SERUM AMINOTRANSFERASES IN CHRONIC KIDNEY DISEASE PATIENTS: A HOSPITAL BASED COMPARATIVE STUDY

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ABSTRACT

Estimation of serum aminotransferase levels play important role in the diagnosis and monitoring of hepatic diseases. Studies suggest that in patients with chronic kidney disease, especially in those under hemodialysis, the reference ranges of the serum aminotransferases might not be reflective of hepatic function. Due to this, diagnosis and management of liver diseases in such patients becomes quite challenging. This study aims to estimate and compare serum aminotransferases levels of hemodialysis patients and healthy controls. Seventy-five patients undergoing hemodialysis in Nepal Medical College Teaching Hospital for at least three months were included in the study as cases and apparently healthy individuals with no active illness and regular medication use for the past three months and were recruited as controls. Predialysis blood samples were drawn and were analyzed for serum aminotransferases and other blood parameters. The median serum AST and ALT values for hemodialysis patients were 15 U/L and 21 U/L, while for the healthy controls, it was 30 U/L and 36 U/L and the differences were statistically significant ($p < 0.001$). Among the hemodialysis patients, serum AST was positively correlated with eGFR ($\rho = 0.247$, $p = 0.033$) and negatively correlated with serum creatinine levels ($\rho = -0.307$, $p = 0.007$). Hence, serum aminotransferases levels were found to be low in patients with impaired kidney function compared to those with normal kidney function.

KEYWORDS

Aminotransferase, chronic kidney disease, hemodialysis, liver disease

***Received on**: February 15, 2023*
***Accepted for publication**: May 26, 2023*

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DOI: https://doi.org/10.3126/nmcj.v25i2.56054

INTRODUCTION

Serum aminotransferases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), play an important role in diagnosing and monitoring liver diseases. Generally, serum aminotransferase levels rise beyond the normal range in patients with liver diseases.[1] However, many studies have suggested that the serum AST and ALT levels were towards the lower reference ranges in the patients with chronic kidney disease (CKD) on hemodialysis (HD) with or without liver disease compared to the patients with normal renal function.[2-5] Because of this, the diagnosis of liver diseases in CKD patients has become a challenge. Various studies suggest that CKD patients, especially those on HD, are more likely to develop hepatic infections.[6-9] Past studies showed that the CKD patients on HD infected with the Hepatitis C virus (HCV) have higher aminotransferase serum levels than those on HD who are not infected.[10,11] Such HCV-infected CKD patients on HD still have lower aminotransferase levels than the infected patients whose renal functions are preserved.[12,13] Serum aminotransferases levels may be normal even when an active hepatic injury occurs in such patients.[14]

Hence, the reliability of using standard reference values of aminotransferases to detect liver disease in patients on chronic dialysis therapy has been questionable.[2,15,16] Such unexpected and unpredicted reduction in aminotransferases levels in patients with CKD could complicate the diagnosis and management of liver damage. Many past and recent studies have hinted toward the need for revising the cut-off values for serum aminotransferases levels in patients with CKD. They even suggested adopting lower "normal" values of aminotransferases to increase the sensitivity of liver function tests among dialysis patients.[2,17]

This study aims to estimate and compare serum AST and ALT levels of CKD patients with HD and healthy controls. It may help to evaluate the need to establish a new reference range of these enzymes among CKD patients. We believe it will benefit clinicians in diagnosing and managing liver problems in CKD patients in the future.

MATERIALS AND METHODS

Ethical approval for the study was taken from Nepal Medical College Institutional Review Committee (IRC No.: 048-077/078). A cross-sectional study was conducted from July 2021 to July 2022 that included CKD patients aged 18 years and older under maintenance HD in the dialysis unit of Nepal Medical College Teaching Hospital (NMCTH) for at least three months. Viral serology was performed to exclude Hepatitis B, HCV, and HIV. Apparently healthy volunteers who attended the hospital for a routine health checkup with no complaint or major illness in the past 3 months were enrolled as controls. Active alcoholics, pregnant women, and those below 18 years were excluded. Also, those under medications that affect liver enzymes were excluded. All the participants were requested to provide consent. In case of refusal, the next eligible respondent was approached. Demographic details and medical history were noted. Serum estimations of AST, ALT, urea, creatinine, sodium, and potassium were done using an automated wet chemistry method (P500 Diatron, reagents of Medicon Hellas SA, Attiki, Greece). Serum AST and ALT within the range of 0-37 IU/L and 0-40 IU/L were considered normal, as mentioned in the manufacturer's manual. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) equation formula for both CKD cases and healthy controls. The equation to calculate eGFR as per National Kidney Foundation is $eGFR = 175 \times (\text{Serum Creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ [if female] x 1.212 [if Black].[18]

