Primary Hyperparathyroidism: Renal Calcium Excretion in Patients with and without Renal Stone Disease before and after Parathyroidectomy

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Abstract. The effect of parathyroidectomy on renal calcium excretion per 24 hours in patients with primary hyperparathyroidism with and without a history of renal stone disease was evaluated. Altogether, 91 patients operated on for primary hyperparathyroidism formed the study group for preoperative analysis. Of these patients, 42 were evaluated 1 to 3 years postoperatively. The median preoperative serum calcium level was 2.92 mmol/L, and it was the same for patients with or without renal stones. Preoperatively we found no differences in renal calcium excretion between patients with and without renal stone disease. The median renal calcium excretion was 6.80 mmol/24 hr. At 1 to 3 years after successful parathyroidectomy the group with renal stone disease had higher renal calcium excretion than the group without renal stones ($p = 0.03$). The reduced effect of parathyroidectomy on renal calcium excretion in the patients with renal stone disease indicates that factors not related to the hyperparathyroid state could contribute to disturbances in renal calcium excretion and hence stone formation. In conclusion, the pathologic basis for renal stone formation in patients with primary hyperparathyroidism might not be the hyperparathyroid state alone; stone formation could be related to other predisposing factors as well. Therefore, although parathyroidectomy can cure hyperparathyroidism, the curative effect on renal stone disease should be reconsidered.

The classic manifestations of primary hyperparathyroidism (pHPT) are bone disease and renal stone disease. Renal stone disease was first described as part of the pHPT syndrome in 1930 [1]. Concomitant with the increasing incidence of pHPT, the frequency of renal stone formers among these patients has decreased from around 80% to 10% to 40% in recent clinical series [2–5]. The increasing incidence of pHPT is due to growing attention to subtle neurophysiologic symptoms, the widespread use of routine serum calcium analysis, and the development of specific, sensitive parathyroid hormone tests [6].

A specific pathophysiologic mechanism for stone formation generated by pHPT is not likely because a substantial number of the pHPT patients never experience renal stones. There is no correlation between the severity of the biochemical and pathologic findings associated with pHPT and the risk of renal stone disease. Borderline increased serum calcium is reported to characterize pHPT patients with renal stones in several series [2, 4, 7].

The formation of calcium-containing renal stones among pHPT patients is to a large extent attributed to hypercalciuria [8], although other stone-promoting factors and tubular dysfunction have been debated [7]. Hypercalciuria has been shown to be more prominent among pHPT patients with a history of renal stones than among those without renal stones [3, 4]. Excretion of urinary calcium is reduced after successful parathyroidectomy [9, 10], and renal stone disease associated with pHPT is considered cured after correction of hypercalcemia [8, 11], although this paradigm has been questioned lately [12].

As hypercalciuria is considered the main pathogenic factor for renal stone formation in pHPT, we find it of interest to investigate the effect of parathyroidectomy on renal calcium excretion in pHPT patients with and without renal stone disease before and after successful parathyroidectomy.

Materials and Methods

Among 101 consecutive patients with surgically verified pHPT, 91 remained normocalcemic (serum calcium < 2.61 mmol/L) postoperatively and form the study group. Their median age was 57 years (range 15–83 years), with a male/female ratio of 1:3. The median preoperative serum calcium level was 2.92 mmol/L (reference range 2.20–2.60 mmol/L). Eighty-five patients (93%) had parathyroid adenoma with a median weight of 865 mg (range 120–12,880 mg). Six patients (7%) had hyperplasia and a median weight of 650 mg (range 210–1230 mg). Thirty-four patients (37%) had renal stone disease defined as stones in the pelvis, ureter, or both on preoperative urograms or a history of renal stones (Table 1).

Prior to surgery the serum and a 24-hour urine collection were analyzed for calcium and creatinine content. Serum samples were obtained in the morning when patients were fasting, at the beginning or end of the urine collection period. Serum and urine samples were analyzed by standard automated laboratory methods in the daily hospital routine. Samples were collected and analyzed prospectively and the values recorded on separate forms and stored separately, with copies in the clinical files. For the first 42 patients the control examination 1 to 3 years postoperatively

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Table 1. Clinical profile.

