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Renal bone disease

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The term, «renal bone disease» includes a variety of lesions known as osteitis fibrosa, osteomalacia, aplastic bone disease, and mixed lesion.

Osteitis fibrosa is most likely the reflection of high PTH levels and secondary hyperparathyroidism. Aplastic bone disease and osteomalacia are different expressions of aluminum toxicity and mixed lesion may represent a transitional form between secondary hyperparathyroidism and aluminum toxicity.

Frequency

The frequency of these various lesions varies according to the geographic location and type of dialysis. In a prospective unselected type of population, we evaluated 142 hemodialysis patients, age ranging from 23-75 years with a mean of 52 ± 14 [1]. The criteria for selection of the patients in this study was the willingness of these patients to undergo bone biopsy. In addition, repeated dialysate aluminum concentration was consistently less than 5 mcg/l. None of these patients received any vitamin D therapy. Of the 142 patients evaluated, 96 had osteitis fibrosa or mixed lesion. Thirty-six patients had dialysis osteomalacia and 10 patients had aplastic bone disease. Although the incidence of these lesions may vary from place to place, various other studies recently have shown a similar frequency of these lesions in the dialysis population.

Symptomatology

We followed these patients for up to 38 months. The most common symptom observed in these patients was bone pain which may become totally disabling; this is more frequently so in patients with aluminum induced bone disease. The pain was generally vague and deep seated and found in the low back, hips, legs, or knees. It varied in intensity and often was aggravated by gravitational stress and weight bearing. We observed that patients with osteitis fibrosa had a much lesser frequency of bone pain than those with aluminum induced bone disease. In fact, the majority of patients with osteitis fibrosa were free of bone pain throughout the years of follow-up. On the other hand, greater than 50 % of patients with aluminum induced bone disease had bone pain. Muscle weakness is another symptom of renal osteodystrophy. It characteristically involves the proximal muscle and initially, the patient may notice difficulty in climbing chairs or rising from a sitting position; as the condition progresses, there may be difficulty in walking or in raising from a supine to a sitting position. As has been shown with bone pain, the incidence of muscle weakness is much lower in patients with osteitis fibrosa than in those with aluminum induced bone disease. Greater than 85 % of these patients were free of muscle weakness while at the end of the follow-up period, greater than 50 % patients with aluminum induced disease had muscle weakness.

Bone fracture is a common problem in patients with severe aluminum toxicity. In the United Kingdom where the occurrence of dialysis encephalopathy is very common, as many as 30 % of dialysis patients may have been afflicted in some units. This was related to a high concentration of aluminum in the dialysate of those units. Fractures involved primarily the axial skeleton such as the rib, vertebral bodies, hips, and even the long bones. These patients may develop scoliosis and substantial loss of height and may have profound disability. As you have seen with the previous symptoms, the incidence of bone fractures is low in patients with osteitis fibrosa as it is much higher in patients with aluminum toxicity.

Biochemical parameters

Hyperphosphatemia is prevalent in most dialysis patients. Various factors affect serum levels in these patients; of these, the most important are dietary intake and the ingestion of phosphate binding gels. When dietary phosphate intake increases to greater than 2 grams/day, the serum phosphate cannot be controlled with ingestion of phosphate binding gels [2]. Patients with overt secondary hyperparathyroidism may have more hyperphosphatemia than those lacking this

