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ARAŞTIRMA / RESEARCH

Risk factors for development of rejection in kidney transplant patients

Böbrek nakilli hastalarda rejeksiyon gelişimi için risk faktörleri

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Abstract

Purpose: The aim of this study was to evaluate the parameters that may be a risk factor for the development of rejection in our patient population.
Materials and Methods: The results of the biopsies performed in our organ transplantation unit were evaluated retrospectively. Demographic data of the patients about primary renal disease, concomitant disease and laboratory data in the time of biopsy were recorded. Forty-nine biopsies made for 45 patients and the results were compared.
Results: The most common cause of kidney biopsy was acute renal injury (34 biopsies, 69.4%). Histopathological examination revealed rejection in 23 (46.7%) biopsies. BK nephropathy was detected in 4 patients (8,1%), while the calcineurin inhibitor toxicity was found in 10 patients (20.5%). Chronic allograft nephropathy was observed in 11 biopsies (22.6%) and recurrent glomerulonephritis was detected in 1 biopsy (2.1%). Serum glucose, uric acid and total cholesterol levels were higher and hemoglobin levels were lower in the rejection group. By logistic regression analysis, uric acid and glucose elevation were defined as independent risk determinants for the development of rejection.
Conclusion: Hyperuricemia and hyperglycemia may predict the development of rejection after renal transplantation.

Keywords:. kidney transplantation, rejection, uric acid, hyperglycemia

Öz

Amaç: Bu çalışmada, kendi hasta populasyonumuzda böbrek nakil rejeksiyonu gelişimi için risk faktörü olabilecek parametrelerin değerlendirilmesini amaçladık.
Gereç ve Yöntem: Organ nakli ünitemizde yapılan nakil böbrek biyopsilerin sonuçları retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, primer böbrek hastalıkları, eşlik eden hastalıkları ve perkütan iğne biyopsisi anındaki laboratuar verileri kaydedildi. 45 hastaya yapılan 49 adet biyopsi verileri karşılaştırıldı.
Bulgular: Böbrek nakilli 45 hastaya yapılan toplam 49 biyopsi incelendiğinde biyopsi yapılma endikasyon sıklığı en sık olarak 34 biyopsi (%69.4) ile akut böbrek hasarı idi. Histopatolojik inceleme ile 23 (% 46.7) biyopside rejeksiyon saptandı. BK nefropati saptanan biyopsi sayısı 4 iken (%8.1), ilaç toksisitesi olarak kalsinörin inhibitörü toksisitesi 10 biyopside (%20.5) ve kronik allograft nefropatisi de 11 biyopside (%22.6) görüldü. 1 biyopside (%2.1) tekrarlayan glomerulonefrit saptandı. Rejeksiyon saptanan grup rejeksiyon saptanmayan grupla karşılaştırıldığında biyopsi anında serum glukoz, ürik asit ve total kolesterol düzeylerinin yüksek, hemoglobin değerlerinin daha düşük olduğu belirlenmiştir (hepsi için. Lojistik regresyon analizi ile, ürik asit ve glukoz yüksekliği rejeksiyon gelişimi için bağımsız risk belirleyicileri olarak tanımlanmıştır.
Sonuç: Hiperürisemi ve hipergliseminin böbrek nakli sonrası rejeksiyon gelişimini öngörebileceği düşünülmüştür.

Anahtar kelimeler: Böbrek nakli, rejeksiyon, ürik asit, hiperglisemi

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INTRODUCTION

Rejection is one of the most important reasons of graft dysfunction after renal transplantation. Acute and chronic rejection may have negative impacts on short and long-term graft survival rates. Defining the risk factors of rejection may increase patient and graft survival[1,2].

Immunologic events are the most important problems in organ transplantation. Rejection has two types, namely, antibody-mediated rejection and T cell-mediated rejection. Antibody-mediated rejection is associated with rapid decrease in graft function, macroscopic hematuria, oliguria, sodium and fluid retention, edema, hypertension, painful enlargement of graft kidney, fever, rapid increase in acute phase reactants, and fast deterioration of kidney function. Although determination of anti-donor antibodies, colored Doppler renal ultrasonography, and radionuclide investigation may help diagnosis, the final diagnosis is made by graft kidney biopsy[3].

