The Relationship Between Pre-Transplant Serum Phosphorus Before Kidney Transplantation with Early Graft Dysfunction

Boshra Hasanzamani,[1] Nasrin Karimi,[2] Mahin Ghorban Sabbagh,[1] Hasan Mahrad Majd[3]

[1]Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Mashhad University of Medical Sciences, Mashhad, Iran
[3]Clinical Research development Unit, Mashhad University of Medical Sciences, Mashhad, Iran

Keywords. delayed graft function, kidney transplantation, phosphorus, chronic kidney disease

Original Paper

Introduction. Pre-transplant serum phosphorus level is shown to be associated with some transplant outcomes in patients with chronic kidney disease. However, its association with Delayed graft function (DGF) has an aura of ambiguity. DGF means either the patient needs dialysis during the first week after transplantation or the creatinine level is ≥ 3. This study was aimed to assess the relationship between pre-transplant serum phosphorus levels with DGF.

Methods. A total of 306 patients, who had undergone kidney transplantation in the Montaserieh organ transplantation hospital in Mashhad, Iran, during 2016 to 2019; were enrolled in this study. Demographic data and clinical characteristics of patients including dialysis type and duration, donor type, medications, pre-transplant serum levels of calcium, phosphorus and DGF development were measured. Then, all patients were divided into five groups according to their serum phosphorus: $P < 3.5$, $3.5 \leq P < 5.5$, $5.5 \leq P < 7.5$, $7.5 \leq P < 9.5$, and $P \geq 9.5$ mg/dL. The association with DGF was evaluated by statistical analysis.

Results. Patients age ranged from 18.00 to 64.00 years old, with an average of 37.08 ± 10.9. About 55.6% of them were men, and 26.1% came up with DGF. Among patients with DGF, 36.25% were recipients with pre-transplant phosphorus level of $3.5 \leq P < 5.5$ and 50% of $5.5 \leq P < 7.5$.

Conclusion. Our study suggested that pre-transplant serum phosphorus might be associated with an increased risk of delayed graft function. Further studies are needed to assess, whether adjusting serum phosphorus level before kidney transplantation could reduce delayed graft function or not.

IJKD 2021;15:148-54
www.ijkd.org

INTRODUCTION

As chronic kidney disease (CKD) progresses and glomerular filtration rate (GFR) declines, CKD's clinical and laboratory complications emerge. CKD is associated with disorders of mineral and bone metabolism that manifest as hypocalcemia and hyperphosphatemia which lead to calcium deposition in extra-osseous tissues like vascular bed and soft tissue, end up with calciphylaxis.[1]

Hyperphosphatemia can induce vascular calcification. Forty (40) to 92% of patients on dialysis have evidence of vascular calcification,[2] and atherosclerotic plaques are significantly more calcified in patients with end-stage renal disease.[3,4] Serum phosphorus level is associated with mortality, cardiovascular disease, and kidney

function loss in CKD patients.[5] It has been shown that serum phosphorus level over 6.5 to 7 mg/dL is significantly associated with increased mortality in CKD patients, and serum phosphorus in the range of 3.5 to 5.5 mg/dL is considered to be an optimal level in therapeutic guidelines.[6] Renal transplantation is the treatment of choice for ESRD patients. After kidney transplantation, almost all of the graft recipients from live donors and about half of the cadaveric grafts maintain a good renal function and serum creatinine reaches average level.[7]

It is supposed that successful renal transplantation could normalize metabolic and endocrine disorders, that lead to dialysis associated secondary hyperparathyroidism, in a few months after transplantation; however, despite proper renal function the disease persists in many kidney recipients even one year after transplantation, and some of these patients require parathyroidectomy.[8]

Delayed graft function (DGF) is the most common kidney transplant complication encountered in the immediate post- transplantation period (met in the initial days after surgery); that, despite several medical considerations before surgery, occurs in 8 to 50% of kidney transplants from cadaveric donors in USA.[9]

