The prevalence of vitamin D deficiency and insufficiency in calcium oxalate stone formers in Ontario, Canada, and the impact of vitamin D supplementation

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ABSTRACT

Introduction: Low vitamin D is a possible risk factor among calcium oxalate (CaOx) stone formers, although its routine assessment and the role for supplementation remain controversial. This study aimed to examine the prevalence of low vitamin D in a large Canadian cohort and to assess the impact of replacement therapy on metabolic and radiographic outcomes.

Methods: A retrospective review of patients with CaOx stones who underwent a full metabolic evaluation, including two 24-hour urine collections in a multidisciplinary metabolic stone clinic, was conducted to determine the prevalence of 25-hydroxy vitamin D (25-OH vitamin D) deficiency/insufficiency. A subset of patients receiving vitamin D supplementation was assessed longitudinally for changes in metabolic parameters and stone growth and compared to a cohort with normal values.

KEY MESSAGES

- Vitamin D deficiency and insufficiency are very common among calcium oxalate stone formers
- 25-hydroxy vitamin measurement should be a routine component of an in-depth metabolic stone disease assessment
- Nutritional vitamin D supplementation (D2/D3) in stone patients who are deficient or insufficient is not associated with an increased risk of stone progression

Results: Among 748 patients, 64% had low vitamin D levels at baseline. These patients were more likely to be younger (53 [42.5–61] years vs. 57 [44–67], p<0.001), have a higher body mass index (BMI) (29.3 [25.7–33.3) kg/m^2 vs. 27.5 [24.3–31.9], p<0.001), and to be male (53.6 vs 44.4%, p=0.019). Among 83 patients receiving vitamin D with a mean followup of 4.8 years, none became hypercalcemic. Serial imaging demonstrated 41% had an increase in stone burden over time, which was not significantly different from those not requiring supplementation.
Conclusions: Low vitamin D is very common among Canadian CaOx stone formers and should be a routine part of an in-depth metabolic workup. Vitamin D administration can be safely recommended to stone formers without risk of inducing stone progression.

INTRODUCTION

Renal stone disease is growing in prevalence across the globe.[1] Recent data from the Global Burden of Disease study noted between 1990-2019 that there has been a 48.57% increase in the incidence of stone disease.[2] A review of Canadian data also suggests an increase in stone disease incidence from 277/100 000 population in 2013 to 290/100 000 in 2018.[3] While similar factors may be responsible for the increasing rates seen globally it has also been acknowledged that there may be unique dietary, cultural, environmental and metabolic features within regions that may be responsible.[4]

In Canada as in most industrialized countries, calcium oxalate (CaOx) stones are the most common composition, accounting for 80% of all cases.[5] Dietary risk factors including low fluid intake, excess dietary sodium, consumption of oxalate-rich foods and excessive protein intake, alongside metabolic risk factors include hyperparathyroidism, renal tubular acidosis, sarcoidosis and inflammatory bowel disease.[6]

Within North America, vitamin D deficiency has been reported to affect 42% of Americans and appears to be even more prevalent in the Canadian population.[7-9] Numerous studies suggest a significant relationship between below normal 25-hydroxyvitamin D (25-OH vitamin D) levels and CaOx stone formation.[10-15] In a Canadian population of stone formers studied by Elkoushy et al., 80.2% were found to be vitamin D deficient.[10]

While vitamin D supplementation is proposed as a beneficial public health measure for addressing deficiency in the general population, the safety of supplementation in the stone population has been questioned for fear of exacerbating or inciting hypercalciuria.[14-16] Although there are reports of vitamin D repletion without inducing adverse effects in stone formers, concerns regarding supplementation remain particularly in patients with a hypercalciuric predisposition.[17-21]

The aim of our study was to examine the prevalence of 25-OH vitamin D deficiency in a large cohort of Canadians with CaOx stones and to explore the impact of nutritional vitamin D (D2 or D3) supplementation on radiographic and metabolic outcomes.

