Vitamin D and Kidney Stones

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This review explores the relationship between vitamin D supplementation and lithogenesis. A causal relationship has been assumed despite myriad studies demonstrating that therapeutic doses of vitamin D do not increase lithogenic risk. Select stone formers may be at increased risk for recurrence with vitamin D supplementation, possibly from *CYP24A1* gene mutations. Additionally, the evidence for who is vitamin D deficient, and the benefits of supplementation in those not at risk for rickets, is sparse. Concerns may be avoidable as vitamin D screening appears unnecessary in most patients, and superior pharmacology is available which increases bone density, while decreasing stone formation. UROLOGY 139: 1–7, 2020. © 2020 Elsevier Inc.

In this review, we explore the relationship between vitamin D and lithogenic risk, and propose alternatives for stone formers who require pharmacologic intervention for bone health. The most recent National Health and Nutrition Examination Survey reports that the prevalence of kidney stones in the United States has almost tripled since 1980. The lifetime prevalence for stones is currently at 8.8% and more prevalent in men though women are closing the gap.[1] Calcium stones are by far the most common type of stone, comprising more than 85% of all stones.[2] Renal calculi are associated with increased body mass index, weight gain, diabetes,[1] as well as diets heavy in animal protein and sodium, while they are inversely related to fluid intake, potassium, and dietary calcium.[2] Higher urine calcium excretion is a significant risk factor for kidney stones and is associated with low bone mineral density (BMD)[3] and fractures.[4]

Considering that intestinal absorption of calcium results in a significant proportion of calciuria in stone formers,[5] there is a theoretical risk that vitamin D supplementation may increase intestinal absorption and lithogenesis. Recent data have shown no risk of kidney stones with vitamin D supplementation in the general population.[6] However, whether vitamin D ingestion or elevated serum levels results in stones in known stone formers or genetically predisposed subgroups remains an open question. Vitamin D deficiency has been associated with a wide range of diseases and as such, a surge in testing and prescriptions has ensued.[7] The overlap between frequent vitamin D supplementation and higher prevalence of kidney stones has led to exploration of a causal relationship. The question has importance since the benefits of screening for vitamin D and supplementing it in response to low values appears to offer little benefit, even in those with reduced BMD.

GENESIS OF CALCIUM KIDNEY STONES

Calcium stone formation is a complex physiological process, extensively investigated with multiple purported mechanistic models, the details of which are beyond the scope of this review. While much is still unknown, the broad prerequisites for stone formation are higher supersaturation, crystallization, growth, and aggregation. The complex chemical properties of urine such as pH, polyionic content, concentrations of promoters, and inhibitors all contribute. A common urinary abnormality in calcium stone formers is higher urine calcium excretion, the explanation of which is often not found. Such patients are said to have idiopathic calcium stones. Genetic factors are undoubtedly important but implicated genes do not fully account for the evidence for significant heritability.

As most stones are composed of calcium, its metabolism and dietary mechanisms of control are of strong interest. Importantly, calcium restriction does not reduce stone formation. In fact limiting dietary calcium increases lithogenic urine factors and can lead to bone demineralization,[2] a phenomenon found to be more pronounced in stone formers, a population already at increased risk for vitamin D inadequacy,[8] decreased BMD, and fracture.[4] Curhan et al in a large prospective study found an inverse risk for dietary calcium intake and kidney stones.[2] The authors proposed that calcium ingestion binds dietary oxalate, reducing its absorption by the bowel and subsequent excretion in the urine. Calcium supplements on the other hand have been associated with an increased risk of stones. Failure to administer oral calcium supplements at the same time as dietary oxalate may provide an explanation for the discrepancy. There may be implications for which formulation of calcium supplement is used, as calcium citrate may be less lithogenic than calcium carbonate.[9] Vitamin D is integral in calcium homeostasis and bone metabolism and its supplementation has been a topic of some controversy in both stone formers

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and nonstone formers alike with regards to bone density, necessity, safety, and efficacy.