Acute T cell-mediated rejection mostly occurs between the third and the sixth post-transplant months and its incidence gradually decreases after the sixth post-transplant month. It develops as a result of T-cell activation. Acute T cell-mediated rejection is associated with decrease in graft function and acute inflammation. Early diagnosis and treatment of acute T cell-mediated rejection increases the possibility of preservation of kidney function. Acute T cell-mediated rejection may be misdiagnosed as cyclosporine and tacrolimus nephrotoxicity, acute tubular necrosis or infection. Although cyclosporine and tacrolimus levels may be helpful for differential diagnosis, they may be misleading. Dynamic and static renal scintigraphy, colored doppler renal ultrasonography and microbiological evaluations may be used in order to differentiate acute T cell-mediated rejection from infections. However, graft biopsy is required for final diagnosis. Especially after the use of cyclosporine and tacrolimus, acute cellular rejection may be subclinical and asymptomatic. Over time, this may lead to irreversible graft damage. Histopathological evaluation is important to direct treatment and prognosis[4].

The 2009 KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guideline defined renal biopsy indications for renal transplantation as persistent and unexplained increase in serum creatinine that has not returned to baseline after treatment of acute rejection, new onset of proteinuria, unexplained proteinuria ≥ 3.0 g per 24 hours, and failure to achieve expected kidney function within the 1-2 months after renal transplantation despite the surveillance of delayed function every 7-10 days5. "Protocol biopsy" is the type of biopsy that does not harm the renal functions of renal transplant patients with high rejection risks. Today, protocol biopsy is only suggested for surveillance of patients with high rejection risk since it does not have an impact on graft survival. Indication practices of renal biopsy vary among centers[6,7]. On the other hand, "indicated biopsy", which is done in renal transplant patients for various reasons, still holds its importance8.

Recognition of risk factors for the development of rejection may increase patient and graft survival. In this study, we aimed to evaluate the parameters that may be a risk factor for the development of rejection in our patient population.

MATERIALS AND METHODS

The study was conducted at the Nephrology Transplantation Clinic of the Diskapi Yilidirm Beyazit Education and Research Hospital with the participation of 45 participants, who had been monitored between 1 January 2013 and 31 May 2017. Written informed consent was obtained from all participants. All patients were included in the study after signing informed consent forms. The study was performed in accordance with Declaration of Helsinki. The study design was approved by local ethical committee (date: May 15, 2017; reference number: 38/33).

Renal biopsy was made due to progressive renal dysfunction, hematuria, or proteinuria. All of the participants had biopsy at least once whereas one patient had biopsy three times and two patients had twice. So, we analyzed a total of 49 renal biopsies made in 45 participants. The results of routine tests conducted during the diagnosis, treatment and follow-up periods were taken from the patient records. No intervention was made by the researchers to the routine treatment process.

Statistical analysis

Analysis of data obtained from 45 patients participated in the study is analyzed by using Statistical Package for the Social Sciences (SPSS) for Windows computer program (release 22.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics

of patient's demographic and laboratory features is expressed for quantitative variables, frequency and percentage (%) are expressed for qualitative variables. Normality tests of quantitative variables are analyzed by using "Kolmogorov-Smirnov and Shapiro Wilk". "One Way Analysis of Variance (ANOVA)" is used for comparison of two or more where variables were normally distributed. Groups of control's and patients' quantitative variables are compared with "Independent Samples –T Test". For Qualitative variables "Chi-Square and Fisher's Exact Tests " were used.

Possible risk factors for the rejection were analyzed by using "Multivariate Binary Logistic Regression Analysis". Statistical tests were applied at 95% confidence level and conclusions were evaluated by calculating the *p*-value.

