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Association of Liver Enzymes and Chronic Kidney Disease Patients with or without Hemodialysis

Khaleda Akhter[1,*], Farnaz Nobi[2,ORCID], Shanjida Sultana Juthy[3,Orcid], Samira Khatun[4,ORCID], Madhabi Karmaker[5,ORCID]

Abstract

Background: Chronic kidney disease (CKD) is a growing global health concern, often associated with hepatic dysfunction. Liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) are commonly used to assess liver function. However, their diagnostic significance in CKD patients, particularly those undergoing hemodialysis, remains unclear.

Aim of the study: This study aimed to evaluate the liver enzyme profile in CKD patients with or without hemodialysis to determine potential alterations in hepatic biomarkers and their clinical implications.

Methods: A cross-sectional study was conducted at Dhaka Medical College and Hospital over one year, involving 135 participants divided into three groups: CKD patients without hemodialysis (Group A, n=45), CKD patients undergoing hemodialysis (Group B, n=45), and healthy controls (Group C, n=45). Serum ALT, AST, and ALP levels were measured and analyzed using SPSS.

Results: ALT and AST levels were significantly lower in CKD patients (both with and without hemodialysis) compared to healthy controls ($p < 0.001$). However, ALP levels were significantly elevated in hemodialysis patients ($p < 0.001$). These findings suggest a potential misinterpretation of normal hepatic enzyme reference ranges in CKD patients, leading to diagnostic challenges in liver disease assessment.

Conclusion: The study highlights the need for revised liver enzyme reference ranges in CKD patients. ALT and AST levels may not be reliable markers of liver disease in this population, whereas ALP elevation could be linked to CKD-related bone metabolism disorders. Further large-scale studies are recommended to refine diagnostic criteria and improve clinical management.

Keywords: Chronic kidney disease; liver enzymes; ALT; AST; ALP; Hemodialysis; Hepatic dysfunction

Introduction

Chronic kidney disease (CKD) has emerged as a major global health concern, gradually becoming one of the leading causes of death and disability worldwide. The Kidney Disease Improving Global Outcomes (KDIGO) defines CKD as structural or functional abnormalities of the kidneys, with or without decreased glomerular filtration rate (GFR) <60 mL/min/1.73m² or evidence of kidney damage lasting ≥3 months [1]. In 2015, the burden of CKD was estimated at 109.9 million cases in high-income countries (men: 48.3 million, women: 61.7 million), whereas lower-middle-income countries bore a much heavier burden,

Affiliation:
[1]Major, Combined Military Hospital, Dhaka, Bangladesh
[2]Department of Nephrology, Kidney Foundation Hospital and Research Institute, Dhaka, Bangladesh
[3]Kidney Foundation Hospital & Research Institute, Dhaka, Bangladesh
[4]Dialysis Medical Officer, Department of Nephrology, Rajshahi Medical College Hospital, Rajshahi, Bangladesh
[5]Department of Medicine, Dhaka Medical College Hospital, Dhaka, Bangladesh