VITAMIN D METABOLISM

Vitamin D is a fat-soluble vitamin, inactive in its natural form and obtained largely and efficiently from sunlight-stimulated synthesis in the skin, and less so from diet. Vitamin D undergoes hydroxylation in the liver by 25-hydroxylase (*CYP2PR1*) resulting in 25-hydroxyvitamin D_3. Subsequent hydroxylation, largely in the kidney, by 1α-hydroxylase (*CYP27B1*) results in the production of the bioactive form 1,25-dihydroxyvitamin D_3 (calcitriol). Calcitriol binds to intracellular receptors in target tissues, promoting transcription of a variety of relevant genes. The primary function of calcitriol is promotion of enteric calcium absorption. However it also directly suppresses release of parathyroid hormone (PTH), promotes renal and intestinal phosphate absorption, and regulates osteoblastic function and bone resorption. 24-hydroxylase (*CYP24A1*) deactivates 1,25-dihydroxyvitamin D_3 to calcitroic acid (Fig. 1). It also acts on the precursor 25-hydroxyvitamin D_3, under the control of several negative feedback mechanisms, to prevent its conversion to the active form. This deactivating enzyme, (to be discussed in detail below), may play a critical role in patients with nephrocalcinosis and kidney stones, particularly in the setting of vitamin D supplementation.[10]

As vitamin D directly stimulates intestinal calcium absorption, it has been extensively studied to determine if elevated levels increase urine calcium excretion and contribute to calcium stone formation. In prospectively followed cohorts of men and women, calcitriol levels were elevated in unselected stone formers and were independently associated with a higher risk of kidney stones. Serum calcium and PTH were not.[11] Additionally ketoconazole, a potent inhibitor of vitamin D synthesis (via 1α-hydroxylase, *CYP27B1*), (Fig. 1) effectively reduced serum calcitriol and urinary calcium in some but not all patients with higher urine calcium excretion.[12] While urine calcium proportionally increases with intestinal absorption in normal individuals, patients with higher urine calcium excretion show an exaggerated calciuric response at any level of intestinal absorption. Moreover, calcium stone formers have higher urinary calcium compared to nonstone formers regardless of calcium intake from diet.[5] It seems clear that while vitamin D can increase intestinal uptake of calcium, there are likely other mechanisms of increased calciuria than pure intestinal over absorption.

