Original Article

A comparative study of serum aminotransferases in chronic kidney disease with and without end-stage renal disease: Need for new reference ranges

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Abstract

Background: Hepatic diseases are common among chronic kidney disease patients and liver function tests particularly serum liver enzymes play an important role in diagnosing and monitoring these patients. Serum aminotransferase levels commonly fall near the lower end of the range of the normal values in patients of chronic kidney disease (CKD). High-levels of serum alkaline phosphatase (ALP) can occur in these patients due to renal osteodystrophy. Thus, the recognition of liver damage in these patients is challenging. **Aim:** To compare the levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and ALP among three groups - CKD patients without end stage renal disease (ESRD), patients with ESRD and healthy controls. **Materials and Methods:** A retrospective, hospital-based study was carried out from 100 patients' records from each group and serum AST, ALT and ALP values were noted. **Results:** Our study showed that serum AST and ALT levels were significantly lower in CKD patients both without and with ESRD compared to controls. Further, these two enzyme levels were also significantly lower in CKD patients with ESRD compared to CKD patients without the condition. Serum ALP levels were significantly higher in patients with and without ESRD as compared to the controls. However, the values did not differ significantly between patients with and without ESRD. **Conclusion:** Levels of serum aminotransferases were low in CKD with and without ESRD and the levels become lower as the severity of CKD increases. Thus, the study established the need for separate reference ranges of serum aminotransferase in different stages of CKD.

Key words: Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, chronic kidney disease, end-stage renal disease, liver enzymes

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Introduction

Chronic kidney disease (CKD) consists of a wide spectrum of conditions associated with a progressive decline in kidney functions and abnormal glomerular filtration rate (GFR).[1] According to the recent guidelines of the National Kidney Foundation (Kidney Dialysis Outcomes Quality Initiatives), CKD is classified into 5 stages based on estimated GFR (eGFR).[2] Stage 1 refers to eGFR ≥ 90 mL/min/1.73 m2 along with demonstrable kidney damage such as persistent proteinuria, abnormal blood and urine chemistry etc. Next, stage 2, 3 and 4 corresponds to eGFR of 60–89 mL/min/1.73 m^2, 30–59 mL/min/1.73 m^2 and 15–29 mL/min/1.73 m^2 respectively.[2] The main aim of treatment in these 4 stages of CKD is to slow down the progression of CKD along with cardiovascular disease risk estimation and management of complications.[1] CKD stage 5 corresponds to eGFR of <15 mL/min/1.73 m^2 and is also known as end stage renal disease (ESRD). In this stage, due to the accumulation of electrolytes, toxins and fluids, death can occur unless treated by renal replacement therapy, either by dialysis or by renal transplantation.[1]

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In patients with CKD, the most common associated chronic liver diseases are hepatitis B and C.[3] In an Indian study with 134 patients on hemodialysis, 5.9% turned out to be hepatitis C virus (HCV) positive whereas 1.4% of the patients had hepatitis B virus (HBV) infection. A dual infection was seen in 3.7% of the patients.[4] Another study showed that the prevalence of HCV infection among dialysis patients ranged between 0.7% and 18.1% in different Asia-Pacific countries, whereas the prevalence of HBV infection ranged between 1.3% and 14.6%.[5] Added to these, is the burden of alcoholic liver diseases. Therefore, CKD patients often need to be regularly monitored with liver function tests particularly serum level of liver enzymes for their concomitant liver diseases.

Serum levels of enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) are commonly used to assess and monitor hepatic diseases. The reference values for these laboratory tests are as follows: Serum ALT: 7–41 U/L, serum AST: 12–38 U/L and serum ALP: 33–96 U/L.[6] It has been reported that the level of serum aminotransferases commonly fall near the lower end of the range of the normal values in patients of CKD.[7] Studies among hemodialysis patients also show a similar decrease in serum aminotransferases.[8] In studies among patients infected with HCV, it was shown that HCV infected patients who also have CKD and are undergoing hemodialysis have lower serum levels of ALT than those with normal renal function.[9,10] Thus, recognition of liver damage in CKD patients poses a challenge to laboratory medicine specialists and is hampered by the reduction in aminotransferases leading to underestimation of the disease load.[11] In this regard, it has been suggested that serum aminotransferase cut-off values should be modified for screening for viral hepatitis in patients undergoing peritoneal dialysis. Although the exact cause of low serum aminotransferase levels in CKD remains controversial, possible reasons include pyridoxine deficiency and/or the presence of an inhibitory substance in the uremic milieu.[12-14] A recent study also speculated that hemodilution could be involved in reducing serum ALT levels in CKD.[15]

