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The relationship between uric acid levels and graft function in renal transplant patients who discontinued steroid therapy.

Relación entre niveles de ácido úrico y función del injerto en pacientes de trasplante renal que interrumpieron la terapia con esteroides

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RESUMEN

Introducción: Con frecuencia se registran niveles elevados de ácido úrico en receptores de trasplantes renales que pueden estar asociados a disfunción de aloinjerto. El presente estudio tiene por objeto examinar la relación entre los niveles de AU y la función del injerto en pacientes que interrumpieron la terapia con esteroides. **Métodos**: En este estudio retrospectivo en un solo centro participaron 56 pacientes con interrupción de la terapia con esteroides de un total de 678 pacientes con TR receptores de trasplante de donantes vivos en el período 1999-2020. La edad promedio de la población de estudio fue de 45,8 ± 8,8 años. En el estudio se registraron causas de la interrupción de la terapia con esteroides, niveles de creatinina concurrentes con niveles de ácido úrico antes y después de la interrupción de la terapia con esteroides (promedio de 3,9 ± 2,1 años), números de rechazo agudo, datos demográficos, duraciones del período de diálisis y trasplante, medicación (uso de inmunosupresores, antihipertensivos), datos de laboratorio, números de desajuste del antígeno leucocitario humano (HLA), presión arterial (PA), índice de masa corporal, números de rechazo agudo retardado (DAR) (3 meses después del trasplante). **Resultados:** Se observó que los niveles de creatinina y ácido úrico aumentaron tras interrumpir la administración de esteroides, con una relación significativa entre ambos (p<0,001). Se identificó una correlación estadísticamente significativa entre el aumento en los niveles de creatinina tras la interrupción de la terapia de esteroides y la supervivencia del injerto con un mayor desajuste de HLA: 39 pacientes (el 69,6%) con desajuste ≥2 y 17 (el 30,4%) pacientes con desajuste <2 (p=0,049). No se encontró una relación significativa entre el número de DAR antes y después de la interrupción del tratamiento con esteroides, así como en los niveles de creatinina tras la interrupción de la terapia con esteroides. **Conclusión:** De acuerdo con el modelo obtenido como resultado del análisis lineal multivariable, la hiperuricemia y los números de desajuste de HLA (p=0,048 y p=0,044, respectivamente) constituyen factores predictivos independientes para la disfunción del injerto en pacientes que interrumpen la terapia con esteroides. En consecuencia, se deben tener en cuenta los efectos negativos del modelado para la supervivencia del injerto a largo plazo en pacientes que

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planean proseguir con regímenes con reducción de la administración esteroides.

PALABRAS CLAVE: Trasplante renal; ácido úrico; función del injerto; rechazo agudo retardado; antígeno leucocitario humano.

ABSTRACT:

Introduction: High uric acid levels are commonly encountered in kidney transplant recipients, and can be associated with allograft dysfunction. Our study aims to examine the relationship between UA levels and graft function in patients discontinuing steroids. **Methods:** In this single-center-retrospective study, 56 patients discontinued steroid therapy from among 678 RT patients transplanted from living donors between 1999-2020 were included. The mean age of the study group was 45.8±8.8 years. Causes of steroid discontinuation, creatinine levels concurrent with uric acid levels before and after steroid discontinuation (mean 3.9 ± 2.1 years), acute rejection numbers, demographics, durations of dialysis and transplantation, medications, laboratory data, human leukocyte antigen (HLA) mismatch numbers, blood-pressure (BP), body mass index, delayed acute rejection (DAR) numbers (3 months post-transplantation) were all recorded. **Results:** Creatinine and uric acid levels were seen to have increased after steroid discontinuation, there was a significant relationship between them ($p<0.001$). Statistically significant correlation was found between increased creatinine levels after steroid discontinuation and graft survival with higher HLA mismatch; 39 (69.6%) patients with mismatch ≥2, and 17 patients with mismatch <2 (30.4%) ($p=0.049$) . No significant relationship was found between DAR numbers before and after steroid discontinuation, and creatinine levels after steroid discontinuation. **Conclusion:** Per model obtained as a result of multivariate linear analysis, hyperuricemia and HLA mismatch numbers ($p= 0.048$ and $p= 0.044$, respectively) are independent predictive factors for graft dysfunction in patients discontinuing steroids. Accordingly, negative effects of modeling should be kept in mind for long-term graft survival in patients who plan to continue with steroid-sparing regimens.

