

How to Cite:

Hothefa, B. K., AlKazaz, F. F., & Naser, S. H. (2022). Bone status and renal transplantation. *International Journal of Health Sciences*, 6(S6), 6926–6934. <https://doi.org/10.53730/ijhs.v6nS6.11950>

Bone status and renal transplantation

Baqer K. Hothefa

Chemistry Department, College of Science, Mustansiriyah University, Iraq

*Corresponding author email: bakerloveyou@gmail.com

Fatin F. AlKazaz

Chemistry Department, College of Science, Mustansiriyah University, Iraq

Salwa H. Naser

Chemistry Department, College of Science, Mustansiriyah University, Iraq

Abstract--Renal transplant is the organ transplant of a kidney into a patient with end-stage kidney disease (ESRD). It is important to regularly monitor the new kidney's function by measuring serum creatinine and other laboratory measurements at least every three months for the rest of the person's life. The pathophysiology underlying bone disorders after transplantation are resulted from a complex interplay of factors. Current review aims to investigate the bone status of the patients after renal transplant by evaluating their physical and clinical bone tests(PTH ,vit D3,ALP,Ca,P,Mg and DEXA scan). The clinical utility of serum markers of bone turnover . para thyroid hormone levels drop by half in the first six months following transplantation, but remain elevated in almost half of kidney transplant patients two years later. Levels of 1,25-dihydroxy vitamin D [1,25(OH)2D] have been linked to improved kidney function. After kidney transplantation, serum calcium generally follows a biphasic pattern. After 3-6 months after transplantation, hypercalcemia has been recorded in about 5%–15% of patients. Hypophosphatemia is frequent in the early post-transplant period, with 50% of acute kidney transplant patients experiencing it. The increase in the hormone PTH, which works to withdraw these elements from the bones and replace them in the blood, causes a decrease in bone density due to the change in bone metabolism during and after the kidney transplantation process, as well as the increase in the time period after the transplant process. In conclusion recipients kidney transplant were suffered of osteopenia and osteoporosis after transplantation surgery. Therefore it should prognosis the tests of bone turnover.

Keyword--renal transplantation, end-stage kidney disease (ESRD), serum, pathophysiology.

Introduction

Kidney transplantation is the optimal treatment for improving survival and quality of life for patients with end-stage kidney disease (ESKD) ⁽¹⁾ The objective throughout the early stages is to avoid acute rejection and infection. After 3–6 months, the focus shifts to preserving transplant function and preventing long-term immunosuppressive drug problems (the medication used to suppress the immune system to prevent rejection). Outpatient follow-up, immunosuppressive medicine, acute and chronic rejection management, and complication avoidance are among the topics highlighted. ⁽²⁾ When it comes to solid organ transplantation, one of the most difficult immunological challenges is detecting non-self-structures in the donor cells. In organ transplantation, human leukocyte antigens (HLA) are the most significant non-self-antigens. Patients might also develop antibodies to targets other than HLA. ⁽³⁾ Over the last decade, researchers have looked at a variety of non-HLA antibody targets in kidney transplantation.

Recent research suggests that non-HLA mismatches between donors and recipients are important in the development of acute rejection and long-term kidney allograft outcomes. ⁽⁴⁾ However, the problems seen in these individuals in the first year following transplantation need hospitalization. These problems are mostly caused by immunosuppressive medicines or infections caused by the immune system being suppressed. ⁽⁵⁾ Post-transplantation neurological complications are common; 30-60% of the patients are at the risk of neurological complications ⁽⁶⁾. Neurological complications increase the mortality rate of the patients and they are not the same for all patients⁽⁷⁾Immunosuppressive medicines, stroke, peripheral neuropathy, infection, and malignant tumors are all examples of post-transplantation neurological problems. The neurological poisoning of immunosuppressive medicines causes a slew of post-transplant problems. ⁽⁸⁾.

