Studying Risk Factors Association with Osteoporosis in Post Kidney Transplantation Patients

Angham Ahmed Hasan¹, Munaf H. Zalzala², Hassan M. Abbas Al-Temimi³

¹Department of Clinical Pharmacy, College of pharmacy, University of Baghdad, Iraq
²Department of Pharmacology and Toxicology, College of pharmacy, University of Baghdad, Iraq
³Baghdad Medical City, Baghdad, Iraq

Article History:
Received on: 14.04.2019
Revised on: 07.07.2019
Accepted on: 11.07.2019

Keywords:
osteoporosis, renal transplant, T – score, gender, age, immunosuppressant drugs

ABSTRACT

Osteoporosis that associate with kidney transplantation is an important cause of morbidity to the patients that warranted extensive study about possible causes of osteoporosis in order to implement several steps to reduce this risk. The current work aimed to investigate possible association between post kidney transplant immunosuppression therapy type and developing the osteoporosis and evaluate the bone mass by using dual X-ray absorptiometry (DXA) post-renalal transplant. A case-control, conducted in kidney transplant center – medical city complex for one year period (from October 2018 till April 2019), Seventy - five kidney transplant patients were participated in the present study including (21 females & 54 males). All patients were examined for their bone density using DEXA scan (T – score) and those with cut-point ≤ -2.5 were diagnosed as having osteoporosis (lumber and hip bones were examined). The prevalence of osteoporosis and osteopenia was significantly higher in transplant patients compared to control for bone lumber and hip bone (for lumber bones: 33.3% vs 2.7%l for hip bones: 60% vs. 14.7%). T score was significantly lower in the transplant patients compared to control for both lumber (-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 spinal bone, while; the BMI and calcium were the predictors of osteoporosis for hip bones. In conclusion, Osteoporosis in post-renal transplant patients have a high rate of osteoporosis compared to the general population, post-renal transplant drugs (Cyclosporine, MMF, etc.) did not increase the risk of osteoporosis, and body mass index and female gender were risk factors for osteoporosis.

INTRODUCTION

Kidney function to maintain stable internal equilibrium by eliminating excess water, electrolytes, and other byproducts, through the formation of ultra filtrate from the plasma by the filtration action of glomerulus system, which can serve as a system for reabsorption or section of other materials and byproduct (Bailey et al., 2015).

The mainstay of treatment of ESRD is either dialysis (temporary solution), or a kidney transplant. Transplant results in a better outcome in comparison to dialysis (in terms of clinical and QOL bene-
fits) (Wolf et al., 1999). However, transplant had its drawbacks, including low availability of kidney from donors, use of chronic immunosuppressant medications and others factors; these factors together with superior 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 (Fritsche et al., 2000).

In order to prevent graft loss caused by an immune reaction, several protocols develop, these protocols will prevent acute rejection. Currently, reduction of side effects caused by these protocols become as important as their role in reducing the incidence of acute rejection. In the present time, intensive immunosuppression in the early stages of the transplant becomes a paramount, followed by maintenance protocol to reduce the risk of rejection (Wiseman and Cooper, 2015; Shawkat et al., 2018).

However, many of these drugs have a side effect that will result in more deterioration of bone density and osteoporosis. Osteoporosis is a disease that associated with low bone mass and density, micro architectural disruption, and increased skeletal fragility. 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 (Stein and Shane, 2013). The current work aimed to investigate possible association between post kidney transplant immunosuppression therapy type and developing the osteoporosis and evaluate the bone mass by using dual X-ray absorptiometry (DXA) post-renalal transplant.

**MATERIALS AND METHODS**

**Study design**

This is a cross-sectional study of a cohort for patients who admitted to kidney transplant center – medical city complex for one year period (from October 2018 till April 2019).

**Patients**

Seventy - five kidney transplant patients were participated in the present study, including (23 females & 52 males). The age range was (15 - 65) years. Apparently, healthy thirty 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)
2. More than 6 months’ post kidney transplant operation

**Exclusion criteria**

1. Endocrine disease: (e.g. hyperthyroidism and hyperparathyroidism)
2. Inflammatory disease: (e.g. rheumatoid arthritis (RA))
3. Gastrointestinal disease: (e.g. Malabsorption)
4. Lung disease: (e.g. cystic fibrosis)

**Bone density assessment**

DEXA scan was used for the assessment of bone density, with T – score ≤ -2.5 to define osteoporosis and between -1.0 to -2.5 to define osteopenia, according to WHO criteria (Ensrud and Crandall, 2017).

