Abnormal Bone and Mineral Metabolism in Kidney Transplant Patients – A Review

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Key Words

Kidney transplant · Hyperparathyroidism, secondary · Mineral metabolism · Bone disease, post-transplant

Abstract

Background/Aims: Abnormal bone and mineral metabolism is common in patients with kidney failure and often persists after successful kidney transplant. **Methods:** To better understand the natural history of this disease in transplant patients, we reviewed the literature by searching MEDLINE for English language articles published between January 1990 and October 2006 that contained Medical Subject Headings and key words related to secondary or persistent hyperparathyroidism and kidney transplant. **Results:** Parathyroid hormone levels decreased significantly during the first 3 months after transplant but typically stabilized at elevated values after 1 year. Calcium tended to increase after transplant and then stabilize at the higher end of the normal range within 2 months. Phosphorus decreased rapidly to within or below normal levels after surgery and hypophosphatemia, if present, resolved within 2 months. Low levels of 1,25(OH)₂ vitamin D typically did not reach normal values

until almost 18 months after transplant. **Conclusion:** This review provides evidence demonstrating that abnormal bone and mineral metabolism exists in patients after kidney transplant and suggests the need for treatment of this condition. However, better observational and interventional research is needed before advocating such a treatment guideline.

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Introduction

Over the past 15 years the number of kidney transplants in the United States has steadily increased, with 14,519 transplants performed annually between 2000 and 2002 [1]. Along with the increase in the number of procedures, patient survival has progressively improved; 1-year survival is now over 90% [2] and transplantation is viewed as a life-saving and reliable treatment for patients with end-stage kidney disease. As patient survival has improved, focus has moved towards reducing patient morbidity and improving quality of life and long-term outcomes.

Secondary hyperparathyroidism (HPT) is present in all facets of chronic kidney disease (CKD). Prior to initiating maintenance dialysis, parathyroid hormone (PTH) levels increase with declining levels of kidney function [3]. In dialysis patients, elevated PTH, calcium (Ca), and

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phosphorus levels are associated with greater morbidity and mortality, and correcting these biochemical markers may improve outcomes in CKD patients [4, 5]. However, even after an otherwise successful kidney transplantation, this condition does not always resolve, although its prevalence, progression, and relationships with patient outcomes are not as well studied [6, 7]. The role of PTH variations is generally understood in the context of bone disease [8]. In kidney transplant patients, the etiology of bone disease is complex reflecting a combination of factors that are associated with renal osteodystrophy in earlier CKD stages and dialysis, as well as the factors unique to the post-transplant stage including immunosuppressive therapy, hormonal disturbances, and insufficient graft functioning [6].

We performed a review of the literature to provide a general overview of the natural history and prevalence of HPT in kidney transplant patients. The current nomenclature of CKD-mineral and bone disorder (CKD-MBD) is based upon the evaluation of three dimensions including: (a) laboratory abnormalities of calcium, phosphate, PTH, alkaline phosphatase, or vitamin D metabolism; (b) bone disease – abnormalities in bone turnover, mineralization, volume, linear growth, or strength, and (c) calcification of vascular or other soft tissue [8]. While all of these components are critical for the full characterization of CKD-MBD, the focus of this review is on the key biochemical components.

A better understanding of the epidemiology of HPT and its role in the clinical course of kidney transplant patients may help optimize treatment for these patients and improve their clinical outcomes.

Methods

Search Strategy

We reviewed the published literature to identify studies evaluating HPT in kidney transplant patients. Relevant publications were identified by searching MEDLINE for English language articles published from January 1990 to October 2006. The search incorporated Medical Subject Headings and key words related to HPT, including hyperparathyroidism, parathyroid hormone, PTH, phosphorus, hyperphosphatemia, calcium, and hypercalcemia, as well as terms related to kidney transplant including kidney transplant and kidney allograft. Additional articles were identified by reviewing bibliographies of reviews and accepted articles as well as articles identified by experts in the field.

