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Impact of tacrolimus on bone metabolism after kidney transplantation

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ABSTRACT

Bone disease is a common clinical problem after kidney transplantation. To date, studies investigating the effects of tacrolimus (TAC) on bone metabolism in vivo or vitro yielded conflicting data. This study was carried out to discuss the relationship between TAC blood concentrations and bone metabolism status in kidney transplant recipients. 72 kidney recipients whose time since transplantation more than 5 months (5–51 months) were divided into two groups by the TAC blood concentrations, high TAC group (TAC≥6 ng/mL) and low TAC group(TAC<6 ng/mL), respectively. Bone mineral density (BMD) of lumbar vertebrae L1–L4 and neck of the femur and allied biochemical markers (TRAP-5b, B-ALP, 25-(OH)D, PTH, beta-CrossLaps, N-MID Osteocalcin, Ca, PO4) were measured simultaneously. Our results showed that 27.78% of our patients had bone loss and the loss rates were statistical different between the high TAC group and low TAC group in kidney recipients (45.5% vs 20.0%, $P=0.026$). Correlation analysis showed that TAC concentrations were positively correlated with tartrate-resistant acid phosphatase-5b (TRAP-5b) in male recipients ($r=0.287$, $P<0.05$). In conclusion, kidney transplant recipients with high TAC blood concentrations are at risk of bone loss, and TAC may cause bone disorders involved in accelerated bone resorption.

1. Introduction

Although kidney transplant recipients now benefit from greatly improved graft and patient survival by using of immunosuppressant drugs [1], posttransplant bone disease, as one of frequent long-term complications after kidney transplantation, adversely affects the quality of life and must be of concern [2,3]. Risk factors that have been suggested to have a role in the pathogenesis of alterations of bone metabolism after transplantation include high cumulative dosage of corticosteroids, long-term use of other immunosuppressant drugs (calcineurin inhibitor, CNI), chronic inflammatory damage of kidney function and preexisting bone disorders [4].

The initial decline in bone mineral density (BMD) immediately after transplantation has been largely attributed to high cumulative doses of glucocorticoids [5]. Nevertheless, a cross-sectional study with a minimal follow-up of 5 years after kidney transplantation found that >50% of transplant recipients were found to be osteoporotic with an increased fracture rate, and no correlation was observed between BMD and steroid-cumulative dosage [6], indicating that unwanted changes of bone metabolism persist beyond the initial period after kidney transplantation and other immunosuppressive agents may have an impact on bone status.

Tacrolimus (TAC), a calcineurin inhibitor, is one of the most common immunosuppressant agents used after kidney transplant. With its narrow therapeutic range, therapeutic drug monitoring is necessary to maintain the blood concentrations within a target window and individualized therapy [7]. However, the recipients carry the risk of adverse reactions induced by TAC lifelong such as bone disorders. Although in vivo and in vitro studies of the action of TAC on bone have yielded conflicting results, a number of studies have shown that TAC causes bone disorders partly by disturbing the balance of RANK–RANKL–OPG system or by inhibiting the extracellular signal-regulated kinases 1/2 (ERK 1/2) [8,9] and causes osteopenia in mice, rats, and humans when administered systemically [10–12]. Therefore, we determined serum levels of bone markers and BMD of kidney transplant recipients to assess the impact of TAC on bone metabolism status after kidney transplantation.

2. Materials and methods

2.1. Participants

This cross sectional study included a total of 72 kidney allograft recipients who underwent living-related donor kidney transplantation between 2007 and 2011 at West China Hospital of Sichuan University.

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate transcarbamylase; BUN, Serum urea nitrogen; URIC, Uric acid; CREA, Creatinine; CysC, Cystatin C; TRAP-5b, Tartrate-resistant acid phosphatase-5b; B-ALP, Bone-specific alkaline phosphatase; Ca, Total calcium; PO4, Inorganic phosphate; PTH, Parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; WBC, White blood count; Hb, Hemoglobin; RBC, Red blood count; GLU, Blood glucose; BMD, Bone mineral density; BMI, Body Mass Index; ERK ½, Extracellular signal-regulated kinases 1/2.

