World of Science: Journal on Modern Research Methodologies

Volume 3 Issue 1, Year 2024
ISSN: 2835-3072
https://univerpubl.com/index.php/woscience

Detection the Associated Factors and Medications Used in Renal Transplantation of Osteoporosis Patients

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Article Information

Received: Nov 13, 2023
Accepted: Dec 22, 2023
Published: Jan 06, 2024

Keywords
Patients.

ABSTRACT

Background: *Osteoporosis is considered one of the complications that occur post renal transplantation. The pathophysiology of underlying bone disorders after renal transplantation results from a variety of causes, such as immunosuppression drugs and alterations in the parathyroid hormone level, vitamin D level as well as changes in mineral metabolism.*

Aim of study: *to detect the associated factors and medications used in renal transplantation of Osteoporosis in a sample of Iraqi patients.*

Patients and Methods: *A cross sectional study conducted in Baghdad Renal Transplant Center in Iraq, over a period of 12 months from Jan-2017 to Dec-2017 on 90 candidate (67 males and 23 females). A Questionnaire used to collect data, history was taken, thorough examination was done including height and weight to estimate BMI, all participants were sent for serum creatinine, serum calcium, serum phosphorus, parathyroid hormone, vitamin D.*

Results: *Mean age of study patients was 37.48 ± 12.96 years; 74.4% were males and 77.8% were married. 51.1% of them had normal body mass index and 71.1% lived in urban areas. The cause of renal transplant was unknown in 72.2% of cases and 93.3% of the patients did renal transplant once. Serum Calcium was normal in 70% of them. Osteoporosis was seen in 47.8% of cases. Diabetes mellitus, causes of renal failure and number of renal transplant, Vitamin D deficiency were considered as significantly associated with osteoporosis after renal transplantation.*

Conclusions: *There is a high prevalence of osteoporosis among Iraqi patients after renal transplantation. And they included several complications such as renal failure, number of renal transplantation and vitamin D deficiency were significant risk factors that associated with osteoporosis after renal transplantation.*

Introduction

Several factors have been demonstrated to be associated with osteopenia after renal transplantation including preexisting bone diseases, secondary hyperparathyroidism, and low bone mineral density due to advanced age and/or vitamin D deficiency, as well as post-transplant immunosuppressive therapy, steroid dose, and ongoing disorder in the phosphate-calcium-parathyroid hormone-vitamin D axis (1,2).

More recent publications of prospective trials that included patients managed with contemporary immunosuppression protocols have reported bone loss of only 0.1%–5.7% in the lumbar spine (3).

Loss of bone mass after kidney transplantation leading to osteopenia or osteoporosis occurs primarily in the first 12 months, predominantly in cortical bone. The most rapid decrease in bone mineral density (BMD) measured by dual-energy X ray absorptiometry occurs in the first six months' post-transplantation, and seems to slow down thereafter, possibly reflecting reduced corticosteroid dose. Osteoporosis characterized by reduced bone mass, impaired bone quality and a propensity to fracture. (4) This may be an issue in the post renal transplant population also. Multiple studies suggest that low bone turnover disease is common and is a major problem post renal transplant (5,6).

There are several factors that may precipitate or worsen hypercalcemia after successful kidney transplantation: Persistently elevated serum PTH, Correction of hyperphosphatemia, Improved 1,25(OH)2 vitamin D production from the allograft (2). So, this study amid to detect the association between this complication of Osteoporosis and other factors as causes of renal failure, electrolytes disturbances, medications used in post renal transplantation

Patients and Methods

Ethical consideration

Approval was taken from the Committee of Arab Board of Medical Specialization, oral consent was taken from each candidate to be enrolled in the study and confidentiality was taken in consideration.

Study design and setting

Across sectional study was conducted in Baghdad Renal Transplant Center in Iraq over a period of 12 months from Jan-2017 to Dec-2017 , a total of 90 patients (67 males and 23 females) aged 12 – 65 years who undergone a renal transplantation in the Iraqi center of renal transplant in Al-Shaheed Ghazi Al- Hareery Teaching Hospital were enrolled in the study. The data were collected through direct interview using a special questionnaire, history was taken and clinical examination was done including height and weight to calculate body mass index (BMI) which calculated according to the following formula:

BMI = Body weight(Kg) / Height(m)2, a normal BMI ranges between 18.5 -24.9 Kg/m2

Laboratory methods

Six ml of venous blood was taken from each candidate, and put in EDTA tube and send for measurement of serum creatinine, serum calcium, serum phosphorus, parathyroid hormone. Only 78 patients from the 90 patient was send for vitamin D.

Reference range of serum creatinine is (60 – 120mmol/l), for serum calcium is (8.5- 10.5 mg/dl), for serum phosphorous is (2.48 – 4.34), parathyroid hormone (16 – 75 pg/ ml), and vitamin D (> 50 nmol /L) (7).

Statistical analyses

The data analysed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Pearson's Chi–square test was used to assess statistical association between bone density levels and multiple variables. A level of P – value less than 0.05 was considered significant.

