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Renal Hypercalciuria and Metabolic Acidosis Associated with Medullary Sponge Kidney: Effect of Alkali Therapy*

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Summary. Sixteen patients with medullary sponge kidney (MSK) and renal stones underwent evaluation of calcium metabolism and acid base balance. Six normal subjects and eight patients with non-MSK absorptive hypercalciuria served as control. Nine (56%) were hypercalciuric and seven (44%) were normocalciuric (N-MSK). Hypercalciuria was divided into absorptive (AH-MSK, n = 2) and renal leak hyerpcalciuria (RH-MSK, n = 7). The mean of minimal urine pH of RH-MSK group (5.28 ± 0.09 (SE)) was significantly higher than that of normal control (4.78 ± 0.12) and of non-MSK AH (4.80 ± 0.6) during acute acid challenge. The mean of the arterial blood HCO_3 concentration of RH-MSK group was significantly lower than that of two control groups. The urine calcium and a frequency of stone passage were decreased significantly after alkali treatment in RH-MSK.

Key words: Acid-base imbalance – Calcium metabolism disorders – Kidney calculi – Renal tubular acidosis – Sponge kidney

Introduction

Nephrolithiasis is a frequent complication in patients with medullary sponge kidney (MSK) [4, 12]. We have previously shown that about 80% of patients with MSK have renal acidification defects of incomplete distal type [8]. Chronic acidosis caused by renal tubular acidosis results in hypercalciuria, although the mechanisms are still not fully understood [11, 16, 17]. Calcium metabolism in patients with incomplete distal renal tubular acidosis was examined in three patients and it was suggested that alkali treatment had been successful in preventing recurrent calculi in these patients [21]. We have reported that MSK is frequently associated with renal hypercalciuria [6, 7] and recent reports confirmed hypercalciuria was present in about 40 to 90% of the patients with MSK [13, 15].

Methods

Patients Selection

Calcium metabolism was studied in sixteen patients with MSK (6 mean and 10 women). The diagnosis of MSK was made by previously established criteria [10]. One patient who had a parathyroid adenoma two and half years prior to present study was included (Renal hypercalciuria MSK, No. 6, Table 1). None of the patients with MSK received alkali-therapy before the study. Unilateral and segmental MSK were excluded from the study. All subjects had normal creatinine clearance.

The control group consisted of six normal volunteers (four men and two women, mean age ± SE, 28 ± 2) and eight patients with absorptive hypercalciuria (seven men and one woman, mean age ± SE, 41 ± 3). Patients with absorptive hypercalciuria were selected from the patients with recurrent nephrolithiasis. Hypercalciuria was defined as a calcium excretion greater than 180 mg/day and 3.7 mg/day/kg B.W. on calcium restricted diets (300 mg/day), both of these values are 2 standard deviations (SD) above the mean of the normal control. Absorptive hypercalciuria was defined as a urinary calcium excretion less than 0.110 mg calcium/mg creatinine during a fasting state and greater than 0.260 mg calcium/mg creatinine after calcium loading, both of these values are equivlanet to mean plus 2 SD of the normal control [1, 14]. Renal hypercalciuria was defined as fasting urinary calcium excretion greater than 0.110 mg calcium/mg creatinine. In addition fasting urinary calcium excretion was measured without taking the preceding calcium-restricted diet on nine healthy menopausal women (age, 61 ± 2).

Informed consent was obtained from every subject.