METHODS

We performed a retrospective review of a prospectively collected database of adults aged 18 years and older, seen in the Metabolic Stone Clinic at St. Joseph's Hospital in London, Ontario, Canada between 2005 – 2019. This is a tertiary urolithiasis referral center serving southwestern Ontario, with a catchment population of 2.5 million residents based on 2024 census data.[22] This study was approved by the Health Sciences Research Ethics Board at Western University, and all patients provided written informed consent.

Patients included in this study had a history of CaOx stones confirmed by stone analysis and were evaluated with a comprehensive metabolic assessment which included two 24-hour urine collections and serum biochemistry including a baseline serum 25-OH vitamin D level. Patients with missing data, incorrectly collect 24-hour urine collections, or a diagnosis of primary hyperparathyroidism were excluded. The serum 25-OH vitamin D level was analyzed in a central laboratory. We classified patients as 25-OH vitamin D deficient (<50 mmol/L), insufficient (50 – 75 mmol/L), or sufficient (75 – 250 mmol/L) based upon recommended guidelines.[23] Patients found to be vitamin D deficient or insufficient were counselled to receive supplemental vitamin D (D2 or D3) with doses ranging from 1000- 4000 international units (IU) per day at the discretion of the treating physician. These patients underwent repeat metabolic testing at least 6 months after initiation of vitamin D supplementation and thereafter until normal values were achieved. Doses of vitamin D supplementation were titrated up based on patients' response until normalization occurred. Of note, calcium supplementation was not routinely co-prescribed.

Our primary outcome measure was the prevalence of 25-OH vitamin D deficiency in our cohort. As secondary outcomes, we compared the clinical and biochemical characteristics between patients with 25-OH vitamin D deficiency, insufficiency and sufficiency. In addition, stone progression was compared between age and sex matched cohorts of vitamin D sufficient and supplemented vitamin D deficient or insufficient patients. Baseline and follow-up Kidney Ureter Bladder (KUB) films were compared, and a greater than 50% increase in total stone burden was considered significant.

Descriptive statistics were used to summarize the characteristics of included patients. The distribution of data was evaluated using the Kolmogorov-Smirnov test. Continuous data is presented as median (25^{th} – 75^{th} percentile). Characteristics of patients with insufficient, deficient, and sufficient vitamin D levels were assessed using the Kruskall-Wallis test with Bonferroni's post-hoc correction. Categorical data was compared with the X^2 test. Chi-square Fischer exact test was used to compare patients that had initially low vitamin D levels that went on to receive vitamin D supplementation with those individuals having normal vitamin D levels and not receiving supplementation. *P* values <0.05 were considered significant and IPSS V.25 was utilized for the statistical analyses.

RESULTS

A total of 748 patients with a stone composition confirming at least 50% CaOx were identified. Among this group, 64% had below normal vitamin D levels (34% deficient and 27% insufficient) on initial evaluation. Compared to the cohort of patients with normal vitamin D levels, those with deficient or insufficient levels were younger [53 (42.5-61) years vs 57 (44-67) p<0.001], had a higher body mass index (BMI) [29.3 (25.7 – 33.3) kg/m^2 vs 27.5 (24.3 – 31.9) *P*<0.001] and were more likely to be male [(53.6 vs 44.4%) *P*=0.019)]. The finding of secondary hyperparathyroidism was more common in the patients with low vitamin D (p<0.001). Among patients with insufficient or deficient vitamin D levels, 8.4% had secondary hyperparathyroidism. In addition, sarcoidosis was found in 2 (0.3%), osteoporosis had been previously documented in 159 (21.2%), 2.8% had inflammatory bowel disease and 1.2% had previous gastric bypass surgery. A comparison of 24-hour urine and blood work results at baseline assessment for those patients with normal or below normal vitamin D are displayed in Tables 1 and 2 respectively.

