

Evaluation the Risk Factors that are Associated with Osteoporosis in Post Kidney Transplantation in a Sample of Iraqi Patients

Angham A. Hasan ^{*,1}, Munaf H. Abd alrazak ^{**} and Hassan M. Abbas Al-Temimi ^{***}

* Department of Clinical Pharmacy, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

** Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq

*** Ministry of Health and Environment , Baghdad, Iraq.

Abstract

Renal transplantation is a principal treatment option for end-stage kidney failure. Bone loss and fracture are serious complication of kidney transplantation, associated with morbidity and mortality. The pathogenesis of post transplantation bone loss is multifactorial and complex. There are changes in the normal bone remodeling system which will lead to more accelerated osteoporotic changes compared to normal individuals. The current work aimed to investigate the incidence of osteoporosis in post kidney transplant patients when compared to the general population. And study the relationship between post kidney transplant immunosuppression therapy and osteoporosis and determine some biochemical changes. Also to evaluate the bone mass and the possible correlation between demographic data and the development of osteoporosis. A case control study, conducted in the Kidney Transplant Center – Medical City Complex during the period (from October 2018 till April 2019), seventy-five kidneys transplant patients were participated in the present study including (23 females & 52 males). Apparently healthy seventy-five subjects were selected to participate as a normal group for comparison (control) including (35 females and 40 males). All participants were examined for their bone density using DEXA scan (T – score) and those with cut– point ≤ -2.5 were diagnosed as having osteoporosis (lumbar and hip bones were examined). The prevalence of osteoporosis and osteopenia was significantly higher in transplant patients compared to control for lumbar and hip bone (for lumbar bones: 33.3% vs. 2.7% for hip bones: 60% vs. 14.7%). T- score was significantly lower in the transplant patients compared to control for both lumbar (-1.9 ± 0.8 vs. -1.1 ± 0.7) and hip bones (-2.3 ± 0.9 vs. -1.3 ± 0.8). In logistic regression analysis; only gender and BMI were the predictors of osteoporosis for lumbar bone, while; the BMI and serum calcium were the predictors of osteoporosis for hip bones. In conclusion, Osteoporosis in post-renal transplant patients is high when compared to general population, only corticosteroids significantly increase risk of osteoporosis, biochemical marker serum level in post kidney transplant patients are significantly different when compared with the general population but did not increase risk of osteoporosis and Body mass index is a risk factor for both lumbar and hip bones osteoporosis, while gender and serum calcium are risk factors for osteoporosis in lumbar and hip ;respectively.

Keywords: Osteoporosis, Renal transplant, T – score, Immunosuppressant drugs.

تقييم علاقة عوامل الخطورة مع هشاشة العظام في عينة من المرضى العراقيين الذين يخضعون لعمليات زرع الكلى