Disordered mineral metabolism is a common complication of CKD that begins early in the course of disease and progressively worsens as patients approach ESRD.⁽⁹⁾ Hyperphosphatemia, hypocalcemia, deficits of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and substantially high levels of parathyroid hormone (PTH) and fibroblast growth factor 23 are all symptoms of disturbed mineral metabolism in ESRD (FGF23).⁽¹⁰⁾ Individually and in aggregate, these alterations are associated with increased risks of cardiovascular disease, fracture, and death.⁽¹¹⁾ Although restoring normal kidney function by transplanting a healthy kidney might be expected to fully reverse disordered mineral metabolism due to ESRD, most existing data suggest that transplantation only partially corrects certain alterations.⁽¹²⁾ Furthermore, presence of a healthy allograft that can respond to the hormonal effects of lingering elevations in PTH and FGF23 levels can precipitate de novo alterations in mineral metabolism, including hypercalcemia and hypophosphatemia.^{19,20} Posttransplant hypercalcemia and hypophosphatemia present clinicians with management challenges because they may jeopardize graft function and bone health and exacerbate fracture and cardiovascular risk.⁽¹³⁾ The post kidney transplant period should be considered a unique phase in the natural history of disordered mineral metabolism associated with CKD that requires dedicated investigation.¹⁴

Few studies have systematically studied mineral metabolism in the posttransplant period. Among those that did, most previous studies were small, single-center, brief, and failed to measure a comprehensive panel of mineral metabolites.⁽¹⁴⁾ As a result, the frequency of hypercalcemia, hypophosphatemia, and persistent hyperparathyroidism during the first year after kidney transplantation remain incompletely characterized. We conducted the current prospective, observational study to examine the evolution of persistent hyperparathyroidism and associated alterations in mineral metabolism during the first year after kidney transplantation.

Experimental

The materials were used in present study purchased as following, Alkaline Phosphatase, Calcium, Magnesium, Phosphorus, Vitamin D3 and Parathyroid hormone. All patients and healthy subjects fasted for approximately 10-14 hours before drawing blood. About 10 ml of venous blood samples were taken tube without adding anticoagulant. Blood samples were left for 30 minutes at room temperature to coagulate and then the sera were separated by centrifuge at 1500 ×g for 10 min. Hemolyzed samples were discarded and the sera were stored and frozed at -17° C until time of analysis. The SPSS version 26.0 was used for t-test statistical analyses to obtaining the results. Also, mean and standard deviation (mean±SD) utilized to explain the results. The one hundred twenty samples classified three groups according to their period after transplantation.

- Group I as a patients less than 6month kidney transplant
- Group II as a patients from 6month to 5 years kidney transplant
- Group III as a patients more than 5 years kidney transplant
- Group IIII as a control group

Results and Discussion

Table 1-1
ANOVA Test clinical parameters in patients G1, G2, G3 and control groups

Parameters	C SD ±Mean	G1 SD± Mean	G2 SD± Mean	G3 SD± Mean	P Value
PTH pg/mL	67.70±18.22	85.44±28.26	125.80±63.88	187.57±83.57	*0.0001
ALP(U/L)	72.97±14.63	101.87±33.24	99.48±42.19	89.17±25.65	*0.001
D3 ng/mL	29.01±8.50	19.16±5.80	20.79±7.39	16.66±8.26	*0.0001
Ca(mmol/mL)	9.68±0.32	9.64±0.47	9.36±0.50	9.04±1.16	*0.001
P(mg/dL)	3.41±0.26	3.00±0.62	3.10±0.59	3.36±0.67	*0.01
Mg(mg/dL)	2.2±0.25	0.25±0.31	9.01±0.21	3.8±0.56	*0.0001
DEXA	0.55±0.21	-0.89±0.36	-1.94±0.89	-2.72±0.672	*0.0001

