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Short Communication

Oral calcium supplementation associated with decreased likelihood of nephrolithiasis prior to surgery for hyperparathyroidism

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Abstract: We aimed to assess the impact of oral calcium supplementation (OCS) on the prevalence of nephrolithiasis among a cohort of patients undergoing surgery for primary hyperparathyroidism (PHPT). There were 339 patients undergoing surgery for PHPT with detailed past medical history data that were analyzed. 73 patients (22%) had a history of nephrolithiasis prior to parathyroid surgery. Nephrolithiasis was more common among men than women (40% *vs* 15%, $P < 0.001$), despite the predominance of women (73% of patients) with hyperparathyroidism. 83 patients (25%) used OCS. OCS was associated with a lower prevalence of nephrolithiasis (9.6% *vs* 25.4% without OCS, $P = 0.002$). This protective effect included both men and women (rates of nephrolithiasis with and without supplements: men 19% *vs* 46%, $P = 0.027$; women 7% *vs* 17%, $P = 0.04$). The mechanism for the apparent protective effect of OCS on rates of nephrolithiasis is unclear, and further research is required to elucidate the variable penetrance of nephrolithiasis among PHPT patients.

Key words: calcium, hypercalcemia, hyperparathyroidism, nephrolithiasis.

Introduction

While most cases of hyperparathyroidism diagnosed in the modern era are asymptomatic, calcium-based nephrolithiasis is the most common sequel of the syndrome, identified in 1–5% of patients with recurrent renal stones.[1] Most hyperparathyroid patients do not suffer nephrolithiasis, however, and the factors which determine stone formation among patients with markedly elevated parathyroid hormone (PTH) levels are incompletely characterized. In particular, the impact of oral calcium supplementation (OCS) on the incidence of nephrolithiasis among these patients remains incompletely defined.

Calcium restriction has been recommended in the past for patients with primary hyperparathyroidism (PHPT), but others argue that this restriction exacerbates the illness by further elevating PTH levels. PHPT patients with elevated levels of vitamin D will become more hypercalciuric with added dietary calcium, while those patients with normal vitamin D levels will not.[2] As optimal levels of oral calcium intake in PHPT patients remain undefined, we conducted a retrospective study of nephrolithiasis rates with or without OCS among PHPT patients prior to parathyroid surgery.

Methods

The section of Endocrine Surgery at the University of California, San Francisco (UCSF) maintains a prospective registry of patients treated for various endocrine surgical diagnoses. Under supervision by the UCSF institutional review board, the database was queried for all men and women undergoing parathyroidectomy for PHPT since 1995. There were 1033 such records; of these 339 (32.8%) included a detailed past medical history checklist.

These records were reviewed for gender, age, dietary factors, the use of OCS, comorbid illness and rates of nephrolithiasis. Rates of nephrolithiasis were compared between those with and without a history of OCS, and were analyzed for association with other potential risk factors for nephrolithiasis, including history of bone fracture, history of gout, smoking, and parathyroid pathology. Statistical significance of associations was assessed with the χ^2 or *t*-tests, and odds ratios (OR) were calculated with exact 95% confidence intervals (CI). The OR for nephrolithiasis among patients taking OCS was also adjusted for gender, age, gout history, and bone fracture history using logistic regression. Analyses were performed with Stata for Macintosh, version 9 (Stata Corp., College Station, TX, USA).

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Results

Characteristics of the 339 patients are summarized in Table 1. 23% of the men and 25% of the women reported OCS use, $P = 0.62$). The mean patient ages were 55.8 ± 12.1 and 58.0 ± 13.9 for those with and without a history of nephrolithiasis ($P = 0.23$). 39.8% of the men in the study gave a history of nephrolithiasis, compared to 14.6% of the women ($P < 0.001$).

Rates of nephrolithiasis varied significantly with OCS history. 9.6% of the PHPT patients taking OCS reported a history of stones, versus 25.4% of those not taking OCS ($P = 0.002$) (Table 2). The OR for nephrolithiasis was 0.31 (95% CI 0.12–0.70) among those taking OCS compared to those not taking OCS. The difference in prevalent nephrolithiasis was greatest in the male cohort, among whom nephrolithiasis rates were 10.8% and 54.2% for patients taking versus not taking OCS, OR 0.28 (95% CI 0.06–0.98). Among women, there was also a significantly lower rate of stones among those taking versus not taking OCS, 6.5% versus 17.4%, OR 0.33 (95% CI 0.08–0.99). The OR for nephrolithiasis adjusting for gender, gout history, and fracture history was 0.30 (95% CI 0.13–0.68).

PHPT patients with a history of bone fracture had a 30% rate of nephrolithiasis compared to 20% of those with no history of bone fracture ($P = 0.14$). Those with and without a history of gout had 31% and 21% rates of nephrolithiasis, respectively ($P = 0.33$). There was no difference between rates of bone fracture among patients taking or not

Table 1 Patient characteristics

	n	(%)
Gender		
Men	93	(27.4)
Women	246	(72.6)
Ethnicity		
Caucasian	269	(79.4)
Other	70	(20.6)
OCS use (all patients)		
Yes	83	(24.5)
No	256	(75.5)
OCS use (men)		
Yes	21	(22.6)
No	72	(77.4)
OCS use (women)		
Yes	62	(25.2)
No	184	(74.8)
Stone history (all patients)		
Yes	73	(21.5)
No	266	(78.5)
Stone history (men)		
Yes	37	(39.8)
No	56	(60.2)
Stone history (women)		
Yes	36	(14.6)
No	210	(85.4)

OCS, oral calcium supplementation.

taking OCS (13% *vs* 12%). Smoking, ethnicity, and specific parathyroid pathology had no impact on rates of nephrolithiasis or bone fracture.