Methods of Investigation

All subjects were advised to avoid calcium-rich food for one week prior to hospitalization where the metabolic studies were conducted. During the first four days, the subjects were given a diet containing a daily calcium content of 300 mg. A 24-h urine sample was collect-

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Table 1. Urinary calcium and cyclic AMP

Group	Age/sex	Calcium excretion[a]		Calcium to creatinine ratio		Urine cyclic AMP (n · mol/100 ml GFR)	
		mg/day	mg/day/kg B.W.	fasting	loadings[b]	fasting	loadings[b]
Control							
(1) Normal ($n = 6$)		129 ±10	2.38 ±0.27	0.056 ±0.010	0.197 ±0.013	3.94 ±0.36	1.85 ±0.40
(2) Absorptive hypercalciuria ($n = 8$)		284 ±8	4.71 ±0.18	0.089 ±0.010	0.323 ±0.017	3.32 ±0.39	2.51 ±0.23
Medullary sponge kidney							
(3) Normocalciuria							
1	52/M	123	1.89	0.044	0.126	2.03	0.36
2	61/M	157	2.92	0.060	0.170	5.07	8.22
3	44/F	158	3.05	0.082	0.403	5.85	3.44
4	59/M	162	2.38	0.040	0.209	5.61	3.93
5	26/F	161	3.05	0.072	0.215	4.19	3.86
6	55/F	112	1.77	0.035	0.070	–	–
7	52/F	151	2.79	0.054	0.175	–	–
Mean	49.9	146	2.55	0.055	0.197	4.55	3.96
SE	±4.5	±8	±0.21	±0.007	±0.013	±0.69	±1.25
P vs normal		NS	NS	NS	NS	NS	NS
(4) Renal hypercalciuria							
1	28/M	248	3.82	0.245	0.288	4.97	2.51
2	49/F	282	7.29	0.307	0.713	6.41	4.29
3	56/F	188	4.88	0.303	0.335	3.48	2.43
4	59/F	192	4.50	0.258	0.512	11.49	5.70
5	45/F	249	4.22	0.221	0.358	3.30	2.31
6	50/F	266	4.67	0.176	0.319	6.23	4.64
7	29/F	226	5.95	0.170	0.320	7.13	5.60
Mean	45.1	236	5.05	0.240	0.406	6.14	3.93
SE	±4.6	±14	±0.45	±0.021	±0.058	±1.05	±0.57
P vs normal		$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	NS	$P < 0.02$
P vs normocalciuric MSK		$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	NS	NS
(5) Absorptive hypercalciuria							
1	41/M	262	5.14	0.069	0.319	4.58	3.48
2	52/M	248	4.28	0.097	0.275	4.37	3.82

[a] Calcium excretion on a 300 mg calcium diet
[b] Data obtained after 850 mg calcium load
Statistical comparisons were determined using Student's *t*-test

ed on day 4 and analyzed for calcium and creatinine. On day 5, a 3-h urine sample was collected from 6:00 to 9:00 a.m. after fasting since 7:00 p.m. of the day before. A venous blood sample was then drawn for determination of calcium, phosphate and creatinine. An oral load of 850 mg of calcium was given between 9:00 and 9:30 a.m. in the form of a mixture of synthetic diet and calcium lactate. The synthetic diet (Boncolon, dinner, Otsuka Pharmaceuticals, Tokyo, Japan) contained 70 mg calcium, 66 mg phosphorus, 2,340 mg sodium chloride, and 185 K calories; calcium lactate provided the remaining 780 mg of calcium. A 3-h urine sample was collected at 1:00 p.m. Creatinine, calcium and cyclic-AMP were determined for fasting and loading urine samples. On a separate day, NH_4Cl loading test [20] was done on these patients. The detailed method was described elsewhere [8]. Seven patients with renal hypercalciuria and five patients with normocalciuria and low plasma bicarbonate repeated the same calcium balance studies after a period of more than one year (12 ~14 months) during which time they were receiving 2 to 4 g sodium bicarbonate daily. The amount of sodium bicarbonate was determined depending on the plasma bicarbonate and body weight.

Urine clacium was determined by an atomic absorption spectrophotometry, and cyclic AMP by an assay kit (Yamasa, Tokyo, Japan). Plasma calcium, phosphate, and creatinine were measured by an autoanalyzer (Hitachi 736 autoanalyzer, Tokyo). Statistical analysis was performed by the Student's t-test or chi-square test. The data were shown as mean ± SE.

