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ROLE OF THE URINARY CALCIUM IN THE GROWTH OF CALCIUM STONE

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We analyzed the relationship between the rate and clinical factors. The growth rate per year of the stone was measured by Nabeshima's method in 29 male patients with renal calcium stones including 7 pure calcium oxalate (CaOx) stones and 22 mixed calcium oxalate and calcium phosphate (CaOx-CaP) stones. The 24-hour urinary excretion of calcium, phosphate, uric acid and magnesium were assayed under an ambulatory free diet in 5 patients with CaOx stones and 15 with CaOx-CaP stones. The relationship between the growth rate and the urinary excretion of stone-forming parameters was examined. We found a significant positive correlation between the growth rate of calcium stones and the urinary excretion of calcium ($p<0.02$). In addition, the growth rate of CaOx-CaP stone was significantly higher than that of pure CaOx stone ($p<0.05$). In conclusion, urinary calcium is important for the growth of renal calcium stones.

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Key words: Growth of calcium stone, Urinary calcium, Stone composition

INTRODUCTION

The nidus of nephrolith is initially formed in the renal tubulus. When this nidus is excreted in the renal pelvis and lodged there for a long time, the crystal aggregates on the surface of the nidus and the clinical stone develops. The growth of the renal calcium stone is closely associated with the crystal formation, growth and aggregation. The crystal formation occurs in the supersaturated urine with respect to calcium oxalate and calcium phosphate, the components of the calcium stone.

Urinary pH also affects crystal formation. The calcium oxalate (CaOx) crystal is formed when the pH is below 6.2, while that of calcium phosphate (CaP) is formed at a pH beyond 6.2[1]. Several stone-growth promoting factors have been proposed, such as male, renal pelvic stone, high output of urinary calcium and low value of urinary magnesium/calcium[2] The purpose of this study is to determine how stone-forming parameters especially urinary excretion of calcium influence stone growth.

METHODS

We investigated the relationship between the composition and the size of renal and ureteric calcium stones in 376 male patients treated at Sagamihara National Hospital from 1980 to 2001. The analysis of the composition of stones obtained by spontaneous passage, surgery and extracorporeal shockwave lithotripsy (ESWL) by means of infrared spectroscopy revealed 175 calcium oxalate (CaOx) stones and 201 mixed calcium oxalate and calcium phosphate (CaOx-CaP) stones, which included 158 CaOx-CaP stones predominantly calcium oxalate(CaOx>CaP) and 43 CaOx-CaP stones predominantly calcium phosphate (CaOx<CaP). We considered the stone to be CaOx stone if the rate of phosphate in it was less than 2%. Among these patients, we could examine the growth rate of renal calcium stones per year by means of the method described by Nabeshima et al.[2] only in 29 patients including 7 with a CaOx stone and 22 with a CaOx-CaP stone including 18 CaOx>CaP stones and 4 CaOx<CaP stones. The stone growth was observed for 6 to 123 months, with a mean observation period of 40 months. The growth rate per year was defined as follows; (the stone volume at the end of the observation − the volume at the start) × 1/the volume at the start × 1/year of the observation × 100%. The 24-hour urinary excretion of calcium, phosphate, uric acid and magnesium was measured in 20 of these 29 patients under an ambulatory free diet. Collected urine during 24 hours at room temperature without adding any antibacterial agent was measured immediately after collection was completed by the following method: calcium; methylxylenol method, phosphate; enzyme colorimetric method, uric acid; uricase peroxidase method and magnesium; xylidyl blue method. Dietary management to prevent stone recurrence was not done except for recommendation of water intake. Patients with primary hyperparathyroidism and treated with allopurinol, uricosuric agents, diuretics and steroid hormones were excluded from the present study. The relationship between the composition and the size of calcium stones was statistically analyzed by the chi squared test. The correlation between the growth rate of the stone and 24-hour urinary excretion of each stone-forming parameter was analyzed by Fisher's z-test. The growth rate was compared between CaOx stones and CaOx-CaP stones by Student's t test. The data were considered statis-

tically significant at $p<0.05$.

