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# Role of Citric Acid in Primary Hyperparathyroidism with Renal Lithiasis

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**Summary**. Nephrolithiasis is presented in 18-40% of patients with primary hyperparathyroidism. Our work suggests that citrate, an inhibitor of calcium salts, could be involved in the presence of renal lithiasis because hyperparathyroid stone formers show less citrate elimination than nonstone formers.

**Key words**: Primary hyperparathyroidism, renal lithiasis, citrate

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Primary hyperparathyroidism (pHPT) is a disease characterized by skeletal involvement and/or renal lithiasis (RL) as main complications (1, 2, 3, 4). In diseases with increased bone resorption, bone components are released to extracellular fluid. Bone is the main reservoir of citric acid, and it is known that citrate inhibits both nucleation and crystal growth of calcium salts (1, 5). The aim of the present work is to evaluate the role of citric acid in the development of RL in patients with pHPT and the possible role of parathormone (PTH) on citric acid metabolism.

## Material and Methods

Diagnostic criteria: We defined pHPT after surgical findings (adenoma or hyperplasia) and/or biochemical parameters (hypercalcemia with elevated iPTH serum levels). RL was confirmed by X-ray or echographic techniques or by recent history of at least one calculi passed. Bone involvement (BI) was defined if alkaline phosphatase serum levels were higher than 13 K.A.U. or urinary hydroxyproline/creatinine ratio above 0.035. We defined hypocitraturia when urinary citrate elimination was less than 320 mg/24 hours. Patients: Forty three unselected patients with pHPT were chosen. Nineteen had RL (9 men, 10 women) and 24 did not have RL (4 men and 20 women). We excluded patients who had a secondary metabolic disease associated with RL.
Methods - Serum and 24 hours-urine: Creatinine was assessed by Jaffe's reaction, citrate by citrate lyase, calcium and magnesium by atomic absorption spectrophotometry and phosphate by Fiske and Subbarrow. Serum: Alkaline phosphatase by Bessey Lowry, and iPTH by RIA. In 24 h-urine: Diuresis, pH by glass electrode, and hydroxyproline by the Kivirikko method.

## Results and Discussion

RL is a complication in pHPT and its incidence is 18-40% (1, 2, 3, 4, 6) in that pathology. We found that 40% of patients with pHPT were stone formers. We, like Pak (3), found a female preponderance in nonstone formers group, whereas the two sexes have an equal incidence in patients with pHPT with RL.

Fig. 1: The incidence of hypocitraturia in pHPT patients with or without RL, in each case with or without BI (43 patients).

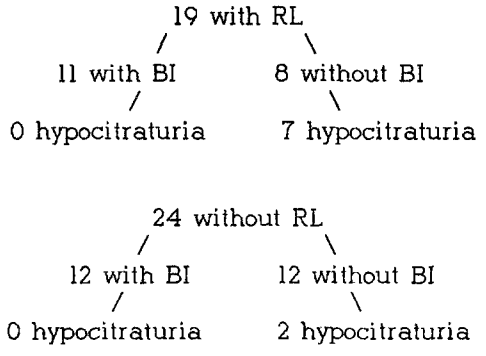


Table 1: Serum and urine biochemical values of 43 patients with pHPT.

| | Patients with RL Mean ± SD (n=19) | Patients without RL Mean ± SD (n=24) |
|---|---|---|
| Serum | | |
| Creatinine (mg/dl) | 1.05 ± 0.27 | 0.96 ± 0.21 |
| Citrate (mg/dl) | 2.51 ± 0.73 | 2.69 ± 0.80 |
| Calcium (mg/dl) | 11.07 ± 0.51 | 10.94 ± 0.77 |
| Phosphate (mg/dl) | 2.86 ± 0.48 | 2.81 ± 0.43 |
| AP (K.A.U.) | 12.24 ± 2.5 | 10.94 ± 2.59* |
| PTH (pg/ml) | 1345 ± 1280 | 794 ± 786 |
| Urine (mg/mg Cr) | | |
| Citrate | 0.39 ± 0.25 | 0.55 ± 0.21* |
| Calcium | 0.19 ± 0.11 | 0.25 ± 0.09* |
| Phosphate | 0.71 ± 0.20 | 0.77 ± 0.23 |
| Hydroxyproline | 0.04 ± 0.01 | 0.04 ± 0.01 |
| Ccr (ml/min) | 100 ± 31 | 91 ± 26 |
| RTC (%) | 87 ± 10 | 77 ± 16* |
| PhTR (%) | 75 ± 9 | 72 ± 10 |
| TmP/GFR | 2.22 ± 0.6 | 2.06 ± 0.5 |

AP: Alkaline phosphatase, Ccr: Creatinine clearance, RTC: Citrate tubular resorption, PhTR: Phosphate tubular resorption, TmP/GFR: Maximal phosphate resorption. *: $p < 0.05$.