Inclusion Criteria

The study population included adult patients (≥ 18 years of age) who had undergone kidney transplantation. Studies assessing patients with multiple organ transplants were excluded. Inter-

ventional and observational studies were included if detail on the severity or temporal assessment of HPT-associated biochemical measures, which included PTH, Ca, phosphorus, and $1,25(\text{OH})_2$ vitamin D, were provided. Articles reporting transplant-related outcomes were excluded if markers for HPT were not assessed. Also, studies were excluded if the study population was restricted by one of the key biochemical markers (e.g., only patients with normal post-transplant PTH were accepted) or if the study sample size was ≤ 30 . However, studies with a population size ≤ 30 were included for assessing biochemical measures immediately (1–14 days) after kidney transplant since studies with larger populations were not identified. Studies evaluating treatment of HPT were not included. Finally, case reports and review articles were excluded.

Data Abstraction

A standardized abstraction form was used to collect data describing population characteristics, sample size, and biochemical markers. A second reviewer independently validated abstracted data. Units of measure were converted between metric and SI units based on conversion factors supplied by the National Kidney Foundation [9]. Mean biochemical marker values were pooled by averaging results from each study.

Results

Literature Review

Our search strategy returned 557 articles. After applying inclusion criteria to article abstracts, 424 articles were eliminated and 133 submitted for full article review. Based on our inclusion criteria, 38 publications reporting data on the natural progression of HPT in kidney transplant patients and associated outcomes were accepted. Analyses were based on data from 2,486 patients enrolled in 38 studies.

Biochemical Markers of CKD-MBD

Parathyroid Hormone

PTH levels were consistently below pre-transplant (month = 0) levels 6 months after surgery with reported decreases between 19 and 71% (median 54%; $n = 10$ studies; 380 subjects) [10–19]. PTH levels immediately (≤ 2 weeks) after surgery, however, were variable with 2 studies reporting decreases [11, 17] and 2 reporting increases [10, 13]. The effect of kidney transplant on PTH levels occurred primarily during the first 6 months and only minimal changes were noted after this point. Between post-transplant months 6 and 12, additional decreases in PTH were reported in 3 studies (range 8–27%; median 16%; 192 subjects) [14, 16, 20] and increases noted in 6 (range 5–38%; median 8.7%; 212 subjects) [11, 12, 17–19, 21]. Two studies reported PTH levels between post-transplant

Fig. 1. Percent change in PTH levels for various short- and long-term time intervals after transplant. Changes in PTH were based on the PTH level during the first time point of the range. Each data point represents results from a single study at that time interval. The number of studies represented in each time interval is indicated in parentheses; a single study can be represented in multiple time intervals.

months 12 and 24; both studies noted minimal change (<3%) [12, 21]. Figure 1 summarizes the changes in PTH levels for various post-transplant time periods. PTH levels were generally reported as mean versus median values, the latter would better represent the skewed distribution of PTH levels.

Although PTH levels tended to decrease after kidney transplant surgery [12–15, 17–20], PTH levels remained elevated in a subset of patients. At time points greater than 2 years after transplant, >50% of patients still had elevated PTH levels [22–24] and this trend continued more than 5 years after surgery [22, 25]. At time points greater than 5 years, only 1 study reported fewer than 50% of their patients (27.4%) with elevated PTH values [26]. The definition of normal PTH values varied among studies.

Of note is that kidney function did not return to normal in all transplant patients and when post-transplant patients were stratified by kidney function, PTH levels were significantly higher in the group with worse kidney function [21, 22].

Calcium

Ca levels exhibited a transient decrease from pre-transplant (week = 0) levels immediately (≤ 2 weeks) after surgery [11, 17], followed by an increase between post-transplant weeks 2 and 26 [11, 17, 20, 27]. Six months after surgery Ca levels stabilized and levels varied less than 5% between post-transplant months 6 and 12 (range –5.0 to

1.3; median –1.6; n = 7 studies; 418 subjects) [11, 12, 16–21, 28] and less than 2% between months 12 and 24 [12, 21]. Figure 2 summarizes changes in Ca levels for various post-transplant time periods.