Data on 83 patients who received vitamin D supplementation at a mean follow-up of 4.8 years (range 0.6-14) was available. Sixty-nine percent of patients were able to normalize their vitamin D after supplementation. Of the patients who continued to have a low vitamin D level despite supplementation 42% had an identifiable risk factor including sarcoidosis (7%), inflammatory bowel disease (23%), and prior gastric bypass (12%). No patients developed an above normal vitamin D on follow-up. Nineteen patients (23%) developed hypercalciuria during follow up, however 42% of these patients also had an elevated urinary sodium which may have been the more significant factor in raising urinary calcium excretion. The baseline and follow up metabolic test values in those who received supplementation are summarized in Table 3.

Serial imaging demonstrated that 41% of the 83 patients receiving vitamin D supplementation had evidence of stone progression, defined as a greater than 50% increase of stone burden from baseline. However, patients who remained vitamin D deficient despite supplementation were more likely to demonstrate an increase in stone burden (71%) versus those who were vitamin D replete (35%). Furthermore, 56% of patients (n=19) who developed hypercalciuria with supplementation were found to have an increase in their stone burden. Baseline and follow up metabolic test results in those patients who demonstrated interval stone growth during follow-up are outlined in Table 4.

Of the patients who had a normal vitamin D at initial metabolic testing, 35% demonstrated radiographic evidence of stone progression at a median follow up of 6.6 years. When this cohort was age and sex matched to the cohort of patients receiving supplementation for vitamin D deficiency, there was no statistical difference in the risk of stone progression on serial imaging (p=0.522).

DISCUSSION

Renal stone disease is a common condition that afflicts 11% of people during their lifetime.[24] In the United States in 2000, the estimated cost of kidney stone health care was almost $2.1 billion

dollars, with estimates that this figure could exceed $4.1 billion dollars by 2030.[25] Recurrence rates are also high with 50% of patients developing another stone within 10 years of the initial presentation without targeted prevention.[26] Numerous genetic, anatomic, environmental, dietary and metabolic risk factors can contribute to urinary stone formation.[27] The impact of diet and metabolic conditions has been linked to the rising incidence of stone formation throughout the world.[28] Depending on the geographic location, specific factors implicated include access to safe water sources, impact of climate change and rising temperatures, dietary practices and latitude.[29]

In northern latitudes the effects of vitamin D deficiency have been attributed to various health risks and noted to be more common in patients with nephrolithiasis.[10] Chronic vitamin D deficiency can lead to hypocalcaemia and secondary hyperparathyroidism, which contribute to increased risks of osteoporosis and fractures.[30-31]

Osteoporosis is a major health concern with approximately 2 million individuals living with osteoporosis in Canada.[32] Amongst this group hip fractures are a major health risk, estimated to occur in 150 per 100,000 people annually.[32-33] Currently, the annual cost of osteoporosis care exceeds $4.6 billion CAD and is expected to increase exponentially with the aging population and high prevalence of vitamin D deficiency.[33]

Other detrimental effects of vitamin D deficiency among adults include myalgias, bone pain, and weakness, while children may present with rickets, developmental delay, irritability and fractures.[30] An increased risk of cardiovascular disease, cancer, infectious disease, type 2 diabetes and autoimmune disorders have also been associated with vitamin D deficiency, but not causally linked to date.[31,34-35]

Vitamin D belongs to a group of fat-soluble compounds and primarily found as naturally synthesized vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol).[37] The active form of vitamin D regulates multiple bodily functions, including the absorption, excretion, and storage of calcium.[37] Vitamin D may be obtained from the diet, supplements, or through ultraviolet sunlight exposure.[37] Oily fish, mushrooms, egg yolks, and fortified milk are common dietary sources of vitamin D_2 and D_3.[37] Vitamin D_3 absorption from ultraviolet light is reliant on the time and intensity of exposure, and an individual's skin pigmentation.[38]

The role of vitamin D-mediated calcium homeostasis and its role in kidney stone formation has been of considerable interest. A meta-analysis of stone formers and healthy individuals identified that stone formers have increased titres of circulating $1,25(OH)_2D$ (active form).[45] The potential concern about this increase in active vitamin D is that stone formers may be at risk of hypercalcemia and hypercalciuria.[21] Other meta-analyses however, suggest that despite vitamin D supplementation the risk of stone disease is not increased.[17-20] The potential role of the gut microbiota on vitamin D metabolism and its impact on urinary stone formation has been investigated.[46] While research in this area has been limited, it is an intriguing concept worthy of further evaluation.