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syndrome [3], suggesting that some of the phosphate may not come from the diet but from bone. The serum phosphate level is much higher in patients with overt secondary hyperparathyroidism than in those with aluminum toxicity [1]. Hypocalcemia is a common feature of dialysis patients; as many as 40 % of uremic patients showed significant hypocalcemia [4]. The presence of a high serum calcium is very suggestive of either aluminum-induced bone disease or overt hyperparathyroidism. Nevertheless, in a large group of patients we evaluated, serum calcium levels were higher in patients with osteitis fibrosa than in those with osteomalacia or aplastic bone disease [1]. An increase in serum alkaline phosphatase is commonly encountered in patients with secondary hyperparathyroidism while in those with aluminum toxicity, it is much lower, sometimes below normal levels. The serum levels of PTH are commonly elevated in dialysis patients. Assays utilizing either the intact PTH or the amino terminal which are more specific for increased parathyroid gland function are currently available. PTH levels are substantially elevated in those patients with secondary hyperparathyroidism while patients with aluminum induced bone disease have mild elevation, normal or even low levels of PTH. The serum aluminum levels in dialysis patients can be significantly elevated in patients with osteomalacia and aplastic bone disease while in those without significant aluminum burden (mostly secondary hyperparathyroidism and osteitis fibrosa), usually the levels are below 50 mcg/l. Unfortunately, there is a large deviation and only in extreme cases can a diagnosis of a specific lesion be made based on the PTH and serum aluminum values. This is the reason why there has been some attempt at non-invasive diagnosis of this problem with the DFO test that we will discuss shortly.

Histopathology

Osteitis fibrosa is characterized by an increased bone resorption and formation with a progressive increase in peritrabecular fibrosis. The trabecular bone surface is occupied by resorption cavitis filled with osteoclasts. In addition, increased numbers of osteoblasts overlie the newly formed unmineralized matrix of bone. As this process becomes clear, the marrow space is filled with fibrous tissue, creating the typical osteitis fibrosa.

Osteomalacia is characterized by an excess of unmineralized osteoid tissue; this arises from impairment of mineralization of the protein matrix of bone. The major feature of osteomalacia is an increase in the width of unmineralized osteoid. This is also found to a certain extent in osteitis fibrosa due to the delay in osteoid mineralization which is formed so rapidly. However, patients with osteomalacia also show a lack of cellular activity with very few osteoblasts and osteoclasts. Also, there is no endosteal fibrosis in osteomalacia. Double tetracycline labeling identified an impaired mineralization rate in patients with osteomalacia. With the aluminum stain, it has been shown that a great majority of osteomalacic patients have large deposits of aluminum in the mineralization front. The characteristic pattern is linear deposition of aluminum along the interface between trabecular bone and osteoid. The degree of osteomalacia correlates closely with bone aluminum content.

Aplastic bone disease is another type of bone lesion observed in dialysis patients. This entity is most likely also a result of aluminum toxicity. It is characterized by features similar to those observed in osteomalacia. The major difference is the absence of large osteoid seams.

Mixed bone lesion is the final subgroup of patients which exhibits wide osteoid seams combined with features of osteitis fibrosa. This lesion most likely represents a transitional form between secondary hyperparathyroidism and aluminum toxicity.

Pathogenesis

Pathogenic factors involved in the causation of osteitis fibrosa are hyperphosphatemia, a decreased calcemic response to PTH, and most importantly, a deficit of calcitriol. With the appropriate control of serum phosphate and use of calcitriol, the severity of secondary hyperparathyroidism and osteitis fibrosa has been ameliorated significantly. Thus, today there are fewer cases of severe overt secondary hyperparathyroidism.

Osteomalacia and aplastic bone disease reflect different expressions of aluminum bone toxicity. In the early days, aluminum contamination of the dialysate was a common cause of severe dialysis dementia as well as osteomalacia [5]. With the introduction of water purification systems such as reverse osmosis, the incidence of acute severe aluminum bone toxicity has significantly decreased [6]. However, a more insidious form of aluminum bone disease has been reported now in our dialysis units. Most likely the source of aluminum is the heavy use of aluminum containing phosphate binders. It has been shown that there is a slow but toxic accumulation of aluminum via intestinal absorption in patients with renal insufficiency [7, 8]. The potential danger of aluminum containing gels was initially raised in the 1960's but this warning was overlooked [9]. The dietary intake of phosphate is quite high in North America compared to other areas of the world. The amount of aluminum hydroxide prescribed to dialysis patients in North America has been greater than in many other countries. A small but significant amount of aluminum can be absorbed when normal

