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A study of recurrent stone formers with special reference to renal tubular acidosis

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Abstract Forty-five patients with recurrent renal stone were examined for distal renal tubular acidosis (dRTA) defects by acid challenge test (150 mg ammonium chloride/kg body weight). Their 24-h urine samples were analysed for creatinine, calcium, oxalic acid, inorganic phosphorus, uric acid, magnesium and citric acid. One-hour urine samples before acid load and hourly samples for the 7 h following acid challenge test were collected and analysed for creatinine, calcium, citric acid, inorganic phosphorus, titratable acidity, and ammonium. The incidence of distal RTA defect was 22.2% in the patients examined. The major biochemical characteristics in RTA patients compared with patients without RTA were: (a) significantly higher urinary pH, (b) significantly lower excretion of citric acid, (c) no significant difference in calcium excretion and (d) a tendency toward lower titratable acidity and ammonium excretion.

Key words Recurrent stone formers · Renal tubular acidosis

In the Indian state of Rajasthan which has a population of over 35 000 000, recurrent idiopathic urinary tract calcium stone disease is a major health problem [7, 8, 14, 18]. Although the cause of calcium stone formation is multifactorial and largely unknown, in some patients it is due to a defect of distal renal tubular acidification (dRTA). The percentage of such cases can vary widely in different populations. Rampton et al. [17] found it to be present in only 0.1% of stone patients, while Backman et al. [3] reported an incidence of 31%. In an earlier study, we observed it to be present in 24% of cases [1]. This led us to investigate a selected group of recurrent renal tract stone formers for the presence of dRTA.

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Patients and methods

Forty-five radiologically proven renal stone formers admitted to surgical wards or attending the out-patient clinic of the general hospital RNT Medical College Udaipur, were selected for this study. They comprised 42 males (age range 21–58 years) and 3 females (aged 38, 31 and 46 years). All secondary causes of stone formation were excluded. The 24-h urine samples were collected in clean glass bottles containing 10 ml concentrated hydrochloric acid as preservative. Fresh urine samples were collected for citric acid analysis and the data were computed on a 24-h basis from 24-h urinary volume. For the acid challenge test, ammonium chloride packed in gelatin capsules was given in a dose of 150 mg/kg body weight to the subjects after a heavy breakfast. The subjects were put on an unrestricted diet and were ambulatory. Approximately 200 ml water/h was given to the subjects throughout the experiment. A 1-h urine sample was collected prior to the ammonium chloride loading, and thereafter hourly urine samples were collected for 7 h after the acid challenge. The urine samples were collected in clean double-distilled water-washed glass bottles which were immediately corked. The pH was measured by pH meter. Titratable acidity, ammonium, creatinine, magnesium, calcium, oxalic acid, inorganic phosphorus and uric acid were analysed in all the samples using standard biochemical procedures. Statistical analysis was carried out using Student's *t*-test.

Results

Of the 45 recurrent renal stone formers, 10 (22.2%) were found to have a defect of RTA. These patients could not acidify their urine pH below 5.0 after ammonium chloride loading. The 24-h urine chemistry

Table 1 Urinary profile of recurrent stone formers (mg/24 h)

Parameters	Recurrent stone formers	
	Without RTA	With RTA
pH	5.81 ± 0.55	6.33 ± 0.60*
Volume	1564 ± 494	1330 ± 498
Creatinine	1178 ± 274	1045 ± 221
Calcium	217 ± 77	197 ± 49
Citric acid	336 ± 96	250 ± 63**
Magnesium	55 ± 15	52 ± 18
In phosphorus	409 ± 145	372 ± 76
Uric acid	309 ± 101	269 ± 126
Oxalic acid	45 ± 14.8	45 ± 11

* P value < 0.02; ** P < 0.01

indicated that the patients with the dRTA defect had significantly lower citric acid excretion ($P < 0.01$) and higher urinary pH ($P < 0.02$) than the patients without the RTA defect. No significant differences were observed in the excretory pattern of the remaining parameters (Table 1). On the day of the acid challenge test, a 1-h urine sample was collected before acid load after giving 200 ml water. In this pre-load urine sample, citric acid excretion was also lower ($P < 0.05$). Ammonium and titratable acid excretion also tended to be lower in this group. In the post acid challenge samples, an adequate reduction in pH was observed only in the patients without the RTA defect. Calcium, inorganic phosphorus, titratable acidity and ammonium excretion increased in the patients without dRTA (Tables 2, 3). Citric acid excretion decreased considerably after acid load in the patients without the dRTA defect.

Discussion

In this study the incidence of distal renal tubular acidosis in these recurrent stone formers was 22.2%. A higher incidence of the condition in women has been reported [5, 19]; however, none of the three female patients in this study had the defect, but the number of patients is too small for any conclusions to be drawn. In an earlier study the incidence of dRTA was found to be 24% in the local stone-forming population comprising 50 patients [1, 16]. No comparable study in an Indian population is available. The incidence of this syndrome reported in the literature is highly variable. The prevalence of dRTA in the population at large has been assessed [4, 12, 17].

In both children and adults dRTA is certainly an inherited condition in most cases. The abnormal gene appears to be inherited as an autosomal dominant trait with full expression in affected members. Sporadic cases with no family history of the disease may represent new mutations or may occur secondary to a variety of renal diseases [6]. As in our previous studies [15] and from indirect evidence, we infer that the cases in this study had an acquired cause. In support of this, the stones formed were found to be composed of a mixture of calcium oxalate and phosphate with a predominance of oxalate, whereas the characteristic stone in dRTA is composed of calcium phosphate.

