Original Article

A Comparison between Silent and Symptomatic Renal Stones in Primary Hyperparathyroidism

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Abstract

Background: Nephrolithiasis is a common complication of primary hyperparathyroidism (PHPT), and in a subgroup of patients stones are clinically silent. Patients with silent and symptomatic stones may differ biochemically. There is a scarcity of data available comparing patients with silent and symptomatic renal stones in PHPT. **Aims:** To characterize patients with PHPT with nephrolithiais and to compare patients with silent and symptomatic stones. **Materials and Methods:** We reviewed clinical data of 186 patients with PHPT managed at our center from January 1996 to December 2017. Silent renal stones were defined as ultrasonography finding of renal stones without symptoms. Symptomatic renal stones were defined as those with symptoms or a history of graveluria or any procedure for nephrolithiasis. A 5-mm diameter was set as the cut-off between micro- and macrolithiasis. We compared those with ($n = 95$) and without ($n = 91$) stones, and, among stone formers, those with symptoms ($n = 66$) and silent ($n = 29$) were compared. **Results:** There was no significant difference between stone formers and nonstone formers with respect to biochemical parameters. Patients with silent renal stones had significantly lower serum calcium and higher phosphate, than those with symptomatic stones. Most (75%) patients with silent renal stones had microlithiais, while only a fifth (22%) with symptomatic renal stones had microlithiasis. **Conclusion:** Nephrolithiasis is a common complication of PHPT. Most patients with silent renal stones had microlithiasis and biochemical features of less severe disease. Patients with silent renal stones may represent early mild stage of PHPT.

Keywords: Microlithiais, nephrolithiasis, primary hyperparathyroidism, silent renal stones

Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder in the West after diabetes mellitus and thyroid disorders.[1] The renal manifestations of PHPT include nephrolithiasis, nephrocalcinosis, azotemia, hypercalciuria, and hyperchloremic metabolic acidosis. The reported prevalence of nephrolithiasis in PHPT ranges from less than 10% to more than 70%.[2-4] We have previously documented renal involvement (nephrolithiasis and/or nephrocalcinosis) in about two-thirds of patients with PHPT.[5] Because even asymptomatic renal stones in patients with PHPT warrant parathyroid surgery, all such patients should be evaluated for renal stones.[6]

It has been recently reported that in a subgroup of PHPT patients, stones are clinically silent.[7,8] To the best of our knowledge, there is a single study available comparing patients with silent and symptomatic renal stones in PHPT.[9] The aim of our study was to characterize patients with PHPT with renal stones and to compare patients with silent and symptomatic stones.

Materials and Methods

The study included 186 cases of PHPT diagnosed and managed at our center from January 1996 to December 2017. A diagnosis of PHPT was established by the presence of persistent hypercalcemia and concomitant raised or inappropriately normal serum intact parathyroid hormone (iPTH). The records were reviewed for age, sex, and laboratory data. The laboratory data included measurement of serum total calcium, phosphate, alkaline phosphatase (ALP), iPTH, 25-hydroxy vitamin

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Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_558_18

How to cite this article: Misgar RA, Sehgal A, Masoodi SR, Wani AI, Bashir MI, Malik AA, *et al*. A comparison between silent and symptomatic renal stones in Primary hyperparathyroidism. Indian J Endocr Metab 2019;23:46-9.

D (25-OHD), albumin, and 24-h urinary calcium. As a routine, we measured 24-h urine calcium and creatinine, serum calcium, albumin, creatinine, phosphate, and ALP by automated techniques. The normal laboratory range was 8.5–10.5 mg/dL for serum calcium and 2.5–4.5 mg/dL for serum phosphate. Serum iPTH was measured by DXI 800, Beckman Coulter Chemiluminescence random access analyzer (Brea, CA, USA) following the manufacturer's protocol. The reference range for PTH levels is 12–88 pg/mL. Serum 25-OHD was measured by radioimmunoassay until 2012 and by chemiluminescence thereafter. Estimated glomerular filtration rate (eGFR) was assessed using CKD-EPI creatinine equation.

All our patients underwent renal ultrasonography (US) for diagnosis of renal stones. Renal US was performed using a 3- to 5-MHz wide-band convex transducer. A 5-mm diameter was set as the cut-off between micro- and macrolithiasis. Silent renal stones were defined as US finding of renal stones without symptoms. Symptomatic renal stones were defined as those with symptoms or a history of graveluria or any procedure for nephrolithiasis. The study was approved by hospital ethics committee.