subjects ingest aluminum hydroxide with a 4 to 10-fold rise in serum aluminum. A small but variable rise in plasma aluminum also occurs. In patients with renal failure, this absorbed aluminum will accumulate. Close correlation between serum aluminum levels and the amount of aluminum containing gels has been found both in adults and children. Various studies have shown that the change from phosphate binders containing aluminum to some other binders is usually followed by a marked decrement in serum plasma aluminum levels [10]. Our previously mentioned study showed that a substantial number of patients treated with appropriately treated dialysate water still had a high incidence of aluminum toxicity, clearly suggesting that the source of aluminum may have been the use of aluminum containing phosphate binders [1]. Another clinical manifestation of aluminum toxicity includes aluminum encephalopathy, microcytic anemia, and most recently congestive heart failure. The possibility of aluminum toxicity in the myocardium was suggested to us by a follow-up study of our patients with osteomalacia [1]. At that time, deferoxamine was not available for therapy. During this three year period of follow-up, 13 of the patients died (30 %), the majority from myocardial problems. We have recently evaluated the possible role of aluminum accumulation in the myocardium in 50 stable asymptomatic hemodialysis patients [11]. Cardiac status was assessed by echocardiography; a deferoxamine test together with bone biopsy was performed to determine the magnitude of aluminum accumulation. Thus, an increase in serum aluminum after DFO and stainable cortical bone aluminum were taken as parameters of bone aluminum load. Fourteen of the 50 patients had no cortical bone aluminum. These patients had a lower left ventricular mass and an increased velocity of circumferential fiber shortening as compared with the other 36 patients with aluminum in their bone. A correlation was observed between left ventricular mass and the aluminum burden. Thus, patients with an increased aluminum load had a larger ventricular mass with a decrease in myocardial contratility suggesting that aluminum accumulation on the myocardium even in those patients which may be asymptomatic may have an important toxic effect.

Differential diagnosis

As we have shown earlier, in extreme cases, patients with osteitis fibrosa usually have high parathyroid hormone levels and high serum alkaline phosphatase levels with significant hyperphosphatemia and hypocalcemia. In addition, these patients usually had low serum aluminum levels. On the other hand, patients with aluminum induced bone disease usually have normo- or hypercalcemia, low serum alkaline phosphatase, inappropriately normal or slightly elevated PTH levels and the serum aluminum usually is in excess of 100 mcg/l. Unfortunately, there is a large number of patients who fall in the gray zone in which diagnosis is difficult. In order to rule out aluminum toxicity, the deferoxamine infusion test, a non-invasive test, has been useful. This agents has a high affinity for aluminum and the rise of plasma aluminum has been measured after a standardized infusion of deferoxamine to assess the tissue stores of aluminum. The maximal increment of plasma aluminum occurs 18 to 24 hours after the infusion of deferoxamine, 40 mg/kg/hr, given over 2 hours after dialysis. The correlation between the increment in plasma aluminum after DFO test with bone aluminum content is closer to the correlation between the plasma basal aluminum levels and the same parameters of bone aluminum loading. An increment of plasma aluminum greater than 40 mcg/l provided 81 % specificity for aluminum related bone disease; however, only 59 % of patients with aluminum related bone disease were detected. At the other extreme, only 6 % of patients with aluminum related bone disease showed an increment of plasma aluminum less than 200 mcg/l. Thus, in general, the increment in plasma aluminum after DFO reflects total tissue stores of aluminum rather than the aluminum localized on the bone forming surface. However, still there will be a good number of patients in whom bone biopsy will be needed to make the final diagnosis of aluminum induced bone disease. The performance or bone biopsy becomes very important in the patient in whom parathyroidectomy is being contemplated. Thus, the presence of hypercalcemia and high PTH levels does not necessarily indicate overt secondary hyperparathyroidism and significant bone aluminum may be present. It has been shown that such patients are likely to develop severe features of overt osteomalacia following parathyroidectomy. Thus, it is mandatory to perform a bone biopsy in any patients who are considered for parathyroidectomy.