انغام احمد حسن^{*}،¹، مناف هاشم عبد الرزاق^{**} و حسن محمد عباس^{***}

* فرع الصيدلة السريرية ، كلية الصيدلة ، جامعة بغداد ، بغداد ، العراق

** فرع الادوية والسموم ، كلية الصيدلة ، جامعة بغداد ، بغداد ، العراق .

*** وزارة الصحة والبيئة ، بغداد ، العراق

الخلاصة

عملية زرع الكلى تعتبر العلاج الرئيسي لمرضى المراحل الاخيرة للفشل الكلوي. هشاشة وتكسر العظم تعتبر من المضاعفات الخطيرة لعملية زرع الكلى وتكون مرتبطة مع تفاقم حاله وزيادة خطر الوفاة للمريض. أن عملية تطور فقدان العظم ما بعد زرع الكلى تكون معقدة و متعددة العوامل. حيث ان بعد عملية الزرع تحدث تغييرات في النظام الطبيعي لإعادة تصميم العظم وهذا يؤدي الى التسريع أكثر في هشاشة العظم مقارنة بالأشخاص العاديين. هذه الدراسة صممت للتحقق في حدوث هشاشة العظم في مرضى زرع الكلى مقارنة بالأشخاص الاصحاء و لمعرفة العلاقة المحتملة بين نوع العلاج المناعي بعد زرع الكلى وهشاشة العظام. ولدراسة التغيرات الكيميائية الحيوية في بعض المؤشرات في مصل مرضى زرع الكلى وايضا لتقييم كتلة العظام وإيجاد العلاقة المحتملة بين البيانات الديموغرافية وتأثيرها على هشاشة العظام. تم إجراء عملية مراقبة لحالة الحالات في مركز زراعة الكلى - مجمع مدينة الطب وللمدة (من أكتوبر ٢٠١٨ إلى أبريل ٢٠١٩) ، وشارك خمسة وسبعون مريضاً في عملية زرع الكلى في هذه الدراسة ، بما في ذلك (٢٣ من الإناث و ٥٢ من الذكور). كان مدى العمر (١٥ - ٦٥) سنة. تم اختيار خمسة وسبعون من الأشخاص الاصحاء للمشاركة كمجموعة طبيعية للمقارنة بما في ذلك (٣٥ من الإناث و ٤٠ من الذكور).

¹Corresponding author E-mail: pharmacistangham@yahoo.com

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وكان مدى العمر (١٥ - ٦٥). تم فحص جميع المرضى لمعرفة كثافة العظام باستخدام فحص كثافة العظام (درجة تي)، وتم تشخيص المصابين بنقطة $\geq ٢,٥$ على أنهم مصابون بهشاشة العظام (تم فحص عظام الفقرات القطنية والورك)، بالإضافة إلى ذلك تم قياس نسبة هرمون الغدة خلف الدرقية، فيتامين دي، الزلال، الفوسفاتيز القلوية، الفوسفات، والكالسيوم في مصل الأشخاص المشاركين في الدراسة. كان متوسط مدة الزرع ٤ سنوات، تلقى غالبية المرضى الميكوفينولات (٩٨,٧٪)، في حين أن ٥٠,٧٪ يستخدمون التكروليموس، ٣٤,٧٪ يستخدمون السيكلوسبورين و ٩,٣٪ يستخدمون سيروليمس. وجميع المرضى كانوا يستخدمون الكورتيكوستيرويد النسبة المئوية لمعدل انتشار كانت أعلى بكثير في مرضى زرع الكلى مقارنة بالأشخاص العاديين في عظام الفقرات القطنية وعظم الورك (لعظام العمود الفقري: ٦٠٪ مقابل ١٤,٧٪ بالنسبة لعظام الورك: ٣٣,٣٪ مقابل ٢,٧٪). كانت درجة تي أقل بكثير في مرضى زرع الكلى مقارنة بالتحكم لكل من الفقرات القطنية (-١,٩ ± ٠,٨ مقابل -١,١ ± ٠,٧) وعظام الورك (-٢,٣ ± ٠,٩ مقابل -١,٣ ± ٠,٨). كان هناك علاقة عكسية كبيرة بين مؤشر كتلة الجسم ودرجة تي في الأشخاص العاديين (درجة تي = -٠,٢٨٥)، في حين أن هذه العلاقة تصبح مباشرة وهامة لمرضى الدراسة (درجة تي = ٠,٤٠١) لعظام الفقرات القطنية، وكان هناك ارتباط معنوي مباشر بين درجة تي والجنس في مجموعات الدراسة فقط (درجة تي = ٠,٢٣٢) بالنسبة لعظم الورك. وتحليل الانحدار اللوجستي وجد أن الجنس ومؤشر كتلة الجسم كانت عوامل تنبئ بهشاشة عظام الفقرات القطنية، في حين كان مؤشر كتلة الجسم والكالسيوم عوامل تنبئ بهشاشة العظام لعظام الورك. نستنتج من هذه الدراسة أن نسبة هشاشة العظام لدى مرضى زرع الكلى أعلى مقارنة مع الأشخاص الأصحاء، عفاً عن الكورتيكوستيرويد عامل خطوره وبشكل كبير لهشاشة العظام، مستوى المؤشرات الكيميائية الحيوية في مصل مرضى زرع الكلى يختلف بشكل كبير عن الأشخاص الأصحاء لكنها لا تعتبر عوامل خطورة لهشاشة العظام، مؤشر كتلة الجسم هي عامل خطورة لهشاشة عظام الفقرات القطنية ويعتبر مؤشر كتلة الجسم عامل خطورة لهشاشة العظام في عظام الفقرات العنقية وعظم الورك كما يعتبر الجنس ومستوى الكالسيوم في المصل عوامل خطورة لهشاشة عظام الفقرات القطنية والورك، على التوالي.

