Association of Metabolic Syndrome and Hyperuricemia in the Recipients of Kidney Transplants: A Single-Center Study

Maryam Salari,[1] Mohammad Ali Yaghoubi,[2] Maryam Miri,[1] Hassan Mehrad-Majd,[3] Maryam Hami[1]

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

Keywords. hyperuricemia, kidney transplantation, metabolic syndrome, uric acid

Original Paper

Introduction. The prevalence of hyperuricemia shows an increasing trend among kidney transplant recipients. The association between metabolic syndrome and hyperuricemia among the recipients of kidney transplants may consequently lead to reduction in graft survival. In this regard, the present study aimed at comparing the kidney transplant recipients with and without metabolic syndrome in terms of the prevalence of hyperuricemia.

Methods. This cross-sectional study was carried out on kidney transplant recipients who were referred to the Kidney Transplant Clinic of Montaserieh Organ Transplant Hospital, Mashhad University of Medical Sciences, from 2019 to 2020. The serum uric acid, anthropometric data, renal function, glucose levels, and lipid profile of the study participants were evaluated.

Results. According to our findings, higher mean uric acid levels were reported in recipients with metabolic syndrome (6.9 ± 1.51 mg/dL), compared to recipients without metabolic syndrome (6.11 ± 1.47 mg/dL; $P < .001$). It was also found that 55.6 and 38.5% of the cases with and without metabolic syndrome had hyperuricemia, respectively ($P < .05$). Additionally, the results showed no significant association between hyperuricemia and the number of metabolic syndrome criteria ($P > .05$). A comparison between recipients with and without hyperuricemia revealed significantly lower levels of tacrolimus in the hyperuricemia group ($P < .05$). Regarding serum Tacrolimus levels, no significant difference was found between recipients with and without metabolic syndrome ($P > .05$). Moreover, there was no significant difference between recipients with and without hyperuricemia ($P > .05$) or metabolic syndrome ($P > .05$) in terms of serum cyclosporine level.

Conclusion. The findings of the current study indicate that kidney transplant recipients suffering from metabolic syndrome have higher mean serum levels of uric acid than those without metabolic syndrome.

IJKD 2023;17:100-7
www.ijkd.org
DOI: 10.52547/ijkd.7141

INTRODUCTION

Metabolic syndrome (MS) consists of a cluster of disorders co-existing with hyperinsulinemia, obesity, dyslipidemia, and hypertension, which increase the risk of type II diabetes, heart failure, and stroke.[1] The association between MS with impaired long-term renal allograft functions and poor survival in kidney transplant recipients has

been confirmed in the literature.[2-4] According to the National Health and Nutrition Examination Survey, the rate of MS has increased in the general population in recent years worldwide.[5]

Kidney transplant recipients are at increased risk of developing metabolic disorders, such as obesity, impaired glucose, and fat metabolism, as a result of immunosuppressive drugs and dietary diversity in the post-transplant period.[1,6] There are some evidence that indicate higher prevalence of MS in kidney transplant recipients, compared to the general population; accordingly, its rate has been estimated from 10 to 45% and 32 to 59% in the general population and transplant recipients, respectively.[7,8] The prevalence of 52.8% for MS in kidney transplant recipients has been reported in the Iranian population.[9] According to the literature, MS is known as a risk factor for diabetes mellitus and chronic kidney disease in the general population. In addition, chronic graft dysfunction, post-transplant diabetes mellitus, and cardiovascular disease can be observed in kidney transplant recipients as well.[10,11]

On the other hand, there will be an increased risk of development of new kidney disease merely due to elevated levels of uric acid. More, the association between hyperuricemia and MS has been reported in some studies in normal populations; however, this association is not known as a causal factor.[12] A strong association between renal dysfunction and hyperuricemia has been confirmed in the literature.[10] Hyperuricemia is more common among kidney transplant recipients, compared to the general population; it has been observed in 30 to 84% of transplant recipients.[13]

The use of cyclosporine and diuretics, followed by obesity and diabetes mellitus could develop hyperuricemia among kidney transplant recipients, which may reduce patient survival.[14] Hyperuricemia has been introduced as a risk factor for cardiovascular and kidney failure.[12] The literature has shown that hyperuricemia exacerbates cyclosporine-induced nephropathy.[15] An increase incidence of hyperuricemia from 25 to 80% after a long time use of cyclosporine has been reported in kidney transplant recipients.[16]

It seems that the association between MS and hyperuricemia leads to a reduction in graft longevity and an increased risk of heart failure in kidney transplant recipients. This study aimed at comparing the recipients of kidney transplant with and without MS regarding the frequency of hyperuricemia.

