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Non-viral Causes of Liver Enzymes Elevation in Post Renal Transplant Patients

Amna Khattak[1], Mirza Muhammad Dawood[1], Zakia Rahman[2], Sardar Alam[3], Rafaqat Hussain[3], Muhammad Izaz[4], Wasia Ullah[5]

[1]Department of Chemical Pathology, Rehman Medical Institute, Peshawar, KP, Pakistan.
[2]NUST School of Health Sciences, National University Science and Technology, Islamabad, Pakistan.
[3]Department of Urology, Institute of Kidney Diseases, Peshawar, KP, Pakistan.
[4]Department of Anaesthesia, Lady Reading Hospital, Peshawar, KP, Pakistan.
[5]District Medical Entomologist, Health Department, KP, Pakistan.

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Correspondence to: Col. Mirza Muhammad Dawood
Consultant Chemical Pathology, Rehman Medical Institute, Peshawar, KP, Pakistan.
Email: mirza.dawood@rmi.edu.pk

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ABSTRACT

Background: Following kidney transplantation, liver enzyme elevations (LEE) are often observed and can result from a number of causes, such as immunosuppressive medications, viral infections, and other underlying illnesses. **Objectives:** The aim of this study was to ascertain the incidence of LEE and identify the risk factors related to it. **Patients and Methods:** 200 KTRs who had received a transplant and were clear of HBV and HCV infections were included in the study. In kidney transplant recipients (KTRs) who tested negative for hepatitis B surface antigen (HBsAg) and hepatitis C virus antibodies (HCV Ab) and were free of other liver illnesses. Between December 2022 and May 2023, 200 kidney transplant patients (113 men and 87 women) participated in this observational perspective analysis. All recipients had their liver enzyme levels and other biochemical markers, such as complete blood counts, cyclosporine levels, and serum creatinine, assessed. Based on the amount of time that had passed following the transplant, the participants were split into three groups: Group I (less than three months), Group II (4–12 months), and Group III (more than a year post-transplant). **Results:** Incidence of LEE was greatest in male recipients ($P < 0.001$) and older individuals ($P < 0.001$). Patients who received kidneys from deceased donors were more likely to have elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) than those who received kidneys from living donors (10.4% vs. 5.6% for AST and 23.8% vs. 14.8% for ALT, respectively, $P < 0.001$). ALT had the greatest incidence of increase among the liver enzymes, occurring in 34.3% of patients. Following transplantation, ALT and AST levels were considerably higher in the first three months and decreased in the fourth to twelve months ($P < 0.001$). Both univariate and linear regression studies showed a negative relationship between liver enzyme levels and renal allograft function, which grew stronger over time. Furthermore, it was shown that, although this association waned with time, cyclosporine blood levels were strongly correlated with abnormal liver enzymes. Additionally, there was a correlation between LEE and these individuals' anemia. **Conclusion:** In kidney transplant recipients, especially in the early post-transplant phase, liver enzyme increases are a frequent and noteworthy observation. All kidney transplant recipients should have their aminotransferases, particularly ALT, regularly and serially monitored in order to identify liver malfunction early and treat any problems.

INTRODUCTION

The most frequent etiological agents that cause liver dysfunction after kidney transplantation are hepatitis B virus (HBV) and hepatitis C virus (HCV), making chronic liver disease (CLD) a serious and frequently disregarded complication in kidney transplant recipients (KTRs) (1,2). The most common cause of post-transplant hepatitis, which contributes to both acute and chronic liver damage in these patients, is HCV infection (3). The incidence and frequency of HBV and HCV infections in patients receiving haemodialysis and kidney transplantation have significantly decreased in recent years due to improvements in screening and immunisation techniques (1, 4-7). Nephrologists are now more aware of additional possible causes of liver disease in KTRs as a result of this drop, which has prompted them to expand their diagnostic methods. Even with these advancements, liver problems continue to be a major source of morbidity and death for

this patient group, requiring close observation and prompt treatment. It is commonly known that elevated levels of liver enzymes, specifically alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), are indicators of hepatocellular damage. These enzymes indicate the degree and severity of hepatocyte injury, making them important markers of liver dysfunction (8). In clinical practice, serum aminotransferase levels—particularly ALT—are often used to evaluate liver health. Regular monitoring of these enzymes is essential in kidney transplant recipients, who are frequently taken hepatotoxic medicines such immunosuppressive drugs, statins, and allopurinol. In this patient population, elevated liver enzymes may indicate possible hepatotoxicity from viral infections or drug-induced liver damage (DILI), requiring immediate therapeutic intervention (9).