Therapy

The cornerstone of management includes prevention of hyperphosphatemia by modest dietary phosphate restriction and administration of phosphate binders, dietary supplements of calcium, the use of appropriate dialysate calcium concentration, and calcitriol. We will focus primarily on the use of calcitriol, especially the oral vs intravenous use of vitamin D. It is our impression that the majority of patients with osteitis fibrosa will benefit from calcitriol therapy. Thus, in the 1970's, there were studies showing the beneficial effect of calcitriol in patients with osteitis fibrosa [13, 14]. A

significant increment in serum calcium, a decrease in alkaline phosphatase as well as in PTH levels, together with improved bone histology was observed. In addition, the majority of patients had significant clinical improvement. Unfortunately, there was an incidence of 20-30 % of hypercalcemia.

Recently, it has been demonstrated that calcitriol directly inhibits PTH secretion. Thus, Silver et al. have shown that in isolated parathyroid cells, the suppressive effect of calcitriol on cytoplasmic mRNA coding for preproparathyroid hormone [15]. With the advent of the intravenous form of calcitriol, the theoretical use of this sterol intravenously becomes more attractive. Thus, recent evidence in hemodialysis patients with osteitis fibrosa, suggests a direct affect of intravenously administered calcitriol on PTH secretion [16]. This is not surprising since the parathyroid gland possesses abundant receptors for calcitriol. We have just finished a study in which we evaluated the intravenous effect of calcitriol on parathyroid hormone secretion independent of hypercalcemia. Before we present details of our study, it is appropriate to briefly review parathyroid hormone function in normals and in patients with chronic renal failure. The secretion of PTH appears to be regulated in a sigmoidal relationship over a narrow range of plasma calcium. Recently, it has been shown that in vitro, isolated parathyroid cells from uremic patients require higher extracellular calcium concentration than normal cells to suppress PTH secretion [17]. The set point of calcium, that is the concentration of calcium required to induce 50 % suppression in PTH release, is shifted in these cells. Dialysis patients have been shown to have an abnormal set point of calcium [18]. Thus, these patients with overt hyperparathyroidism and biopsy proven osteitis fibrosa exhibited a marked increase in PTH while hypocalcemia was produced with a low serum calcium dialysis. It is of interest that 5 of these patients had significant increments in PTH even at a moderately decreased serum calcium levels (less than 9 mg/dl), suggestive of an increased sensitivity of the parathyroid gland to changes in serum calcium concentration.

We evaluated parathyroid gland function with a hypo and hypercalcemia stimulus performed before and after 10 weeks of 2 mcg of intravenous calcitriol at the end of each dialysis. Hypo and hypercalcemia were evaluated with a low (1.0 mEq/l) and high calcium (4.0 mEq/l) dialysis before and after 10 weeks of intravenous calcitriol therapy. To avoid hypercalcemia during calcitriol administration, the dialysate calcium was reduced to 2.5 mEq/l. Parathyroid hormone values from dialysis- induced hypo and hypercalcemia were plotted against serum calcium and the sigmoidal relationship between PTH and calcium was evaluated. Basal PTH levels fell from 902 ± 126 pg/ml to 466 ± 152 pg/ml ($p < .01$) after therapy without any significant changes in serum calcium concentration. The calcium-PTH sigmoidal curve shifted to the left and downward after calcitriol therapy (fig. 1). The maximal PTH response during hypocalcemia decreased after calcitriol from 1661 ± 485 pg/ml before calcitriol to 1081 ± 280 pg/ml after ($p < .05$). The PTH level at maximal inhibition due to hypercalcemia decreased