KEYWORDS: renal transplant; uric acid; graft function ; delayed acute rejection; human leukocyte antigen

INTRODUCTION

The relationship between high serum uric acid levels and renal, cardiovascular, and metabolic disorders have been defined since the 19th century [1].Several epidemiological studies substantially suggested that chronic hyperuricemia was an independent risk factor for hypertension, cardiovasculer disease (CVD) , and chronic kidney disease [2,4]. Therefore, it is crucial to consider serum uric acid levels when profiling patient. The evidence suggests that serum UA levels above 6 mg/dl is considered abnormal [5].Overall, hyperuricemia can induce renal and cardiovascular injury both directly and indirectly through well-known mechanisms of tissue damage [6]. Several studies have reported that elevated serum UA levels correspond with reduced kidney transplant survival [3,7]. Immunosuppressive agents initiated after renal transplantation (RT) have variable effects on serum UA levels [8]. Previous studies have shown that steroids increase UA excretion [9]. The aim of our study is to examine the relationship between UA levels and graft function in patients who discontinued steroids.

MATERIAL AND METHODS

Study Population

In this single center retrospective study (conducted by Tepecik Training and Research Hospital, The Renal Transplant Program, Izmir, Turkey), 56 patients who underwent kidney transplantation from living donors (n=678) between 1999-2020 and who did not receive steroids were included. The average age of our study group [41 (73.2%) males and 15 (26.8%) females] was 45.8±8.8 years. In our patients, the reasons for not using steroids were osteoporosis (n=9; 16.1%), avascular necrosis of the femoral head (n=6; 10.7%), dermatological reasons (n=1; 1.2%) and patients who stop taking steroids themselves (n=40; 71.5%). Exclusion criteria included inability to provide consent, pregnancy, New York Heart Association class III or IV congestive heart failure, gout disease, history of kidney stones , metabolic syndrome, human immunodeficiency virus infection, multiple myeloma, renal cancer, smoking, cirrhosis, history of malignancy, history of end-stage renal disease, proteinuria, being under 18, allopurinol use, diabetes mellitus, obesity, inflammation, history of ischemic coronary disease, hypertension, Cytomegalovirus and Polyomavirus nephropathy, renal transplantation

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for less than 2 years, chronic allograft nephropathy, and early acute rejection (EAR, within the first three months).

Acute or chronic rejection based on clinical and laboratory findings was proven by transplant kidney biopsy. Initially pulse steroid therapy was given and if no response was achieved treatment pursued with antithymocyte globulin. The number of acute rejections before and after steroid discontinuation was recorded.

The study protocol was approved by the local ethics committee of the center and is in accordance with the principles of the Declaration of Helsinki. Subjects agreed to the informed consent requirement.

Clinical, laboratory and demographic characteristics of the study population including dialysis vintage, duration of transplantation, immunosuppressive and other medications, body mass index, number of HLA mismatches, BP and delayed acute rejection (DAR) (three months post-transplantation) were recorded.

The UA levels before and after steroid discontinuation at an average of 3.9 ± 2.1 years and the concurrent creatinine levels and the number of acute rejections were recorded.

Immunosuppressive therapy protocol:

All patients were given basilixumab as induction treatment on Days 0 and 4. Routine immunosuppression consisted of tacrolimus (0.1 to 0.2 mg/kg/day orally divided dose), mycophenolate mofetil (1000 mg orally twice daily), and prednisolone (5 mg/day orally). Patients whose steroids were discontinued continued to take tacrolimus (0.1 to 0.2 mg/kg/day orally divided dose) and mycophenolate mofetil (1000 mg orally twice daily).

Statistical analysis:

Statistical analysis was performed with SPSS software (Statistical Package for the Social Sciences, version 11.5, SSPS Inc, Evanston, Ill, United States). Results were considered as statistically significant if the P value was <0.05. Data are shown as the mean ± SD. Comparisons between the 2 groups were performed by means of the student t test (Paired Samples test) for normally distributed continuous variables and with the Mann-Whitney U test for non-normally distributed continuous variables. For comparisons of categorical variables, we used the chi-square test. Cox regression (multiple linear regression) analysis was used to measure the effect of the UA level, acute rejection, and HLA mismatch on creatinine.