The impact of immunosuppressive treatments and other viral infections, such as cytomegalovirus (CMV) and herpes simplex virus (HSV), are important factors in the differential diagnosis of post-transplant hepatic dysfunction. Tacrolimus and cyclosporine (CsA), two immunosuppressive medications frequently used in kidney transplantation, are known to worsen liver damage and may make it more difficult to determine the underlying cause of hepatic impairment (9). Tacrolimus, a macrolide used as an immunosuppressant following transplantation, has a limited therapeutic index and pharmacokinetics that vary across and within individuals, making clinical management challenging. Tacrolimus interacts with a number of other medications used in transplant therapy that are also known as CYP3A and/or P-glycoprotein inhibitors and/or inducers since it is a substrate of cytochrome P450 (CYP) 3A enzymes and P-glycoprotein (10).

Surprisingly few studies have examined the prevalence and clinical consequences of liver enzyme elevations (LEE) in KTRs, despite the fact that these elevations are clinically significant. The prevalence and development of LEE over time after transplantation have received little attention in the literature, which has mostly concentrated on the etiological mechanisms causing liver dysfunction. This gap in the literature emphasizes the necessity of more research on the long-term consequences, risk factors, and prevalence of LEE in kidney transplant patients. The results of these research may have a major influence on clinical care and monitoring plans for liver problems in KTRs, which would eventually enhance patient outcomes and quality of life.

Objectives

In order to determine the prevalence of non-viral causes of liver enzymes elevation in post renal transplant patients and identification of possible risk factors of liver enzymes elevation.

MATERIALS AND METHODS

Ethical approval

This study was approved by the Ethical Committee of Rahman Medical Institute Peshawar, Pakistan

Study Population

In order to ensure that all participants in this trial were free of any other liver-related conditions, a cohort of 200 renal transplant recipients (RTRs) were first examined for the presence of hepatitis B surface antigen (HBsAg) and hepatitis C virus antibodies (HCV Ab) in the Department of Nephrology and Renal Transplant, Chemical Pathology Section of the Department of Pathology, Rehman Medical Institute, Peshawar. Two hundred patients in all, 113 men and 87 women, were chosen from this group. Each participant had a blood sample taken, and 1327 samples in total were processed. Routine biochemical markers such as serum creatinine (SCr), cyclosporine (CsA) trough levels (C0), 2-hour post-dose cyclosporine levels (C2), and liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were measured in these samples. Based on the amount of time that had passed following their transplant, the patients were divided into three groups:

- **Group No. 1st**: less than 3 months' post-transplantation
- **Group No. 2nd**: 4-12 months' post-transplantation
- **Group No. 3rd**: more than 1-year post-transplantation.

These categories were established in order to evaluate the evolution of liver enzyme levels and renal function over time after transplantation.

Data Collection

Both clinical and demographic characteristics were included in the extensive data gathering process. These included both the donor's and the recipient's gender, their ages, and the donor's source (dead or alive). Each recipient's blood urea, lipid profiles, haemoglobin (Hb), uric acid, and fasting blood sugar (FBS) were measured biochemically. Following transplantation, all patients were monitored for at least six months. The ethics committee gave the study its ethical approval.

Protocol of Treatment and Follow-Up

All participants received immunosuppressive treatment based mostly on cyclosporine (CsA), with most patients also getting azathioprine, prednisolone, and mycophenolate mofetil. Anti-thymocyte globulin induction treatment was used in situations of high sensitization, especially for patients receiving second or third transplants or those with higher panel reactive antibodies.

During the first month following transplantation, blood samples were taken weekly for standard laboratory testing, and participants were routinely evaluated through clinical exams. Up until three months following transplantation, follow-up was conducted every two weeks. following that, tests were conducted monthly for the first year and then every one to two months after that.

