Correlation of Pretransplant Hyperglycemia and Delayed Graft Function in Kidney Transplantation

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Introduction. Hyperglycemia is common and a contributing factor to the undesirable outcomes in kidney transplant recipients. This study investigates the relationship of pretransplant blood glucose levels and the occurrence of delayed graft function among kidney transplant recipients without a diagnosis diabetes mellitus before transplantation.

Materials and Methods. Eighty-one patients on long-term hemodialysis with no history of clinically diagnosed diabetes mellitus were enrolled in this study. Correlation of the occurrence of delayed graft function with age, gender, donor source, underlying cause of kidney failure, insulin resistance, and blood glucose levels before transplantation was evaluated.

Results. There was a significant correlation between abnormal glucose metabolism categories and occurrence of delayed graft function (P = .004). Logistic regression analysis showed that fasting blood glucose before kidney transplantation is an independent predictor of delayed graft function immediately after transplantation (odds ratio = 1.042, P = .04).

Conclusions. Hyperglycemic patients have an increased risk for delayed graft function and should be treated by more potent immune therapy and further restriction of blood glucose regulation in peritransplantation period.

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INTRODUCTION

Some studies have shown that patients with diabetes mellitus (DM) have an increased risk of allograft rejection.[1] However, this is not a settled issue, with reports that DM had no influence on graft survival.[2] Hyperglycemia is a common and contributing factor to the outcome of kidney transplantation.[3,4] Hyperglycemia is also common following kidney transplantation among patients without a history of DM. Hyperglycemia accentuates renal ischemic injury, enhances antigen presentation and apoptosis, and increases inflammatory responses in kidney transplantation. This study was performed to investigate the relationship of pretransplant serum glucose levels and occurrence of delayed graft function (DGF) among uremic patients without a pretransplant diagnosis of DM.

MATERIALS AND METHODS

Eighty-one kidney transplant candidates on long-term hemodialysis with no history of clinically diagnosed DM (48 men and 33 women) were included in this study. They were going to receive a kidney transplant at the kidney transplant centers of Ghaem Hospital and Imam Reza Hospital, in Mashhad, Iran, from September 2008 to March 2009. Informed consent was obtained from all of the patients. The study was approved by the

Mashhad University of Medical Sciences Research Ethics Committee.

The participants' demographic and clinical data were collected. Fasting blood glucose (FBG) and glucose tolerance test were measured on the day before transplantation and on days 3, 7, 14, and 21 after transplantation. The American Diabetes Association criteria were used for definitions of posttransplant DM (FBG ≥ 7.0 mmol/L or 2-hour postload glucose ≥ 11.1 mmol/L), impaired fasting glucose (FBG ≥ 5.6 mmol/L and < 7.0 mmol/L), impaired glucose tolerance (2-hour postload glucose ≥ 7.8 mmol/L and < 11.1 mmol/L), and normal glucose tolerance (FBG < 5.6 mmol/L and 2-hour postload glucose < 7.8 mmol/L). Requirement of dialysis in the 1st week after transplantation was defined as DGF.[5] The basal values of glucose and insulin, as measured by radioimmunoassay, were used to calculate indexes of insulin resistance, beta-cell function, and insulin secretion, according to the homeostasis equations, before transplantation and on days 3, 7, 14, and 21 after transplantation. Because reporting beta-cell function in isolation could be misleading,[6] we normalized percentile of beta-cell function by insulin sensitivity, wherever necessary; eg, 50% beta-cell function in the presence of 200% insulin sensitivity was normalized to 100%.

Continuous variables were compared between the two groups of patients with and without DGF using the Student *t* test when normally distributed; otherwise, the Mann-Whitney test was used. Categorical variables were compared using the chi-square test and Fisher exact test, as appropriate. The 1-way analysis of variance was used for analysis of variance for quantitative dependent variables by a single factor (independent) variable. Logistic regression analysis was used to explore the impact of each putative independent determinant on the dependant factor, which was DGF. Multinomial logistic regression was used for evaluation of predictor variables' effect on glucose metabolism categories. A *P* value less than .05 was considered significant.

RESULTS

There were 11 patients with DGF, of whom 8 were diagnosed with acute rejection and 3 with acute tubular necrosis, according to kidney biopsy results, renal scintigraphy, and the clinical course. Table 1 summarizes the characteristics of the kidney recipients with and without DGF.