MATERIALS AND METHODS

This cross-sectional study investigated kidney transplant recipients who were referred to the Kidney Transplant Clinic of Montaserieh Organ Transplant Hospital, Mashhad University of Medical Sciences, from 2019 to 2020.

Inclusion and Exclusion Criteria

The study included individuals aged more than 18 years who had kidney transplant for a minimum of six months, as well as a stable graft function (serum creatinine $\leq$ 2 mg/dL) for at least the last three months. Individuals with diabetes mellitus, pregnancy, active infections, and those receiving mammalian target of rapamycin (mTOR) inhibitors, such as everolimus or sirolimus as immunosuppression, were excluded from the study.

Study Design

Based on the 32% prevalence of hyperuricemia reported among Iranian population in the study of Einollahi *et al.*,[14] and considering: $\alpha = 0.05$, $d = 0.25$, and $\beta = 0.2$; 131 participants were enrolled in this research. Finally, the number of participants were increased to 150 to increase the power of the study. In all the study participants, immunosuppressive medications included cyclosporine or tacrolimus in combination with azathioprine, mycophenolate mofetil or mycophenolic acid along with prednisolone.

The participants' demographic characteristics and anthropometric data (age, gender, body mass index [BMI], waist circumference, weight, and height), as well as the type of transplant (living or cadaveric), systolic and diastolic blood pressure, the length of time passed after transplantation, the number of transplants, and the type and dose of medications were collected and recorded in a data extraction form.

The height was measured in standing position, and the weight was measured with a single scale for all the study participants. The waist circumference was measured at the midpoint between the iliac crest and the lowest rib and BMI was calculated with the use of weight and height. The modification of diet in renal disease (MDRD) formula was

used for calculation of glomerular filtration rate and evaluation of graft function. Blood pressure was measured twice from the dominant arm with an interval of 5 to 6 minutes by using a mercury sphygmomanometer.

Hypertension was diagnosed according to the mean systolic blood pressure higher than 130 mmHg or mean diastolic blood pressure higher than 85 mmHg.[6] The recipients receiving treatment with antihypertensive agents were also diagnosed as hypertensive.

Moreover, 5 mL of blood was extracted after 12 hours fasting from brachial vein to assess serum creatinine, high-density lipoproteins (HDL), triglyceride, cholesterol, glucose, and uric acid levels. The serum of the extracted blood samples was separated by using a centrifuge and then stored at minus 4 to 8 °C. All analyses were performed by using a BT3500 auto-analysis device and Pars Azmoon Company kits. To investigate the serum levels of cyclosporine and tacrolimus, 3 mL of blood was extracted 12 hours after taking the last dose of the medications and collected in a container containing ethylene diamine tetra acetic acid. The samples were stored in refrigerator at minus 4 to 8 °C, and the Electro Chemi Luminescence method with a Cobas e 411 analyzer device (Roche Company) was used to measure the serum level of the mentioned medications.

The diagnosis of metabolic syndrome was based on the definition by the modified Asian Adult Treatment Panel III (ATP III) model provided that at least three of the five following criteria were present:

1) Waist circumference > 92 cm in both females and males.
2) Triglyceride ≥ 150 mg/dL or a specific treatment on this lipid abnormality.
3) HDL < 40 for males and HDL < 50 for females or a specific treatment for this lipid abnormality.
4) Hypertension ≥ 130 mmHg and diastolic blood pressure ≥ 85 mmHg or the use of antihypertensive medication.
5) Fasting blood sugar ≥ 100 mg/dL or the use of antidiabetic agents.

Hyperuricemia was defined in females and males as serum uric acid levels of ≥ 6 and 7 mg/dL, respectively. The prevalence of hyperuricemia was subsequently evaluated in recipients with and without MS, and then they assigned into two groups according to their MS status (according to the definition of the modified Asian ATP III model). In the next step, the relationship between MS and hyperuricemia was independently assessed by considering the transplanted kidney function.

