53.8% of stone formers from two major stone clinics in Boston and Rhode Island had serum vitamin D less than 30 ng/ml. Recently, we reported serum 25(OH)D concentrations among 757 adult stone formers in the Third United States National Health and Nutritional Examination Survey (NHANES III), and found that the mean serum level was 29 ng/ml.[3]

$1,25(OH)_2D$ is a key regulator of calcium homeostasis, and as 80% of kidney stones are calcium based, use of vitamin D is thought to increase the risk of stone formation. This is consistent with the observation that stone formers have a higher serum $1,25(OH)_2D$ concentration.[4] At this time, there is no consensus in the management of nutritional vitamin D supplementation in patients with kidney stone disease who are vitamin D deficient. In clinical practice, physicians often withhold calcium and vitamin D supplementation in stone formers even when they are vitamin D deficient.[5] However, this practice has led to other clinical problems, most notably deteriorating bone condition, as reduced bone mineral density is highly prevalent in kidney stone formers,[6–8] and nutritional vitamin D supplementation is important in maintaining dynamic calcium and bone balance.[9–12] Here, we will provide an in-depth review of existing literature that addressed the role of vitamin D in calcium handling among stone formers and its link to kidney stone disease.

Genetic Studies

Genetic predisposition to calcium based kidney stone disease has long been recognized. Hypercalciuric nephrolithiasis has been found to be a familial disorder in more than 35% of patients.[13] Twin studies have shown that the proband concordance rate in monozygotic twins (32.4%) was significantly greater than the rate in dizygotic twins (17.3%; $P < 0.001$), consistent with a genetic influence.[14] Even though kidney stones can develop in certain monogenic disorders, that is, Dent disease and hypophosphatemic rickets with hypercalciuria, family-based association study suggested a polygenic pattern of inheritance in most familial cases.[15] Several genes have been tested through linkage analysis in a cohort of 47 French Canadian pedigrees with calcium stones and idiopathic hypercalciuria. Candidate genes included those encoding 25(OH)D 1α-hydroxylase, VDR, calcium sensing receptor (CaR), uromodulin, osteocalcin, and osteopontin. Of these genes, only the *VDR* locus showed

linkage with kidney stone formation.[16–19] The linkage between VDR and kidney stone formation was later confirmed in a study of Northern Indian families.[20]

In addition to gene linkage analysis, case–control association studies also examined the relationship between *VDR* polymorphism and kidney stone formation. Mossetti *et al*.[21] examined *VDR* polymorphisms of BsmI and TaqI alleles in recurrent stone formers with idiopathic hypercalciuria, and found a particular homozygous haplotype that was associated with more aggressive kidney stone disease manifested by a higher familial incidence and younger age at onset. It was also associated with higher urinary supersaturation of calcium oxalate and lower urinary citrate excretion. Two other independent groups have reported an association of *VDR* gene TaqI polymorphism with recurrent kidney stone formation in both Japanese adults and Turkish children.[22,23] There are other *VDR* polymorphisms that have been reported in hypercalciuric stone formers;[24,25] however, these findings are still controversial.[26,27] More importantly, none of the *VDR* polymorphisms have been identified to have an association with kidney stone formation in a recent genome-wide association study from Iceland and The Netherlands.[28] Instead, *Claudin*-14 gene variants had a significant association with stone formation. Claudin-14 is expressed in the kidney and regulates paracellular permeability at epithelial tight junctions.

