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Original Article

The Relationship between Graft Function and Liver Function after Kidney Transplantation: A Retrospective Cohort Study

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HIGHLIGHTS

- Liver enzymes can consider the rejection possibility of kidney transplant recipients (KTR).
- Some factors like inflammation factors like erythrocyte sedimentation rate (ESR or sed rate) and C-reactive protein (CRP can consider for rejection.
- Liver function test abnormalities cannot adequately predict the rejection.

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ABSTRACT

Introduction
After kidney transplantation, several factors should be checked to predict the risk of rejection. Liver enzymes are such predicting factors so liver function test abnormalities (LFTA) can consider the rejection possibility in kidney transplant recipients (KTR).

Methods
Through a retrospective cohort study, 659 KTR were studied. The source of all grafts was from deceased donors. Amongst these cases, 67 patients showed a significant rise in creatinine as the rejection indication. Several liver indexes like alanine transaminase (ALT), aspartate transaminase (AST), direct bilirubin (Bil D), total bilirubin (Bil T), and liver ultrasound reports, gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), prothrombin time (PT) INR in addition to creatinine were examined for three-six post-transplant in KTR.

Results
Our study exposed that liver functional tests regularly had considerable statistical differences between KTR with creatinine increase and with no creatinine increase. Despite these differences between the two groups AST, ALT and ALP serum levels were still within the normal range in both groups. The same result was seen over the Bil D, and Bil T.

Conclusions
Liver function test abnormalities can not adequately predict the rejection. Some other elements should be taken into consideration like inflammation factors like erythrocyte sedimentation rate (ESR or sed rate), and C-reactive protein (CRP).

Keywords: Kidney Transplantation; Liver Function Test; Creatinine; Allografts

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Introduction

Renal transplantation is a surgical procedure to place a healthy kidney from a live or deceased donor into a person whose kidneys no longer function properly. Renal transplantation classically is categorized as deceased-donor (formerly known as cadaveric) or living-donor transplantation. Renal transplantation is known as the chief progress of modern medicine which makes high-quality life years for patients with irreversible kidney failure (end-stage renal disease (ESRD)) worldwide (1). Until 2013, more than two thousand kidney transplants have been reported from Iran (2).

Transplant rejection as the fourth leading cause of the end-stage renal disease is still the biggest limitation in renal transplant procedures and 10%-50% of rejection occurs in the first six months after transplant (3-5). In the United States, 5469 kidney transplants established end-stage kidney failure in 2008 with no known exact reason (6). Maybe graft rejection happens because of dysregulated fibrosis, drug toxicity, or progressive "chronic allograft nephropathy" (7-9). According to de novo donor-specific HLA antibodies (dnDSA) posttransplantation has been linked to greater graft failure rates. Acute renal transplant glomerulopathy (ARTG) is a glomerular inflammation principally of 4.3-14 % of all renal allografts that happens in the first three months after transplantation (10). Acute vascular rejection (AVR) is a fibrous thickening of the arterial intimal layer that consequenced in early renal failure (11). The therapeutic regimen of renal transplant recipients is including medication strategies, infection prevention, smoking cessation, clinic visit attendance, and following guidelines concerning alcohol intake, diet, and exercise (12). Medication strategies for transplant rejection are based on the conventional immunosuppressive protocols made of the triple therapy: a calcineurin inhibitor, an adjunctive agent, corticosteroids (13). To find the trends in kidney function during one year after transplant the serum creatinine is taken into the account. A serum creatinine less than 1.6 mg/dl at 6 and 12 months post-transplantation resulted in a considerably minor rate of graft loss at 3 years versus a serum creatinine level > 1.5 mg/dL (14-16). Analysis of liver function test abnormalities in kidney transplant recipients can support the result of creatinine and evaluation the risk of transplant rejection (17).

Despite the significance of the said fact and the high prevalence of post-renal transplant liver enzyme elevation, few studies have examined liver enzyme status as a risk factor in the incidence of post-renal transplant creatinine increase courses. The present study aims at evaluating the relationship between post-kidney transplant increase courses with creatinine significance and liver function tests in kidney transplant patients.