الكلمات المفتاحية: هشاشة العظام، عملية زرع الكلى، فحص كثافة العظام (درجة تي)، الادوية المثبطة للمناعة

Introduction

The primary function of Kidney is to maintain stable internal equilibrium by eliminating excess water, electrolytes, and other byproducts, through the formation of ultrafiltrate from the plasma by the filtration action of glomerulus system, which can serve as a system for reabsorption or secretion of other materials and byproduct⁽¹⁾.

The main stay of treatment of end stage renal failure (ESRF) is either dialysis (temporary solution), or kidney transplant. Transplant result in better outcome in comparison with dialysis⁽²⁾. However, transplant had its drawbacks, including low availability of kidney from donors, use of chronic immunosuppressant medications and others factors; these factors together with superiors outcome compared to dialysis lead to the development of criteria for selective candidates for the operation to include as many as possible patients to benefit from transplantation⁽³⁾.

In order to prevent graft loss that caused by immune reaction, several protocol develop, these protocols will prevent acute rejection. Currently reduction of side effects that caused by these protocols become as important as their role in reducing the incidence of acute rejection. In the present time, intensive immunosuppression therapies in the early stages of the transplant become a paramount, followed by maintenance protocol to reduce the risk of rejection⁽⁴⁾.

However, many of these drugs have side effects that will result in more deterioration of bone density and osteoporosis. Osteoporosis disease that show reduction in bone mass, micro architectural disruption, and enhanced skeletal fragility, with subsequent low bone strength and high rates of fracture⁽⁵⁾. After renal transplantation, there are changes in the normal bone remodeling system which will lead to more accelerated osteoporotic

changes compared to normal individuals, while for transplantation-related bone loss results from both an increase in the rate of resorption and a decrease in the rate of bone formation⁽⁶⁾. The current work aimed to investigate the incidence of osteoporosis in post kidney transplant patients when compared to the general population, and study the relationship between post kidney transplant immunosuppression therapy and osteoporosis and determine some biochemical changes. Also to evaluate the bone mass by using dual X-ray absorptiometry (DEXA) and the possible correlation between demographic data and the development of osteoporosis.

Subjects and Method

Study design

A case control study applied in Kidney Transplant Center – Medical City Complex during the period from October 2018 till April 2019.

Patients and controlled subjects

Seventy-five kidney transplant patients were participated in the present study including (23 females & 52 males). The age range was (15 - 65) years. Apparently seventy five healthy subjects were selected to participate as a normal group for comparison (control) including (35 females & 40 males). The age range of these subjects was (15 - 65). The follow up of kidney transplant patients was made by specialist's surgeon.

Inclusion criteria

1. Patient age range (15 -65) years.
2. More than 6 months' post kidney transplant operation

Exclusion criteria

1. Endocrine diseases.
2. Inflammatory diseases.
3. Gastrointestinal diseases.
4. Lung disease.
5. Patients using drug that effect calcium level.

Bone density assessment

DEXA scan was used for the assessment of bone density, with T – score $\leq - 2.5$ to define osteoporosis and between $- 1.0$ to $- 2.5$ to define osteopenia ⁽⁷⁾.

