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# Correlation Between 1.25 Dihydroxyvitamin D Serum Levels and Fractional Rate of Intestinal Calcium Absorption in Hypercalciuric Nephrolithiasis. Role of Phosphate

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**Summary**. Different mechanisms could explain the elevated calcium elimination, the main cause of calcium oxalate renal stones. Our results suggest that phosphate levels are decreased in patients with absorptive hypercalciuric nephrolithiasis and elevated serum dihydroxyvitamin D. This could be the reason why in this group of patients oral phosphate treatment prevented hypercalciuria and renal lithiasis.

**Key words**: Hypercalciuric renal lithiasis, $1.25(OH)_2D_3$, phosphate

It is known that the active metabolite of vitamin D, $1.25(OH)_2D_3$, regulates intestinal calcium absorption (1). Hypercalciuric nephrolithiasis (HN) has been recognized as the main cause of calcium renal stones. Different mechanisms could explain the cause of elevated urinary calcium excretion: renal, absorptive and bone resorption (2). A decrease in renal intracellular phosphorus concentration induces an increase in $1.25(OH)_2D_3$ serum values, with consequent increase in intestinal calcium absorption and hypercalciuria. Our objective has been to prove if a phosphate disturbance could be demonstrated in absorptive hypercalciuric nephrolithiasis and consequently prevented with phosphate oral supplementation.

## Materials and Methods

Diagnostic criteria: Hypercalciuria was diagnosed when urinary calcium levels were higher than 300 mg/24 h in men and 250 mg/24 h in women or upper than 4 mg/kg/day in both sexes.

Patients: Fifty eight patients affected with HN (36 men and 22 women) were studied. Patients with renal tubular acidosis, persistent urinary tract infections, chronic renal failure or elevated PTH serum levels were excluded. Patients were divided into three groups: group I with normal $\alpha$ and normal $1.25(OH)_2D_3$ serum levels, group II with high $\alpha$ and normal $1.25(OH)_2D_3$ serum levels and group III with high $\alpha$ and high $1.25(OH)_2D_3$ serum levels. Ten patients from group II and 10 patients from group III were treated with elemental phosphorus (1.5 g/day) during six months (ammonium dihydrogen phosphate, potassium dihydrogen phosphate and manganese glycerophosphate; Sandoz).

Methods: Serum and 24 h urine: creatinine (Jaffe's reaction), uric acid (uricase), phosphate (Fiske and Subbarow), calcium and magnesium (atomic absorption spectrophotometry). Serum: PTH (RIA), $1.25(OH)_2D_3$ by radio receptor assay (normal range: 18-50 pg/ml) and fractional rate of calcium ($\alpha$) using a Ca-47 isotope (normal range: 0.4-0.8 $h^{-1}$).

## Results and Discussion

Intestinal calcium absorption has been studied by direct (3) and indirect (4) methods. In the present work a direct method has been used (3). Serum $1.25(OH)_2D_3$ levels correlated linearly with $\alpha$ ($r = 0.42$: $p < 0.05$) in these patients, as it was expected, because this vitamin D metabolite mediates intestinal calcium absorption (1). When HN subjects were divided into three groups (Table 1), patients from group II with normal serum $1.25(OH_2D_3$ levels and high $\alpha$ presented a lower urinary calcium excretion than patients from group I and group III.

Table 1: Serum and urine biochemical values in 58 HN patients.

| | Group I Mean ± SD (n=20) | Group II Mean ± SD (n=19) | Group III Mean ± SD (n=19) |
|---|---|---|---|
| Sex (m/f) | 10/10 | 13/6 | 10/6 |
| Age (years) | 44.53 ± 9.76 | 46.92 ± 6.97 | 48.20 ± 10.31 |
| $\alpha$ ($h^{-1}$) | 0.60 ± 0.11 | 1.02 ± 0.13 | 1.04# ± 0.16 |
| $1.25(OH)_2D_3$ (pg/ml) | 34.76 ± 7.84 | 36.20 ± 6.64 | 67.87#$ ± 12.8 |
| Serum | | | |
| Phosphate (mg/dl) | 3.02 ± 0.37 | 3.10 ± 0.50 | 3.06 ± 0.46 |
| Calcium (mg/dl) | 10.02 ± 0.49 | 9.87 ± 0.45 | 9.91 ± 0.26 |
| Urine | | | |
| Calcium/Creatinine (both in mg/24h) | 0.22 ± 0.07 | 0.18 ± 0.04 | 0.22$ ± 0.07 |
| Calcium (mg/kg/24h) | 4.77 ± 1.4 | 4.56 ± 0.6 | 4.77 ± 1.4 |
| Ccr (ml/min) | 119 ± 28 | 115 ± 25 | 125 ± 21 |
| PhTR (%) | 80 ± 6.8 | 79 ± 6.9 | 80 ± 6.2 |
| TMP/GFR | 2.49 ± 0.49 | 2.53 ± 0.66 | 2.59 ± 0.49 |