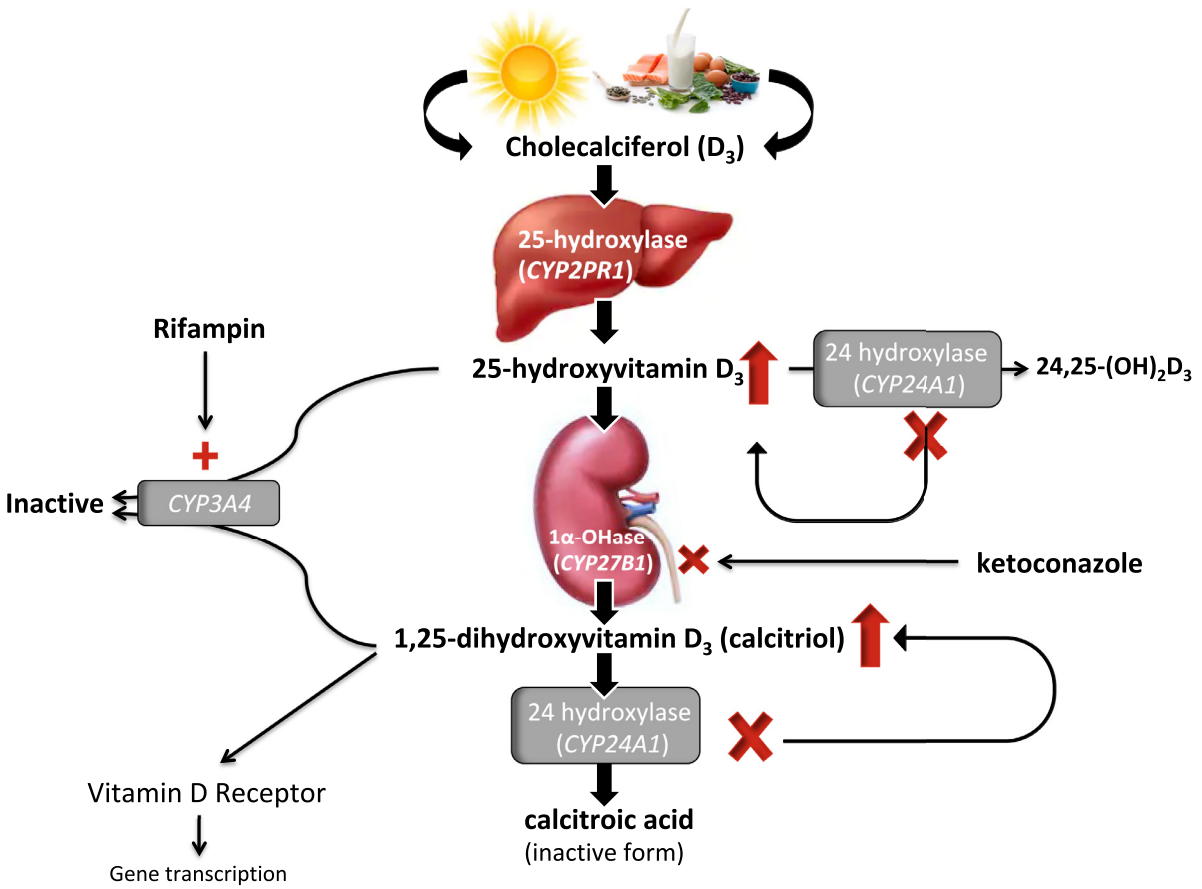

Figure 1. The metabolic pathway for vitamin D along with activating and inhibiting factors. (1α-OHase, 1alpha-Hydroxylase; 24,25-$(OH)_2D_3$, 24,25-dihydroxycholecalciferol). (Color version available online.)

Despite the above data, stimulation of intestinal calcium absorption and higher urinary calcium excretion as the result of vitamin D supplementation is not an inevitability, due to tight regulatory mechanisms. Both gene transcription and enzymatic activity of 1α-hydroxylase (CYP27B1, the activating enzyme) is upregulated by PTH, low serum calcium and phosphate, and downregulated by 1,25-dihydroxyvitamin D_3. Additionally, CYP24A1 (the deactivating enzyme) is upregulated through various genetic and epigenetic mechanisms, causing degradation of 1,25-dihydroxyvitamin D_3 in order to attenuate bioavailability and prevent hypercalcemia. Considering this regulation, why should stone formers, even with vitamin D supplementation, have elevated calcitriol levels?

GENETIC VARIATIONS IN VITAMIN D METABOLISM IN STONE FORMERS

Various mechanisms have been proposed to answer this question, with recent evidence suggests the answer may be related to mutations in *CYP24A1*, creating an inability to deactivate calcitriol (Fig. 1), as evidenced in idiopathic infantile hypercalcemia.[10] Schlingmann et al demonstrated that in children with idiopathic infantile hypercalcemia, significant nephrocalcinosis and hypercalcemia were seen in the setting of suppressed serum PTH and markedly elevated 1,25-dihydroxyvitamin D_3 due to *CYP24A1* mutations. These mutations were also identified in a second cohort who suffered severe hypercalcemia following vitamin D boluses.[10] As expected, *CYP24A1* knockout mice show hypercalcemia and nephrocalcinosis after exogenous vitamin D administration.[13] While *CYP24A1* mutations have been identified in calcium stone formers, the exact prevalence is unknown. These individuals can be distinguished from idiopathic stone formers by low PTH levels with elevated calcitriol values. 24, 25-dihydroxyvitamin D levels are reduced.