**Laboratory procedure**

A 5 ml venous blood sample from each participant were collected and then sent for laboratory analysis in the Medical City Complex campus, serum calcium, phosphate, ALP, vitamin D3, PTH, and albumin measurement were recorded. For serum calcium, PO4, ALP, and albumin spectrophotometry methods was used in the measurement of serum levels, while for vitamin D and PTH immune florescent assay was used.

**Statistical analysis**

For assessment of continuous variables, independent t-tests 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 8.2.1 (San Diego, California USA), p-value considered when appropriate to be significant if less than 0.05.

**RESULTS AND DISCUSSION**

The study included 150 participants, mean age of patients was not significantly different in the study group compared to control (38.4±11.5 vs 44.9±6.6 years, respectively), with age range from 18 – 64 years, for both control and study age group between 40 – 49 years was the most common (40.4% and
26.7%, respectively). BMI was significantly lower in the study group compared to control (25.2±3.8 vs 27.0±7.5 kg/m², respectively), 46.2% of the control was obese while 47.5% of the study group had normal BMI. There was no significant difference in gender between both groups, with male to female distribution rate (1.14:1 vs 2.26:1, respectively), as illustrated in Table 1.

The prevalence of osteoporosis and osteopenia was significantly higher in transplant patients compared to control for bone lumber and hip bone (see Table 3), also; T score was significantly lower in the transplant patients compared to control for both lumber and hip bones, as illustrated in Table 2 and Figure 1 and Figure 2.

The BMI and calcium were the predictors of osteoporosis for spinal bone, as illustrated in Table 3. Only gender and BMI were the predictors of osteoporosis for hip bone, as illustrated in Table 4.

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) (Rachner et al., 2011). 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 (Malluche et al., 2009).

In the present study mean age of transplant patients were 40.9 ± 12.2 years, with 73.3 % of them distributed between 39 – 59 years, our findings were similar to those of Coco et al. (2003) study which included 59 kidney transplant patients with mean age of 45.5 ± 13 years (Coco et al., 2003), also in agreement with Walsh et al. (2009) study which included 93 transplant patients (divided into two group 46 received Pamidronate and 47 did not receive treatment) with mean age for treatment was (46.1 ± 12.77 years) and for control (46.1 ± 12.93 years) (Walsh et al., 2009), our patients were younger than patients included in the Smerud et al. (2012) study with mean age 51.4 ± 13.8 years for all the 129 transplant patients (Smerud et al., 2012), also lower than other study with mean age of 50.7 ± 15.5 years for 49 control transplant patients (Torregrosa et al., 2010).

In the present study, mean T – score for spinal -1.9±0.8, while for hip bone, it was -2.3±0.9 in the study group. In Marcen et al. (2006) study, for the lumbar bones (L2-L4) T-score, - 1.88±0.99, and for the femoral neck was - 1.52±0.88, which is similar to our findings Marcén et al. (2007). In Mazzaferro et al. (2006) study, T – the score was - 1.290 ± 1.286, which higher than our study (Mazzaferro et al., 2006). In Durieux et al. (2002) study, T – the score was ~2 ± 1.3 at the lumbar spine and ~1.9 ± 1.2 at the femoral neck which is similar to our findings (Durieux et al., 2002).

In this 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. (2017) 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, which is in disagreement with our findings since osteoporosis in our study is higher (Gregorini et al., 2017). In Marcén et al. (2007) study, 20% had normal BMD in the lumbar spine; 52.5% had osteopenia, and 27.5% had osteoporosis (which mean lower osteoporosis rate and higher osteopenia rate compared to our findings). While for femoral neck, 35.0% had normal BMD; 50.0% had osteopenia; and 15.0%, osteoporosis (which is similar to our findings) (Marcén et al., 2007). In Durieux et al. (2002) study, in the lumbar spine, 37% had osteoporosis, and 44% had osteopenia. While for the femoral neck, 37% had osteoporosis and 40% had osteopenia (which is similar to
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/m²), mean ± SD           | 27.0±7.5      | 25.2±3.8      | 0.068   |
| Gender, n (%)                    |               |               | 0.065   |
| Female                           | 35 (46.7%)    | 23 (30.7%)    |         |
| 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%)    |         |
| Ca corrected, mean ± SD          | 9.0±0.4       | 9.5±0.7       | <0.001  |
| PO4, mean ± SD                   | 4.1±0.6       | 3.3±0.6       | <0.001  |
| ALP, mean ± SD                   | 65.6±17.7     | 101.2±35.8    | <0.001  |
| Vitamin D3, mean ± SD            | 22.5±15.0     | 22.9±13.4     | 0.871   |
| PTH, mean ± SD                   | 39.4±22.8     | 82.6±66.9     | <0.001  |
| Albumin, mean ± SD               | 3.8±0.6       | 3.6±0.3       | 0.002   |

Table 2: Assessment of the bone status

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

our findings) (Durieux et al., 2002). In Marcen et al. (2006) study, 41.9% had osteopenia, and 14% had osteoporosis (Marcen et al., 2006).