On the other hand, plasma ALP levels can originate from liver, bone, intestine and placenta. In general, the isoenzymes from liver and bone contribute to the majority of the circulating enzyme levels. Therefore, in a patient of liver disease serum ALP level is an important marker for screening and monitoring. However, in a CKD patient, renal osteodystrophy could result in a significant increase in the bone isoenzyme of ALP contributing to high serum ALP level. In fact, higher ALP has been associated with increased mortality in predialysis CKD as well as patients on maintenance hemodialysis.[16]

Thus, the interpretation of serum aminotransferase levels in different stages of CKD patients with possible concomitant liver disease presents a diagnostic dilemma. Though some studies have recorded the serum liver enzyme levels in CKD patients with a background of hepatitis, studies on serum liver enzyme levels in different stages of CKD without hepatitis are few and far in between. The paucity of information in this particular clinical scenario, more so among the Asian population, underlines the importance of a controlled study. Thus, this study was carried out to study the serum levels of liver enzymes in an attempt to emphasize on the need for new reference ranges in CKD patients, particularly in ESRD patients. In this regard the study aimed to compare serum AST, ALT, and ALP levels among CKD patients without ESRD, CKD patients with ESRD and healthy controls in a South-Indian coastal population.

Materials and Methods

The study was a retrospective study carried out by analyzing patient records in the department of Biochemistry at a medical college in Southern India. The study was approved by the institutional research committee and ethics committee, which follow the guidelines set by the Helsinki declaration.

File numbers of CKD patients attending nephrology OPD were collected between April 1, 2013 and June 30, 2013. File numbers of patients attending the hospital for routine health check during the same period were also collected as healthy controls. The case files of the patients were retrieved from the records department of the hospital. Records of both CKD patients and control subjects with documented history of liver disease and drugs which affect liver enzymes were excluded from the study. The following data were collected from each of the files: Age, sex, serum urea, serum creatinine, serum ALT, serum AST, and serum ALP values. The serum parameters in all cases had been measured using automated routine chemistry analyser (Roche Cobas Integra 400 plus, Roche Diagnostics Limited, Switzerland) with commercial kits (Roche cobas c packs, Roche Diagnostics Limited, Switzerland) according to manufacturer's protocol. Values from the same machine were chosen to minimize inter-machine variation.

Estimated GFR was calculated in each case by the formula - Equation from the Modification of Diet in Renal Disease study: eGFR (mL/min/1.73 m2) =1.86× $(PCr)^{-1.154}$ × $(age)^{-0.203}$, multiplied by 0.742 for women and multiplied by 1.21 for African Americans.[17] Based on eGFR, all the collected CKD patient files were divided into two groups: Group A had eGFR >15 mL/min and were called CKD without ESRD and Group B had eGFR <15 mL/min and were called CKD with ESRD. Group C consisted of the control

Group (apparently healthy individuals) who had eGFR above 90 mL/min. Therefore, Group A patients included CKD patients belonging to stage1–4 and Group B had patients belonging to stage 5 of CKD according to National Kidney Foundation (Kidney Dialysis Outcomes Quality Initiatives) criteria. The major contrasting feature between these two groups was the treatment modality whereby Group B patients needed dialysis, but Group A patients did not.

Using this methodology, 171 patient files were allotted in Group A, 119 patient files were allotted in Group B and 205 patients were in Group C. The first 100 consecutive patient files according to their hospital number in each group were included in the study and statistical analysis.

Statistical study

The categorical data were analyzed using SPSS statistical software (v 16; IBM Corporation, Armonk, NY, USA). Mean and standard deviations of age, serum AST, ALT and ALP, were calculated in all the three groups. The means of the different parameters in three groups was compared by means of one-way analysis of variance. These comparisons were followed by *post-hoc* comparisons between groups by means of the Duncan's test and a $P < 0.05$ was considered statistically significant. The gender distribution was also compared among the three groups using Chi-square test.

Results

The demographic profiles of all the subjects under study are shown in Table 1. There was no statistically significant difference ($P > 0.05$) among the mean ages of the three groups. When the three groups were analyzed according to sex, no significant difference ($P > 0.05$) was observed between the percentages of females in the three groups.

The statistical analysis of serum AST, ALT and ALP levels among the three study groups is shown in Figure 1. AST levels were significantly lower in both Group A (18.48 ± 4.14) and Group B (10.08 ± 3.49) as compared to controls in Group C (30.5 ± 10.75), ($P < 0.001$). There was also a statistically significant lowering of serum AST levels in patients belonging Group B as compared to patients in Group A ($P < 0.001$). Similarly serum ALT levels [Figure 1] were also significantly lower in both Group A (16.82 ± 4.38) and Group B (8.3 ± 3.58) as compared to Group C (26.94 ± 13.07) ($P < 0.001$).