RESULTS

45 patients were included in the study. Reasons for End Stage Renal Disease (ESRD) of the renal transplant patients were shown in Table 1. Etiology of renal failure was as follows: diabetes for six patients (13.3%), hypertension for 16 patients (35.6%), glomerulonephritis for 13 patients (28.9%), post renal factors for five patients (11.1%) and unknown for five patients (11.1%).

Table 1. Etiology of renal failure.

Primary Kidney Disease	n (%)
Hypertension	16 (35.6)
Glomerulonephritis	13 (28.9)
Diabetes	6 (13.3)
Postrenal causes	5 (11.1)
Unknown	5 (11.1)

n: number of the patients %: percentage

Table 2 shows the indications of the 49 biopsies made in 45 patients (Table 2. Indications of Renal Biopsy). Accordingly, acute renal injury is the primary reason of indications with 34 biopsies (69.4%), followed by nephrotic range proteinuria with 7 biopsies (14.3%), non-nephrotic proteinuria with 5 biopsies (10.2%) and microscopic hematuria with 3 biopsies (6.1%).

Table 2. Indications of Renal Biopsy

Indications	n (%)
Acute kidney injury	34(69.4)
Nephrotic range proteinuria	7(14.3)
Non-Nephrotic proteinuria	5(10.2)
Microscopic hematuria	3(6.1)

n: number of the renal biopsy %: percentage

Table 3. Histopathological results.

Results	n (%)
Rejection	23 (46.7)
Acute antibody-mediated rejection	8 (16.3)
Chronic antibody-mediated rejection	7 (14.2)
Acute T cell-mediated rejection	4 (8.1)
Chronic T cell-mediated rejection	4 (8.1)
Chronic allograft nephropathy	11 (**22.6**)
Calcineurin inhibitor toxicity	10 (**20.5**)
BK nephropathy	4 (8.1)
Recurrent glomerulonephritis	1 (**2.1**)

n: number of the renal biopsy %: percentage

Table 4. Demographic and laboratory features of the patients at the time of biopsy

Parameter(unit)	Patient (n=45)
Age (years)	38.8±9.59
Gender	
Female (n, %)	11(24.4%)
Male (n, %)	34 (75.6%)
Diabetes mellitus (n, %)	6 (13.3%)
Hypertension (n, %)	16 (35.5%)
Atherosclerotic cardiovascular disease (n, %)	3 (6.6%)
Smoking (n, %)	4 (8.8%)
Stroke (n, %)	2 (4.4%)
Dialysis vintage (years)	7.3±4.611
Dialysis type	
Hemodialysis (n, %)	42 (93.3%)
Peritoneal dialysis (n, %)	2 (4.4%)
Preemptive kidney transplantation (n, %)	1 (2.2%)
Donor type	
Living (n, %)	30 (66.6%)
Deceased (n, %)	15 (33.4%)
Transplantation time (years)	4.91±1.83
Hemoglobin (g/dL)	10.64±1.33
Glucose (mg/dL)	89±19.29
Albumin (g/dL)	3.81±0.568
Uric acid (mg/dL)	7.49±1.26
Urea (mg/dL)	70.57±35.07
Creatinine(mg/dL)	2.86±1.1
GFR (ml/min/1.73m^2)	40.05±14.77
Total Cholesterol (mg/dL)	191.42±29.09
Triglyceride (mg/dL)	171.91±53.30
CRP (mg/L)	10.75±8.55
CSA level (ng/ml)	366.8±183.33
TAC level (ng/ml)	5.88±4.98
Sirolimus level (mg/ml)	3.79±1.70
Everolimus level (ng/ml)	4±0

DM, Diabetes Mellitus; HT, Hypertension; GFR, Glomerular Filtration Rate; CRP, C Reactive Protein; CSA, Cyclosporine A; TAC, Tacrolimus

Table 3 demonstrates the histopathological results of the 49 biopsies. The results were acute T cell-mediated rejection (n=4, 8.1%) and acute antibody-mediated rejection in 8 biopsies (n=8, 16,3%) Chronic T cell-mediated rejection (n=4, 8.1%) and chronic antibody-mediated rejection (n=7, 14.2%). C4d staining was positive in all of the antibody-mediated rejections in kidney transplant biopsies. BK nephropathy was found in 4 biopsies (8.1%), calcineurin inhibitor toxicity was detected in 10 biopsies (20.5%), and chronic allograft nephropathy was found in 11 biopsies (22.6%). Recurrent glomerulonephritis was detected in one patient (2.1%).