Parameter	All patients	With renal stones	Without renal stones	p
No. (% of total)	91 (100%)	34 (37%)	57 (63%)	—
Age (years)	57.0 (15–83)	53.5 (18–78)	62.8 (15–83)	0.05*
Male/female ratio	1:3 (23:68)	1:2 (12:22)	1:4 (11:46)	NS
Serum creatinine (mmol/L)	0.093 (0.05–0.22)	0.093 (0.05–0.20)	0.094 (0.06–0.22)	NS
Serum calcium (mmol/L)	2.92 (2.41–3.98)	2.93 (2.41–3.61)	2.92 (2.50–3.98)	NS
Urine calcium (mmol/L)	4.80 (0.5–10.0)	4.65 (1.1–10.0)	4.97 (0.5–10.0)	NS
Urine calcium excretion (mmol/24 hr)	6.80 (0.9–23.8)	6.54 (2.0–13.6)	6.97 (0.9–23.8)	NS
Frequency of hypercalciuria (%)[a]	54 (49 patients)	53 (18 patients)	54 (31 patients)	NS
Frequency of hyperplasia (%)	7 (6 patients)	9 (3 patients)	5 (3 patients)	NS
Frequency of adenoma (%)	93 (85 patients)	91 (31 patients)	95 (54 patients)	NS
Weight of excised tissue (mg)	800 (120–12,880)	640 (135–12,880)	977 (120–10,000)	NS

Values are presented as medians with ranges in parentheses.
[a]Excretion of calcium per 24 hours was > 6.2 mmol for women and > 7.5 mmol for men.
*Statistical significance of differences was evaluated by the Mann-Whitney or Fisher's exact test, with Bonferoni correction.

Table 2. Effect of parathyroidectomy on calcium excretion and concentration in the urine.

Parameter	Preoperatively			Postoperatively		
	With renal stones	Without renal stones	p	With renal stones	Without renal stones	p
No. (% of total)	19 (45%)	23 (55%)		19 (45%)	23 (55%)	
Urine calcium excretion (mmol/24 hr)	6.81 (3.9–11.8)	7.32 (1.9–23.8)	0.89	4.93 (2.0–9.3)	2.99 (0.7–9.5)	0.03*
Urine calcium concentration (mmol/L)	5.10 (2.3–10.0)	5.03 (2.1–9.2)	0.95	2.63 (1.1–7.5)	2.40 (0.6–7.5)	0.13

Values are presented as medians with ranges in parentheses.
*Statistical significance was evaluated by the Mann-Whitney test.

comprised the history, a urogram, and serum and urine examinations. Altogether, 30 patients were examined after 3 years and the remaining 12 patients after 1 year.

Differences in median values of continuous data were analyzed by the Mann-Whitney test and differences in proportions by Fischer's exact test. The level of significance was $p \le 0.05$. The Bonferoni correction was performed when comparing a large number of variables.

Results

The patients with and without a history of renal stone disease were compared concerning their clinical profile and the effect of parathyroidectomy. The clinical profile is illustrated in Table 1. Only age differed significantly between the two groups ($p = 0.05$). The group with stones was 9 years younger than the no-stone group. There was a tendency toward more male patients and lower weight of excised pathologic tissue in the stone group. Preoperatively there were no differences in 24-hour calcium excretion between the two groups. Neither the concentration of calcium in the urine nor the frequency of hypercalciuria differed between the two groups.

The effect of parathyroidectomy is illustrated in Table 2 for the 42 patients evaluated postoperatively. This group was comparable to the total group regarding gender, age, serum and urine values, and histopathology, as shown in Table 3. After parathyroidectomy the 24-hour calcium excretion was reduced from a median 7.32 mmol to a median 2.99 mmol in the no-stone group, a reduction of 59%. In the stone group 24-hour calcium excretion was reduced from a median 6.81 mmol to a median 4.93 mmol, a reduction of 28%. Postoperatively the 24-hour calcium excretion was significantly higher in the stone group than in the no-stone group ($p =$

Table 3. Evaluated group compared to the total group.

Parameter	Total group	Evaluated group
No. (% of total)	91 (100%)	42 (46%)
Age (years)	57 (15–83)	54 (18–72)
Male/female ratio	1:3 (23:68)	1:4 (9:33)
Frequency of stone disease (%)	37 (34 patients)	45 (19 patients)
Serum calcium (mmol/L)	2.92 (2.41–3.98)	2.90 (2.50–3.98)
Serum creatinine (mmol/L)	0.093 (0.05–0.22)	0.086 (0.07–0.19)
Frequency of hypercalciuria (%)[a]	54 (49 patients)	55 (23 patients)
Frequency of hyperplasia (%)	7 (6 patients)	5 (2 patients)
Frequency of adenoma (%)	93 (85 patients)	95 (40 patients)
Weight of excised tissue (mg)	800 (120–12,880)	800 (170–5000)

[a]Excretion of calcium per 24 hours was > 6.2 mmol for women and > 7.5 mmol for men.

0.03). The concentration of calcium in the urine showed a nonsignificant tendency to be higher in the stone group than in the no-stone group after parathyroidectomy ($p = 0.13$).

Renal stones recurred in 3 of 19 patients (16%) during follow-up. There were no differences in renal calcium excretion before or after parathyroidectomy (data not shown) between these three patients and the rest of the stone group.