RESULTS

Patients with CaOx stones had a significantly higher rate of stones less than 10 mm compared to those with CaOx>CaP stones and CaOx<CaP stones, respectively. However, no significant difference was found between the size of CaOx>CaP stones and CaOx<CaP stones (Table 1). The patient's age, composition of stone, observation period, growth rate, 24-hour urinary excretion of stone-forming parameters and urine volume per day are summarized in Table 2. The excretion of calcium alone showed a significant positive correlation between the growth rate and 24-hour urinary excretion of stone forming parameters (Fig. 1). Six of eight calculi with a 24-hour calcium excretion of more than 300 mg per day showed an extremely high growth rate. No significant correlation was found between the growth rate and 24-hour urinary excretion of phosphate, uric acid and magnesium. With regard to the relationship between 24-hour urinary excretion of calcium and other stone-forming parameters, significant positive correlations were found between calcium and phosphate (Fig. 2), and uric acid. The mean growth rate per year of CaOx stones was 21.0± 24.5% (n=7), while those of CaOx>CaP, CaOx< CaP and CaOx-CaP were 92.4±98.8% (n=18), 210.9±236.7% (n=4) and 108.0±135.9% (n=22),

Table 1. Relationship between composition and size of stone (male patient)

Composition	Size of stone		Total
	<10 mm	10 mm<	
CaOx	163*#	12	175
CaOx>CaP	108	50	158
CaOx<CaP	29	14	43
Total	300	76	376

*: $p<0.01$ compared with CaOx>CaP, #: $p<0.01$ compared with CaOx<CaP, CaOx: calcium oxalate stone, CaOx>Cap: mixed calcium oxalate and calcium phosphate stone prerdominantly calcium oxalate, CaOx<CaP: mixed calcium oxalate and calcium phosphate stone predominantly calcium phosphate.

Table 2. Patient data

Case	Age	Composition	Observed months	Growth rate (%/year)	24 hour urinary excretion (mg/day)				Urine (ml/day)
					Calcium	Phosphate	Uric acid	Magnesium	
1	54	CaOx	54	73.1	247	701	591	99	2,750
2	44	CaOx	36	9.3	249	734	504	—	2,770
3	35	CaOx	33	20.4	262	752	621	135	3,740
4	18	CaOx	123	26.2	114	630	407	67	670
5	55	CaOx	26	4.2	231	1,191	855	—	3,000
6	36	CaOx	11	11.7	—	—	—	—	—
7	44	CaOx	28	2.3	—	—	—	—	—
8	35	CaOx>CaP	42	4.9	444	810	624	84	3,000
9	21	CaOx>CaP	10	175	528	1,135	714	149	1,860
10	63	CaOx>CaP	13	167	349	749	599	66	3,120
11	52	CaOx>CaP	16	38.6	273	893	447	108	4,700
12	48	CaOx>CaP	48	8.9	336	897	1,047	78	2,300
13	57	CaOx>CaP	43	124	384	1,550	986	130	3,100
14	47	CaOx>CaP	28	73.3	154	616	429	50	1,600
15	49	CaOx>CaP	62	2	215	426	521	100	1,760
16	65	CaOx>CaP	46	247	307	889	702	—	1,940
17	50	CaOx>CaP	84	4.8	244	505	583	129	2,350
18	37	CaOx>CaP	11	60.4	285	1,041	912	130	2,160
19	43	CaOx>CaP	37	14.5	92	357	616	104	2,880
20	55	CaOx>CaP	17	2.4	—	—	—	—	—
21	24	CaOx>CaP	6	366	—	—	—	—	—
22	36	CaOx>CaP	20	85.2	—	—	—	—	—
23	56	CaOx>CaP	54	8.3	—	—	—	—	—
24	81	CaOx>CaP	59	62.1	—	—	—	—	—
25	30	CaOx>CaP	38	87.8	—	—	—	—	—
26	46	CaOx<CaP	31	389	370	711	682	102	3,630
27	48	CaOx<CaP	110	3.4	287	904	578	140	2,470
28	34	CaOx<CaP	6	441	448	929	885	139	2,950
29	66	CaOx<CaP	54	11.1	—	—	—	—	—

CaOx: calcium oxalate stone, CaOx>Cap: mixed calcium oxalate and calcium phosphate stone predominantly calcium oxalate, CaOx<CaP: mixed calcium oxalate and calcium phosphate stone predominantly calcium phosphate.