Table 2. Acid-base status and plasma calcium and phosphate concentration

Group	Minimal urine pH[a]	Arterial blood pH	Arterial blood HCO_3^- mEq/l	Plasma calcium mg/dl	Plasma phosphate mg/dl
Control					
(1) Normal ($n = 6$)	4.78 ±0.12	7.38 ±0.01	25.0 ±0.2	9.6 ±0.2	3.2 ±0.1
(2) Absorptive hypercalciuira ($n = 8$)	4.80 ±0.06	7.39 ±0.01	25.5 ±0.5	9.4 ±0.2	2.9 ±0.2
Medullary sponge kidney					
(3) Normocalciuria					
1	5.26	7.38	19.8	9.3	2.3
2	5.17	7.39	26.5	9.6	3.2
3	5.05	7.30	18.9	9.6	3.2
4	5.33	7.39	23.6	9.7	3.0
5	5.68	7.37	17.3	9.9	3.2
6	5.70	7.41	22.6	9.4	3.3
7	4.98	7.39	26.3	9.4	4.1
Mean	5.31	7.38	22.1	9.6	3.2
SE	±0.10	±0.01	±1.4	±0.1	±0.2
P vs normal	$P < 0.01$	NS	NS	NS	NS
(4) Renal hypercalciuria					
1	5.44	7.38	23.9	9.4	2.3
2	5.23	7.37	21.1	9.0	2.9
3	4.94	7.39	22.0	9.0	3.0
4	5.11	7.41	21.6	9.0	2.9
5	5.19	7.39	25.3	8.6	2.4
6	5.72	7.40	21.9	8.8	2.6
7	5.30	7.43	22.0	9.6	2.7
Mean	5.28	7.40	22.5	9.1	2.7
SE	±0.09	±0.01	±0.6	±0.1	±0.1
P vs normal	$P < 0.01$	NS	$P < 0.01$	$P < 0.05$	$P < 0.02$
P vs normocalciuric MSK	NS	NS	NS	$P < 0.01$	$P < 0.05$
(5) Absorptive hypercalciuria					
1	4.82	7.40	26.2	9.4	3.9
2	5.07	7.39	26.3	9.0	3.0

[a] Minimal urine pH represents the minimal urine pH observed during acute acid challenge

Results

Urinary Calcium Excretion and Cyclic AMP (Table 1)

Seven (44%) of the 16 patients with MSK were normocalciuric and 9 (56%) were hypercalciuric. Seven of 9 hypercalciuric patients were renal calcium leak type and 2 were absorptive type. Normocalciuric patients showed normal calcium excretion patterns before and after calcium loadings except one (No. 3), who had an exaggerated increase in calcium excretion after loading.

The urinary excretion of cyclic AMP in the patients with normocalciuric MSK was not different from that in the normal control during fasting and loading. The fasting urinary cyclic AMP levels in renal hypercalciuric MSK tended to be higher than normal although it was not statistically significant. However, during loading periods, the urine cyclic AMP in the patients with renal hypercalciuric MSK was higher than that in normal control and that in the patients with non-MSK absorptive hypercalciuria.

Six of seven with renal hypercalciuria were female and most of them were menopausal age. Therefore we compared fasting urinary calcium to creatinine ratio between this group and healthy menopausal group. The ratio was 0.239 ± 0.025 in female renal hypercalciuria and MSK and 0.115 ± 0.021 in healthy menopausal grroup. These values are significantly different ($P < 0.01$).