Statistical Analysis

The collected data were analyzed in SPSS (version 22), and the descriptive data were presented by using frequency, percentage, and mean ± SD. Analytical analysis was performed by the chi-square test (or if necessary, Fisher's exact test) for categorical data and an independent t-test for interval data. The assessment of the normality of data was performed by using the Kolmogorov-Smirnov test. A P value of < .05 was considered statistically significant.

The study adhered to the principles of the Declaration of Helsinki. The research procedure and objectives were explained to the participants, and informed written consent was obtained from them. Furthermore, they were informed that they could withdraw from the study at any time during the research period. The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences (Code: 971361).

RESULTS

The current study included 150 kidney transplant recipients out of which 88 (56.7%) were males. The mean age of the participants with and without MS were 42.22 ± 10.71 and 37 ± 12.6 years, respectively. The recipients with MS were older than those without MS (P < .05).

In total, cadaveric kidney recipients accounted for 86 (57.3%) of cases while living kidney recipients were 64 (42.7%) of the cases. The comparison of demographic characteristics and clinical information of participants with and without MS is presented in Table 1.

The mean BMI of the participants was 23.49 kg/m^2, and the mean duration of dialysis including hemodialysis and peritoneal dialysis was 27.87 ± 18.67 months. In addition, the corresponding lengths were 28.32 and 18.75 months in samples receiving hemodialysis and peritoneal dialysis, respectively. The mean lengths of dialysis in recipients with and without MS were 27.63 ± 1.83 and 28.12 ± 2.6, respectively (P > .05). Table 2

Table 1. Demographic Characteristics and Clinical Information in Patients With and Without MS

Categorical Variables	With Metabolic Syndrome		Without Metabolic Syndrome		*P*
	number	%	number	%	
Gender					
Male	48	66.7	40	51.3	.056*
Female	24	33.3	38	48.7	
Type of Transplantation					
Live	27	37.5	37	47.4	.21*
Cadaveric	45	62.5	41	52.6	
Number of Transplantations					
Once	69	95.8	72	92.3	.36*
Twice	3	4.2	6	7.7	
Type of Dialysis					
Hemodialysis	70	97.2	75	96.2	.71*
Peritoneal Dialysis	2	2.8	3	3.8	
Causes of Kidney Failure					
Hypertension	42	58.3	57	73.1	.27**
Idiopathic	11	15.3	9	11.5	
Glomerulonephritis	8	11.1	8	10.8	
Reflux Nephropathy	7	9.7	2	2.6	
Polycystic Kidney Disease	4	5.6	0	0	
Hereditary Diseases	0	0	2	2.6	
Dialysis Duration, mo	27.63 ± 1.83		28.12 ± 2.64		.789
Type of Treatment					
Tacrolimus	22	30.6	41	52.6	.0060
Cyclosporine	50	69.4	37	47.4	

*Chi-square
**Fisher's exact test

Table 2. Anthropometric Criteria and Laboratory Data in Patients With and Without MS

Variables	With Metabolic Syndrome		Without Metabolic Syndrome		*P*
	Mean	SD	Mean	SD	
Weight, kg	71.8	11.9	62.1	12.3	< .005
Height, cm	166.5	8.7	163.2	9.5	.02
Waist Circumference, cm	94.48	11.07	83.17	9.69	< .005
BMI, kg/m^2	25.3	3.84	22.85	3.64	< .005
Creatinine Level, mg/dL	1.3	0.2	1.2	0.3	.27
GFR, mL/min	59.8	17.8	64.5	20.2	.13
Systolic Blood Pressure, mmHg	130.18	13.29	122.13	14.33	< .005
Diastolic Blood Pressure, mmHg	85.13	10.59	86.27	7.32	.89
Triglyceride, mg/dL	189.68	7.69	114.22	4.06	< .005
HDL, mg/dL	40.75	1.3	47.03	1.76	< .005
FBS, mg/dL	96.5	1.68	88.38	1.69	< .005

*Independent *t*-test

presents the anthropometric criteria and laboratory data in recipients with and without MS.