Precision medicine has made genetic testing more widely available and less expensive, with potential applicability in stone disease. Multiple, potentially clinically relevant monogenic causes of idiopathic nephrolithiasis have been identified. Enhanced diagnosis through genotyping is available and has been suggested for both diagnostic and therapeutic purposes.[14] Heterozygosity of *CYP24A1* mutations may predispose to stone formation; therefore screening with 25(OH)D serum levels (which would be high), and 24, 25(OH) vitamin D levels (which would be low) should be considered before prescribing vitamin D supplementation in stone formers to avoid exacerbation of calciuria. Patients who merit screening and genetic testing are those with high normal to high serum calcium levels with suppressed PTH levels.

Other genetic pathways may offer further insight into the calciuric predisposition to vitamin D and urolithiasis. Vitamin D receptor (VDR) polymorphisms may cause an exaggerated response resulting in higher urine calcium excretion, and sib-pair linkage studies have found vitamin D allelic variation in idiopathic stone formers.[15] Studies attempting to identify VDR single nucleotide polymorphisms in stone formers have produced mixed results.[16] Heterogeneity between studies and variables like gender, race, ultraviolet exposure, and lifestyle are notable limitations. Another candidate gene implicated in calcium stone-forming predisposition is the calcium sensing receptor, CaSR, coded by *CASR*. Located in both the kidney and parathyroid gland, these receptors have a protective effect on calcification and calcium-phosphate precipitation. Alterations in expression change the normal homeostasis between water, calcium, and phosphate.[17] Promoters of this gene contain responsive elements to VDR, and calcium sensing receptor agonists may inhibit arterial calcifications provoked by vitamin D.[17] While recent genome wide association studies have identified 4 novel susceptible nephrolithiasis loci, further studies are needed to elucidate the mechanisms of nephrolithiasis in those genetically predisposed.[18] Despite extensive study, the exact genes responsible for stone-forming heritability remain elusive.

Genetic hypercalciuric stone-forming (GHS) rats are selectively bred to maximize urinary calcium excretion and are ideal for studying the genetics and pathophysiology of nephrolithiasis.[19] GHS rats excrete up to 10 times as much urinary calcium on a standard diet and generate calcium phosphate stones, or calcium oxalate stones when hydroxyproline (an oxalate precursor) is added to their diet.[20] Principally, the mechanism seems to be an intestinal absorption of calcium mediated by an increased number of VDRs.[19] GHS rats also have increased VDRs in both bone and kidney implicating skeletal resorption, as well as failure to resorb filtered calcium, in lithogenesis.[20] When given calcitriol, bone resorption and urinary calcium increased significantly compared to controls. Administration of the calcitriol precursor, cholecalciferol, produced kidney stones in these rats though oral calcium did not.[21] GHS rats mirror common metabolic abnormalities in idiopathic stone formers and though the genetic picture remains incomplete, they offer further insight into the complex polygenetics predisposing humans to lithogenesis.

Ultimately elevated calcitriol levels increase calciuria and kidney stones.[11] However the relationship of circulating 25-hydroxyvitamin D_3 (the direct precursor to calcitriol) to kidney stone formation is less clear, and arguably more important as it is the accepted clinical measurement of vitamin D status. Meta-analysis show mixed results regarding 25-hydroxyvitamin D_3 levels correlating with lithogenic risk.[22] Elevated circulating 25-hydroxyvitamin D_3 and 1,25 dihydroxyvitamin D_3 were noted in hypercalciuric, but not normocalciuric stone formers. Some included studies demonstrated elevated 1,25 dihydroxyvitamin D_3 in normocalciuric stone formers vs controls, but were not statistically significantly different.[22] The role of multiple genetic polymorphisms and lifestyle differences likely represent variables not controlled for in the above data. The lack of consistent effect of these vitamin D metabolites highlights the complexity of calcium

homeostasis and stone formation with further study needed to identify phenotypic subgroups that may be at risk with supplementation.

