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A Study Of Serum Aminotransferase Levels In Subjects With Chronic Kidney Disease Attending A Tertiary Care Hospital In Perambalur.

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ABSTRACT

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.To estimate and compare the serum aminotransferase levels between subjects with CKD and apparently healthy controls. This prospective cross-sectional observational study was conducted for a duration of six months from January 2018 to June 2018 among subjects attending the out-patient department in Department of Nephrology, Dhanalakshmi Srinivasan Medical College Hospital located in Perambalur. The study involved two groups of subjects named Group A and B. Subjects in Group A were 30 patients with chronic Kidney Disease (CKD) but without end stage renal disease (ESRD) (eGFR >15 ml/min/ 1.73m^2) and Group B consisted of 30 apparently healthy subjects without any known renal disorders .All tests were performed using automated routine chemistry analyser with commercial kits (Roche, Germany) according to manufacturer's protocol. : In the current study, Group A subjects with CKD (stage 1 to 4) had a mean age (± S.D) of 49.4 (± 12.4) years in comparison to 48.2 (± 13.4) years in Group B subjects and this difference was not statistically significant (p = 0.723). There was no statistically significant difference between the two groups in terms of gender distribution. 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.

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

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem because of its high prevalence, morbidity and mortality. The prevalence of CKD ranges from <1% to 17% across varies parts of India. The etiology of CKD is complex, multifactorial and varies from between different regions of the country while the predominant etiological factor being hypertension and diabetes mellitus CKD is classified into 5 stages based on estimated Glomerular Filtration Rate (eGFR)[3]. Stage 1 represents eGFR ≥ 90 ml/min/1.73m^2 with signs of kidney damage while stage 2, 3 and 4 represent eGFR values between 60-89, 30 -59 and 15-29 ml/min/ 1.73m^2 [1]. In India, about 50% of the patients with advanced CKD report to the health facility for the first time only when the eGFR falls below 15 ml/min/ 1.73m^2 which is stage 5 also known as end stage renal disease (ESRD). The reasons for this worrisome fact being inaccessible and unaffordable renal replacement therapy in health facilities, absence of efficient screening programs besides insufficient awareness about the disease. In ESRD, accumulation of electrolytes, toxins and fluid retention occurs which necessitates renal replacement therapy in the form of dialysis or renal transplantation [5].The most common chronic liver disorder associated with CKD is hepatitis B and C infection A south-Indian study reported the prevalence of hepatitis C infection in 5.9% and hepatitis B infection in 1.4% besides dual infection in 3.7% of CKD patients on hemodialysis [2]. Added to these hepatitis infections is the ever-growing burden of alcoholic liver disease which was reported to be the commonest cause of cirrhosis responsible for 35% of cirrhosis . Due to these reasons, CKD patients frequently need screening with liver function tests for coexisting liver diseases [3]. The mainstay in the assessment of liver function is the estimation of serum aminotransferase levels such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT). They are the most frequently used and specific indicators of hepatocellular necrosis and the level of elevation of these enzymes above the reference range indicates the type and severity of liver damage. ALT is primarily localized to liver while AST is also present in many tissues like heart, kidney, brain and skeletal muscle [4]. The reference values for these laboratory tests are Serum ALT: 7–41 U/L, serum AST: 12–38 U/L and serum ALP: 33–96 U/L. Studies have reported that serum aminotransferase levels in CKD patients are usually lower than healthy subjects and frequently fall near the lower border of the normal reference range [11]. Many researchers have reported even lower levels of serum aminotransferases in CKD subjects on hemodialysis than CKD patients without renal replacement therapy and those with normal renal function [5]. The factors associated with lower levels of serum aminotransferase in CKD patients include hemodilution due to fluid retention, low levels of pyridoxine and high levels of homocysteine. In patients with hepatitis B or C infection, the cause for low transaminase levels are lower viremia after dialysis, high hepatocyte growth factor (HGF) and raised levels of serum alpha-interferon. In fact, some researchers have expressed that a new reference range should be used for these patients for early diagnosis of liver disease and to avoid underestimation of the problem [6]. Because of these reasons, diagnosis of liver damage in CKD subjects poses a challenge in terms of estimation of aminotransferase levels.With this background, this study was planned to analyse the levels of serum aminotransferases among subjects with CKD from a rural population attending a tertiary care hospital in comparison to healthy controls [7].