C: control group

G1: less than 6 months Kidney Transplant

Significant at $P \leq 0.05$

G2: more than 6 months less 5 years Kidney Transplant

no Significant at $P \leq 0.05$

G3: more than 5 years Kidney

The results of the PTH show the decrease in the value of the hormone during a period of 3 to 6 months(G1) due to the idle and income patent of the parathyroid gland during this period and then it continues its work by absorbing the Calcium from the bones to the blood and excessive secretion of the hormone is a risk indicator of osteoporosis, as it works to withdraw calcium from the bones and excrete it in the blood to obtain a normal percentage of calcium in the blood, and this explains the reason why calcium during the first months is a normal rate After the first year to 5 years of transplantation(G2), the level of PTH increased to compensate for the decrease in the value of calcium, but it is insufficient or not equal to the normal value, so the calcium in this period is less than calcium in the first months, due to hyperparathyroidism during the first months. Much more after this period, so calcium during the first period of implantation is normal and begins gradually decline, which is a very dangerous indicator of osteoporosis.

The current results of PTH support the finding data of Lou I, Foley D, Odorico SK, Levenson G, Schneider DF, Sippel R, Chen (2015)⁽¹⁵⁾ PTH reduces by 50% after 6 months but stays high in approximately 45 percent of kidney transplant recipients 2 years after transplantation due to changes in calcium, phosphorus, and vitamin D3 levels linked with improved renal function, according to researchers. Bonarek H, Merville P, Bonarek M, Moreau K, Morel D, Aparicio M (2004)⁽¹⁶⁾ They found that PTH levels drop rapidly (by about 50%) during the first 3-6 months, which they attribute to a decrease in parathyroid functional mass; however, beyond this first period, the drop in PTH is more gradual. Perrin P, Caillard S, Javier RM, Braun L, Heibel F, Borni-Duval C, Muller C, Olagne J, Moulin B(2013)⁽¹⁷⁾ They came to the conclusion that high PTH levels are associated with considerable bone loss in the hip, with PTH being more catabolic to cortical than trabecular bone. Persistent hyperparathyroidism (PTH.130 ng/L) was found to be an independent risk factor for fracture in a single-center study of 140 kidney transplant patients after three months, with a 7.5-fold increase in fracture risk.

The results for phosphorous in the study were consistent with other studies from Wolf M, Weir MR, Kopyt N, Mannon RB, Von Visger J, Deng H, Yue S, Vincenti(2016)⁽¹⁸⁾ they showed that level of phosphate in the first kidney transplantation period is low, because of the It is usually self-limiting, reflecting an improvement in excretory kidney function that supported in current study is that phosphate levels are low for patients in the first 6 months of kidney transplantation (G1)and begin to rise as the time period for kidney transplant increases due to the increase in the value of the PTH, which works to compensate for phosphorus from the bones in the blood.

Result of Ca their level for patients during the first months of implantation is high(G1), due to the excessive activity of the parathyroid gland and thus the rise in the parathyroid hormone during the first three months., and thus a decrease in the value of calcium, which is also caused by a deficiency in the value of vitamin D3 this study are agreement with the following study by Bonthuis M, Busutti M, van Stralen KJ, Jager KJ, Baiko S, Bakkaloglu S, et al. Mineral. (2015)⁽¹⁹⁾ . Hypercalcemia is common after kidney transplantation and has been reported in 11–31% of kidney transplant within 1 year. Evenepoel P, Van Den Bergh B, Naesens M, De Jonge H, Bammens B, Claes K (2009)⁽²⁰⁾ . Stop taking calcium

supplements via intravenous injection and vitamin D3 through pills that were given in the stages of kidney failure and stop giving them during kidney transplantation affect the value of calcium and lead to a decrease in its value in the long run, but the effect is slight.