***Corresponding author:**
Khaleda Akhter, Major, Combined Military Hospital, Dhaka, Bangladesh

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with 387.5 million cases (men: 177.4 million, women: 210.1 million) [2]. The increasing prevalence of CKD worldwide has prompted the recognition of CKD as a public health crisis, particularly in Asia and other parts of the world. In addition to renal dysfunction, CKD patients are often at increased risk of concurrent chronic liver diseases, with hepatitis B and C being the most prevalent among these comorbidities. Hepatitis C infection, for instance, has been observed in between 0.7% and 18.8% of dialysis patients in the Asia-Pacific region, while hepatitis B prevalence ranges from 1.3% to 14.6% in these populations [3]. Dialysis modality plays a significant role in the transmission of these infections, with hemodialysis patients exhibiting higher rates of seroconversion for hepatitis B and C viruses compared to peritoneal dialysis patients. Hepatic infections in CKD patients are associated with increased mortality, primarily due to complications such as cirrhosis and hepatocellular carcinoma [4]. For assessing and monitoring hepatic diseases in CKD patients, serum enzyme levels such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) are commonly used biomarkers. The reference ranges for these enzymes are 7–41 U/L for ALT, 12–38 U/L for AST, and 33–96 U/L for ALP [5]. In CKD patients, serum aminotransferase levels often fall near the lower end of the normal range, and this trend is similarly observed in patients undergoing hemodialysis. Studies have reported that patients with hepatitis C infection and CKD undergoing hemodialysis exhibit serum ALT levels lower than those of individuals with normal renal function [6,7]. While the exact cause for the lower serum aminotransferase levels remains unclear, possible explanations include pyridoxine deficiency or the presence of an inhibitory substance in the uremic environment. Additionally, hemodilution has been suggested as a contributing factor [8]. Alkaline phosphatase, mainly produced by the liver and bones, is vital for diagnosing and monitoring hepatic disease. In CKD patients, elevated ALP is often linked to renal osteodystrophy. Among those on maintenance hemodialysis, increased bone isoenzyme levels of ALP are associated with coronary calcification and higher mortality rates [9]. Furthermore, Studies indicate that ALT and AST levels in CKD patients, regardless of renal replacement therapy, tend to be at the lower end of the normal range. Thus, normal enzyme levels do not exclude liver disease, complicating the diagnosis, management, and follow-up of hepatic dysfunction [10]. The aim of this study was to evaluate the status of liver enzymes in chronic kidney disease patients with or without hemodialysis.

Materials and Methods

This cross-sectional study was conducted in the Department of Nephrology at Dhaka Medical College and Hospital, Dhaka, over a one-year period from October 2018 to September 2019. Total 135 people were participated in the study where 90 people had CKD. The study population consisted of three groups:

Group A (n=45): diagnosed case of CKD without hemodialysis

Group B (n=45): diagnosed case of CKD with hemodialysis

Group C (n=45): Healthy control group

A non-randomized purposive sampling method was used to select participants based on specific inclusion and exclusion criteria.

Inclusion criteria

- Participants must be above 18 years of age.
- Patients diagnosed with CKD who are not undergoing hemodialysis are eligible.
- Patients diagnosed with CKD who are undergoing hemodialysis are eligible.

Exclusion criteria

- Patients with acute kidney injury are excluded.
- Patients with CKD for less than one year are not included.
- Individuals with a history of chronic liver disease are excluded.
- Patients who consume alcohol more than 40 grams per day for males and 20 grams per day for females are excluded.
- Pregnant and postpartum women are not included.
- Patients taking medications that affect liver enzymes, such as statins or rifampicin, are excluded.

Ethical Consideration

The researcher ensured that all ethical considerations related to the study were properly addressed. Formal ethical clearance was obtained from the ethical review committee of Dhaka Medical College before conducting the study. Confidentiality of both participants and their information was strictly maintained, and unauthorized individuals were not given access to the data. Informed written consent was obtained from all study participants, with clear explanations provided regarding the nature and purpose of the study, the study procedures, and the participants' rights, including their freedom to refuse, accept, or withdraw from participation at any stage. Additionally, participants were informed that they would not receive any financial benefits from their involvement in the study.

Data collection technique

Following attending in department of Nephrology all patients were assessed and managed accordingly. After selection of participants according to the inclusion and

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exclusion criteria, they were approached for inclusion of study. Following information about the study aim, objectives and procedure, informed written consent was taken from each participant. Appropriate data were collected by using a preformed data collection sheet. The study variables included demographic information, liver enzyme levels, kidney function status, and various laboratory investigations. Demographic data such as age and sex were recorded for all participants. Liver enzyme levels were assessed by measuring alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Kidney function status was evaluated through serum creatinine levels and estimated glomerular filtration rate (e-GFR). Additionally, several laboratory investigations were conducted, including urine routine examination (Urine R/E), serum calcium, serum phosphate, intact parathyroid hormone (iPTH), complete blood count (CBC), and ultrasonography of the whole abdomen (USG of W/A). ALT, AST, and ALP serum levels were determined by an automated kinetic method for blood samples, which were taken from all three groups. After that compare the serum levels of AST, ALT, and ALP among all groups. All collected information were stored in separate data record form.