Laboratory procedure

A 5 ml venous blood sample from each participant was collected and then sent for laboratory analysis in the Medical City Complex campus, serum (calcium, phosphorous (PO₄), alkaline phosphatase (ALP), vitamin D₃, parathyroid hormone(PTH), and albumin) measurement were recorded.

Statistical analysis

For the assessment of continuous variables, independent t – test was used, while for categorical variables chi square test used, ordinal logistic regression analysis used to examine the risk of osteoporosis (in which the order of category from lowest to highest was normal bone, osteopenia, and

osteoporosis). All analysis carried out using SPSS version 22.0.0 (Chicago, IL) and GraphPad Prism version 8.2) San Diego, California USA), p value considered when appropriate to be significant if less than 0.05

Results

The study included 150 participants, mean age of patients was not significantly different in the study group compared to control (40.9±12.2 vs. 38.4±11.5 years, respectively), with age range from 15 – 65 years, the commonest age group for both study and control group was between 40 – 49 years (26.7% vs. 28.0%, respectively). BMI was significantly lower in the study group compared to control (25.2±3.8 vs. 27.0±7.5 kg/m², respectively). There was no significant difference in gender between study and control groups .with male to female ratio (2.26:1 vs.1. 14:1, respectively), as illustrated in table.1.

Table 1. Assessment of demographic, clinical, and laboratory data.

Variables	Control	Study	p-value
Number	75	75	-
Age (years), mean ± SD	38.4±11.5	40.9±12.2	0.191 #
BMI (kg/m ²), mean ± SD	27.0±7.5	25.2±3.8	0.068 #
Gender, n (%)			
Female	35 (46.7%)	23 (30.7%)	0.065 #
Male	40 (53.3%)	52 (69.3%)	
Transplant duration (years), median (IQR)	-	4.0 (2.0 – 7.0)	-
Treatment, n (%)	-		-
MMF	-	74 (98.7%)	-
Cyclosporine	-	26 (34.7%)	-
Sirolimus	-	7 (9.3%)	-
Tacrolimus	-	38 (50.7%)	-
S.Ca (mg/dl), mean ± SD	9.0±0.4	9.5±0.7	<0.001#
S.PO ₄ (mg/dl), mean ± SD	4.1±0.6	3.3±0.6	<0.001#
S.ALP(U/L), mean ± SD	65.6±17.7	101.2±35.8	<0.001 #
S.VitaminD ₃ (ng/ml), mean ± SD	22.5±15.0	22.9±13.4	0.871 *
S.PTH(Pg/ml), mean ± SD	39.4±22.8	82.6±66.9	<0.001#
S. Albumin(mg/d), mean ± SD	3.8±0.6	3.6±0.3	0.002#
* Significant difference indicates p-value <0.05, compared to control			
# Non-significant difference indicates p-value ≥0.05			
MMF: Mycophenolatemofetile			
S.ALP: Serum Alkaline phosphatase, S.Ca: Serum calcium, S.PTH: Serum parathyroid hormone, S.PO ₄ : Serum phosphorus.			

The prevalence of osteoporosis and osteopenia was significantly higher in transplant patients compared to control for bone lumbar and hip bones (Figure 1 and 2), also; T-Score was

significantly lower in the transplant patients compared to control for both lumbar and hip bones - as illustrated in table;2.

Table 2. Assessment of bone status.

