

The Prevalence and Risk Factors of Osteoporosis in Thai Renal-Transplant Patients

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Objectives: To determine the prevalence and risk factors of osteoporosis after renal transplantation in Thai patients.

Material and Method: A single-center cross-sectional study of bone mineral density was conducted in 102 Thai renal allograft recipients. Correlations were made between the clinical parameters and the occurrences of osteoporosis.

Results: The prevalence of osteoporosis was 24.5%, 9.8% and 26.4% at lumbar vertebrae, hip region, and any sites, respectively. Binary logistic regression analysis revealed that cumulative dosage of steroids was significantly correlated with osteoporosis of the lumbar spine ($p = 0.023$, adjusted OR = 1.005), while body mass index ($p = 0.005$, adjusted OR = 0.738) and age ($p = 0.052$, adjusted OR = 1.077) were correlated with osteoporosis of the hip region.

Conclusion: Osteoporosis is common in Thai renal allograft recipients, particularly of the lumbar vertebrae. Cumulative dosage of steroids is the most important risk factor of low BMD of the lumbar vertebrae.

Keywords: Osteoporosis, Renal Transplantation, Dual Energy X-ray Absorptiometry

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Renal transplantation is the best treatment of patients with end-stage renal disease. The restoration of renal function not only dramatically increases patient survival but also improves their quality of life. Despite the significant improvement of renal and patient survival, critical skeletal complications may occur in patients with functioning grafts. High prevalence of osteoporosis was reported early after transplantation and this leads to serious morbidities such as bone fracture and bone pain⁽¹⁻⁷⁾. The prevalence of osteoporosis was increasingly associated with duration after transplantation. The prevalence of osteoporosis and bone fracture was reported to be up to approximately 50 percent of patients in Western countries⁽⁶⁾. Importantly, the prevalence of osteoporosis was even higher than long-term dialysis patients^(1, 8).

Despite the fact that steroid has direct effects on osteoblastic activities, many factors have been proposed in the pathogenesis of post-transplant bone loss⁽⁹⁻¹²⁾. Calcineurin inhibitors, persistent hyperparathyroidism, hypophosphatemia, abnormal vitamin D metabolism, and genetic susceptibility are among the critical factors which are otherwise modifiable⁽¹³⁻²⁰⁾.

More than 2,000 renal transplantations and 300 new cases per year were performed in Thailand. However, no osteoporosis study has been conducted in transplant patients. The aim of the present study was to determine the prevalence and risk factors of both early- and late-onset osteoporosis in Thai renal allograft recipients in King Chulalongkorn Memorial Hospital center.

Material and Method

Patients

There were 102 renal allograft recipients of the King Chulalongkorn Memorial Hospital who

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received their first-time transplantation for at least 6 months. The patients met the following criteria: older than 18 years of age, serum creatinine less than 2 mg/dl without significant changes during last 3 months, and none of vitamin D, calcitonin or any antiresorptive drugs administration after renal transplantation. Electronic medical database were reviewed for the following parameters: age, gender, menopausal status, body weight, body mass index, cause of renal failure, dialysis mode and time before transplantation, type of renal allograft, time since transplantation, and cumulative dose of steroid and cyclosporine A. The study was approved by the Ethics Committee for human research of the Faculty of Medicine, Chulalongkorn University, and each patient provided informed consent.

Blood biochemistry

Serum levels of urea nitrogen, creatinine, calcium, phosphorus and magnesium were measured at the time of patient entry. Plasma intact parathyroid hormone (iPTH) levels were assayed by electrochemiluminescence immunoassay (ECLIA, Roche, IN, USA).

Bone Densitometry

Bone mineral density (BMD) of the first to the fourth lumbar spine and the non-dominant hip was measured by dual-energy x-ray absorptiometry with a Hologic QDR series, Delphi W Model (Waltham, MA, USA). Vertebral bone density represented the average of four vertebrae (the 1st to 4th lumbar vertebrae). Hip bone density represented the average of four regions (femoral neck, greater trochanter, intertrochanteric crest and Ward's triangle). Results were expressed as Z scores relative to mean normal values for subjects of the same age and gender and as T scores for sex-matched young adults. Pre-transplant measurement of bone densitometry was not performed. World Health Organization's (WHO) diagnostic criteria of osteoporosis were applied to define osteoporosis (T score below -2.5) and osteopenia (T score between -1 and -2.5).

Statistical analysis

The statistical analysis was performed by using SPSS software version 11.5. Results are expressed as mean \pm standard deviation (SD). Student's T-test was used to compare continuous variables between two groups. Binary logistic regression analysis and linear regression analysis were used to assess the effects of the different parameters. A *p* value of less than 0.05 was considered statistically significant.