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All patients received a triple immunosuppressive therapy consisting of steroids plus TAC plus Mycophenolate Mofetil (MMF). Exclusion criteria were as follows, age<18 years, thyroid or parathyroid disorders, postmenopausal women, diabetes mellitus, gastrointestinal disease, and other diseases that affect bone mass (Cushing's syndrome, acromegaly). Baseline data included age, sex, height, weight, days posttransplantation, cumulative dosages of prednisolone. To avoid the well-described effects of the initial using of high-dose steroid on bone metabolism, we only included patients whose time since transplantation more than 5 months (5–51 months) (after a 5 months period, kidney recipients were administrated a low dose glucocorticoid, and could keep a stable TAC blood drug level). We divided those 72 patients into two groups according to the blood levels of TAC [13] at the time when performed the BMD test: 22 patients showing high concentrations of TAC (TAC≥6 ng/mL) and another 50 patients with low levels (TAC<6 ng/mL).

The Human Research Subjects Committee in our hospital approved this study. The sources of organs included in our study were all legal.

2.2. Laboratory examinations

After giving informed consent, all patients underwent bone mineral densitometry (BMD) at the lumbar vertebrae L1–L4 and neck of the femur using dual-energy X-ray Absorptiometry (Expert-IDXA bone densitometer; Lunar Corp., Wisconsin). The result was expressed as T score as recommended by the World Health Organization.

The following serum biochemical parameters were measured using Roche Modular-P800 automatic biochemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany): (1) liver function parameters: alanine aminotransferase (ALT) (normal range<55 IU/L), aspartate transcarbamylase (AST) (<46 IU/L), (2) kidney function parameters: serum urea nitrogen (BUN) (3.30–8.22mmol/L), Uric acid (URIC) (240–490 umol/L), creatinine (CREA) (53–140umol/L), Cystatin C (CysC) (0.51–1.09 mg/L), (3) bone resorption and formation markers: osteoclast-specific tartrate-resistant acid phosphatase-5b (TRAP-5b) (1.3–4.82 U/L) was determined by ELISA (TRACP 5b Assay Kit, IDS, UK), bone-specific alkaline phosphatase (B-ALP) (11.4–24.6ug/L) was determined by Beckman Unicel DXI800 analyzer (Beckman Coulter Inc., California, USA), beta-CrossLaps (0.300–0.584 ng/mL) and N-MID Osteocalcin (11–43 ng/mL) were determined by Roche E170 Elecsys (Roche Diagnostics GmbH, Mannheim, Germany), (4) parameters affecting bone metabolism: total calcium (Ca) (2.1–2.7 mmol/L), inorganic phosphate (PO4) (0.81–1.45 mmol/L), both were determined by Roche Modular-P800 automatic biochemistry analyzer, parathyroid hormone (PTH) (1.60–6.90 pmol/L) was determined by Roche E170 Elecsys (Roche Diagnostics GmbH, Mannheim, Germany), 25-hydroxyvitamin D [25(OH)D] (47.7–144nmol/L) was determined by ELISA (25-Hydroxy Vitamin D Kit, IDS, UK), (5) TAC blood concentrations were determined by SIEMENS V-TWIN clinic medicine concentration analyzer (Siemens Healthcare Diagnostics Inc., Deerfield, USA), and (6) other parameters: white blood count (WBC) (4.0–10.0 10^9/L), hemoglobin (Hb) (male 120–160 g/L; female 110–150 g/L) and red blood count (RBC) (male 4.0–5.5 10^{12}/L; female 3.5–5.0 10^{12}/L) were determined by Sysmex XE-2100 automatic hematology analyzer (Sysmex, Kobe, Japan), blood glucose (GLU) (3.9–5.9mmol/L) was determined by Roche Modular-P800 automatic biochemistry analyzer.