In our study, we found a very high prevalence of 25-hydroxyvitamin D deficiency and insufficiency in CaOx stone formers. Surprisingly and concerningly, we noted younger male

patients had higher rates of vitamin D inadequacy, as well as those patients with higher BMIs. A higher rate of vitamin D insufficiency in obese patients has been observed previously and attributed to a number of possible factors including lesser bio-availability due to trapping in fat stores, insulin resistance and reduced outdoor physical activity and sunlight exposure.[47,48]

Among patients found to be deficient and prescribed supplementation, 14% developed hypercalciuria over 6 months of follow-up but 42% of these patients were found to have an elevated urinary sodium, implicating another potential cause rather than vitamin D supplementation alone. None of the patients on supplementation developed hypercalcemia or vitamin D levels above the normal range. The majority of patients on supplementation did not have any change in stone burden during the study interval. Post-hoc exploratory analysis did not identify groups at particular risk of stone progression. When compared to a cohort of patients with a normal vitamin D at baseline and not prescribed supplementation, there was no significant difference in stone growth on follow up.

Given the general health risks of vitamin D deficiency, and its high prevalence among calcium stone formers it seems prudent to include an assessment of vitamin D levels in the metabolic evaluation and to provide supplementation if patients are deficient or insufficient. We suggest a starting supplementation dose of 1000-2000 IU daily for patients with insufficient vitamin D levels (50-75 nmol/L) and 3000-4000 IU daily for those with deficient levels (<50 mmol/L). In those patients receiving vitamin D supplementation periodic reassessment of vitamin D and urinary calcium, every 6 to 12 months should be considered, allowing for dose modification as needed. Patients with evidence of secondary hyperparathyroidism and an elevated PTH level, should have their PTH reassessed every 6 months until it has normalized.

Several published studies have questioned the value of screening for Vitamin D deficiency and supplementation for the general population or for bone health preservation. It should be highlighted however, that these cohorts did not include stone patients, and therefore their recommendations cannot be extrapolated to our population.[49,50]

The strengths of this review include the large sample size allowing an assessment of vitamin deficiency/insufficiency prevalence. We were also able to assess not only the metabolic impact of vitamin D administration, but also the potential effect on stone burden through serial imaging over a mean follow up duration of 4.8 years. Limitations of this work include the retrospective methodology and our inability to confirm patient compliance and adherence to the recommended dose of vitamin D supplementation. However, we were able to compare patients' follow-up vitamin D levels. Stone burden was assessed through serial KUB x-rays over time; while CT imaging would have been more accurate it may also have led to unnecessary radiation exposure for many patients. In addition, given the variation in follow-up intervals we calculated stone growth as a percent increase instead of change in absolute size which may have been less accurate. Furthermore, we did not have available information regarding stone related events including emergency room visits, surgery or stone passage during the follow up period. As our patients were cared for in a tertiary care centre, it is possible our cohort is not representative of

more community-based practices. Moreover, the prevalence of vitamin D deficiency/insufficiency noted in our study population may be significantly different from sub-tropical or tropical regions.

CONCLUSIONS

Vitamin D deficiency/insufficiency is highly prevalent in a Canadian population of CaOx stone formers. Vitamin D evaluation should be a routine part of the in-depth metabolic evaluation of CaOx stone formers, due to the potentially detrimental effects of undetected and untreated deficiency or insufficiency. Supplementation does not appear to affect urine calcium levels significantly in those who are deficient or insufficient, nor does it appear to influence the burden of stone disease in the majority of patients.

