

Correlation between Liver Enzymes and Chronic Kidney Disease Iraqi Patients With or Without Hemodialysis

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Abstract: In CKD patients liver enzymes to be in the lower levels of normal reference range value, while ALP is high due to renal osteodystrophy. As a result the diagnosis and follow up of liver disease in these patients are dilemma and challenging.

Aims: The need for new reference ranges of liver enzymes in chronic kidney disease patients for accurate diagnosis and assessment of any liver disease and its progression.

Settings and Design: A cross sectional study, which was conducted from January 2014 to January 2015.

Methods and Material: Fifty patients in each group were enrolled in the current study according to inclusion criteria and each one was sent for: serum aminotransferases, total serum bilirubin, serum albumin, PT & INR, renal function test and serum electrolyte, virology screen, CBC and abdominal ultrasound.

Statistical analysis used: One way ANOVA was used to analyze the statistical significance of the 3 groups. All analyzed were performed using SPSS version 22 software package.

Results: The chronic kidney disease patients had lower serum aminotransferases when compared to normal population; and AST level was lower in hemodialysis patients only, while ALT levels were not significantly differed with both groups.

Conclusions: A normal level of serum aminotransferases in chronic kidney disease patient does not exclude liver disease in those patients. We need new normal reference ranges of liver enzymes in chronic kidney disease patients for accurate diagnosis, assessment, monitoring, treatment, and follow up of any liver disease.

Keywords: Chronic kidney disease, Hemodialysis, Liver enzymes.

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I. Introduction

The most common chronic liver diseases among CKD patients are hepatitis B and C. [1]The prevalence of hepatitis C virus infection is significantly higher in hemodialysis patients than general population[2], which associated with increased mortality rate mostly due to hepatocellular carcinoma & cirrhosis[3, 4].

Dialysis modality has been identified as a major risk factor of infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), with significantly higher rates of seroconversion observed in hemodialysis compared with peritoneal dialysis [5-9].

Many studies showing significant variability in HBV and HCV prevalence has been reported across South America, North America, Europe and Asia [5, 8, 10-13] and even across dialysis units within the same country [8, 11, 12].

In one Iraqi study the prevalence rate of hepatitis B virus infection in HD patients was 9.75% [14]; while another study showed that the prevalence rate of hepatitis C virus infection among Iraqi patients was 40.3% [15].

Some studies show the prevalence rates of hepatitis C virus infection are 5.5% for dialysis patients in Brazil, 14.4% in US, and 68% for those in Saudi Arabia[12, 16, 17]. In European countries the prevalence rates of hepatitis C virus infection among hemodialysis patients vary markedly : 3.4% in Netherlands, 15% in Hungary, 3% in UK, 16% in Italy, and 44% in Poland[18, 19]. In Middle East, the prevalence rates: 34.6% in Jordan, 49% in Syria, and 55.7% in Saudi Arabia[20-22].

The prevalence of hepatitis C infection among dialysis patients ranged between 0.7% and 18.8% in different Asia-Pacific countries, whereas the prevalence of hepatitis B infection ranged between 1.3% and 14.6%[23].

In another study, hepatitis C virus was positive about 5.9% whereas hepatitis B was positive about 1.4%. A dual infection was seen in 3.7% of patients [24].

Furthermore, the possible link between non alcoholic fatty liver (NAFLD) and CKD has also attracted research interest and recent data suggest an association between these two conditions. These findings have fuelled concerns that NAFLD may be a new and added risk factor of the development and progression of CKD. NAFLD and CKD share some important cardiometabolic risk factors and possible common pathophysiological mechanisms, and both are linked to an increased risk of incident CVD events [25-28].

Some studies have shown that patients with chronic kidney disease (CKD) without renal replacement therapy may have lower serum levels of liver enzymes than those with normal renal function; and those with hemodialysis may have lower serum levels of liver enzymes than CKD patients without renal replacement therapy and those with normal renal function[29-31].

Another study shows that the frequency of raised serum alanine aminotransferase (ALT) concentrations in patients who are infected with the hepatitis C virus (HCV) and have chronic renal failure (CRF) that requires hemodialysis (HD) therapy has been reported to be between 4 and 67% [32-34]. On the other hand, between 54 and 75% of patients with HCV antibodies (anti-HCV) without CRF have increased ALT levels.[35] On the basis of these considerations, the ALT levels are assumed to be poor predictors of hepatocellular damage in the chronic HD population.[32,33]

II. Subjects and Methods

The current study are a cross sectional study, which was conducted from January 2014 to January 2015, that include the comparison of serum aminotransferases between three groups of patients: patients who were attending hemodialysis unit in Baghdad teaching hospital, chronic kidney disease patients not on hemodialysis who were admitted to the medical ward in Baghdad teaching hospital, and normal (healthy) population.

The patients and normal individuals were selected according to the following exclusions criteria:

Age <20 and > 70 years ,BMI >25, Acute kidney injury, Chronic kidney disease <1 year, Hemodialysis < 1 year if on dialysis, History of chronic liver disease, Patients who consumed > 40 gm/day in male and > 20 gm/day in female of alcohol. Patients who receive drugs which affect liver enzymes. Pregnant and post partum women, Patients with ALT and AST values greater than 2 times the upper limits of normal, Abnormal prothrombin time & INR, Patients with features of liver disease especially fatty liver on abdominal ultrasounds, Hepatitis B or C positive patients, The study was approved by Research Ethics Committee at Baghdad teaching hospital, all patients and normal individuals included signed an informed consent form after receiving information about the study. After that the following data were collected:

Age, Sex, BMI, Alcohol history, Smoking history Past medical history, Drug history.

