Kidney International, Vol. 52 (1997), pp. 1412–1421

NEPHROLOGY FORUM

Disorders of bone and mineral metabolism after renal transplantation

Principal discussant: PABLO U. MASSARI

Hospital Privado-Centro Médico de Córdoba, and Catholic University of Córdoba, Córdoba, Argentina

CASE PRESENTATION

A 27-year-old transplant patient was admitted to the Hospital Privado-Centro Médico de Córdoba for a core decompression procedure on both femoral heads and a bone biopsy of the iliac crest. He had received a cadaveric graft 18 months prior to this admission after receiving chronic hemodialysis for 14 months. His renal failure was due to chronic glomerulonephritis of undefined cause. At the time of transplantation, his intact PTH serum level was 132 pg/dl and the serum aluminum concentration was 139.6 μg/liter (Table 1). He was given immunosuppression therapy of steroids and cyclosporine. Diuresis began on the seventh postoperative day after a period of presumed acute tubular necrosis. Acute rejection (Banff I/II on the biopsy specimen) occurred on postoperative day 12, and he was given a series of intravenous boluses of methylprednisolone (250 mg twice daily for 3 days). The rejection resolved and he was discharged from the hospital on postoperative day 20; his serum creatinine was 2.2 mg/dl.

He pursued most of his previous activities, but 15 months after transplantation he started to complain of pain in both hips. Radiographic examination disclosed no abnormalities. A bone scan showed a moderate and diffuse increase in uptake of the tracer, compatible with hyperparathyroidism, but no focal hot areas. He was treated with analgesics and advised to refrain from physical activity. Two months later, his symptoms worsened, and subtle radiologic changes were evident on both femoral heads. A nuclear magnetic resonance (NMR) imaging study showed clear evidence of bilateral osteonecrosis. His symptoms immediately disappeared after core decompression of both hips, and he was discharged but advised to use crutches and limit his walking for 3 months. Iliac crest bone biopsy findings disclosed resolving osteomalacia with increased osteoclastic activity and a few small deposits of aluminum. Bone aluminum content was 14.7 μg/g. Six months after the core decompression, he was free of symptoms. An NMR study showed consolidation of the lesion on the right hip but clear evidence of progression on the left side.

The Nephrology Forum is funded in part by grants from Hoechst Marion Roussel, Incorporated; Amgen, Incorporated; Merck & Co., Incorporated; Dialysis Clinic, Incorporated; and R & D Laboratories.

DISCUSSION

DR. PABLO U. MASSARI (*Chief, Renal Service, Hospital Privado-Centro Médico de Córdoba, and Professor of Medicine, Catholic University of Córdoba, Córdoba, Argentina*): This young patient with chronic renal failure received a successful cadaveric renal transplant after a relatively short period on the waiting list. After transplantation he experienced several of the bone and mineral problems known to occur in this condition (Table 2); these abnormalities have been reviewed elsewhere [1, 2]. At the time of transplantation, he had evidence of aluminum overload and probably low-turnover bone disease, as indicated by low serum PTH (132 pg/dl) and alkaline phosphatase levels (55 IU/liter) and a high serum concentration of aluminum (139.6 μg/liter). Within two weeks after transplantation, both PTH and alkaline phosphatase levels rose and the serum aluminum declined rapidly in association with persistent urinary aluminum excretion. Later, while otherwise doing well clinically, he was struck by one of the most debilitating bone conditions in a renal transplant patient: avascular bone necrosis of the femoral heads.

Post-transplant bone and mineral disorders could be classified, according to their pathogenesis and appearance time, into two groups of entities: those bone disorders related to pre-transplant renal osteodystrophy that persist after transplantation, and those arising de novo after appropriate renal function has been restored (Table 2). Overlapping of these disorders is not rare. I will review both types of syndromes with a focus on the problems suffered by the patient presented today. Normalization of changes in mineral and bone metabolism and structure do not occur as fast as other metabolic processes do after renal function is restored. Consequently, bone conditions present before transplantation can persist for prolonged periods and can become symptomatic before their complete reversal. These persistent pre-transplant disorders are: hyperparathyroidism (HPT), aluminum bone disease, and dialysis-related amyloid bone disease.

Persistent pre-transplant disorders

Hyperparathyroidism. When a renal graft starts to function properly, it does so in a setting characterized by: (*1*) negative calcium and positive phosphate balances that had been only partially and intermittently corrected by dialysis and administration of calcitriol and oral calcium [2]; (*2*) low production of

Table 1. Serum and urinary biochemical values and immunosuppressive drug doses

	Pre-transplant	Day 15	Day 30	Day 90	18 months
Serum					
Creatinine, *mg/dl*	12.8	3.8	2	1.8	1.4
Calcium, *mg/dl*	9.2	8.4	9.8	9.5	9.4
Phosphate, *mg/dl*	4.8	2.8	3.3	1.9	3
Alkaline phosphatase, *IU/liter*	55	89	92	128	279[a]
Intact PTH, *pg/ml*	132	430	250	128	100
Aluminum, *μg/liter*	139.6	105	73.8	36.6	–
Urine					
Aluminum, *μg/liter*	–	153.8	249.1	145.4	–
Aluminum/creatinine, *μg/mg*	–	2.84	2.73	1.04	–
Immunosuppression					
Prednisone, *mg/day*	–	500[b]	45	25	10
Cyclosporine, *mg/day*	–	520	320	300	240

[a] 61% as bone alkaline phosphatase.
[b] As i.v. pulses of methylprednisolone × 3 days.

Table 2. Disorders of bone and mineral metabolism after renal transplantation

Persistent pre-transplant disorders
Hyperparathyroidism
Aluminum bone disease
Dialysis-related amyloid bone disease
De novo bone and mineral disorders
Renal tubular dysfunction
Renal tubular acidosis
Renal tubular hypercalciuria
Non-PTH-related hypophosphatemia
Painful legs syndrome
Avascular bone necrosis
Immunosuppression-related bone disease (drugs and cytokine-induced)

calcitriol and impediments to the genomic and non-genomic actions of the hormone [3]; (*3*) continuous stimulation of PTH synthesis and secretion due to overexpression of the PTH gene in parathyroid cells, recruitment of more cells into an active secretory state, and hypertrophy and hyperplasia of the parathyroid gland [4]; and (*4*) resistance to the calcemic action of PTH [1]. Normalization of glomerular filtration and tubular function rapidly eliminates phosphate and uremic toxins and restores effective calcitriol production, all of which contribute to reversing the preceding abnormalities and suppress parathyroid gland hyperfunction. But securing the involution of parathyroid gland hyperplasia is neither rapid nor easy; it can take months or even years to normalize the size of the glands and reach basal PTH secretion [5]. Moreover, glands with nodular hyperplasia, which are known to have reduced density of calcitriol receptors [6] and which probably have low expression of the membrane calcium sensor receptor [7], especially those with monoclonal proliferation, might never return to normal size and function [4]. McCarron et al studied 15 patients with post-transplant HPT, giving intravenous infusions of calcium and EDTA to evaluate the parathyroid function curve [8]. Patients with post-transplant HPT displayed a curve with a slope similar to normals but with a shift to the right, indicating a conserved sensitivity to extracellular calcium concentration but augmented basal PTH secretion. The same group also demonstrated that basal PTH secretion correlates with gland size [9].

Several other factors can influence the involution of HPT in these patients. Duration and intensity of pre-transplant HPT correlates positively with the time-course and severity of persistent post-transplant HPT [10]. Also, we have recently shown that pre-transplant aluminum overload can influence post-transplant parathyroid function, especially during the early post-transplant months [11]. Moreover, continuous production of calcitriol in normal amounts by the graft seems to be a key factor in the involution of HPT [12]. Serum calcitriol levels correlate well with graft function and consequently calcitriol production might not be sufficient to inhibit PTH secretion in patients with poor initial function [13]. Steiner and colleagues demonstrated a marked decrease in both N-terminal and C-terminal levels in a group of 10 stable normocalcemic hyperparathyroid renal transplant patients after an average of 5 months on vitamin D and calcium therapy [14]. Finally, the use of drugs that can impair intestinal calcium absorption (steroids) [15] or block calcitriol synthesis (ketoconazol) [16] also can interfere with the involution of HPT after renal transplantation.