Table 4 shows demographic and laboratory features of the patients at the time of biopsy (Table 4. demographic and laboratory features of the patients at the time of biopsy). Average age of the patients was 38.8±9.59 years. 11 patients were female (24.4%). Co morbidity analysis reveals that 6 patients (13.3%) had diabetes mellitus (DM), 16 (35.5%) had hypertension (HT), 3 (6.6%) had atherosclerosis. Pre-transplant period was 7.3±4.611 years. During the pre-transplant period, 42 patients (93.3%) were on hemodialysis, 2 patients (4.4%) were on peritoneal dialysis. One patient (2.2%) had preemptive kidney transplantation. 30 patients (66,6%) received transplant from living donors. The average period between primary diagnosis and transplantation was 4.91±1.83 years. Laboratory features of the patients at the time of biopsy can be seen in table 4.

Table 5. Comparison of the renal biopsy results of the rejection and non-rejection patients with their demographic characteristics and laboratory features at the time of biopsy

Parameter	Rejection (+) group (n=22)	Rejection (-) group (n=27)	P value
Age (years)	38±10	40±9	0.399
Gender Male (n, %)	20(90.9%)	18(66.7%)	0.043
DM (n, %)	5(22.7%)	7(25.9%)	0.682
HT (n, %)	8(36.4%)	13(48.1%)	0.407
Aterosclerotic cardiovascular disease (n, %)	3(6.6%)	-	-
Smoking (n, %)	4(8.8%)	-	-
Stroke (n, %)	2(4,4%)	-	-
Dialysis vintage(years)	9,32±4,64	5,67±3,96	0,005
Dialysis type			
HD (n, %)	20(90.9%)	26(96.3%)	0.191
PD (n, %)	2(9.1%)	-	-
Preemptive kidney transplantation (n, %)	-	1(3.7%)	-
Hemoglobin(g/dL)	10.22±1.04	10.99±1.47	0.044
Glucose(mg/dL)	96.95±15.68	82.52±19.79	0.008
Albumin(g/dL)	3.70±0.50	3.92±0.61	0.178
Uric acid(mg/dl)	8.06±1.02	7.03±1.28	0.004
Urea(mg/dL)	64.77±30.13	75.30±38.56	0.301
Creatinine Baseline value before /biopsy (mg / dl)	2.21±1.12	2.13±1.04	0.790
Creatinine Current (mg / dl)	3.03±1.06	2,.73±1.15	0.363
GFR epi/ Baseline value before biopsy (ml/min/1.73m^2)	45.40±18.54	44,99±23,22	0.949
GFR epi current (ml/min/1.73m$^{2)}$	37.64±12.63	42.03±16.28	0.306
T-Chol(mg/dl)	204.00±33.06	181.19±20.92	0.005
TG (mg/dl)	186.86±62.53	159.74±41.76	0.076
CRP (mg/L)	13.75±8.25	8.32±8.15	0.025
CSA level(ng/ml)	380.25±255.77	357.83±144.94	0.881
TAC level(ng/ml)	5.60±7.15	6.09±2.51	0.772
Sirolimus level (mg/ml)	3.80±1.70	0±0	-
Everolimus level(ng/ml)	0±0	4±0	-

DM, Diabetes Mellitus; HT, Hypertension; HD, Hemodialysis; PD, Peritoneal Dialysis; GFR, Glomerular Filtration Rate; T-chol, Total Cholesterol; TG, Triglyceride; CRP; C Reactive Protein; CSA, Cyclosporine A; TAC, Tacrolimus

Table 6. Logistic regression model for defining histopathologic risk factors that trigger posttransplant development of acute or chronic rejection (model p = 0.004, constant -14.684).