Vitamin D and Intestinal Calcium Absorption in Stone Formers

Vitamin D is crucial in regulating calcium absorption in the small intestine. $1,25(OH)_2D$ stimulates the expressions of several calcium transport proteins in the duodenum, including an apical calcium channel – transient receptor potential vanilloid member 6 (TRPV6), calbindin that regulates intracellular transport, and Ca-ATPase that is important for the removal of calcium from the basolateral side.[29,30]

Existing studies have demonstrated that there is an enhanced intestinal calcium absorption in a subgroup of patients with idiopathic hypercalciuria,[31–33] and the high intestinal calcium absorption in these patients is likely a primary process, rather than a response to urinary calcium loss. Pak *et al*.[34] examined a group of stone formers with idiopathic hypercalciuria and demonstrated an increased renal calcium excretion after an oral calcium load, and normalized urinary calcium excretion when intestinal calcium absorption was limited by fasting or by cellulose phosphate. There are two proposed mechanisms:[35] a response to inappropriately high serum $1,25(OH)_2D$ concentration, or an enhanced intestinal vitamin D response under normal $1,25(OH)_2D$ levels. In a genetic rat model with idiopathic hypercalciuria, administration of $1,25(OH)_2D$ resulted in an enhanced *VDR* gene expression and prolonged in-vivo half-life of VDR mRNA in the duodenum of hypercalciuric rats, but not in normocalciuric controls.[36] In the same rat model with normal serum concentrations of $1,25(OH)_2D$, intestinal cells contained twice the abundance of VDR compared with normocalciuric controls, suggesting an enhanced intestinal vitamin D response.[37] It is important to note that the affinity of VDR for its ligand was not different between hypercalciuric rats and normal controls, and the enhanced intestinal calcium absorption was independent of parathyroid hormone (PTH) concentration.[38] In humans, Favus *et al*.[39] examined the expression of VDR in peripheral blood monocytes of 10 male stone formers with idiopathic hypercalciuria, and found more than twice the amount of VDR among stone formers as compared to their age-matched controls. Unfortunately, the VDR expression in intestinal cells was not examined in their study.

Although $1,25(OH)_2D$ is able to enhance intestinal calcium absorption in stone formers with idiopathic hypercalciuria, the role of nutritional vitamin D use in calcium absorption is unclear. The intestinal cells possess 1-α hydroxylase,[40] providing local $1,25(OH)_2D_3$ critical in maintaining the intestinal autocrine/paracrine vitamin D system. Thus far, no study has examined the independent effect of 25(OH)D on intestinal calcium absorption in stone formers prospectively.

Vitamin D and Renal Calcium Reabsorption in Stone Formers

In the kidney, activation of CaR is important in reducing paracellular calcium reabsorption in the thick ascending limb (TAL) of the loop of Henle.[41] It also inhibits PTH-induced apical calcium entry at the TAL,[42] and has been shown to block calcium exit from tubular cells by suppressing Ca-ATPase activity.[43] CaR expression is regulated by active vitamin D, and is PTH independent.[42,44,45] Furthermore, CaR is able to up-regulate VDR gene expression,[46] and therefore may create a self-amplifying process to potentiate vitamin D action on renal calcium handling.

Studies have shown that a subgroup of patients with idiopathic hypercalciuria fail to reduce urinary calcium excretion under dietary calcium restriction or fasting,[47,48] suggesting a primary disorder in renal tubular calcium reabsorption. The underlying mechanism is still not clear, although the vitamin D dependent overexpression of renal CaR might be the cause. Several studies have shown that high $1,25(OH)_2D$ concentration associates with increased urinary calcium excretion.[49,50] In addition, VDR expression in the kidney may also be upregulated,[36,37] allowing an enhanced vitamin D response despite a normal serum $1,25(OH)_2D$ concentration.

Even though $1.25(OH)_2D$ has been shown to associate with higher urinary calcium excretion,[4,51,52] less is known about the

effect of nutritional vitamin D supplementation on renal calcium handling among stone formers. Eisner *et al*.[2] examined the correlation between serum 25(OH)D concentration and 24-h urine calcium among 169 adult stone formers (~46% had calcium based stones). Univariate analysis revealed no difference in urinary calcium excretion between stone formers with normal serum 25(OH)D concentrations and those with 25(OH)D concentrations less than 30 ng/ml (231.5 mg/day vs. 246.4 mg/day, $P = 0.5$). Age-adjusted regression analysis also failed to show any type of association between serum 25(OH)D concentration and the amount of 24-h urine calcium [β regression coefficient = −0.31, 95% confidence interval (CI) −1.9 to 1.3]. Finally, in multivariate regression analysis adjusted for demographics and other known risk factors for stone disease, serum 25(OH)D concentration was again not associated with urinary calcium excretion (β = 0.08, 95% CI −1.3 to 1.5). The study, however, did not adjust for most of the confounding dietary factors.