RESULTS

The demographic and clinical characteristics of the patients are shown in **Table 1**.

Table 1: Demographic and Clinical Features of the Patients (n=56)

		Mean Value (SD)
Age (y)		45±8.8
Gender (female/male)		15/41
Living-related donor		56
Duration of dialysis pretransplantation (mo)		21.4±25.3
Total Transplant duration (years)		13.3± 4.6
Time After Steroid Discontinuation (years)		3.9± 2.1
Body mass index (kg/m²)		21.7± 3.7
HLA mismatch	<2	n= 39(%69.6)
	≥2	n=17 (%30.4)

The predominant cause of renal failure was hypertensive nephropathy (primary hypertensive ones) (n=35, 62.5%) followed by polycystic kidney disease (n=11.2, 20.0%), stone (n=5.6, 10%), unknown (n=5.3, 9.5%) and glomerulonephritis (n=1.1, 2%). The BP of patients in the primary hypertensive group was under control with 10 mg of amlodipine. There was no statistically significant difference between the BP of the patients using amlodipine before and after steroid discontinuation (p> 0.05), and UA levels did not differ significantly (p> 0.05). No significant difference was found in UA levels between men and women (p<0.05). No significant relationship was found between age, gender, pre-transplantation dialysis duration, total transplant duration, duration after steroid

discontinuation, and body mass index and graft survival (p>0.05). However, an increase was observed in UA and creatinine levels after the cessation of steroid therapy. A significant correlation was observed between creatinine and UA levels (p<0.001) after steroid discontinuation (**Table 2**).

Table 2: Uric acid, creatinine, blood pressure and delayed acute rejection before and after steroid discontinuation.

	Before steroid discontinuation (n=56)	After steroid discontinuation (n=56)	P-value
Uric acid (mg/dl)	5.7±1.1	9.2±1.3	<0.001
Creatinine (mg/dl)	1.27±0.33	2.51±0.62	<0.001
Blood Pressure (BP) (mmHg)	125/85	128/86	>0.05
Number of Delayed Acute Rejection (LAR)	3 (5.4%)	19 (33.19%)	<0.001

HLA mismatches of the patients were evaluated. A statistically significant correlation was found between increased creatinine levels after steroid discontinuation and graft survival with higher HLA mismatch numbers; 39 (69.6%) patients with mismatch of ≥2, and 17 patients with mismatch of <2 (30.4%) (p=0.049).

There was no significant correlation between the steroid discontinuation and the number of LAR and creatinine levels (p:0.535, p: 0.147, respectively). Although the number of DAR increased after steroid discontinuation, it was not statistically significant.

Also, predictive risk factors for graft dysfunction; UA levels and the number of HLA mismatch were analyzed using a multivariate Cox proportional hazards model. The UA levels after discontinuation of steroids and number of HLA mismatches were found an independent risk factors for graft dysfunction (p=0.048 and p=0.044).

DISCUSSION

In this study, the relationship between hyperuricemia prevalence and graft survival in renal transplant patients using steroids was investigated after steroid discontinuation. The prevalence of hyperuricemia is higher in posttransplant patients compared to the healthy population [10]. In a study among kidney recipients the prevalence of hyperuricemia was 70% and 80% at the baseline and at 2.2 years after transplantation, respectively [3]. In our study, we observed that the discontinuation of streroids contributed to the increase in UA levels. Steroids are known to increase uric acid excretion [9]. Moreover, posttransplant maintenance immunosuppressive drugs have an effect on UA metabolism involving its excretion and absorption. Tacrolimus, for example, increases UA levels through reduction of urate excretion [8]. Initially all patients in the study group used tacrolimus and mycophenolate mofetil and prednisolone as maintenance immunusuppression regimen.

Acute rejection (AR) is a common complication in renal transplantation and is associated with reduced graft survival.3 It can occur in less than three months (EAR) or after three months of transplantation (DAR) [11]. Early Acute Rejection (EAR) had no adverse effect on long-term renal graft function if they were successfully treated [12]. In the recent years, the incidence of EAR has decreased due to the introduction of newer immunosuppressive agents [13]. The main factors

for a more successful long-term allograft outcome are immunological [14,15].