Persistent HPT, perhaps the most common mineral disturbance in the transplant patient, is almost invariably present in the early post-transplant period [5, 10, 17, 18], but it generally resolves in a few months. Hypercalcemia, usually of mild degree and without clinical consequences, is its most frequent biochemical marker. In our experience, 23% of 47 consecutive transplant patients developed hypercalcemia within the first three months (Fig. 1) [18], but the calcium level exceeded 12 mg/dl in only 10%; the hypercalcemia was self-limited in every case, as it resolved spontaneously before the first year after transplantation. Most of the patients with post-transplant hypercalcemia also had elevated serum PTH levels, but it is notable that 4 of our hypercalcemic patients (2 at day 30 and 2 at day 60 post transplantation) had low values of PTH concomitantly with a high serum aluminum concentration [18]. Rarely, hypercalcemia exceeds 13 mg/dl and/or can have a protracted course, becoming symptomatic and eventually compromising graft function [19]. This syndrome is usually seen in patients with severe, uncontrolled pre-transplant HPT [5]. They rarely require surgical treatment and are best served by conservative measures and by avoiding fluid deprivation and administration of agents that can worsen hypercalcemia, such as oral calcium and vitamin D supplements, and thiazide diuretics.

Hypophosphatemia, another manifestation of persistent HPT, has a higher incidence than hypercalcemia (30% versus 50%) [18] during the first year after transplantation because of the coexistence of non-PTH-mediated phosphaturia [20]. Two decades ago, post-transplant hypophosphatemia was associated with osteomalacia [21], but more recent observations have not revealed osteomalacia in bone biopsy specimens from patients with post-transplant hypophosphatemic HPT [22]. Using nuclear magnetic resonance spectroscopy, Higgins et al found evidence that depletion of intracellular phosphate compounds and the use of steroids are associated with the development of hypophosphatemia [23]. This observation is important in relation to the pathogenesis of hypophosphatemic and steroid-induced myopathy. Protracted post-transplant hypophosphatemia might require oral or intravenous phosphate replacement to prevent osteomalacia and myopathy. Steiner et al [14] and Dumoulin et al [24] have shown that oral calcium and vitamin D supplements can reduce PTH levels

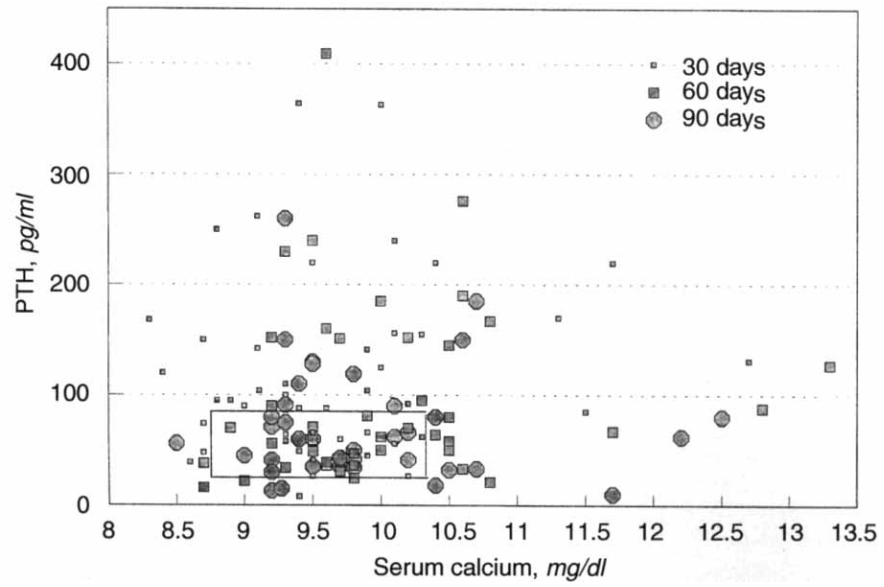

Fig. 1. Distribution of serum calcium and simultaneous PTH levels at 30, 60, and 90 post-transplant days in 47 consecutive patients. Rectangle indicates normal values.

and increase renal tubular phosphate reabsorption in patients with normolcalcemic, hypophosphatemic, post-transplant HPT.

What are the indications for surgical treatment of post-transplant HPT? It seems advisable to consider subtotal parathyroidectomy or ethanol injection only for patients with symptomatic, protracted hypercalcemia; deterioration of graft function; or soft-tissue calcifications and worsening bone disease. All these sequelae are rare in today's transplant experience [19, 25, 26].

Aluminum bone disease. A 1993 report indicated that the incidence of aluminum-related bone disease in patients with chronic renal failure who receive dialysis treatment is decreasing [27], but this entity has not disappeared. Aluminum accumulation still occurs as a major finding or in combination with other types of renal osteodystrophy in large reported series of bone biopsies in dialysis patients [27–29]. Moreover, overexposure to aluminum from contaminated dialysate (that is, high levels of aluminum in the water supply used to prepare the dialysate) seems to be quite prevalent in South America. We recently found that 57% of 47 consecutive transplant patients had serum aluminum levels higher than 40 μg/liter just prior to transplantation [11], as did the patient presented today. Although serum levels are not a good marker of aluminum bone disease [30], the high and prolonged rate of urinary aluminum excretion shown by today's patient (Table 1) is certainly a good indicator of the whole-body aluminum burden [31, 32]. Moreover, 18 months after transplantation, a bone biopsy in our patient disclosed evidence of recovering osteomalacia and an elevated bone aluminum content. Several reports have shown that renal transplantation is a successful therapy for aluminum-related bone disease, but it takes probably longer than one year to significantly reduce bone aluminum content [33–35].

Besides bone disease, aluminum intoxication is associated with an increased risk of soft-tissue calcium deposition [28] and, more important, more shortened survival in dialysis patients [28, 36]. Also, patients with aluminum intoxication have an increased incidence of infectious complications after transplantation [37, 38]. Therefore, it seems advisable to increase urinary aluminum

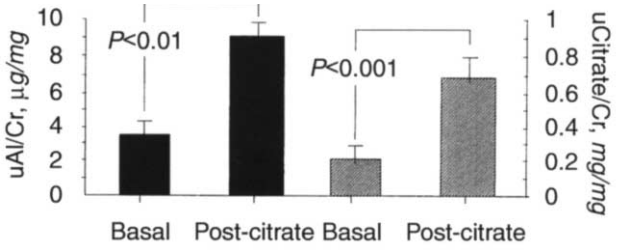

Fig. 2. Effect of an acute oral load of potassium citrate on urinary excretion of citrate and aluminum in renal transplant patients (n = 8). Values shown are mean ± 1 SE.

elimination in transplant patients. In 1984, Malluche et al accomplished this by administering deferoxamine [39], but deferoxamine therapy is not without risks, and it involves repeated intravenous administration.

Urinary aluminum elimination increases dramatically during the immediate post-transplant period. This rise occurs contemporaneously and correlates positively with urinary phosphate excretion. We believe that this correlation also might have therapeutic implications [40]. Because a recent experimental model in the rat suggested that citrate can increase urinary aluminum excretion [41], we are currently testing a protocol of oral potassium citrate administration in transplant patients. Very preliminary results show a marked increase in urinary aluminum excretion after a single dose (Fig. 2). If more detailed and extended studies confirm this approach, potassium citrate administration would seem to be an easy and rational way to accelerate aluminum detoxification in these patients.