VITAMIN D SUPPLEMENTATION AND KIDNEY STONE RISK

In the largest study to date on vitamin D and kidney stones, 3 well-characterized cohorts were studied: men in the Health Professionals Follow-up Study and women in the Nurses' Health Studies I and II.[6] In nearly 200,000 men and women with long-term prospective follow-up, no association was found between vitamin D intake and risk of stones after multivariate adjustment. The Nurses' Health Studies II group had a suggestion of higher risk with a *P* value of .02; however the confidence interval included 1.0.[6] The indications for vitamin D supplementation in these individuals was unknown and few in the cohort had vitamin D intake greater than 2000 IU per day; the authors concluded that in "typical amounts" there is no association between vitamin D and kidney stones.[6] Prior studies are largely in agreement, including previous analysis of Health Professionals Follow-up Study.[23] This finding was corroborated in more than 2000 patients, demonstrating no association between elevated 25-hydroxyvitamin D_3 and stones and no association with vitamin D supplementation and stone risk, albeit with short follow-up and a low stone incidence.[24]

The majority of interventional studies and meta-analyses confound the true role of vitamin D as causative in stone formation by the concomitant administration of calcium supplementation.[25-27] Though dietary calcium is inversely related to calcium stone formation, nonfood-based calcium supplementation is positively associated with stones.[2] Vitamin D with calcium supplements increased stones in the hypercalciuric rat.[21] The US Preventive Services Task Force (USPSTF) found adequate evidence that supplementation with vitamin D *and* calcium increases the incidence of kidney stones.[28] This finding is based on evidence from 3 randomized controlled trials (n = 39,659), where combined vitamin D and calcium supplementation for 4-7 years increased the incidence of kidney stones; the pooled absolute risk difference was 0.33% (0.06%-0.60%) and the pooled RR was 1.18 (1.04-1.35).[28] In the Women's Health Initiative (WHI), postmenopausal women taking 400 IU vitamin D and 1000 mg elemental calcium had an increased incidence of kidney stones (HR 1.17, 95% CI 1.02-1.34). Though the hazard ratio is modest, the large numbers of women taking supplementation makes the risk clinically significant.[26] Whether lithogenesis would be curbed if calcium citrate instead of calcium carbonate were used, or timing supplements with meals[9] along with vitamin D remain open questions. Notably, Curhan et al found no significant association between the use of daily calcium supplementation and kidney stones, protective or otherwise. The authors also speculate that this could have been due to the timing of supplementation, as dietary calcium curbed lithogenesis.[2] Another more recent study from 2019 from Malihi et al demonstrated no increased risk of stone formation or serum calcium with high-dose vitamin D supplementation (without calcium), with a more than 3 year median follow-up.[29]

Despite the WHI results, it is unlikely that the marginal expected increase in serum 25(OH)D with 400 IU resulted in hypercalcemia (and subsequent increased urine calcium), especially considering the relatively low baseline levels in that cohort.[26]

In known stone formers with vitamin D deficiency, Leaf et al found that vitamin D supplementation did not significantly increase mean urine calcium excretion. Some patients had increases, while others had decreases, suggesting that vitamin D supplementation is best monitored by following 24 hour urine collections.[30] Jorhi et al did note an increase in 24-hour urine calcium among stone formers with vitamin D supplementation, and although not statistically significant (P = .06) 6 of 26 patients who began with "normal" calcium excretion transitioned to significantly higher levels.[31] Could these exceptions be the aforementioned population with *CYP24A1* or VDR polymorphisms? The authors suggest as much, however no assessment of *CYP24A1* or other mutations was made in either study. Despite differences in formulation and duration of vitamin D between these 2 studies it is reasonable to conclude that it is perhaps appropriate to monitor urinary calcium excretion in stone formers with vitamin D supplementation.[31]

IS VITAMIN D SUPPLEMENTATION NECESSARY?