Statistical analysis

The data were analyzed by IBM SPSS statistics software version 22. Variables were presented as mean ± standard deviation or frequency (%) as appropriate. Continuous variables were compared between the two groups by independent sample *t*-test for parametric data and Wilcoxon rank-sum test for nonparametric data. Categorical data were compared by Chi-square/Fisher's exact test. A *P* value <0.05 was considered statistically significant.

Results

The demographic and biochemical data of this PHPT cohort are described in Table 1. Of 186 patients, renal stones were present in 95 (51%). Table 2 shows the comparison between stone formers (silent and symptomatic, $n = 95$) and nonstone formers ($n = 91$). There was no significant difference between the two groups with respect to age and biochemical parameters. The stone formers, however, had significantly lower body mass index (BMI) than nonstone formers.

Table 3 shows the comparison between patients with symptomatic ($n = 66$) and silent ($n = 29$) renal stones. Patients with silent renal stones had significantly lower serum calcium and higher phosphate than those with symptomatic stones. The mean serum calcium in patients with silent renal stones was 11.1 ± 0.4 mg/dL, whereas the mean serum calcium in patients with symptomatic renal stones was 12.3 ± 1.3 mg/dL ($P = 0.002$). The mean serum phosphate in patients with silent renal stones was 2.7 ± 0.6 mg/dL, whereas the mean serum phosphate in patients with symptomatic renal stones was 2.2 ± 0.7 mg/dL ($P = 0.016$). Patients with silent renal stones also had lower iPTH (169 ± 143 vs 322 ± 314 pg/mL) and 24-h urinary calcium (293.8 ± 199.2 vs 357 ± 183.3 mg) than patients with symptomatic renal stones, but this did not reach statistical significance. Most (75%) patients with silent renal stones had microlithiais, whereas only a fifth (22%) with symptomatic renal stones had microlithiasis. We found no significant difference between the two groups for eGFR and serum 25-OHD levels.

Table 1: Demographic and biochemical characteristics of the cohort of patients with PHPT ($n = 186$)

Parameter	Mean ± SD	Median	Normal range
Age (years)	47.8±14.1	49.5	-
Sex (M/F, %)	22/78	-	-
BMI (kg/m^2)	24.3±4.9	24.3	18.5-22.9
Serum calcium (mg/dL)	12.1±1.4	11.7	8.5-10.5
Serum phosphate (mg/d;)	2.4±0.7	2.3	2.5-4.5
Serum ALP (U/L)	235.3±347	151	30-140
iPTH (pg/mL)	311±321	193	12-88
25-OHD (ng/mL)	23±18	18	≥30
Serum creatinine (mg/dL)	1±0.5	0.9	0.5-1.5
24-H urinary calcium (mg)	334.8±209.4	292	4 mg × kg/24 h
eGFR (mL/min/1.73 m^2)	81.3±32.4	81.6	-

SD: Standard deviation; BMI: Body mass index; ALP: Alkaline phosphatase; iPTH: Intact parathyroid hormone; 25-OHD: 25-hydroxy vitamin D; eGFR: Estimated glomerular filtration rate

Discussion

The reported prevalence of renal stones in PHPT is variable, ranging from less than 10% to more than 70% reflecting differences in study populations and the imaging methods used to diagnose renal stones.[2-4] In our series, the prevalence of renal stones was 51%. This high prevalence is affected by the inclusion of patients with silent renal stones due to our routine use of renal US. Other recent studies with routinely performed renal imaging reported a similar or higher prevalence of nephrolithiasis than ours.[8,9]

The etiology and pathophysiology of renal stones in PHPT are not completely understood. Hypercalciuria is considered to be only one of the major risk factors. However, the impact of hypercalciuria on the risk of renal stones has not been entirely clarified because studies have reported conflicting results. Several studies have documented increased renal calcium excretion in patients with PHPT with renal stones.[9-11] It is important to note that in our series, there was no significant difference between the stone formers and nonstone formers with respect to any of the biochemical parameters. Similarly, in our series, there was no significant difference in 24-h urinary calcium excretion between stone formers and nonstone formers, although the mean value was higher in stone formers. Our finding that the biochemical variables appear to be unreliable in the prediction of renal stones in PHPT is in agreement with previous studies and a large clinical review.[2,12,13] Factors beyond the urinary calcium load may be of paramount importance for the genesis of nephrolithiasis in PHPT. The risk of nephrolithiasis has been associated with other biochemical and local urinary factors in PHPT.[14] There is a mounting evidence for an association between nephrolithiais