The frequencies of normal and impaired glucose tolerance, impaired FBG, and newly diagnosed DM in the two groups are shown in Table 2. As shown in this table, impaired glucose tolerance and previously undiagnosed DM were highly frequent among the patients. It is noteworthy that 5 of 11 patients with DGF had an undiagnosed DM and 7 of 11 with DGF had either an impaired glucose tolerance test or an undiagnosed DM. Table 3 lists the mean FBG levels in the two groups, which were comparable between the DGF and no DGF group before and after transplantation, except for the measurements 1 week after transplantation which were significantly higher among patients with DGF.

The duration of hemodialysis before transplantation was significantly longer in the patients with DGF (*P* = .03; Table 1). Comparing the patients with and without DGF showed no differences regarding age, gender, donor source, body mass index, systolic and diastolic blood

Table 1. Demographic and Clinical Characteristics of Kidney Allograft Recipients With and Without Delayed Graft Function

Characteristic	Delayed Graft Function		*P*
	No	Yes	
Age, y	32.38 ± 13.52	26.18 ± 9.67	.14
Male gender	42 (60.0)	8 (72.7)	.42
Body mass index, kg/m^2	20.64 ± 4.41	20.057 ± 4.62	.74
Dialysis duration, mo	20.66 ± 24.99	26.27 ± 18.55	.03
Pretransplant serum creatinine, mg/dL	8.19 ± 3.09	9.50 ± 3.17	.27
Pretransplant systolic blood pressure, mm Hg	137.83 ± 22.94	137.63 ± 21.85	.97
Pretransplant diastolic blood pressure, mm Hg	83.80 ± 1.42	86.54 ± 10.87	.54
Donor source			
Living unrelated	53 (75.7)	6 (54.5)	
Cadaver	17 (24.3)	5 (45.5)	.14

*Values in parentheses are percents.

Table 2. Blood Glucose Tests Results Before Transplantation in Patients With and Without Delayed Graft Function

Glucose Tests Results	Delayed Graft Function		*P*
	No	Yes	
Normal glucose tolerance	13 (18.6)	4 (36.4)	.18
Impaired fasting blood glucose	1 (1.4)	0	.86
Impaired glucose tolerance	51 (72.9)	2 (18.2)	< .001
Diabetes mellitus	5 (7.1)	5 (45.4)	< .001

Table 3. Mean Fasting Blood Glucose Levels Before and After Transplantation in Patients With and Without Delayed Graft Function

Fasting Blood Glucose, mg/dL	Delayed Graft Function		*P*
	No	Yes	
Before transplant	80.79 ± 21.07	95.42 ± 29.53	.50
Day 3	92.67 ± 31.13	104.44 ± 20.01	.82
Day 7	73.92 ± 24.20	99.5 ± 38.19	.02
Day 14	84.3 ± 22.66	97.90 ± 34.85	.47
Day 21	81.28 ± 23.34	101.50 ± 43.81	.32

Table 4. Logistic Regression Analysis of the Effect of Fasting Blood Glucose Before Transplantation , Quartiles of beta Cell Function, and Duration of Dialysis Before Transplantation on Development of Delayed Graft Function

Factor	B	P	Exp(B)
Fasting blood glucose	0.041	.04	1.042
Dialysis duration	-0.008	.56	0.992
Quartiles of beta cell function	0.001	.82	1.001
Constant	-4.797	.01	0.008

Table 5. Mean beta Cell Function Before and After Transplantation in Patients With and Without Delayed Graft Function

Beta Cell Function*	Delayed Graft Function		*P*
	No	Yes	
Before transplant	113.97 ± 60.81	94.29 ± 36.04	.26
Day 3	75.08 ± 50.60	68.44 ± 56.00	.39
Day 7	136.05 ± 60.35	82.60 ± 46.26	.005
Day 14	94.25 ± 68.64	72.40 ± 41.63	.11
Day 21	131.58 ± 77.37	90.15 ± 53.58	.22

*Beta cell function was normalized by insulin sensitivity percentage.