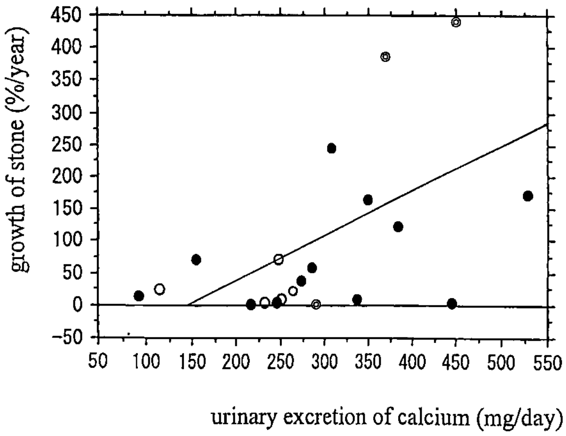

Fig. 1. Relationship between the growth rate of stone per year and 24-hour urinary excretion of calcium under ambulatory free diet in patients with renal calcium stone. There was a positive correlation between the growth rate of stone and the urinary excretion of calcium ($\gamma=0.513$; $p=0.0147$, $y=0.625x-87.546$). Calcium oxalate stone (○), mixed calcium oxalate and calcium phosphate stone predominantly calcium oxalate (●), mixed calcium oxalate and calcium phosphate stone predominantly calcium phosphate (◎).

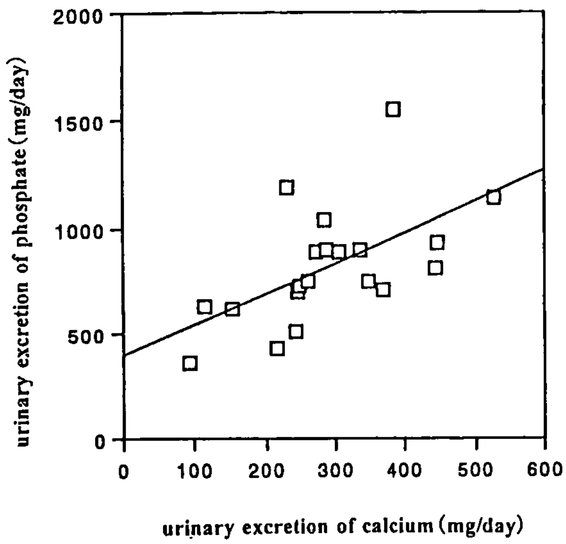

Fig. 2. Relationship between 24-hour urinary excretion of calcium and that of phosphate under ambulatory free diet in patients with renal calcium stone. There was a positive correlation between the urinary excretion of calcium and that of phosphate ($\gamma=0.579$; $p=0.0065$, $y=1.446x+400.230$).

respectively. A statistically significant difference was noted between the growth rate of CaOx stones and those of CaOx>CaP and CaOx-CaP stones, respectively ($p<0.05$). The 24-hour urinary excretion of calcium was higher in patients with CaOx-CaP stone (314±114 mg/day) than those with CaOx stones (221±61 mg/day), but not significantly.

DISCUSSION

It has been generally accepted that urinary calcium and oxalate play an important role in stone formation. In the present study, we showed that urinary calcium excretion is an important factor for the growth of calcium stones. In addition, we have also demonstrated a characteristic stone growth pattern dependent on stone composition.

Sutor et al. reported that CaOx stones were more likely to be expelled than CaOx-CaP stones and that CaOx stones were lighter than CaOx-CaP stones in weight[3]. Table 1 also shows the similar results. From this, we can safely say that CaOx stones are smaller than CaOx-CaP stones. The fact that CaOx stones are small and CaOx-CaP stones large suggests that CaOx stones grow slowly while CaOx-CaP stones grow rapidly.

It has been reported that patients with CaOx stones excrete significantly more acidic urine with a lower calcium[4] and higher oxalate[5] content than those with CaOx-CaP stones. In this study, we found that the 24-hour urinary excretion of calcium was higher in patients with CaOx-CaP than in those with CaOx, although the difference between them was not statistically significant, probably due to the small number. The slow growth of CaOx stones in the high-oxalate and low-calcium urine and rapid growth of CaOx-CaP stones in the normal oxalate and high-calcium urine lead us to consider that urinary calcium plays a more important role in the growth of calcium stone than urinary oxalate does. In addition, we found a positive correlation between urinary calcium and phosphate excretion probably due to recent trends in dietary habit such as excess intake of animal protein and alcohol ingestion which result in increased excretion of urinary calcium as well as phosphate[6] We consider that increased urinary calcium excretion and phosphate excretion are responsible for the fast growth of CaOx-CaP stones.