Table 2: Comparison between stone formers and nonstone formers[a]

Parameter	Patients without renal stones (*n*=91)	Patients with renal stones (*n*=95)	*P*
Age (years)	49.4±13.9	46.2±14.2	0.115
Sex (M/F, %)	21.9/78	22.1/77.9	0.543
BMI (kg/m^2)	25±4.9	23.6±4.8	**0.04**
Serum calcium (mg/dL)	12±1.5	12.2±1.3	0.465
Serum phosphate (mg/dL)	2.4±0.6	2.3±0.7	0.312
iPTH (pg/mL)	319±309	302±299	0.754
25-OHD (ng/mL)	23±17	22±18	0.665
Serum creatinine (mg/dL)	1±0.5	1±0.4	0.674
24-H urinary calcium (mg)	319.5±231.7	349.5±185.2	0.333
eGFR (mL/min/1.73 m^2)	82.5±35.1	80±29.6	0.606

BMI: Body mass index; iPTH: Intact parathyroid hormone; 25-OHD: 25-hydroxy vitamin D; eGFR: Estimated glomerular filtration rate. [a]Data expressed as mean±SD

Table 3: Comparison between patients with symptomatic and silent renal stones[a]

Parameter	Symptomatic (*n*=66)	Silent (*n*=29)	*P*
Age (years)	46±14.3	46.9±13.7	0.844
Sex (M/F, %)	31.7/68.2	9/91	0.002
BMI (kg/m^2)	23.6±4.8	23.8±5.7	0.867
Serum calcium (mg/dL)	12.3±1.3	11.1±0.4	**0.002**
Serum phosphate (mg/dL)	2.2±0.7	2.7±0.6	**0.016**
iPTH (pg/mL)	322±314	169±143	0.102
25-OHD (ng/mL)	22±18	24±21	0.642
Serum creatinine (mg/dL)	1±0.5	0.8±0.2	0.180
24-H urinary calcium (mg)	357±183.3	293.8±199.2	0.291
eGFR (mL/min/1.73 m^2)	79.5±30.3	83.7±24.4	0.650
Microlithiasis/ macrolithiasis (%)	22/78	75/25	<0.001

BMI: Body mass index; iPTH: Intact parathyroid hormone; 25-OHD: 25-hydroxy vitamin D; eGFR: Estimated glomerular filtration rate. [a]Data expressed as mean±SD

and calcium-sensing receptor gene polymorphisms in patients with PHPT.[15,16] A surprising finding in our study was that nonstone formers had a significantly higher BMI than stone formers. This is in contradiction to the reported positive association between risk of renal stones and BMI.[17,18]

In our series, patients with silent renal stones showed a significantly higher prevalence of microlithiasis. Microlithiasis was present in 75% of patients with silent renal stones when compared with 22% of patients with symptomatic renal stones. This remarkable high prevalence of microlithiasis in patients with silent renal stones in all probability accounts for the lack of symptoms. Similar results have been reported recently in the single study which compared silent and symptomatic renal stones in PHPT by Elena Castellano *et al.*[9] They also reported some features of more severe disease, including higher PTH levels and lower 25-OHD levels in patients with silent renal stones.[9] The limitation of this study was that the subgroup of patients with silent renal stones was relatively small. In contradiction in our series, lower calcium and higher phosphate and lower average iPTH in patients with silent renal stones point to a less severe disease in these patients. Thus, patients with silent renal stones may represent an early mild stage of PHPT.

To the best of our knowledge, our study is only the second study that compares patients with PHPT with silent and symptomatic renal stones. Our study has a relatively large subgroup of patients with silent renal stones when compared with the previously published single study. However, our study has some limitations. First, we did not evaluate other parameters involved in pathophysiology of nephrolithiasis, although such evaluations are now recommended by the current guidelines.[6] Second; our patients were not genotyped for the calcium-sensing receptor gene, which is known to be associated with nephrolithiasis in patients with PHTP.