Discussion

We examined the excretion of calcium in the urine in pHPT patients with and without renal stone disease before and 1 to 3 years after successful parathyroidectomy. The preoperative serum calcium levels and urinary calcium excretion per 24 hours were equal in patients with and patients without renal stones. After correcting hypercalcemia by parathyroidectomy, calcium excre-

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tion was reduced in both groups of patients. Compared to patients without renal stone disease, however, the stone formers showed higher calcium excretion postoperatively, indicating that factors other than hyperparathyroidism may play a role in these patients. Such a factor could be idiopathic hypercalciuria. Previously the effect of parathyroidectomy on calcium excretion in the urine has been evaluated only for pHPT patients as a whole, showing an overall reduction of calcium excretion [9, 10].

In a series from the Mayo Clinic by Söreide et al. [4], surgically verified pHPT patients with renal stones had higher preoperative calcium excretion than patients without renal stones, in contrast to our results. Preoperative serum calcium levels were equal for patients with or without a history of renal stones, as in our series, but serum calcium levels were lower in the series from the Mayo Clinic than in our series. Söreide et al. did not present postoperative data. The higher preoperative calcium excretion in stone patients compared to no-stone patients in the Mayo Clinic series might indicate that preoperative differences in calcium excretion, unrelated to the hyperparathyroid state, can be present with moderately elevated serum calcium levels, but that they disappear with higher levels and hence higher calcium excretion. This is in accordance with our findings, where preoperative serum calcium and calcium excretion were higher than in the Mayo Clinic series, and levels of calcium excretion between stone and no-stone patients differed only postoperatively when serum calcium levels were normalized.

Both renal stone disease and pHPT are common and might therefore by chance occur in the same patients. Owing to the epidemiology of renal stone disease, renal stones are likely to occur by coincidence in 5% of a pHPT population, which is confirmed in pHPT series identified by serum calcium screening [6]. The prevalence of pHPT in screened populations is 1% to 2%, far exceeding the expected percentage [13, 14]. Patients with renal stone disease are routinely screened for pHPT. Selection bias might therefore result in a frequency of renal stones among pHPT patients exceeding the expected 5%. Our group has lately shown that after successful treatment of pHPT recurrence of renal stones among the patients with a history of such stones is comparable to the recurrence rate among patients with idiopathic renal stone disease [12]. The present biochemical observations further support that the relation between stone disease and pHPT should be reconsidered.

Conclusions

The pathologic basis for renal stone formation in pHPT patients might not be only the hyperparathyroid state, it could be related to other predisposing factors, such as idiopathic hypercalciuria. Elevated calcium excretion due to pHPT could contribute to stone formation.

The effect of parathyroidectomy on stone formation among pHPT patients with renal stones as the only manifestation can be evaluated safely only by a prospective, randomized study that includes pHPT patients with minimally elevated serum calcium. Such a study would be difficult to conduct for ethical reasons, considering the potential effect on stone formation and other health risks compared to the few complications and the high success rate of parathyroid surgery [15]. It would demand a large number of patients and a long period of follow-up to present sufficient statistical power to answer the question: Does parathy-

roidectomy reduce the number of new stones for patients with pHPT and a history of renal stones?

Parathyroidectomy does not eliminate the risk of stone recurrence according to our previous study [12]. The present study supports these findings. It remains to be shown to what extent parathyroidectomy reduces the frequency of renal stones for the individual pHPT patient with renal stone disease.

Résumé. On a évalué les effets de la parathyroïdectomie sur l'excrétion rénale du calcium par 24 h chez le patient atteint d'hyperparathyroïdie primaire avec ou sans antécédent de lithiase rénale. Quatre-vingt-onze patients opérés pour hyperparathyroïdie primaire ont fait l'objet de cette étude d'analyse préopératoire. Quarante-deux patients ont été évalués un à trois ans postopératoire. La médiane du taux de calcium sérique préopératoire a été de 2.92 mmol/L, identique pour les patients avec, ou sans lithiase rénale. En préopératoire, nous n'avons retrouvé aucune différence d'excrétion rénale de calcium entre les patients avec ou sans lithiase rénale. La médiane d'excrétion rénale de calcium a été de 6.80 mmol par 24 heures. Un à trois ans après une parathyroïdectomie avec succès, l'excrétion calcique du groupe de patients avec la maladie lithiasique du rein était plus élevée par rapport au groupe de patients sans lithiase rénale (*p* = 0.03). L'effet de réduction de la sécrétion calcique de la parathyroïdectomie chez les patients lithiasiques indique que des facteurs sans rapport avec l'hyperparathyroïdie pourrait contribuer aux perturbations de l'excrétion calcique, et alors, à la formation de calculs. En conclusion, la pathogenèse de la formation lithiasique chez le patient atteint d'hyperparathyroïdie primaire pourrait non seulement être en rapport avec l'hyperparathyroïdie mais aussi en rapport avec d'autres facteurs prédisposants. Ainsi même si la parathyroïdectomie peut guérir l'hyperparathyroïdie primaire, il faut mettre en doute son rôle dans la cure de la lithiase rénale.