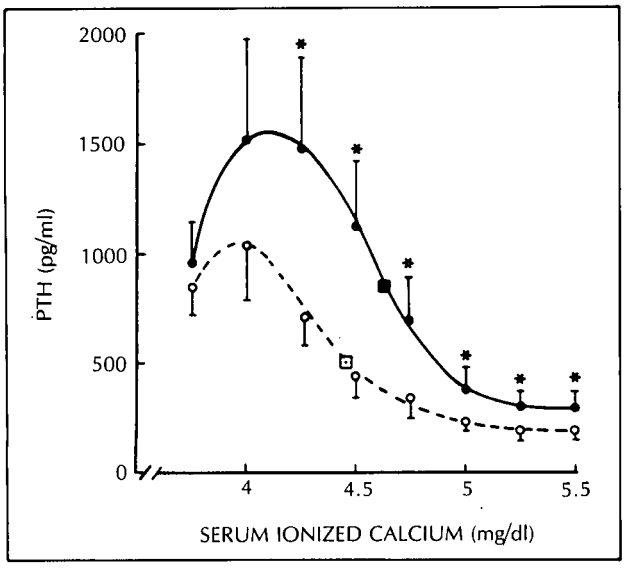

Fig. 1.—The sigmoidal serum ionized calcium-PTH curve before (solid line) and after (dashed line) ten weeks of intravenous calcitriol therapy is shown. The set point is represented by a solid square before and an open square after calcitriol.

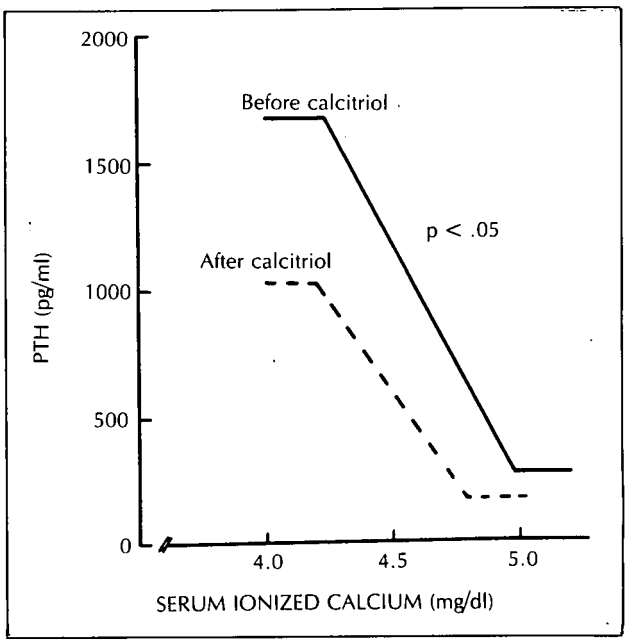

Fig. 2.—The change in the slope of the sigmoidal calcium-PTH curve before and after (-----) ten weeks of intravenous calcitriol therapy is presented.

from 281 ± 76 pg/ml before calcitriol to 192 ± 48 pg/ml after ($p < .05$). The slope of the sigmoidal curve changed significantly after calcitriol therapy (fig. 2). The set point of calcium, however, did not change with calcitriol therapy.

In summary, ten weeks of intravenous calcitriol therapy decreased PTH concentration across a wide range of serum calcium levels, shifting the calcium-PTH sigmoidal curve toward normal (left and downward). This result demonstrated a direct inhibitory effect of intravenous calcitriol on parathyroid function in dialysis patients with secondary hyperparathyroidism.

The role of intravenous calcitriol in the management of patients with secondary hyperparathyroidism is not clear. At present, comparative studies showing the beneficial effect of this new form of therapy are not available. However, this type of therapy may be appropriate in certain groups of patients such as: 1) the non-compliant patient prescribed oral calcitriol; 2) the patient with overt secondary hyperparathyroidism in whom the administration of oral calcitriol usually induced significant hypercalcemia; 3) in general, in those cases with a significant increment in parathyroid hormone levels with the hope that the medical parathyroidectomy may be achieved; 4) finally, another possible and beneficial use of intravenous calcitriol may in the post-parathyroidectomy stage when severe hypocalcemia may develop resulting in multiple fractures. In this situation, the administration of intravenous calcitriol has proven to be beneficial in maintaining the serum calcium within a reasonable level.