The results of vitamin D3 show a decrease in its value for patients, the decreasing continues with the increase in the time of transplantation, and this decrease is one of the most important reasons that lead to osteoporosis in kidney transplant recipients, in addition to the lack of health awareness among patients to take this vitamin because of its great importance to compensate for the deficiency in this vitamin. Current results are compatible with the following studies: McGregor, R.; Li, G.; Penny, H.; Lombardi, G.; Afzali, B.; Goldsmith, D3. 2014⁽²¹⁾ Low serum vitamin D levels are frequently found in the immediate post-transplant period, and also in long-term graft recipients. In about one third of post-renal transplant recipients, even after successful engraftment, vitamin D3 levels tend to be low when compared to healthy individuals. Calcitriol levels fall in the post-transplant period, which is attributed to the use of steroids and other immunosuppressive medications. Steroids inhibit the activity of one α hydroxylase, potentially leading to a reduction in calcitriol levels. Obi Y, Hamano T, Ichimaru N, Tomida K, Matsui I, Fujii N, et al. 2014⁽²²⁾

Hypovitaminosis D3, defined by serum levels of D3 less than 30 ng/ml, is common among patients referred for kidney transplantation. It occurs mainly during the first months after transplantation and may be related to limited sunlight exposure and sun blockers use, hepatic dysfunction and use of Glasgow Coma Scale, which may increase catabolism of vit D3. Study demonstrated that vitamin D deficiency predicted a rapid decline in renal function in kidney recipient patients. Magnesium results show that there is an increase in magnesium with the increase in the time period of kidney transplantation, and this increase comes with an increase in the value of the parathyroid hormone as well as a decrease in calcium and vitamin D3 due to the relationship between magnesium and these factors. In PTH with an increase in the time period and also the functions of Mg to transport calcium, and we notice an increase in Mg with a decrease in calcium, as it works to transfer the largest possible amount of calcium from bones to the blood to reduce calcium deficiency. Vitamin D3 inhibits the absorption of magnesium with an increase in this vitamin in the blood and with decrease in D3 and increase in thyroid hormone. We note an increase in magnesium with an increase in the time period for kidney transplantation. This was supported in a study. Yu AS. Swaminathan 2001⁽²³⁾ suggest a role for parathyroid hormone (PTH) in regulating magnesium absorption, but the role of vitamin D and its active metabolite 1,25 dihydroxyvitamin D is more controversial. Phytates in the diet bind to magnesium and impair its absorption. Vetter T, Lohse MJ. 2002⁽²⁴⁾ No single hormone has been shown to be specifically related to magnesium homeostasis. Several hormones including PTH is the most important. PTH increases reabsorption in the distal tubules by a cyclic AMP mediated process.

The results of the DEXA

Scan in figure 3-8 are supported by the fact that a decreasing in bone density with an increased time after kidney transplant compared to healthy subjects.

due to the change in bone metabolism and compensation that occurs from the bones in the blood and the apparent decrease in bone density, which exposes the person to fractures due to the weak structure of the bones. these results are compatible of the study of Iyer SP, Nikkel LE, Nishiyama KK, Dworakowski E, Cremers S, Zhang C, McMahon DJ, Boutroy S, Liu XS, Ratner LE, Cohen DJ, Guo XE, Shane E, Nickolas (2014).⁽²⁵⁾ Syrazah Salam, Pierre Delanaye, Richard Eastell, and Arif Khwaja (2016) ⁽²⁶⁾ Bone and mineral disorders occur frequently in kidney transplant recipients and are associated with a high risk of fracture, morbidity, and mortality. There is a broad spectrum of often overlapping bone diseases seen after transplantation, including osteoporosis as well as persisting high- or low-turnover bone disease. Carolina A. M. Kulak, Victoria Z. C. Borba, Jaime Kulak Júnior, Melani Ribeiro Custódio , (2014)⁽²⁷⁾ reported that Bone loss is a common complication that occurs in transplant recipients. Osteoporosis and fragility fractures are serious complication , mainly in the first year post transplantation.

