Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation

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Background. Bisphosphonates can prevent bone mineral density loss after renal transplantation, but their effect on trabecular mineralization and bone morphology, two key factors of bone stability, remains unknown.

Methods. In a 6-month, randomized, placebo-controlled study, 20 kidney transplant recipients received either 4 mg zoledronic acid or placebo twice within 3 months after engraftment. At transplantation and after 6 months, mean trabecular calcium concentration and trabecular morphometry were measured in bone biopsies. Bone mineral density (BMD) of the femoral neck and the lumbar spine were evaluated by dual-energy x-ray absorptiometry, and serum biochemical markers of bone metabolism were determined monthly.

Results. Trabecular calcium content increased significantly in the zoledronic acid group, but remained unchanged in the placebo group. BMD at femoral neck showed no change in the zoledronic acid group, but decreased in the placebo group. BMD of the lumbar spine was increased in the zoledronic acid group without change in the placebo group. High-turnover bone disease resolved similarly in both groups, as evidenced by a significant decrease of eroded bone surface, osteoclast and osteoblast surface. Serologic markers of bone formation and resorption were significantly lower in zoledronic acid-treated patients throughout the study. Kidney transplant function was stable after zoledronic acid therapy.

Conclusions. Our results show that administration of zoledronic acid improves the calcium content of cancellous bone after kidney transplantation. The beneficial effect of bisphosphonate therapy is further evidenced by an increase of lumbar spine BMD, and stabilization of femur BMD.

Renal transplantation is the treatment of choice for end-stage renal failure. However, post-transplant osteodystrophy is a major problem, especially in the first months after transplantation, because about 10% of bone density is lost during this period [1]. The bone disease is multifactorial and resembles a mixture of pathophysiologically different entities. Pre-existing causes of osteodystrophy are secondary hyperparathyroidism, vitamin D metabolic disorders, parathyroid hormone resistance of bone cells, patient immobility, hypogonadism, amyloidosis, or aluminum toxicity [2]. Furthermore, steroid or immunosuppressive treatment of underlying renal disease, and long-term use of loop diuretics contribute to bone loss [3]. In addition, the main cause of terminal renal failure is diabetic nephropathy, and diabetes itself causes osteoporosis [4]. Some of these factors cease after successful renal transplantation, but new, and even worse, causes of osteodystrophy arise. Among these are high steroid doses in the immediate post-transplant period, calcineurin antagonist type of immunosuppression, renal tubular impairment of calcium and phosphorus reabsorption, and the aggravation of the metabolic disturbances in diabetic patients.

Early, as well as late, post-transplant bone loss has been studied thoroughly by densitometry and bone morphometry in children and adults [5, 6]. Changes in bone architecture, however, have been investigated only in two small studies. Julian et al [1] reported sequential changes in bone morphology in 20 young patients without diabetes and major comorbidity, and more than one half of these patients had been transplanted preemptively. Even in this best-case scenario, histomorphometry revealed an imbalance in bone remodeling caused by a decreased rate of bone formation and prolonged formation periods [1]. Briner et al [7] investigated the bone-sparing effect of a low-dose steroid regimen in 20 patients
with sequential transiliac crest biopsies and found an increase in cancellous bone volume, but no resolution of metabolic bone abnormalities 2 years after transplantation.

Several investigators conducted prospective treatment studies in patients with post-transplant osteodystrophy, but used only densitometry or biochemical markers of bone turnover as a treatment outcome variable. Densitometry and biochemical markers, however, are not suitable to uncover morphologic-architectural changes and are only of moderate value to discriminate between the various causes of renal osteodystrophy and to define patients at risk for fractures [8–10]. Therefore, more sensitive methods of bone mineralization and bone architecture measurements such as bone mineralization density distribution measurement (BMDD) (i.e., the degree of trabecular calcium content in a given bone specimen and bone morphometry) are necessary to guide therapeutic intervention and evaluate treatment success. The diverse pathophysiologic entities of the skeletal changes allow discrimination between morphologically distinctly different types of renal osteodystrophies [8, 11]. The mineralization density and distribution can be evaluated on bone biopsy specimen by quantitative backscattered electron imaging, a method that has been proved to be sensitive in the detection of small changes in the mineralization pattern due to bisphosphonate treatment of patients and in animal studies [12–14]. Furthermore, BMDD allows discrimination between changes in bone volume and the degree of mineralization, which is not possible with conventional x-ray densitometry. Hence, it is possible that x-ray densitometry reveals high bone mass in regions of reduced bone matrix mineralization and thus impaired mechanical stability.