Acid-base status and plasma calcium and phosphate (Table 2)

Minimal urine pH during acute ammonium chloride loading test were not different between normal control and the pa-

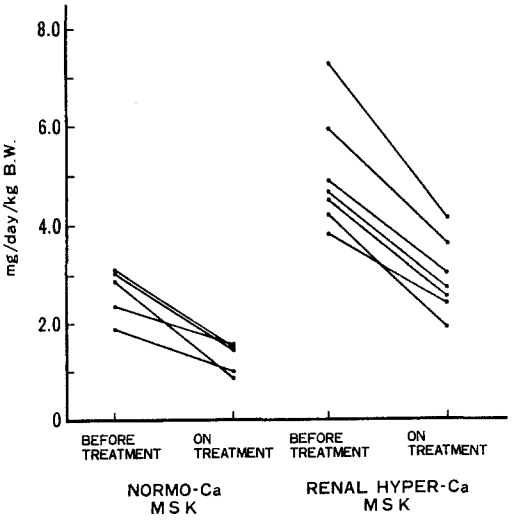

Fig. 1. The changes in urinary calcium excretion by the alkali-teratment

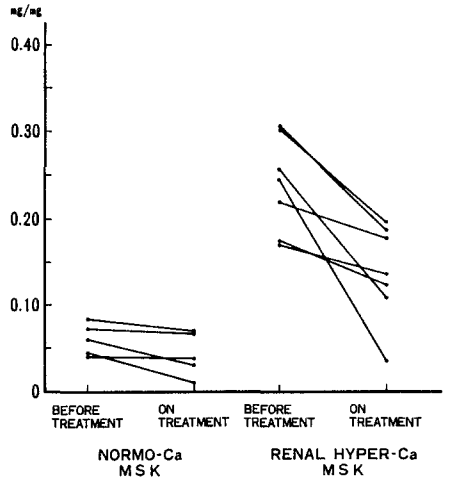

Fig. 2. The changes in the ratios of fasting urinary calcium to creatinine by the alkali-treatment

tients with non-MSK absorptive hypercalciuria. All subjects of these two control groups could lower their urine pH below 5.10. In contrast, three of seven patients with normocalciuric MSK and two of seven patients with renal hypercalciuric MSK could not lower their urine pH below 5.10. In contrast, three of seven patients with normocalciuric MSK and two of seven patients with renal hypercalciuric MSK could not lower their urine pH below 5.33, the mean minimal urine pH plus 2 SD from the normal control values. The mean minimal urine pH of normocalciuric and renal hypercalciuric MSK groups were significantly ($P <$ 0.01) higher than that of normal control and the patients with non-MSK absorptive hypercalciuria.

Arterial blood pH remained normal and was not different among the three groups. Plasma bicarbonate tended to be low in the patients with normocalciuric MSK but not significantly different. It was significantly lower in the patients with renal hypercalciuric MSK than in normal control and the patients with normocalciuric MSK.

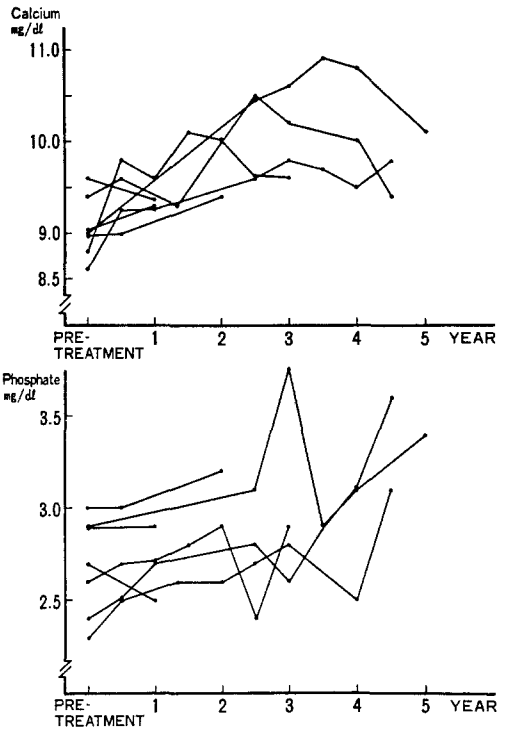

Fig. 3. The changes in plasma calcium and phosphate levels during alkali-treatment in the patients with MSK and renal hypercalciuria

