Hyperglycemia After Kidney Transplantation
Frequency and Risk Factors

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Introduction. Kidney transplantation and its conventional treatment can lead to increased risk of diabetes mellitus outbreak in normoglycemic recipients. Also, uncontrolled hyperglycemia may increase allograft loss and decrease patient survival. We aimed to assess the frequency of hyperglycemia in transplant patients and its risk factors.

Materials and Methods. A retrospective study was performed on 3342 adult kidney transplant recipients between 2008 and 2010. Demographic and laboratory data were collected. All laboratory tests were done in a one laboratory, and hyperglycemia was defined as a fasting plasma glucose level greater than 125 mg/dL. Univariable and multivariable logistic regression analyses were used to determine the risk factors of hyperglycemia following kidney transplantation.

Results. There were 2120 men (63.4%) and 1212 women (36.3%) included in the study. The prevalence of hyperglycemia was 22.5%. Hyperglycemia was significantly higher in patients with cytomegalovirus infection ($P = .001$), elevated serum creatinine ($P < .001$), low high-density lipoprotein cholesterol ($P = .01$), and increased blood levels of cyclosporine ($P < .001$). After adjusting for covariates by multivariate logistic regression, the hyperglycemia rate was significantly higher for patients with a cyclosporine trough level greater than 250 ng/mL ($P < .001$), a serum creatinine level greater than 1.5 mg/dL ($P < .001$), and a high-density lipoprotein cholesterol less than 45 mg/dL ($P = .03$).

Conclusions. This study indicated that hyperglycemia is a common metabolic disorder in Iranian kidney transplant patients. Risk factors for hyperglycemia were higher cyclosporine level, impaired kidney function, and reduced high-density lipoprotein cholesterol values.

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INTRODUCTION

Diabetes mellitus (DM) is considered as one of the most costly diseases, and one of the most important causes of end-stage renal disease (ESRD) through the world.[1-5] Hyperglycemia is also a common complication among transplant patients without a history of DM. Although the new potent immunosuppressant agents have improved short-term and long-term outcomes after transplantation, these drugs can cause greater prevalence of hyperglycemia.[6] In addition, DM may increase the risk of cardiovascular disease, infection, nephropathy, neuropathy, and retinopathy.[7]

Although some studies have shown that kidney

transplant recipients with DM have an increased risk of allograft rejection,[8-10] many studies indicated similar patient and graft survival rates in diabetic transplant patients with a good control of blood glucose level as compared to general transplant recipients without DM.[3,11-13] There are limited available data about the prevalence of hyperglycemia after kidney transplantation among Iranian transplant recipients.[3,14-16] Therefore, we aimed to evaluate the frequency of hyperglycemia in kidney transplant patients and its risk factors in a large kidney transplant population in Iran.

MATERIALS AND METHODS

Patient Population

We carried out a retrospective analysis of laboratory data of all adult patients (age > 18 years) who underwent kidney transplantation at 8 teaching hospitals of Tehran, Iran, referred to Gholhak laboratory during a period from 2008 to 2010. Living-related and deceased kidney transplants were both included. We excluded patients who suffered from transient hyperglycemia due to steroid pulse, incomplete data, and rejected allograft. We obtained the 14 986 laboratory data in 3342 kidney transplant recipients within the period of the study. Ethical approval was obtained from the local Ethics Committee of Baqiyatallah University.

Data Collection

Data recorded for any of the patients were age, sex, fasting plasma glucose level, serum creatinine concentration, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDLC), uric acid, hemoglobin, trough level of cyclosporine, and cytomegalovirus antigen (CMV Ag). Cytomegalovirus pp65 antigenemia was detected by Brite Turbo (IQ Products, Groningen, Netherlands), and cyclosporine levels were determined with Cobas Mira-Plus analyzer (Roche, Basel, Switzerland).

Hyperglycemia Definition

We defined hyperglycemia as a fasting plasma glucose level greater than 125 mg/dL, according to the World American Diabetes Association.[17]

Immunosuppressive Regimen

The maintenance immunosuppression was based on cyclosporine (Neoral, Novartis, Basel, Switzerland), plus mycophenolate mofetil or azathioprine and prednisolone in all patients. The amount of cyclosporine given to transplant patients was mostly based on blood levels of the drug. Cyclosporine monitoring using its trough levels was periodically performed at different times and dose was adjusted, as necessary. In our treatment strategy, target therapeutic ranges for cyclosporine levels were 200 ng/mL to 300 ng/mL in 1 to 3 months, 100 ng/mL to 250 ng/mL in 4 to 12 months, and 100 ng/mL to 150 ng/mL in more than 1 year after transplantation.

Statistical Analysis

Statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, III, USA). All numeric data were presented as mean ± standard deviation. Differences between the categorical variables were compared using the chi-square test or the Fisher exact test. The Student *t* test was used for evaluating continuous quantitative variables. The univariable linear regression and multivariable logistic regression were performed for risk factors associated with hyperglycemia. A *P* value level less than .05 was considered significant.

RESULTS

Characteristics of Patients

There were 3342 kidney transplant patients, 2120 men (63.4%) and 1212 women (36.3%), referred to a single laboratory from 8 Transplant Centers. The majority of the patients (93.4%) received a kidney from a living donor (85.2% unrelated and 8.2% related). The mean age of the recipients was 37 ± 16 years (range, 18 to 79 years). The majority of the patients were followed up more than 1 year (92.6%), while 3.5% of the recipients had 3 to 12 months of follow-up, and 3.9% less than 3 months. Patients with hyperglycemia were older compared to normoglycemic recipients (Table 1). The prevalence of hyperglycemia was 22.5%.