In general, Ca levels stabilized at the higher end of the normal range for non-dialysis patients (10.4 mg/dl; 2.6 mmol/l) although elevated Ca levels were still observed 12 months after surgery [12, 18–21, 28]. The percent of patients with high Ca tended to decrease after kidney transplant although elevated Ca levels persisted in a subset of patients. At time points greater than 2 years (median 53.6 months) depending on the study (n = 5), between 1.4 and 47% of patients (median 10.0% of patients) had elevated Ca levels [21–23, 25, 29]. The normal Ca range varied among studies.

Stratification of patients by either S-Cr or CrCl did not reveal a difference in Ca levels [21, 30, 31]. Ca levels were measured between 2 and 47 months after transplant. However, one study reported that S-Cr in patients categorized with either high (mean 10.72 mg/dl; 2.68 mmol/l), or low (mean 9.72 mg/dl; 2.43 mmol/l) calcium 12 months after kidney transplant, SrCr was significantly higher in the high calcium group [36].

Phosphate

Phosphate levels, which were elevated prior to surgery, decreased rapidly after transplantation falling to within or below the normal range for patients with normal kidney function (range 2.43–4.13 mg/dl; 0.78–1.32 mmol/l)

Fig. 2. Percent change in Ca levels for various short- and long-term time intervals after transplant. Changes in Ca were based on the Ca level during the first time point of the range. Each data point represents results from a single study at that time interval. The number of studies represented in each time interval is indicated in parentheses; a single study can be represented in multiple time intervals.

Fig. 3. Percent change in phosphorus levels for various short and long-term time intervals post-transplant. Changes in phosphorus were based on the phosphorus level during the first time point of the range. Each data point represents results from a single study at that time interval. The number of studies represented in each time interval is indicated in parentheses; a single study can be represented in multiple time intervals.

in the first postoperative month [11, 12, 17, 27]. The hypophosphatemia was transient, and within 3 months all reported that the increased post-surgery mean phosphorus levels were within the normal range [11, 12, 19-21, 27].

Phosphate levels were stable 6 months after surgery; only 2 of 8 studies assessing phosphorus levels between post-transplant months 6 and 12 reported changes in

phosphorus greater than 10% (range -1.0 to 18.1; median 7.3%; n = 8 studies; 382 subjects) [11, 12, 16-21] and only minimal changes (-1%) were reported between 12 and 24 months [12, 21]. Figure 3 shows changes in phosphorus levels at various post-transplant time periods.

Although mean phosphorus levels were within normal limits by the end of the 2nd month after transplant, hypophosphatemia was still observed in between 1.6 and

Fig. 4. Average percent of patients with a diagnosis of low BMD from various studies. If more than 1 data point was reported in a study for a specific site of diagnosis, the rates were averaged and represented as a single data point in the summary figure. Osteoporosis diagnoses were based on WHO definitions of T score <-2.5 . n = Number of studies reporting the percentage of subjects with osteoporosis.

39% of patients 6 months after transplant [12, 17, 25]. Definitions of a normal phosphorus range also varied across studies.

Phosphorus levels in kidney transplant patients were not dependent on kidney function as assessed by stratification of patients by S-Cr or CrCl [21, 30–32]. Phosphorus levels were measured between 2 and 47 months after transplant.

1,25(OH)₂ Vitamin D

Baseline 1,25(OH)₂ vitamin D tended to fall outside and below the normal range (range 33.3–83.3 pg/ml; 80–200 pmol/l), and then increased slowly after surgery to within normal limits by month 12 [12, 16, 18, 21]. In one study, low 1,25(OH)₂ vitamin D levels were reported in 48% of patients 6 months after transplantation [12] and this trend persisted as evidenced by a second study which reported low 1,25(OH)₂ vitamin D levels in 25% of the study population more than 5 years later (mean time after transplant 84.4 months) [33].