Data Processing and Analysis

After data checking they were inputted into Microsoft excel sheet (version 2010) and then transcribed into statistical software. Finally, after data editing and compilation, data was analyzed by using the Package for Social Sciences (SPSS Inc., Chicago, IL, version 22.0 for Windows). Statistical analyses was carried out using descriptive statistics. For normally distributed data, continuous variables were expressed with a mean and standard deviations & means were compared using student´s t test, ANOVA test. Qualitative or categorical variables were described as frequencies and proportions & proportions were compared using Chi square. Statistical tests was two-sided and performed at a significance level of p =<0.05.

Results

A total of 135 patients were included in the study, divided equally into three groups (Group A, Group B, and Group C), each consisting of 45 participants. The mean age was significantly lower in Group C (41.58 ±9.26 years) compared to Group A (47.47 ±10.92 years) and Group B (47.97 ±10.93 years) ($p = 0.006$). The gender distribution was similar across groups, with no significant differences ($p = 0.810$) (Table 1). The etiology of chronic kidney disease (CKD) was compared between Group A and Group B in Table 2. A significant difference was observed in the prevalence of glomerulonephritis, affecting 35.6% of Group A and 44.4% of Group B ($p = 0.035$). Obstructive nephropathy was present in 11.1% of Group A patients but absent in Group B. Other CKD causes such as hypertension, diabetes, polycystic kidney disease (PCKD), and systemic lupus erythematosus (SLE) showed no significant differences. In terms of disease duration, Group A had a higher proportion (60%) of patients with a disease duration of 1-3 years, while Group B had more patients (53.3%) in the 3-6 years category. The mean disease duration was 2.72 ±2.13 years in Group A and 4.66 ±3.00 years in Group B, though no significant difference was observed ($p = 0.194$) (Table 3). The distribution of CKD stages showed that Group A had 88.9% of patients in Stage 4, while Group B had 100% in Stage 5, with a significant difference ($p < 0.001$) (Table 4). Laboratory findings revealed significant differences across the groups in Table 5. Serum creatinine was highest in Group B (8.95 ± 1.49 mg/dL), followed by Group A (5.44 ± 1.97 mg/dL), and lowest in Group C (0.97 ± 0.12 mg/dL) ($p < 0.001$). Group A had a higher eGFR (24.64 ± 5.26) compared to Group B (6.71 ± 1.55) ($p < 0.001$). Significant differences were also observed in serum calcium, phosphate, PTH, ALT, AST, and ALP levels ($p < 0.001$). The relationship between serum liver enzyme levels and CKD patients with or without hemodialysis showed that ALP was significantly higher in Group B (100% elevated), compared to Group A (17.8% elevated), while ALT and AST remained normal in both groups ($p < 0.001$) (Table 6).

Table 1: Demographic characteristics of the study population (N=135).

Variables	Group A (n=45)		Group B (n=45)		Group C (n=45)		P-value
	n	%	n	%	n	%	
Age (years)							
18-30	4	8.9	3	6.7	7	15.6	0.176*
31-40	8	17.8	10	22.2	15	33.3	
41-50	16	35.6	12	26.7	10	22.2	
51-60	12	26.7	14	31.1	13	28.9	
>60	5	11.1	6	13.3	0	0	
Mean±SD (in years)	47.47±10.92		47.97±10.93		41.58±9.26		0.006**
Gender							
Male	27	60	25	56	24	53.3	0.810*
Female	18	40	20	44	21	46.7	

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Table 2: Probable etiology of chronic kidney disease (CKD) patients (N=90).

Etiology	Group A (n=45)		Group B (n=45)		P-value
	n	%	n	%	
Glomerulonephrits	16	35.6	20	44.4	0.035*
Hypertension	2	4.4	2	4.4	
Diabetes mellitus	14	31.1	16	35.6	
PCKD	3	6.7	3	6.7	
SLE	4	8.8	3	6.7	
Obstructive nephropathy	5	11.1	0	0	
Others	1	2.2	1	2.2	

Table 3: Disease duration of CKD patients of study population (N=90).