Results

Patient characteristics (Table 1)

There were 102 renal allograft recipients (52 males and 50 females) who participated in this study. Mean age was 46.2 ± 10.7 years (18-68 years). Causes of renal failure were unknown in most patients (56%). Hemodialysis was the most common type of renal replacement therapies before transplantation (97%). Duration of dialysis therapy was 20.3 ± 16.5 months (1-87 months). Sixty five percent of the allografts were from deceased donors. Duration of transplantation was 47 ± 38 months (6 months to 17 years).

Biochemical parameters (Table 1)

The mean serum creatinine and creatinine clearance were 1.4 ± 0.5 mg/dl and 63.9 ± 21.2 ml/min, respectively. All patients had normal levels of serum calcium, phosphorus and magnesium. Half of the patients (49%) had serum levels of intact parathyroid hormone (iPTH) exceeding normal range (88.78 ± 71.55 pg/ml) (Fig. 1). Linear regression analysis revealed that duration of dialysis therapy had a correlation with serum levels of iPTH ($r = 0.47$, $P < 0.001$).

Bone mineral density

Osteoporosis of lumbar vertebrae, hip region, and any sites was observed in 24.5%, 9.8% and 26.4% of studied patients, respectively. Meanwhile, osteopenia of the same regions increased to 47.1%, 56.9%, and 56.9%, respectively (Table 2). The mean T score of lumbar spine and hip region were -1.58 ± 1.30 and -1.30 ± 0.92 , respectively. With respect to gender and menopausal status, post menopausal female patients had the lowest T-score of both lumbar and hip regions (-1.78 ± 1.81 and -1.47 ± 1.25 , respectively), whereas the pre menopausal female patients had the highest

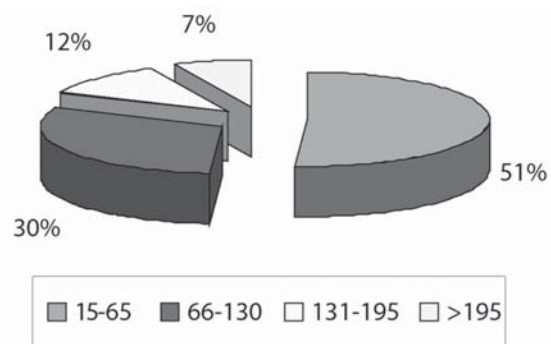


Fig. 1 Percentage of patients in different iPTH levels

Table 1. Clinical characteristics of participants

Clinical Characteristics	Result
Gender (male/female)	52 / 50
Postmenopausal female / all female	23 / 50
Average age (years)	46.2 ± 10.7
Body weight (kg)	65.3 ± 13.8
Body mass index	25.1 ± 5.2
Causes of renal failure (cases)	
- diabetic mellitus	18
- glomerulonephritis	13
- ADPKD ^a	10
- obstructive uropathy	4
- unknown	57
Mode of dialysis before transplantation (cases)	
- Hemodialysis	99
- CAPD ^b	3
Type of transplantation	
- LRKT ^c	36
- CDKT ^d	66
Dialysis time before transplantation (months)	20.3 ± 16.5
Time since transplantation (months)	47 ± 38
Cumulative steroids dose per body weight (mg/kg)	165 ± 98
Cumulative cyclosporine A dose per body weight (mg/kg)	3501 ± 2617
Serum creatinine (mg/dL) (0.5 - 1.2) ^e	1.40 ± 0.50
Creatinine clearance (ml/min)	63.90 ± 21.20
Serum calcium (mg/dL) (9 - 11) ^e	9.40 ± 0.40
Serum phosphorus (mg/dL) (2.5 - 4.8) ^e	3.60 ± 0.60
Serum magnesium (mg/dL) (1.7 - 2.8) ^e	1.80 ± 0.20
Serum intact parathyroid hormone (pg/mL) (15 - 65) ^e	88.78 ± 71.55

results were expressed in mean ± SD

^aAutosomal dominant polycystic kidney disease, ^bChronic ambulatory peritoneal dialysis

