INTRODUCTION

Renal osteodystrophy represents the syndrome of altered divalent ion metabolism and skeletal symptoms which arise when kidney function fails. Hyperparathyroidism and reduced production of the active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (1,25(OH)2D3), are almost always present in renal failure and they are critical factors in the syndrome of renal osteodystrophy. In this chapter we outline the management of renal osteodystrophy. For more comprehensive discussion on the subject, the reader is referred to recently published review articles (1, 2).

TREATMENT OF SPECIFIC PATHOGENIC FACTORS

There are several factors that are critical in the pathogenesis of renal osteodystrophy; these include: (1) hypocalcemia and secondary hyperparathyroidism; (2) phosphate retention and hyperphosphatemia; (3) reduced renal production and low plasma levels of 1,25-dihydroxyvitamin D; and (4) metabolic acidosis. These factors should be managed specifically and in combination, if possible, to prevent and reverse the progression and clinical signs and symptoms of renal osteodystrophy. Therefore, the objectives of management of renal osteodystrophy should be aimed: (1) to keep the blood concentration of calcium as near as normal to prevent the development of secondary hyperparathyroidism or, if this has already occurred, to suppress parathyroid hypersecretion and hyperplasia; (2) to keep the blood levels of phosphorus as near normal as possible; (3) to maintain blood acid-base status normal; and (4) to supplement active vitamin D sterol(s). These therapeutic maneuvers will keep divalent ion homeostasis as near normal as possible and potentially prevent and even reverse the skeletal abnormalities and extraskeletal calcification.

Hypocalcemia and secondary hyperparathyroidism

Oral supplement of calcium should be considered in patients with moderate-to-advanced chronic renal failure and those on regular dialysis for the following reasons. First, intestinal calcium absorption is impaired in these patients. Second, the dietary calcium content in these patients will be reduced, in general, to 400–700 mg/day, because the diet of these patients contains smaller quantities of dairy products (3). It has been shown that supplemental oral calcium, in forms of calcium carbonate, calcium citrate, or calcium lactate, to increase the total elemental calcium intake to 1.5 g or more per day can bring about the neutral to positive calcium balance in these patients (4–6). In addition, calcium carbonate also is capable of binding phosphorus in the intestine; this may help in reducing serum phosphorus levels.

Mild to moderate renal failure

There is no unified opinion regarding when supplemental calcium should be added in the course of chronic renal failure. Intestinal calcium absorption may not be reduced in patients with GRF greater than 50 ml/min (7, 8); thus supplemental calcium should be considered in those who have GFR less than 50 ml/min or serum creatinine greater than 2–3 mg/dl. Calcium carbonate (Titralac, Tums, etc.) is the first choice since it contains a higher fraction of calcium (40% of calcium carbonate is elemental calcium), is inexpensive, tasteless and thus relatively well tolerated by the patients. Moreover, this compound can bind a certain amount of phosphorus in the intestine. Elemental calcium comprises 12% of calcium lactate and 18% of calcium gluconate, thus larger quantities of these compounds need to be given to provide comparable amounts of elemental calcium. To maximize the intestinal absorption of calcium, it is best to give the calcium in divided doses several times throughout the day rather than administering it in one or two doses.

It is important that supplemental calcium not be given until serum phosphorus levels are stabilized within normal range. Serum phosphorus levels in these patients with mild to moderate renal failure are usually in normal range. However, if the serum phosphate level increases above normal range, it should be controlled appropriately with dietary phosphate restriction and phosphate binding antacids.

Advanced renal failure and patients on regular dialysis

In patients with far advanced renal failure with GFR less than 10 ml/min and in patients undergoing chronic dialysis, it is reasonable to recommend calcium supplement to provide –1.0 g/day of elemental calcium. Serum calcium was as well as phosphate levels should be monitored carefully and regularly. If serum calcium exceeds 10.5 mg/dl the quantity of oral calcium should be halved. In patients with serum calcium levels less than 8 mg/dl, the quantity of calcium should be increased. It
is important to remember that calcium supplements should never be initiated until the serum phosphate levels are controlled to below 5.5 mg/dl. Otherwise, oral calcium supplementation in the presence of elevated serum phosphate will increase the calcium × phosphate product, thereby predisposing to extraskeletal calcification.

