Evaluation and Comparison of Hepatic Enzymes in Different CKD Categories

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ABSTRACT

Background: Chronic Kidney Disease is a global public health issue, with increasing incidence. It consists wide spectrum of renal conditions that lead to progressive decline in renal function and abnormal GFR. Liver disorders are common among chronic kidney diseases. LFT's particularly play a vital role in the diagnosis and monitoring CKD patients. Currently, eGFR considered being the most valuable parameter for diagnosing CKD. But it has some limitations, it is not done routinely in apparently healthy people, secondly, GFR has different normal values for different ethnic groups so the formulae for calculating eGFR being used in west might not be applicable in eastern population and vice versa. **Objectives:** This study was carried out to compare hepatic enzymes of patients with different stages of chronic kidney disease. **Materials and methods:** A total of 257 persons were recruited. Cases were divided into two subgroups based on the glomerular filtration rate (GFR). Subgroup 1: 85 Cases had GFR <15, subgroup 2: 99 cases with GFR > 15 and Subgroup 3: 73 normal healthy controls. The hepato-renal profile was done for all cases and controls.

Results: Hepatic transferases in the patients undergoing dialysis fell into the normal range. But the same enzymes showed a marked elevation in the patients with chronic kidney disease having non-invasive treatment. Alkaline phosphatase showed mark elevation for both groups A and B as compared to normal controls.

Keywords: Chronic kidney disease, liver function, hepatic enzymes, glomerular filtration rate, end stage renal disease.

INTRODUCTION

Chronic kidney disease is defined as kidney damage for ≥ 3 months (measured in terms of structural or functional damage), presented with or without a change in glomerular filtration rate. These derangements can be assessed by identifying the biochemical markers of kidney damage i.e. urea and creatinine[(1)]. Chronic kidney disease is gradually becoming a global threat. According to the Global burden of disease study, in 1990 CKD was ranked 27th in the list of major killers, but its rank drastically gained momentum and rose to 18th in 2010 [(2)].

In Kingdom of Saudi Arabia, the dynamics of chronic kidney disease are also changing very rapidly. Mortality due to CKD is 17.8 per 100,000 populations [(3)]. Different studies were conducted in the Kingdom to establish a prevalence of chronic kidney disease. The efforts were also made to categorize chronic kidney disease in different stages according to glomerular filtration rates using different formulas of eGFR including Cockcroft-Gault equations, MDRD-3(Modification of Diet in Renal Disease MDRD3 formula), and the CKD-EPI. The results showed a prevalence of chronic kidney disease which was 5.7 %, irrespective of the stage of kidney disease, there is no significant difference of the prevalence of chronic kidney disease among different population distributed on the basis of different socio-economic, educational and behavioral patterns[(4)].

The outcome in the patients with chronic kidney disease is also not very promising. A major portion of the population suffering from chronic kidney disease develops end stage renal failure, insulin resistance, hypercholesterolemia, uremia and encephalopathy[(5)]. The number of diseases affected disability days is also increased. On the other hand, the mortality rate due to multisystem organ failure (hepatic failure, stroke etc.) is also greatly increased[(6)].

Hepatic transferases and phosphatases are the markers of hepato-cellular inflammation and damage to the hepatocytes. The enzymes or biomarkers follow a definite pattern of wax and wane in different diseases. In the patients with chronic kidney disease, different studies showed the tranferases and phosphatses with a specific pattern. They fall on the lower limit of the normal range as compared to the normal population[(7)]. The fall of this transferase is irrespective of the stage of kidney disease, dialysis or extent of hepatic or kidney

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damage. So these same patterns present the challenge to the clinician that hampers the assessment of disease load. It is also reported that the patients who are on hemo-dialysis for end stage renal disease, suffer from hepatitis C virus at any time in due course of the disease. This also encumbers the assessment of treatment modalities for this viral infection due to a specific pattern of hepatic enzymes[8].

Alkaline phosphate is the second most important hepatic enzyme, mainly originated from liver, bone and placenta. But major prevalence is excreted from the liver. Previous studies showed that in the patients with chronic kidney disease phosphatase tends to appear on the upper side of the normal range. The rise in ALP levels in chronic kidney disease could be due to impaired degradation and function of parathyroid hormone and vitamin D which leads to osteo-dystrophy and thus a higher amount of phosphatase is liberated into the serum[9].

