Azotemic Renal Osteodystrophy; Clinical Features and Bone Pathology

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Synopsis

During the hemodialysis treatment of 543 uremic patients for 10 years, significant complications concerning metabolic calcium disturbances, subperiosteal resorption, calcification of soft tissue or peripheral vessels, and fractures were noted. Significant elevation of alkaline phosphatase was induced for 5 years under hemodialysis using 5.0-6.0 mg/dl dialysate calcium, but not under 7.5 mg/dl dialysate calcium. Plasma immunoreactive parathyroid hormone (iPTH) values were abnormally high with a few exceptions, without relationship to serum calcium levels. Among the patients with chronic renal failure on dietary control, osteomalacic changes were predominant, but their iPTH values were not always elevated. When the patients were treated for a long time with hemodialysis, the mixed type of osteomalacia and osteitits fibrosa appeared. Administration of dihydrotachysterol and 1α-hydroxycholecalciferol to the patients on hemodialysis changed the mixed type of osteomalacia and osteitis fibrosa to the osteomalacic type with the marked reduction of osteoid seam thickness.

Azotemic renal osteodystrophy is a difficult complication to the end-stage chronic renal failure. It becomes increasingly important as the uremic state is sustained for a long term by hemodialysis (Kim, et al., 1968, Pendras, 1969). The pathogenesis responsible for the development of azotemic renal osteodystropy is not fully understood. However, impaired vitamin D metabolism, hypocalcemia, hyperphosphatemia, decreased intestinal absorption of calcium, hyperparathyroidism, abnormal collagen metabolism etc. are the contributing factors. Especially, the conversion process of 25-hydroxycholecalciferol (25-OH-D₃) to 1α, 25-dihydroxycholecalciferol (1α, 25-(OH)₂-D₃) is impaired in patients with chronic renal failure (Mawer et al., 1973). This vitamin D metabolic disturbance may play a major role in azotemic renal osteodystrophy.

Bone changes may develop even in patients with less advanced chronic renal failure (Bonucci et al., 1975; Malluche et al., 1975). Osteomalacia accompanied by osteitis fibrosa was detected by the pathological studies. In patients on maintenance hemodialysis, the bone changes often progress including the deminisching density (Bonomini, 1975). The synthesized analogues of active vitamine D such as dihydrotachysterol (DHT) and 1α-hydroxycholecalciferol (1α-OH-D₃) have been shown to be beneficial in the treatment of azotemic renal osteodystrophy (Kaya et al., 1970; Peacock et al., 1974).

In the present report, azotemic renal osteodystrophy is described in both clinical
features and bone histology. Furthermore, the evaluation of treatments with DHT and 1α-OH-D₃ was performed.

Patients and Methods

Intermittent hemodialysis was carried out in 543 patients between ages of 10 to 78 years, at the end-stage of chronic renal failure by various causes during these 10 years in our center. The length of hemodialysis treatment ranged from a month to 10 years and 8 months, the average of 32 months. They had been treated twice a week for 8 to 10 hr each for the first 5 years, with the dialysate calcium concentration of 6.0-6.5 mg/dl (mainly 6.0 mg/dl) except for a short period of 5.0 mg/dl. For the second 5 years, they were treated 3 times a week as a rule, 5 to 6 hr each, with the dialysate calcium concentration of 7.5 mg/dl with a short test period of 8.0 mg/dl. Dialysis bath had contained 33 mEq/L of acetate for the first 5 years, and 35-37 mEq/L for the second 5 years respectively. Patients were recommended to take 1.0 g/kg or 1.2-1.5 g/kg body weight dietary protein under treatment for twice or 3 times a week, to take and 35-30 cal/kg.

The 12 patients with chronic renal failure of various degrees in the residual kidney function were 31 to 71 years of age. They had 5 to 30 ml/min of glomerular filtration rate (GFR), respectively.

Superiour iliac crest biopsies were performed using a trephine (5 mm in diameter) under local or generalized anesthesia. Undecalcified sections, 100 μm in thickness, were stained with Tetrachrom. An integrating eyepiece was used to assess osteoid surface and resorption surface area. And osteoid seam thickness was measured.

Results

Frequency of complications concerning azotemic renal osteodystrophy

The general states of the patients in the standpoint of serum total calcium, inorganic phosphate, total protein and plasma bicarbonate were relatively fair for recent 5 years rather than for early 5 years.

Subperiosteal resorption 18.2%, soft tissue calcification 15.7%, peripheral vessel calcification 9.6%, deformation of vertebra 8.7%, tubular bone fracture 5.7%, and vertebral compression fracture 2.6% were observed in 543 patients (Fig. 1). In the other dialysis center using 5.0 mg/dl dialysate calcium for almost 5 years, frac-

![Fig. 1. Complications concerning azotemic renal osteodystrophy observed in 10 years treatment. High frequency of tubular bone fracture in the other center using 5.0 mg/dl dialysate calcium is remarkable.](image-url)
tures occurred 3 times as frequent as our results.