pressure, insulin sensitivity, insulin resistance, and the underlying disease resulting in end-stage disease. There was a correlation between quartiles of beta cell function before transplantation and occurrence of DGF (P = .04), while no correlation was found between quartiles of insulin resistance or insulin sensitivity before transplantation and the subsequent DGF. In the logistic regression model in which the FBG, quartiles of beta cell function, and duration of dialysis before transplantation were entered, the only predictor factor correlated significantly with DGF was FBG (odds ratio = 1.042, P = .04; Table 4). In subsequent measurements until the end of the 3rd week, only beta cell function at the end of the 1st week of transplantation and FBG at the same time showed a significant difference between the two groups (P = .005 and P = .01, respectively; Tables 3 and 5) This was in spite of no differences regarding cumulative corticosteroid and cyclosporine dose between the two groups. At this point of time, multinomial logistic regression analysis evaluating the effect of evolving discriminatory factors, cumulative corticosteroid and cyclosporine dose administered until then and serum creatinine level on the dependant factor (glucose metabolism categories) showed that the only discriminator of different four categories of blood glucose derangements was serum creatinine level (Table 6). This was equally reflected in the more elevated mean FBG level in the patients with DGF compared with those with normal allograft function at the end of the 1st week after transplantation (P = .02; Table 3). Accordingly, we witnessed a significantly less insulin secretion as assessed by normalized beta cell function obtained by insulin resistance modeling at the end of the 1st week after transplantation in the patients with DGF (P < .001). On the 7th day

Table 6. Multinomial Logistic Regression Analysis on the 7th Day After Transplantation Comparing the Effect of Predictor factors on Glucose Derangement Categories*

Factor	Category			
	Impaired Glucose Tolerance		Diabetes Mellitus	
	P	Exp(B)	*P*	Exp(B)
Creatinine	.51	1.21	.01	3.44
Corticosteroid	.43	1.00	.59	1.00
Cyclosporine	.71	0.99	.22	1.00

*The categories of impaired glucose tolerance and diabetes mellitus were compared with normal glucose tolerance as the reference category.
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after transplantation, again we found a significant negative correlation between FBG and beta cell function both normalized and non-normalized insulin sensitivity (r = -0.419, *P* = .002 and r = -0.369, *P* = .008; respectively).

DISCUSSION

In our study, abnormal glucose metabolism was highly frequent in uremic pretransplantation patients; insulin resistance, hormonal imbalances, systemic inflammation, oxidative stress, excess parathyroid hormone, and chronic acidosis are uremia-associated causes of abnormal glucose metabolism.[7-10] Other researchers have also found the abnormal glucose metabolism prevalent in uremic patients before engraftment.[11] In our study, the pretransplantation abnormal glucose metabolism was associated with an increased occurrence of DGF in patients without diagnosed DM. Impaired 2-hour postload glucose tolerance test and undiagnosed DM before transplantation significantly correlated with the occurrence of DGF. Others have also found an association of hyperglycemia on allograft function in the early period after kidney transplantation.[12] Brennan and coworkers[13] showed that diabetic etiology of kidney disease is a the dominant risk factors for DGF after living donor kidney transplantation, and DGF strongly predisposes the patient to acute rejection. Indeed, in our study, acute rejection was the dominant cause of DGF (defined as requirement of hemodialysis in the first week after transplantation). On the contrary, Van Den Berg and colleagues[14] found no apparent impact of increased posttransplant blood glucose levels on clinical outcome in kidney transplant recipients; however, they studied the effect of the first 48 hours after kidney transplantation and not pre-operative serum glucose levels.

Our analysis did not support the proposed possible hypotheses to explain the association between different abnormal glucose metabolism categories and DGF, such as the ideas that patients with abnormal glucose metabolism have higher body mass indexes, are more likely to be older, and have received more cadaveric kidney allografts. The explanations more likely reflects physiologic subcellular rather than demographic or epidemiologic differences between those with and whit out glucose metabolism abnormalities.