Effects of alkali-therapy on plasma and urinary calcium (Figs. 1–4)

Sodium bicarbonate therapy was conducted on every patient with renal hypercalciuric MSK and five patients with normocalciuric MSK. In the patients with renal hypercalciuric MSK, urinary calcium excretion decreased from 5.05 ± 0.45 to 2.91 ± 0.29 mg/day/kg B.W. ($P < 0.01$, Fig. 1). In five normocalciuric MSK who received alkali-treatment, urinary calcium excretion decreased from 2.66 ± 0.23 to 1.27 ± 0.15 mg/day/kg B.W. ($P < 0.005$). During fasting, the ratio of urinary calcium to creatinine also decreased from 0.240 ± 0.020 to 0.137 ± 0.021 ($P < 0.01$, Fig. 2), with the latter value, however, still higher than that of normal control group (0.056 ± 0.010, $P < 0.01$). In normocalciuric MSK, fasting urinary calcium to creatinine ratio also decreased from 0.060 ± 0.008 to 0.043 ± 0.012, but the change was not significant.

Plasma calcium levels increased gradually from 9.1 ± 0.1 mg/dl to normal range and plasma phosphate also increased in renal hypercalciurig group (Fig. 3). Figure 4 shows the frequency of spontaneous stone passage. Stones/100 patients/year were decreased from 153.1 to 48.6 ($P < 0.05$) with alkali-treatment in patients with renal hypercalciuria. Six of seven patients with renal hypercalciuric MSK had

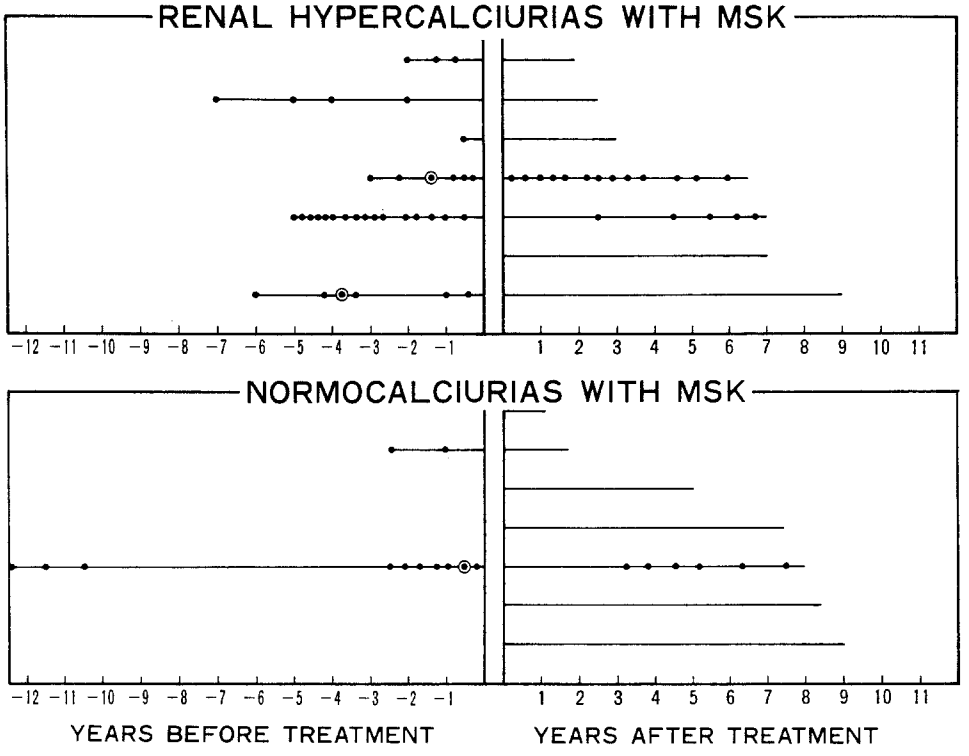

Fig. 4. The frequency of spontaneous stone passage. · represents the spontaneous stone passage ⊙ represents the surgical removal of ureter stone

experienced spontaneous stone passage. In contrast, only one of seven patients with normocalciuric MSK had experienced it ($P < 0.05$ by chi-quare test). Therefore, urinary calcium level is thought to be related to the frequency of stone formation in the patients with MSK.