MATERIALS AND METHODS

This retrospective comparative study was conducted in the Nephrology department of King Saud University Hospital from 2015 to 2016.

The study participants were included on the following basis.

Inclusion criteria:

For cases:

Patients with chronic kidney diseases
Adult and geriatric population (age more than 18)
Saudi national

For controls

- Healthy subjects
- Adult and geriatric population (age more than 18)
- Saudi national

Exclusion criteria

- For cases and controls:
- Age <18
- Those with positive serological markers for HBV, HCV, HIV or a chronic liver disease
- Suffering from any infectious disease.
- Pregnant or postpartum women.
- Non-Saudi population

The data was collected for 184 patients after ensuring complete anonymity by using hospital management information system (HMIS). These patients were further divided into two sub groups on the basis of estimated glomerular filtration rate eGFR. The first group comprised of a total of 85 individuals having a GFR less than 15, the second sub-group comprised of 99 individuals having a GFR more than 15. The third group comprised of 73 healthy age matched individuals having a GFR more than 90.

The blood samples were taken from the controls after describing the entire procedure and purpose of the study and by following good aseptic measures and phlebotomy practice. Written consent was also taken from the controls. A total of 5 ml of blood was taken from each control using a Becton Dikinson (b-d) syringe in a yellow top gel tube. After formation of a clot, the sample was centrifuged at 6000 rpm for 4 minutes and serum was obtained for liver function tests and renal function tests.

Advia 1800™ based on photometery was used for the normal chemistry analysis. Urea and creatinine were done in renal function tests and Alanine amino tranferase (ALT), Aspartate amino transferase (AST) and Alkaline phosphatase were carried out in liver function tests.

The eGFR was calculated by using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. The single equation for CKD-EPI is as:

$$\mathbf{GFR = 141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018\ [if\ female] * 1.159\ [if\ black]}$$

Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. Online resource calculator was used for the calculation of CKD-EPI equation[10].

The study was done according to the ethical board of Imam Muhammad Ibn Saud Islamic university.

Statistical analysis was performed using SPSS 23. Mean and SD was calculated for numerical values while frequencies for qualitative were variables. For comparison of LFT's and RFT's in group's t-Test, and p-value was applied

RESULTS

Among 257 candidates which were selected for this study, 124 were males and 133 were female (Fig-1). These selectees were further divided into three further subgroups based on their estimated glomerular filtration rate.

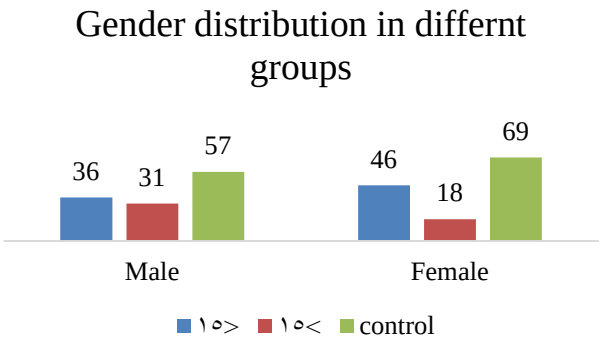

Fig. 1: Gender distribution in the included subgroups

In group A (Patients having GFR less than 15) alanine amino tranferase showed a mean of 27.91 with a standard deviation of 30.14, in group B (Patients having GFR more than 15) the mean with standard deviation was 93.12±288.62, as compared to the mean in controls which was 23.64±10.93. Aspartate amino transferase also showed the similar pattern of leaps and bound like ALT in three groups. The mean with standard deviation of AST in group A was 25.25±23.77, and in group B the mean was 438.66±1819.20 as compared to the controls which were 20.48±6.12. (Table 1)

The mean of alkaline phosphatase in group A was 159.98±129.91 and in group B it was 231.45±296.97. In controls the mean of ALP was 77.60±24.04. (Table 1)