Discussion

The pathophysiology of nephrolithiasis in the setting of PHPT is generally accepted to be related to resorptive hypercalciuria driven by excess PTH, but the precise relationship between PHPT and nephrolithiasis remains incompletely characterized. The prevalence of symptomatic nephrolithiasis among PHPT patients has fallen from over 50% in the early 1980s to approximately 15–20%,[1] presumably due to earlier detection of subclinical PHPT with serum screening; but the heterogeneity of the disease – why some PHPT patients form kidney stones, some develop bone fractures, some suffer both problems, and some neither – is not well understood. Similarly unclear is why PHPT is more common among women than men, yet the majority of PHPT patients who exhibit nephrolithiasis are male.

Paillard *et al*. have proposed that PHPT patients may be divided into two groups – one with autonomous PTH secretion and another with an 'altered setpoint' for PTH secretion that remains somewhat suppressible. They also noted differences among PHPT patients who presented with nephrolithiasis and those who presented with bone pathology. The stone formers were more likely to have elevated vitamin D levels with moderately elevated PTH levels, whereas those with bone loss typically had normal or low calcitriol levels but severely elevated PTH levels.[3] Another study likewise found that bony manifestations of PHPT tend to be more severe in patients with low levels of Vitamin D.[4] A third study concluded, in contrast, that higher elevation in PTH levels – along with levels of vitamin D, serum calcium, and urinary calcium and oxalate – did predict stone formation among PHPT patients.[5]

Significant progress has been made in the past several decades in elucidating the relationship between dietary calcium and nephrolithiasis. Classical dogma taught that stone forming patients without PHPT should minimize calcium intake; mounting evidence, however, has required a reevaluation of the relationship between calcium intake and stone development. In a randomized controlled trial, a normal calcium load with a low salt, low protein, unregulated calcium diet was superior to a low calcium diet in prevention of stone formation.[6] Further analysis revealed that the low calcium diet led to an increase in urinary oxalate and phosphate excretion, presumably due to decreased availability of calcium in the lumen of the gut to bind excess oxalate. Calcium supplementation using calcium citrate has likewise been proven in a randomized trial to decrease oxalate excretion and stone risk profiles among postmenopausal women.[7]

Current recommendations for patients with PHPT advise a diet which is neither excessive nor restrictive with respect to calcium. One small, recent study found that OCS among patients with low dietary calcium intake modestly reduced serum PTH levels and increased bone mineral density.[8] Perhaps conversely, Odvina *et al*. found that PHPT with nephrolithiasis patients had a two-fold greater hypercalciuric response to an oral calcium load than PHPT patients without nephrolithiasis.[9] Related to the observations discussed above regarding the relevance of vitamin D to PHPT pathophysiology, Locker *et al*. found that PHPT patients with elevated levels of vitamin D become more hypercalciuric with added dietary calcium, whereas PHPT patients with normal vitamin D levels do not.[2]

Our analysis found no association between parathyroid pathology and the prevalence of nephrolithiasis. One prior study found that among patients with parathyroid adenoma, the location of the adenoma correlated with the presence of kidney stones. Their series of 90 patients with surgically treated PHPT showed that 91% of those with kidney stones had adenomas in the left inferior parathyroid gland, and 69% of those without kidney stones had adenomas in the right inferior gland. They suggested that perhaps distinct active PTH fragments may be made from different parathyroid glands.[10] They did not, however, speculate regarding the autonomous versus suppressible nature of the adenomas based on location in the neck, nor did they analyze patients with hyperplasia rather than adenoma.

The present finding, that OCS is associated with a lower risk of stone formation in patients with PHPT, leads to several interesting, albeit speculative, hypotheses. It may be that OCS in these patients, as in other recurrent stone-forming patients, binds dietary oxalate and thus decreases urinary oxalate levels. Alternatively, OCS may lead to transiently elevated serum calcium levels, causing functional suppression of parathyroid adenomas with set point derangements, thereby lowering serum PTH levels and decreasing calcium and phosphate resorption. Finally, it may be that oral calcium suppresses vitamin D synthesis in these PHPT patients, decreasing stone formation by other pathways.

There are clear limitations to this study: this is a retrospective review of a non-urological database which was created to study neither nephrolithiasis nor OCS use. As such, there is likewise inadequate analysis of additional covariates – in particular serum and urine chemistry levels – which may explain the association between OCS use and nephrolithiasis. Indication for and type and duration of OCS use are not available in this cohort, nor is information on the severity or frequency of nephrolithiasis episodes. Furthermore, the subset of registry patients with detailed past medical history data was not selected at random, which may be a source of bias.

Table 2 Summary of incidence of nephrolithiasis among patients reporting or not reporting a history of oral calcium supplementation (OCS)

n (Row percentage) [column percentage]	No nephrolithiasis	Nephrolithiasis	Total
No OCS use	191	65	256
	(74.6%)	(25.4%)	(100%)
	[71.8%]	[89.0%]	[75.5%]
OCS use	75	8	83
	(90.4%)	(9.6%)	(100%)
	[28.2%]	[11.0%]	[24.5%]
Total	266	73	339
	(78.4%)	(21.5%)	(100%)
	[100%]	[100%]	[100%]

While this association between OCS use and decreased rates of nephrolithiasis does not imply causality – and we certainly would not suggest treatment of PHPT patients with OCS based on these data alone – the decrease in stone rates is at once dramatic and intriguing. Explaining the variability in stone formation among PHPT patients may offer insight into the pathophysiology of nephrolithiasis. We consider these results hypothesis-generating, and are currently accruing PHPT patients to a prospective study which will include more detailed medical history and serum and urinary chemistry analysis before and after surgery.

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