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Management of Calcium and Bone Abnormalities in Hemodialysis Patients

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In chronic renal failure, hyperphosphatemia, hypocalcemia, hyperparathyroidism, reduced activation of vitamin D, decreased level of calcium-sensing receptor, osteitis fibrosa, and osteomalacia are features related to calcium abnormalities. Hyperparathyroidism is a risk factor for survival of hemodialysis patients as well as hypoparathyroidism, which is another feature in hemodialysis patients. Treatment of these abnormalities includes control of parathyroid hormone (PTH) secretion, counteracting hyperphosphatemia, correction of hypocalcemia, and others. Various kinds of vitamin D analogs have been introduced recently in addition to calcitriol and alfacalcidol, which have a rather long history (eg, maxacalcitol and falecalcitriol). Sevelamer is a newly developed phosphate binder to treat soft-tissue calcification.

KEYWORDS hyperphosphatemia, hypocalcemia, hyperparathyroidism Vitamin D analogs, phosphate binder

In association with the development of chronic renal failure, hyperphosphatemia, hypocalcemia, increased parathyroid hormone (PTH) level, decreased 1,25 (OH)2D, and decreased levels of calcium-sensing receptors are the main features related to calcium abnormalities. The initial event has been regarded to be retention of phosphate as a result of impaired excretion of phosphate and the increased production of PTH with decreased suppression of parathyroid gland activity by 1,25(OH)2D. Persistent hyperparathyroidism causes bone disease (osteitis fibrosa). In addition, vitamin D deficiency leads to osteomalacia. Thus, osteitis fibrosa and osteomalacia are basic bone pathologic processes in chronic renal disease. Adynamic bone disease has been recognized, especially in association with aluminum administration. Aluminum is deposited in the calcification front and this is associated with increased osteoid tissues and low bone turnover. However, such low bone turnover was observed even after the use of aluminum was ceased.

A survey on blood levels of intact PTH among dialysis patients in Japan was started in 1998, evaluating the effect of duration of hemodialysis. Patients treated with hemodialysis for 15 to 20 years showed the highest value of intact PTH (389.76 pg/mL) compared with other groups.[1]

The effect of intact PTH levels on 1-year survival rates of hemodialyzed patients was analyzed and it was shown that the relative risk was significantly higher in the group with intact PTH levels of 30 to less than 60 pg/mL (relative risk = 1.175), and that with intact PTH levels of 30 to less than 60 pg/mL (relative risk = 1.357),[1] when relative risk was set as 1.000 in the group with intact PTH levels of 60 to less than 120 pg/mL. However, the group with intact PTH levels of 30 to less than 60 pg/mL did not show significant effect of the risk when the values of intact PTH were corrected by serum calcium × phosphate, whereas hyperphosphatemia is another risk factor for 1-year survival. When patients treated with vitamin D were compared with those not treated with vitamin D analogs, the former group showed significant reduced risk ($r = .760$) compared with the latter.[1]

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Abnormalities Associated With Derangement of Calcium Metabolism in Chronic Renal Failure

Abnormalities in chronic renal failure are results of overproduction of PTH and/or the underproduction of calcitriol by the kidney. They include hypocalcemia, hyperphosphatemia, immunologic dysfunction, and abnormal lipid and glucose metabolism. There have been many intervention methods for each of these abnormalities (Table 1).

Methods for Reducing PTH Levels

The target level of intact PTH is supposed to be within 3 times that of the normal range. Quarles et al[2] proposed the optimum range of intact PTH as 100 to 165 pg/mL for patients undergoing hemodialysis. Methods for PTH reduction include parathyroid gland intervention, administration of vitamin D analogs and phosphate binders, and have been proposed in addition to calcimimetics, which are under investigation. These methods are described in Table 2.

Systemic Use of Vitamin D Analogs

Calcitriol and Alfacalcidol

Calcitriol and alfacalcidol have been introduced to hemodialysis patients who exhibited hyperparathyroidism associated with hypocalcemia and hyperphosphatemia. It is already more than 20 years since the introduction of these drugs. Each of them has its unique characteristics. Calcitriol shows a high peak after administration and the effect on PTH may be mediated by increasing serum calcium levels and/or has a direct effect on the parathyroid glands. The intravenous administration of larger doses has been approved recently. Alfacalcidol is effective after it is converted to calcitriol in the liver. Although the peak is not as steep as in the case of calcitriol, the eventual concentration of calcitriol is higher than alfacalcidol when a dose of .25 μg of calcitriol and .5 μg of alfacalcidol were compared at 12 weeks of administration.[3] Both calcitriol and alfacalcidol have been used for the purpose of pulse treatment, giving 3 to 5 μg twice/wk of calcitriol or 8 μg/wk of alfacalcidol.