In most studies, the reported incidence of DGF ranges from 20 to 50% in deceased donors and 4 to 10% in living donor kidney transplant recipients.[10] Clinical manifestations of DGF vary along a spectrum of severity from a slightly slowing decrease in serum creatinine to prolonged oliguria requiring dialysis. DGF consequences include prolonged hospitalization, higher cost (burden financial) of transplantation, more complex immunosuppressive regimens, and an adverse effect on the rehabilitation programs of allograft recipients.[9] It has been demonstrated that DGF is associated with poor long term patient and graft survival.[9-13] Since DGF imposes significant adverse effects on patient and graft survival and also to improve renal transplantation outcomes, this is widely approved to identifying risk factors that could contribute to DGF. Several studies have addressed this issue.[9-12,14-23] The risk factors identified by different researchers could be generally categorized in three main fields: 1) donor-related: as age, expanded criteria donor, donor's comorbidity like hypertension and stroke-caused death, high BMI, right sided renal graft, positive panel reactive antibody, HLA mismatching; 2) Recipient-related: age, high BMI, smoking, comorbidities like ischemic cardiomyopathy and dyslipidemia, dialysis type and duration before transplantation, gender, ethnicity, pre-transplant hemoglobin, transfusion history, serum calcium, and phosphorus levels; and 3) Surgery related: cold ischemic time, anastomotic time, allograft handling and maintenance.

The role of pre-transplant serum phosphorus level in DGF is controversial. In native kidneys, phosphaturia can cause calcium-phosphate deposition in the tubules, which may trigger a local inflammatory response and lead to tubular obstruction and, ultimately, to kidney failure. These mechanisms may recur in the renal transplant and play a role in graft dysfunction.[24] The crystal deposition creates a focus of inflammation that may progress to fibrosis and renal failure.[25] The present study addressed the pre-transplant serum phosphorus' association with DGF.

MATERIALS AND METHODS

After checking for exclusion criteria, 306 patients who had undergone renal transplantation in Montaseriah organ transplantation hospital, in Mashhad, Iran; 2016 to 2019 were enrolled in this study. All the patients had filled out the informed consent form to be included in this study. Exclusion criteria included: poor compliance, other causes of kidney dysfunction such as infection, surgical complications, high serum levels of the drug, severe liver disease, peritonitis over the past three months, having dementia, unstable blood sugar, and blood pressure. Data were collected from Montaseriah organ transplant hospital's archive in Mashhad, Iran. Demographic data, underlying disease, dialysis type and duration, transplant medications, pre-transplant calcium and phosphorus levels, donor type (live or cadaveric), and DGF development were recorded. Calcium level was not corrected with serum albumin, because it has been reported that in CKD patients, albumin-corrected calcium cannot accurately estimate ionized calcium.[26]

DGF was defined as the need for dialysis during the first week after transplantation or creatinine at the fifth day ≥ 3 mg/dL. The Patients were divided into five groups according to their pretransplant serum phosphorus: $P < 3.5$, $3.5 \leq P < 5.5$, $5.5 \leq P < 7.5$, $7.5 \leq P < 9.5$, $P \geq 9.5$ mg/dL, and

DGF development was assessed in each group.

Continuous variables were evaluated by student t-test and categorical variables by the chi-square test. Significant values were considered as $P < .05$. All data were analyzed by SPSS version 22.

RESULTS

A total of 306 patients aged 18 to 64 years old (mean age 37.08 ± 10.9 years old), consisting of 170 (55.6%) men, were enrolled. ESRD causes included diabetes 32 (10.5%), hypertension 65 (21.2%), autosomal dominant polycystic kidney disease (ADPKD) 15 (4.9%), vesicoureteral reflux 14 (4.6%), glomerulonephritis 46 (16%), unknown 115 (37.6%), and other causes 16 (5.2%).

The medications used were from two main categories: The first group was calcineurin inhibitors (113 (36.9%) cyclosporine, 193 (63.1%) tacrolimus) and the second group was anti-metabolites (169 (55.2%) mycophenolate mofetil (CellCept), 137 (44.8%) mycophenolic acid (Myfortic)). The baseline characteristics of the 306 patients are summarized in Table 1.