The only prospective study of the effect of nutritional vitamin D use on urinary calcium excretion was reported by Leaf *et al*.[53] They recruited 29 stone formers with baseline urinary calcium excretion of 150–400 mg/day and with inadequate vitamin D store defined as serum 25(OH)D concentration less than 30 ng/ml. All participants received 8 weeks of oral ergocalciferol at a weekly dose of 50 000 IU. At the end of the study, despite a significant increase of serum 25(OH)D concentration, the mean 24-h urine calcium excretions were not different before and after the treatment (257 ± 54 vs. 255 ± 88, $P = 0.9$). Individually, 11 of 29 participants had an increase in urinary calcium excretion of at least 20 mg/day, but these 11 participants also had increases in urinary sodium and urea nitrogen excretions, suggesting a confounding effect from diet. The major limitation of the study is the large intrapersonal variations in urinary calcium excretion, which compromised the overall statistical power of the study. In addition, total body calcium balance was not examined. Despite these limitations, the study did provide direct evidence that nutritional vitamin D repletion in stone formers with low vitamin D does not appear to increase urinary calcium excretion, even among those with high baseline urinary calcium excretion. Therefore, vitamin D supplementation may lead to a positive calcium balance and be beneficial for maintaining bone health without increasing the risk for stone formation.

Vitamin D and Bone Mineral Loss in Stone Formers

Bone serves as a reservoir for calcium and is also important in maintaining calcium homeostasis. An abnormal bone-plate phenotype and growth-plate phenotype was found in VDR or 1α-hydroxylase knockout mice.[54] $1,25(OH)_2D$ has a direct effect on bone by inducing osteocalcin and osteopontin, which are important for new bone formation and bone resorption, respectively.[55,56] In addition, it regulates osteoblastic differentiation,[11] and can promote osteoblast-mediated osteoclast formation.[57] Therefore, $1,25(OH)_2D$ maintains dynamic bone balance via its effects on both bone formation and resorption.

In a genetic rat model with idiopathic hypercalciuria, rats fed with a low-calcium diet continue to have inappropriately high urinary calcium excretion, suggesting that abnormal bone mineral wasting accounts for the negative calcium balance.[58,59] In patients with idiopathic hypercalciuria, calcium balance study using calcium-restricted di*et al*so confirmed this finding.[47] Fuss *et al*.[60] measured radius bone mineral content (BMC) by single-photon absorptiometry, and found a significantly reduced BMC in 123 male stone formers compared with nonstone forming controls. Furthermore, BMC appears to correlate negatively with fasting urinary calcium excretion among stone formers.[61] Recently, Heller *et al*.[62] performed a histomorphometric analysis of iliac crest biopsies from nine stone formers with absorptive hypercalciuria and nine matched controls. Compared with controls, the stone formers had lower indices of bone formation (osteoblast surface/bone surface 1.8 ± 2.1% vs. 3.0 ± 1.5%, $P = 0.04$) and relatively higher indices of bone resorption (osteoclast surface/bone surface 0.4 ± 0.2% vs. 0.2 ± 0.2%, $P = 0.05$). Furthermore, a short course of alendronate treatment in these stone formers corrected fasting urinary calcium to creatinine ratio (0.14 ± 0.06 to 0.06 ± 0.04, $P = 0.001$), reduced 24-h urine calcium by 48 mg ($P = 0.06$), and significantly improved the estimated calcium balance ($P = 0.007$). The study again proved that excessive bone resorption contributed to the urinary calcium loss in stone formers, despite high intestinal calcium absorption.