The peripheral vessel calcification was a remarkable complication in our center, accumulating rapidly with the progress of the treatment.

Correlation between dialysate calcium concentration and serum alkaline phosphatase levels

The patients treated with 6.0 mg/dl dialysate calcium, revealed significant elevation of alkaline phosphatase for 5 years. No significant elevation was recognized in the patients treated with 7.5 mg/dl dialysate calcium. The dialysate against 5.0 mg/dl calcium however, brought about a striking elevation for 5 years (Fig. 2).

Plasma immunoreactive parathyroid hormone (iPTH)

5 of 6 patients who had 6.1–14 ml/min GFR and were under dietary control, showed normal values of plasma iPTH. On the other hand, 53 of 54 patients on long term hemodialysis with 7.5 mg/dl dialysate calcium showed abnormal increasing levels, regardless of the normocalcemic (iPTH 2.23 ± 1.87 ng/ml, n=28) or hypocalcemic (2.37 ± 1.66 ng/ml, n=26) state of the patients.

Fig. 2. Dialysate calcium concentrations are responsible for elevation of serum alkaline phosphatase. 6.0 mg/dl and 5.0 mg/dl dialysate calcium may deteriorate azotemic renal osteodystrophy.
Moreover, high values of iPTH were observed in the plasma from 29 of 30 patients with normal alkaline phosphatase. After 5 hours hemodialysis using 7.5 mg/dl dialysate calcium plasma iPTH values somewhat decreased, but fully recovered until the next hemodialysis (Fig. 3). These results indicate the difficulty in the effective suppression of the secondary hyperparathyroidism by 7.5 mg/dl dialysate calcium.

**Bone histology**

Bone histologic changes can be classified into the following 4 groups by histomorphometry with reference to normal control values (Mori et al., 1976) as shown in Fig. 3.

![Fig. 3. Serial changes of plasma iPTH under hemodialysis with 7.5 mg/dl dialysate calcium. Hyperparathyroidism is not effectively suppressed.](image)

![Fig. 4. Bone histologic changes can be classified into 4 groups by histomorphometry. Osteoid excess (O) group, resorption excess (R) group, bidirectional excess (O/R) group and normal range (N) group. Normal maximum limits of osteoid surface and resorption surface area show mean ± 2SD from the values of controls (Mori et al. 1976).](image)
4. The osteoid excess group corresponds to osteomalacia that is caused by vitamin D deficiency, and the resorption excess group reflects osteitis fibrosa due to secondary hyperparathyroidism. Bidirectional excess osteoid and resorption group is considered to be the mixed type of both osteomalacia and osteitis fibrosa. Normal values of osteoid and resorption indicate the normal group. Thickness of osteoid seam is measured from an aspect of osteomalacia.

(1) Patients under dietary control period

No patients out of 12 fitted to the normal range group. Seven belonged to the osteoid excess group. One showed resorption excess and 4 settled in bidirectional excess (Fig. 5). Therefore, in patients under dietary control, osteomalacic changes were frequently observed rather than osteitis fibrosa.

(2) Patients on long term hemodialysis period

42 patients were examined in 3 series according to the length of hemodialysis treatment as follows: 19 (14 males, 5 females) treated for between 1-11 months, 10 (5 males, 5 females) treated for between 12-35 months, and 13 (7 males, 6 females) treated for between 36-85 months. Osteomalacia, osteitis fibrosa and the mixed type of both changes are distributed rather evenly in the patients treated for 1-11 months (Fig. 6). Based on these results, it seems most likely that the hemodialysis treatment caused secondary hyperparathyroidism. In addition, the mixed type of both osteomalacia and osteitis fibrosa was common but simple osteomalacia or osteitis fibrosa seemed to appear when the treatment exceeded 36 months (Fig. 7).

Fig. 5. Bone histomorphometry revealed osteomalacic changes to be the main feature in 12 patients under dietary control period.
Fig. 6. Bone histomorphometry in 19 and 10 hemodialysis patients who were treated for between 1-11 and 12-35 months respectively.

Fig. 7. Bone histomorphometry in 13 hemodialysis patients who were treated for 36-85 months. Hemodialysis treatment introduced the development of secondary dyperparathyroidism.
Evaluation of DHT and 1α-OH-D₃ treatments by bone histology

0.125–0.375 mg/day of DHT was administered for 4–10 months in 5 patients on hemodialysis. They were 31–62 years old, 3 males and 2 females, and were treated by hemodialysis for 4–10 months.