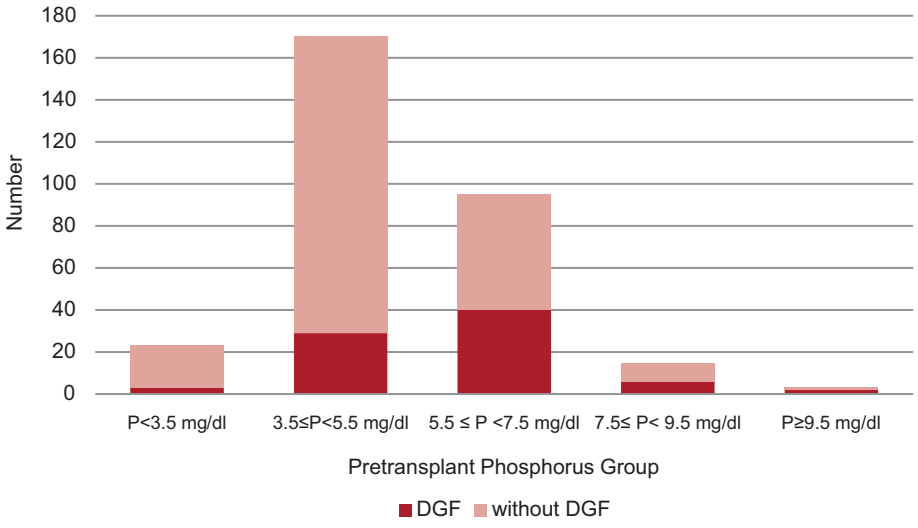
Table 1. Baseline Characteristics of Patients Included in the Study

Variables	n (%) or mean ± SD
Age, y	37.08 ± 10.9
Gender (Male)	170 (55.6)
Donor	
Cadaveric	241 (78.8)
Live	65 (21.2)
Dialysis	
Hemodialysis	269 (87.9)
Peritoneal dialysis	23 (7.5)
Preemptive	14 (4.6)
Dialysis Time, mo	28.46 ± 16.94
Calcium, mg/dL	8.79 ± 0.9
Phosphorus, mg/dL	5.1 ± 1.3
Ca-P Product	45
ESRD cause	
Diabetes	32 (10.5)
Hypertension	65 (21.2)
ADPKD	15 (4.9)
Vesicoureteral reflux	14 (4.6)
Glomerulonephritis	49 (46)
Unknown	115 (37.6)
Other	16 (5.2)

Abbreviations: SD, standard deviation; Ca-P, calcium phosphate.

DGF developed in 80 (26.1%) patients. Patients were divided into five groups according to their pre-transplant serum phosphorus levels: $P < 3.5$, 23 (7.5%); $3.5 \leq P < 5.5$, 170 (55.6%); $5.5 \leq P < 7.5$, 95 (31%); $7.5 \leq P < 9.5$, 15 (4.9%); and $P \geq 9.5$, 3 (1%) mg/dL. DGF developed in 3 (3.75%) of group 1, 29 (36.25%) in group 2, 40 (50%) in group 3, 6 (7.5%) in group 4, and 2 (2.5%) in group 5; respectively. 69 (86.25%) of patients with DGF were among the second and third groups with a pre-transplant serum phosphorus 3.5 to 7.5 mg/dL. Total numbers of patients with and without DGF in each phosphorus group are presented in figure. Fischer's exact test revealed a significant relationship between pre-transplant serum phosphorus and incidence of DGF ($P < .001$).

The relationship between different factors and



DGF in 5 Pretransplant Phosphorus Groups (Abbreviation: DGF, delayed graft function; P, phosphorus).

DGF such as age, gender, pre-transplant calcium and phosphorus levels, donor type, dialysis type and duration, ESRD cause, and used medications was studied and summarized in Table 2. The mean duration of dialysis in patients with DGF was 33.3 ± 16.31 months and in patients, without DGF it was 26.75 ± 16.86 months; which showed a significant relationship with DGF ($P < .05$).

The mean pre-transplant serum phosphorus level in patients with DGF was 5.79 ± 1.46 mg/dL, and in patients; without DGF it was 4.86 ± 1.2 mg/dL. Serum phosphorus was significantly associated with the development of DGF ($P < .001$). The mean value of calcium-phosphorus product in patients with DGF was 51.55 ± 13.89, and in the patients; without DGF, was 42.68 ± 12.39. This relationship was also significant by the t-test ($P < .001$). The relationship between the donor type (living or cadaveric) and DGF was assessed by the chi-square test, which showed a close to considerable value ($P = 0.057$). Hemodialysis, as a dialysis type,showed a substantial association with DGF by the chi-square test ($P < .05$). There was no meaningful relationship between ESRD causes, age, gender, pre-transplant serum calcium levels, and DGF in our study ($P > .05$, $P > .05$, $P > .05$, and $P > .05$; respectively).

DISCUSSION

In this retrospective study among 306 kidney transplant patients, DGF occurred in 26.1%, which was similar to previous studies. We showed a statistically significant relationship between pre-transplant phosphorus level and calcium phosphorus product with DGF.