The cause of bone loss in stone formers is not clear. Exposure to high doses of $1,25(OH)_2D$ has been shown to stimulate bone resorption and decrease collagen synthesis.[63] In genetic hypercalciuric stone forming rats with normal levels of serum $1,25(OH)_2D$, bone contains higher levels of VDR and has increased sensitivity to exogenous $1,25(OH)_2D$ when compared with the bone from control animals,[58] suggesting an enhanced bone response to active vitamin D. Recently, in a mouse model with reduced trabecular and cortical bone thickness, low BMC, and secondary hypervitaminosis D caused by targeted ablation of *TRPV5* gene, treatment with a vitamin D analogue (likely acts as a vitamin D antagonist) led to a partial restoration of bone phenotype and improved mineralization as shown by bone microarchitecture analysis and quantitative backscattered electron imaging.[64] Although excessive $1,25(OH)_2D$ action may lead to abnormal bone mineralization in the stone forming population, evidence is lacking regarding the effect of nutritional vitamin D supplementation on bone in patients with kidney stone disease, especially in those with vitamin D deficiency.

Link Between Vitamin D Store and Risk of Kidney Stone Formation

There have been a few epidemiological/interventional studies examining the link between body vitamin D store and kidney stone

formation ([2-4,51-53,65,66]). In a small study involving 160 stone formers and 217 controls, Netelenbos *et al*.[65] failed to show any significant difference in serum 25(OH)D concentrations between stone formers and nonstone formers. We examined the independent association of high serum 25(OH)D concentration with prevalent kidney stone disease among participants of NHANES III.[3] Out of 16 286 adult participants, 757 reported history of previous kidney stones. Concentrations of serum 25(OH)D were not different between stone formers and nonstone formers (P = 0.6). Higher 25(OH)D concentration was not associated with increased odds ratio (OR) for previous kidney stones (OR = 0.99; 95% CI 0.99–1.01) after adjustment for age, sex, race, history of hypertension, diabetes, BMI, diuretic use, and serum calcium. Furthermore, after we divided 25(OH)D concentrations into quartiles, or into groups using higher cutoffs (e.g., 40 and 50 ng/ml), there were still no significant differences in stone formation among group comparisons. Our study suggested that stone formers do not carry an increased vitamin D store in the form of serum 25(OH)D concentration. In addition, higher serum concentrations of 25(OH)D do not appear to increase the risk of kidney stone disease. However, our study has several limitations including the cross-sectional study design that prevented us from establishing any causal relationships.

Table 1. Summary of studies examining the link between vitamin D and risk of kidney stone formation

Investigators	Study participants	Interventions	Study outcomes	Findings
Epidemiological studies				
Eisner BH, *et al*.[2]	169 adult stone formers from Boston and Rhode Island	n/a	24-h urine calcium	Serum 25(OH)D concentration was not associated with urinary calcium excretion
Tang J, *et al*.[3]	Adult NHANES III participants, include 757 prevalent stone formers, 15 529 nonstone formers	n/a	Prevalent kidney stone disease	There was no difference in concentrations of serum 25(OH)D between prevalent stone formers and control individuals. Higher serum vitamin D concentration was not associated with increased risk of prevalent kidney stone disease
Shakhssalim N, *et al*.[4]	106 adult male recurrent calcium kidney stone formers, 109 age and sex matched controls	n/a	Serum levels of $1,25(OH)_2D$, parathyroid hormone, calcitonin, estradiol and testosterone	Serum $1,25(OH)_2D$ levels in stone formers were significantly higher than controls (P<0.001). Serum $1,25(OH)_2D$ levels were also associated with higher urinary excretion of calcium and phosphorus in stone formers.
Giannini S, *et al*.[51]	75 adult calcium stone formers	n/a	Urinary calcium and oxalate excretions	There was a positive correlation between serum $1,25(OH)_2D$ concentration and urinary calcium excretion (P<0.001) and urinary oxalate excretion (P<0.003)
Jarrar K, *et al*.[52]	111 adult stone formers (57 with calcium stones), 44 controls	n/a	Concentrations/quantifications of calcium, phosphate and uric acid in serum/urine	Serum $1,25(OH)_2D$ level correlated positively with urinary calcium excretion in calcium stone formers and controls.
Netelenbos JC, *et al*.[65]	160 calcium stone formers, 217 controls	n/a	Serum 25(OH)D and $1,25(OH)_2D$	No difference in concentrations of serum 25(OH)D, and $1,25(OH)_2D$ between stone formers and control individuals.
Berlin T, *et*	108 adult male stone formers	n/a	Serum 25(OH)D	There was a positive association between urinary