Table 1-2
The correlation coefficients and p-value for D3,PTH and ALP level and other parameters for patient with G3 group

Parameters	G3					
	PTH		D3		ALP	
	r	P	r	P	r	P
Age	-0.163	0.437	0.085	0.685	0.398	*0.049
Height	-0.026	0.900	0.000	1.000	0.011	0.958
Weight	-0.262	0.206	0.163	0.436	0.404	*0.045
BMI	-0.329	0.109	0.212	0.309	0.484	*0.014
Ca	-0.569	**0.003	0.450	*0.024	0.303	0.141
	0.499	*0.011	-0.325	0.113	-0.219	0.294
Mg	-0.035	0.869	-0.070	0.739	0.026	0.902
Na	-0.040	0.850	0.441	*0.027	0.006	0.976
K	-0.043	0.837	-0.039	0.855	0.228	0.273
Cl	0.117	0.576	-0.020	0.926	-0.292	0.156
Total Protein	-0.399	*0.048	0.473	*0.017	0.236	0.256
Glucose	0.021	0.922	-0.007	0.972	0.240	0.248
Bu	0.448	*0.025	-0.171	0.413	-0.409	*0.043
Cre	0.586	**0.002	-0.169	0.418	-0.427	*0.033
Alb	0.169	0.419	0.044	0.835	-0.143	0.495
Globin	-0.471	*0.017	0.431	*0.032	0.301	0.143

*: correlation significant at $p \leq 0.05$

**: correlation significant at $p \leq 0.01$

r: Pearson correlation coefficient

G3: more than 5 years Kidney Transplant

For patients with kidney transplant after 5 year i.e.G3 the correlation study for three parameter PTH,vit D3,and ALP with all other studied parameters had obtained the following :

There is a positive moderate correlation between PTH and ,P (r=0.499), Bu(r=0.448),and strong with Cre(r=0.586).

And a negative correlation between PTH and Ca($r=-0.569$), Total Protein ($r=-0.399$) and Globin($r=-0.471$).

For Vit D3 has a positive correlation with Ca($r=0.450$), Na($r=0.441$), Total Protein ($r=0.473$) and globin($r=0.431$)

Finally ALP has a positive correlation with Age($r=0.398$), weight($r=0.404$), and BMI($r=0.484$) and negative correlation with Bu($r=0.409$) and Cre($r=0.427$).

Table 1-3 demonstrated the PTH performance with (0.965) area under the curve (AUC), 84% sensitivity and 93.3% specificity at > 94 pg/mL cutoff value

Table 1-3
ROC curve analysis of test variables for patients in G3 and control groups

Test variable	Sensitivity %	Specificity %	Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
						Lower Bound	Upper bound
PTH	84.0	93.3	0.965	0.0202	0.000	0.876	0.996

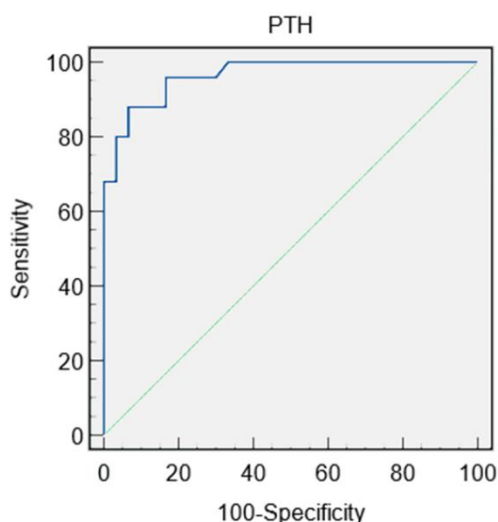


Figure 1-1. ROC curve of PTH for patients and control groups

Aim of Study

The current study aimed to evaluate the Bone Status of the patients after transplanted their Kidney in different period. To achieve the aim it should determine PTH, vit D3, ALP, Ca, P, and Mg in sera of patients after transplanted their Kidney and DEXA scan through three periods less than 6 months (G1), between 6 months to 5 years (G2) and more than 5 years (G3) and compare with healthy control group.

Conclusion

According to the result obtained from this work it includes the following points:

- PTH, Mg, ALP level significantly increase With an increase in the time period after kidney transplant.
- Ca, P, Vit D3 level significantly decrease With an increase in the time period after kidney transplant.
- DEXA scan It shows a significant loss in bone density with the increase in the time period after kidney transplantation, and it shows the presence of osteoporosis expected after 5 years of kidney transplantation.

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