Variables	Control	Study	p-value
Number	75	75	-
T – score, mean ± SD			
Spine bone	-1.1±0.7	-1.9±0.8	<0.001
Hip bone	-1.3±0.8	-2.3±0.9	<0.001
Lumbar bone, n (%)			
Normal	39 (52.0%)	14 (18.7%)	<0.001
Osteopenia	34 (45.3%)	36 (48.0%)	
Osteoporosis	2 (2.7%)	25 (33.3%)	
Hip bone, n (%)			
Normal	43 (57.3%)	7 (9.3%)	<0.001
Osteopenia	21 (28.0%)	23 (30.7%)	
Osteoporosis	11 (14.7%)	45 (60.0%)	

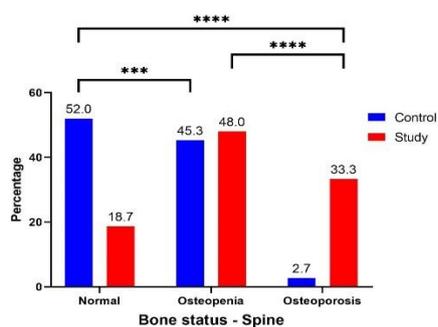


Figure 1. Osteoporosis status for spinal (lumbar) bones . *** Highly significant difference (p-value < 0.001). **** Very highly significant difference (p-value < 0.0001)

Only gender and BMI were the predictors of osteoporosis for lumbar bone, as illustrated in Table 3, while The BMI and serum calcium were the

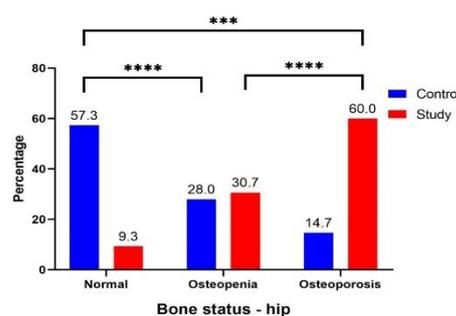


Figure 2. Osteoporosis status for hip bone *** Highly significant difference (p-value < 0.001) **** Very highly significant difference (p-value < 0.0001)

predictors of osteoporosis for hip bone, as illustrated in table 4

Table 3. Ordinal regression analysis of the predictor of osteoporosis for lumbar bone in the study group

	β	OR	95%CI	p-value
Age	0.020	1.020	0.984-1.057	0.284
Gender (female)	-1.107	3.026	1.118-8.188	0.029 *
BMI	0.163	0.850	0.748-0.966	0.013 *
Transplant duration	0.047	1.048	0.961-1.143	0.286
MMF	-	-	-	-
Cyclosporine	0.252	1.286	0.516-3.208	0.589
Sirolimus	0.035	1.036	0.249-4.317	0.961
Tacrolimus	-0.162	0.850	0.362-2.0	0.710
S.PO4	0.141	1.151	0.562-2.358	0.700
S.ALP	-0.003	0.997	0.986-1.008	0.591
S.Vitamin D3	0.011	1.011	0.977-1.047	0.522
S.PTH	0.001	1.001	0.995-1.008	0.644
S.Albumin	-0.023	0.977	0.275-3.475	0.971
S.Calcium	-0.315	0.730	0.379-1.406	0.346

β: Ordinal logistic regression analysis,OR: odd ratio, CI: confidence interval
 It cannot be calculated for MMF
 *Significant relationship between variables (p-value<0.05)

Table 4. Ordinal regression analysis of the predictor of osteoporosis for hip bone in the study group.

	β	OR	95%CI	p-value
Age	0.017	1.017	0.979-1.056	0.377
Gender (female)	0.933	2.543	0.951-6.802	0.063
BMI	-0.139	0.870	0.760-0.996	0.043 *
Transplant duration	-0.007	0.933	0.917-1.076	0.872
MMF	-	-	-	-
Cyclosporine	0.279	1.321	0.511-3.419	0.566
Sirolimus	-0.646	0.524	0.098-2.807	0.451
Tacrolimus	0.023	1.023	0.414-2.527	0.961
S.PO4	-0.444	0.642	0.292-1.409	0.269
S.ALP	0.002	1.002	0.989-1.014	0.790
S.Vitamin D3	0.020	1.020	0.982-1.061	0.308
S.PTH	0.002	1.002	0.995-1.009	0.542
S.Albumin	0.417	1.517	0.384-5.995	0.552
S.Calcium	-0.665	0.514	0.265-0.997	0.049 *