	Odds ratio	% 95 CI	P
Dialysis vintage (years)	0.923	0.756-1.126	0.428
Hemoglobin (g/dl)	0.853	0.502-1.451	0.558
Glucose (mg/dl)	1.063	1.003-1.126	0.040
Uric acid (mg/dl)	2.034	1.056-3.917	0.034
Total cholesterol (mg/dl)	1.030	0.999-1.061	0.58

Immunosuppressive therapies received by the patients at the time of biopsy were as follows: 29 patients (64.4%) received mofetil mycophenolate (MMF) + tacrolimus (TAC) + Steroid, 5 patients (11.1%) received MMF+cyclosporin (CSA) + Steroid, 4 patients (8.8%) received Azathioprine (AZA)+TAC+Steroid, 3 patients (6.6%) received AZA+CSA+Steroid, 2 patients (4.4%) received MMF+Everolimus+Steroid, and 2 patients (4,4%) received MMF+Sirolimus+Steroid.

Histopathological diagnosis was as follows: 23 biopsies were diagnosed with rejection, which was followed by chronic allograft nephropathy (CAN) (11 biopsies), calcineurin inhibitor toxicity (CIN) (10 biopsies), BK nephropathy (4 biopsies), and recurrent nephropathy (1 biopsy).

Table 5 compares the 23 biopsies that were diagnosed with rejection with the 26 non-rejection biopsies (4 BK nephropathy, 1 recurrent glomerulonephritis, 10 CIN, 11 CAN) (Table 5 Comparison of the renal biopsy results of the rejection and non-rejection patients with their demographic characteristics and laboratory features at the time of biopsy). The comparison found no difference between the rejection and non-rejection patients in terms of age (p=0.399, p>0. 05). However, male gender had more rejection (p=0,043, p<0.05).

Regarding co-morbidity, we found no difference between the rejection and non-rejection patients in terms of DM and HT frequency (p=0.682, p=0.407). We also found that all the 3 patients with coronary artery disease, 2 patients with stroke and 4 smokers were in the group of rejection.

We found statistically significant difference between the rejection and the non-rejection patients in terms of dialysis vintage (p=0,005, p<0.05). Besides, glucose, uric acid, total cholesterol (TC), and C reactive protein (CRP) levels were significantly higher in the rejection group (p=0.008, p=0.004, p=0.005, p=0.025 p<0.05). Finally, hemoglobin was lower in the rejection group (p=0.044).

There was no statically significant difference between rejection and non-rejection groups in terms of albumin, triglyceride, creatinine and glomerular filtration rate (GFR) (p=0.178, p=0.076, p=0.363, p=0.306, p>0.05). CSA and TAC levels were similar in both groups (p=0.881, p=0.772 p>0.05). We could not make statistical comparison for the patients who received mammalian target of rapamycin inhibitors (mTORi) since all of the patients that received sirolimus were in the rejection group whereas the patients that received everolimus were all in the non-rejection group.

Serum, glucose, uric acid, and total cholesterol levels of the rejection group at the time of biopsy were higher whereas hemoglobin value was lower (p<0.05). We conducted logistic regression analysis to determine the independent risk factors for rejection. As a result, uric acid and glucose were determined as independent risk markers for rejection development (p<0.05) (Table 6. Logistic regression model for defining histopathological risk factors that trigger post-transplant development of acute or chronic rejection).

DISCUSSION

Kidney transplantation is the most effective way for the treatment of end stage renal failure because of a significant survival advantage and a better quality of life[9]. This study aimed to evaluate the parameters that may pose a risk for the development of rejection that had renal biopsy.