Duration of disease (years)	Group A (n=45)		Group B (n=45)		P-value
	n	%	n	%	
01-Mar	27	60	17	37.77	0.056
03-Jun	13	28.9	24	53.3	
>6	5	11.11	4	8.8	
Mean±SD (years)	2.72±2.13		4.66±3.00		0.194**

Table 4: Stages of CKD in study population (N=90).

Stages of CKD	Group A (n=45)		Group B (n=45)		P-value
	n	%	n	%	
Stage-4	40	88.9	0	0	<0.001*
Stage-5	5	11.1	45	100	

Table 5: Laboratory findings among patients (N=135).

Variables	Group A (n=45)	Group B (n=45)	Group C (n=45)	P-value
S. Creatinine (mg/dL)	5.44 ± 1.97	8.95 ± 1.49	0.97 ± 0.12	<0.001*
eGFRMDRD	24.64 ± 5.26	6.71 ± 1.55	N/A	<0.001**
Serum Calcium (mg/dL)	8.10 ± 0.69	7.79 ± 0.72	9.36 ± 0.41	<0.001*
Serum Phosphate (mg/dL)	5.28 ± 0.39	7.54 ± 0.75	3.91 ± 0.43	<0.001*
PTH (pg/ml)	155.58 ± 27.72	350.16 ± 52.14	22.82 ± 5.00	<0.001*
Serum ALT (U/L)	20.16 ± 4.15	17.49 ± 5.04	33.42 ± 4.57	<0.001*
Serum AST (U/L)	22.35 ± 2.96	17.73 ± 4.41	30.56 ± 4.86	<0.001*
Serum ALP (U/L)	84.77 ± 11.97	117.38 ± 13.73	27.62 ± 5.78	<0.001*

Table 6: Relationship of serum liver enzyme levels with CKD patients with or without hemodialysis (N=90).

Liver enzymes level		Group A (n=45)		Group B (n=45)		P-value*
		n	%	n	%	
ALT	↑↑	0	0	0	0	<0.001*
	↔	45	100	45	100	
AST	↑↑	0	0	0	0	
	↔	45	100	45	100	
ALP	↑↑	8	17.8	45	100	
	↔	37	82.2	0	0	