The new bisphosphonate zoledronic acid (Zometa®, Novartis, Basel, Switzerland) potently inhibits osteoclastic bone resorption and has been shown to prevent osteoporosis associated with estrogen deficiency, and halt progression of osteolysis [15–17]. Zoledronic acid has not been investigated for corticosteroid-induced osteoporosis, but convincing data are available for other bisphosphonates, such as etidronate [18]. Besides the reduction of bone turnover, zoledronic acid has been shown to directly decrease type II collagen degradation in patients with Paget’s disease [19]. Zoledronic acid is two to three orders of magnitude more potent than pamidronate in bone resorption assays, but showed a threefold greater renal tolerability [20, 21].

So far, no controlled study on the effect of bisphosphonate therapy on bone morphology and mineralization density distribution for the prevention of post-transplant osteopathy exists.

METHODS

Patients

We consecutively recruited 28 adult hemodialysis patients, who received their first or second cadaveric renal allograft. Patients were enrolled independently of the cause of renal failure, time on renal replacement therapy, or bone disease. Hemodialysis was performed in all patients according to the Dialysis Outcome Quality Initiative (DOQI) guidelines [22]. Out of the 28 patients enrolled, 24 received 0.25 to 0.5 μg 1,25 (OH)₂ vitamin D₃ per day. Patients who had had previous or current treatment with either calcitonin or bisphosphonates, or with hypocalcemia, were excluded from the study.

Procedures

The study protocol was approved by the Institutional Review Board and each patient provided informed consent. Twenty of the 28 enrolled patients, who met the inclusion criteria of serum creatinine below 2 mg/dL within 2 weeks after transplantation, and a representative bone biopsy core obtained during the transplant procedure, were randomly assigned to an intravenous infusion of 4 mg zoledronic acid or placebo in 250 mL saline over 15 minutes. Eight of the 28 patients did not meet the study inclusion criteria. Two patients died within the first week after transplantation due to cardiac arrest, four patients had a serum creatinine above 2 mg/dL 2 weeks after transplantation, the bone biopsy specimen was not adequate in one patient, and one patient withdrew consent before the first zoledronic acid/placebo infusion.

A second infusion at the same dose was administered 3 months later. Therapy and randomization were supplied by Novartis (Basel, Switzerland). All patients received 1000 mg of daily calcium citrate, but no vitamin D supplementation (Maxi-Kalz®, Asta Medica, Vienna, Austria). The immunosuppressive regimen consisted of methylprednisolone, mycophenolate mofetil, and cyclosporine. Two patients in the placebo group and one patient in the zoledronic acid group received tacrolimus instead of cyclosporine.

Bone histology and histomorphometry were performed on transcortical bone biopsies obtained from the iliac crest during and 6 months after kidney transplantation as described by Bordier, Miravet, and Hioco [23], using the Meunier Bone Biopsy device (luminal diameter 7 mm = 0.28 inch; Groupe Lépine, Lyon, France). Due to the design of the study (cadaver kidney transplantation), the time point of transplantation was unknown and, thus, tetracycline labeling was not feasible. The specimens were then undecalcified embedded in plastic and cut into 5 μm thick sections. After standard staining, histologic analysis was performed by one pathologist (G.D.), who was blinded for the clinical and biochemical
status, as well as the randomization group of the patients. Renal osteodystrophy was classified according the Del-ling criteria, as reported previously [11]. By these criteria three different groups of renal osteodystrophy are identi-fied (types I, II, and III). If compared to the classification of Malluche and Faugere [24], renal osteodystrophy type II would equal osteomalacic low-turnover bone disease and renal osteodystrophy type III would equal predominant hyperparathyroid, or high-turnover bone disease. Mixed uremic osteodystrophy would spread over both groups depending of whether osteoidosis (renal osteo-dystrophy type II) or osteoidosis and fibroosteoclasia (renal osteodystrophy type III) predominates. Renal os-teodystrophy type I is mainly characterized by fibro-os-teoclasia and bone marrow fibrosis and was not present in any of our patients. Three-dimensional morphometric analysis was carried out as described previously [11]. According to Parfitt et al [25], the following parameters were evaluated: trabecular bone volume and osteoid volume, both expressed as the percentage of tissue volume; osteoid surface, expressed as the percentage of trabecu-lar bone surface; osteoblast surface; expressed as the osteoid surface covered with osteoblasts, and as percent-age of trabecular bone surface; osteoclast surface, ex-pressed as the osteoid surface covered with osteoclasts, and as the percentage of trabecular bone surface; and eroded surface, expressed as percentage of trabecular bone surface.