al.[66]				calcium excretion and serum 25(OH)D level
Interventional study				
Leaf DE, *et al*.[53]	29 adult stone formers from New York Presbyterian Hospital, with urinary calcium excretion 150–400 mg/day and serum 25(OH)D <30 ng/ml.	Ergocalciferol 50 000 IU weekly × 8 weeks	24-h urine calcium before and after vitamin D supplementation	No change in mean 24-h urine calcium excretion

$1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; NHANES, National Health and Nutritional Examination Survey.

The Women's Health Initiative is a double-blinded, placebo-controlled trial, which randomly assigned 36 282 postmenopausal women in the United States to 1000 mg elemental calcium plus 400 IU of vitamin D_3 daily (*n* = 18 176) or placebo (*n* = 18 106), for an average of 7 years. Wallace *et al*.[67] reported a modest increase of kidney stone risk among participants in the intervention group. Among all participants, 449 (0.35%) in the intervention group and 381 (0.30%) in the placebo group developed kidney stone during the trial period, with a stone hazard ratio of 1.17 (95% CI 1.02–1.34). However, the study was limited by low adherence rate, only 60–63% took at least 80% of the assigned medication for the first 3 years of the study. Subsequent analysis among adherent women showed a hazard ratio of 1.21 (95% CI 0.98–1.50) and the association was no longer significant. The study also did not assess the effect of vitamin D on stone formation independent of calcium, especially considering that high calcium intake can increase the half-life of nutritional vitamin D.[68]

Conclusion

Vitamin D is important in regulating calcium balance in kidney stone formers via its actions on skeletal mineralization, intestinal calcium absorption, and kidney calcium reabsorption (Fig. 1). Most of the existing evidence does not indicate that a high vitamin D store is associated with an increased risk of kidney stone formation. Standard course of vitamin D repletion among stone formers with inadequate vitamin D also does not appear to increase urinary calcium excretion, although the effect of long-term maintenance vitamin D therapy remains to be determined. As vitamin D deficiency is highly prevalent in the stone forming population, we still need large-scale prospective study to establish the safety and efficacy of nutritional vitamin D therapy in this unique patient population.