Table 2 Urinary profile of recurrent stone formers without RTA before and after acid challenge test (mg/g creatinine)

	pH	Calcium	In phosphorus	Citric acid	Titratable acidity	Ammonium
Pre load	5.8 ± 0.48	157 ± 80	272 ± 183	269 ± 162 (314 ± 86)	2201 ± 1211	960 ± 717
I	5.53 ± 0.58	241 ± 161	384 ± 392	204 ± 128 (229 ± 82)	1479 ± 1267	937 ± 591
II	4.98 ± 0.42	259 ± 150	346 ± 339	164 ± 120 (124 ± 93)	1585 ± 1138	1100 ± 843
III	4.79 ± 0.39	289 ± 171	421 ± 410	120 ± 99 (104 ± 59)	1648 ± 1136	1078 ± 843
IV	4.73 ± 0.32	360 ± 371	494 ± 407	122 ± 110 (86 ± 39)	1176 ± 1463	1313 ± 1052
V	4.70 ± 0.22	407 ± 370	577 ± 417	105 ± 69 (73 ± 33)	2484 ± 2035	1315 ± 963
VI	4.73 ± 0.23	363 ± 266	545 ± 251	92 ± 61 (58 ± 49)	2365 ± 1816	1324 ± 1022
VII	4.71 ± 0.24	333 ± 313	467 ± 278	90 ± 78 (68 ± 25)	2116 ± 1593	1124 ± 694

Normal range of citric acid excretion in local population is given in parentheses

Table 3 Urinary profile of recurrent stone formers with RTA before and after acid challenge test (mg/g creatinine)

	pH	Calcium	In phosphorus	Citric acid	Titratable acidity	Ammonium
Pre load	6.23 ± 0.42*	174 ± 77	233 ± 117	145 ± 64*	1418 ± 881	846 ± 613
I	5.89 ± 0.54	165 ± 127	165 ± 135	115 ± 20	891 ± 554	813 ± 750
II	5.44 ± 0.17**	287 ± 204	250 ± 108	103 ± 39	1521 ± 1284	855 ± 791
III	5.53 ± 0.39***	274 ± 249	256 ± 188	115 ± 52	1209 ± 918	864 ± 292
IV	5.58 ± 0.51***	292 ± 237	333 ± 214	235 ± 199*	1852 ± 1716	1111 ± 781
V	5.59 ± 0.49***	220 ± 116	305 ± 185	173 ± 129	1236 ± 535	779 ± 328
VI	5.62 ± 0.44***	275 ± 114	395 ± 226	147 ± 92	1464 ± 981	968 ± 438
VII	5.71 ± 0.39***	275 ± 142	343 ± 182	133 ± 51	1283 ± 630	804 ± 390

* P value < 0.05; ** P value < 0.01; *** P value < 0.001

The secretion of H^+ depends upon a luminal membrane proton pump and a voltage-dependent transport system, with the reabsorption of sodium creating a transepithelial voltage potential, leading to H^+ excretion. It also depends on the ability of the distal nephron to maintain a steep intraluminal H^+ gradient. The primary functional abnormality in dRTA is an inability of the distal nephron to establish an H^+ gradient. These functional abnormalities cause an impaired capacity of the kidney to acidify the urine, resulting in a lower phosphate and titratable acid secretion. Two other important biochemical defects are seen concomitantly, namely, hypercalciuria and hypocitraturia [13].

Some workers suggest that the criteria for the diagnosis of dRTA is an inability to acidify the urine below a pH of 5.5 following an acid load, whilst others place the lower limit at pH 5.0. To exclude any doubt, we considered only those patients who were unable to reduce their urinary pH to 5.0 after receiving 150 mg ammonium chloride per kilogram body weight. In this series, the patients with dRTA showed no significant difference in 24-h urinary excretion of creatinine, magnesium, inorganic phosphate, uric acid and oxalic acid from those with no RTA defect; nor did they show any significant difference in calcium excretion. In contrast, Albright et al. [2] reported that hypercalciuria was a significant characteristic of nephrolithiasis due to dRTA. This is a claim supported by others: Wrong and Feest [20] and Harrington et al. [9] found hypercalciuria to be present in 27% and 23% of patients, respectively. Nutahara et al. [12] suggest that hypercalciuria in stone formers with dRTA may not necessarily be due to the acidification defect.

In stone formers with dRTA, 60% were noted to have hypocitraturia (citric acid excretion < 300 mg/24 h). This incidence was significantly greater than that of those without an acidification defect. Nicar et al. [11] reported hypocitraturia in 75% of patients with dRTA and Caruana and Buckalew [6] observed it to be present in 100%. Malasit et al. [10] have suggested that hypocitraturia could be used as a screening test for dRTA. Hypocitraturia is considered to be an important risk factor for stone formation.

Urine samples collected before and after acid challenge showed that in pre-load samples of the dRTA patients there was no significant difference in calcium but citric acid excretion was significantly lower. Interestingly, the dRTA patients did not show a fall in urinary citric acid after acid load, whereas in patients without RTA it progressively decreased. This change appears to be mainly the function of pH. As expected, titratable acidity and ammonium excretion in pre-load and post-challenge period tended to be lower. These remained more or less unchanged in all the samples examined, whereas both of them increased in stone patients without RTA. Precise comparable data are not available in the literature.

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