Results

General characteristics

The distribution of study patients by general characteristics is shown in table (1). Study patient's age ranged from 12 to 65 years with a mean of 37.48 years and standard deviation (SD) of ± 12.96 years. The highest proportion of study patients was found in age group 30 - 49 years (53.3%).

Regarding gender and residence, most of the patients were males (74.4%) and 71.1% of them were from urban area.

Concerning BMI level and marital status, the highest proportion of study patients had normal BMI level (51.1%) and the majority of them were married (77.8%).

Table 1: Distribution of study patients by general characteristics

Variable	No. (n=79)	Percentage (%)
Age (Years)		
< 19	42	26.7
10 - 49	24	53.3
≥ 39	84	20.0
Gender		
Male	67	74.4
Female	23	25.6
Residence		
Urban	64	71.1
Rural	26	28.9
BMI Level		
Under Weight	21	23.3
Normal	46	51.1
Over Weight	9	10.0
Obese	14	15.6
Marital status		
Married	70	77.8
Unmarried	20	22.2

Risk Factors of renal failure

The distribution of study patients by risk factors of renal failure is shown in table (2). In this study, the highest proportion of study patients didn't show a known risk factor for renal failure. (72.2%)

Table 2: Distribution of study patients by risk factor of renal failure

Risk factor of transplantation	No. (n=79)	Percentage (%)
Unknown	56	72.2
Nephrotic Syndrome	11	12.2
PCKD	5	5.6
Bladder Dysfunction	1	1.1
SLE	1	1.1
uncontrolled DM	7	7.8

Drug used after renal transplantation

Table (3) shows the distribution of study patients by drug used after renal transplantation. In this

study, all of study patients were using steroid (100%) and the highest proportion of study patients were using MMF, cyclosporin and azathioprine (97.8%, 73.3 and 97.8% respectively), on the other side the highest proportion of study patients were not using tocrolimus and sirolimus (78.9% and 91.1% respectively).

Table 3: Distribution of study patients by Post renal drag used

Drug used after renal transplantation	No. (n=79)	Percentage (%)
Steroid		
Yes	90	100.0
MMF		
Yes	88	97.8
No	2	2.2
Cyclosporin		
Yes	66	73.3
No	24	26.7
Tocrolimus		
Yes	19	21.1
No	71	78.9
Sirolimus		
Yes	8	8.9
No	82	91.1
Azathioprine		
Yes	2	2.2
No	88	97.8

Investigation

Table (4) shows the distribution of study patients by investigation. The highest proportion of study patients was having normal level of S. Calcium and S. Phosphate (70% and 91.1% respectively).

Regarding parathyroid hormone level, most of patients had high level of parathyroid hormone (57.8%) . Concerning Vit.D, the total number of study patients in this study was 78, most of them had low level of Vit.D (59%).

Table 4: Distribution of study patients by investigation

Investigation	No. (n=79)	Percentage (%)
S. Calcium		
Low	27	30.0
Normal	63	70.0
S. Phosphate		
Low	4	4.4
Normal	82	91.1
High	4	4.4
Parathyroid hormone		
Normal	38	42.2
High	52	57.8
Vit.D	**No=78**	
Low	46	59.0
Normal	32	41.0

Table (5) shows the association between bone density and investigation. The highest proportion of osteoporosis was seen among patients with low level of vit D (73.9%) with significant association (P=0.001) between Vit.D and bone density levels. There was no significant association between bone density and other investigations. ($P \geq 0.05$).

Table 5: Association between bone density level and investigation.

Variable	Bone Density Level			Total (%) n=79	P- value
	Group A Normal n= 8 (%)	Group B Osteopenia n= 39 (%)	Group C Osteoporosis n= 43 (%)		
S. Calcium					
Low	2 (7.4)	12 (44.4)	13 (48.1)	27 (30)	**0.948**
Normal	6 (9.5)	27 (42.9)	30 (47.6)	63 (70)	
S. Phosphate					
Low	0 (0.0)	3 (75.0)	1 (25.0)	4 (4.4)	**0.686**
Normal	8 (9.8)	34 (41.5)	40 (48.8)	82 (91.2)	
High	0 (0.0)	2 (50.0)	2 (50.0)	4 (4.4)	
Parathyroid hormone					
Normal	3 (7.9)	19 (50.0)	16 (42.1)	38 (42.2)	**0.551**
High	5 (9.6)	20 (38.5)	27 (51.9)	52 (57.8)	
Vit.D	**n=6**	**n=34**	**n=38**	**n=78**	
Low	1 (2.2)	11 (23.9)	34 (73.9)	46 (59.0)	**0.001**
Normal	5 (15.6)	23 (71.9)	4 (12.5)	32 (41.0)	

Number of renal transplantation

Table (6) shows the distribution of study patients by number of renal transplantation. The majority of study patients were undergone renal transplantation for the first time (93.3%).

Table 6: Distribution of study patients by number of renal transplantation

No. of renal transplantation	No. (n=79)	Percentage (%)
First	**84**	**93.3**
Second	**6**	**6.7**

Bone Density

The distribution of study patients by bone density level is shown in figure (1). In this study, 8.9% of study patients had normal bone density level 43.3% of them showed osteopenia and 47.8% of them showed osteoporosis.