The mean values of the uric acid level in recipients with and without MS were 6.9 ± 1.51 and 6.11 ± 1.47 mg/dL, respectively; which was significantly higher in patients with MS ($P < .001$). Furthermore, there was a 55.6% prevalence of hyperuricemia among patients having MS and a 38.5% prevalence among patients lacking MS ($P < .05$). There was no significant correlation between hyperuricemia and the number of MS criteria evaluated by Fisher's exact test ($P > .05$) (Table 3).

The serum levels of tacrolimus and cyclosporine showed no difference between recipients with and without MS ($P > .05$ and $P > .05$, respectively). Moreover, the prescribed dosage of tacrolimus

Table 3. Number of Criteria of MS and the Prevalence of Hyperuricemia

The Number of Criteria	With Hyperuricemia		Without Hyperuricemia		*P*
	Number	%	Number	%	
Zero	5	33.3	10	66.7	0.12
One	16	40	24	60	
Two	9	39.1	14	60.9	
Three	28	59.6	19	40.4	
Four	11	57.9	8	42.1	
Five	1	16.7	5	83.3	

and cyclosporine was higher in recipients with MS, compared to those without MS ($P < .05$ and $P < .05$, respectively). A comparison of serum levels and dosage of cyclosporine in recipients with and without hyperuricemia did not reveal any significant differences ($P > .05$). Moreover, recipients with hyperuricemia had lower serum levels of tacrolimus than those without hyperuricemia ($P < .05$). However, regarding the prescribed dosage of Tacrolimus, there was no difference between recipients with and without hyperuricemia ($P > .05$) (Table 4).

The relationship between the criteria of MS and serum levels, as well as the dosage of cyclosporine and tacrolimus are presented separately in Tables 5 and 6.

DISCUSSION

The results of the current study showed that kidney transplant recipients with MS had significantly higher uric acid levels than their counterparts without MS. Moreover, serum tacrolimus levels were found to be higher in recipients with hyperuricemia, compared to those without hyperuricemia; however, it was not different in recipients with and without MS. The serum cyclosporine levels were not different in transplant recipients with and without MS or hyperuricemia.

Kidney transplant recipients are at risk of obesity, hypertension, and diabetes mellitus, commonly known as MS. Recently, the level of uric acid has been reported as an important factor for MS in kidney transplant recipients.[14] Our findings revealed higher levels of serum uric acid in the recipients of kidney transplant with MS, compared to recipients without MS, which is in line with the results of other studies.[4,17,18]

In the study of Ohashi *et al.* on the relationship between MS and kidney function in living donor kidney transplant recipients, MS was reported in 12.2% of patients. They showed that donors who were diagnosed with MS had a greater likelihood of developing hyperuricemia than those without MS; accordingly, hyperuricemia was prevalent in 34% of donors with MS and 10.1% of those without MS.[19] The results of a study conducted by Cicero *et al.* indicated that the risk of developing

Table 4. Comparison of Serum Level and Prescribed Dose of Tacrolimus and Cyclosporine in Patients With and Without MS and Hyperuricemia

Variables	Cyclosporine		*P*	Tacrolimus		*P*
	Mean	SD		Mean	SD	
Serum Level, ng/mL						
With Metabolic Syndrome	104.9	27.9	.62	5.6	1.6	.44
Without Metabolic Syndrome	107.8	2.55		5.4	1.1	
Dose, mg/kg/d						
With Metabolic Syndrome	3	0.8	.005	0.18	0.17	.04
Without Metabolic Syndrome	2.5	0.85		0.11	0.08	
Serum Level, ng/mL						
With Hyperuricemia	107.5	27.4	.64	5.1	1	.03
Without Hyperuricemia	104.8	26.5		5.8	1.4	
Dose, mg/kg/d						
With Hyperuricemia	2.9	0.8	.35	0.13	0.07	.89
Without Hyperuricemia	2.7	0.8		0.12	0.15	

Table 5. Comparison of Serum Levels of Cyclosporine and Tacrolimus in Patients With and Without the Criteria of MS