Serum phosphorus level is associated with mortality and cardiovascular events in dialysis patients and kidney recipients as well as affecting

Table 2. Comparison Between DGF Groups According to Different Demographic Characteristics and Serum Factors

Variables	DGF n (%) or Mean ± SD	Without DGF n (%) or Mean ± SD	*P*
Age	38.38 ± 11.26	36.61 ± 10.76	> .05
Gender			
Men	61.3	53.5	> .05
Women	38.7	46.5	
Calcium, mg/dL	8.89 ± 0.92	8.75 ± 0.9	> .05
Phosphorus, mg/dL	5.79 ± 1.46	4.86 ± 1.27	< .001
Calcium Phosphate Product	51.55 ± 13.89	42.68 ± 12.39	< .001
Donor			
Cadaveric	28.6	71.4	> .05
Live	16.9	83.1	
Dialysis			
Hemodialysis	28.3	71.7	< .05
Peritoneal Dialysis	17.4	82.6	
Pre-emptive	0	100	
Dialysis Time, mo	33.3 ± 16.31	26.75 ± 16.86	< .05
ESRD Cause			
Diabetes	31.3	68.8	> .05
Hypertension	32.3	67.7	
ADPKD	26.7	73.3	
Vesicoureteral Reflux	0.0	100	
Glomerulonephritis	30.6	69.4	
Unknown	22.6	77.4	
Other	25	75	
Pretransplat Phosphorus Groups, mg/dL			
P < 3.5	13	87	< .001
3.5 ≤ P <5.5	17.1	82.9	
5.5 ≤ P < 7.5	42.1	57.9	
7.5 ≤ P < 9.5	40.0	60.0	
P ≥ 9.5	66.7	33.3	

Abbreviations: DGF, delayed graft function; ADPKD, autosomal dominant polycystic kidney disease; ESRD, end stage renal disease; P, phosphorus.

patients and graft survival.[25]

However, serum phosphorus could be well adjusted by medications (such as phosphate binders, vitamin D analogs, and calcimimetics) and also adherence to dietary restrictions. Therefore, if further studies prove that pre-transplant phosphorus level as a definite risk factor for DGF, we would be able to take essential steps in preventing DGF. Several studies have been performed on serum phosphorus and DGF with different results. A survey by Calabia *et al* in 2009 on the effects of bone and mineral metabolism parameters before kidney transplant on early outcomes in 449 patients, pre-transplant calcium and phosphorus levels and PTH didn't show any significant relationship with DGF.[18] In this study the mean serum phosphorus in patients with DGF was 5.7 ± 1.8, and in patients, without DGF; it was 5.5 ± 1.5 mg/dL. This finding may be due to relatively lower levels of serum phosphorus in these patients. Moreover, this study with a relatively small number of patients could not be representing of all kidney recipients' population. Roodnat *et al.* reported an association between PTH, but not phosphorus, and increased graft failure.[27] In 2011, Sampaio *et al.* studied pre-transplant serum phosphorus and post-transplant outcomes in 9384 kidney recipients; they reported that pre-transplant serum phosphorus had a significant relationship with all-cause mortality and cardiovascular events, but not with DGF.[25] Despite an acceptable sample size and variable levels of phosphorus in this study, it had some limitations. They mentioned that medications that could influence serum phosphorus were not available and not considered. It is possible that recipients with a similar phosphorus levels have different degree of severity regarding the metabolic bone disorder, and therefore different levels of vascular damage.

Some studies showed similar results with our research. A cohort study conducted by Sampaio and colleagues found that serum phosphorus levels were associated with kidney transplant prognosis. In this study, it was shown that serum level of phosphorus higher than 5 mg / dL increases the risk of DGF. They also showed that at serum phosphorus levels greater than 9.5 mg / dL, the mortality rate was significantly higher than phosphorus level ranges between 3.5 to 5.5 mg / dL.[26]

In a study conducted by Ahmadi *et al.*, they examined the relationship between calcium, phosphorus, parathyroid hormone, and DGF. In this study, it was concluded that patients with DGF had higher amounts of phosphorus levels and also in these patients the product of calcium-phosphorus was at the top.[29] Another study by Chang *et al.* on 241 kidneys transplant patients followed for one year showed that high levels of phosphorus were a risk factor for primary impaired renal function.[33]