β : Ordinal logistic regression analysis, OR: odd ratio, CI: confidence interval
It cannot be calculated for MMF
*Significant relationship between variables (p-value<0.05)

Discussion

Disturbances in bone metabolism are common complications that affect patients after successful renal transplantation. The usual method for assessing BMD by DXA scan in which osteoporosis defined as T score ≤ -2.5 standard deviation (one standard deviation represent the average of young adult) ⁽⁸⁾. BMD in patients who have undergone renal transplantation has been reported to decrease by a mean of 5.5% to 19.5% during the first 6 months but only 2.6% to 8.2% between months 6 and 12 after surgery ⁽⁹⁾.

In the present study, mean age \pm SD of transplant patients were 40.9 ± 12.2 years, with 73.3% of them distributed between 30 – 59 years, this result is close to Coco et al; study which included 59 kidney transplant patients with mean age of 45.5 ± 13 years ⁽¹⁰⁾, also in agreement with Walsh et al; study which included 93 transplant patients with mean age \pm SD for treatment was (46.1 ± 12.77 years) and for control (46.1 ± 12.93 years) ⁽¹¹⁾. In this study patients were younger than patients included in the Smerud et al; study with mean age 51.4 ± 13.8 years for all the 129 transplant patients ⁽¹²⁾, also lower than other study with mean age of 50.7 ± 15.5 years for 49 control transplant patients ⁽¹³⁾.

In the present study, mean T – score for lumbar- 1.9 ± 0.8 while for hip bone it was -2.3 ± 0.9 in study group. In Marcén et al study, for the lumbar bones (L2-L4) T-score, -1.88 ± 0.99 , and for femoral neck was -1.52 ± 0.88 , which is close to present findings ⁽¹⁴⁾. In Mazzaferro study, T – score was -1.290 ± 1.286 which higher than current study ⁽¹⁵⁾. In Durieux et al study, T – score was -2 ± 1.3 at the lumbar spine and -1.9 ± 1.2 at the femoral neck which is close to current study ⁽¹⁶⁾.

In the current study, the prevalence of osteoporosis, osteopenia, and normal bone for spinal bone were 33.3% ,48.0% ,and 18.7% ;while for hip bone it was 60.0% ,30.7% ,and 9.3% .

In Gregorini et al, a retrospective cohort study, 60.3% of the patients had normal bone, while osteopenia and osteoporosis were present in 24.6% and 15.1%, respectively ⁽¹⁷⁾, which is in disagreement with the current study since osteoporosis in the current study is higher. In Marcén et al study, 20% had normal BMD in the lumbar spine; 52.5% had osteopenia and 27.5% had osteoporosis. While for femoral neck, 35.0% had normal BMD; 50.0% had osteopenia; and 15.0%, osteoporosis (which mean lower osteoporosis rate when compared to the present result) ⁽¹⁴⁾. In Durieux et al; study agree with current study for the lumbar spine 37% had osteoporosis, and 44% had osteopenia, but disagree for the femoral neck 37% had osteoporosis and 40% had osteopenia ⁽¹⁶⁾. In Marcen et al study, 41.9% had osteopenia and 14% had osteoporosis ⁽¹⁸⁾.

The high rate of osteoporosis that observed in this study can be explained by the long duration of transplantation that can will more progressive bone disease, also all patient received corticosteroids (CS) and for extended period of time, since CS is known to cause bone loss by its inhibitory effect on osteoblast cells, and activation of osteoclastic activity, reduction of Ca absorption from the GIT, enhance renal Ca excretion, and increased secretion of PTH⁽¹⁹⁾.

In the present study, 34.7% of the patients received cyclosporine (CsA) (as part of combination therapy), also there is no significant relationship between CyA with osteoporosis, (with OR, 95%CI = 1.286 ,0.516-3.208; for lumbar bone and = 1.321 ,

0.511-3.419 for hip bones), which is in agreement with Martín-Fernández⁽²⁰⁾.