The treatment of aluminum induced bone disease includes the cessation of any aluminum supply to the patient. This includes a regular monitoring of the dialysate concentration of aluminum in a given dialysis unit and the discontinuation of aluminum containing gels which is the major source of aluminum accumulation today. Dietary phosphorus intake should be reduced to 800-900 mg/day to lower the requirement of phosphate binding agents. Alternative to aluminum containing phosphate binders are either calcium carbonate or magnesium carbonate. Calcium carbonate reduces the intestinal absorption of phosphate although not all patients can tolerate calcium carbonate because of hypercalcemia and/or side effects such as diarrhea and constipation. Calcium carbonate should be ingested with meals with a dose adjusted in proportion to the amount of phosphorus contained in each individual meal to minimize the absorption of calcium. The use of lower calcium dialysate concentration, i.e., 2.0-2.5 mEq/l will often permit the use of calcium carbonate with less risk of hypercalcemia. In those patients who cannot restrict phosphorus intake adequately, or who are unable to take adequate an dose of calcium carbonate, aluminum gels and calcium carbonate can be used in combination in lower and safe doses. Magnesium carbonate given in conjunction with a magnesium free dialysate solution has been employed successfully as an alternative phosphate binding agent. However, this preparation is not available on the market at the present time and if used, must be prepared by the in-hospital pharmacy.

The administration of the chelating drug, deferoxamine, has changed the prognosis of patients with aluminum induced bone disease. This agent markedly enhances the removal of aluminum during dialysis. There are two mechanisms by which deferoxamine enhances aluminum removal during dialysis: First, it mobilizes aluminum from the tissues stores, thereby raising the total aluminum levels in plasma and secondly, it increases the fraction of plasma aluminum that is ultrafilterable. Thus, aluminum removal increases from 50-300 mcg during 4 hours of hemodialysis before deferoxamine to 4-8 mg during the same 4 hours of hemodialysis after infusion of deferoxamine. The use of deferoxamine results in a significant improvement in the clinical status of the patient. Improvement in clinical symptomatology has been universal in all studies. After treatment with deferoxamine for one year, bone biopsy showed decreased surface staining for aluminum and increased bone formation. Therapy with deferoxamine is not without side effects. Hypotension, cataracts and retinal abnormalites, and infections due to yersinia, salmonella, and Rhizopus (mucormycosis) have been observed in patients receiving deferoxamine. To minimize these risks, the dose of deferoxamine should be kept to a minimum, i.e., less than 1.0-1.5 g/week. We have recently evaluated the role of deferoxamine therapy administered during one year in 20 patients with aluminum associated bone disease. In addition, we assessed parathyroid gland function as it has been shown previously. In comparison of findings before and after DFO therapy, we observed the following: 1) A decrease in stainable trabecular bone aluminum and an increase in osteoblastic osteoid, osteoclasts and bone formation rate. 2) A shift of the PTH-calcium curve to the right. Thus, for similar levels of serum calcium, PTH concentration was increased after DFO. 3) An increase in PTH concentration at the serum calcium level required for maximal PTH inhibition. 4) Significant clinical improvement in the majority of patients. This study suggests that aluminum removal from bone may improve bone histology as well as parathyroid gland function.

References

1. Llach F, Felsenfeld AJ, Coleman MD, Keveney JJ, Pederson JA and Medlock TR: The natural course of dialysis osteomalacia. *Kidney Int* (suppl. 18):S74, 1986.