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 section of PTH (Coco et al., 2003).

In the present study, 34.7% of the patients received CyA (as part of combination therapy), also there no significant relationship between CyA with osteoporosis, (with OR, 95%CI = 1.286, 0.516-3.208; for spinal bone and, = 1.321, 0.511-3.419; for hip bones), which in agreement with Martin-Fernández et al. (2017).

This can be explained by the lack of effect of CyA on bone, or since the decrease in BMD in transplant recipients is difficult to evaluate because CyA...
Angham Ahmed Hasan et al. “Int. J. Res. Pharm. Sci., 11(1), 200-206

Table 3: Ordinal regression analysis of the predictor of osteoporosis for spinal 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   |
| PO4              | 0.141| 1.151| 0.562-2.358      | 0.700   |
| ALP              | -0.003| 0.997| 0.986-1.008      | 0.591   |
| Vitamin D3       | 0.011| 1.011| 0.977-1.047      | 0.522   |
| PTH              | 0.001| 1.001| 0.995-1.008      | 0.644   |
| Albumin          | -0.023| 0.977| 0.275-3.475      | 0.971   |
| Calcium          | -0.315| 0.730| 0.379-1.406      | 0.346   |

OR: odd ratio, CI: confidence interval
It cannot be calculated for MMF

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   |
| PO4              | -0.444| 0.642| 0.292-1.409      | 0.269   |
| ALP              | 0.002| 1.002| 0.989-1.014      | 0.790   |
| Vitamin D3       | 0.020| 1.020| 0.982-1.061      | 0.308   |
| PTH              | 0.002| 1.002| 0.995-1.009      | 0.542   |
| Albumin          | 0.417| 1.517| 0.384-5.995      | 0.552   |
| Calcium          | -0.665| 0.514| 0.265-0.997      | 0.049   |

OR: odd ratio, CI: confidence interval
It cannot be calculated for MMF

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 (Marčen et al., 2007). In the present study, there was no correlation between the use of sirolimus and osteoporosis, which is in agreement with other studies (Hsu et al., 2016).

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 associated with osteoporosis risk.

Osteoporosis after kidney transplantation is multifactorial, while pathophysiologic mechanisms responsible for this condition are not completely elucidated. Pre-transplantation risk factors include the duration of dialysis, high or low parathormone (PTH) levels and preexisting bone disease.

is usually administered together with glucocorticoids (Martín-Fernández et al., 2017).
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 addition to the classical osteoporosis risk factors such as age and female gender (Dounousi et al., 2015).

CONCLUSIONS

Osteoporosis in post-renal transplant patients have a high rate of osteoporosis compared to the general population. Post-renal transplant drugs (Cyclosporine, MMF, etc.) did not increase the risk of osteoporosis, and Body mass index and gender were risk factors for osteoporosis.

REFERENCES

Bailey, M. A., Shirley, D. G., Unwin, R. J. 2015. Renal Physiology. In Comprehensive clinical nephrology. Philadelphia. Elsevier Saunders. 5th Edition.

Coco, M., Glicklich, D., Faugere, M. C., Burris, L., Bognar, I., Durkin, P., Malluche, H. 2003. Prevention of Bone Loss in Renal Transplant Recipients: A Prospective, Randomized Trial of Intravenous Pamidronate. Journal of the American Society of Nephrology, 14(10):2669–2676.

Dounousi, E., Leivaditis, K., Eleftheriadis, T., Liakopoulos, V. 2015. Osteoporosis after renal transplantation. International Urology and Nephrology, 47(3):503–511.

Durieux, S., Mercadal, L., Orcel, P., Dao, H., Rioux, C., Bernard, M., Bagnis, C. I. 2002. Bone mineral density and fracture prevalence in long-term kidney graft recipients. Transplantation, 74(4):496–500.

