ability to assess adequately the overall impact of the BP load upon the heart [8]. When LV thickening is found the clinical record should be carefully reviewed and blood pressure should be assessed using state-of-the art methods such as ambulatory blood pressure monitoring in the interdialytic period [11] and exercise BP monitoring. Search for additional evidence of target-organ damage, e.g. thickening of the aortic or the carotid artery wall should also be carried out. This laborious and time-consuming approach will certainly complicate our lives and those of our patients. The alternative, however, would be to risk inadequate treatment of arterial hypertension and relentless progression of LVH.

## The role of antihypertensive treatment

The aim of effective antihypertensive treatment must be (i) to lower BP below the (currently controversial) risk threshold and (ii) to achieve reversal of LVH without perturbing LV functional properties [3]. It is beyond the scope of this short communication to discuss control of hypervolaemia. Treatment using antihypertensive medication may reverse LVH by two mechanisms (i) resetting of central and peripheral haemodynamics (which is a long-term process) and (ii) reversal of LVH by non-haemodynamic mechanisms of the drugs (which may be a matter of weeks). Reversal of LVH occurs more rapidly with ACE inhibitors than with calcium-channel blockers or beta blockers [12]. The protean effects of these drugs, however, renders it difficult to delineate to what extent the benefit is related to arterial and venous dilatation, reduction of the arterial stiffness [8], inhibition of systemic RAS, enhanced activity of the kinin system, or inhibition of cardiac growth independent of haemodynamic effects [3,12]. In theory, accelerated regression of LVH in the face of incomplete lowering of BP may cause damage by upsetting the balance between myocardial contractility and hydraulic work load. This does not appear to be a clinical problem. In the absence of further information on the detailed mechanisms, it is wise to combine treatment with ACE inhibitors and calcium-channel blockers in patients with difficult to control hypertension [6].

It follows from the above that the ideal treatment of LVH is currently not available, but recent progress has gone a long way to make LVH a problem that can be rationally managed by the clinical nephrologist.

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# Treatment of hyperparathyroidism—why is it crucial to control serum phosphate?


Diego Brancaccio, Maurizio Gallieni and Mario Cozzolino

Renal Unit, Ospedale San Paolo, University of Milan, Italy


The reasons for failure of phosphate control in uremic patients and the therapeutic interventions that can be taken have been recently reviewed [1–4]. Briefly, what should be done for every dialysis patient is the following: restriction of dietary intake of phosphate, optimization of dialysis efficiency, correction of metabolic acidosis and use of phosphate binders, possibly avoiding aluminum gels.


*Correspondence and offprint requests to*: Diego Brancaccio, MD, Renal Unit, Ospedale San Paolo, via A. di Rudinì, 8, 20142 Milan, Italy.

## What is the role of phosphate in the genesis of abnormal calcium metabolism in renal failure?

Which are the reasons why we should do all of this? When more than 20 years ago Slatopolsky and Bricker [5] formulated the 'trade off' hypothesis, they clearly established that phosphate restriction *prevents* hyperparathyroidism in renal failure: a decline in glomerular filtration rate while eating a regular diet is accompanied by a progressive rise in PTH levels, while limiting phosphate intake prevents the development of secondary hyperparathyroidism. This conclusion was drawn from the experimental data at a time when the role of calcitriol was not known but this is generally still valid today.

It was later demonstrated that in moderate renal failure phosphate restriction is followed by an increase in the production of calcitriol [6], which in turn suppresses PTH synthesis and secretion directly and by increasing serum calcium levels. However, in advanced renal failure calcitriol levels do not change after phosphate restriction, but PTH levels improve, indicating a direct action of phosphate on PTH secretion, independent of calcium and calcitriol [7,8]. This issue has been recently studied in detail by Kilav *et al.* [9]: they showed that hypophosphatemic, normocalcemic rats with normal serum $1,25(OH)_2D_3$ levels had decreased PTH mRNA levels, indicating that hypophosphatemia itself decreases PTH mRNA levels without a contribution of calcium or vitamin D. Moreover, they provided additional evidence that the effect of hypophosphatemia was not mediated by vitamin D. It was documented that the effect was not transcriptional: in nuclear transcript run-on assays there was no difference in the transcription of PTH from rats on a low phosphate diet as compared to a normal diet. Slatopolsky *et al.* [10] provided evidence that in parathyroid glands of normal rats *in vitro*, high phosphate levels have a direct stimulatory effect on PTH secretion with no difference in PTH mRNA, suggesting a post-transcriptional mechanism; in addition, they showed that phosphate restriction in uremic rats prevents parathyroid gland growth and secondary hyperparathyroidism independent of ionized calcium and $1,25(OH)_2D_3$. Almaden *et al.* [11] evaluated the effect of phosphate on PTH secretion *in vitro* using fresh parathyroid gland tissue from parathyroidectomized patients: they also demonstrated that phosphorus has a direct stimulatory effect on PTH secretion.

## The different pathophysiologies in early and in advanced renal failure

It therefore appears that the relationship between calcium, phosphate, PTH, and calcitriol in the dialysis patient is peculiar insofar as the pathophysiology is completely different from the patient with mild to moderate renal insufficiency. In mild renal failure, the hypersecretion of PTH is initially appropriate, since it tends to normalize serum phosphate, calcitriol and calcium levels; in the long term, however, PTH loses its ability to maintain normophosphatemia when the GFR falls below 30 ml/min. Because of the inhibitory effect of PTH on proximal phosphate reabsorption, the fraction of the filtered phosphate that is reabsorbed can fall from the normal 80 to 95% to as low as 15% in severe renal failure. At this point, PTH is unable to further increase phosphate excretion but continues to promote phosphate release from bone, resulting in persistent hyperphosphatemia if intake of phosphate is not diminished, leading to the development of a vicious cycle. In addition, secondary hyperparathyroidism may at this stage contribute to the hyperphosphatemia by continuing to enhance the release of calcium phosphate from bone. The combination of marked hyperphosphatemia and normal or low-normal plasma calcium concentration will result in an elevated calcium-phosphate product and a tendency for metastatic calcification, i.e. calcium phosphate precipitation into arteries, joints, and soft tissues.

