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Increased Bone Turnover Markers after Renal Transplantation

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ABSTRACT

Bone remodeling is a process that occurs continuously in a seemingly inactive tissue like bone. Because of decreased vitamin D synthesis, phosphorus retention and decreased calcium blood concentration, patients with chronic renal failure (CRF) develop secondary hyperparathyroidism^{1–5}. Elevated PTH levels shifts balance between osteoblast and osteoclast activity in favor of osteoclast activity and, therefore, bone resorption. Bone metabolic disorder that affects patients with CRF is called renal osteodystrophy (ROD)^{1–5}. We presume that renal transplantation reverses bone metabolism disorder and our goal was to establish whether osteoblast and osteoclast activity returns to the levels of healthy individuals.

Key words: chronic renal failure, renal transplantation, bone markers

Introduction

Bone is a very dynamic organ that gives our organism maximal strength with minimal mass¹. There is constant activity in bone that is called bone remodeling. Osteoblasts continuously form new bone and osteoclasts resorb the old one. In healthy individuals there is balance between osteoblast and osteoclast activity. Among other diseases, chronic renal failure also affects bone metabolism and remodeling. Because of phosphate retention, decreased blood calcium and vitamin D levels, patients with CRF develop secondary hyperparathyroidism. It is known that parathyroid hormone (PTH) is major regulator of bone turnover^{2,3}. An excess of PTH shifts balance between osteoblast and osteoclast activity in favor to osteoclast activity and therefore bone resorption⁴. Disturbances in bone metabolism in CRF patients are called renal osteodystrophy (ROD).

To evaluate osteoblast and osteoclast activity we have measured bone specific alkaline phosphatase (BAP) and tartrate-resistant acid phosphatase isoform 5b (TRAP 5b). BAP is exclusively produced by osteoblast and is degraded in the liver⁵. TRAP 5b is produced by osteoclasts during bone resorption. It correlates with osteoclast activity and does not cumulate in renal insufficiency^{6,7}.

We presume that renal transplantation reverses bone metabolism disorder. The aim of this study was to see whether the levels of bone markers that represent the activity of osteoblasts and osteoclasts return to the value of the control group.

Patients and Methods

Blood sampling

To avoid circadian variations, venous blood was drawn in the morning after overnight fast. Blood samples were collected three times in transplantation group (at the day of transplantation, 6 and 12 months after – Tx0, Tx6 and Tx12 group) and once in control group. The samples were centrifuged and sera aliquoted and stored at –80°C. No repeated thawing and freezing cycles occurred.

Transplantation group

The study population was consisted of 17 kidney allograft recipients (age range 25–67 years, 15 male and 2 female) who were enrolled at the moment of transplantation and followed up 6 and 12 months post transplant.

All patients were with stable graft function (serum creatinine 1.5 ± 0.3 mg/dL), free of infections, liver dysfunction and 3 of them had undergone subtotal parathyroidectomy. The immunosuppressive therapy included prednisone, mycophenolate mofetil and tacrolimus. Time on dialysis prior to transplantation in average was $94 \pm 96,6$ months. The study was approved by institutional ethics committee and written informed consent was obtained from all participants.

Control group

A control group of 23 healthy individuals matched for sex and age was studied at the same time. Inclusion criteria for this group were no bone and renal diseases, no therapy with medications that affect normal bone formation and normal PTH levels.

Biochemical markers

Intact PTH (iPTH) was measured using IMMULITE/IMMULITE 1000 Intact PTH (Siemens Medical Solution Diagnostics, Deerfield, USA). Assay is highly specific for intact PTH, with low crossreactivity to most PTH fragments. The CV's of intra- and interassay were $< 8\%$, and the sensitivity is 3 pg/mL (0.3 pmol/L).

Bone specific alkaline phosphatase (BAP) was measured with immunoassay from MetraBAP (Metra Biosystems, Mountain View, CA, USA). The intra- and inter assay CV is also $< 8\%$. The minimum detection limit of the assay is 0.7 U/L.

Tartrate-resistant acid phosphatase isoform 5b (TRAP5b) was estimated using immunocapture enzyme assay MetraTRAP5b (Metra Biosystems, Mountain View, CA, USA), whose detection limit was 0.2U/L and intra-interassay CV's were $< 3\%$.