Risk Factors of Hyperglycemia After Transplantation

Hyperglycemia patients had significantly higher rates of CMV infection, elevated plasma cyclosporine levels, and increased plasma creatinine levels as compared to normoglycemic recipients (Tables 1 and 2). Although hyperglycemia patients had higher low-density lipoprotein cholesterol, this difference

Table 1. Patient Characteristics and Laboratory Data in Hyperglycemic and Normoglycemic Kidney Transplant Recipients*

Variable	Kidney Transplant Recipients		*P*
	Normoglycemic	Hyperglycemic	
Mean recipient age, y	35.8 ± 15.6	46.9 ± 12.0	< .001
Recipient sex, %			
Male	62.8	66.4	
Female	37.2	33.6	.37
Positive CMV antigen, %	4.7	11.7	< .001
Mean cyclosporine trough level, ng/mL	182 ± 121	230 ± 150	< .001
Mean serum creatinine, mg/dL	1.54 ± 0.97	1.79 ± 1.20	< .001
Mean HDLC, mg/dL	49 ± 15	47 ± 17	.15
Mean LDLC, mg/dL	101 ± 35	105 ± 36	.74
Mean hemoglobin, g/dL	12.5 ± 2.2	12.1 ± 2.3	.31

*HDLC indicates high-density lipoprotein cholesterol and LDLC, low-density lipoprotein cholesterol.

Table 2. Predictive Laboratory Data for Hyperglycemia in Kidney Transplant Recipients*

Variable	Kidney Transplant Recipients			*P*
	All	Normoglycemic	Hyperglycemic	
Trough level of Cyclosporine, %				
> 250 ng/mL	24.4	21.2	35.3	
≤ 250 ng/mL	75.6	78.8	64.7	< .001
Serum creatinine, %				
> 1.5 mg/dL	37.9	35.8	45	
≤ 1.5 mg/dL	62.1	64.2	55	< .001
HDLC, %				
> 45 mg/dL	47.5	52.1	46	
≤ 45 mg/dL	52.5	47.9	54	.02
Hemoglobin, %				
> 11 g/dL	26.7	32.2	25.1	
≤ 11 g/dL	73.3	67.8	74.9	.01

*HDLC indicates high-density lipoprotein cholesterol.

was not significant ($P = .70$). Despite no significant correlation was seen between hyperglycemia and hemoglobin or HDLC concentrations as quantitative values, higher than normal levels of these biochemical markers (qualitative) had significant relationships (Table 2).

In univariable regression, the prevalence of hyperglycemia was significantly higher in patients with CMV infection ($P = .001$), impaired kidney allograft function ($P < .001$), low HDLC ($P = .01$), and elevated plasma cyclosporine levels ($P < .001$). After adjusting for covariates by multivariable logistic regression, hyperglycemia was significantly more frequent in patients with a plasma cyclosporine through level greater than 250 ng/mL (95% confidence interval, 0.27 to 0.98, $P < .001$), a plasma creatinine greater than 1.5 mg/dL (95% confidence interval, 0.93 to 0.98, $P < .001$), and an HDLC level lower than 45 mg/dL (95% confidence interval, 0.95 to 0.99, $P = .03$).

DISCUSSION

In the current study, hyperglycemia was a frequent problem among kidney transplant recipients. Perez-Flores and colleagues showed that hyperglycemia was a common complication after kidney transplantation and it was present in 65% of their patients.[18] The incidence of posttransplant DM ranges from 2% to 50% of cases in different series, reflecting wide variations in the definition of the disorder, the population, and the immunosuppressive regimen.[19] Hyperglycemia is a common and contributing factor to the outcome of kidney transplantation. Our study was able to confirm these findings by showing an increased risk of kidney allograft impairment associated with posttransplant DM.[8,20,21] Unless adequately controlled, DM after transplantation enhances the risk of kidney allograft loss.[21]

Several risk factors have been previously described for the development of hyperglycemia

after transplantation, which include advanced age, male donor, infections (hepatitis C, Epstein-Barr virus, and CMV), obesity,[13] immunosuppressive agents (particularly prednisolone and cyclosporine), and dyslipidemia.[22] In our study, high blood level of cyclosporine seemed to be an important factor for the development of altered glucose metabolism. We also demonstrated our hyperglycemic patients had significantly higher rates of CMV infection as compared to normoglycemic cases, which matches with other studies.[23,24] Conversely, two small studies showed that there was no significant correlation between DM and CMV infection after kidney transplantation.[25,26] We were also able to demonstrate a significant increased risk of hyperglycemia in advanced age, which is consistent with other studies.[26-30] Although no significant correlation was seen between hyperglycemia and hemoglobin concentration, hyperglycemic recipients were more likely to be anemic as compared to normoglycemic patients; this finding matches with other study.[28]

The main limitation of the present study resides in its retrospective design. As a result, data about family history, body mass index, metabolic syndrome, and blood pressure were not accessible. However, we believe that this limitation exists in nearly any retrospective studies using secondary data collection. Therefore, we could not consider all confounding factors in this study.

CONCLUSIONS

This study indicated that hyperglycemia is a common metabolic disorder in Iranian kidney transplant patients. These results confirmed the importance of appropriate cyclosporine level control among patients undergoing kidney transplantation.

CONFLICT OF INTEREST

None declared.

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