In our study, dialysis type as hemodialysis and the duration of dialysis before transplantation showed a significant relationship with DGF. This issue has been addressed in previous studies. Some of them reported similar results.[19,21] In a survey by Joachim, which was a Meta-analysis and reviewed the articles from 1980 to 2014, they reported that peritoneal dialysis before transplantation is associated with a lower risk of DGF compared with hemodialysis.[22] In our study, hemodialysis as a type of dialysis was significantly associated with DGF. However, this finding could be of low statistical value and power owing to relatively fewer patients on peritoneal dialysis. Although, in a study by Vanholder that was a case-control with an equal number of patients on hemodialysis and peritoneal dialysis, DGF occurred in hemodialysis patients more frequently.[20] However, in some studies, dialysis modality did not influence DGF risk.[30,31]

In our study, the duration of dialysis before transplantation had a significant relationship with DGF. Patients with DGF had been on dialysis longer than patients without DGF. A similar finding was described in a study by Mogulla.[10] Considering the above results in several studies, it seems that selecting peritoneal dialysis initially in patients who are transplantation candidates and minimizing the duration on dialysis before transplantation, could be useful steps in reducing DGF risk and better transplantation outcomes.

Our study showed no significant relationship among recipient age, gender or pre-transplant serum calcium with DGF. This could be a result of lower mean age and homogeneity of the patients' age compared with other studies. However, some studies found a significant relationship between the recipient and donor age and DGF.[9,12,14,18] Ahmadi *et al.* showed no meaningful relationship between DGF and recipient age.[28] In this study, all the kidney recipients had living donors with

lower mean age and comorbidities. Taking into consideration of the retrospective nature of this study, we had some limitations; this study lacks some data that could influence DGF incidence, such as donor's age, patients' BMI, smoking status, and cold ischemic times. The medications used before transplantation that could alter serum phosphorus levels were not considered. Hence, further studies with higher sample size, and collaboration of multiple transplantation centers in order to collecting precise and comprehensive information of kidney recipients and donors, would yield better results.

CONCLUSION

In our study, pre-transplant serum phosphorus levels showed significant relationship with developing DGF. Since it has been demonstrated that DGF could influence graft and patient survival, therefore, optimizing serum phosphorus level before renal transplantation, as a modifiable risk factor for DGF, could have a high impact on renal transplant outcomes. Moreover, it seems that choosing peritoneal dialysis modality for transplantation candidates and reducing the duration on dialysis before transplantation as much as possible, may reduce DGF risk and improve patient and graft survival.

Further studies are needed to assess, whether adjusting serum phosphorus level before kidney transplantation could reduce delayed graft function incidence.

ACKNOWLEDGMENT

This study was supported by research project number 961480 as an MD student dissertation (No 961480), at Mashhad University of Medical Sciences. The authors would like to express their sincere appreciation to the staff of the Clinical Research Development Unit of Ghaem Hospital of Mashhad University of Medical Sciences, for facilitating data analysis.

REFERENCES

1. Kasper D, Fauci A, Hauser S, Longo D, Jameson J. Harrison's Principles of Internal Medicine. New York: McGraw-Hill Education; 2015.
2. Cannata-Andia JB, Rodriguez-Garcia M. Hyperphosphataemia as a cardiovascular risk factor -- how to manage the problem. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2002;17 Suppl 11:16-9.
3. Amann K, Gross ML, London GM, Ritz E. Hyperphosphataemia--a silent killer of patients with renal failure? Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 1999; 14(9):2085-7.
4. Schwarz U, Buzello M, Ritz E, et al. Morphology of coronary atherosclerotic lesions in patients with end-stage renal failure. 2000; 15(2):218-23.
5. Voormolen N, Noordzij M, Grootendorst DC, et al. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. 2007; 22(10):2909-16.
6. Massry SG, Coburn JW, Chertow GM, et al. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. 2003; 42(4 SUPPL. 3).
7. Wilkinson AJHoKT, ed. The "first quarter". The first three months after transplantation. 2010; 5:213.
8. Schaeffner ES, Födinger M, Kramar R, Sunder-Plassmann G, Winkelmayer WCJTI. Prognostic associations of serum calcium, phosphate and calcium phosphate concentration product with outcomes in kidney transplant recipients. 2007; 20(3):247-55.
9. Ojo AO, Wolfe RA, Held PJ, Port FK, Schmouder RLJT. Delayed Graft Function: Risk Factors and Implications for Renal Allograft Survival1. 1997; 63(7):968-74.
10. Mogulla MR, Bhattacharjya S, Clayton PA. Risk factors for and outcomes of delayed graft function in live donor kidney transplantation - a retrospective study. Transplant international: official journal of the European Society for Organ Transplantation. 2019; 32(11):1151-60.
11. Yarlagadda SG, Klein CL, Jani AJAickd. Long-term renal outcomes after delayed graft function. 2008; 15(3):248-56.
12. Martínez EG, Mateu LP, Calabuig AS, et al., editors. Delayed graft function after renal transplantation: an unresolved problem. Transplantation proceedings; 2011: Elsevier.
13. Gjertson DWJCt. Impact of delayed graft function and acute rejection on kidney graft survival. 2000; 467-80.
14. Irish W, Ilsley J, Schnitzler M, Feng S, Brennan DJAjot. A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. 2010; 10(10):2279-86.
15. Lebranchu Y, Halimi J-M, Bock A, et al. editors. Delayed graft function: Risk factors, consequences and parameters affecting outcome—results from MOST, A Multinational Observational Study. Transplantation proceedings; 2005: Elsevier.
16. Molnar MZ, Kovesdy CP, Rosivall L, et al. Associations of pre-transplant anemia management with post-transplant delayed graft function in kidney transplant recipients. Clinical transplantation. 2012; 26(5):782-91.
17. Troppmann C, Gillingham KJ, Benedetti E, et al. Delayed graft function, acute rejection, and outcome after cadaver renal transplantation. The multivariate analysis. Transplantation. 1995; 59(7):962-8.
18. Rodrigo Calabia E, Ruiz San Millán JC, Gago Fraile