Ensrud, K. E., Crandall, C. J. 2017. Osteoporosis. Annals of Internal Medicine, 167(3):17–32.

Fritsche, L., Vanrenterghem, Y., Nordal, K. P., Grinyo, J. M., Moreso, F., Budde, K., Neumayer, H. H. 2000. Practice variations in the evaluation of adult candidates for cadaveric kidney transplantation. Transplantation, 70(10):1492–1497.

Gregorini, M., Sileno, G., Pattonieri, E. F., Corradetti, V., Abelli, M., Ticozzelli, E., Rampino 2017. Understanding Bone Damage After Kidney Transplantation: A Retrospective Monocentric Cross Sectional Analysis. Transplantation Proceedings, 49(4):650–657.

Hsu, B. G., Chen, Y. C., Ho, G. J., Shih, M. H., Chou, K. C., Lin, T. Y., Lee, M. C. 2016. Inverse Association Between Serum Osteoprotegerin and Bone Mineral Density in Renal Transplant Recipients. Transplantation Proceedings, 48(3):864–869.

Malluche, H. H., Monier-Faugere, M. C., Herberth, J. 2009. Bone disease after renal transplantation. Nature Reviews Nephrology, 6.

Marcen, R., Caballero, C., Pascual, J., Teruel, J. L., Tenorio, M., Ocana, J., Villafruela, J. J., Burgos, F. J., Fernandez, A. M., Muriel, A., Ortuno, J. 2006. Lumbar bone mineral density in renal transplant patients on neoral and tacrolimus: a four-year prospective study. Transplantation, 81:826–831.

Marcén, R., Caballero, C., Uriol, O., Fernández, A., Villafruela, J. J., Pascual, J., Ortunño, J. 2007. Prevalence of Osteoporosis, Osteopenia, and Vertebral Fractures in Long-Term Renal Transplant Recipients. Transplantation Proceedings, 39(7):2256–2258.

Martín-Fernández, M., Rubert, M., Montero, M., Piedra, C. 2017. Effects of Cyclosporine, Tacrolimus, and Rapamycin on Osteoblasts. Transplantation Proceedings, 49(9):2219–2224.

Mazzaferrro, S., Diacinti, D., Proietti, E., Barresi, G., Baldinelli, M., Pisani, D., Pugliese, F. 2006. Morphometric X-ray absorptiometry in the assessment of vertebral fractures in renal transplant patients. Nephrology Dialysis Transplantation, 21(2):466–471.

Rachner, T. D., Khosla, S., Hofbauer, L. C. 2011. Osteoporosis: now and the future. The Lancet, 377(10):62349–62354.

Shawkat, A. J., Jwaid, A. H., Awad, G. M., Fawzi, H. 2018. Evaluation of osteopathy in patients with beta-thalassemia major using different iron chelation therapies. Asian Journal of Pharmaceutical and Clinical Research, 11(11):467–471.

Smerud, K. T., Dolgos, S., Olsen, I. C., Åsberg, A., Sagedal, S., Reisaeter, A. V., Hartmann, A. 2012. A 1-Year Randomized, Double-Blind, Placebo-Controlled Study of Intravenous Ibandronate on Bone Loss Following Renal Transplantation. American Journal of Transplantation, 12(12):3316–3325.

Stein, E., Shane, E. 2013. Osteoporosis in Organ Transplant Patients, volume 56. Chapter, San Diego. Osteoporosis (Fourth Edition).

Torregrosa, J. V., Fuster, D., Gentil, M. A., Marcen, R., Guirado, L., Zarraga, S., Bravo, J., Burgos, D., Monegal, A., Muxi, A., Garcia, S. 2010. Open-label trial: effect of weekly risedronate immediately after transplantation in kidney recipients. Transplantation, 89:1476–1481.

Walsh, S. B., Altmann, P., Pattison, J., Wilkie, M.,
Yaqoob, M. M., Dudley, C., Cunningham, J. 2009. Effect of Pamidronate on Bone Loss After Kidney Transplantation: A Randomized Trial. American Journal of Kidney Diseases, 53(5):856–865.

Wiseman, A. C., Cooper, J. E. 2015. Prophylaxis and Treatment of Kidney Transplant Rejection. Comprehensive clinical nephrology. 5th Edition.

Wolfe, R. A., Ashby, V. B., Milford, E. L., Ojo, A. O., Ettenger, R. E., Agodoa, L. Y. C., Port, F. K. 1999. Comparison of Mortality in All Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant. New England Journal of Medicine, 341(23):1725–1730.