In patients on chronic dialysis treatment, serum calcium levels just prior to each dialysis should be in normal or near normal range. Calcium balance and serum calcium levels in these patients can also be affected by the dialysate calcium concentration. Studies have shown that dialysate calcium concentration below 6.0 mg/dl may enhance the progression of secondary hyperparathyroidism and renal osteodystrophy; thus, progressive loss of bone mineral and of total body calcium content, and progressive rise in serum alkaline phosphatase activity may be seen (12, 13). There is no firm evidence, however, that dialysate calcium concentration higher than 6.5 mg/ml can prevent and/or reverse the secondary hyperparathyroidism and have definite beneficial effects on renal osteodystrophy. Rather, such dialysate calcium concentration may result in a sustained hypercalcemia in these patients. Thus, it is generally recommended that dialysate calcium concentrations be 6.0–6.5 mg/dl. It is obvious that purification of water used for dialysis is essential since untreated water may contain 0.5–1.0 mg/dl of calcium. Regardless of dialysate calcium concentration, appropriate use of dietary restriction of phosphate with phosphate binding antacids, dietary calcium supplementation, and judicial use of 1,25(OH)2D3 are still critical to control divalent ion metabolism and secondary hyperparathyroidism in patients on chronic dialysis.

Patients with more advanced renal failure may be somewhat more prone to develop hypercalcemia with excessive oral calcium supplementation since they do not have the renal route for calcium excretion should the net calcium absorption increases more than is expected. Some uremic patients who have mild hypercalcemia (serum calcium 10.5–11.5 mg/dl) may be asymptomatic: other patients may exhibit symptoms of hypercalcemia such as anorexia, nausea, vomiting, mental confusion, lethargy with only a modest hypercalcemia. Further, patients with advanced renal failure and those on chronic dialysis may develop acute elevation of blood pressure (9) or pruritus (10, 11) with hypercalcemia.

Prevention of phosphate retention and hyperphosphatemia

The hyperphosphatemia of uremia is one of the major factors responsible for the development of hypocalcemia and thus the development and progression of secondary hyperparathyroidism and renal osteodystrophy (14–16). Thus, prevention of hyperphosphatemia is one of the key elements in the management of renal osteodystrophy.

The dietary intake of phosphorus is primarily dependent upon the intake of meat and dairy products. The usual daily phosphate intake in normal adults in the United States ranges from 1.0 to 1.8 g (3). Theoretically, one could reduce the dietary phosphate intake in proportion to the fall in GFR in patients with mild to moderate renal failure. If one eliminates or restricts dairy products with low (40 g/day) protein intake, the dietary intake of phosphorus could be reduced to approximately 60% of normal, i.e., 600–900 mg/day (3). Further reduction in dietary phosphate intake by the further restriction of protein and dairy products may not be acceptable for most patients. It is therefore evident that further restriction of dietary phosphate intake in proportion to the decrease in GFR is extremely difficult and may not be practical in patients with advanced renal failure and GFR less than 30 ml/min. Thus, phosphate binding antacids must be added to restrict the intestinal absorption of phosphate.

The aluminum-containing antacids are used to restrict intestinal absorption of phosphate. These antacids bind to phosphate in the intestinal tract and make phosphate nonabsorbable in the gut. Both aluminum hydroxide and aluminum carbonate are available as liquid gels, tablets, and capsules. Liquid gels are more effective in binding phosphate than capsules: however, patient compliance is usually better with the latter. These preparations should be given with each meal aiming to maintain the serum phosphate concentrations between 3.5 and 5 mg/dl. If serum phosphate levels decrease too much or remain unchanged at elevated levels, the dosage of antacids should be altered accordingly. In addition to the administration of these aluminum-containing antacids, the dietary phosphate content should be restricted to 0.8 to 1.0 g/day; otherwise, the efficacy of antacids may be reduced. This is because antacids not only bind phosphate in the diet thus preventing its absorption, but they also bind phosphate secreted in the intestinal tract thus effectively remove excess phosphate from the body. The presence of excessive phosphate in the diet may saturate the binding capacity of the antacids thereby preventing the removal of phosphate from the body.

It is equally important to avoid decreasing serum phosphate levels lower than normal. Too aggressive treatment can result in severe hypophosphatemia and phosphate depletion, which can aggravate the uremic bone disease and cause osteomalacia (17, 18).

In rare patients serum phosphate levels remain in normal range or even lower than normal despite severe renal failure. Such patients do not require any phosphate binding antacids. The author has seen a patient on regular dialysis who remained hypophosphatemic with a normal diet and without any antacids and who even required phosphate supplementation to maintain low normal serum phosphate levels.

Mild to moderate renal failure

It may be generally thought that serum phosphate levels may be modestly elevated in patients with mild to moderate chronic renal failure with GFR ranging 40–70 ml/min. On the contrary, serum phosphate levels in these patients are on the average normal to low normal (7, 19). This may not be compatible with the so-called 'trade-off hypothesis' (20) which explains that hy-