Does hypophosphataemia induce hypoparathyroidism in pre-dialysis patients?

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Relationship between phosphorus and hypoparathyroidism

In the first set of clinical observations, we studied 23 patients with biochemical abnormalities suggesting renal osteodystrophy [10]. The group included 15 males (65%) and eight females (35%), with a mean age of 51.1 ± 12.6 years (mean ± standard deviation) and creatinine clearance of 20.8 ± 13.3 ml/min/1.73 m². The undecalcified bone biopsy showed three patients with hyperparathyroid bone disease (13%), eight with mixed bone disease (34.8%), four with osteomalacia (OM; 17.4%) and eight with ABD (34.8%). No stainable aluminium or iron was detected at the bone surface. They had not taken any vitamin D or calcium supplement, phosphate binders, anti-convulsants or corticosteroids. When compared with the other histological subgroups, ABD patients showed a more preserved renal function (creatinine clearance = 32.8 ± 14 vs 14.4 ± 7.5 ml/min/1.73 m²) and did not show any acidosis.

Within the whole population, a serum phosphorus concentration ≤3.5 mg/dl was predictive of ABD (P = 0.001). In the low turnover group (OM plus ABD), serum total calcium was 9.2 ± 1.6 mg/dl, and a significant positive correlation was observed between serum phosphorus and amino-terminal PTH (n = 12; r = 0.68; P < 0.05). Furthermore, in ABD patients, serum total calcium was normal (9.9 ± 1.1 mg/dl), and the lowest serum phosphorus (3.1 ± 0.9 mg/dl) was associated with the lower PTH, 10.3 ± 3.3 pmol/l (normal values: 14–27 pmol/l), clearly indicating a relative hypoparathyroidism. On the other hand, OM patients showed greater serum PTH (44.5 ± 13.3 pmol/l) and phosphorus (5.0 ± 1.5 mg/dl) and a more deteriorated renal function (creatinine clearance = 10.8 ± 2.0 ml/min/1.73 m²). These results suggest that a low serum phosphorus could be responsible for the low PTH observed in ABD patients. This assumption was reinforced by the fact that our pre-dialysis patients had a low phosphorus intake (651 ± 315 mg/day; n = 17). Overt malnutrition was not observed, since all but two patients showed normal body mass index (23 ± 3 kg/m²).
Hypophosphataemia and hypoparathyroidism in pre-dialysis patients

The mechanisms by which low phosphorus intake and/or low serum phosphorus could induce hypoparathyroidism are not clear. Some possibilities could be considered: (i) less physicochemical interaction with serum calcium [11]; (ii) less direct stimulation of the parathyroid gland by the phosphorus itself [12]; and (iii) blocking of the parathyroid gland due to increased calcitriol resulting from a lesser action of phosphorus on 1α-hydroxylase activity [4,13]. As serum calcium was normal, it is difficult to implicate hypercalcaemia as a cause of the low PTH. On the other hand, the third mechanism might be operating in our patients with low bone turnover, since in this group a significant negative correlation between serum calcitriol and PTH was found (Figure 1). Furthermore, calcitriol concentrations in ABD patients, although not significant, were greater than those observed in the other patients (48.1 ± 37.3 vs 26.7 ± 14.4 pg/ml). It has been shown that administration of vitamin D to pre-dialysis patients was capable of inducing ABD [9]. In this study, serum calcitriol concentrations were high and PTH was within the normal range, i.e. not as high as could be expected in the uraemic condition, suggesting a relative hypoparathyroidism. Our ABD patients, on the contrary, were not given vitamin D supplements. Since these patients live in a sunny country, a high exposure to sunlight, combined with a less deteriorated renal function and a low phosphorus intake, may have played a role in determining the greater calcitriol levels observed [4,14]. However, a direct action of calcitriol on the parathyroid gland of ABD patients has to be proven.

In another group of pre-dialysis patients, now selected for showing low bone mineral density (median of L2/L4 T-score = −2.63), a high prevalence of low turnover bone disease was also found (n = 38; 95%). They were 40 patients (25 males and 13 females), with a median age of 52.5 years and creatinine clearance of 26.5 ml/min/1.73 m² [15]. Again, ABD patients (n = 21) showed a significant positive correlation between serum phosphorus and intact PTH (normal values: 15–65 pg/ml; Figure 2). In the ABD subgroup, the median of serum phosphorus was 3.6 mg/dl (range = 1.9–6.2 mg/dl) and intact PTH was 76 pg/ml (6–409 pg/ml). Some patients showed serum phosphorus and PTH somewhat greater than those observed in our first study. These results are in agreement with those of Hernandez et al. [16] who found a high prevalence of ABD with low PTH in uraemic pre-dialysis patients. However, in their study, mean serum phosphorus was greater than ours, perhaps due to a more deteriorated renal function. Coen et al. [17] have stressed the possibility that pre-dialysis patients may change their histological pattern of bone disease. If we consider that better preserved renal function and low serum phosphorus favour the occurrence and are markers of ABD, the findings of more decreased renal function and high serum phosphorus could be indicative of histological changes. Yet, in our two studies, OM patients showed a more severe renal failure combined with both higher phosphorus and PTH [15]. A strong association between osteopenia and low turnover bone disease was observed in those pre-dialysis patients. In fact, as for ABD, this was the first time we found patients with such diagnosis associated with a clear sign of bone disease, as is osteopenia, quantified by dual photon bone absorptiometry.

An attempt to reverse hypoparathyroidism with phosphorus supplementation

More recently, in order to verify if we could reverse the hypoparathyroidism observed in low turnover bone disease, we have provided an oral phosphorus supplement (neutral complex phosphate) to 18 pre-dialysis patients with normal/low serum phosphorus and low PTH, or with ABD diagnosed through bone biopsy [18]. As can be seen in Table 1, patients were given phosphorus for two consecutive months, in daily doses of 0.5 g during the first month and 1.0 g during the second month. Throughout that period, serum creatinine did not change, suggesting maintenance of renal function. Urinary phosphorus excretion increased significantly, indicating a good compliance by the
patient with the prescription; on the other hand, serum phosphorus did not change. Serum ionized calcium and calcitriol decreased and PTH increased significantly. Such an increase was not excessive, representing 42% of the basal values, despite the high phosphorus intake during the study. Yet, with the use of 0.5 g of phosphorus, no increase in PTH was observed. These results show that the parathyroid activity in low-turnover bone disease patients can be increased with the use of phosphorus supplements; the moderate response of PTH suggests that there are other factors regulating the activity of the parathyroid gland. Again, the increase in PTH could be due to a direct action of phosphorus on the parathyroid gland and/or a reduction in both calcitriol and ionized calcium [11–13]. Further studies are necessary to determine the actual action of phosphorus in such a condition.

References

9. Cohen-Solal ME, Sebert JL, Boudailliez B et al. Non-aluminic adynamic bone disease in non-dialyzed uremic patients: a new use of phosphorus supplements; the moderate response of PTH suggests that there are other factors regulating the activity of the parathyroid gland. Again, the increase in PTH could be due to a direct action of phosphorus on the parathyroid gland and/or a reduction in both calcitriol and ionized calcium [11–13]. Further studies are necessary to determine the actual action of phosphorus in such a condition.