Discussion

Medullary sponge kidney is an anatomic abnormality confined to the medullary portion of the kidney. Our cases represent the fully developed form of the anatomic defect in bilateral kidneys. These patients constituted about 2% of our stone forming population. Segmentally or unilaterally affected cases are excluded from the studies.

MSK is associated with increased frequency of calcium containing renal stones [4, 12, 15]. Part of the explanation for the frequent development of kidney stones may be the anatomic abnormality with resultant stasis of urine and infection [9]. However, a high frequency of hypercalciuria has been recognized in MSK patients with renal stones, and O'Neill et al. investigated the types of hypercalciuria [13]. Among seventeen patients examined by them, fifteen were hypercalciuric but most common type was absorptive (12 patients, 71%) and only three patients (18%) had renal hypercalciuria. In contrast to their results, seven patients (44%) had renal hypercalciuria in our series. The difference in frequency of renal hypercalciuria between their and our studies, however, is not statistically significant.

The patients with MSK have a defect in urine acidification of distal type [8] and resultant low plasma bicarbonate in the renal hypercalciuric MSK patients (Table 2). Chronic metabolic acidosis caused by renal tubular acidosis or by the administration of acid produces hypercalciuria [2, 11, 16, 19]. Hypercalciuria was initially thought to be the result of increased filtered load of calcium which was dissolved from bone by acidosis [19], but it was demonstrated later to arise from a depressed renal tubular reabsorption of calcium [11, 16, 17]. Therefore hypercalciuria cuased by acidosis takes the form of renal-leak.

The correction of metabolic acidosis resulted in the decrease in urinary calcium excretion and the frequency of spontaenous stone passage in patients with renal hypercalciuria. This suggests that renal hypercalciuria in patients with MSK was caused by metabolic acidosis and the level of urine calcium was related to the frequency of stone formation. However, similar grade reductions in plasma bicarbonate and impairment of urinary acidification ability were present in normocalciuric patients with MSK. It, therefore, seems likely that patients with MSK vary considerably with respect to their hypercalciuric response to metabolic acidosis. In addition, the fact that two patients with renal hypercalciuric MSK continued to pass stones after treatment suggests the participation of multifactorial causes in stone formation.

The urinary excretion of cyclic AMP with calcium loading in the patients with renal hypercalciuric MSK was significantly higher than the normal control (Table 1). The secondary hyperparathyroidism has been reported in renal hypercalciuria [14] or in distal renal tubular acidosis [3]. However, recent reports have doubled parathyroid hyperfunction in renal hypercalciuria [5, 18]. In fact, in our

studies, fasting urinary cyclic AMP were not different among the groups and loading urinary cyclic AMP levels were not different among MSK groups irrespective state of urine calcium. The evaluation of hyperfunctioning parathyroid gland awaits further studies [18].

In conclusion, a metabolic study of 16 patients with bilateral MSK and renal stones has shown that 56% were hypercalciuric and most of them were renal-leak type. Hypercalciuria in addition to the distorted collecting duct anatomy may augment the risk of stone formation. The high frequency of stone formation in hypercalciuric patients with MSK stood in sharp contrast to the low frequency of stone formation in normocalciuric patients with MSK. Since correction of the underlying metabolic abnormality reduce the incidence of renal stones, patients with MSK deserve a careful metabolic evaluation and appropriate therapy.

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