However, new immunosuppressive agents have a little effect on chronic graft dysfunction and long-term renal allograft survival is still a concern [16]. Recent research has confirmed that with new immunosuppressive therapy, an EAR is no longer a risk factor of long-term graft failure and chronic allograft nephropathy [17]. In contrast, another research showed that only DAR have adverse effects on long-term graft function [18]. Another study showed that EAR were not significant risk factors of chronic graft loss compared with DAR [11].

In our study, although there was a significant increase in the number of DAR with steroid discontinuation, but no effect was found on graft survival. We concluded that DAR treatments are introduced effectively to our patients. The discontinuation of the steroid may not be the only cause, but it may have triggered DAR [19].

HLA compatibility is one of the best methods to define immunological compatibility between kidney transplant donors and recipients. Certain studies show no statistically significant difference in graft survival in donor pairs in the case of HLA mismatch, but in other studies, the presence of HLA mismatch negatively affects the development of acute rejection attacks and graft survival [20,21]. A linear negative relationship was found between HLA mismatch and transplant survival rates [22]. In our study, a significant negative correlation was found between HLA mismatch and graft survival strongly supporting the negative effects of HLA mismatches on the graft as well as the negative effects of high UA levels after steroid discontinuation.

Hyperuricemia contributes to kidney dysfunction by several mechanisms. Elevated UA levels may cause progression of renal injury by activating the renin-angiotensin system and resulting in increases in both systemic and glomerular pressures, and cyclooxygenase-2 [12,23]

In this study, we excluded patients with secondary hypertension, and patients with controlled primary BP on more than one-drug regimen. In another study the effect of serum UA level on endothelial damage and inflammation markers in renal allograft recipients was determined [24]. Gerhardt et al showed that in hyperuricemic patients allograft survival decreased significantly at 2, 4 and 5 years compared to normouricemic patients [25]. Our study also emphasizes that the elevation of UA, which may have developed with the cessation of steroids, negatively affects the graft functions.

In our study, the low number of normouricemic patients after steroid discontinuation in RT patients (the major limitation of our study) suggested that steroid discontinuation was an additional factor for the occurrence of posttransplant hyperuricemia. Concluding that hyperuricemia alone has an adverse effect on a failing survivor would not be correct. One should keep in mind that subclinical rejection attacks not reflected in the clinic during follow-up may negatively affect graft survival.

CONCLUSION

According to the model obtained as a result of multivariate linear analysis in our study, hyperuricemia and the number of HLA mismatch are independent predictive factors for graft dysfunction in patients with steroid discontinuation. The negative effects of the modeling factors used in our study should be kept in mind in terms of long-term graft survival in patients who are planned to discontinue steroids. While making predictions for graft survival in patients planned to have steroid discontinuation, our study might provide a guidance in this regard; but we wanted to emphasize the need for multi-center studies with more cases, considering our limitations.

We declare that we are responsible for the article's scientific content in the Copyright Transfer Form of the accepted article. These responsibility areas include study design, data collection, analysis and interpretation, writing, preparation and scientific review of the contents, and approval of the final version of the article.

LIMITATIONS

Our study is not randomized and the number of patients is small. Randomized studies are needed on this subject. We screened 678 patients who discontinued steroids in our center between 1999-2020 (n=56). We keep the inclusion criterias very strict and highly selected cases were included in this study.

Due to the number of patients with steroid discontinuation and patients with normal UA levels was very low, the graft survival of these two group patients could not compared and this is the

major limitation of the present study.

Confirming the role of UA in progressive renal disease as well as in cardiovascular disease in the transplant population will necessitate larger sample sizes to allow for the adjustment of confounding variables, as well as clinical trials of maneuvers for altering UA levels.

Until such studies can be realized, hyperuricemia remains a promising marker for progressive renal allograft dysfunction and cardiovascular disease after renal transplantation.

A study in larger series comparing the same graft function may provide more detailed and robust information for the relationship between uric acid level in transplant patients before and after steroid withdrawal. Our results should be supported by further studies.

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