The analysis of the primary etiologies in Table 1 shows that hypertension was the primary reason of renal failure for 16 patients (35.5%), which was followed by glomerulonephritis for 13 patients (28.8%) and diabetes for 6 patients (13.3%). Our findings are parallel to the study of Seyahi et al., who analyzed the records of the Turkish Nephrology Association and found HT (18%),

glomerulonephritis (14%), pyelonephritis 9%) and DM (8%) as the reasons of renal failure in Turkish transplant patients[10].

Histopathological results of 45 patients in this study reveals that CAN detected in 11 biopsies (22.4%)- was the second most frequent biopsy result after rejection. Calcineurin inhibitor toxicity as drug toxicity was found in 10 biopsies (20,4%), which was followed by acute antibody-mediated rejection in 8 biopsies (16.3%), chronic antibody-mediated rejection in 7 biopsies (14.2%), BK nephropathy, acute T cell-mediated rejection and chronic T cell-mediated rejection in 4 biopsies each (8.1%), and recurrent glomerulonephritis in 1 biopsy (2,03%). In this sense, rejection was found as the most frequent histopathological result of this study.

We compared the clinic, demographic and laboratory features of the rejection and non-rejection patients. Age was not statistically significantly different between groups (p=0.399) while male gender had more rejection (0.043). Studies about the relationship between the gender of the donors and receivers found conflicting results. An important difference between the female and male receivers is the higher sensitivity of the female receivers to the human leucocyte antigens, and perhaps to other antigens, because of pregnancy and menstruation[11] (11). The study of Almond et al, which analyzed the risk factors of chronic rejection for 587 renal transplant patients, found chronic rejection in 103 patients and stated acute rejection episodes, CsA dosage < 5 mg/kg/day at 1 year, infections, female gender as risk factors[12]. In this sense, unlike our findings, Almond et al. found female gender as a risk factor for chronic rejection.

In this study CRP was higher in rejection group. Higher CRP in rejection, which may be considered as an indicator of inflammation, is an expected finding and this is supported by other studies. The study of Maury and Teppo analyzed CRP and other acute phase proteins to predict renal allograft rejection and found that although serum amyloid A (SAA) and beta 2-microglobulin are better markers, CRP may be useful to aid the early recognition and verification of acute allograft rejection[13]. In the study of Fink et al. CRP was significantly higher in the chronic allograft nephropathy group in respect to control group[14].

In Our study serum glucose, uric acid and total cholesterol levels were higher in rejection group whereas hemoglobin values were lower at the time of biopsy (p<0,05). In Logistic regression analysis higher uric acid and glucose levels were found to be independent risk markers for rejection (p<0.05).

Higher uric acid level is a modifiable risk factor for cardiovascular diseases[15]. Experimental models show that hyper-uricemia attenuates nitric oxide generation and activation of renin angiotensin aldosterone system that simulates vascular smooth muscle cell proliferation. Renal arteriolar hypertrophy decreases renal perfusion. Hyper-uricemia plays a role in inflammation, endothelial dysfunction and chronic renal disease pathogenesis[16].

Limited number of studies on uric acid in renal transplantation found conflicting results. The study of Akgul et al in 133 renal transplant patients found that uric acid level had no effect on the development of CAN during the first year after transplantation[17]. Similarly, the study of Meier-Kriesche et al. in 852 renal transplant patients found no association between uric acid levels that were measured one month after transplantation and 3-years renal function[18]. The study of Kim et al did not find any association between elevated uric acid and graft outcome and proposed that the effect of uric acid may be an indicator of nutritional status[19].

Unlike these findings above, Gerhardt et al. analyzed 5-year post-kidney transplantation records of 350 kidney transplant recipients and found that hyperuricemic kidney transplant recipients had a lower renal survival rates compared to normouricemic patients (68.8% and 83.3%, respectively)[20]. Similarly, the study of Akalin et al., in 307 renal transplant patients for six months, found an association between hyper-uricemia and CAN[21]. Harrian et al. analyzed 212 recipients of living donor kidneys and found an association of hyperuricemia with graft failure[22]. Retrospective analysis of Kun et al. after three-year follow-up of renal transplant patients found a higher level of graft loss for the hyperuricemic patients[23]. Finally, recent study of Deok et al.in 241 transplant patients, found an association between hyperuricemia and renal allograft fibrosis[24].