Data were entered into Microsoft Excel and analyzed using SPSS-16. The Shapiro-Wilk test was performed to see the distribution of continuous variables. Since all the variables deviated significantly from the normality, non-parametric tests were employed for the analysis. The numerical data were expressed as a median and interquartile range. Mann-Whitney U test was used to compare the mean rank between the comparison groups. Spearman's correlation analysis was done to see the association between continuous hepatic and renal parameters. P value <0.05 was considered statistically significant.

RESULTS

A total of 150 participants were enrolled in the study. Among them, 75 were CKD patients on maintenance HD, and 75 were apparently healthy individuals. The sex-wise distribution of the participants in CKD groups and controls is shown in Fig. 1. The median age of the overall participants was 50 years, with the average ages of the CKD groups and healthy controls being 48 and 51 years, respectively. Table 1 shows the descriptive statistics of age and laboratory

Table 1: Comparison of study parameters between the study groups

Variables	Total population[a]	CKD group[a] (n = 75)	Healthy controls[a] (n = 75)	P- value[b]
Age (years)	50 (38-62)	48 (36-62)	51 (41-62)	0.343
AST (U/L)	24 (15-33.25)	15 (11-27)	30 (22-41)	**<0.001**
ALT (U/L)	29 (17-45.25)	21 (14-33)	36 (24-54)	**<0.001**
Urea (mg/dl)	47 (26.75-133.27)	132.7 (111-155)	27 (22-32)	**<0.001**
Creatinine (mg/dl)	2.35 (0.9-10)	10 (8-12.1)	0.9 (0.8-1)	**<0.001**

Notes: [a]Median (figure in the parenthesis indicates the inter-quartile range). [b]Mann-Whitney U test. P < 0.05 considered statistically significant and indicated in bold typing.

Table 2: Comparison of study variables between the study groups based on sex

Variables		CKD group[a] (n = 75)	Healthy controls[a] (n = 75)	P-value[b]
Age (years)	M	50 (37-69)	53 (41-67.25)	0.381
	F	48 (34.5-55.75)	50 (34-60)	0.827
AST (U/L)	M	15 (10-27)	34 (25-44)	**<0.001**
	F	15.5 (11.25-28.5)	25 (19-232)	**0.005**
ALT (U/L)	M	26 (15-360	47 (27-62)	**<0.001**
	F	17.5 (14-29)	32 (20-37)	**0.008**
Urea (mg/dl)	M	129 (110-166)	27 (22.25-32)	**<0.001**
	F	135 (114.25-143.88)	26 (22-31)	**<0.001**
Creatinine (mg/dl)	M	10.6 (8.2-12.7)	1 (0.9-1.07)	**<0.001**
	F	9.1 (7.12-11.65)	0.8 (0.7-0.9)	**<0.001**

Notes: [a]Median (figure in the parenthesis indicates the inter-quartile range). [b]Mann-Whitney U test. P < 0.05 considered statistically significant and indicated in bold typing.

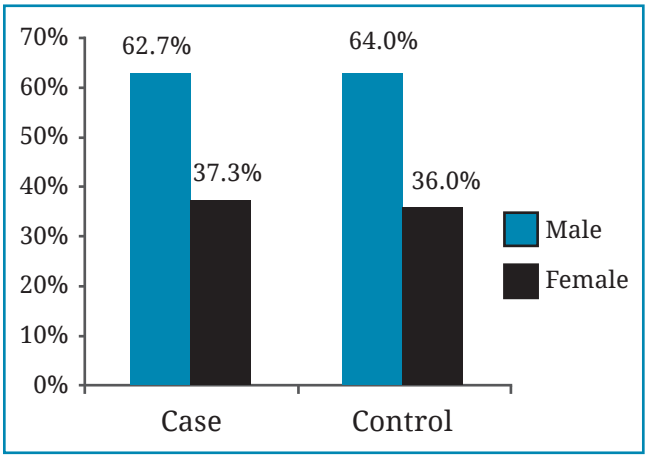

Fig. 1: Sex-wise distribution of the study participants

parameters between CKD groups and healthy controls. The median serum AST and ALT values among cases were 15 U/L and 21 U/L, while for the healthy controls, it was 30 U/L and 36 U/L (Table 1). The differences were statistically significant ($p < 0.001$). Similar results were obtained when the parameters were compared separately for males and females (Table 2).