Low levels of 25-(OH)D have been associated with a host of adverse events including fractures, falls, cardiovascular disease, colorectal cancer, diabetes, depression, cognitive decline, and death.[32] Randomized trials of vitamin D supplementation have generally not supported these associations as causal in nature. With regards to bone health, meta-analysis looking at supplementation in *asymptomatic* vitamin D deficient populations found a reduction in the average number of falls but no reduction in fractures; a decrease in risk of death was found but was not sustained when excluding trials with older institutionalized women.[32] The WHI study did find a small increase in BMD in asymptomatic patients with supplementation but no reduction in fractures.[27] As such the US Preventive Services Task Force has found insufficient evidence to recommend screening in men and premenopausal women, and recommends against daily supplementation of 400 IU or less of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women.[28] Hansen et al, in an randomized controlled trial of postmenopausal women with 25-(OH)D levels less than 30 ng/mL showed no difference between placebo, low- or high-dose cholecalciferol in terms of BMD, muscle function, muscle mass, or falls.[33] More recently, a 2019 randomized controlled trial from the University of Calgary followed healthy adults over a 3-year

period and demonstrated *reduced* BMD, both radial and tibial, with large increases in vitamin D dosage using 400 IU as a reference point.[34]

Historically, vitamin D assays were ordered for an established role in metabolic bone health. However the possible (and much publicized) nonskeletal benefits of vitamin D garnered interest in its pleiotropic, nonbone effects.[35] Observational studies demonstrate an inverse relationship between 25-(OH)D and a wide range of disorders, and as a result a marked increase in testing and supplementation ensued worldwide in recent years.[7] No benefit was found with vitamin D supplementation with regards to cardiovascular disease or cancer in the asymptomatic primary preventative setting.[36] Additionally, a recent large systematic review of 34 interventional studies showed no nonskeletal benefit from vitamin D supplementation, though elderly women had a slight reduction in all-cause mortality.[37] Though the controversy has not been settled, the fact that little benefit of supplementation has been borne out across myriad studies makes it likely that low levels of 25-(OH)D are the result, not the cause, of poor health.[37]

In response to the evolving data, attempts have been made to curb testing. The American Society for Clinical Pathology launched its "Choosing Wisely" initiative recommending against population-based screening for 25-(OH)D, as they determined that the test offers no benefit.[38] Additionally, Manson et al note that clinical and research applications of vitamin D levels are largely based on misinterpretation and misapplication of reference values, and that fears of a vitamin D deficiency "pandemic" are unfounded.[39] The recommended dietary allowance of 20 ng/mL for bone health is often used as a "cut point," when in fact it is the upper end of a spectrum of need, and the majority (97.5%) of the population has a requirement of that or less.[39] Thus, routine screening and supplementation in asymptomatic patients likely has little benefit and may present a theoretical harm in some genetically predisposed stone formers.

TREATMENT OF REDUCED BMD IN STONE FORMERS

Symptomatic populations with nontraumatic fractures, liver or kidney dysfunction or malabsorptive diseases clearly will need intervention for bone health, and stone formers are no exception. Indeed, a history of kidney stones and higher urine calcium excretion predispose to lower BMD[3] and are independently associated with a higher risk of wrist fracture in both men and women.[40] Additionally, in patients presenting with urolithiasis, the prevalence of inadequate vitamin D levels was more than 80% and associated with metabolic abnormalities on stone work-up, making this population particularly prone to having supplementation recommended.[8] How then to treat the at-risk stone former with osteopenia or osteoporosis? Screening for *CYP24A1* mutations is available and may have utility; however alternative pharmacology is available that increases BMD with the added benefit of stone prevention, and has even been suggested empirically for at-risk stone formers.[41]