Resumen. Se evaluaron los efectos de la paratiroidectomía sobre la excreción renal de calcio de 24 horas en pacientes con hiperparatiroidismo primario con y sin historia de cálculos renales. Noventa y un pacientes fueron operados por hiperparatiroidismo primario, los cuales constituyeron el grupo de estudio para el análisis preoperatorio; 42 pacientes fueron evaluados 1 a 3 años después de la operación. El valor medio del calcio sérico preoperatorio fue 2.92 mmol/L, valor que fue igual para los pacientes con y sin cálculos renales. En la evaluación preoperatoria no hallamos diferencias en la excreción renal de calcio entre los pacientes con y sin cálculos. La excreción renal media fue de 6.80 mmol por 24 horas. Uno a tres años luego de una paratiroidectomía exitosa, el grupo con enfermedad litiásica renal exhibió una excreción renal de calcio mayor en comparación con el grupo libre de cálculos (*p* = 0.03). El bajo efecto de la paratiroidectomía sobre la excreción renal de calcio en los pacientes con cálculos indica que existen factores no relacionados con el estado de hiperparatiroidismo que contribuyen a las alteraciones en la excreción renal de calcio y, consecuentemente, a la formación de cálculos. En conclusión, las bases patológicas para el proceso de formación de cálculos renales en pacientes con hiperparatiroidismo primario puede ser no sólo el estado hiperparatiroideo, sino relacionado con otros factores predisponentes. Por consiguiente, aunque la paratiroidectomía puede curar el hiperparatiroidismo, el efecto curativo sobre la enfermedad litiásica renal debe ser reconsiderado.

References

1. Barr DP, Bulger HA. The clinical syndrome of hyperparathyroidism. Am. J. Med. Sci. 1930;179:449–476
2. Chan AK, Duh Q-Y, Katz MH, et al. Clinical manifestations of primary hyperparathyroidism before and after parathyroidectomy. Ann. Surg. 1995;222:402–414
3. Silverberg SJ, Shane E, Jacobs TP, et al. Nephrolithiasis, and bone involvement in primary hyperparathyroidism. Am. J. Med. 1990;89: 327–334
4. Söreide JA, van Heerden JA, Grant CS, et al. Characteristics of patients surgically treated for primary hyperparathyroidism with and without renal stones. Surgery 1996;120:1033–1037

5. Udén P, Chan A, Duh Q-Y , et al. Primary hyperparathyroidism in younger and older patients: symptoms and outcome of surgery. World J. Surg. 1992;16:791–798

6. Heath H III. Clinical spectrum of primary hyperparathyroidism: evolution with changes in medical practice and technology. J. Bone Miner. Res. 1991;6:63–70

7. Pak CYC, Nicar MJ, Peterson R, et al. A lack of unique pathophysiologic background for nephrolithiasis of primary hyperparathyroidism. J. Clin. Endocrinol. Metab. 1981;53:536–542

8. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. N. Engl. J. Med. 1992;327:1141–1150

9. Fuss M, Pepersack T, Corvilain J, et al. Infrequency of primary hyperparathyroidism in renal stone formers. Br. J. Urol. 1988;62:4–6

10. Pak CYC. Effect of parathyreoidectomy on crystallization of calcium salts in urine of patients with primary hyperparathyroidism. Invest. Urol. 1979;17:146–148

11. Jabbour N, Corvilain J, Fuss M. et al. The natural history of renal stone disease after parathyroidectomy for primary hyperparathyroidism. Surg. Gynecol. Obstet. 1991;172:25–28

12. Mollerup CL, Lindewald H. Renal stones and primary hyperparathyroidism: natural history of renal stone disease after successful parathyroidectomy. World J. Surg. 1999;23:173–176

13. Lundgren E, Rastad J, Thrufjell E, et al. Population-based screening for primary hyperparathyroidism with serum calcium and parathyroid hormone values in menopausal women. Surgery 1997;121:287–294

14. Palmér M, Jakobsson S, Åkerström G, et al. Prevalence of hypercalcemia in a health survey: a 14-year follow-up study of serum calcium values. Eur. J. Clin. Invest. 1988;18:39–46

15. Kjellman M, Sandelin K, Farnebo L-O. Primary hyperparathyroidism: low surgical morbidity supports liberal attitude to operation. Arch. Surg. 1994;129:237–234