2.3. Statistical analysis

Statistical analysis was performed using SPSS16.0 software (SPSS Inc., Chicago, IL). Data that met normal distribution were expressed as mean ± SD and *t*-test was used to compare the difference between two groups. Otherwise, data were expressed as mean (median, extreme value) and Mann–Whitney test was used. Pearson correlation analysis was used to analyze the relationship between TAC blood concentrations and bone metabolism parameters. P-values<0.05 were regarded as statistically significant.

3. Results

3.1. Demographic and clinical characteristics

A total of 72 kidney transplant recipients with an average age of 36.36 ± 8.18 years were studied and included 48 male and 24 female patients. The results of comparison between low TAC group and high TAC group showed that there were statistically significant in gender ($P<0.05$). The clinical and laboratory features of two groups were summarized in Table 1. To exclude possible impact of unmatched sex on other parameters, we conducted stratified analysis in subsequent related analysis.

3.2. Bone mass measurement

According to the World Health Organization's (WHO) diagnostic criteria, T score below −2.5 at the femoral neck and/or the lumbar site was defined as osteoporosis and T score between −1.5 and −2.5 at same sites was osteopenia. We applied these criteria to define low bone mass (T score below −1.5 at any site of femoral neck and/or the lumbar). Our results showed that there were 27.78% patients had bone loss. We observed that the bone loss rates were significant statistical different between the high TAC group and low TAC group in kidney recipients (45.5% vs 20.0%, $P=0.026$, Table 2).

Table 1
Comparison of two groups with respect to the clinical and laboratory features.

	Low TAC group (n=50)	High TAC group (n=22)	*p*
Gender (M:F)	28:22	20:2	0.003*
Age (years)	36.64 ± 7.90	35.81 ± 9.36	0.056
Days posttransplantation (mo)	18.06 (15.00; 6–51)	16.86 (14.00; 6–34)	0.507
BMI (kg/m^2)	22.49 ± 3.49	22.06 ± 2.70	0.222
Liver function parameters			
ALT (IU/L)	23.39 ± 15.00	25.24 ± 16.10	0.356
AST (IU/L)	21.55 ± 8.35	26.33 ± 13.65	0.189
Renal function parameters			
BUN (mmol/L)	6.66 ± 1.19	6.48 ± 1.94	0.684
CREA (umol/L)	108.99 ± 21.68	110.38 ± 28.76	0.838
CysC (mg/L)	1.28 ± 0.25	1.38 ± 0.44	0.664
URIC (umol/L)	351.48 ± 65.32	399.67 ± 90.83	0.287
Metabolic effects of FK506			
GLU (mmol/L)	4.99 ± 0.45	5.10 ± 0.55	0.130
Hb (g/L)	138.09 ± 23.30	139.57 ± 18.16	0.144
RBC (10–12/L)	4.68 ± 0.80	4.73 ± 0.57	0.113
WBC (10–9/L)	6.69 ± 2.12	6.53 ± 1.88	0.437
Metabolic of Ca and PO4			
Ca (mmol/L)	2.30 ± 0.11	2.36 ± 0.14	0.354
PO4 (mmol/L)	1.01 ± 0.18	1.03 ± 0.21	0.452
25(OH)D (nmol/L)	38.07 ± 14.74	39.51 ± 17.43	0.538
Cumulative dosage of steroids (mg)	4517.8 (3900.0; 1400–13200)	2723.3 (2100.0; 1200–6000)	0.101

BMI: Body Mass Index, ALT: alanine aminotransferase, AST: aspartate transcarbamylase, BUN: serum urea nitrogen, CREA: creatinine, CysC: Cystatin C, URIC: uric acid, GLU: blood glucose, Hb: hemoglobin, RBC: red blood count, WBC: white blood count, Ca: total calcium, PO4: inorganic phosphate, 25(OH)D: 25-hydroxyvitamin D.

* Significant differences (P<0.05) were depicted in gender, time since transplantation and Ca levels. Days posttransplantation and cumulative dosage of steroids were expressed as mean (median, extreme value), others were mean ± SD.