Statistical analysis

Statistical analysis was performed using Statistica 8 software (StatSoft, Inc., Tulsa, OK, USA). All results were expressed as median and range, or mean \pm SD. Differences between the groups were analyzed using Student t-test and one-way ANOVA, following Duncan's post hoc test. A probability level of 0.05 was chosen for statistical significance.

Results

In healthy controls concentrations of iPTH were within assay normal range (1.6–6.9 pmol/L), whereas in Tx0 group iPTH values exceeded significantly normal range with the median of 86 pmol/L ($p < 0.001$). Other two transplantation groups showed lower iPTH values compared to Tx0 group with median 12.4 pmol/L in Tx6 group, and 10.4 pmol/L in Tx12 group (level of significance for Tx6 and Tx12 group versus Tx0 was $p < 0.001$). Compared to controls Tx6 and Tx12 group had elevated levels of iPTH, although this increase was mild ($p < 0.33$; 0.31, respectively; Figure 1).

BAP values in control group were below estimated median for the assay used, and in our hands median value measured is 12.3 U/L. In Tx0 group BAP had similar values as in control group with median 12.05 U/L. Post transplantation groups showed increased BAP values compared both to control and Tx0 group. In Tx6 group BAP median was 32.97 U/L, and in Tx12 group 29.83 U/L. Observed differences were statistically significant (Tx6 versus control $p < 0.02$; Tx12 versus control $p < 0.001$; Tx12 versus Tx0 $p < 0.001$; Figure 2).

Median concentration of TRAP5b in controls was 2.0 U/L. Unlike controls, Tx0 group had increased values of TRAP5b with median 3.7 U/L, but no statistical significance was observed (Figure 3). In Tx6 group TRAP5b values resembled to those in control group with median 2.2 U/L. The highest value of TRAP 5b was noticed in Tx12 group with median 4.1U/L. Differences of TRAP5b concentrations between control and Tx12 group were statistically significant ($p < 0.001$).

Discussion and Conclusion

This study evaluated 17 kidney transplant recipients to determine alterations of bone markers during one year after transplantation, and their correlation with

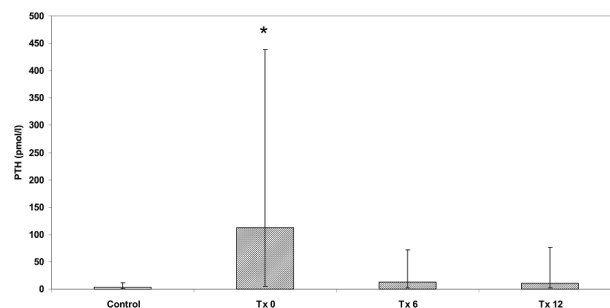


Fig. 1. PTH median and minimal-maximal range in examined groups; control group, Tx0 = at the time of transplantation, Tx6 = six months after transplantation, Tx12 = twelve months after transplantation, * statistically significant versus control, Tx6 and Tx12.

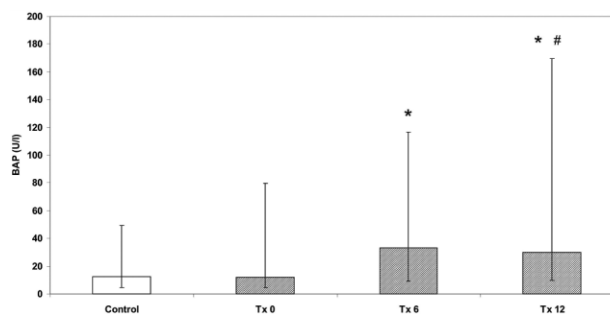


Fig. 2. BAP median and minimal-maximal range in examined groups; control group, Tx0 = at the time of transplantation, Tx6 = six months after transplantation, Tx12 = twelve months after transplantation, * statistically significant versus control; # statistically significant versus Tx0.