Variables	Serum Levels of Cyclosporine, ng/mL		*P*	Serum Levels of Tacrolimus, ng/mL		*P*
	Mean	SD		Mean	SD	
Waist Circumference						
Abnormal	106.5	26.9	.92	5.5	1.2	.89
Normal	105.9	27		5.4	1.3	
FBS Levels						
Abnormal	109.8	25.88	.48	5.4	2	.76
Normal	105	27.22		5.5	1	
Triglyceride Level						
Abnormal	107.2	29.98	.702	5.2	1.1	.85
Normal	107.6	23.5		5.6	1.3	
HDL						
Abnormal	107.8	25	.58	5.4	1.5	.83
Normal	104.6	28.4		5.5	1.1	
Hypertension						
Abnormal	107.7	27.8	.34	5.7	1.3	.08
Normal	101.6	23.8		5.1	1.1	

Table 6. Comparison of Dosage of Cyclosporine and Tacrolimus in Patients With and Without the Criteria of MS

Variables	Cyclosporine, mg/kg/d		*P*	Tacrolimus, mg/kg/d		*P*
	Mean	SD		Mean	SD	
Waist Circumference						
Abnormal	2.7	0.86	.45	0.14	0.09	.63
Normal	2.8	0.86		0.13	0.14	
FBS Level						
Abnormal	2.6	0.9	.38	0.20	0.22	.03
Normal	2.8	0.85		0.11	0.07	
Triglyceride Level						
Abnormal	3.1	0.78	.002	0.16	0.07	.63
Normal	2.5	0.85		0.12	0.14	
HDL						
Abnormal	2.9	0.79	.22	0.18	0.17	.02
Normal	2.7	0.9		0.1	0.07	
Hypertension						
Abnormal	2.8	0.8	.83	0.13	0.15	.77
Normal	2.8	0.79		0.14	0.08	

MS in the presence of elevated uric acid levels were 2.69 and 2.12 times higher in females and males, respectively.[20] Another study performed by Bombelli *et al.* indicated that uric acid levels could increase the risk of MS by 1.3 times more likely.[21]

Hyperuricemia is considered the main complication in organ transplant recipients, especially in kidney and heart recipients. Some evidence has showed that the risk of cardiovascular events increased with elevated blood uric acid levels independent of renal function.[22] Furthermore, decreased glomerular filtration rate, immunosuppressant therapy, aging, obesity, and MS are reported to be the main risk factors for post-transplant hyperuricemia.[23]

There are controversies regarding the effect of uric acid effects on graft function. Recently, the higher uric acid level has been introduced as a risk factor for graft survival; however, the effects of hyperuricemia on the transplant recipients' health and graft survival have not been studied well until now. Chronic allograft dysfunction is suggested to be a complication of hyperuricemia in transplant recipients in some studies, whereas other studies have reported the increased level of uric acid only as a marker of decreased glomerular filtration rate.[23]

Like our study, Ohashi *et al.* showed that kidney

transplant recipients with MS were older than those without MS. The mean values of fasting blood sugar, BMI, triglycerides, and systolic and diastolic blood pressure were significantly higher in individuals with MS than their counterparts without MS. Moreover, transplant recipients with MS had significantly lower HDL levels.[19] These findings were confirmed by our study, except that diastolic blood pressure showed no difference between recipients with and without MS. In a study by Luan *et al.* the MS and new-onset diabetes mellitus were evaluated after kidney transplant.[18] More, they showed that 53.1% of transplant recipients had MS while 15.2% of them developed new-onset diabetes mellitus in one year after transplantation.[4]

Immunosuppressive medications play a significant role in metabolic abnormalities, and consequent MS. Immunosuppressive medications inhibit the insulin signaling pathways in skeletal muscle and liver, leading to a reduction in postprandial glucose uptake. The use of immunosuppressive medications also disrupts the inhibition of hepatic glucose production and increases the production of very-low-density lipoprotein and lipolysis in adipose tissues, which leads to an increase in the circulating triglycerides and free fatty acids, and consequently intensifies insulin resistance.[24] Moreover, the immunosuppressant leads to increased blood pressure and weight.[25]

Hyperlipidemia is commonly observed in kidney transplant recipients receiving immunosuppressive medications.[26] Tacrolimus increases the risk of diabetes mellitus, and the inhibitory effect of the agent on insulin secretion in response to glucose loading after kidney transplant is well-known.[27] Cyclosporine causes hyperlipidemia with a significant increase in total cholesterol, triglycerides, and LDL cholesterol.[28] However, in the present research, no difference in serum tacrolimus level was found in recipients with and without MS. Nonetheless, a higher rate of serum tacrolimus levels was reported among recipients with hyperuricemia. Moreover, recipients with and without MS or hyperuricemia showed no difference in terms of serum cyclosporine levels.