On the other hand serum ALP levels [Figure 1] were significantly higher in Group A (121.24 ± 59.77) ($P < 0.001$) and Group B (112.5 ± 77.98) ($P = 0.02$) as compared to Group C (72.72 ± 0.71). No statistically significant difference was observed between the ALP values of Groups A and B ($P = 1.00$).

Discussion

Chronic kidney disease patients are an important group of patients with chronic co-morbidities, who require regular laboratory investigations. Within this group, there are significant differences in the biochemical milieu of patients depending upon the different stages of CKD. Hepatic co-morbidities,

Table 1: Demographic characteristics of the three study Groups-A, B, C

Parameters	Group A CKD without ESRD	Group B CKD with ESRD	Group C Controls	*P*
n	100	100	100	
Age in years (mean±SD)	50.06±11.74	48.02±12.43	49.54±11.07	0.667*
Range in years	25-70	23-66	30-72	
Female (%)	44 (44)	42 (42)	36 (36)	0.698*

**P* value not statistically significant (*P*>0.05). SD: Standard deviation; CKD: Chronic kidney disease; ESRD: End stage renal disease

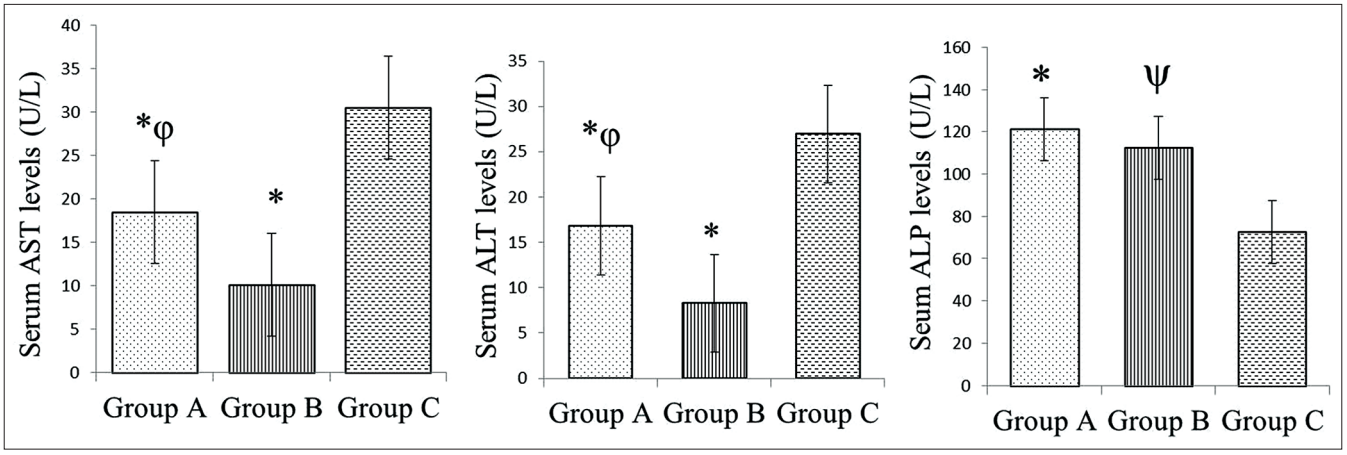

Figure 1: The values are expressed as the means ± standard deviation for the number of cases (*n*) in each group of subjects. Statistical comparisons were made by one way ANOVA followed by *post-hoc* analysis as described in the methods. *: $P < 0.001$ versus Group C (controls), φ: $P < 0.001$ versus Group B (chronic kidney disease [CKD] with end stage renal disease [ESRD]), ψ: $P = 0.02$, no statistically significant difference in alkaline phosphatase levels between Group A (CKD without ESRD) and Group B, $P = 1.00$

particularly hepatitis B and hepatitis C are frequent among patients with CKD.[3-5] In this scenario, liver function tests particularly serum liver enzymes play an important role in diagnosis and monitoring of liver damage in these patients. Therefore, we carried out the study, to know if there is any significant difference between serum AST, ALT, and ALP levels among three groups namely CKD patients without ESRD, CKD patients with ESRD and healthy controls, thereby emphasizing on the urgent need for new reference ranges of these enzymes in CKD patients.