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FIGURES AND TABLES

Table 1. Comparison of baseline 24-hour urine values among sufficient, insufficient, and deficient vitamin D CaOx stone-formers

	Sufficient vitamin D	Insufficient vitamin D	Deficient vitamin D	p
Volume (L/d)	1.97 (1.40–2.70)	1.7 (0.3–5.0)	1.4 (0.4–4.01)	0.002*
Sodium (mmol/d)	145 (96–190)	150 (25–549)	160.5 (34–281)	0.162
Creatinine (mmol/d)	11.9 (9–15.4)	13.1 (4.1–39.6)	14.2 (5.2–23.9)	0.013
Phosphate (mmol/d)	27 (19–34)	28 (3–84)	27 (0.89–50)	0.141
Urate (mmol/d)	3.1 (2.3–4.1)	3.3 (0.6–9.8)	3.6 (1.2–5.5)	0.148
Calcium (mmol/d)	5.1 (3.3–7.5)	5.1 (0.5–16.6)	4.05 (1–10.8)	0.148
Urea (mmol/d)	348.8 (262.2–460)	372 (94–950)	354 (112–553)	0.279
Oxalate (mmol/d)	316 (232–417.5)	324 (42–574)	324 (165–751)	0.50
Citrate (mmol/d)	2.90 (1.95–4)	2.8 (0–10.6)	2.07 (0–6.09)	0.134
Urine pH	6 (5.5–6.5)	6 (5–8.5)	6 (5–7.5)	0.001*

Continuous data presented as median (25^{th}–75^{th} percentile). *Statistically significant.

Table 2. Comparison of baseline serum biochemistry among sufficient, insufficient, and deficient vitamin D CaOx stone-formers

	Sufficient vitamin D	Insufficient vitamin D	Deficient vitamin D	p
Sodium (mmol/L)	140 (139–141)	140 (132–146)	140 (135–144)	0.875
Potassium (mmol/L)	3.9 (3.7–4.2)	3.9 (3–5.1)	3.8 (3.1–4.7)	0.092
Chloride (mmol/L)	103 (101–104)	102 (96–110)	103 (99–106)	0.423
HCO_3- (mmol/L)	27 (25–28)	26 (18–35)	25 (14–29)	0.054
Urea (mmol/L)	5.5 (4.3–7.1)	5.2 (2.4–13.6)	4.85 (2.9–12)	0.006
Creatinine (mmol/L)	75 (65–87)	73 (36–232)	73 (51–163)	0.308
Calcium (mmol/L)	2.32 (2.25–2.39)	2.3 (2.1–3.12)	2.29 (1.91–2.77)	0.031
Phosphate (mmol/L)	0.97 (0.86–1.1)	0.96 (0.52–1.9)	0.89 (0.62–1.2)	0.296
Urate (mmol/L)	316.5 (263.5–387)	331 (126–630)	301.5 (182–513)	0.741
PTH (pmol/L)	3.8 (3– 4.8)	4.3 (0.9–19.8)	5.95 (2.6–16)	<0.001*

Continuous data presented as median (25^{th}–75^{th} percentile). *Statistically significant.

Table 3. Followup 24-hour urine and serum biochemistry for deficient and insufficient CaOx stone formers who received vitamin D supplementation