^cLiving-related kidney transplantation, ^dCadaveric kidney transplantation

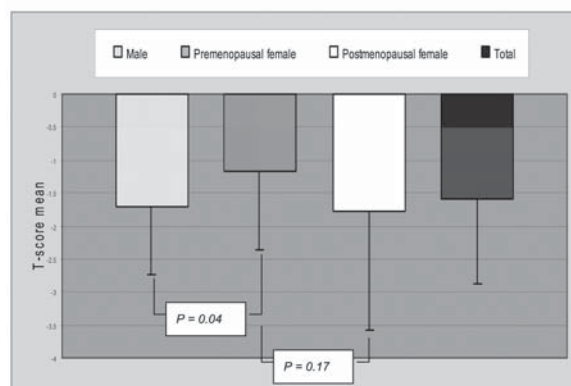
^enormal value of each parameters

Table 2. Prevalence of osteopenia and osteoporosis at different regions

Region	Normal N (%)	Osteopenia N (%)	Osteoporosis N (%)	Total
L1-4	29 (28.4)	48 (47.1)	25 (24.5)	102
Total Hip	34 (33.3)	58 (56.9)	10 (9.8)	102
Any sites	17 (16.7)	58 (56.9)	27 (26.4)	102

T score of both regions (-1.16 ± 1.21 and -1.22 ± 0.99 , respectively) (Fig. 2, 3).

Patients with osteoporosis of lumbar spine had cumulative dosage of steroid and cyclosporine A higher than those without osteoporosis (207 ± 138 vs 151 ± 76 ; $p=0.01$) (4390 ± 3596 vs 3212 ± 2161 ; $p=0.04$). Furthermore, patients with osteoporosis of hip had lower body weight and body mass index than those without osteoporosis (53.9 ± 11.8 vs 66.5 ± 13.5 ; $p=0.006$) (21.9 ± 4.8 vs 25.4 ± 5.1 ; $p=0.04$) (Table 3, 4).

**Fig. 2** Mean T-score at lumbar vertebrae according to sex and menopausal status

Cumulative dosage of steroid was the most significant factor of osteoporosis of the lumbar vertebrae either by binary logistic regression analysis ($p=0.023$, adjusted OR = 1.005) or by linear regression

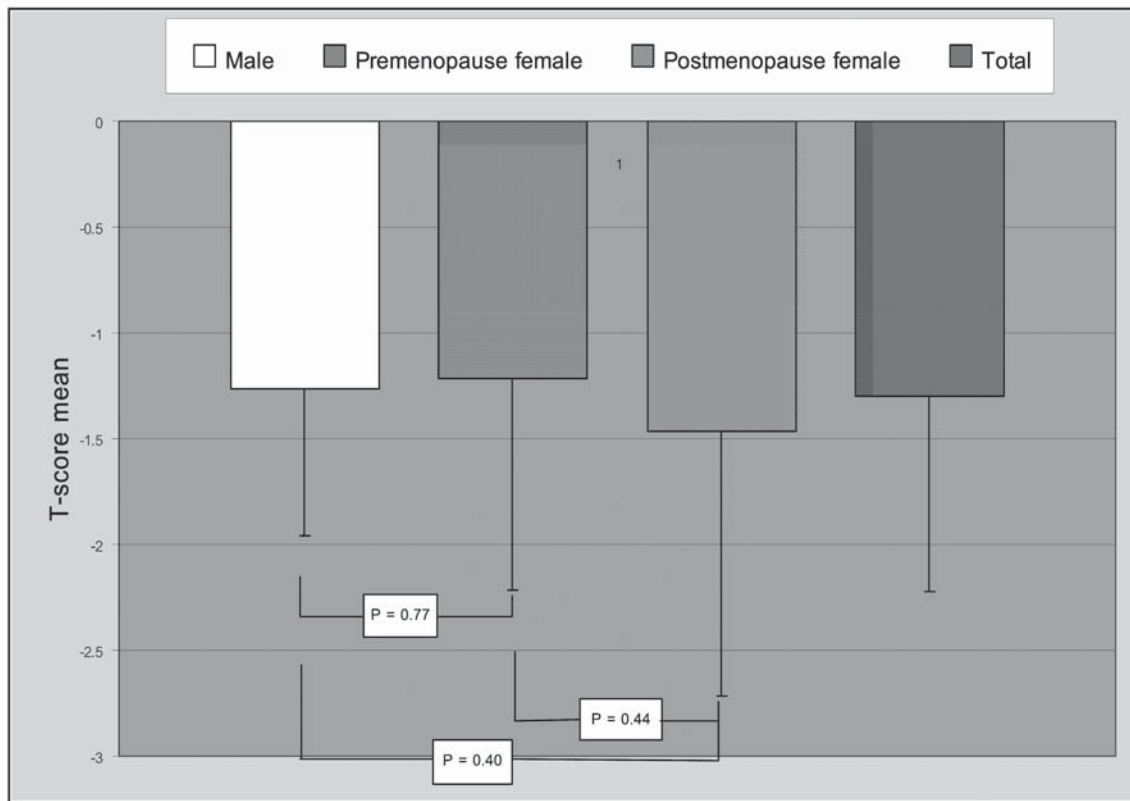


Fig. 3 Mean T-score at hip region according to sex and menopausal status

analysis ($p = 0.006$, $r = -0.27$). Alternatively, body mass index and age were correlated with osteoporosis of the hip region by binary logistic regression analysis ($p = 0.005$, adjusted OR = 0.738 and $p = 0.052$, adjusted OR = 1.077, respectively). The linear regression analysis showed similar correlation between BMI, age and osteoporosis of the hip ($p < 0.001$, $r = 0.49$ and $p = 0.016$, $r = -0.23$, respectively).