In 7 patients between ages of 20 and 65 years (4 males and 3 females) subjected to 1–54 months hemodialysis were given 1–10 μg/day of 1α-OH-D₃ for 3–12 months. Both DHT and 1α-OH-D₃ treatments generally reduced resorption surface area, and the 1α-OH-D₃ treatment tended to decrease osteoid surface area simultaneously (Fig. 8). Thickness of osteoid seam showed a remarkable reduction as follows, 14.3 ± 3.6 to 10.1 ± 1.8 μm by DHT, 12.2 ± 2.8 to 8.4 ± 1.5 μm by 1α-OH-D₃.

Discussion

For the prevention of azotemic renal osteodystrophy, the administration of almitrine for hyperphosphatemia (Pendras, 1966) or large amount of calcium for hypocalcemia (Davidson and Pendras, 1967) had been attempted. The adjustment of dialysate calcium concentrations against hypocalcemia have been discussed (Goldsmith et al., 1971). However, the azotemic renal osteodystrophy is not a negligible complication in long term hemodialysis (Ritz et al., 1971). We also paid great attention to prevent the complication, but the results were not satisfactory as shown in this report.

Elevation of alkaline phosphatase in course of long term hemodialysis is essentially dependent upon the calcium concentration of the dialysate (Massry et al., 1969). The dialysate calcium of 6.0 mg/dl were not sufficient in our result. By contrast, 5.0 mg/dl dialysate calcium induced no vascular calcifications but many fracture in the other center. The 7.5 mg/dl dialysate calcium are insufficient to suppress plasma iPTH in our results, but 8.0 mg/dl may be useful (Goldsmith et al., 1971). The higher calcium concentration of dialysate would be harmful, particularly if the serum phos-
June 1979

phosphate levels are not well controlled. It was pointed out many years ago that chronic renal failure might be accompanied by osteomalacia (Barber, 1926) or osteitis fibrosa (Albright et al., 1935), or both (Follis and Jackson, 1943). Osteomalacia is due to lack of vitamin D and osteitis fibrosa is derived from hyperparathyroidism (Stanbury et al., 1969).

We observed that osteomalacic changes rather than osteitis fibrosa were predominant in patients with chronic renal failure with GFR of 5-30 ml/min. Bonucci et al. (1975) pointed out that osteomalacia is the main pathological feature in 60% of 40 patients with 3-40 ml/min GFR. By Maluiche et al. (1975), the primary changes of hyperparathyroidism exhibited mineralisation defect below 40 ml/min GFR. Another report (Bordier, 1975) suggested that osteomalacia was superimposed on the early stage of osteitis fibrosa in the progressive course of chronic renal failure.

A number of investigators have reported the bone changes in patients on long term hemodialysis (Kaye, 1971; Sherard et al., 1972). The major disorders are osteomalacia, osteitis fibrosa and osteoporosis. Abnormal collagen metabolism in bone was also mentioned (Avioli, 1973). Serial bone biopsies revealed the progression of osteomalacia and osteitis fibrosa in maintenance hemodialysis (Bonomini, 1975). We also recognized the advancing pattern of bone disease in the course of hemodialysis.

Dialysate calcium concentrations were responsible for bone disease (de Veber, 1970; Jowsey et al., 1972). High-calcium dialysate may improve bone disease through suppressing secondary hyperparathyroidism (Goldsmith et al., 1971).

Both DHT and 1α-OH-D₃ are analogues of active vitamin D. When hydroxylated in the liver at the 25 position, those have similar steric configurations to 1α, 25-(OH)₂-D₃. Synthetic 1α, 25-(OH)₂-D₃ corrects the calcium balance and increases the serum calcium (Brickman et al., 1972) in uremic patients.

We observed beneficial effects on long-term hemodialysis patients with hypocalcemia and elevated alkaline phosphatase by the administration of both remedies. In the bone histologic study, both DHT and 1α-OH-D₃ decreased resorption surface area. Furthermore, osteoid surface area was reduced by 1α-OH-D₃. Both remedies diminished the osteoid seam thickness.

DHT had effects on osteitis fibrosa (Kaye et al., 1970) and osteomalacia (Hill et al., 1975; Cordy, 1976) in hemodialysis patients. DHT decreased high value of iPTH (Malekzadeh et al., 1977). The use of 1α-OH-D₃ is beneficial to the intestinal malabsorption of calcium (Peacock et al., 1974), hypocalcemia (Nielsen et al., 1976), vascular calcification (Pierides et al., 1976), bone mineral content (Catto et al., 1975) and the high level of iPTH (Brownjohn et al., 1977), but its effect on osteitis fibrosa and osteomalacia still remains inconclusive (Naik et al., 1976).

References

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