Definitions of Terms

This cohort's liver enzyme upper limit of normal (ULN) was set at 40 IU/L for alanine aminotransferase (ALT), aspartate aminotransferase (AST), and 316 IU/L for alkaline phosphatase (ALP). Serum creatinine (SCr) values above 2 mg/dl were seen as a sign of renal allograft failure. Additionally, according to earlier research, individuals were classified as having increased ALT levels if their ALT levels were higher than 27 IU/L, which is considered the upper limit of normal for dialysis patients without liver disease (11).

Statistical Analysis

SPSS version 21.0 (SPSS Inc., Chicago, Illinois, USA) was used to analyse the data. Quantitative data were presented as mean ± standard deviation (SD) using descriptive statistics, while categorical variables were represented as percentages and frequencies. The ALT and AST levels did not follow a normal distribution, according to the results of the Kolmogorov-Smirnov test (K-S test). Consequently, the associations between liver enzyme levels and continuous variables were investigated using Spearman's correlation analysis. When comparing categorical variables, the chi-square test was used.

The Mann-Whitney U-test was performed to compare the AST, ALT, and ALP levels of male and female recipients. Additionally, aberrant ALT levels were treated as a categorical outcome and used as the dependent variable in a multivariate logistic regression analysis. A p-value of less than 0.05 was deemed to be statistically significant.

RESULTS

Demographic Settings: This study comprised 200 patients, 113 of whom were male (56.5%) and 87 of whom were female (43.5%). The patients' demographic information is shown in Table 1. Kidneys from live, unrelated donors were given to most patients. Liver enzyme levels were higher in older patients than in younger ones. In addition, the liver enzyme levels of male patients were greater than those of female patients. Patients who got kidneys from deceased donors had significantly higher levels of AST and ALT than those who received kidneys from living donors (10.4% and 23.8%, respectively, vs 5.6% and 14.8%, P < 0.001). On the other hand, individuals who received kidneys from living donors had substantially higher ALP levels (17% versus 13%, P = 0.006).

Table 1

Demographic Data of Transplant Patients (n = 200)

Variable	Amounts
Recipients Sex, Male/Female, %	56.5/43.5
Donors Sex, Male/Female, %	83/17
Donor Sources, LRD/LURD/Deceased, %	8.23/84.6/6.6
Times of Transplantation, 1/2/3	190/8/2
ALT, IU/L, Mean ± SD	30.4 ± 46.30
AST, IU/L, Mean ± SD	22.19 ± 29.01
Total Bilirubin, Mean ± SD	1.11 ± 3.10
ALP, IU/L, Mean ± SD	243.30 ± 188.90
Trough-Level of CsA, ng/mL, Mean ± SD	154.9 ± 98.12
2-h Dose CsA, ng/mL, Mean ± SD	518.7 ± 174.3
Age of Recipients, Mean ± SD, years	38 ± 15
Age of Donors, Mean ± SD, years	28 ± 6
BUN, mg/dL, Mean ± SD	52 ± 31
Serum Creatinine, mg/dL, Mean ± SD	1.60 ± 0.91
HDL Cholesterol, mg/dL, Mean ± SD	48.2 ± 15.7
FBS, mg/dL, Mean ± SD	103 ± 46
LDL Cholesterol, mg/dL, Mean ± SD	102.20 ± 34.40
Uric Acid, mg/dL, Mean ± SD	6.1 ± 1.80
Hemoglobin, g/dL, Mean ± SD	12.6 ± 2.2

[1] Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase ; BUN, blood urea nitrogen; Cr, creatinine; CsA, Hb; hemoglobin cyclosporine; FBS, fasting blood sugar;; AST, aspartate transaminase; LDL, low density lipoprotein; HDL, high density lipoprotein LRD, living-related-donor; LURD; living unrelated donor; TB; total bilirubin; Tx; transplantation.

Prevalence: The frequency of liver enzyme abnormalities in each patient and in particular groups is shown in Table 2. The most prevalent abnormality of liver enzymes after donation was ALT increase. Within the first three months after transplantation, ALT and AST values were substantially higher than those during the next four to twelve months (P < 0.001). ALP levels did not, however, alter significantly across the three post-transplantation periods (P = 0.2).