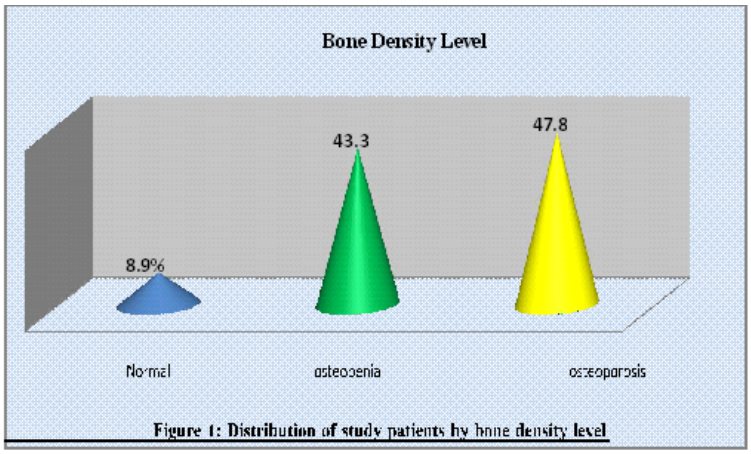

Figure 1: Distribution of study patients by bone density level

Table (7) shows the association between bone density and number of renal transplantation. All patients who did 2nd renal transplantation was diagnosed with osteoporosis (100%) with a significant association (P=0.029) between bone density level and no. of renal transplantations.

Table 7: Association between bone density level and number of renal transplantation.

Variable	Bone Density Level			Total (%) n=79	P- value
	Group A Normal n= 8 (%)	Group B Osteopenia n= 39 (%)	Group C Osteoporosis n= 43 (%)		
Number of renal transplantation					
First	8 (9.5)	39 (46.4)	37 (44.0)	84 (93.3)	
Second	0 (0)	0 (0)	6 (100.0)	6 (6.7)	**0.029**

Discussion

In this study we didn't find any risk factor for renal transplantation in the majority of the studied patients (72.2%), this was in agreement with the Iranian study that included 61 post-transplant patients in 2004, as they observed that unknown cause was the major risk factor that contributed to end-stage renal failure patients (57%) **(8)**.

A different result was obtained in the Chinese study conducted on 31 patients with transplantation in 2003, where unknown causes was found in only 3% of them **(9)**, Also the Egyptian study conducted in 2005 in which Sixty adult male recent renal transplant recipients were enrolled into the study and found that main causes of end- stage renal disease were chronic interstitial nephritis in 23 patients (38%) and the least was hereditary nephritis in 4 patients (6%) **(10)**.

Different results in a study in 2003 in china involved 31 patients with renal transplant, in all study patient's the mean of serum PTH concentration decreased one year after transplantation **(11).** Baseline biochemical investigations performed in Egypt in 2005 showed that average serum calcium levels were found in most of the patients; however, the values were near the lower limit of normal in 35 patients (64%) **(10)**.

In our study osteoporosis was found among those with low levels of vitamin D , this can be explained by the fact that low vitamin D levels leads to physiological increase of PTH (secondary hyperparathyroidism) and an increase in bone resorption and a decrease in the bone density level and bone mineralization. The vitamin D deficiency can explained due to dietary restriction, reduced sun exposure, and the fact of decreased skin synthesis of vitamin D in patients with chronic illness. **(12, 13)**

These difference observed between studies can be attributed to the fact that patients were in different post transplantation durations and disturbances in biochemical and hormonal levels is seen more in the first months after transplantation. The number of renal transplantations in the same patient was significantly associated with osteoporosis (P=0.029), where all patients who did 2nd renal transplantation had osteoporosis (100%), this may be explained by the recurrent courses of long term corticosteroid administration beside other comorbidities risk factors of osteoporosis. An agreement was observed with Turkish study in 2010 that included 70 patients with renal transplants, they noticed at a median duration of 23 months after renal transplantation, osteopenia or osteoporosis was observed among 30 (42.9%) or 30 (42.9%) of the 70 patients, respectively, and agreed in that it was significantly associated with vit D level (P = 0.26), in addition to no relation observed between density and age, gender, use of a vitamin D preparation, immunosuppressive regimen, post-transplantation period, levels of iPTH or 25 hydroxyl vitamin D3 (25OH vit D), exposure to tacrolimus or cyclosporine (P > 0.05) **(14)**.

The differences observed between previous studies might be attributed to the difference in sample size in each study, as a study with larger sample size may show more significant relationship between them in comparison to that of that with small sample size, furthermore, Factors that have been suggested to have a role in the pathogenesis of osteoporosis after transplantation include high daily and cumulative dosage of corticosteroids, the type and duration of immunosuppressive agents persistent hyperparathyroidism, may have contributed to these differences **(11)**.

Conclusion

There is a high prevalence of osteoporosis among Iraqi patients after renal transplantation. And they included several complications such as renal failure, number of renal transplantation and vitamin D deficiency were significant risk factors that associated with osteoporosis after renal transplantation.

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