Conclusion

In conclusion, our study reconfirms that nephrolithiasis is a common complication of PHPT. This study also underlines some distinctive features of patients with silent renal stones in comparison to those with symptomatic renal stones. The most striking finding was that most patients in the silent group had microlithiasis, while this was the case in only a minority of patients with symptomatic renal stones. We are reporting for the first time that patients with silent renal stones had biochemical features of less severe disease in the form of low serum calcium and higher serum phosphate when compared with those with symptomatic renal stones and that they may represent early mild stage of PHPT.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ruda JM, Hollenbeak CS, Stack BC Jr. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995 to 2003. Otolaryngol Head Neck Surg 2005;132:359-72.
2. Rejnmark L, Vestergaard P, Mosekilde L. Nephrolithiasis and renal calcifications in primary hyperparathyroidism. J Clin Endocrinol Metab 2011;96:2377-85.

3. Odvina CV, Sakhaee K, Heller HJ, Peterson RD, Poindexter JR, Padalino PK, *et al.* Biochemical characterization of primary hyperparathyroidism with and without kidney stones. Urol Res 2007;35:123-8.
4. Suh JM, Cronan JJ, Monchik JM. Primary hyperparathyroidism: Is there an increased prevalence of renal stone disease? Am J Roentgenol 2008;191:908-11.
5. Misgar RA, Dar PM, Masoodi SR, Ahmad M, Wani KA, Wani AI, *et al*. Clinical and laboratory profile of primary hyperparathyroidism in Kashmir Valley: A single-center experience. Indian J Endocr Metab 2016;20:696-701.
6. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, *et al*. Guidelines for the management of asymptomatic primary hyperparathyroidism: Summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 2014;99:3561-9.
7. Cassibba S, Pellegrino M, Gianotti L, Baffoni C, Baralis E, Attanasio R, *et al.* Silent renal stones in primary hyperparathyroidism: Prevalence and clinical features. Endocr Pract 2014;20:1137-42.
8. Cipriani C, Biamonte F, Costa AG, Zhang C, Biondi P, Diacinti D, *et al.* Prevalence of kidney stones and vertebral fractures in primary hyperparathyroidism using imaging technology. J Clin Endocrinol Metab 2015;100:1309-15.
9. Castellano E, Attanasio R, Latina A, Visconti GL, Cassibba S, Borretta G. Nephrolithiasis in primary hyperparathyroidism: A comparison between silent and symptomatic patients. Endocr Pract 2016;23:157-62.
10. Söreide JA, van Heerden JA, Grant CS, Lo CY, Ilstrup DM. Characteristics of patients surgically treated for primary hyperparathyroidism with and without renal stones. Surgery 1996;120:1033-7.
11. Viccica G, Cetani F, Vignali E, Miccoli M, Marcocci C. Impact of vitamin D deficiency on the clinical and biochemical phenotype in women with sporadic primary hyperparathyroidism. Endocrine 2017;55:256-65.
12. Berger AD, Wu W, Eisner BH, Cooperberg MR, Duh QY, Stoller ML. Patients with primary hyperparathyroidism – Why do some form stones? J Urol 2009;181:2141-5.
13. Bandeira F, Caldas G, Freese E, Griz L, Faria M, Bandeira C. Relationship between serum vitamin D status and clinical manifestations of primary hyperparathyroidism. Endocr Pract 2002;8:266-70.
14. Starup-Linde J, Waldhauer E, Rolighed L, Mosekilde L, Vestergaard P. Renal stones and calcifications in patients with primary hyperparathyroidism: Associations with biochemical variables. Eur J Endocrinol 2012;166:1093-100.
15. Vezzoli G, Tanini A, Ferrucci L, Soldati L, Bianchin C, Franceschelli F, *et al.* Influence of calcium-sensing receptor gene on urinary calcium excretion in stone-forming patients. J Am Soc of Nephrol 2002;13:2517-23.
16. Scillitani A, Guarnieri V, Battista C, De Geronimo S, Muscarella LA, Chiodini I, *et al.* Primary hyperparathyroidism and the presence of kidney stones are associated with different haplotypes of the calcium-sensing receptor. J Clin Endocrinol Metab 2007;92:277-83.
17. Park S, Pearle MS. Pathophysiology and management of calcium stones. Urol Clin North Am 2007;34:323-34.
18. Stamatelou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. Kidney Int 2003;63:1817-23.