Table 2

Prevalence of Liver Enzymes Elevation after Kidney Transplantation (n = 200)

Abnormal Variable	Overall (%)	Group I (<3 months) (%)	Group II (4-12 months) (%)	Group III (>12 months) (%)	P value
ALT	34.3	62.3	53	29	<0.001
AST	6.7	13.4	10.6	5.6	<0.001
ALP	16.5	18.9	16.7	16.2	0.2

[1] Abbreviations: AST; aspartate transaminase ALP; alkaline-phosphatase; ALT; alanine-aminotrans-ferase;.
[2] P value; < 0.05.

Correlation of Liver Enzyme Tests and Other Biochemical Parameters

Univariate Analysis: The relationship between liver enzyme levels and other biochemical markers is shown in Table 3. Serum creatinine levels showed a negative correlation between elevated liver enzymes and renal function. Furthermore, there was a noteworthy correlation between the blood levels of cyclosporine (CsA) and liver enzymes, including ALT and ALP. Anemia and fasting blood sugar (FBS) were also linked to elevated liver enzyme levels. The characteristics of the lipid profile showed a mild but significant connection with ALP.

Table 3

Correlation between Liver Enzyme Levels and Other Parameters

Variables	AST (P value)	ALT (P value)	TB (P value)	ALP (P value)
Trough Level of CsA	<0.001 (0.17)	<0.001 (0.29)	<0.001 (0.11)	0.1 (-0.02)
2-hours post dose CsA	<0.001 (0.13)	<0.001 (0.23)	<0.001 (0.14)	0.001 (-0.07)
Age of Recipient	0.06 (0.02)	<0.001 (0.07)	<0.001 (0.09)	<0.001 (-0.06)
Age of Donor	0.6 (-0.007)	0.8 (-0.004)	0.08 (0.04)	0.1 (0.02)
Serum Creatinine	<0.001 (-0.12)	<0.001 (-0.07)	<0.001 (-0.02)	<0.001 (-0.07)
FBS	0.6 (0.006)	<0.001 (0.09)	0.083 (0.03)	<0.001 (0.1)
HDL Cholesterol	0.15 (0.02)	0.08 (0.03)	<0.001 (0.1)	<0.001 (-0.09)
LDL Cholesterol	0.4 (0.01)	0.06 (0.03)	0.1 (-0.03)	0.008 (0.04)
Uric Acid	0.004 (-0.04)	<0.001 (-0.09)	0.6 (0.009)	0.09 (-0.02)

Hemoglobin	<0.001 (0.09)	0.001 (0.06)	<0.001 (0.4)	<0.001 (0.09)

[1] Abbreviations: ALT, alanine aminotransferase; AST, aspartate trans-aminase ; CsA; cyclosporine; ALP; alkaline phosphatase, Hb; hemoglobin, HDL; high density lipoprotein; LDL, low density lipoprotein; TB, total biliruben. [2] P value; < 0.05.

Multivariate Regression Analysis: An ALT level of more than 27 IU/L was considered abnormal in recipients whose serum creatinine levels were more than 2 mg/dL. Renal impairment was found to be an independent risk factor for aberrant ALT levels in individuals with increased serum creatinine by multivariate logistic regression analysis (Exp (B) = 0.48, 95% CI: 0.32-0.73, P = 0.001).

The study identifies notable variations in liver enzyme levels according to biochemical correlations, donor type, and demographic characteristics. Male patients were more likely to have elevated liver enzymes within the first three months following transplantation. While ALP had a modest connection with lipid profiles, ALT and AST had strong relationships with renal function and CsA levels.

DISCUSSION

Hepatocellular damage is indicated by an increase in liver aminotransferases, particularly aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Surprisingly few studies have looked at liver enzyme levels and the risk factors that are linked to them in kidney transplant recipients, despite the significance of monitoring liver enzyme elevations (LEE) following kidney transplantation. There is currently little information available on the frequency and clinical importance of liver enzyme abnormalities following kidney transplantation.

200 kidney transplant recipients (113 men and 87 women) participated in this study, which showed that liver enzymes are commonly raised in these patients, with ALT abnormalities making up about 34% of cases. According to other research, between 7% and 67% of kidney transplant recipients have liver disease (references 12–15). This discrepancy might be explained by variations in the diagnostic standards applied in various investigations. AST and ALT values more than 40 IU/L were deemed abnormal for individuals with serum creatinine (SCr) levels less than 2 mg/dL. On the other hand, ALT levels over 27 IU/L were considered abnormal for recipients with SCr > 2 mg/dL.