Thiazides are well established and recommended by both the American Urological Association and European Association of Urology for calcium stone prevention with a 47% reduction in relative risk of recurrence shown in meta-analysis.[42] Thiazides increase calcium absorption directly in the distal tubule and indirectly in the proximal tubule reducing calciuria. As a result retained calcium increases BMD in men at a rate of 8% and 3% per year at the spine and hip, respectively.[43] These results were corroborated in a large population-based case-control study of over 40,000 patients in Denmark treated for hypertension. The authors reported a 17% reduction of forearm fracture, and a 10% reduction of any fracture with current thiazide use after adjustment for confounders.[44] Pak et al demonstrated similar improvements in spine, femoral neck and radial shaft density with thiazides and potassium citrate resulting in essentially a complete cessation in stone formation.[45] Thiazides confer a risk of hypokalemia, resulting in hypocitraturiathus potassium citrate supplementation is recommended.

Hypocitraturia is exceedingly common among stone formers and potassium citrate independently reduces kidney stone recurrence by increasing urinary citrate, and reducing calcium excretion.[42] Chronic acid loads, a common consequence of high-protein diets, are not only associated with lithogenesis,[23] but decreased bone mass as well.[46] Jehle et al in a randomized, prospective controlled trial of postmenopausal women with osteopenia, demonstrated the efficacy of potassium citrate in reducing urine calcium, increasing urinary citrate, and significantly increasing bone mass.[46] Presumably these effects occur by neutralization of dietary protons and decreased urine calcium excretion. The same group presented similar findings in osteoporotic elderly patients with potassium citrate administration for 24 months, improving bone microarchitecture.[47] Side effects include gastrointestinal upset and diarrhea. If hyperkalemia is of concern then sodium citrate may be considered; however this does not reduce urine calcium excretion and may increase stone formation.

The preferred therapy for bone health is bisphosphonate administration. This is a well-established class of therapy for osteoporosis which effectively inhibits bone resorption.[48] In a randomized controlled trial Giusti et al found improvement in BMD and reduced 24-hour urine calcium with alendronate in osteoporosis associated with higher urine calcium excretion. The benefits to bone health and urinary calcium were significantly increased with concurrent thiazide use.[49] Bisphosphonates produced the same results in stone formers in a prospectively-followed cohort while curbing lithogenic activity.[50] Weisinger et al demonstrated decreased 24-hour urinary calcium excretion with bisphosphonate use in 18 hypercalciuric stone formers along with reduced bone turnover and increased lumbar spine BMD. Normocalciuric controls did not see a reduction in urinary calcium suggesting a role for bone

resorption in lithogenesis.[51] Extensive study of bisphosphonates show them well tolerated and safe; however despite the data there is significant resistance to their use. Myriad adverse events including gastrointestinal intolerance, atypical femoral fractures, and osteonecrosis of the jaw (ONJ) have been observed; however these are rare and have been difficult to reproduce.[52] ONJ has received particular attention and despite findings in case reports and series, no causal prospective studies exist. ONJ appears most often with the higher doses used in advanced cancer and multiple myeloma, with the incidence less than 1 in 100,000 per patient-year exposure.[52] Finally, a dramatic effect of zoledronic acid to prevent fractures was also demonstrated in osteopenic women; one would expect lower urinary calcium and lithogenic benefit in osteoperotic women as well, a group more prone to fracture. [53]

CONCLUSION

Kidney stones have significant cost and quality of life implications. The prevalence in relation to obesity and diet is indisputable. Widespread screening for vitamin D leading to supplementation does not appear to have contributed to kidney stone risk in the general population at therapeutic doses. Elevated calcitriol in known stone formers does pose an increased lithogenic risk and vitamin D may increase stones in patients with *CYP24A1* mutations. Genetic testing, while possibly useful for prevention, is not available or necessary for much of the world's population. The evidence for vitamin D's benefit in adults who are not at risk for rickets is sparse, and superior pharmacology can increase BMD while decreasing stones with minimal and manageable side effects.

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