Delayed graft function is thought to be initiated in the early posttransplant period by allograft injury and the inflammatory response to that injury. We hypothesize that pretransplantation hyperglycemia may directly increase the risk of DGF. This may be due to several mechanisms; high glucose levels may exacerbate warm ischemic damage, with the resulting tissue injury. It is known that hyperglycemia worsens renal ischemic injury in experimental models,[15] signifying a direct role for glucose. High glucose levels have a direct vasoconstrictor effect in nondiabetic renal vessels,[15] culminating in endothelial dysfunction through hyperosmolarity, oxidant formation, and protein kinase C activation.[16] Other studies have shown the incidence of DGF to be increased in patients with DM.[17] In addition, high glucose levels may have a pro-coagulant effect.[18]

Hyperglycemia increases antigen presentation and co-stimulation. Glucose-induced ischemia/reperfusion injury and oxidative stress enhances expression of major histocompatibility complex class I and class II antigens on allograft cells and subsequently dendritic cells.[19,20] Also production of chemokines that induce expression of major histocompatibility complex antigens are augmented,[21] and the tissue response to interferon-gamma is increased by the presence of high glucose concentrations.[19] Peripheral dendritic cells are activated by reactive oxygen species.[20] Apoptosis is triggered by reperfusion injury, and inhibition of apoptosis by ischemia-reperfusion prevents inflammation.[22] Apoptosis is also enticed by hyperglycemia that can cause reperfusion-induced inflammation and tissue injury.[13-15] Also co-stimulatory molecules are upregulated directly by hyperglycemia, and indirectly, by glucose-enhanced ischemia and oxidative stress.[16]

There are other possible mechanisms for hyperglycemia-induced allograft dysfunction; hyperglycemia causes an exaggerated inflammatory response to ischemia/reperfusion and rejection.[22-24] More nuclear factor-kappa B is produced in hyperglycemic states,[25] resulting in upregulation of both cellular and humoral mediators of inflammation. Adhesion molecules including intercellular adhesion molecule-1 and vascular endothelial growth factor are overexpressed by hyperglycemia.[26] Increased phosphorylation of platelet cell adhesion molecule-1and expression

of CD18, vascular cell adhesion molecule-1, and E-selectin work together to enhance the adhesion and transendothelial migration of monocytes.[27,28] Both the production and activity of cytokines including tumor necrosis factor-alpha and interferon-gamma may be increased by hyperglycemia.[19] Amplified production of transforming growth factor-beta 1 in hyperglycemia also decreases the production of IL-10.[29] Reactive oxygen species, generated in patients with higher plasma glucose level, lead to the induction of pro-inflammatory cytokines.[29,30]

Following steroid therapy and surgery, occurrence of hyperglycemia is a marker of the insulin resistance. This new metabolic milieu is characterized by hypertension, dyslipidemia, hyperinsulinism, and increased levels of circulating advanced glycation end-products, leptin, tumor necrosis factor-alpha, interleukins 1, 6, and 12.[10,31] These cytokines act concomitantly with hyperglycemia to induce kidney allograft injury.

Interestingly, in patients with DGF we found a remarkably more elevated FBG and less beta cell function at the end of the1st week after transplant. Patients with the DGF have abnormalities of the overstimulated immune system, resulting in an augmented cytokine responsiveness that may predispose to beta cell injury. We hypothesize this can be interpreted as the effect of continued uremic milieu and oxidative stress and acidosis on beta cells function in patients with DGF, mirrored in significantly higher FBG and less insulin secretion compared with patients with no DGF.[10,32] Others, although in long-term follow-up, have also shown that beta cell function rather than insulin resistance is the main contributing factor to the development of posttransplant glucose metabolism derangements.[33,34]

CONCLUSIONS

Impaired glucose tolerance test and undiagnosed DM are highly prevalent among patients on long-term dialysis. We suggest there is a significant correlation between these glucose metabolism derangements and occurrence of DGF if the patients undergo kidney transplantation. Logistic regression analysis showed that FBG before transplantation is an independent predictor of DGF immediately after transplantation. Impaired insulin secretion, as assessed by normalized beta cell function obtained at the end of the 1st week after transplantation, rather than insulin resistance is the probable cause of more elevated FBG in patients with DGF. This can be interpreted as a consequence of the persistence of the uremic state and stimulated immune system in the group of patients with DFG. Hyperglycemic patients who have an increased risk for DGF should be treated by more potent immune therapy, and more restrict blood glucose regulation in peritransplantation period may improve kidney allograft function.

CONFLICT OF INTEREST

None declared.

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