The most prevalent liver enzyme abnormality in our sample, especially in the first three months after transplantation, was ALT abnormalities. This result is consistent with a prior study that included 189 kidney transplant recipients and found that 41% of patients had abnormal liver enzymes. Interestingly, 22% of patients saw brief increases in aminotransferases over the first three months. As the fourth leading cause of death following kidney transplantation, chronic liver disease continues to be a serious consequence. Although they may have longer allograft function, patients with chronic liver enzyme deficiencies are more likely to die from non-hepatic infections (references 16–17). The clinical management of tacrolimus, a macrolide used as immunosuppressant after transplantation, is complicated by its narrow therapeutic index in combination with inter- and intra-individually variable pharmacokinetics. As a substrate of cytochrome P450 (CYP) 3A enzymes and P-glycoprotein, tacrolimus interacts with several other drugs used in transplantation medicine, which also are known CYP3A and/or P-glycoprotein inhibitors and/or inducers

According to a research by Malekzadeh et al., 14.2% of paediatric kidney transplant recipients had liver disease; just one instance was identified in the first month following the transplant, and the others showed up after the third month. According to their results, only one patient had increased alkaline phosphatase (ALP), and ALT levels were greater than AST levels. In their investigation, liver dysfunction was caused by cytomegalovirus (CMV) infection in one instance and azathioprine toxicity in eight cases. Similar to this, although ALT levels in our research were higher than AST levels, most occurrences of hypertransaminasemia happened in the first three months following transplantation.

The incidence of abnormal liver enzymes was strongly impacted by the kidney allograft's origins. In contrast to alive donor transplants, our results showed that liver enzyme abnormalities were more common in deceased donor transplants. This finding is consistent with previous research (references 19–21). According to a 1987 study by Lorber et al., 49% of recipients of renal allografts treated with cyclosporine (CsA) had post-transplant hepatotoxicity. These included high levels of lactate dehydrogenase (LDH) (84%), ALT (73%), AST (47%), bilirubin (48%), and ALP (59%). In their cohort, abnormal liver enzymes frequently resolved on their own, occurring soon after transplantation and doing so in 82% of instances. With an average of 225 ± 17 ng/mL, the CsA levels in these individuals were comparatively high.

Despite being less severe, our results support the link between aberrant liver enzymes and CsA levels. We were able to rule out azathioprine's hepatotoxic effects because our patients did not get it. We found a correlation between higher liver enzymes and lipid profiles, renal allograft performance, and CsA blood levels. Patients who get CsA frequently have brief, moderate increases in their aminotransferase levels. Elevations that are significant or persistent call for a thorough assessment that includes a liver biopsy if required and screening for viral hepatitis. Our results emphasize how crucial it is for kidney transplant recipients to have regular liver function checks, particularly in the early post-transplant phase.

Limitations of the Study

This study's primary shortcomings are its observational perspective design, the omission of non-alcoholic fatty liver disease, which is the leading cause of chronic liver disease globally, and the failure to screen for hepatitis E virus infection in individuals with increased liver enzymes. Additionally, not all kidney transplants with abnormal ALT had liver biopsies and genetic testing. It should be

mentioned that the gold standard for diagnosing hepatic damage is a liver biopsy.

Nevertheless, it is costly, intrusive, and potentially dangerous. Furthermore, we were unable to estimate the influence of the following factors on liver enzyme levels following kidney transplantation: ischaemia time, ALP bone isoenzyme, body mass index, medications that affect liver enzymes, such as statins, and the status of opportunistic infections following kidney transplantation. Prednisolone and mycophenolate mofetil were also administered to most individuals. Only a few individuals were treated with azathioprine, and we didn't look into how it affected the liver enzymes. Abnormal liver enzymes are frequently observed in kidney transplant recipients. Age, gender, donor source, renal allograft function, anemia, and CsA blood levels were all associated with the LEE. Following kidney transplantation, all patients should have their aminotransferases, especially ALT, monitored on a serial basis.

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