Serum markers	**Initial**	**Followup**	**p**		**24-hour urine collection**	**initial**	**Followup**	**p**
Sodium (mmol/L)	140 (134–146)	140 (135–199)	0.158		Volume (L/d)	2.1 (0.25–4.2)	2.2 (0.9–4.5)	0.502
Potassium (mmol/L)	3.9 (3.1–4.8)	4 (2.4–5.1)	0.870		Sodium (mmol/d)	158 (25–388)	164 (29–471)	0.229
Chloride (mmol/L)	102 (96–107)	102 (79–108)	0.005		Creatinine (mmol/d)	13.1 (1.8–25)	13.2 (5.8–34.5)	0.006
HCO_3- (mmol/L)	26 (20–33)	26 (21–35)	0.541		Phosphate (mmol/d)	29 (2–61)	27.5 (11–71)	0.034
Urea (mmol/L)	5.6 (2.9–14.1)	5.75 (2.7–9.5)	0.163		Urate (mmol/d)	3.4 (0.6–9.2)	3.2 (0.9–8.6)	0.009
Creatinine (mmol/L)	73 (47–148)	75.5 (53–140)	0.707		Calcium (mmol/d)	6.7 (0.3–14.2)	5.5 (0.8–18)	0.379
Calcium (mmol/L)	2.3 (1.91–2.61)	2.34 (2.04-2.69	0.054		Urea (mmol/d)	380.5 (38–862)	395 (175–927)	0.369
Phosphate (mmol/L)	0.98 (0.68–1.38)	0.94 (0.56–1.35)	0.548		Oxalate (mmol/d)	331.5 (103–980)	373.5 (144–796)	0.091
Urate (mmol/L)	319 (106–569)	3.2 (0.9–8.6)	0.740		Citrate (mmol/d)	2.99 (0–8.50)	3.5 (0.1–13.8)	0.549
PTH (pmol/L)	3.8 (0.3–16.8)	3.65 (1.4–18.8)	0.007		Urine pH	6 (5.5–6.5)	6 (5.5–6.5)	0.251
Vitamin D (nmol/L)	56 (13–73)	91 (22–258)						

Continuous data presented as median (25^{th}–75^{th} percentile).

Table 4. Followup 24-hour urine and serum biochemistry for CaOx stone formers who demonstrated interval stone growth during the followup period

Serum markers	Initial	Followup	p	24-hour urine collection	Initial	Followup	p
Sodium (mmol/L)	140 (134–146)	140 (135–199)	0.158	Volume (L/d)	2.1 (0.25–4.2)	2.2 (0.9–4.5)	0.502
Potassium (mmol/L)	3.9 (3.1–4.8)	4 (2.4–5.1)	0.870	Sodium (mmol/d)	158 (25–388)	164 (29–471)	0.229
Chloride (mmol/L)	102 (96–107)	102 (79–108)	0.005	Creatinine (mmol/d)	13.1 (1.8–25)	13.2 (5.8–34.5)	0.006
HCO_3- (mmol/L)	26 (20–33)	26 (21–35)	0.541	Phosphate (mmol/d)	29 (2–61)	27.5 (11–71)	0.034
Urea (mmol/L)	5.6 (2.9–14.1)	5.75 (2.7–9.5)	0.163	Urate (mmol/d)	3.4 (0.6–9.2)	3.2 (0.9–8.6)	0.009
Creatinine (mmol/L)	73 (47–148)	75.5 (53–140)	0.707	Calcium (mmol/d)	6.7 (0.3–14.2)	5.5 (0.8–18)	0.379
Calcium (mmol/L)	2.3 (1.91–2.61)	2.34 (2.04–2.69	0.054	Urea (mmol/d)	380.5 (38–862)	395 (175–927)	0.369
Phosphate (mmol/L)	0.98 (0.68–1.38)	0.94 (0.56–1.35)	0.548	Oxalate (mmol/d)	331.5 (103–980)	373.5 (144–796)	0.091
Urate (mmol/L)	319 (106–569)	3.2 (0.9–8.6)	0.740	Citrate (mmol/d)	2.99 (0–8.50)	3.5 (0.1–13.8)	0.549
PTH (pmol/L)	3.8 (0.3–16.8)	3.65 (1.4–18.8)	0.007	Urine pH	6 (5.5–6.5)	6 (5.5–6.5)	0.251
Vitamin D (nmol/L)	56 (13–73)	91 (22–258)					

Continuous data presented as median (25^{th}–75^{th} percentile).