Dialysis-related amyloid bone disease. Cystic bone lesions secondary to deposition of fibrillar beta amyloid in periarticular bone is the most recently described form of renal osteodystrophy [42]. I will only mention here that transplantation produces a rapid disappearance of symptoms but that the cystic lesions persist for many years [43–45]. We need more information on the natural

history of this disorder after transplantation and its relationship with increased production and high blood levels of beta-2 microglobulin [46].

After transplantation, complications can develop that are particular to the patient with a functioning graft. Several tubular dysfunctions can alter mineral metabolism in these patients, such as renal tubular acidosis [47, 48], renal hypercalciuria [49], and non-PTH-related hypophosphatemia [20]. I will not discuss these syndromes today; instead we shall move on to other, more prevalent and clinically disabling entities.

Post-transplant disorders

Painful legs syndrome. This syndrome, described in recent years in transplant patients [50–54], includes pain over the long bones, mostly localized to the knees and ankles, without evidence of joint inflammation. The pain is often symmetrical, interferes with walking, is not relieved by rest, and often awakens the patient at night. The leg pain arises during the first or second month after transplantation and resolves spontaneously in a few weeks. Occasionally, patients have the symptoms for more than a year. The real frequency of the syndrome is unknown. Informal communication with several transplant centers leads to the impression that in its mild and very transient form, the syndrome is quite common. However, the incidence of the "full-blown" picture has been approximately 10% in some series [50, 51]. Lucas et al found a clear relationship between the appearance of the painful legs syndrome and the initiation of cyclosporine therapy [50]. Others also have implicated cyclosporine based on the fact that symptoms improved with administration of vasodilating calcium-channel blockers [53]. Plain radiographs of bones, as well as bone scans, are of no diagnostic value. Magnetic resonance imaging shows changes compatible with so-called stress or insufficiency fractures [52], and epiphyseal impaction has been suggested as the underlying structural abnormality [51]. The syndrome does not correlate with previous or current markers of HPT, and its pathogenesis is not known. One can only speculate on its relation with the next two syndromes that I will discuss.

Avascular bone necrosis. One of the most disabling skeletal complications of renal transplantation, avascular bone necrosis (ABN), was first described more than 30 years ago [55]. As the patient presented today exemplifies, this complication usually appears between six months and the second year after transplantation; the maximal incidence is in the first year [56–63]. Clinically, it presents with pain in the hip, which is by far the most frequently affected site [57]. Pain is severe enough to impede walking. Both hips generally are affected, and several other bones are affected in more than 30% of patients [57]. Several papers have reported a decreasing incidence of this complication, from about 30% prior to the introduction of cyclosporine down to 0%–4% since the introduction of cyclosporine [60–63], but several other factors also are associated with the lower incidence of ABN. These include lower steroid doses [60], better control of pre-transplant HPT [62], and better clinical and nutritional condition of the patient at the time of transplantation [59].

The pathogenesis of ABN is not entirely clear [64]. Infiltration by lipid-laden cells producing high tissue pressure inside the femoral head, in turn leading to an impediment in blood perfusion and the resulting ischemic tissue necrosis, seems to be the most accepted hypothesis [64]. This local phenomenon has been corroborated by direct pressure measurement during core decompression procedures [64]. The role played in the pathogenesis of ABN by factors other than steroids, such as HPT, nutrition, prolonged bed rest, and cytokines, is not understood. Diagnosis usually is made by imaging techniques; plain radiographs usually demonstrate only advanced ABN, as evidenced by areas of subcortical condensation and later cortical fractures and collapse. Bone scanning reveals earlier but nonspecific findings [65]. Nuclear magnetic imaging seems to be the method of choice for diagnosis, as it allows for earlier detection and prognostic inferences [66, 67]. When the lesions are recognized in their early stages, before the appearance of cortical fractures and collapses, a core decompression procedure can offer relief in some instances [68, 69]. It brings immediate pain relief, but it has not been shown to change the course of bone destruction [70]. Collapsed lesions and those associated with degenerative joint changes are better managed by total hip replacement [71].

Immunosuppression-related bone disease. Also called post-transplant osteopenia [72], immunosuppression-related bone disease (IRBD) is defined in terms of low bone-mineral density as assessed by dual photon absorptiometry or computerized densitometry, mostly of the axial skeleton. Many groups, including our own, are greatly concerned because IRBD has appeared in many patients and is thought to be progressive and associated with a higher incidence of bone fracture [73–81]. Horber and coworkers calculated, on the basis of determinations of bone mineral content by dual-energy, x-ray absorptiometry, that the average transplant patient loses approximately 40 g (10%) of bone calcium salts, mostly from the trabecular compartment, during the first five months of having a functioning graft [76]. The attainment of a normal "peak bone mass" can be compromised by many disease conditions occurring during the first three decades of life [82]. Not surprisingly, then, we found a positive correlation between bone-mineral density and age at transplantation [79]. Thus, early, pre-transplant factors could influence post-transplant bone mineral content [79]. Nevertheless, we do not have a clear understanding of the pathogenesis and natural history of IRBD, because data from bone biopsies are scant. Several investigators have shown that vertebral bone-mineral density falls dramatically, some 6% to 10% from the pre-transplant levels, by the sixth month post transplantation [72–74]. This decline is already apparent by the third month [73] and continues to decline for as long as 18 months. These findings led Bagni and colleagues to suggest that this loss of bone mineral content is permanent and progressive [77]. In more prolonged observations, however, we and others have noted that bone-mineral content reverted to basal levels by the second year [76, 78, 80]. Moreover, studies of patients at various time periods since renal transplantation (including many after several years) found that the demineralization is not progressive, is not a universal phenomenon, and bears no relationship to time since transplantation, time on hemodialysis, or patient age [79–81]. Some investigators have noted a correlation between the fall in bone-mineral density and the severity of pre-transplant HPT [74, 83–85]. This observation is most intriguing because trabecular or spongy bone of the axial skeleton is not the site most affected in HPT bone disease [86]. A lesser degree of cortical bone-mineral content loss also has been reported; it is seen less frequently and it resolves fairly rapidly [73–76].

Many [78, 81, 84] but not all [72, 74, 79] studies have found a correlation between the total cumulative dose of steroids and the

Table 3. Systemic and local effects of steroids on bone and mineral metabolism

Hormonal disturbances
Decreased production of gonadal and pituitary hormones
Impairment of growth hormone anabolic effects
Impairment in vitamin D action
Disturbances in renal calcium and phosphate handling
Increased urinary calcium excretion
Increased urinary phosphate excretion
Alteration in intestinal calcium absorption
Non-vitamin D-mediated decrease
Local effects on bone metabolism
Inhibition of osteoblast activity
Suppression of procollagen and osteocalcin production
Increased bone resorption
Inhibition of cytokine gene expression (IL-1, IL-6, TNF, TGFβ)
Increased sensitivity of bone to PTH

amount of bone mineral loss; still another study noted a correlation only with the number of acute rejection episodes treated with intravenous steroid pulses [78]. Wolpaw et al showed a significant negative correlation between the total cumulative steroid dose and the adjusted vertebral bone density; this correlation was evident only in patients who had received more than 30 g of the drug [81]. Torres et al have impressive evidence that pre-transplant hyperparathyroidism is the main determinant of early vertebral bone mineral loss, but that the recovery of bone mineral content after the first year following transplantation is associated with the presence of the so-called "favorable" common alleles (bb) of the vitamin-D receptor; these data strongly suggest a genetic determinant as the main factor in late post-transplant bone density [85].

As I stated earlier, our understanding of this entity is limited because few studies have included bone biopsies with dynamic bone histomorphometric evaluation. The 1991 study by Julian et al that included repeated bone biopsies at six months post transplantation disclosed resolving osteitis fibrosa with "de-novo" development of adynamic bone disease [72]. Velasquez-Forero and colleagues reported adynamic bone disease to be the most frequent finding in bone biopsies performed in late (mean, 84 months) post-transplant periods in patients with normal renal function and low bone-mineral density [87]. They incriminated steroids and bone iron deposits as the most likely causes of the low turnover bone disease. Also, Sherrard and coworkers studied specimens from bone biopsies performed before and at 18 months post transplantation in 26 patients and noted a diminution of resorption and osteoclast activity with evidence of "uncoupling" of bone formation and bone dissolution, which they attributed to steroids [88].