The correlation of hepatic enzyme levels with both serum creatinine level and eGFR was evaluated separately for CKD patients and healthy controls. Among CKD groups, serum AST levels had a significant, albeit weak, positive correlation with eGFR ($\rho = 0.247$; $p = 0.033$) and a negative correlation with serum creatinine values ($\rho = -0.307$; $p=0.007$) (table 3). The serum

Table 3: Spearman's correlation of serum aminotransferases with serum creatinine and eGFR among CKD group

Group	Liver enzymes		Creatinine	eGFR
CKD Group (N = 75)	AST	ρ	-0.307	0.247
		P-Value	**0.007**	**0.033**
	ALT	P	-0.046	0.127
		p-Value	0.693	0.279

Notes: P- values obtained from Spearman's correlation analysis. P<0.05 considered statistically significant and indicated in bold typing. ρ denotes Spearman's rank correlation coefficient.

AST levels did not correlate significantly with renal parameters in healthy controls. The serum ALT levels had no significant correlation with eGFR and serum creatinine in both groups.

DISCUSSION

Evaluation and monitoring of hepatic comorbidities in patients with CKD under HD based on serum aminotransferase levels could be misleading. In this study, we compared serum aminotransferase levels between CKD patients under HD, without hepatic dysfunctions, and healthy controls to see whether renal failure affected their levels.

There was no significant difference in age between the comparison group (p = 0.343). However, the median age of the CKD patients was 48 years which is low compared to the average age of similar patients in their developed counterparts.[19,20] This is a matter of concern and has been discussed in our previous papers as well.[21,22] Lack of awareness, low access to proper healthcare facilities, especially at earlier stages of the disease, financial insecurities, and increasing prevalence of hypertension and diabetes mellitus among youths could be possible attributing factors.[5]

In our study, serum AST and ALT levels were significantly lower in CKD patients with HD than in healthy controls (p < 0.001). Similar results were obtained when serum aminotransferase levels were compared between the groups separately for males and females. The patients under HD had median serum AST and ALT levels on the lower side of the reference range. Many earlier and recent studies have also conformed to these results.[2,4,23] Similar findings were also reported in a recent study from Nepal.[23] Furthermore, serum aminotransferase levels have also been reported to be significantly lower in CKD patients without ESRD as compared to healthy controls but higher than in CKD patients with ESRD.[2] Various studies have also compared the pre and post-dialysis levels of hepatic enzymes in patients with ESRD where significant increments in post-dialysis aminotransferase levels were noted.[24,25] In contrast, the study from Nepal reported no significant differences in aminotransferase levels before and after dialysis.[23]

These findings pose a significant challenge in assessing liver functions in HD patients, given the fact that hepatic complications are more likely in such individuals.[6,7] Many hypotheses have been put forward to explain the lower serum aminotransferase levels among CKD patients; however, they remain controversial. Some of them include clearance of aminotransferases during the HD session; high lactate serum levels that consume significant NADPH resulting in low aminotransferase levels; inhibition of enzyme activities by uremic factors; and the deficiency of pyridoxine, an essential cofactor for aminotransferase synthesis.[2,5] While some of them have already been disproved,[4] none seem to corroborate seamlessly with the overall narrative.

Establishing newer reference ranges of serum aminotransferases for CKD patients; suitable disease-specific cut-off values of these enzymes to estimate hepatic dysfunctions, or using more sensitive and specific biomarkers in such patients could resolve these clinical uncertainties.

The serum aminotransferase levels were significantly lower among CKD patients under maintenance HD compared to healthy controls. Assessment of liver function in CKD patients with the older reference range could be misleading.

Limitations: We could not exclude all the hepatic disorders, especially autoimmune hepatitis and non-alcoholic fatty liver disease in our study due to budget constraints. This was the major limitation of our study.

ACKNOWLEDGEMENTS

We are very much grateful to our participants of hemodialysis unit and the staffs.

Conflict of interest: None

Source of research fund: None

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