Measurements of BMDD were performed using a quantitative backscattered electron imaging method described previously [12, 14]. This method is based on the phenomenon that the backscattering coefficient of the electrons is dependent on the atomic number of the target material. In the case of bone tissue the backscattered electron signal is directly proportional to the mineral content (calcium content) of the tissue. BMDD was quantified by the BMDD-parameter Ca_{mean}, describing the weighted mean calcium (Ca) concentration of the imaged bone area. The full width at half maximum of the peak is a measure of the homogeneity of the distribution. All measurements were blinded for quantitated backscattered electron imaging, histomorphometric, and biochemical analysis.

Bone mineral density measurements (BMD) were performed with dual-energy x-ray absorptiometry and a QDR-4500 scanner (Hologic, Waltham, MA, USA), using the manufacturer’s recommended standard procedures for the posteroanterior lumbar spine at L1-L4, and for the proximal femur at the femoral neck, trochanter, intertrochanteric region, total region, and Ward’s triangle. The projectional BMD values were given in grams per centimeter squared, and the individual patient’s results were expressed as z scores and t scores. The diagnostic bone-mass threshold for defining osteoporosis in individu-als without fractures was set at a t score less than −2.5.

Blood samples for biochemical bone markers were drawn immediately before transplantation and monthly during follow up in all twenty patients. Bone alkaline-phosphatase was measured by immunosorbent enzyme-linked assay (ELISA), osteocalcin, intact parathyroid (iPTH) and type I collagen peptides (crosslaps) by elec-tro-chemiluminescence and 1,25(OH)2 D3 by a radio-immuno assay.

Statistical analysis

All results are expressed as mean ± SE or median and range when appropriate. Sample size calculation revealed a minimum of 10 patients in each group to detect a >2% difference in mean BMDD giving an α of <0.05 and β = 0.8. We estimated that 80% of patients would meet the inclusion criteria and post-randomization discontinuation rate would be 10%.

Either the two-tailed Student t test for paired data or the non-parametric Wilcoxon sign rank test was used for differences in the same group at different time points. The Student t test for unpaired data or the Mann-Whitney U test were used for differences between the groups. Bonferroni-Holm correction was used for multiple comparisons. To evaluate the difference in trabecular calcium concentration between the zoledronic acid and placebo group at 6 months, a multiple linear regression model adjusted for baseline differences was used. A P value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics were similar in both treatment groups, with the exception of BMDD and osteoclast surface. Six patients withdrew their consent for a second biopsy, thus only 14 bone biopsies were performed at the end of the study. One of the second bone biopsy specimens contained mainly callous bone, possibly after a foregoing microtrauma and was not suited for further analysis. In summary, a total of seven (pre- and post-) specimens were available from the zoledronic acid group, and six (pre- and post-) specimens from the placebo group. Therefore, baseline and 6 months’ data on bone morphology and BMDD are given only for these 13 patients. The cumulative dose of methylprednisolone in the first 6 months after transplantation averaged 2.9 ± 0.4 g in the 10 placebo patients and 3.0 ± 0.8 g in the 10 zoledronic acid-treated patients. In the six placebo and seven zoledronic acid patients with complete bone biopsy studies, the methylprednisolone doses were 2.4 ± 0.7 and 2.7 ± 0.6 g respectively.