Glucocorticoids have long been known to have deleterious effects on bone [reviewed in 15, 89]. Clinical manifestations include bone demineralization, bone pain, and fractures, which occur more commonly in vertebral bone [89]. These effects are time- and dose-dependent. Although these side effects occur even with low-dose anti-inflammatory therapy [90], they are less prevalent [91] or absent [92] when steroids are administered as replacement therapy. The time course, localization, and recovery of steroid-induced osteopenia in non-transplant patients is quite similar to that in renal transplant patients [108, 109]. The mechanisms of steroids' effects on bone include several systemic and local factors (Table 3), but these mechanisms are beyond the scope of this review.

Of particular interest in renal transplant patients are the effects on the expression of cytokine genes. Recent information has surfaced regarding cytokines' effects on bone metabolism in normal and disease conditions [93, 94], including renal osteodystrophy [95]. Glucocorticoids suppress expression of the bone-resorbing cytokines, IL-1, IL-6, and TNF; but glucocorticoids also suppress TGFβ, which promotes bone formation [96]. During the rejection process, blood levels of IL-1, IL-6, and TNF can rise [97] and thus can exert their effects on target bone cells. In short, when a patient is receiving glucocorticoid therapy for an inflammatory disease, the net effect on bone is the result of the complex interaction of the drug and the cytokines IL-1, IL-6, TNF, and TGFβ.

But transplant patients are usually immunosuppressed with another drug that can affect bones: cyclosporine. The development of high-turnover bone disease from cyclosporine in a rat model has caused much concern [98], but some authors do not attach any importance to the clinical relevance of such a mechanism [99]. Moreover, the immunosuppressive effect of cyclosporine entails the activation of nuclear transcription factors that in turn induce production of IL-6, one of the most potent bone-resorbing agents [100, 101]. Unfortunately, no experimental model is yet available in which resolving uremic bone disease has been studied in the company of steroid and cyclosporine administration. Clearly, we need more information to better define the natural history, pathogenesis, diagnosis, and treatment of immunosuppression-related bone disease.

QUESTIONS AND ANSWERS

DR. NICOLAOS E. MADIAS (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts, USA*): You suggested that the extracellular calcium-sensing receptor might be involved in the pathophysiology of the hyperparathyroidism associated with end-stage renal disease. Does any evidence indicate that, indeed, the receptor either has different characteristics or is dysregulated in this disorder?

DR. MASSARI: As I mentioned, Dr. Slatopolsky's group recently published a paper describing, in a model of vitamin-D deficient rat, that expression of the calcium-sensing receptor in renal and PTH gland cells is upregulated by calcitriol [7]. Although I am not aware of any published work investigating these phenomena in uremic models, differential expression of this receptor probably is one of the mechanisms involved in uremic hyperparathyroidism.

DR. MADIAS: I was interested in your observation that administration of potassium citrate increases urinary aluminum excretion. As you know, administered citrate is rapidly oxidized to bicarbonate and induces bicarbonaturia. Any elevation in urinary citrate excretion largely reflects changes in renal metabolism rather than excretion of administered citrate. Moreover, citrate increases intestinal aluminum absorption. Did your patients have bicarbonaturia? Did administration of bicarbonate increase their urinary aluminum excretion? Also, have you tested administration of sodium citrate, rather than potassium citrate?

DR. MASSARI: In humans, the fractional excretion of citrate is 10% to 35%. It is known that the reabsorbed citrate is rapidly oxidized to bicarbonate [102], but urinary citrate increases substantially after an oral load [102]. We have not looked for the

presence of bicarbonaturia after the oral administration of potassium citrate. We have not yet tested the effect of sodium citrate or sodium bicarbonate on urinary aluminum excretion. Aluminum does not seem to have an affinity for bicarbonate [103]. At the prevailing pH of plasma, citrate behaves as a trivalent anion. Consequently, it could be that in our studies we are obtaining a chelation effect on tissue aluminum, a complex that is readily filtered and excreted in urine. Note that aluminum has a very high affinity for citrate [103]. We cannot exclude the possibility that our results are due to interference with the tubular reabsorption of aluminum.

DR. JOHN T. HARRINGTON (*Dean, Tufts University School of Medicine, Boston*): Could you comment on the specific causes of non-PTH-induced phosphaturia after renal transplantation?

DR. MASSARI: Hypophosphatemia and hyperphosphaturia are a common finding after renal transplantation [18]. Several years ago, Rosenbaum et al showed that transplant patients with hypophosphatemia had renal phosphate wasting that could not be explained on the basis of their PTH levels and that the high phosphate clearance persisted after PTH suppression induced by calcium infusion [20]. They postulated a tubular defect in phosphate reabsorption or a heightened sensitivity to PTH as the explanation for these findings. More recently, Higgins et al [23] and Vrtovsnik and coworkers [104] showed that steroids have a marked phosphaturic effect and that they appear to be the main factor in post-transplant, non-PTH induced, hypophosphatemia. Decreased tubular reabsorption of phosphate during post-transplant acute tubular necrosis could contribute to these phenomena in early post-transplant periods, as could other drugs like acyclovir, which also has a phosphaturic effect [105].

DR. MANUEL MARTINEZ-MALDONADO (*Vice Chair and Professor of Medicine, Emory University, Atlanta, Georgia, USA*): Is there any evidence that aluminum can affect the calcium sensor either by altering its conformation or substituting for calcium? Could this in turn affect PTH secretion?

DR. MASSARI: In a recent Nephrology Forum, Hebert noted that the particular molecular conformation of the calcium-sensing receptor makes it well suited for binding with other bivalent and trivalent cations [106]. Although I am not aware of any information regarding interaction of aluminum with the calcium-sensing receptor, what you mention is a very attractive possibility that merits further investigation.

DR. SAULO KLAHR (*Simon Professor and Co-chairman, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA*): There is no question that aluminum directly affects PTH secretion, as Slatopolsky et al showed many years ago [107]. I just want to make some general comments on the overall issue of secondary hyperparathyroidism and bone disease. The natural history of this disease has changed substantially since the mid-1960s. Perhaps our group was overzealous in terms of treating dialysis patients aggressively to bring PTH down to normal values. We know now that uremic patients need PTH levels two to three times the normal values to have a nearly normal bone metabolism and that normal levels of PTH in these patients lead to adynamic bone disease. What should the PTH level be in a renal transplant recipient?

DR. MASSARI: This is certainly a very important point, Dr. Klahr. We do not know what the appropriate level of PTH should be after renal transplantation, but I would guess that the problem is confined to those patients with persistently poor renal function and those who received high doses of immunosuppressive drugs. Nevertheless, if the studies by Sherrard and colleagues are confirmed [88], we might have to re-evaluate our concept of appropriate PTH levels for patients with normal renal function and adynamic, immunosuppression-related bone disease.

DR. MADIAS: You showed a correlation between GFR and serum phosphate and calcitriol levels in patients following transplantation. What about patients with persistent post-transplantation hyperparathyroidism, hypophosphatemia, and well-maintained graft function? Do these patients have supranormal levels of calcitriol?

DR. MASSARI: Garabedian et al showed that in children with sub-normal renal function, calcitriol levels were not appropriate for the degree of hypophosphatemia [12]. Moreover, in spite of the fact that several patients had high levels of calcitriol, a "normal type" correlation did not exist between serum PTH and calcitriol levels. It seems that the main determinant of post-transplant calcitriol levels is the GFR [13].

DR. J. CARLOS AYUS (*Professor of Medicine, Baylor College of Medicine, Houston, Texas, USA*): What are the indications for treatment with calcitriol and/or calcium supplements in transplant patients with incomplete recovery of renal function and persistent hyperparathyroidism? What are the indications for parathyroidectomy in these patients?