Our study showed that serum AST and ALT levels were significantly lower in CKD patients without ESRD and CKD patients with ESRD compared to controls. Further, these two enzyme levels were also significantly lower in CKD patients with ESRD compared to CKD patients without ESRD. Several recent studies have also revealed that serum ALT levels are lower in patients with CKD compared with individuals with normal renal function.[8-10,18-20] Although fewer authors have discussed AST levels in patients with CKD, the results of those studies also showed a lower AST level in CKD patients compared to controls.[11,21] Further, a study done in Italy demonstrated lower AST and ALT levels among dialysis patients compared to predialysis patients with CKD in addition to the lower level of aminotransferases in CKD compared to healthy individuals.[7] Our results are broadly similar to the results of the above mentioned studies. However, only a few studies have analyzed both AST and ALT levels together. Among those studies, only the study from Italy to the best of our knowledge, has compared the enzyme levels between CKD patients with and without ESRD and healthy controls as we have done in our study.[7] Therefore, the present study is the first of its kind done in the Indian population and depicts a similar lowering of serum aminotransferases as the severity of the CKD increases. Further, our study is a rare study which has studied the serum aminotransferase levels in CKD patients without ESRD. In this scenario, setting up of new reference ranges for serum aminotransferases in CKD patients both with and without ESRD, assumes great significance to prevent missing out on diagnosing hepatic dysfunction in CKD.

The pathophysiological mechanism for this reduction in the serum aminotransferase levels in patients with CKD remains controversial. The possible mechanisms include reduction in pyridoxal-5-phosphate which is a coenzyme of aminotransferase, presence of ultraviolet absorbing materials and high levels of uremic toxins. Other possibilities include decreased synthesis and inhibition of release of AST and ALT from hepatocytes or accelerated clearance from serum.[7,12-14,22] One of the studies showed an increase in serum AST after hemodialysis probably due to the removal of an inhibitory substance during the dialysis.[12] This increase in serum AST may not be due to the removal of urea alone because the addition of urea to normal serum is not associated with decreased AST activity. In contrast, another study reported that the mean serum Vitamin B6 and pyridoxal phosphate levels in dialysis patients were not significantly reduced as compared to controls. So, the authors concluded that decreased serum AST and ALT levels in dialysis patients are not a result of Vitamin B6 deficiency.[21] A low serum aminotransferase level could also be due to water retention and hemodilution in patients of CKD.[18]

Serum ALP is an important parameter in the liver function test panel and aids in diagnosing the type of jaundice in patients without CKD. However, this diagnostic importance of ALP is masked in CKD patients, as it is a well-established fact that serum ALP level increases in patients with CKD.[16] In fact, in CKD patients without liver disease serum ALP can be elevated in high-turnover bone disease.[23-25] In addition, higher levels of serum ALP are associated with increased mortality in CKD patients.[16,26] In spite of this knowledge, we included the parameter in our study to reiterate the nonspecificity of serum ALP in CKD, further underlining the importance of correct interpretation of serum AST and ALT levels in CKD patients, more so in patients with CKD with ESRD. This in turn, reflects the urgent need for correct reference ranges for serum aminotransferases in CKD patients with and without ESRD. In our study, the serum ALP levels were significantly higher in CKD patients with and without ESRD as compared to the controls. However, the values did not differ significantly between CKD patients with and without ESRD. In most normal individuals, approximately 95% of the total ALP activity is derived from bone and liver sources in 1:1 ratio.[27] Polyacrylamide gel electrophoresis is the most reliable method of determination of the tissue origin of ALP. Bone derived ALP is heat-labile whereas liver-derived ALP is not. Therefore, exposure of the serum to elevated temperatures can determine the tissue source of elevated levels of ALP. Since neither polyacrylamide gel electrophoresis nor heat-testing of serum ALP are routinely done in a clinical laboratory setting, determination of the tissue source of high ALP in CKD patients with suspected hepatobiliary dysfunction is difficult.

This study was a retrospective analysis of patient files, performed in a hospital-based setting, a limiting factor for the generalization of the findings. Further, the causes of renal failure in the CKD patients were not analyzed which precludes any discussion on the relation between the mechanism of renal failure and the lowering of serum aminotransferases. Therefore, further studies are needed to explore the causal links between CKD severity and lowering of serum aminotransferases.

Conclusion

Thus, our study reinforces the fact that the serum aminotransferase levels tend to remain lower in CKD patients compared to the normal population, and the levels are further reduced in CKD patients with ESRD. As a result, a serum aminotransferase value falling within the current normal reference range does not rule out hepatobiliary pathology in CKD patients. Therefore, the diagnosis and monitoring of hepatitis and cirrhosis in different stages of CKD patients presents a significant challenge in laboratory medicine. Our study, though a retrospective study with a small sample size emphasizes the urgent need for large-scale, well-planned, controlled studies to determine a separate normal reference range of serum aminotransferases in different stages of CKD.

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