MATERIALS AND METHODS

This prospective cross-sectional observational study was conducted for a duration of six months from January 2018 to June 2018 among subjects attending the out-patient department in Department of Nephrology, Dhanalakshmi Srinivasan Medical College Hospital located in Perambalur. The protocol of the study was approved by the Institutional Ethical committee of Dhanalakshmi Srinivasan Medical College Hospital. The study involved two groups of subjects named Group A and B. Subjects in Group A were 30 patients with chronic Kidney Disease (CKD) but without end stage renal disease (ESRD) (eGFR >15 ml/min/ 1.73m^2) and Group B consisted of 30 apparently healthy subjects without any known renal disorders selected with the following exclusion criteria: pregnancy, medications altering liver enzymes, previous documented liver disorders, history of alcoholism, recent surgery, severely ill patients. Estimated GFR was calculated using Modification of Diet in Renal Disease (MDRD) formula: eGFR (mL/min/1.73 m2) $=1.86\times (S.Cr)^{-1.154}\times (age)^{-0.203}$ x 0.742 (if women) x 1.21 (if black) [15]. Informed written consent was taken from all the subjects after explaining the purpose of the study. Data regarding age, sex, urea, creatinine, serum AST and ALT levels were collected from each subject. About 5 ml of fasting venous samples were collected from each subject for biochemical analysis. Sample Collection was carried out under aseptic precaution; Plasma was separated from the whole blood cells after centrifugation. All the biochemical tests were done in the laboratory under Department of Biochemistry, Dhanalakshmi Srinivasan Medical College Hospital. All tests were performed using automated routine chemistry analyser with commercial kits

(Roche, Germany) according to manufacturer's protocol.All the data were firstly entered to Microsoft Excel 2010 and then the spreadsheets were used for statistical analysis in the SPSS version 16.0. Continuous variables were tested for normal distribution initially and independent samples 't' test was used for comparison of continuous variables between two groups. For all statistical analysis, a p value of <0.05 was used to reject the null hypothesis.

RESULTS

In the current study, Group A subjects with CKD (stage 1 to 4) had a mean age (± S.D) of 49.4 (± 12.4) years in comparison to 48.2 (± 13.4) years in Group B subjects and this difference was not statistically significant (p = 0.723). As shown in Table 1, there was no statistically significant difference between the two groups in terms of gender distribution. The comparison of urea and creatinine and eGFR levels are provided in Table 2. The comparison of serum aminotransferase levels between the 2 groups is depicted in Figure 1 and 2.

Table 1: Demographic data of the study subjects (n=60)

Variable	Group	N	Mean age in years	Std. Deviation	Student 't' test p value
Age	A	30	49.4	12.42	0.723
	B	30	48.2	13.42	
Variable	Group	N	Male	Female	Chi-square test p value
Gender	A	30	21	9	0.781
	B	30	20	10	

Table 2: Renal parameters of the study subjects (n=60)

Variable	Group	N	Mean (mg/dl)	Std. Deviation	Student 't' test p value
Urea	A	30	92.4	38.1	<0.001*
	B	30	28.2	5.4	
Creatinine	A	30	4.82	10.12	0.034*
	B	30	0.812	0.142	

Table 3: Comparison of serum transaminase levels of the study subjects (n=60)

Variable	Group	N	Mean (mg/dl)	Std. Deviation	Student 't' test p value
AST (IU/L)	A	30	21.8	8.75	0.011*
	B	30	28.2	10.09	
ALT (IU/L)	A	30	17.7	6.7	<0.001*
	B	30	30.4	11.02	

DISCUSSION

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). 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 (eGFRStage 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 ^{2} respectively. Aminotransferases [9]. Since, the 1970s, studies have shown that AST and ALT serum levels were decreased in CKD patients undergoing HD. It was hypothesized that this reduction could be caused by factors such as the withdrawal of aminotransferases during the HD session; the high lactate serum levels, which, during biochemical dosages, would rapidly consume Nicotinamide Adenine Dinucleotide Phosphate (NADPH) and result in low levels of aminotransferases; the presence of uremic factors that would inhibit the activity of these enzymes; and, finally, the deficiency of pyridoxine, a cofactor for the synthesis of the aminotransferases. 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 [10]. 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. Studies among hemodialysis patients also show a similar decrease in serum aminotransferases [11]. 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[12] 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. 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 [7, 15]. 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 [11,14]. 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. The results of our study showed that the serum levels of AST and ALT (transaminases) were significantly low in CKD patients without ESRD as well as in ESRD patients as compared to controls; even though the mean values of transaminases in CKD without ESRD and ESRD groups were within the reference range only [15]. There was a marked difference in these levels between CKD without ESRD and CKD with ESRD though not statistically significant. Serum ALP, GGT, amylase and lipase levels were significantly increased in CKD without ESRD and in CKD with ESRD patients as compared to controls. ALP, amylase, and lipase were raised in ESRD as compared to CKD with no ESRD. There was a strong negative correlation between estimated GFR and the serum ALP levels and pancreatic enzymes (amylase and lipase) in all CKD patients taken together as well as in both subgroups (CKD without ESRD and with ESRD). Reduction in transaminase levels in CKD patients with and without ESRD was also observed in few studies 13-16 which are in support of our study results. Studies among hemodialysis patients also show a similar decrease in serum aminotransferases level [12]. 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. Hence using the present reference ranges for serum aminotransferases in CKD patients both with and without ESRD, might result in missing a diagnosis of hepatic dysfunction in CKD. The use of standard reference values for aminotransferases to help detect liver disease is, therefore, less useful in patients undergoing chronic dialysis therapy [5,12,15].

CONCULSION

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.

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