Phosphate imbalance: a culprit or victim in renal failure?

Hyperphosphatemia is a common problem in patients with end-stage renal disease. In this issue, Goodman (1) gives an extensive review on the novel management of renal bone disease, the result of secondary hyperparathyroidism, and associated hyperphosphatemia.

On the contrary, hypophosphatemia is not an uncommon disorder in post-renal-transplant patients. More than 50% of post-renal-transplant patients in a major renal unit in Hong Kong have hypophosphatemia (2). Phosphate supplements may be needed during the early post-transplant period to correct hypophosphatemia (2).

The kidneys have an important role in the maintenance of phosphate balance. About 80% to 85% of the phosphate filtered at the glomeruli is reabsorbed. Glomerular filtration rate (GFR) declines with renal failure. With the initial fall in GFR, filtered phosphate load as well as excretion are diminished. The net effect will be phosphate retention and a small increase in the plasma phosphate concentration. This small increase in phosphate will combine with ionized calcium. The lowered ionized calcium level stimulates secretion of parathyroid hormone (PTH) and results in secondary hyperparathyroidism, as proposed in the “trade-off” hypothesis (3,4). However, the initial minor increase in phosphate may not be sufficient to cause a significant hypocalcemia to enhance hypersecretion of PTH (5). Recent studies have demonstrated that phosphate may directly enhance PTH secretion (6). In early chronic renal failure, phosphate retention suppresses 1α-hydroxylase activity, thus the renal synthesis of 1,25-dihydroxyvitamin D3 that has inhibitory effect on the parathyroid gland. Dietary phosphate restriction may restore vitamin D3 levels and diminish PTH secretion (7,8).

The initial hypersecretion of PTH is appropriate in the sense that it inhibits phosphate reabsorption in proximal tubules and lowers the plasma phosphate concentration towards normal. However, in the long run, the hyperparathyroidism is maladaptive. Chronic exposure to high levels of PTH can lead to potentially serious bone disease. In addition, PTH fails to increase phosphate excretion when GFR declines to less than 20 mL/min. At this point, decreased phosphate excretion and increased phosphate release from bone by PTH would result in persistent hyperphosphatemia, if phosphate intake is not diminished. A vicious cycle is developed as hyperphosphatemia stimulates further PTH release directly (9).

Following successful renal transplantation, hypophosphatemia may develop secondary to urinary phosphate wasting. Although this complication may be due to hyperparathyroidism-dependent or -independent mechanisms (10), pretransplant serum phosphate level is significantly higher in hypophosphatemic than the normophosphatemic group (2). Oral phosphate supplementation is the common treatment. Unfortunately, administration of oral phosphate may exacerbate hyperparathyroidism due to its complexion with calcium and lowering intestinal calcium absorption.

To break the viscous cycle of hyperphosphatemia-hyperparathyroidism, maintaining normal plasma phosphate is the mainstay of therapy in chronic renal failure. The review by Goodman (1) in this issue outlines all the possible ways to control hyperphosphatemia. The use of newer and potentially safer phosphate binder (sevelamer), calcimimetic agents, as well as nocturnal hemodialysis has been proposed and proven effective in lowering hyperphosphatemia and thus hyperparathyroidism. However, these treatments are associated with increased cost and they are usually instituted after hyperphosphatemia and secondary hyperparathyroidism are established.

In advanced chronic renal failure with creatinine clearance below 15 to 20 mL/min, patients are referred to nephrologists. They are then started on a combination of low protein, low phosphate diet and phosphate binders. These measures may help to lower serum PTH levels, but patients have to comply with a rather monotonous diet. Milk, cheese, eggs, meat, fish, peas, beans, soya products, and cereals have to be reduced or restricted. Compliance to this diet is doubtful and benefit is questionable at this stage.

Coburn et al (11) suggested that the optimal benefits of preventing secondary hyperparathyroidism are best achieved when creatinine clearance is still within the 25- to 60 mL/min range. Lower phosphate level may also slow down the progression of renal failure (12). Long-term survivors with non-progressive chronic renal failure have unusually low plasma phosphate. This supports the
view that hyperphosphatemia has an independent deleterious effect. To prevent the progression of renal failure and its complications, more research on the effect of phosphate on renal failure and PTH secretion should be carried out at the early stage of renal failure when the creatinine clearance is still above 50%.

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REFERENCES