Outcomes in Kidney Transplant Patients

Cardiovascular outcomes in kidney transplant patients were infrequently reported in the context of HPT. In one study, the association between PTH and cardiovascular risk was indirectly assessed by evaluating the relationship between PTH and common carotid intima

media thickness (CC IMT) [19]. In kidney transplant patients CC IMT was increased and as post-transplantation PTH levels declined significant reductions in CC IMT were noted at 6 and 12 months. PTH levels were shown to be significantly and independently associated with CC IMT, while graft function, Ca, and phosphorus did not show an association. A second study looked at rates of hypertension in post-transplant patients. Stratifying patients by PTH levels ($>$ or <80 pg/ml, 8.8 pmol/l) did not differentially impact rates of hypertension [14].

Low bone mineral density (BMD; T score <-2.5) was frequently diagnosed in kidney transplant patients [24, 25, 34–41]. Averaging all data, the percent of patients with low BMD from primarily cortical bone sites was greater than that from primarily trabecular bone sites (fig. 4). However, stratifying study results by time after transplant and body site reveals differences for lumbar spine, but not femoral neck. In these studies, the average percent of patients diagnosed with low BMD within the first 6 years after transplant at the lumbar spine was 35%, but only 22% after 6 years. In a more cortical site, the femoral neck, 21% of patients were diagnosed with low BMD during the first 6 years after transplant, and 22% after 6 years.

Temporal changes in BMD for femoral neck and lumbar spine were similar across studies assessing BMD over multiple time points [12, 15, 18, 20, 22, 39]. In general, BMD decreased in both the femoral neck and lumbar spine the first 3 months after transplant. By month 6, BMD measurements in these regions were relatively stable and by month 9 some studies reported modest increases [20, 39]. In one study with longer follow-up (47–71 months), no changes were reported in lumbar spine BMD [31].

Elevated PTH levels negatively impacted BMD-related outcomes in kidney transplant patients. Patients with higher post-transplant PTH levels tended to have significantly greater BMD loss than patients with lower post-transplant PTH levels [27, 31, 42] although one study reported no difference [14]. While most studies found a significant correlation between BMD and PTH [23, 24, 27, 28, 33, 38], this correlation was not documented by all authors [18, 25, 40, 43]. The relationship between post-transplant PTH and BMD loss appears to be site- [27, 28] and gender-specific [27]. The association between baseline PTH levels and BMD loss appears to be site-specific [20, 28], time-dependent (i.e. post-transplant) [20] and gender-specific [28].

Length of dialysis was not associated with the severity of BMD loss in kidney transplant patients [15, 20, 28, 33,

39, 43–45], although one study reported a significant correlation between T scores and dialysis duration for the femoral neck and radius but not the spine [37]. Similarly, kidney function in kidney transplant patients was not associated with BMD [25, 30, 31, 33, 39, 40, 44, 45].

Discussion

This review summarizes the natural history of HPT in kidney transplant patients and describes the association between biochemical markers of persistent HPT and BMD loss. The totality of published results suggests that HPT is a continuing issue in transplant patients.

The biochemical markers of HPT demonstrated distinct patterns during the initial period after kidney transplant. PTH levels decreased significantly during the first 3 months after transplant but tended to stabilize at elevated levels after 1 year. Low Ca levels tended to increase after transplant and stabilize at the higher end of the normal range within 6 months. Phosphate decreased rapidly after transplant to within or below normal levels but tended to resolve within 2 months; elevated PTH likely contributes to hypophosphatemia, especially in patients with a restored glomerular filtration rate. Disturbances in 1,25(OH)₂ vitamin D persisted longer and, in general, levels did not reach normal until almost 12 months after transplant.

In longer-term studies of transplant patients, disturbances in mineral metabolism persisted in a subset of patients. In particular, elevated PTH levels were seen in over 50% of the study population 2 years after transplantation. Ca levels also remained elevated but in a smaller percentage of patients (range 1.4–47%). Similarly, low levels of phosphate and 1,25(OH)₂ vitamin D persisted in some patients 6 months and more than 5 years, respectively, after transplant.