We analyzed the stone structure of the calcium stones. CaOx stones are classified into 3 groups according to their components, CaOx-monohydrate (COM), CaOx-dihydrate (COD), and CaOx-mono and dihydrate. COM stones are smoothly surfaced, and hard stones composed of COM crystals arrangied orderly and tightly. COD stones are irregularly surfaced and brittle stones consisting of COD crystals arranged at random[7]. COD stones are more common than COM stones among patients with higher urinary calcium excretion levels and with a higher urinary pH and significant differences have not been found between the urinary excretion of oxalate in patients with COM stones and those with COD stones[8] In addition, the CaOx component in the majority of CaOx-CaP stones has been shown to be COD rather than COM and the interspace of COD to be occupied by CaP components[9]

From these findings we speculate that the low growth rate of the COM-type CaOx stone is due to the lower urinary calcium excretion as well as small interspaces between COM crystals, and the higher growth rate of the CaOx-CaP stones is due not only to higher calcium and phosphate excretion but also to the large interspaces between COD crystals.

From a therapeutic standpoint, we consider that diet therapy such as recommendation of water intake and restriction of excess intake of animal protein, alcohol and salt may help to prevent the increase of calcium stones by lowering urinary calcium[10] Thiazide therapy may be needed especially in patients with a 24-hour urinary calcium excretion of more than 300 mg.

In this study, we could not measure the urinary oxalate and citric acid concentrations. In addition, it is not known how high molecular weight inhibitors or promoters affect the growth of calcium stones. The full understanding of the growth of calcium stones awaits future studies.

In conclusion, the urinary calcium excretion is an important factor for the growth of calcium containing stones. The growth rate of CaOx-CaP stones is higher than that of CaOx stones.

REFERENCES

1) Robertson WG, Peacock M and Nordin BEC: Calcium crystalluria in recurrent renal stone former. Lancet **2**: 21–24, 1969
2) Nabeshima S, Masai M, Shimazaki T, et al.: Prognostic factors influencing the growth of renal calculi. Jpn J Urol **85**: 1593–1600, 1994
3) Sutor DJ and Wooley SE: Some data on urinary stones which were passed. Br J Urol **47**: 131–135, 1975
4) Murayama T, Sakai N, Yamada T, et al.: Role of the diurnal variation of urinary pH and urinary calcium in urolithiasis: a study in outpatients. Int J Urol: **8**: 525–532, 2001
5) Ueda H: Urinary oxalate excretion in the patients with upper urinary tract calculi. Jpn J Urol **76**: 338–347, 1985
6) Zechner O, Latal D, Pflüger H, et al.: Nutritional risk factors in urinary stone disease. J Urol **125**: 51–54,1981
7) Koide T, Itatani H, Yoshioka T, et al.: Clinical manifestations of calcium oxalate monohydrate and dihydrate urolithiasis. J Urol **127**: 1067–1069, 1982
8) Pierratos AE, Khalaff H, Cheng PT, et al.: Clinical and biochemical differences in patients with pure calcium oxalate monohydrate and calcium oxalate dihydrate kidney stones. J Urol **151**: 571–574, 1994
9) Tanikawa K, Matsushita K and Matsuzaki S: The Japanese Symposium For Urolithiasis Research **3**: 29–34, 1993
10) Lifshitz DA, Shalhav AL and Lingeman JE: Urolithiasis—Patient evaluation and medical treatment. In: Treatment of Urolithiasis. Edited by Akimoto M, Higashihara E, Kumon H, et al. ed., pp 37–59, Springer-Verlag, Tokyo, 2001

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和文抄録

カルシウム結石の増大における尿中カルシウムの役割について

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尿路結石の増大についての検討はきわめて少ない．われわれはカルシウム結石の増大率を測定し，これに影響を与える臨床的因子について検討した．

29例の男子腎結石（純蓚酸カルシウム結石7例，蓚酸結石および燐酸カルシウム混合結石22例）を対象として鍋島らの方法により結石増大率を測定した．29例中20例（蓚酸カルシウム結石5例，蓚酸カルシウム燐酸カルシウム混合結石15例）において24時間尿中カルシウム，リン，尿酸，マグネシウムを外来自由食下で測定した．結石増大率と尿中結石関連物質排泄量の関係について検討した．

結石増大率と24時間尿中カルシウム排泄量の間に有意な正の相関関係が認められた．また，蓚酸カルシウム燐酸カルシウム混合結石の増大率は蓚酸カルシウム結石のそれより有意に高かった．

尿中カルシウムはカルシウム結石の増大に重要な影響を与えるものと思われた．

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