M, et al. Changes in the pre-transplant bone-mineral metabolism do not affect the initial outcome of the renal graft. 2009; 29(2):143-9.

19. Resende L, Guerra J, Santana A, Mil-Homens C, Abreu F, da Costa A, editors. Influence of dialysis duration and modality on kidney transplant outcomes. Transplantation proceedings; 2009: Elsevier.
20. Vanholder R, Heering P, Van Loo A, et al. Reduced incidence of acute renal graft failure in patients treated with peritoneal dialysis compared with hemodialysis. 1999; 33(5):934-40.
21. Goldfarb-Rumyantzev AS, Hurdle JF, Scandling JD, Baird BC, Cheung AKJAJoKD. The role of pretransplantation renal replacement therapy modality in kidney allograft and recipient survival. 2005; 46(3):537-49.
22. Joachim E, Gardezi AI, Chan MR, Shin J-I, Astor BC, Waheed SJPDI. Association of pre-transplant dialysis modality and post-transplant outcomes: a meta-analysis. 2017; 37(3):259-65.
23. Tugmen C, Sert I, Kebabci E, et al. Delayed Graft Function in Kidney Transplantation: Risk Factors and Impact on Early Graft Function. Progress in transplantation (Aliso Viejo, Calif). 2016; 26(2):172-7.
24. Evenepoel P, Lerut E, Naesens M, et al. Localization, etiology and impact of calcium phosphate deposits in renal allografts. 2009; 9(11):2470-8.
25. Sampaio MS, Molnar MZ, Kovesdy CP, et al. Association of pretransplant serum phosphorus with posttransplant outcomes. 2011; 6(11):2712-21.
26. Gauci C, Moranne O, Fouqueray B, et al. Pitfalls of measuring total blood calcium in patients with CKD. 2008; 19(8):1592-8.
27. Roodnat JI, van Gurp EA, Mulder PG, et al. High pretransplant parathyroid hormone levels increase the risk for graft failure after renal transplantation. 2006; 82(3):362-7.
28. Ahmadi F, Ali-Madadi A, Lessan-Pezeshki M, et al. Pre-transplant Calcium-Phosphate-Parathormone Homeostasis as a Risk Factor for Early Graft Dysfunction. 2008; 19(1):54-8.
29. Sapir-Pichhadze R, Parmar K, Kim SJ. Pretransplant serum phosphate levels and outcomes after kidney transplantation. Journal of nephrology. 2012; 25(6):1091-7.
30. Molnar MZ, Mehrotra R, Duong U, et al. Dialysis modality and outcomes in kidney transplant recipients. Clinical journal of the American Society of Nephrology: CJASN. 2012; 7(2):332-41.
31. Yang Q, Zhao S, Chen W, et al. Influence of dialysis modality on renal transplant complications and outcomes. Clinical nephrology. 2009; 72(1):62-8.

Correspondence to:
Boshra Hasanzamani, MD
Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
E-mail: hasanzamanib@mums.ac.ir

Received October 2020
Revised December 2020
Accepted February 2021