Table 1: Hepatic enzymes in different groups

	ALT			AST		
	<15	>15	Control	<15	>15	control
Mean	27.917	93.120	23.645	25.254	438.662	20.481
Std. Deviation	30.141	288.622	10.935	23.770	1819.203	6.122
	ALP			eGFR		
	<15	>15	<15	>15	<15	>15
Mean	159.981	231.457	159.981	231.457	159.981	231.457
Std. Deviation	129.919	296.970	129.919	296.970	129.919	296.970

Table 2: Correlation of eGFR with hepatic enzymes

Correlations of eGFR						
	Age	ALT	AST	ALP	Creatinine	BUN
<15	.132	.120	.106	-.013	-0.807	-0.255
>15	-.209	.244	.217	.184	-0.84	-0.465
Controls	-0.599	-.163	-.167	.075	-0.451	-0.286

Renal functions and hepatic enzymes of patients falling in the group A showed a positive correlation with eGFR except for alkaline phosphatase. Urea, creatinine, ALT, AST, ALP of the patients belonging to group B showed a positive correlation with eGFR as compared to the controls which showed a negative correlation with hepatic enzymes (except ALP), urea and creatinine.

Table 3: Significance of means between different groups

Significance of means between different groups			
	between Cases (<15&>15)	<15 & controls	>15 & controls
ALT	.002	<0.001	<0.001
AST	.0003	<0.001	<0.001
ALP	.0013	<0.001	<0.001
Creatinine	<0.001	<0.001	<0.001
BUN	.029	<0.001	<0.001

Students-T test was applied to compare the significance of means between different groups. All the parameters were found to have a significant association with eGFR (cut off the value of significance p=0.05).

DISCUSSION

Defining the chronic kidney disease in terms of stages is a tiresome task. The controversy stands that the classification must predict the outcome of the disease. So after the implementation of KDOQI, the classification was done on the basis of estimated GFR and albuminurea [(11)]. The criteria for establishing this classification is important because a huge bulk of patients suffer from co-morbidities like metabolic bone diseases and end stage renal failure. The measurement of hepatic enzymes can also help the clinician in determining the prognosis of this disease

Hepatic enzymes showed a specific pattern at different stages of chronic kidney disease. These may also be used as an indicator of the progress of chronic kidney disease. Our study showed that in group A the aminotransferases were at the lower side of the normal range. This is due to the fact that ALT and AST washed out due to the hemo-dialysis as compared to the group B (patients on the conventional treatment of CKD) which showed a value of ALT and AST that is almost double the normal range or group C (normal controls) which showed the normal value of transferases. Here we found our study is in a complete harmony to the previous studies[(12)]. There are a few authors who also suggested that the values of transfereases depend on the method of dialysis. But our data was in consistency with Hung et al who found out that the method of dialysis has no effect in determining the quantity of transferases in serum[(13)].

On the other hand, alkaline phosphatase showed a definite but a slight variation in the three groups. It was also washed out by dialysis. The mean of group A in our study was a little lower than group B. This is due to the fact that alkaline phosphatase has multiple sources in the body. Bones are one of them and at the end stage renal disease which require dialysis; derangements of calcium and phosphate occurred. These derangements are due to impaired metabolism and reactionary deficiency of parathyroid hormone which in turn leads to an increase mobilization of calcium from the bone into the serum. This metabolic bone disease leads to a continuous higher amount of alkaline phosphate despite the fact that the patient is on dialysis[(14)].

Ray *et al.* also suggested alanine amino transferase and aspartate amino trasnferase at the lower normal limit as compared to the control population, and alkaline phospatase on an upper limit in target group as compared to control population[(8)]. Hence we find our study in a complete concordance with the previous studies.

CONCLUSION

Our study concluded two major patterns of hepatic enzymes. The first pattern was transferases which were much lower in patients on dialysis and controls, as compared to the patients falling in the group not having hemodialysis. Alkaline phosphatase in both studied groups was normal but it was much higher than the controls.

RECOMMENDATIONS

This study should be conducted on a larger scale to determine the reference values of hepatic enzymes in different stages of chronic kidney disease. These reference values should also be extracted and classified on the basis of age and gender.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

Confidentiality and patient privacy:

1. Patient information would not be disclosed under any circumstances.
2. Data entered would be by code numbers, not by patient MR number or the patient's name.
3. Data wouldnot be given to anyone outside the research team.

All the data in the computer would be password protected.

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