Methods

This retrospective cohort study analyzed the data regarding 659 kidney transplants from deceased donors due to brain death, in the period May 2008 to May 2010, at Sina Hospital Clinic. Patient consent undertook before surgery based on the ethical code of the Tehran University of Medical Sciences Ethics committee (IR.TUMS.MEDICINE.REC.1398.342).

For each patient, five post-transplantation assessments were performed at 1, 2,3,4, and 6 months after the kidney graft. The serum levels of creatinine and four liver indices including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and blood urea nitrogen (BUN) were recorded in these five

Table 1. Serum levels of the creatinine and liver enzymes measured at five post-transplant times

Variables	Mean (SD)
Creatinine	
1 month after surgery (U/L)	1.4 (0.4)
2 month after surgery (U/L)	1.3 (0.3)
3 month after surgery (U/L)	1.2 (0.4)
4 month after surgery (U/L)	1.5 (0.4)
6 month after surgery (U/L)	1.2 (0.4)
Aspartate aminotransferase (AST)	
1 month after surgery (U/L)	60.9 (28.8)
2 month after surgery (U/L)	52.6 (21.9)
3 month after surgery (U/L)	45.4 (15.0)
4 month after surgery (U/L)	41.9 (13.1)
6 month after surgery (U/L)	44.2 (15.3)
Alanine aminotransferase (ALT)	
1 month after surgery (U/L)	54.3 (31.5)
2 month after surgery (U/L)	44.7 (20.3)
3 month after surgery (U/L)	76.3 (32.6)
4 month after surgery (U/L)	61.3 (22.7)
6 month after surgery (U/L)	55.8 (20.2)
Alkaline phosphatase (ALP)	
1 month after surgery (U/L)	383.2 (130.9)
2 month after surgery (U/L)	394.6 (145.3)
3 month after surgery (U/L)	380.3 (148.0)
4 month after surgery (U/L)	228.7 (65.4)
6 month after surgery (U/L)	222.3 (59.6)
Blood urea nitrogen (BUN)	
1 month after surgery (U/L)	20.8 (6.3)
2 month after surgery (U/L)	16.0 (7.1)
3 month after surgery (U/L)	14.4 (6.7)
4 month after surgery (U/L)	14.8 (5.0)
6 month after surgery (U/L)	14.1 (5.6)

SD: Standard deviation

Table 2. Prediction of elevated Creatinine (≥2 vs. <2) measured at 3, 4, and 6 months after surgery, using the predictors ALP, ALPT, AST, and BUN

Elevated Creatinine at month	Predictor			AUC (%)	Sensitivity (%)	Specificity (%)
		Month	Cut-off			
CR3	ALP	1	322	87.0	95.8	79.2
		2	278	87.9	91.7	80.8
		3	258	91.8	100	78.9
CR4		1	322	86.9	95.0	78.7
		2	281	87.3	90.0	80.1
		3	258	90.4	100	78.4
CR6		1	322	85.7	93.3	78.1
		2	278	85.6	86.7	79.7
		3	258	90.4	100	77.8
CR3	ALT	1	50	72.7	79.2	81.3
		2	40	64.4	66.7	84.9
		3	50	85.4	87.5	79.7
CR4		1	50	79.0	85.0	81.1
		2	40	71.8	75.0	84.8
		3	48	89.1	90.0	80.3
CR6		1	45	76.4	80.0	83.1
		2	40	69.7	73.3	84.3
		3	44	92.0	100	81.7
CR3	AST	1	25	84.4	79.2	83.8
		2	37	86.1	91.7	76.4
		3	34	85.6	79.2	78.4
CR4		1	42	86.5	90.0	75.0
		2	37	83.2	90.0	75.9
		3	44	82.8	95.0	57.3
CR6		1	42	88.1	100	74.7
		2	37	82.4	86.7	75.3
		3	30	87.4	80.0	81.2
CR3	BUN	1	22.1	86.2	83.3	89.9
		2	18.5	86.0	79.2	84.4
		3	19	97.6	100	89.1
CR4		1	22.1	78.4	75.0	89.2
		2	18.5	84.3	85.0	84.2
		3	19	97.0	100	88.6
CR6		1	22.1	77.6	73.3	88.7
		2	18.5	81.2	80.0	83.5
		3	24.6	95.9	86.7	96.7

AUC: Area Under ROC Curve; ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; AST: Aspartate Transaminase; BUN: Blood Urea Nitrogen

follow-ups.