Based on the study of Neal *et al.*, the occurrence of hyperuricemia was similar in liver transplant recipients undergoing treatment with either cyclosporine or tacrolimus.[29] Other studies confirmed that the use of immunosuppressants, such as cyclosporine, had no effects on uric acid metabolism.[30]

Studies conducted on recipients receiving cyclosporine-free regimens and mTOR inhibitors disapproved the relationship between hyperuricemia and the use of immunosuppressants.[30] In this regard, future studies are recommended to evaluate the effects of using tacrolimus and cyclosporine in transplant recipients with MS.

ADVANTAGES AND LIMITATIONS

This research had some limitations, one of which was its relatively small sample size. Furthermore, because it was a cross-sectional study, no cause-effect link between blood uric acid levels and MS was investigated. Prospective studies with a larger sample size in different ethnic groups are recommended to investigate the relationship of serum uric acid with MS and cardiovascular complications associated with it.

CONCLUSION

The findings of this study indicate that the kidney transplant recipients suffering from MS have higher mean serum levels of uric acid than those without MS.

ACKNOWLEDGMENT

The authors would like to appreciate all people who participated in this study, especially the staff affiliated with Mashhad University of Medical Sciences, Mashhad, Iran.

This study was supported by the research project No. 971361 as a nephrology fellowship thesis at Mashhad University of Medical Sciences, Mashhad, Iran. The authors would like to thank the Clinical Research Development Unit at Ghaem Hospital, Mashhad, Iran, for their assistance in this research.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Samson SL, Garber AJJE, Clinics M. Metabolic syndrome. 2014;43(1):1-23.
2. Anastácio LR, Lima AS, Correia MITD. Metabolic syndrome and its components after liver transplantation: incidence, prevalence, risk factors, and implications. Clinical nutrition. 2010;29(2):175-9.
3. Hricik DE. Metabolic syndrome in kidney transplantation: management of risk factors. Clinical Journal of the

American Society of Nephrology. 2011;6(7):1781-5.