2. Coburn JW, Hartenbower DL, Brickman AS, Massry SG and Kopple JD: Intestinal absorption of calcium, magnesium, and phosphorus in chronic renal insufficiency. In David DS (Ed.): *Calcium Metabolism in Renal Failure and Nephrolithiasis.* New York. John Wiley and Sons, p. 77, 1977.
3. Massry SG, Coburn JW, Popovtzer MM, Shinaberger JH, Maxwell MH and Kleeman CR: Secondary hyperparathyroidism in chronic renal failure: The clinical spectrum in uremia, during hemodialysis and after renal transplantation. *Arch Intern Med* 124:431, 1969.
4. Coburn JW, Popovtzer MM, Massry SG and Kleeman CR: The physiochemical state and renal handling of divalent ions in chronic renal failure. *Arch Intern Med* 124:302, 1969.
5. Parkinson IS, Feest TG, Ward MK, Fawcett RWP and Kerr DNS: Fracturing dialysis osteodystrophy and dialysis encephalopathy: An epidemiological survey. *Lancet* 1:406, 1979.
6. Platts MM, Owen G and Smith S: Water purification and the incidence of fractures in patients receiving home dialysis supervised by a single centre: Evidence for «safe» upper limit of aluminum in water. *Br Med J* 288:969, 1984.
7. Andreoli SP, Bergstein JM and Sherrard DJ: Aluminum intoxication in nondialyzed azotemic children from aluminum containing phosphate binders. *N Engl J Med* 310:1079, 1984.
8. Felsenfeld AJ, Gutman RA, Llach F and Harrelson JM: Osteomalacia in chronic renal failure: A syndrome previously reported only with maintenance dialysis. *Am J Nephrol* 2:147, 1982.
9. Berlyne GM, Ben-Ari J, Pest D, Weinberger J, Stern M, Gilmore J and Levine R: Hyperaluminaemia from aluminum resins in renal failure. *Lancet* 2:494, 1970.
10. Hercz C, Kraut JA, Andress DA, Howard N, Roberts C, Shinaberger JH, Sherrard DJ and Coburn JW: Use of calcium carbonate as a phosphate binder in dialysis patients. *Mineral Electrolyte Metab* 12:314, 1986.
11. London GM, De Vernejoul MC, Fabiani F, Marchais S, Guerin AL, Metivier F, Chappuis P and Llach F: Association between aluminum accumulation and cardiac hypertrophy in hemodialyzed patients. *Am J Kidney Dis* 13:75-83, 1989.
12. Milliner DS, Nebeker HG, Ott SM, Andress DL, Sherrard DJ, Alfrey AC, Slatopolsky E and Coburn JW: Use of deferoxamine infusion test in the diagnosis of aluminum-related osteomalacia. *Ann Intern Med* 101:775, 1984.
13. Voigts AL, Felsenfeld AJ and Llach F: The effects of calciferol and its metabolites on patients with renal failure. I. Calciferol, dihydrotachysterol and calcifediol. *Arch Intern Med* 143:960, 1983.
14. Voigts AL, Felsenfeld AJ and Llach F: The effects of calciferol and its metabolites on patients with chronic renal failure. II. Calcitriol, 1 alpha hydroxyvitamin D_3. *Arch Intern Med* 143:1205, 1983.
15. Silver J, Russell J, Letteri D and Sherwood LM: Vitamin D metabolites suppress cytoplasmic mRNA coding for preproparathyroid hormone in isolated parathyroid cells. *Clin Res* 32:561A, 1984.
16. Slatopolsky E, Weerts C, Thielan J, Horst R, Harter H and Martin KJ: Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25 dihydroxycholecalciferol in uremic patients. *J Clin Invest* 74:2136, 1984.
17. Brown EM, Wilson RE, Eastman RC, Pallotta J and Marynick SP: Abnormal regulation of parathyroid hormone release by calcium in secondary hyperparathyroidism due to chronic renal failure. *J Clin Endocrinol Metab* 54:172, 1982.
18. Voigts A, Felsenfeld AJ, Andress J and Llach F: Parathyroid hormone and bone histology: Response to hypocalcemia in osteitis fibrosa. *Kidney Int* 25:445, 1984.