The elevated creatinine was considered as a creatinine value ≥2 (REF). Then, the liver indices ALT, AST, ALP, and BUN were tested if they could predict the occurrence of significant elevation of creatinine. To do this, the logistic regression model was utilized, taking each of the liver indices as the predictor, and the categorized form of creatinine as the response variable. The literature suggests that the liver indices of the three months after the kidney graft could predict the significant creatinine elevation after the 3rd month. To assess this, the creatinine measures of the 3, 4, and 6 months after the surgery were fitted on the liver indices of the 1, 2, and 3 months after the surgery. These models provided the area under the roc curve (AUC), an index of how good a predictor is in describing a binary response variable, which changes between 0-100 percent. As a guide, the AUCs higher than 80, and 90 % are labeled as good and excellent (18). Other products of the model included cut-off values for the predictor, alongside the sensitivity and specificity of the test.

Kidney transplant patients were included in this study. Our exclusion criteria were chronic viral B, C hepatitis (including HCV Ab, HBsAg, HBc Ab), HIV+, pregnancy, diabetes, alcohol consumption >20 for men and >10 for women, recent consumption (in the last 6 months) of medication like atorvastatin, methotrexate (MTX), carbamazepine, and trifluoperazine affecting liver enzymes. Moreover, patients who had a history of liver disease like (cirrhosis, autoimmune hepatitis (including gamma globulin serum & FANA), Primary biliary cirrhosis, biliary obstruction, hemochromatosis, alpha-1-antitrypsin deficiency, wilson's disease (including serum ceruloplasmin, transferrin saturation percentage), chronic disabling diseases (severe cardiac dysfunction, chronic obstructive pulmonary disease, malignancy), and well-known cancers.

The analysis was performed using the statistical software Stata (ver. 11), and the significance level was chosen to be 0.05.

Results

The mean and standard deviation (SD) of the age of 659 kidney transplant recipients were 55.6 (3.6). In the five post-transplant measurements, the number (percent) of patients with elevated creatinine levels were 29 (4.4%), 20 (3.0%), 24 (3.6%), 20 (3.0%), and 15 (2.3%), respectively. A description of serum levels of creatinine and four liver indices is presented in Table 1. Furthermore, the findings of the logistic regression models are shown in Table 2. Considering these results, it appears that the liver indices measured at the 3rd month are better predictors of the significant creatinine elevation, comparing with the first and second months measurements.

Discussion

The present study aims at studying the mid-term relationship between post-kidney transplant creatinine increase courses and liver function tests in kidney transplant patients. Patients (n=67) with one or more creatinine increase courses were assigned as the case group compared to the control group (n=592). ALT had the highest prevalence among those enzymes that had been investigated in the current study. The changes in liver enzymes after three months from transplantation is a better predictor of creatinine rise versus liver enzyme changes in the first two months from transplantation.

Initial damage to kidney graft encompasses a variety of presentations ranging from very mild to permanent injuries. Graft injury may provide an inflammatory situation, which makes grafts susceptible to acute or chronic graft rejection. Moreover, graft injury may result in the progression of tubular atrophy or interstitial fibrosis that increases the risk of graft rejection (19, 20). Concerning graft injury, urinary markers as valuable tests have been introduced, nevertheless, despite the benefits of urinary markers, their usage in patients with transplanted kidney is limited due to graft anuria following graft injury for several days and even after initiation of diuresis, urine tests are not able to predict the severity of graft injury (21, 22).