The relationships between citrate metabolism and parathyroid gland activity have been reported (1, 7); but the results of these works could be considered of limited value due to the low number of patients studied and the nonspecific method used for citrate assay. The results of our study (Fig. 1; Table 1) show that kidney stone formers with pHPT presented a significant decrease in mean citraturia and a significant increase in mean RTC in comparison to patients with pHPT without RL. On the other hand, citraturia prevents renal stones due to the ability of citrate to form soluble complexes with divalent cations such as calcium and inhibits spontaneous nucleation of crystal growth of calcium salts. Minisola et al. (5) and Rudman et al. (8) showed that kidney is the organ responsible for the low urinary citrate elimination in patients with hypocitraturic RL. This could be due to an increase in RTC that occurred in the proximal tubule, as the brush border membrane contains a special transport system for citrate. We found a higher alkaline phosphatase serum level in patients with RL than in patients without RL; but the number of stone formers with BI (11 from 19; 57.8%) was similar to the number of pHPT patients without RL (12 from 24, 50%). Also we did not find any significant differences in the hydroxyproline/creatinine ratio between both groups. We have found higher calciuria in pHPT nonstone formers than in pHPT stone formers, but mean values of both groups were increased with respect to normal values. When we separated pHPT kidney stone patients with respect to bone turnover status (Table 2), 7 from 8 patients without BI had hypocitraturia and mean urinary citrate levels were lower than the normal range. Simultaneously, these stone formers showed an increase in RTC. Subjects with pHPT, RL and BI presented normocitraturia and hypercalciuria against patients with pHPT and RL but without BI who have hypocitraturia and normocalciuria. These results suggest that the etiology of RL in pHPT is probably multifactorial. In some cases the etiologic factor could be a decrease in citraturia and in others, could be due to hypercalciuria. Citrate serum levels were abnormally high in patients with pHPT (1,7). We found a positive linear correlation between serum citrate and serum calcium values ($r = 0.45$: $p < 0.05$) which have been reported (1). Our results show a significant positive correlation between iPTH serum levels ($r = 0.46$: $p < 0.05$) in patients with pHPT, which suggest that PTH could be involved in citric acid metabolism either because PTH released citric acid from bone or PTH could produce an increase in citrate renal tubular reabsorption.

Table 2: Biochemical values in 19 pHPT stone former patients classified according to their BI..

| | Stone formers with BI (n=11) | Stone formers without BI (n=9) |
|---|---|---|
| Serum | | |
| Creatinine (mg/dl) | 0.94 ± 0.13 | 1.12 ± 0.3 |
| Citrate (mg/dl) | 2.64 ± 0.7 | 2.35 ± 0.76 |
| Calcium (mg/dl) | 11.12 ± 0.55 | 11.01 ± 0.43 |
| Phosphate (mg/dl) | 2.72 ± 0.47 | 3.04 ± 0.47 |
| A.P. (K.A.U.) | 15.12 ± 7.0 | 8.20 ± 2.05* |
| Urine (mg/mg Cr) | | |
| Citrate | 0.53 ± 0.19 | 0.12 ± 0.10* |
| Calcium | 0.24 ± 0.12 | 0.14 ± 0.08* |
| Phosphate | 0.78 ± 0.19 | 0.62 ± 0.17* |
| Hydroxyproline | 0.04 ± 0.01 | 0.03 ± 0.01* |
| Ccr (ml/min) | 102 ± 25 | 99 ± 37 |
| RTC (%) | 81 ± 1 | 94 ± 5* |
| PhTR (%) | 74 ± 8 | 78 ± 9 |
| TmP/GFR | 2.07 ± 0.56 | 2.42 ± 0.60* |

*: $p < 0.05$

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# Advances in Medical Treatment of Renal Stones

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Advances in pharmacotherapy of renal stones are closely linked to the progress made in laboratory diagnostics. Development of lithotripters and the consequent sophisticated means of removing stones has distracted attention from the causes of lithiasis. However, removal of a renal stone only eliminates the consequences of a disease, but not its cause. There is frequently a failure to institute the most important diagnostic measure (collection of stones or disintegrates with a urinary sieve and performance of a qualified stone analysis). Various ESWL centers also do not analyse the stones or only do so by means of the intrinsically unsuitable chemical method. Thus, strategies of follow-up care are already very non-specific or wrong at the beginning of therapy.

It is indispensable to analyse every renal stone or to send all disintegrates collected for analysis. Only X-ray diffraction (7) and infrared spectroscopy (9) can provide exactly reproducible results among the methods of analysis available today. A computer program was developed for infrared spectroscopy which ensures definitive qualitative analysis and allows semiquantitative appraisals (10). By these methods of analysis, some new kinds of renal stones have been discovered (e.g. 2.8 dihydroxyadenine) and a series of sub-groups has been differentiated. The types of stones relevant for practical purposes are:

1. Cystine
   2.8 dihydroxyadenine
   Xanthine
2. Uric acid
   Ammonium urate
   Sodium urate
3. Calcium oxalate
   -Whewellite
   -Weddellite
4. Phosphates
   -Struvite
   -Carbonate apatite
   -Brushite

Particular attention must be paid to the fact that the types of renal stones of metabolic origin listed in the first group are mostly very pure, whereas two thirds of the other stone types are mixed stones. The relative urinary volume is crucial for all types of renal stones, i.e. the relative supersaturation for the respective stone type is significantly lowered with increase of urinary volume. This is shown for calcium oxalate in Figure 1.

The increase of the urine volume is of very great importance in the stone types of metabolic origin, since the lithogenic noxa is always present and constitutes a major risk especially at night.

The requirement for limitations of ascorbic acid administration in the therapy of cystine lithiasis has to be regarded as a crucial advance. By the reductive action of ascorbic acid, it was possible to induce an increased cystine excretion in almost all