Distribution of renal osteodystrophy was similar in both groups at baseline (Table 1). Histomorphologic fea-tures of high-turnover bone disease diminished within 6 months after transplantation as evidenced by a signifi-cant decline of eroded surface, osteoblast surface, and
Table 1. Patients characteristics at baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo (All patients)</th>
<th>Placebo (With two bone biopsies)</th>
<th>Zoledronic acid (All patients)</th>
<th>Zoledronic acid (With two bone biopsies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SE)</td>
<td>49 (16)</td>
<td>54 (5)</td>
<td>55 (18)</td>
<td>58 (3)</td>
</tr>
<tr>
<td>Sex f/m</td>
<td>4/6</td>
<td>3/3</td>
<td>4/6</td>
<td>1/6</td>
</tr>
<tr>
<td>Kidney disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>1</td>
<td></td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td></td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Focal-segmental glomerulosclerosis</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of first/second transplantation</td>
<td>9/1</td>
<td>5/1</td>
<td>8/2</td>
<td>6/1</td>
</tr>
<tr>
<td>Mean months on renal replacement therapy (SE)</td>
<td>32 (10)</td>
<td>40 (11)</td>
<td>43 (14)</td>
<td>40 (7)</td>
</tr>
<tr>
<td>Renal ostestodystrophy (type II/type III)</td>
<td>37</td>
<td>1/5</td>
<td>3/7</td>
<td>2/5</td>
</tr>
</tbody>
</table>

Osteoclast surface in both groups (Table 2). Although mean osteoblast surface and osteoclast surface was comparable between the groups, osteoid surface had increased significantly in patients receiving zoledronic acid but remained unchanged in untreated patients (Table 2). No biochemical or clinical evidence of osteomalacia could be detected in the zoledronic acid-treated patients. Adynamic bone disease in the zoledronic patients could be ruled out because unlike osteomalacia, the histopathology of adynamic bone disease does not include an increase in osteoid formation.

There was a significant difference of mean trabecular calcification (Ca mean) between both groups at baseline, with a higher concentration in patients who were going to receive zoledronic acid. However, at the end of the study, trabecular calcium content had only increased in zoledronic acid-treated patients and remained unchanged in the placebo group (Table 2). Multiple linear regression revealed a significant correlation between baseline values and Ca mean at 6 months (P = 0.03). When adjusted for baseline differences in Ca mean between the zoledronic acid and placebo group, the difference at 6 months failed to reach statistical significance (P = 0.08). The full width at half maximum of the peak did not show any significant difference between the zoledronic acid-treated and non-treated group at baseline and at 6 months, suggesting a homogenous distribution of trabecular calcification.

Dual-energy x-ray absorptiometry measurements were available from all patients at transplantation and after 6 months. Mineral content of lumbar spine (g/cm²) and Z score improved significantly in patients receiving zoledronic acid. In contrast, in placebo-treated patients, BMD of lumbar spine deteriorated significantly (Table 2). Dual-energy x-ray absorptiometry of the femur revealed a significant decrease of BMD of the femoral neck, the Ward's triangle, and trochanter in the placebo group, but not in patients receiving zoledronic acid. BMD of the intertrochanteric region remained unchanged in both groups (Table 2).

DISCUSSION

This study demonstrates that two intravenous infusions of the bisphosphonate zoledronic acid prevented post-transplant bone loss by increasing average trabecular calcium concentration (Ca mean) in renal allograft recipients in the first 6 months after successful transplantation. The weight fraction of mean trabecular calcium increased by 2% in the zoledronic acid group, but was unchanged in the placebo group. Between group differences at 6 months were not statistically significant after
Table 2. Mean (SE) values of histomorphometry, bone mineralization density distribution, and bone mineral density in zoledronic acid and placebo-treated patients