Of 43,380 patients to whom vitamin D analogs were prescribed during the year 2000, alfacalcidol was given to 27,525, calcitriol to 9,071, oral pulse treatment to 885, intravenous pulse therapy to 2,594, and other methods to 3,305 patients.[1] Calcitriol was given intravenously to 4 groups of 162 hemodialyzed patients, to whom placebo, 1, 1.5, or 2 μg was given at the end of each session of hemodialysis for 12 weeks. Intact PTH levels decreased in a dose-dependent manner, with the lowest level at 4 weeks with the dose of 2 μg and at 8 weeks with the dose of 1.5 μg, and the level continued to decrease until 12 weeks with the dose of 1 μg. Serum levels of adjusted calcium increased to 10.5 mg/dL in the 2 groups receiving the higher doses of calcitriol, from 9.49 mg/dL (1.5 μg calcitriol) and 9.22 mg/dL (2 μg calcitriol).[4]

Maxacalcitol

Maxacalcitol (22-oxacalcitriol) is a newly synthesized vitamin D analog that has an oxygen atom at the 22-carbon position and has suppressive action on PTH secretion. Doses of 2.5 to 20.0 μg of maxacalcitol were injected intravenously at each session of hemodialysis 3 times weekly for 26 weeks subsequent to a 26-week pretrial period. Intact PTH levels decreased significantly by more than 30% in 51.6% of the patients. Hypercalcemia, which was diagnosed in 33.1% of patients, was found to resolve or ameliorate immediately after withdrawal or dose reduction of maxacalcitol. Phosphate levels increased to 6.41 mg/dL at the end of the study from 5.79 mg/dL at baseline.[5]

Falecalcitriol

Falexalcitrol (hexafluoro-1, 25-dihydroxycholecalciferol [F6]) is converted to 1, 23, 25-trihydroxycholecalciferol and remains in the cell. Because this newly synthesized compound is equipotent with the mother compound, the effect is fortified as a whole.[6] The effect to suppress PTH levels is more pronounced than to stimulate intestinal calcium absorption. A multicenter study was performed investigating the efficacy and safety of long-term administration of F6 in patients with renal osteodystrophy with secondary hyperparathyroidism caused by chronic

Table 1 Interventions for Abnormalities in Calcium Metabolism in Chronic Renal Failure

	Methods of Intervention
Osteitis fibrosa	Suppression of PTH Surgical PTX Pharmacologic PTX (Ethanol, and so forth) Phosphate binder
Osteomalacia	Vitamin D and vitamin D analogs
Soft-tissue calcification	Suppression of PTH Phosphate binder
Immunologic dysfunction	Vitamin D analogs

Table 2 Suppression of PTH Production

Category of PTH Suppression	Methods
Parathyroid gland intervention	Surgical parathyroidectomy Percutaneous ethanol injection therapy) Direct injection of vitamin D analogs
Systemic administration of vitamin D analogs	Calcitriol Alfacalcidol (oral and injection) Maxacalcitol Falecalcitriol
Phosphate binder	Calcium carbonate Sevelamer
Calcimimetics	

renal failure. F6 was administered every day for 48 weeks, starting from a dose of .3 μg/d and changed whenever necessary according to serum calcium levels. Significant inhibition of bone resorption markers and intact PTH levels were shown.[7] It was found that the increase in serum calcium is not remarkable when F6 was given orally at doses of .15 to .3 μg/d.[8] In most of the studies the incidence of hypercalcemia was not remarkable and the serum phosphate level did not change much.

Sevelamer: A New Phosphate Binder

There have been many discussions on whether or not blood levels of phosphate may be able to stimulate secretion of PTH directly.[9] Sevelamer has been shown to control serum phosphate levels without increasing serum calcium levels as in the case of calcium compound as phosphate binder.

Soft-Tissue Calcification, Especially Arterial Calcification, as a Complication in Chronic Renal Failure and as Control

Although calcification is not so manifest in primary hyperparathyroidism, soft-tissue calcification is observed in subcutaneous tissues, kidneys, and arteries, especially in fingers and pelvis, as described in the literature.[10] In view of the fact that the percentage of cardiovascular death in hemodialyzed patients occupied 37.3% among other causes in 2002 in Japan,[1] the establishment of nontraumatic and concise methods of diagnosis and treatment is needed urgently. Raggi[11] showed that electron beam tomography is a powerful tool to detect different calcification stages in a variety of tissues, and is a sensitive tool for detecting calcified coronary artery and valvular calcifications. Chertow et al[12] showed that sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients.

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