In Advanced Renal Failure, Dietary Phosphorus Restriction Reverses Hyperparathyroidism Independent of Changes in the Levels of Calcitriol

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Dear Sir,

In patients with chronic renal failure (CRF), the restriction of dietary phosphorus results in serum phosphate reduction and improvement of secondary hyperparathyroidism. These data are usually ascribed to a concomitant increase in the production of calcitriol [1, 2]. However, it has been reported in patients with advanced renal failure [3] and in severe experimental renal failure [4, 5] that phosphorus restriction reversed hyperparathyroidism without significant change in plasma calcitriol levels.

The aim of the present investigation was to examine the effects of phosphorus restriction on calcium phosphate metabolism and more especially on plasma calcitriol levels. Our study comprised 23 patients with advanced CRF (GFR: 11.63 ± 3.9 ml/min per 1.73 m²) receiving a diet providing daily, per kilogram body weight, 0.4 g protein of vegetable origin, 3-5 mg of inorganic phosphorus and 35 kcal. The diet was supplemented with ketoanalogues (CSW 20/4, Clintec, France)

and with calcium carbonate to keep unchanged their habitual calcium intake: 758 ± 124 mg/day at the start of the study. No other phosphate binder was prescribed. The patients additionally received a multivitamin preparation providing 1,000 IU of vitamin D₂ per day. Serum calcium, serum phosphorus, serum bicarbonate, PTH activity (intact hormone), calcitriol, alkaline phosphatase and osteocalcin were measured at the start of the study and 3 months later. The evolution of renal function was assessed by ⁵¹Cr-EDTA clearances.

Results were expressed as mean $\pm$ standard deviation (SD). Student's t test was used for paired data. Multiple regression analysis was applied to analyze the relationship between the concentrations of PTH and calcitriol and the different variables.

At the start of the study, PTH concentration was directly correlated with GFR ($r = 0.46$; $p = 0.04$), with inorganic phosphorus ($r = 0.59$; $p = 0.01$) and with osteocalcin ($r = 0.5$; $p = 0.02$). On the other hand, PTH did not correlate with either calcitriol or calcium concentrations, no correlation was found between calcitriol and the other biochemical variables.

After 3 months of phosphorus and protein restriction, GFR did not change significantly from initial values: 11.63 ± 3.98 and 11.00 ± 4.05 ml/min, respectively. During this period, serum bicarbonate increased significantly while alkaline phosphatase, serum inorganic phosphorus and PTH decreased significantly. At the same time, calcitriol levels decreased slightly from 16.91 ± 7.39 to 13.51 ± 6.3 pg/ml (NS), while serum calcium was not significantly modified. Table 1 summarizes the evolution of the different biochemical parameters. Beneficial effects of dietary protein and phosphorus restriction on acidosis and calcium phosphate metabolism have been described in previous studies [6-8].

Although it has been known for 20 years that in patients with CRF dietary phosphorus restriction prevents and ameliorates secondary hyperparathyroidism [9, 10], the mechanisms that may mediate these effects are still controversial. It is generally postulated that phosphorus restriction results in a decrease in serum phosphorus with secondary increase in 25-hydroxyvitamin D 1α -hydroxylase activity and calcitriol production and lastly a decrease in the PTH level favored by the improvement in the calcemic response to PTH [5]. However, it has been reported in severe clinical and experimental uremia that phosphorus restriction could reverse secondary hyperparathyroidism without any change in plasma calcium or plasma calcitriol levels [3-5]. Actually Lucas et al. [3] observed in 7 patients with severe CRF (creatinine clearance : 6.1 ± 0.9 ml/min) that after 3 months on a low-phosphorus diet, plasma concentration of PTH and plasma phosphorus level significantly decreased whereas serum calcitriol levels which were initially below normal, decreased significantly. In 5 uremic dogs (with $\frac{5}{8}$ nephrectomy), Lopez-Hilker et al. [4] pointed out that phosphate intake restriction was able to decrease PTH levels despite normocalcemia and low plasma calcitriol levels. Recently, Rodriguez et al. [5] have shown that, in rats with normal function or with moderate CRF, reduced phosphorus intake increased serum calcitriol levels whereas in animals with a more severe degree of renal failure the same diet did not affect the serum calcitriol level which was not modified by a PTH infusion either. It is likely that in advanced renal failure, calcitriol synthesis which is continually stimulated by the elevated PTH levels and produced at a maximum rate by a reduced renal mass cannot be stimulated by phosphorus restriction anymore.

We confirm that in severe CRF, the beneficial effect of phosphorus restriction on secondary hyperparathyroidism is independent of changes in calcitriol and plasma calcium. The mechanism of this effect is not yet known, Lopez-Hilker et al. [4] have proposed that the improvement of secondary hyperparathyroidism may be related to a direct effect of the low-phosphorus diet which might affect the phospholipid composition of the parathyroid cell membranes modifying local calcium fluxes and/or regulation of calcitriol receptors of the parathyroid cells.

References

Llach F, Massry SG: On the mechanism of secondary hyperparathyroidism in moderate renal insufficiency. *J Clin Endocrinol Metab* 1985; 61:601-606.

Portale AA, Booth BE, Halloran BP, Morris RE: Effect of dietary phosphorus on circulating concentrations of 1,25-dihydroxyvitamin D in children with moderate renal insufficiency. *J Clin Invest* 1984;73:1580-1589.

Lucas PA, Brown RE, Woodhead JS, Coles GA: 1,25-dihydroxycholecalciferol and parathyroid hormone in advanced chronic renal failure: Effects of simultaneous protein and phosphorus restriction. *Clin Nephrol* 1986;25:7-10.

Lopez-Hilker S, Dusso AS, Rapp NS, Martin KS, Slatopolsky E: Phosphorus restriction reverses hyperparathyroidism in uremia independent of changes in calcium and calcitriol. *Am J Physiol* 1990;259:F432-F437.

Rodriguez M, Martin-Malo AA, Martinez ME, Torres A, Felsenfeld AJ, Llach F: Calcemic response to parathyroid hormone in renal failure: Role of phosphorus and its effect on calcitriol. *Kidney Int* 1991;40:1055-1062.

Tessitore N, Venturi A, Adami S, Roncari C, Rugia C, Corgnati A, Bonucci E, Maschio G: Relationship between serum vitamin D metabolites and dietary intake of phosphate in patients with early renal failure. *Miner Electrolyte Metab* 1987;13:38-44.

Barsotti G, Cupisti A, Morelli E, Ciardella F, Giovannetti S: Conventional low-protein diet (CLPD) and special vegan supplemented diet (SD): Effects on metabolic acidosis (MA) and total hydrogen ion excretion in chronic renal failure (CRF) (abstract). 26th Congr EDTA, Göteborg 1989, p 145.

Lefèbvre A, de Vernejoul MC, Gueris J, Goldfarb B: Optimal correction of acidosis changes progression of dialysis progression of dialysis osteodystrophy. *Kidney Int* 1989;36:1112-1118.

9 Slatopolsky E, Bricker NS: The role of phosphorus restriction in the prevention of secondary hyperparathyroidism in chronic renal failure. *Kidney Int* 1973;4:141-145.

10 Barsotti G, Morelli E, Guiducci A, Ciardella F, Giannoni A, Lupetti S, Giovannetti S: Reversal of hyperparathyroidism in severe uremia following very-low-phosphorus diet. *Nephron* 1984;38:54-56.