Although not assessed in this review, an important question to pose is whether treating HPT in kidney transplant patients would improve patient outcomes, similar to improvements in morbidity and mortality associated with the treatment of HPT in dialysis patients [4, 5]. However, observational and interventional studies are limited in transplant patients, especially with respect to clinical outcomes. From the studies we reviewed, one study suggested that elevated levels of PTH negatively impacted CC IMT while a second study failed to demonstrate a differential effect of PTH levels on rates of hypertension.

Elevated PTH levels were associated with loss of bone in kidney transplant patients. Low BMD (T score <–2.5),

however, was frequently diagnosed in kidney transplant patients and has been associated with significant morbidity in these patients [31]. While most studies found a significant correlation between BMD and post-transplant PTH levels, this correlation was not documented by all authors. This inconsistency might be explained by the apparent site-specific [27, 28] and gender-specific [27] nature of this relationship.

Studies of treatments for HPT were excluded from our review. A recent Cochrane review of controlled trials suggested that treating these patients may result in improved BMD, but showed no improvement in the risk of fractures [46]. Specifically, bisphosphonates, vitamin D compounds and calcitonin all had statistically significant effects on BMD of the lumbar spine, and bisphosphonates and vitamin D compounds each had a statistically significant effect on the BMD of the femoral neck. One bisphosphonate study showed a reduction in the risk of graft rejection. The authors concluded that ‘no benefit from any intervention known to reduce risk of fracture from bone disease could be demonstrated to reduce fracture incidence in kidney transplant recipients’.

While this review did not focus on clinical trials of treatments, nonetheless, our search identified non-randomized treatment studies excluded from the Cochrane review. These treatments included parathyroidectomy, vitamin D, and cinacalcet hydrochloride [47–58]. In general, while these treatments were associated with some improvement in laboratory values, the lack of control groups makes inferences about efficacy difficult. The beneficial effects of parathyroidectomy tended to be countered by a decline in kidney function [48, 53]. Controlled studies of these treatments, or others, may provide additional insight into the morbidity and mortality associated with persistent HPT in the kidney transplant population.

There are limitations to this review. This review is limited by the study design of the accepted studies which were cross-sectional and thus lacked adequate controls and rigor for critical assessment. Other variables such as immunosuppressant use, steroid dose, and co-morbid conditions that can affect clinical outcomes independent of HPT were not reviewed. Also, our assessment was limited to variables impacting outcomes associated with HPT.

Additionally, the studies examined were markedly heterogeneous in terms of their design and patient population, which made it difficult to form strong conclusions. Variable patient characteristics included, among other variables, the percent of postmenopausal women, parathyroidectomy, diabetes, time since transplantation, and dialysis vintage. Study protocols varied on exclusion criteria

for the use of co-medications both before and after transplant. Thus, the varying use of medications may have affected bone metabolism. The date of transplant also varied with some studies including transplants occurring as far back as 1973 in their analysis. The date of transplant is associated with the immunosuppressive regimen that was used which has important effects on outcomes.

Laboratory methodologies of the biochemical markers also varied. PTH levels have been shown to be assay-dependent [59]. Ca levels were not consistently reported (some studies measured total Ca, others ionized, and some reported adjusted) making comparisons between studies difficult. Comparisons between studies, and even within studies, for 1,25(OH)₂ vitamin D were difficult since few studies controlled for seasonal variations in this marker.

Conclusion

HPT, which develops during chronic kidney failure, often persists after kidney transplantation. While elevated PTH and Ca levels associated with this disorder have been associated with adverse effects on various outcomes in dialysis patients, observational and interventional studies are limited in transplant patients, especially with respect to clinical outcomes. Treating HPT in kidney transplant patients may have the potential of improving patient outcomes, but more research is needed in these patients to better assess long-term treatment benefits on clinical outcomes.

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