DR. MASSARI: As I mentioned, post-transplant patients with normocalcemia, hypophosphatemia, and hyperparathyroidism can benefit from calcitriol and calcium supplements [14], but appropriate precautions should be taken to avoid hypercalcemia and/or hypercalciuria. The indications for parathyroidectomy or ethanol injection include protracted, symptomatic hypercalcemia, especially when it induces deterioration of renal function, soft-tissue calcification, or worsening bone disease.

DR. AMANDO L. NEGRI (*Staff Nephrologist, Institute for Metabolic Research, Buenos Aires, Argentina*): Cyclosporine produces high-turnover bone disease and could contribute to immunosuppression-induced bone disease. Does tacrolimus have the same effects on bone? Could it have a bone-sparing effect?

DR. MASSARI: Unfortunately that is not the case. Cvetkovic et al have recently shown that tacrolimus produces a similar disorder [108]. This is not surprising if you consider the immunosuppressant mechanism of the drug [100].

DR. HORACIO J. ADROGUÉ (*Professor of Medicine, Baylor College of Medicine*): It seems to me that the comparison of bone and skeletal manifestations after renal transplantation with bone and skeletal changes following heart and liver transplantation might elucidate the role of immunosuppressive drugs independent of other factors like hyperparathyroidism, aluminum, etc. Thus, I suppose that if cyclosporine is responsible for the painful legs syndrome after renal transplantation, which you indicated is quite common, such a syndrome also should be evident after transplantation of other organs if the patient receives the same drugs.

DR. MASSARI: Your observation is very interesting. Information on bone disease after heart or liver transplantation has been surfacing recently. Although I am not aware of any description of the painful legs syndrome after non-renal transplantation, severe osteopenia and a high incidence of bone fracture have been reported [109, 110]. However, pre-transplant clinical conditions, prolonged hospitalization time, as well as the multiple drugs administered to these patients in the post-transplant period all contribute to making comparison difficult.

DR. HARRINGTON: You said that fractional aluminum excretion increased in patients with acute tubular necrosis. Was this only during the period of ATN, or did it last longer? Was absolute excretion higher than in the controls during this same period?

DR. MASSARI: In patients with post-transplant acute tubular necrosis, the difference in fractional excretion of aluminum, as well as in the absolute excretion rate, was still present four weeks after transplantation, but it vanished thereafter.

DR. RODOLFO S. MARTIN (*Instituto de Investigaciones Médicas, Buenos Aires, Argentina*): In the patient presented today, would you say that the appearance of bilateral symptomatic osteonecrosis occurred rather early after transplantation? Don't you think that osteomalacia played a more important pathogenetic role than did avascular necrosis?

DR. MASSARI: This patient had bilateral necrosis of the hip at 15 months after transplantation, about the time of maximal incidence of this complication. Uremic bone disease might play a role in this entity, but it has been reported quite infrequently in dialysis patients.

DR. MADIAS: Have biphosphonates, and in particular alendronate, been used in the treatment of post-transplant osteopenia?

DR. MASSARI: The abstract book for the 1996 ASN meeting in New Orleans contains a report from Dr. Almond from London showing the results of a prospective study with pamidronate to prevent bone loss in these patients. After one year of treatment, treated patients had a marked diminution in bone loss compared to controls. This is the first study utilizing biphosphonates successfully in this condition [111].

DR. MADIAS: You showed data indicating that increased body aluminum correlates with increased mortality rates. As you know, aluminum bone disease tends to be more severe in diabetics. Might the correlation reflect the increased propensity of diabetics to develop this disorder rather than the adverse effect of aluminum per se on survival?

DR. MASSARI: The data published by Chazan et al come from a population of more than 10,000 dialysis patients. Applying the Cox model, these researchers showed that diabetes and serum aluminum levels were independent risk factors for survival [36].

DR. HORACIO REPETTO (*Chief, Pediatric Service, Hospital Nacional A. Posadas, Buenos Aires, Argentina*): Would you comment on the possible explanation for the association between aluminum intoxication and what seems to be a decrease in the immune response against infections?

DR. MASSARI: I think it is an unsettled issue as yet. Tzanno-Martins et al had shown that aluminum-treated rats display a decreased immune response to mitogen as assessed by the lymphoproliferative response, with a decreased lymphocyte helper/cytotoxic ratio and a reduction in IL-2 production [38]. Further studies are needed to clarify the mechanism.

DR. PEDRO SZYLMAN: (*Poria Hospital Renal Unit, Tiberias, Israel*): Do you have information about drug abuse as a risk factor for femoral head aseptic necrosis in patients who have received transplants? Cyclosporine substantially reduces the incidence of post-transplant bone disease and avascular necrosis, but I wonder whether this can be related to a reduction in steroid dosage and general better outcome.

DR. MASSARI: Heavy alcohol ingestion has been associated with avascular bone necrosis. I do not know of any other abused drug implicated with the syndrome. As to the mechanism of the cyclosporine-associated fall in the incidence of avascular bone necrosis, a reduction in steroid dosage seems to be the main factor, but we cannot rule out cytokine-related effects.

ACKNOWLEDGMENTS

This Forum was presented at the Tenth Congress of the Sociedad Argentina de Nefrología, October 1996. The Editors wish to acknowledge the assistance of Sandoz Argentina, Incorporated, for financial support of this Forum. Work done by the authors' group and cited in this review has been done with the aid of grants from the Concejo de Investigaciones Cientificas y Tecnológicas de Córdoba, Argentina, and from the Fundación Nefrológica de Córdoba, Argentina, and in collaboration with the Mineral and Bone Metabolism Research Unit (Dr. Jorge Cannata), University of Oviedo, Spain. The author greatly appreciates the secretarial help of Mariela Hajndel.

Reprint requests to Dr. P. Massari, Chief, Servicio de Nefrologia, Hospital Privado, Centro Medico de Córdoba, Naciones Unidas 346, 5016 Córdoba, Argentina

REFERENCES

1. SLATOPOLSKY E, DELMEZ J: Bone disease in chronic renal failure and after renal transplantation, in *Disorders of Bone and Mineral Metabolism*, edited by COE FL, FAVUS MJ, New York, Raven Press, 1992, p 905
2. DOUTHAT W, MASSARI PU, CANNATA ANDÍA JB: Trastornos del metabolismo óseo y mineral en el transplante renal. *Nefrologia* (Madrid) 14:408–415, 1994
3. HSU CH, PATEL S, VANHOLDER YE: The biological action of calcitriol in renal failure. *Kidney Int* 46:605–612, 1994
4. DRÜEKE T: Nephrology Forum: The pathogenesis of parathyroid gland hyperplasia in chronic renal failure. *Kidney Int* 48:259–272, 1995
5. PARFITT AM: Hypercalcemic hyperparathyroidism following renal transplantation: differential diagnosis, management, and implications for cell population control in the parathyroid gland. *Miner Electrolyte Metab* 8:92–112, 1982
6. KORKOR A: Reduced binding of [^{3}H] 1,25-dihydroxyvitamin D_3 in the parathyroid glands of patients with renal failure. *N Engl J Med* 316:1573–1577, 1987
7. BROWN AJ, ZHONG M, FINCH J, RITTER C, MCCRACKEN R, MORRISSEY J, SLATOPOLSKY E: Rat calcium- sensing receptor is regulated by vitamin D but not by calcium. *Am J Physiol* 39:454–460, 1996
8. MCCARRON D, MUTHER RS, LENFESTY B, BENNET W: Parathyroid function in persistent hyperparathyroidism: Relationship to gland size. *Kidney Int* 22:662–670, 1982
9. MCCARRON D, LENFESTY B, NARASIMHAN N, BARRY J, VETTO M, BENNETT W: Anatomical heterogeneity of parathyroid glands in posttransplant hyperparathyroidism. *Am J Nephrol* 8:388–391, 1988
10. CUNDY T, KANIS JA, HEYNEN G, MORRIS PJ, OLIVER DO: Calcium metabolism and hyperparathyroidism after renal transplantation. *Q J Med* 205:67–78, 1983
11. GARAY G, GROSSO S, DOUTHAT W, FERNÁNDEZ MARTÍN JL, CANNATA J, MASSARI PU: Influence of aluminium overload on the course of post-transplant parathyroid function. *Nephrol Dial Transplant* 11(suppl 3):65–68, 1996
12. GARABEDIAN M, SILVE C, LEVY-BENTOLILA D, BOURDEAU A, ULMANN A, NGUYEN T, LIEBERHERR M, BROYER M, BALSAN S: Changes in plasma 1,25 and 24,25-dihydroxyvitamin D after renal transplantation in children. *Kidney Int* 20:403–410, 1981
13. RIANCHO J, DE FRANCISCO A, DEL ARCO C, AMADO J, COTORRUELO J, ARIAS M, GONZALEZ MACIAS J: Serum levels of 1,25-dihydroxyvitamin D after renal transplantation. *Miner Electrolyte Metab* 14:332–337, 1988
14. STEINER R, ZIEGLER M, HALASZ N, CATHERWOOD B, MANOLAGAS S, DEFTOS L: Effect of daily oral vitamin D and calcium therapy, hypophosphatemia, and endogenous 1–25 dihydroxycholecalciferol on parathyroid hormone and phosphate wasting in renal transplant recipients. *Transplantation* 56:843–846, 1993