Abnormality in liver function tests has been an area of investigation in several studies. OS Dizdar and his colleges conducted a study of over 281 patients with a transplanted kidney. In the mentioned study, in 107 (38%) of patients abnormality in liver function tests have been detected (23), which in comparison to results of the study of Klintmalm et al., (19.7%) is much higher (24). This significant difference in the incidence of liver function test abnormality can be attributed to the difference in drugs that patients used. In our study that was carried out on 659 patients in a single center of kidney transplantation, patients were under the virtually same treatments and no differences did not exist in this regard. Therefore, abnormality in liver function tests between the control and case groups cannot be explained by differences in drugs.

One of the factors that enable to alter liver function enzymes is the source of the allograft. It has been postulated that patients who transplanted from deceased donors are at greater risk of elevation in liver function tests versus patients who transplant from living donors (25, 26). Following the outcomes of B Einollahi et al.,'s study, AST and ALT had much higher levels in patients who received kidney allograft from deceased donors when they compare to patients who received kidney allograft from living donors (25), however, in the current, all patients received grafts from deceased donors and hence, cannot examine the role of kidney graft source.

There is scarcity of studies that pointed out the benefits of

utilizing AST as the factor that can be used in graft injury. Graft injury can be predicted by the rise in creatinine and is strongly associated with rising according to many years of experience. It has been demonstrated that AST can detect the severity of graft injury and the major superiority of AST in comparison to creatinin is the ability of AST in detecting graft injury more sooner than creatinin. As has been postulated, detecting graft injury in the early stages plays a pivotal role in graft survival and better outcomes for graft survival can be expected if it detects in the early stages (22). Despite all of those benefits, there is an important obstacle to using AST as a predicting factor. AST is mainly used as a liver injury factor, on the other hand, it presents in lots of nucleated cells, therefore, AST is not restricted to specific organs or tissue (22).

Liver failure, which is a common complication after kidney transplantation, is the fourth cause of mortality among patients with transplanted kidneys (27, 28). The prevalence of liver dysfunction among 63 children with transplanted kidney was about 14.2% (9 patients). Of 9, only one of them showed an abnormality in liver enzymes in the first month after renal transplantation and the rest of them did not show abnormality in liver enzymes before the first three months following renal transplantation (29). They also claimed that ALT had the highest prevalence among them and only one patient showed a rise in ALP enzyme. Their assessment showed that the hepatotoxicity of 8 patients was a result of azathioprine toxicity and the other one was because of CMV infection. ALT had the highest prevalence in the study of B Einollahi et al., (34.3%), which was similar to the result of our study.

Conclusions

Because of the importance of a rise in the level of creatinine in patients with transplanted kidneys for identifying graft injury, we assessed the possible correlation between the rise in creatinine level and AST, ALT, ALP, and BUN. Findings of the current study revealed that an increase in the level of creatinine in the first 6 months after kidney transplantation correlates with changes in AST, ALT, ALP, and BUN. Moreover, it has been demonstrated that this correlation is more significant and powerful after three months from kidney transplantation compared to the first two months following kidney transplantation.

Authors' contribution

All authors contributed equally.

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Conflict of interest

All authors declare that there is not any kind of conflict of interest.

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Ethical Statement

The study was under the Tehran University of Medical Sciences Ethical Committee (IR.TUMS.MEDICINE.REC. 1398.342).

Data availability

Data will be provided by the corresponding author on request.

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARTG	Acute renal transplant glomerulopathy
AST	Aspartate transaminase
AUC	Area under the roc curve
AVR	Acute vascular rejection
Bil D	Direct bilirubin
Bil T	Total bilirubin
BUN	Blood urea nitrogen
dnDSA	Donor-specific HLA antibodies
ESRD	End-stage renal disease
GGT	Gamma-glutamyl transpeptidase
KTR	kidney transplant recipients
LFTA	Liver function test abnormalities
MTX	Methotrexate
PT	Prothrombin time
SD	Standard deviation

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