<table>
<thead>
<tr>
<th></th>
<th>Base Line</th>
<th>6 Months</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Zoledronic acid</td>
<td>Placebo</td>
</tr>
<tr>
<td>Histomorphometry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Bone volume (BV/TV) %</td>
<td>25 (2)</td>
<td>23 (2)</td>
<td>26 (1)</td>
</tr>
<tr>
<td>Osteoid volume (OV/TV) %</td>
<td>1.4 (0.6)</td>
<td>1.3 (0.5)</td>
<td>2.2 (0.6)</td>
</tr>
<tr>
<td>Osteoid surface (OS/BS) %</td>
<td>48 (9)</td>
<td>47 (8)</td>
<td>53 (4)</td>
</tr>
<tr>
<td>Osteoblast surface (Ob.S/BS) %</td>
<td>7.6 (1.5)</td>
<td>4.4 (1.4)</td>
<td>2.6 (1.3)b</td>
</tr>
<tr>
<td>Osteoclast surface (Oc.S/BS) %</td>
<td>3.2 (0.6)</td>
<td>1.5 (0.3)b</td>
<td>0.4 (0.3)b</td>
</tr>
<tr>
<td>Eroded surface (ES/BS) %</td>
<td>16.8 (3.1)</td>
<td>10.7 (0.8)</td>
<td>5.9 (0.9)b</td>
</tr>
<tr>
<td>Bone mineralization density distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CaMean (wt %)</td>
<td>21.5 (0.2)</td>
<td>21.8 (0.1)b</td>
<td>21.4 (0.2)</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine g/cm²</td>
<td>0.96 (0.04)</td>
<td>0.88 (0.05)</td>
<td>0.93 (0.04)c</td>
</tr>
<tr>
<td>Femoral neck g/cm²</td>
<td>0.74 (0.03)</td>
<td>0.68 (0.04)</td>
<td>0.71 (0.03)</td>
</tr>
<tr>
<td>Femoral neck z score</td>
<td>−0.75 (0.36)</td>
<td>−1.15 (0.32)</td>
<td>−1.11 (0.93)c</td>
</tr>
<tr>
<td>Trochanter g/cm²</td>
<td>0.66 (0.03)</td>
<td>0.59 (0.03)</td>
<td>0.63 (0.03)c</td>
</tr>
<tr>
<td>Trochanter z score</td>
<td>−0.55 (0.33)</td>
<td>−0.98 (0.23)</td>
<td>−0.78 (0.33)c</td>
</tr>
<tr>
<td>Intertrochanteric region g/cm²</td>
<td>1.02 (0.04)</td>
<td>0.92 (0.04)</td>
<td>1.00 (0.05)</td>
</tr>
<tr>
<td>Intertrochanteric region z score</td>
<td>−0.69 (0.31)</td>
<td>−1.18 (0.21)</td>
<td>−0.73 (0.39)</td>
</tr>
<tr>
<td>Ward’s triangle g/cm²</td>
<td>0.61 (0.05)</td>
<td>0.52 (0.05)</td>
<td>0.56 (0.05)</td>
</tr>
<tr>
<td>Ward’s triangle z score</td>
<td>−0.18 (0.39)</td>
<td>−0.56 (0.26)</td>
<td>−0.64 (0.38)c</td>
</tr>
</tbody>
</table>

*a* Indicates significant difference vs. baseline; *b* Indicates difference between placebo and zoledronic acid.

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**Fig. 1.** Time course of biochemical markers of bone formation and resorption in 10 zoledronic acid and 10 placebo-treated renal transplant recipients. The hatched areas indicate the reference range. Symbols are: (□) alkaline phosphatase placebo and (○) zoledronic acid-treated patient groups. Abbreviations are: CTX, type I collagen peptides (crosslaps); bone AP, alkaline phosphatase; iPTH, intact parathyroid gland.
adjustment of the multiple linear regression model for baseline differences in $C_{\text{mean}}$. The likeliest explanation for the mean difference in baseline $C_{\text{mean}}$ of 0.3 weight % after randomization is the relatively small sample size of the study. The increase in $C_{\text{mean}}$ from 21.8 to 22.2 weight % in the zoledronic acid group seems low, but given the small intra- and interassay variations of 0.27 and 0.30%, respectively, are statistically significant. Furthermore, zoledronic acid treatment led to an increase of $C_{\text{mean}}$ close to the reference range, which was determined post-mortem in 20 individuals of wide age range without bone disease, who died in accidents [12]. Osteoid surface increased by 39% in the zoledronic acid group, but was unchanged in the placebo group. Furthermore, BMD of the lumbar spine increased by 31% in the bisphosphonate group, but deteriorated further by 38% ($z$ score) in the placebo group, although all patients were treated concomitantly with 1000 mg calcium citrate daily.