*: Group I vs group II; $p < 0.05$
#: Group I vs group III; $p < 0.05$
$: Group II vs group III; $p < 0.05$

Table 2: Serum and urine biochemical parameters before and after treatment.

| | Group II (n=10) | Group III (n=10) |
|---|---|---|
| Before treatment: | | |
| $\alpha$ ($h^{-1}$) | 0.95 ± 0.20 | 1.10 ± 0.30** |
| $1.25(OH)_2D_3$ (pg/ml) | 38 ± 9 | 74 ± 16** |
| Serum phosphate (mg/dl) | 3.10 ± 0.5 | 3.10 ± 0.7 |
| PhTR (%) | 81 ± 11* | 77 ± 10** |
| TMP/GFR | 2.80 ± 0.60* | 2.50 ± 0.70** |
| Calcium/Creatinine (both in mg/24h) | 0.22 ± 0.04 | 0.26 ± 0.05** |
| After treatment: | | |
| $\alpha$ ($h^{-1}$) | 1.10 ± 0.1 | 0.85 ± 0.3 |
| $1.25(OH)_2D_3$ (pg/ml) | 39 ± 8 | 44 ± 12 |
| Serum phosphate (mg/dl) | 2.80 ± 0.4 | 3.20 ± 0.2 |
| PhTR (%) | 69 ± 7 | 68 ± 8 |
| TMP/GFR | 1.05 ± 0.1 | 1.04 ± 0.3 |
| Calcium/Creatinine (both in mg/24h) | 0.21 ± 0.06 | 0.15 ± 0.05 |

*: Group II before treatment vs group II after treatment; $p < 0.05$

**: Group III before treatment vs group III after treatment; $p < 0.05$

But when calciuria was corrected by body weight we could not find any differences in urinary calcium excretion between the three groups. We, like several groups (4 ,5), could not find a correlation between serum phosphate and serum $1.25(OH)_2D_3$. Other authors (5, 6) studying simultaneously hypercalciuric, normocalciuric and healthy subjects found a significant correlation between low serum phosphate concentration and high serum $1.25(OH)_2D_3$. On the other hand several findings (5, 7) have indicated the stimulatory effects of $1.25(OH)_2D_3$ on phosphate reabsorption, which prevented hypophosphatemia induced by renal phosphate leak or intake phosphate restriction. These findings expressed the difficulties to study the role of phosphate in HN. Patients with absorptive HN presented a decrease in tubular phosphate resorption (PhTR) and in maximal phosphate resorption (TmP/GFR) (5). When 10 patients from group II and 10 patients from group III (Table 2) were treated with phosphorus, absorptive HN patients with normal serum $1.25(OH)_2D_3$ levels presented hypercalciuria and elevated $\alpha$, which indicated that phosphate and $1.25(OH)_2D_3$ were not implicated in the high calcium absorption, so the first etiological cause remains unknown. Oral phosphate administration in absorptive HN patients with high serum $1.25(OH)_2D_3$ conduced to a normalization of active vitamin D metabolite (pg/ml: 74 ± 16 vs 44 ± 12; $p \ll 0.05$), a significant decrease of $\alpha$ ($h^{-1}$: 1.1 ± 0.3 vs 0.85 ± 0.3; $p < 0.05$) and a decrease of urinary calcium excretion (Ca/Cr: 0.26 ± 0.05 v ± 0.15 ± 0.05; $p < 0.05$). These findings suggest that renal phosphate, as a modulator of 1$\alpha$-hydroxylase, could be decreased in patients with absorptive HN and elevated serum $1.25(OH)_2D_3$ levels. This fact could explain why, in this group of patients, phosphate treatment prevented hypercalciuria.

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