Although hyperuricemia has been noted as one of the factors that may affect long-term allograft outcomes, various studies listed above[17,18,19]. defined uric acid not to be an independent risk factor for graft loss. These studies vary in terms of analysis time and statistical methods. Previous studies about hyper-uricemia focused on estimated glomerular filtration rate (eGFR) or graft loss as the final point. Unlike

these studies, the study of Deok et al. underlined the relationship between hyper-uricemia and renal allograft fibrosis[24]. Different from the existing studies, our study conducted logistic regression analysis in order to find out the statistically significant independent risk factors that may be used to detect rejection in the patients who had renal biopsy. Logistic regression analysis revealed that higher uric acid levels may be considered as an independent risk factor for the development of rejection (Table 6, $p<0.05$).

Despite different outcomes, hyper-uricemia has been mostly associated with graft function for the renal transplant patients. However, the relationship between hyper-uricemia and rejection has been unnoticed. Mechanisms related to renal damage include endothelial nitric oxide inhibition and activation of renin angiotensin system. In addition, vasoconstriction simulates vascular smooth muscle cell proliferation. These changes result with progressive renal fibrosis, which is a common histological graft result[16,24]. Due to this reason, we may conclude that hyper-uricemia therapy may improve health outcomes by decreasing fibrosis.

Taking the conflicting findings in the literature into consideration, we may conclude that further clinical studies with the participation of a higher number of patients may be conducted to understand the impact of uric acid levels on rejection.

Hyperglycemia incidence increases with immune suppressive therapy during the post- transplant period. The study of Gerhardt et al. on 350 renal transplant patients found no impact of post-transplant glucose metabolism on graft survival[20]. The study of Ganji et al., which analyzed the relationship between perioperative serum glucose levels and acute rejection in 100 non-diabetic patients found no significant correlation between hyperglycemia, delayed graft function and acute rejection[25]. Retrospective analysis of the study of Sheu et al. in 148 renal transplant patients, found no difference between post-transplant diabetes mellitus (PTDM) and DM patients in terms of acute rejection development[26]. The study of Nampoory et al., indicates poor patient survival in pretransplant diabetes mellitus (pre-TDM) due to coronary artery disease and infections, whereas the pure long-term graft survival was equally good in pre-TDM and nondiabetic transplant (ND) recipients. Acute rejection episodes were more frequently seen in pre-TDM (43%) than ND (33%), however the difference was not statistically significant[27]. However, there are a number of studies that have found an association between hypoglycemia and acute rejection[28,29]. Our study found that serum glucose of the rejection patients at the time of biopsy were higher ($p<0.05$). Logistic regression analysis, which was conducted to reveal statistically significant independent risk factors, defined high glucose level as an independent risk factor ($p<0,05$). Renal outcomes of patients, who underwent renal transplantation, may be improved by hyperglycemia treatment. However, further studies that include a higher number of patients should be conducted in order to verify the findings of our study.

There is no indicator for rejection other than CRP, which shows inflammation. Our findings indicate that hyper-uricemia and hyperglycemia may be used to predict post-transplant rejection. Based on our findings, we may conclude that hyper-uricemia and hyperglycemia therapy may be used for the improvement of renal outcomes of the renal transplant patients. However, further studies including higher number of patients are needed to verify our results.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ME, EG, SÖ; Veri toplama: KGA, ME, ÖY; Veri analizi ve yorumlama: MDA, EGO; Yazı taslağı: ME, EGO, ÖY, GA; İçeriğin eleştirel incelenmesi: MDA, EGO, ÖY; Son onay ve sorumluluk: ME, EGO, ÖY, KGA, SÖ, MDA; Teknik ve malzeme desteği: ME, GA; Süpervizyon: MDA, EG; Fon sağlama (mevcut ise): yok.
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