It has been shown previously that vitamin D, calcitriol, estrogen, or testosterone supplementation is ineffective in preventing post-transplant bone loss [26–30]. Older generation bisphosphonates could not prevent early post-transplant bone loss, but exhibited benefits from 1 year on in preventing further deterioration of existing bone disease [26, 27]. Newer generation bisphosphonates, such as pamidronate and ibandronate, are more potent than first-generation bisphosphonates on an equimolar basis and can prevent the loss in BMD after transplantation [31, 32]. Similar results were obtained in the present study with zoledronic acid. The placebo group patients experienced a reduction in cancellous bone density, and zoledronic acid–treated patients exhibited an increase in lumbar spine mineral density in dual-energy x-ray absorptiometry studies. However, an increase in densitometry scores does not necessarily mean higher bone stability. Logistic regression analysis showed only a weak association between BMD and fracture risk. Per $z$ score unit increase in spine BMD, the odds ratio of developing a fracture within a median of 5 years was 1.57 (1.04 to 2.37, 95% CI) in nontransplanted patients [33]. One of the main determinants of bone strength is bone architecture [34]. Because randomized studies of post-transplant osteopathy in renal patients with fracture rate as end point are unlikely to be conducted, treatment success with regards to changes in bone architecture (micromorphology) can only be evaluated by quantitative histomorphometry of bone biopsy cores. The present study is the first to show that the new-generation bisphosphonate zoledronic acid led to an increase of osteoid surface. Osteomalacia was ruled out by biochemical parameters of bone turnover, but could not be excluded by histomorphology because bone turnover cannot be measured without tetracycline labeling. The increase in BMDD in the zoledronic acid–treated patients, however, suggests an increase in trabecular mineralization and thus argues strongly against osteomalacia in the zoledronic acid group. Adynamic bone disease could be expelled by the increase of osteoid in the zoledronic acid group. Markers of high turnover bone disease such as osteoblast and osteoclast surface and eroded surface improved significantly within the first 6 months after engraftment in both patient groups, which can be attributed to the reduction of the secondary hyperparathyroidism after successful renal transplantation in both groups.

Our findings support the hypothesis of investigators from previous studies, that third-generation bisphosphonates lead to an increase of cancellous bone formation [31, 32]. This could so far only be measured indirectly by dual-energy x-ray absorptiometry of the cancellous vertebrae in comparison to the dual-energy x-ray absorptiometry readings of the cortical femur neck. However, the trabecular mineralization and architecture are more important for the stability and performance of the bone than cortical mineralization [34]. To further analyze the influence of zoledronic acid on cancellous bone, we used several methods. Besides dual-energy x-ray absorptiometry, which, due the high absorption of the cortical layer, is, in particular, insufficient in femoral cancellous bone density measurement, we additionally determined mineralization density distribution and morphometry of bone biopsies. The main finding in the current investigation was the significant increase of $C_{\text{mean}}$, a very sensitive measure of trabecular mineralization with low interindividual variation of results [12]. This result of increased $C_{\text{mean}}$ is in accordance with previous studies on human and animal bone bisphosphonate treatment [13, 14]. The measured increase of calcium content was confirmed by significantly lower serologic markers specific for bone formation (osteocalcin) and increased bone resorption [type I collagen peptides (crosslaps)] in treated patients. Biochemical markers of high-turnover osteopathy, such as iPTH, improved in both treatment groups within the first 6 months after transplantation, mirroring the histomorphologic changes that result from adequate renal transplant function.

**CONCLUSION**

In conclusion, this is the first study to show that post transplant administration of zoledronic acid not only conferred an increase of bone mineralization but, that despite the use of high steroid doses, trabecular calcium content increased and cancellous bone could be stabilized.

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