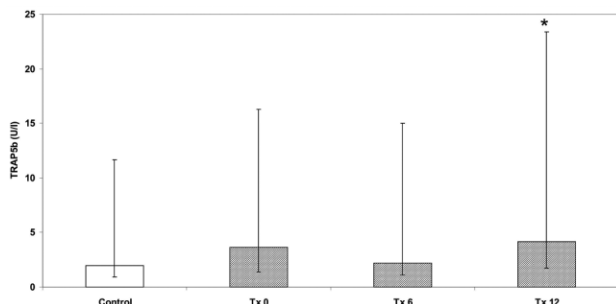


Fig. 3. TRAP5b median and minimal-maximal range in examined groups; control group, Tx0 = at the time of transplantation, Tx6 = six months after transplantation, Tx12 = twelve months after transplantation, * statistically significant versus control.

healthy control serum values. For the first time participants entered the study at the day of transplantation, and were followed twice during first year. We had the rare opportunity to observe dynamic changes of serum values regarding bone metabolism in homogenized and time controlled survey.

Parathyroid hormone (PTH) levels increase with deterioration of kidney function⁸. PTH levels decrease and stabilize one year after renal transplantation⁹. It is well known that elevated PTH affects bone metabolism by stimulating osteoblasts and osteoclasts activity either directly or by modulating cytokines secretion. Such overactivity leads to formation of low quality bone and disorder known as renal osteodystrophy^{4,6}.

It was previously investigated that PTH levels decrease during six months to few years after transplantation^{10,11}. In consistence with these findings we showed that one year following the transplantation PTH values almost reach those in control group. The substantial decline of PTH levels is observed after six months and improvement of hyperparathyroidism continues to first year post transplantation. Because PTH normalizes we hypothesized that osteoblast and osteoclast overactivity

present in CRF also normalize. To prove that thesis we analyzed BAP and TRAP5b as markers of osteoblasts and osteoclasts.

Probably the most studied bone marker besides PTH is BAP. Throughout first year of post transplant period BAP values are persistently higher compared to control group. Also, in our study is seen that BAP unlike PTH increases during time after transplantation. In other studies BAP levels were also higher in the first post transplantation year, in later period decreasing trend began¹². Previously Reinhardt et al. reported incrementation of BAP and osteocalcin in first few months after transplantation and gradual normalization after first year¹³.

The least explored bone marker in kidney transplant recipients is surely, TRAP5b. In previous studies statistically significant correlation was found between TRAP5b and PTH, also it was found negative correlation of TRAP5b with concentration of cyclosporine, prednisone and azathioprine^{14,15}. In study by Malyszko et al. TRAP5b in kidney transplant recipients was within normal range, but their allograft recipients were enrolled in study 1–10 years after transplantation¹⁵. Opposite to their findings TRAP5b in our study is decreased to normal range in first six months, afterwards TRAP5b value increases two times above normal range.

In conclusion it is obvious that patients after renal transplantation, in spite of normalizing PTH values, still have increased osteoblast and osteoclast activity. Observing that, we could say that PTH alone is not the only factor responsible for bone metabolism disturbances. Several studies noticed that immunosuppressive therapy, next to PTH, plays a key role in bone loss after transplantation and that glucocorticoid therapy promotes osteoclast and inhibits osteoblast activity, leading to development of glucocorticoid induced osteoporosis^{16–18}. The course of bone remodeling after renal transplantation is guided multifactorially, so furthermore investigations are needed to establish what factors and how, along with PTH, contribute to osteoblasts and osteoclasts activity.

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POVIŠENI MARKERI KOŠTANE PREGRADNJE NAKON TRANSPLANTACIJE BUBREGA

S A Ž E T A K

Koštana pregradnja je proces koji se neprekidno odvija u naizgled inaktivnom tkivu kao što je kost. Zbog smanjene sinteze vitamina D, retencije fosfora i smanjenja koncentracije kalcija u krvi, bolesnici sa kroničnim bubrežnim zatajenjem razvijaju sekundarni hiperparatireoidizam¹⁻⁵. Povišene vrijednosti PTH pomiču granicu aktivnosti osteoblasta i osteoklasta na stranu aktivnosti osteoklasta i time koštane resorpcije. Koštani metabolički poremećaj koji zahvaća bolesnike sa kroničnim bubrežnim zatajenjem nazivamo renalna osteodistrofija¹⁻⁵. Naša je pretpostavka da transplantacija bubrega popravlja poremećaj koštanog metabolizma, a cilj je ovog rada vidjeti da li će se aktivnost osteoblasta i osteoklasta vratiti na razine prisutne u zdravih pojedinaca.