15. ADLER R, ROSEN C: Glucocorticoids and osteoporosis. *Endocrinol Metab Clin North Am* 23:641–655, 1994
16. MOORE L, ALLOWAY R, ACCHIARDO S, VERA S, SHOKOUH-AMIRI M, GABER A: Clinical observations of metabolic changes occurring in renal transplant recipients receiving ketoconazole. *Transplantation* 61:537–541, 1996
17. CONCEICAO SC, WILKINSON R, FREST TG, OWEN JP, DEWAR J, KERR DNS: Hypercalcemia following renal transplantation: causes and consequences. *Clin Nephrol* 16:235–244, 1981
18. GARAY G, GROSSO S, CANNATA J, MASSARI P, FERNÁNDEZ E, ARTEAGA J, GARZÓN F: Evolución post transplante renal del hiperparatiroidismo secundario (*abstract*). *Nefrología Latinoamericana* 2:139, 1995
19. ZEIDAN B, SHABTAL M, WALTZER WC, WADHWA NK, SIDDARTH P, RAPAPORT FT: Improvement in renal transplant function after subtotal parathyroidectomy in a hypercalcemic kidney allograft recipient. *Transplant Proc* 23:2285–2288, 1991
20. ROSENBAUM R, HRUSKA K, KORDOR A, ANDERSON C, SLATOPOLSKY E: Decreased phosphate reabsorption after renal transplantation: Evidence for a mechanism independent of calcium and parathyroid hormone. *Kidney Int* 19:568–578, 1981
21. MOORHEAD JF, AHMED KY, VARGHESE Z, WILL MR, BAILLOD RA, TATLER GL, FAIRNEY A: Hypophosphataemic osteomalacia after cadaveric renal transplantation. *Lancet* 1:694–697, 1974
22. FELSENFELD A, GUTMAN R, DREZNER M, LLACH F: Hypophosphatemia in long-term renal transplant recipients: effects on bone histology and 1,25-dihydroxycholecalciferol. *Miner Electrolyte Metab* 12:333–341, 1986
23. HIGGINS R, RICHARDSON A, ENDRE Z, FROSTICK S, MORRIS P: Hypophosphatemia after renal transplantation: relationship to immunosuppressive drug therapy and effects on muscle detected by P nuclear magnetic resonance spectroscopy. *Nephrol Dial Transplant* 5:62–68, 1990
24. DUMOULIN G, HORY B, NGUYEN N, HENRIET MT, BRESSON C, REGNARD J, SAINT-HILLIER Y: Acute oral calcium load decreases parathyroid secretion and suppresses tubular phosphate loss in long-term renal transplant recipients. *Am J Nephrol* 15:238–244, 1995
25. D'ALESSANDRO A, MELZER J, PIRSCH J, HANS-SOLLINGER W, KALAYOGLU M, VERNON W, BELZER F, STARLING J: Tertiary hyperparathyroidism after renal transplantation: operative indications. *Surgery* 106:1049–1056, 1989
26. PUNCH J, THOMPSON N, MERION R: Subtotal parathyroidectomy in dialysis dependent and post renal transplant patients. *Arch Surg* 130:538–543, 1995
27. SHERRARD D, HERCZ G, PEI Y, MALONEY N, GREENWOOD C, MANUEL A, SAIPHOO C, FENTON S, SEGRE G: The spectrum of bone disease in end-stage renal failure—An evolving disorder. *Kidney Int* 43:436–442, 1993
28. SHERRARD D, HERCZ G, PEI Y, SEGRE G: The aplastic form of renal osteodystrophy. *Nephrol Dial Transplant* 11(suppl 3):29–31, 1996
29. MONIER-FAUGERE M, MALLUCHE H: Trends in renal osteodystrophy: A survey from 1983 to 1995 in a total of 2248 patients. *Nephrol Dial Transplant* 11(suppl 3):111–120, 1996
30. D'HAESE P, COUTTENYE M, DE BROE E: Diagnosis and treatment of aluminium bone disease. *Nephrol Dial Transplant* 11(suppl 3):74–79, 1996
31. KOO W, KRUG-WISPE S, SUCCOP P, BENDON R, KAPLAN L: Sequential serum aluminium and urine aluminium: creatinine ratio and tissue aluminium loading in infant with fractures/rickets. *Pediatrics* 89:877–881, 1992
32. DAVENPORT A, DAVISON AM, NEWTON KE, TOOTHILL C, WILL WJ, GILES GR: Urinary aluminium excretion following renal transplantation and the effect of pulse steroid therapy. *Ann Clin Biochem* 27:25–32, 1990
33. NORDAL K, DAHL E, HALSE J, AKSNES L, THOMASSEN Y, FLATMARK A: Aluminum metabolism and bone histology after kidney transplantation: a one year follow up study. *J Clin Endocrinol Metab* 74:1140–1145, 1992
34. BERTOLONE G, ADRIANI M, BONUCCI E, BALLANTI P, COSTANTINI S, GIORDANO R, MATTIELLO G, CALCONI G, MARESCA MC, GALARDI N, CALZAVARA P, NORDIO M, PICCOLI A: Dynamics of bone aluminum over one year of functioning renal graft. *Nephron* 64:540–546, 1993
35. DAVID-NETO E, JORGETTI V, SOEIRO N, PEREIRA R, BORELLI A, IANEHEZ L, SABBAGA E, WAJCHEMBERG B, ARAP S: Reversal of aluminum-related bone disease after renal transplantation. *Am J Nephrol* 13:12–17, 1993
36. CHAZAN J, LEW N, LOWRIE E: Increased serum aluminum. An independent risk factor for mortality in patients undergoing long-term hemodialysis. *Arch Intern Med* 151:319–322, 1991
37. DAVENPORT A, DAVISON AM, NEWTON KE, TOOTHILL C, WILL WJ: Aluminium mobilization following renal transplantation and the possible effect on susceptibility to bacterial sepsis. *Q J Med* 289:407–423, 1991
38. TZANNO-MARTINS C, AZEVEDO S, ORII N, FUTATA E, JORGETTI V, MARCONDES M, SILVA DUARTE A: The role of experimental chronic renal failure and aluminium intoxication in cellular immune response. *Nephrol Dial Transplant* 11:474–480, 1996
39. MALLUCHE H, SMITH A, ABREO K, FAUGERE MC: The use of deferoxamine in the management of aluminum accumulation in bone in patients with renal failure. *N Engl J Med* 311:140–144, 1984
40. MASSARI P, GARAY G, GROSSO S, DOUTHAT W, CANNATA J: Time course and functional correlates of post transplant aluminium elimination (*abstract*). *J Am Soc Nephrol* 6:937, 1995
41. COCHRAN M, CHAWTUR V, PHILLIPS J, DILENA B: Effect of citrate infusion on urinary aluminium excretion in the rat. *Clin Sci* 86:223–226, 1994
42. KOCH KM: Nephrology Forum: Dialysis-related amyloid. *Kidney Int* 41:1416–1429, 1992
43. JADOUL M, MALCHEM J, PIRSON Y, MALDAGUE B, VAN YPERSELE C: Effect of renal transplantation on the radiologic signs of dialysis amyloid osteoarthropathy. *Clin Nephrol* 32:194–197, 1989
44. BARDIN T, LEBAIL-DARNÉ JL, ZINGRAFF J, LAREDO JD, VOISIN MC, KREIS H, KUNTZ D: Inhibition of parathyroid hormone and interleukin 1-sH: Dialysis arthropathy: outcome after renal transplantation. *Am J Med* 99:243–248, 1995
45. TAN S, IRISH A, WINEARLS C, BROWN E, GOWER P, CLUTTERBUCK E, MADHOO S, LAVENDER P, PEPYS M, HAWKINS P: Long term effect of renal transplantation on dialysis-related amyloid deposits and symptomatology. *Kidney Int* 50:282–289, 1996
46. MOE S, HACK B, CUMMINGS S, SPRAGUE S: Role of IL-1 beta and prostaglandins in beta2-microglobulin-induced bone mineral dissolution. *Kidney Int* 47:587–591, 1995
47. WILSON DR, SIDDIQUI AA: Renal tubular acidosis after kidney transplantation. *Ann Intern Med* 79:352–361, 1973
48. BATLLE D, MOZES M, MANALIGOD J, ARRUDA J, KURTZMAN N: The pathogenesis of hyperchloremic metabolic acidosis associated with kidney transplantation. *Am J Med* 70:786–796, 1981
49. SPRINGATE J, FILDES R, MAUER S, FELD L: Hematuria and hypercalciuria following renal transplantation. *Transplantation* 41:664–665, 1986
50. LUCAS VP, PONGE L, PLOUGASTEL-LUCAS M, HOURMANT M, SOULILLOU J: Musculoskeletal pain in renal transplant recipients. *N Engl J Med* 325:1449, 1991
51. GOFFIN E, PIRSON Y, BERG B, MALGHEM J, MALDAGUE B, VAN YPERSELE DE STRIHOU C: Epiphyseal impaction as a cause of severe osteoarticular pain of lower limbs after renal transplantation. *Kidney Int* 44:98–106, 1993
52. VANDE BERG B, MALGHEM J, GOFFIN E, DUPREZ T, MALDAGUE B: Transient epiphyseal lesions in renal transplant recipients: Presumed insufficiency stress fractures. *Radiology* 191:403–407, 1994
53. GAUTHIER V, BARBOSA L: Bone pain in transplant recipients responsive to calcium channel blockers. *Ann Intern Med* 121:863–865, 1994
54. STEVENS J, HILSON A, SWENY P: Post-renal transplant distal limb bone pain. *Transplantation* 60:305–307, 1995
55. STARZL T, MARCHIOSO T, PORTER K, MOORE C, RIFKIND D, WADDELL W: Renal homotransplantation. Late function and complications. *Ann Intern Med* 61:470, 1964
56. PIERIDES A, SIMPSON W, STAINSBY D, ALVAREZ-UDE F, ULDALL P: Avascular necrosis of bone following renal transplantation. *Q J Med* 175:459–480, 1975
57. IBELS L, ALFREY A, HUFFER W, WEIL R: Aseptic necrosis of bone