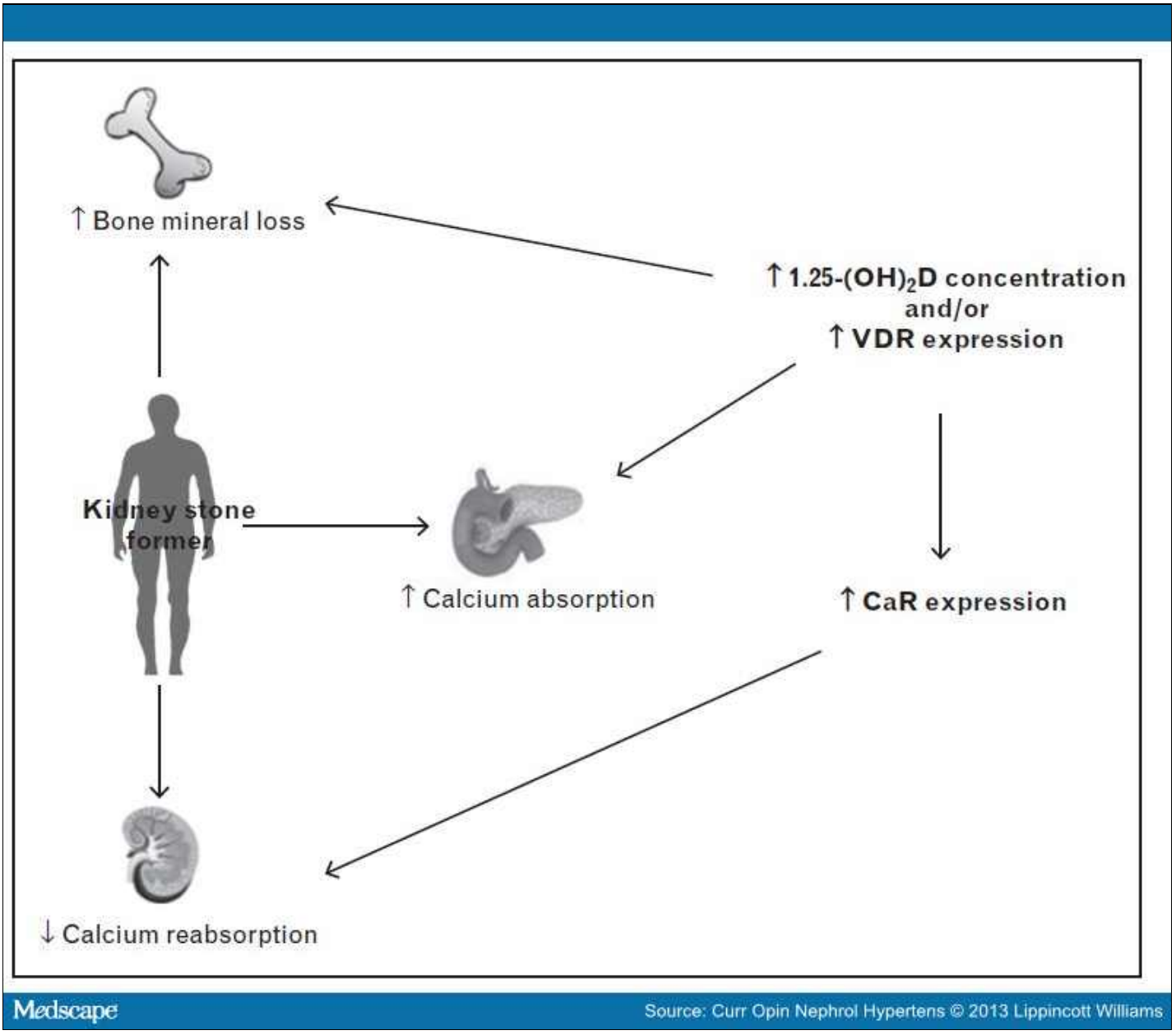

Figure 1.

Calcium handling in kidney stone formers. Stone formers are more likely to have increased calcium absorption through the small intestine, reduced calcium reabsorption in the kidney and increased mineral loss from the bone. Active vitamin D has been linked to these processes either directly or indirectly. 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D; CaR, calcium sensing receptor; VDR, vitamin D receptor.

Sidebar

Key Points

- 1,25$(OH)_2$D is important in regulating calcium balance in patients with kidney stone disease, and may play an important role in kidney stone formation.
- Higher body 25(OH)D store does not appear to be associated with a higher risk of kidney stone disease.
- Short-term nutritional vitamin D supplementation in stone formers with vitamin D deficiency or insufficiency does not appear to increase urinary calcium excretion.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 490–491).

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