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Discussion

In this study, the mean age of the CKD patients without HD was 47.47±10.92 years and undergoing HD was 47.97±10.9 years. Majority were between 41-50 years in group-A CKD which is comparable to other studies [11,12]. In group-A patients, who had CKD but not undergoing HD (hemodialysis), the majority (35.6%) was found in 41-50 years group while in group-B, who had CKD with HD, majority (31.1%) was found in advanced age (51-60 years group). The difference was non-significant statistically. There was a significant difference (p value <0.001) in the mean ages of normal subjects which were significantly lower than both CKD with or without dialysis that is similar with a study in Iraq [10]. Among the study population male were more prevalent. There were 60% was male in group-A and 55.6% male in group-B. The finding of this study was supported by another study done by Bapat et al showed 66% males and 44% females among CKD patients [13]. The male predominance could be due to socio-economic and sociocultural factors. Etiological analysis in both group-A and group-B showed that, the majority causes of CKD was found respectively in two groups were glomerulonephritis (35.6% vs 44.4%), diabetes mellitus (31.1% vs 35.6%). A study done in Bangladesh found that GN was the dominant cause of CKD (67.2%), followed by diabetes (24%), HTN (4.8%), and others (4%) [12]. Similar findings were also found in India [14]. However, none of the above etiology was biopsy proven. Most of the patients in group-A had duration of disease of 1-3 years but in case of group-B it was 3-6years. Mean disease duration in group-A was (2.72±2.13 years) lower than group-B (4.66±3.00 years). There was significant difference (*p*-value <0.05). Haq et al. stated that, most of their CKD patients were newly diagnosed [12]. It means chance of dialysis increased with progression of CKD and duration of disease. In group-A, 22.22% cases were suffering from stage-3, 66.6% were from stage-4 and 11.1% was stage-5 CKD, while 100% in group-B belongs to stage-5 CKD group with significant difference (p<0.001). Allawi et al. in a cross-sectional study found that 100% hemodialysis patients were in stage-5 CKD which is like us [10]. Serum ALT:7-41 U/L, serum AST:12-38 U/L and serum ALP:33-96 U/L were considered normal. Our study found that mean serum ALT levels were 20.16±4.15 U/L in Group A, 17.49±5.04 U/L in Group B, and 33.42±4.57 U/L in Group C, showing significantly lower levels in CKD patients (with or without hemodialysis) compared to the healthy group. A significant difference was also observed between Group A and Group B. Similarly, mean serum AST levels were 22.35±2.96 U/L in Group A, 17.73±4.41 U/L in Group B, and 30.56±4.86 U/L in Group C, with significantly lower levels in CKD patients compared to the healthy group and a significant difference between Group A and Group B. This finding is consistent with study done by Ray et al. who found lower serum ALT and serum AST levels in CKD patients with or without HD as compared to healthy controls [7]. In 2015, Sette and Lopes observed that serum ALT and serum AST levels were low in CKD patients with or without ESRD [15]. This decreased was proportional to the progression of CKD, directly correlated with GFR and negatively correlated with serum creatinine levels [16]. This low level of these liver enzymes (AST, ALT) in CKD patients remains controversial. The possible mechanisms include low level of pyridoxine (B6) which is a coenzyme of aminotransferase, high level of uremic toxin, water retention and hemodilution in advanced CKD, presence of ultraviolet absorbing materials in the blood that could alter the transaminase detection [7,8]. Other possibilities include decrease synthesis and inhibition of release of AST and ALT from hepatocytes into the bloodstream or accelerated clearance from serum [6]. Advanced renal medications negatively impact vitamin B6 status, making deficiency common in hemodialysis patients. Erythropoietin increases B6 utilization for hemoglobin synthesis, while phosphate binders like sevelamer-HCL bind about 30% of B6 intake. With a low molecular weight (MW 245) compared to folate (MW 441) and B12 (MW 1355), B6 also has limited body stores lasting only 3–4 months [17]. Serum ALP level was significantly higher in group-A and group B as compared to group-C. There was also significant difference between group-A and group-B. In this study serum ALP level was 84.77±11.97 U/L in group-A, 117.38±13.73 U/L in group-B and 27.62±5.78 U/L in group-C. Kovesdy et al showed that serum ALP is an important parameter in the assessment, monitoring of liver function as well as diagnosis of type of jaundice in patients without CKD [9]. However, this diagnostic importance of ALP is masked in CKD patients. Because it is well recognized fact that, serum ALP level increase in CKD patients without liver disease due to high turnover bone disease [17,18]. In CKD patients, serum ALT, AST showed a positive correlation with eGFR while ALP showed a negative correlation with eGFR. This finding is consistent with study done by Sette and Lopes who found direct correlation between a reduction in eGFR and a decrease in aminotransferases [16]. It is well established that serum ALT and AST levels fall near the lower limit of normal reference values in CKD patients and the levels are lower in hemodialysis patients. Serum ALP is more in hemodialysis patients than CKD patients without hemodialysis. The degree of decrease in serum ALT, AST as well as increase of ALP is directly proportional to the severity of CKD [19].

Limitations of the Study

- Single centered study.
- Study was conducted in a tertiary care hospital, where most of the patients admitted with moderate to severe renal impairment, results may not reflect the original picture of the country.

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- Another limitation of this study is that it did not measure vitamin B6 (pyridoxine).

Conclusion

In this study, it is observed that serum ALT and AST levels were low and serum ALP was high in CKD patients with or without hemodialysis. So using the present reference ranges for these enzymes in CKD patients leading to misdiagnosis of hepatic diseases. Thus the study established the need for new separate reference ranges for these enzymes in CKD patients for diagnosis, treatment and monitoring of any liver disease.

Recommendations

- CKD patients should screen for hepatic enzymes (ALT, AST, and ALP).
- Further studies with larger sample size are recommended to establish new reference ranges for these hepatic enzymes in various stages of CKD.
- CKD patients who have hepatic enzyme elevation upper limit of the usual reference range, should be cautiously monitored.

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Conflict of interest

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