## Phosphate control—the academic ivory tower versus real life

Now, although we know that in theory we can prevent all of this simply by controlling serum phosphate, things in real life are a little different: serum phosphate is poorly controlled in many dialysis patients and secondary hyperparathyroidism is a common problem. Treatment of secondary hyperparathyroidism with calcitriol is usually (but not always) effective, and sometimes is complicated by the occurrence of hypercalcemia and hyperphosphatemia. Also it is debated whether PTH synthesis and secretion can be controlled at all by medical therapy once parathyroid hyperplasia has developed [12].

## Does hyperphosphatemia interfere with the response to treatment with active vitamin D?

Two main unanswered questions arise: 1. Can we reverse secondary hyperparathyroidism by restricting phosphate intake? And if the answer is yes, how? 2. Can we use calcitriol in the presence of hyperphosphatemia? Conflicting data have been reported on the reversibility of parathyroid gland hyperplasia following calcitriol treatment: a promising report from Japan [13] could not be reproduced by other investigators. In experimental renal failure, Szabo *et al.* [14] have shown that calcitriol may inhibit the development of parathyroid hyperplasia but can not reverse the process. Calcitriol might exert its antiproliferative effect on the parathyroid gland through an inhibition of the replication associated oncogene, *c-myc*, whose expression was stimulated by exposure of parathyroid cells to uraemic serum [15]. As far as the role of phosphate is concerned, a preliminary report from Slatopolsky *et al.* [16] shows that although *in vitro* studies failed

to demonstrate any effect of phosphate on PTH synthesis and secretion, *in vivo* experiments confirmed a significant effect of phosphate restriction on pre-pro PTH mRNA and PTH secretion in advanced renal insufficiency, independent of the levels of calcitriol and calcium. This was confirmed by the study of Kilav *et al.* [8]. Preliminary data from the same group [17] indicate that hypocalcemia, hyperphosphatemia and uremia lead to an increase of parathyroid cell mitoses, while hypophosphatemia completely abolishes them. On the other hand, $1,25(OH)_2D_3$ had no effect on cell mitoses, emphasizing the importance of normal phosphate and calcium in the prevention of parathyroid hyperplasia.

The mechanisms of the inhibitory effect of phosphate restriction on PTH synthesis and secretion are therefore still unknown: it has been postulated that the low-phosphorus diet might affect the phospholipid composition of the parathyroid cell membranes modifying local calcium fluxes and/or regulation of the number or of the conformation of calcitriol receptors of the parathyroid cells.

Although it is not proved whether a combination of calcitriol treatment and phosphate control represents the most effective approach to the treatment of secondary hyperparathyroidism, several facts suggest that this might be the case. First, hyperphosphatemia may cause nonresponsiveness to the inhibitory action of calcitriol on PTH release by the parathyroid gland. Rodriguez *et al.* [18] observed worsening of secondary hyperparathyroidism in two patients receiving appropriate doses of intravenous calcitriol. In these two patients, there was an initial marked decrease in serum PTH in response to intravenous calcitriol, but as severe hyperphosphatemia developed, there was a gradual and steady increase in serum PTH; the change occurred despite the presence of mild hypercalcemia and appropriate blood levels of calcitriol. Second, Quarles *et al.* [19] performed a controlled study of pulse oral versus intravenous calcitriol treatment of severe secondary hyperparathyroidism and failed to document a consistently beneficial effect of either route of administration. Patients had hyperphosphatemia at the beginning and remained hyperphosphatemic throughout the study, furthermore hyperphosphatemia predicted refractoriness to calcitriol therapy. Third, on the other hand, Cannella *et al.* [20] demonstrated that long-term therapy with high-dose i.v. pulses of calcitriol in patients with severe secondary hyperparathyroidism was highly effective if care was taken to achieve good control of serum phosphate levels: the authors observed an 80% decrease of initial PTH levels, a marked improvement of all histomorphometric indices of hyperparathyroid bone disease, and a reduction of the functional mass of the parathyroid glands assessed by parathyroid scintigraphy.

## Phosphate control—the orphan of treatment of the dialysis patient

Optimal control of serum phosphorus in dialysis patients should always be viewed in the context of adequate nutrition and protein intake, keeping in mind the necessity to avoid malnutrition and the consequent higher risk of death [21], we strongly favour better control of intestinal absorption of phosphate by a combination of reduced dietary intake and the use of calcium salts, which are almost always necessary in the anuric well-nourished dialysis patient. In fact, thrice weekly dialysis with 4 h sessions can not counterbalance a normal phosphorus intake [22] although a recent study suggests that slow nocturnal home hemodialysis, performed six nights weekly for 8 h per session resulted in a decreased phosphate level despite a 50% increase in phosphate intake and avoidance of phosphate binders after five months of treatment [23]. However, this dialysis technique is impractical. Therefore, control of hyperphosphatemia in dialysis patients is mandatory: it is difficult but inexpensive and it can improve the action of calcitriol.

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