This can be explained by the lack of effect of CsA on bone, or since the decrease in BMD in transplant recipients is difficult to evaluate because CsA is usually administered together with glucocorticoids⁽²⁰⁾.

Tacrolimus was received in the present study by 50.7% patients (as part of combination therapy), also there was no significant relationship between tacrolimus and osteoporosis, (with OR, 95% CI = 0.850, 0.362-2.0; for lumbar bone and, = 1.023, 0.414-2.527 ; for hip bones). FK506-based regimens may benefit the skeleton by lowering steroid exposure in transplant recipients. In a small group of kidney-transplant recipients followed for 1 year, Goffin et al. ⁽²¹⁾; noted that those who received tacrolimus had a small net increase in bone density compared to a loss observed in those who received cyclosporine.

Sirolimus might impair bone formation by interfering with the proliferation and differentiation of osteoblasts and might contribute to the impairment of osteoclast-mediated bone resorption⁽²⁰⁾. In the present study, only 9.3% of patients received sirolimus, there was no correlation between the use of sirolimus and osteoporosis (with OR, 95% CI = 1.036, .249-4.317; for lumbar bone and, = 0.524, 0.098-2.807 ; for hip bones), it is a more novel immunosuppressive agent that produces lower effects on bone⁽²²⁾.

In the current study, 98.7% of patients received mycophenolate mofetil (MMF) (as a part of combination therapy), and there was no significant relationship between (MMF) and osteoporosis. Mycophenolate mofetil has no influence on bone formation and mass in clinical observations ⁽²³⁾.

Also, the logistic regression analysis revealed that the BMI (OR, 95% CI = 0.850, 0.748-0.966) (and gender (OR, 95% CI = 3.026, 1.118-8.188)) were risk factors that are associated with osteoporosis risk for lumbar bone. While for hip bone, logistic regression analysis for BMI (OR, 95% CI = 0.870, 0.760-0.996), and serum calcium (OR, 95% CI = 0.514, 0.265-0.997) were risk factors that are associated with osteoporosis in hip bone. These results study disagree with the results of another study, where no significant relationship was observed between osteoporosis and gender and body mass index ⁽²⁴⁾. Also differs from another study, where no significant relationship was observed between osteoporosis and serum levels of calcium ⁽²⁵⁾ but it agrees with the same study, regarding non-significant relationship between osteoporosis and serum phosphorus and serum parathyroid hormone level.

Osteoporosis after kidney transplantation is multifactorial, while pathophysiologic mechanisms responsible for this condition is not completely elucidated. Pre-transplantation risk factors include

duration of dialysis, high or low parathyroid hormone (PTH) levels and preexisting bone disease. Post-transplantation risk factors associated with bone loss and/or fractures are deceased kidney donor, immunosuppressive regimen choice (glucocorticoids, calcineurin inhibitors), and time since transplantation, hypophosphatemia and graft dysfunction. Additional risk factors such as postmenopausal status for women and presence of diabetes have been considered as possible culprits, in adjunction to the classical osteoporosis risk factors such as age and female gender⁽²⁶⁾.

Conclusion

Osteoporosis in post-renal transplant patients is high when compared to general population, T-score was significantly lower in the transplant patients when compared to control for both lumbar and hip bone, immunosuppressant therapy (mycophenolate mofetil, tacrolimus, cyclosporine and sirolimus) did not increase the risk of osteoporosis, but corticosteroids significantly increase risk of osteoporosis, Biochemical marker serum level in post kidney transplant patients are significantly different when compared with general population but did not increase risk of osteoporosis. Body mass index is a risk factor for both lumbar and hip bones osteoporosis, while gender and serum calcium are risk factors for osteoporosis in lumbar and hip; respectively.

Conflict of Interest

There are no conflicts of interest.

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