Discussion

Osteoporosis is one of the most common morbidities of renal transplant patients. The first 6-month post-transplantation is the most critical period of rapidly declination of bone mineral density⁽⁵⁾. However, little is known of renal transplant in Asians regarding differences in lifestyle and genetic factor. The present study indicates that osteoporosis is common in Thai renal-transplant patients. Importantly, the prevalence of osteoporosis is not limited to early post-transplant but is also common in the long-term functioning graft patients.

Renal osteodystrophy and osteoporosis are

both common in long-term dialysis Thai patients⁽²¹⁾. These typical skeletal complications could persist, or even increase despite the recovery of renal function after transplantation. Interestingly, the present study shows a higher prevalence of osteoporosis post-transplantation compared to a previous report in dialysis patients⁽²¹⁾. Lumbar vertebrae is one of the most vulnerable sites due to a high proportion of active bone remodeling in the trabecular bone⁽²²⁾. Therefore it is important to manage correctable factors early at the pre-ESRD stage since, as a conclusion from this work; renal osteodystrophy is a continuum problem regardless of the type of renal replacement therapy.

The effects of immunosuppressive treatment on the skeletal system have been studied by several investigators^(2,3,6,10). By univariable and multivariable analysis, the present study supports that cumulative dosage of steroids has a negative impact upon BMD. Many studies have demonstrated that steroids have both direct effects to osteoblastic and osteoclastic activities as well as indirect effects such as an induction of hypogonadism^(9,12,23-25). Steroids could also

Table 3. Mean values of different variables between patient with and without osteoporosis at lumbar vertebrae

Lumbar Vertebrae	Patient without Osteoporosis (Mean (SD))	Patient with Osteoporosis (Mean (SD))	p
Number	77	25	
Age (yrs)	45.4 (10.6)	48.6 (11.0)	0.19
Body Weight (kg)	66.7 (13.7)	60.7 (12.7)	0.06
BMI (kg/m ²)	25.5 (5.1)	23.8 (5.2)	0.18
Time on dialysis (day)	607 (506)	614 (471)	0.95
Time since KT (day)	1,318 (966)	1,694 (1547)	0.15
Cumulative steroid dose (mg/kg)	151 (76)	207 (138)	0.01
Cumulative CycA dose (mg/kg)	3,212 (2161)	4,390 (3596)	0.04
Calcium (mg/dl)	9.40 (0.45)	9.28 (0.51)	0.27
Phosphorus (mg/dl)	3.55 (0.64)	3.73 (0.58)	0.20
Magnesium (mg/dl)	1.83 (0.22)	1.83 (0.15)	0.99
Creatinine (mg/dl)	1.47 (0.5)	1.35 (0.4)	0.30
CCr (ml/min)	62.7 (20.3)	67.5 (24.0)	0.33
iPTH (pg/ml)	95.3 (79.6)	70.7 (37.4)	0.17

Table 4. Mean values of different variables between patient with and without osteoporosis at hip region

Hip region	Patient without Osteoporosis (Mean (SD))	Patient with Osteoporosis (Mean (SD))	p
Number	92	10	
Age (yrs)	45.71 (10.7)	50.3 (10.1)	0.20
Body weight (kg)	66.5 (13.5)	53.9 (11.8)	0.006
BMI (kg/m ²)	25.4 (5.1)	21.9 (4.8)	0.04
Time on dialysis (day)	606 (495)	636 (530)	0.86
Time since KT (day)	1,434 (1162)	1,185 (918)	0.51
Cumulative steroid dose (mg/kg)	164 (101)	173 (63)	0.78
Cumulative CycA dose (mg/kg)	3,488 (2637)	3,623 (2540)	0.87
Calcium (mg/dl)	9.37 (0.47)	9.39 (0.44)	0.91
Phosphorus (mg/dl)	3.58 (0.65)	3.71 (0.39)	0.54
Magnesium (mg/dl)	1.83 (0.22)	1.83 (0.15)	0.90
Creatinine (mg/dl)	1.45 (0.5)	1.31 (0.4)	0.37
CCr (ml/min)	65.1 (21.2)	53.2 (18.4)	0.09
iPTH (pg/ml)	90.3 (74.3)	72.0 (22.9)	0.52