following renal transplantation: experience in 194 transplant recipients and review of the literature. *Medicine* 57:25–45, 1978
58. ELMSTEDT E: Avascular bone necrosis in the renal transplant patient. *Clin Orthop* 158:149–157, 1981
59. PARFREY P, FARGE D, PARFREY N, HANLEY J, GUTTMAN R: The decreased incidence of aseptic necrosis in renal transplant recipients—A case control study. *Transplantation* 41:182–187, 1986
60. FELSON D, ANDERSON J: A cross-study evaluation of association between steroid dose and bolus steroids and avascular necrosis of bone. *Lancet* 1:902–905, 1987
61. LANDMANN J, RENNER N, GACHTER A, THIEL G, HARDER F: Cyclosporine A and osteonecrosis of the femoral head. *J Bone Joint Surg* 69(A):1226–1228, 1987
62. NEHME D, RONDEAU E, PAILLARD F, MOREAU J, NUSSAUME O, KANFER A, SRAER J: Aseptic necrosis of bone following renal transplantation: relation with hyperparathyroidism. *Nephrol Dial Transplant* 4:123–128, 1989
63. COTORRUELO J, DE FRANCISCO A, CANGA E, AMADO J, RIANCHO J, DE BONIS E, ZUBIMENDI J, RUIZ J, SANZ DE CASTRO S, ARIAS M: The influence of immunosuppression on the prevalence of aseptic bone necrosis after renal transplantation. *Transplant Proc* 23:2199–2200, 1991
64. MANKIN H: Nontraumatic necrosis of bone. *N Engl J Med* 326:1473–1480, 1992
65. SPENCER J, MAISEY M: A prospective scintigraphic study of avascular necrosis of bone in renal transplant patients. *Clin Orthop* 194:125–135, 1994
66. HOI KOO K, KIM R: Quantifying the extent of osteonecrosis of the femoral head. *J Bone Joint Surg* 77(B):875–880, 1995
67. HOLMAN A, GARDNER G, RICHARDSON M, SIMKIN P: Quantitative magnetic resonance imaging predicts clinical outcome of bone decompression for osteonecrosis of the femoral head. *J Rheumatol* 22:1929–1933, 1995
68. LEARMONTH J, MALOON S, DALL G: Core decompression for early atraumatic osteonecrosis of the femoral head. *J Bone Joint Surg* 72(B):387–390, 1990
69. MONT M, CARBONE J, FAIRBANK A: Core decompression versus nonoperative management for osteonecrosis of the hip. *Clin Orthop* 324:169–178, 1996
70. MARKEL DC, MISKOVSKY C, SCULCO TP, PELLICCI PM, SALVATI EA: Core decompression for osteonecrosis of the femoral head. *Clin Orthop* 323:226–233, 1996
71. DEO S, GIBBONS C, EMERTON M, SIMPSON A: Total hip replacement in renal transplant patients. *J Bone Joint Surg* 77(B):299–302, 1995
72. JULIAN B, LASKOW D, DUBOVSKY J, DUBOVSKY E, CURTIS J, QUARLES D: Rapid loss of vertebral mineral density after renal transplantation. *N Engl J Med* 325:544–550, 1991
73. KWAN J, ALMOND M, EVANS K, CUNNINGHAM J: Changes in total body mineral content and regional bone mineral density in renal patients following renal transplantation. *Miner Electrolyte Metab* 18:166–168, 1992
74. ALMOND M, KWAN J, EVANS K, CUNNINGHAM J: Loss of regional bone mineral density in the first 12 months following renal transplantation. *Nephron* 66:52–57, 1994
75. GROTZ W, MUNDINGER A, GUGEL B, EXNER V, KIRSTE G, SCHOLLMEYER P: Bone fracture and osteodensitometry with dual energy x-ray absorptiometry in kidney transplant recipients. *Transplantation* 58: 912–915, 1994
76. HORBER F, CASEZ J, STEIGER U, CZERNIAK A, MONTANDO A, JAEGER P: Changes in bone mass early after kidney transplantation. *J Bone Miner Res* 9:1–9, 1994
77. BAGNI B, GILLI P, CAVALLINI A, BAGNI I, MARZOLA MC, ORZINCOLO C, WAHNER H: Continuing loss of vertebral mineral density in renal transplant recipients. *Eur J Nucl Med* 21:108–112, 1994
78. GROTZ W, MUNDINGER A, RASENACK J, SPEIDEL L, OLSCHEWSKI M, EXNER V, SCHOLLMEYER P: Bone loss after kidney transplantation: a longitudinal study in 115 graft recipients. *Nephrol Dial Transplant* 10:2096–2100, 1995
79. MASSARI PU, GARAY G, ULLA MR: Bone mineral content in cyclosporine-treated renal transplant patients. *Transplant Proc* 26: 2646–2648, 1994
80. GROTZ W, MUNDINGER A, GUGEL B, EXNER V, KIRSTE G, SCHOLLMEYER P: Bone mineral density after kidney transplantation. *Transplantation* 59:982–986, 1995
81. WOLPAW T, DEAL C, FLEMING-BROOKS S, BARTUCCI M, SCHULAK J, HRICIK D: Factors influencing vertebral bone density after renal transplantation. *Transplantation* 58:1186–1189, 1994
82. MATKOVIC V, JELIC T, WARDLAW G, ILICH J, GOEL P, WRIGHT J, ANDON M, SMITH K, HEANEY R: Timing of peak bone mass in caucasian females and its implication for the prevention of osteoporosis. *J Clin Invest* 93:799–808, 1994
83. TORREGROSA J, CAMPISTOL J, MONTESINOS M, PONS F, MARTINEZ DE OSABA M: Evolution of bone mineral density after renal transplantation: related factors. *Nephrol Dial Transplant* 10(suppl 6):111–113, 1995
84. MCINTYRE H, MENZIESS B, RIGBY R, PERRY-KEENE D, HAWLEY C, HARDIE I: Long-term bone loss after renal transplantation: comparison of immunosuppressive regimens. *Clin Transplant* 9: 20–24, 1995
85. TORRES A, MACHADO M, CONCEPCIÓN M, MARTIN N, LORENZO V, HERNÁNDEZ D, RODRIGUEZ AP, RODRIGUEZ A: Influence of vitamin D receptor genotype on bone mass changes after renal transplantation. *Kidney Int* 50:1726–1733, 1996
86. SEEMAN E, WAHNER W, OFFORD K, KUMAR R, JOHNSON W, RIGGS B: Differential effects of endocrine dysfunction on the axial and the appendicular skeleton. *J Clin Invest* 69:1302–1309, 1982
87. VELASQUEZ-FORERO F, MONDRAGÓN A, HERRERO B, PEÑA J: Adynamic bone lesion in renal transplant recipients with normal renal function. *Nephrol Dial Transplant* 11(suppl 3):58–64, 1996
88. SHERRARD D, KOPP J, MALONEY N: Bone histologic findings relate to renal transplant bone disease (*abstract*). *J Am Soc Nephrol* 3:881, 1992
89. LUKERT B, RAISZ L: Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 112:352–364, 1990
90. SAITO J, DAVIS J, WASNICH R, ROSS P: Users of low-dose glucocorticoids have increased bone loss rates: a longitudinal study. *Calcif Tissue Int* 57:115–119, 1995
91. ZELISSEN P, CROUGHS R, VAN RIJK P: Effect of glucocorticoid replacement therapy on bone mineral density in patients with Addison's disease. *Ann Intern Med* 120:207–210, 1994
92. MORA S, SAGGION F, RUSSO G, WEBER G, BELLINI A, PRINSTER C, CHIUMELLO G: Bone density in young patients with congenital adrenal hyperplasia. *Bone* 18:337–340, 1996
93. MANOLAGAS SC, JILKA RL: Bone marrow, cytokines, and bone remodeling. *N Engl J Med* 332:305–311, 1995
94. GOLDRING S, GOLDRING M: Cytokines and skeletal physiology. *Clin Orthop* 324:13–23, 1996
95. LANGUB M, KOSZEWSKI N, TURNER H, MONIER FAUGERE MC, GENG Z, MALLUCHE H: Bone resorption and mRNA expression of IL-6 and IL-6 receptor in patients with renal osteodystrophy. *Kidney Int* 50:515–520, 1996
96. ZHOU H, CHOONG P, CHOU S, KARTSOGIANNIS V, MARTIN T, NG K: Transforming growth factor beta 1 stimulates bone formation and resorption in an in-vivo model in rabbits. *Bone* 17(suppl):443S–448S, 1995
97. DALLMAN M, MORRIS P: Immunology of rejection, in *Kidney Transplantation* (4th ed), edited by MORRIS P, Philadelphia, Saunders, 1994, p 8
98. EPSTEIN S: Post-transplantation bone disease: the role of immunosuppressive agents and the skeleton. *J Bone Miner Res* 11:1–7, 1996
99. DUMOULIN G, HORY B, NGUYEN NU, HENRIET MT, BRESSON C, REGNARD J, SAINT HILLIER Y: Lack of evidence that cyclosporine treatment impairs calcium phosphorus homeostasis and bone remodeling in normocalcemic long-term renal transplant recipients. *Transplantation* 59:1690–1694, 1995
100. MURAOKA D, FUJIMOTO K, SUN X, YOSHIOKA K, SHIMIZU K, YAGI M, BOSE H JR, MIYAZAKI I, YAMAMOTO K: Immunosuppressant FK506 induces interleukin-6 production through the activation of transcription factor nuclear factor (NF)-κB. *J Clin Invest* 97:2433–2439, 1996
101. GREENFIELD E, SHAW S, GORNIK S, BANKS M: Adenyl cyclase and interleukin 6 are downstream effectors of parathyroid hormone resulting in stimulation of bone resorption. *J Clin Invest* 96:1238–1244, 1995