4. Luan FL, Langewisch E, Ojo A. Metabolic syndrome and new onset diabetes after transplantation in kidney transplant recipients. Clin Transplant. 2010;24(6):778-83.
5. Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among US adults: NHANES III to NHANES 1999–2006. Diabetes care. 2011;34(1):216-9.
6. Hami M, Sabbagh MG, Sefidgaran A, Mojahedi MJSjokd, transplantation: an official publication of the Saudi Center for Organ Transplantation SA. Prevalence of the metabolic syndrome in kidney transplant recipients: A single-center study. 2017;28(2):362-7.
7. Cheung CY, Chan HW, Liu YL, Chan YH, Wong HS, Chak WL, et al. Prevalence of metabolic syndrome in Chinese renal transplant recipients. Hong Kong Med J. 2008;14(5):379-84.
8. Sharif A, Ravindran V, Dunseath G, Luzio S, Owens DR, Baboolal K. Comparison of rival metabolic syndrome classifications against pathophysiological markers in renal transplant recipients. Transplantation. 2010;89(3):347-52.
9. Jalali G, Hami M, Namaee N, Salehi M, Mojahedi MJ, Hasanzamani B. Relationship between vitamin D deficiency and metabolic syndrome in renal transplant patients in Mashhad, Iran. Shiraz E-Medical Journal. 2017;18(3).
10. Prasad GR. Metabolic syndrome and chronic kidney disease: Current status and future directions. World journal of nephrology. 2014;3(4):210.
11. Porrini E, Delgado P, Torres A. Metabolic syndrome, insulin resistance, and chronic allograft dysfunction. Kidney International. 2010;78:S42-S6.
12. Gaffo AL, Edwards NL, Saag KG. Gout. Hyperuricemia and cardiovascular disease: how strong is the evidence for a causal link? Arthritis research & therapy. 2009;11(4):1-7.
13. Kim KM, Kim SS, Han DJ, Yang WS, Park JS, Park SK. Hyperuricemia in Kidney Transplant Recipients with Intact Graft Function. Transplantation Proceedings. 2010;42(9):3562-7.
14. Einollahi B, Einollahi H, Nafar M, Rostami Z. Prevalence and risk factors of hyperuricemia among kidney transplant recipients. Indian journal of nephrology. 2013;23(3):201.
15. Cirillo P, Sato W, Reungjui S, Heinig M, Gersch M, Sautin Y, et al. Uric acid, the metabolic syndrome, and renal disease. Journal of the American Society of Nephrology. 2006;17(12 suppl 3):S165-S8.
16. Mazzali M, editor Uric acid and transplantation. Seminars in nephrology; 2005: Elsevier.
17. King C, Lanaspa MA, Jensen T, Tolan DR, Sánchez-Lozada LG, Johnson RJ. Uric acid as a cause of the metabolic syndrome. Uric Acid in Chronic Kidney Disease. 2018;192:88-102.
18. Luan FL, Stuckey LJ, Ojo AO. Abnormal glucose metabolism and metabolic syndrome in non-diabetic kidney transplant recipients early after transplantation. Transplantation. 2010;89(8):1034.
19. Ohashi Y, Thomas G, Nurko S, Stephany B, Fatica R, Chiesa A, et al. Association of metabolic syndrome with kidney function and histology in living kidney donors. American Journal of Transplantation. 2013;13(9):2342-51.
20. Cicero AFG, Fogacci F, Giovannini M, Grandi E, Rosticci M, D'Addato S, et al. Serum uric acid predicts incident metabolic syndrome in the elderly in an analysis of the Brisighella Heart Study. Scientific reports. 2018;8(1):1-6.
21. Bombelli M, Quarti-Trevano F, Tadic M, Facchetti R, Cuspidi C, Mancia G, et al. Uric acid and risk of new-onset metabolic syndrome, impaired fasting glucose and diabetes mellitus in a general Italian population: data from the Pressioni Arteriose Monitorate E Loro Associazioni study. Journal of hypertension. 2018;36(7):1492-8.
22. Brodov Y, Chouraqui P, Goldenberg I, Boyko V, Mandelzweig L, Behar S. Serum uric acid for risk stratification of patients with coronary artery disease. Cardiology. 2009;114(4):300-5.
23. Mazali FC, Mazzali M. Uric Acid and Transplantation. Seminars in Nephrology. 2011;31(5):466-71.
24. Klubo-Gwiezdzinska J, Lange M, Cochran E, Semple RK, Gewert C, Brown RJ, et al. Combined immunosuppressive therapy induces remission in patients with severe type B insulin resistance: a prospective cohort study. Diabetes Care. 2018;41(11):2353-60.
25. Knight SR, Morris PJ. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. Transplantation. 2010;89(1):1-14.
26. Riella L, Gabardi S, Chandraker A. Dyslipidemia and its therapeutic challenges in renal transplantation. American Journal of Transplantation. 2012;12(8):1975-82.
27. Kolic J, Beet L, Overby P, Cen HH, Panzhinskiy E, Ure DR, et al. Differential effects of voclosporin and tacrolimus on insulin secretion from human islets. Endocrinology. 2020;161(11):bqaa162.
28. Kockx M, Kritharides L. Cyclosporin A-induced hyperlipidemia. Lipoproteins: Role in health and diseases London: IntechOpen. 2012:337-54.
29. Neal DA, Tom BD, Gimson AE, Gibbs P, Alexander GJ. Hyperuricemia, gout, and renal function after liver transplantation. Transplantation. 2001;72(10):1689-91.
30. Meier-Kriesche H-U, Schold JD, Vanrenterghem Y, Halloran PF, Ekberg H. Uric acid levels have no significant effect on renal function in adult renal transplant recipients: evidence from the symphony study. Clinical Journal of the American Society of Nephrology. 2009;4(10):1655-60.

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

Received September 2022
Revised November 2022
Accepted January 2023