decrease intestinal calcium absorption⁽²⁶⁾ and increase renal calcium loss⁽²⁷⁾. A proper dose prescription is required to avoid its bone density-lowering effect. Of note, the patients at risk are patients with a low body weight or receiving an anti-rejection protocol. Effects of Cyclosporine A on BMD remains debatable⁽²⁸⁻³¹⁾. In the present study, patients with osteoporosis of lumbar vertebrae had a higher steroid exposure compared to those without osteoporosis ($p = 0.04$). Nonetheless, multivariable analysis failed to reveal this association. It, therefore, remains to be proven by other well-controlled studies.

Secondary hyperparathyroidism has been proven to be the critical factor of low BMD, particularly in cortical bone-rich areas. The persistent hyper-

parathyroidism (iPTH > 150 pg/ml) in the renal allograft recipients predicted patients at risk of low BMD of hip and wrist region^(15,17). Half of the patients in the present study had mild to moderate hyperparathyroidism, regardless of the time after transplantation and renal function. Surprisingly, the correlation of iPTH levels and bone density was not seen. The mildly increased levels of iPTH may have minimal effect on bone density. Taken together, one should control the pre-transplant iPTH levels toward the recommended level in order to minimize the problem of post-transplant bone loss.

Age and body mass index are generally accepted to be the predictive factors of osteoporosis in general population. In the present study, the increas-

ing age and decreasing body mass index adversely affected the bone density of the hip region. The findings could lead the authors to create some preventive measurements particularly in specific groups of patients as shown here.

In conclusion, osteoporosis is common in Thai renal allograft recipients, especially in the lumbar vertebrae. Cumulative dosage of steroid has negative impact on bone density of lumbar vertebrae. BMD measurement should be performed in both pre- and post-transplant period at least once yearly. Dosage of steroids should be titrated cautiously. Bisphosphonate treatment is recommended in osteoporosis but the long-term benefits remain to be determined.

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ความชุกและปัจจัยเสี่ยงของโรคกระดูกพรุนภายหลังการปลูกถ่ายไตในผู้ป่วยไทย

นัอด เตชะวัฒนวรรณ, ยิงยศ อวิหิงสานนท์, เกื้อเกียรติ ประดิษฐ์พรศิลป์, คณินิจ กิ่งเพชร, สมพงษ์ สุวรรณวลัยกร, เถลิงศักดิ์ กาญจนบุษย์, สมชาย เอี่ยมอ่อง, เกรียง ตั้งสง่า,

วัตถุประสงค์: เพื่อศึกษาถึงความชุกและปัจจัยเสี่ยง ของโรคกระดูกพรุนภายหลังการปลูกถ่ายไตในผู้ป่วยไทย

วัสดุและวิธีการ: ผู้ป่วยที่ได้รับการปลูกถ่ายไตมานานกว่า 6 เดือนจำนวน 102 ราย ได้รับการตรวจความหนาแน่นของกระดูกเพื่อวินิจฉัยโรคกระดูกพรุน รวมทั้งทำการวิเคราะห์ข้อมูลทางคลินิก เพื่อหาปัจจัยที่มีผลต่อการเกิดโรค

ผลการศึกษา: พบความชุกของโรคกระดูกพรุนที่กระดูกสันหลัง, กระดูกสะโพก, และที่ตำแหน่งใด ๆ ร้อยละ 24.5, 9.8 และ 26.4 ตามลำดับ เมื่อวิเคราะห์ปัจจัยเสี่ยงโดยวิธี binary logistic regression พบว่าที่ตำแหน่งกระดูกสันหลัง ปัจจัยที่เป็นตัวทำนายโรคได้แก่ ขนาดสะสมของยาสเตอรอยด์ ($p = 0.023$, adjusted OR = 1.005) ในขณะที่ตรวจหานี้ มวลกาย ($p = 0.005$, adjusted OR = 0.738) และอายุ ($p = 0.052$, adjusted OR = 1.077) เป็นสองปัจจัยเสี่ยงที่สำคัญที่กระดูกสะโพก

สรุป: โรคกระดูกพรุนเป็นภาวะแทรกซ้อนที่พบได้บ่อย ภายหลังการปลูกถ่ายไตในผู้ป่วยไทย โดยเฉพาะที่บริเวณกระดูกสันหลัง โดยมีขนาดสะสมของยาสเตอรอยด์เป็นปัจจัยเสี่ยงที่สำคัญ