102. HAMM L: Renal handling of citrate. *Kidney Int* 38:728–735, 1990
103. HARRIS W, BERTHON G, DAY J, EXLY C, FLATEN T, FORBES W, KISS T, ORVING C, ZATTA P: Speciation of aluminum in biological systems. *J Toxicol Environ Health* 48:543–568, 1996
104. VRTOVSNIK F, JOURDAIN M, CHERQUI G, LEFEBVRE J, FRIEDLANDER G: Glucocorticoid inhibition of Na-Pi contransport in renal epithelial cells is mediated by protein kinase C. *J Biol Chem* 269:8872–8877, 1994
105. MONTEIRO J, DE CASTRO I, SEGURO A: Hypophosphatemia induced by acyclovir. *Transplantation* 55:680–682, 1993
106. HEBERT S: Nephrology Forum: Extracellular calcium-sensing receptor: Implications for calcium and magnesium handling in the kidney. *Kidney Int* 50:2129–2139, 1996
107. SLATOPOLSKY E: Nephrology Forum: The interaction of parathyroid hormone and aluminum in renal osteodystrophy. *Kidney Int* 31:842–854, 1987
108. CVETKOVIC M, MANN G, ROMERO D, LIANG X, YANFEI M, WEBSTER J, EPSTEIN S: The deleterious effects of long-term cyclosporine A, cyclosporine G, and FK 506 on bone mineral metabolism in vivo. *Transplantation* 57:1231–1237, 1994
109. MEYS E, FONTANGES E, FOURCADE N, THOMASSON A, POUYET M, DELMAS P: Bone loss after orthotopic liver transplantation. *Am J Med* 97:445–450, 1994
110. ROZENBERG S, OBERLIN F, DORENT R, KOEGER A, FRIH L, GANDJBACKCH I, BOURGEOIS P: Study of bone mineral density after cardiac transplantation. *Transplant Proc* 27:1692–1693, 1995
111. ALMOND MK, FAN S, BALL E, EVANS K, CUNNINGHAM J: Randomized prospective study demonstrating prevention of bone loss by pamidronate during the first year after renal transplantation (*abstract*). *J Am Soc Nephrol* 7:1789, 1996