Blood samples were collected and sent to central laboratory at Baghdad teaching hospital for the following parameters: Blood urea, Serum creatinine, Serum electrolytes, Serum ALT and Serum AST, Total serum bilirubin, Total serum protein and serum albumin, Prothrombin time and INR, Complete blood count, Hepatitis screen (HBs Ag, HCV AB), Urinalysis and Abdominal ultrasound.

The serum parameters of biochemistry in all patients had been measured using automated chemistry analyzer (SIEMENS/Dimension RXL – MAX 224512 – AX) according to manufacture protocol. Complete blood count was measured using (CELL-DYN/Ruby). Hepatitis screen was determined by ELISA (BioTek).

The normal reference range of ALT & AST was (0.5-40) in the central laboratory at Baghdad teaching hospital

Estimated GFR was calculated in each case according to the following equations:

- Modification of Diet in Renal Disease (MDRD) equation: $eGFR [ml/min/1.73m^2] = 186 \times (SCr)^{-1.154} \times (\text{age})^{-0.203} \times 1.21[\text{if black}] \times 0.742[\text{if female}]$
- Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: $eGFR = 141 \times \min(PCr/k, 1) \times \max(PCr/k, 1)^{-1.209} \times 0.993 \text{Age} \times 1.018 [\text{if female}] \times 1.159 [\text{if black}]$.

Based on the eGFR and if patient was on hemodialysis or not, the patients were divided into three groups: group A who were on hemodialysis whatever their eGFR; group B who had eGFR < 90 ml/min/1.73 m² (from stage 2 to stage 5) and not on hemodialysis; group C considered the normal population group (apparently healthy individuals) who had eGFR > 90 ml/min/1.73 m².

For hemodialysis patients they were on regular schedule 3 sessions per week, with Na 140, K 2 and HCO₃ 35, and membrane type was polysulfone low flux.

We compared the result of investigations (ALT and AST) for a 50 patients in each group and correlate the findings other parameters, and the effect of hemodialysis on liver enzymes.

Statistical analysis:

Continuous data were tested for Anderson darling test for normality and were found to follow normal distribution, also no significant outliers were found, and so mean and standard deviation were chosen to represent our data.

One way ANOVA was used to analyze the statistical significance of the 3 groups, and then post hoc (Tukey’s test) were used to analyze within group differences.

Discrete variables were described using numbers and percentages, and chi square analyses used for analyzing the defenses in distribution among groups.

All analyzed were performed using SPSS version 22 software package, 0.05 were chosen as level of significance (p value).

III. Results

Table 1 shows a description of demographic profile of the study. 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, while the gender distribution there was no statistically significant difference (p value >0.05) among all groups. There was no significant difference in the body mass index among all groups, and it was less than 25 for all groups as shown in table 1.

Table 1: demographic data of the study

Age	No	Mean	SD	Range		P values
Dialysis	50	50.6400	11.39237	24.00	69.00	<0.001 ^a
CKD	50	53.7000	12.26119	21.00	70.00	
Normal	50	41.6800	9.29437	25.00	60.00	
BMI	No	Mean	SD	Range		P values
Dialysis		21.2400	1.58514	18.00	24.00	0.923
CKD		21.2000	1.69031	18.00	24.00	
Normal		21.3300	1.70117	18.50	24.00	
Gender	Female		Male		P values	
Dialysis	No	21	29		0.602 ^b	
	%	42.0%	58.0%			
CKD	No	26	24			
	%	52.0%	48.0%			
Normal	No	24	26			
	%	48.0%	52.0%			
^a One way ANOVA, post hoc Tukey tests (p value: dialysis vs. CKD = 0.253, dialysis vs. normal <0.001, CKD vs. normal <0.001)						
^b chi square						

These were significant differences in both smoking and alcohol use as shown in table 2; normal subject have 24% of them with active smoking and none with ex smoking, while CKD patient had 10% smoker and 22% as ex smokers, and dialysis patients had 6% of them as smoker and 30% of them as ex smokers as shown in table 2. 18% of dialysis patients were ex alcoholic, 8% of CKD and none of normal subjects as shown in table 2.

Table 2: smoking and alcoholic history in the study

Variables			Dialysis	CKD	Normal	P values		
Smoker	Not smoker	No	32	34	38	<0.001		
		%	64.0%	68.0%	76.0%			
	Active smoker	No	3	5	12			
		%	6.0%	10.0%	24.0%			
	Ex Smoker	No	15	11	0			
		%	30.0%	22.0%	0.0%			
Alcoholic	Not alcoholic	No	41	46	50	0.006		
		%	82.0%	92.0%	100.0%			
	Ex alcoholic	No	9	4	0			
		%	18.0%	8.0%	0.0%			
	Chi square analysis							

Dialysis patients show significantly elevated levels of both urea and creatinine compared to CKD and normal subjects, as shown in table 3. Dialysis patients show significantly lower GFR (for both EPI and MDRD) when compared to CKD patients, as shown in table 3.

Table 3: mean of urea, creatinine, GFR for each group

Variables		Mean	SD	P values (2 tailed)
Urea	Dialysis	175.9800	41.84982	<0.001 ^a
	CKD	106.5800	47.20303	
	Normal	27.3200	6.92655	
Creatinine	Dialysis	9.3820	3.23865	<0.001 ^b
	CKD	5.1080	14.74467	
	Normal	0.8052	0.13414	
GFR _{MDRD}	Dialysis	6.2600	2.78612	<0.001 ^c
	CKD	28.1100	14.16247	
GFR _{EPI}	Dialysis	5.9000	2.44841	<0.001 ^c
	CKD	27.7080	14.75514	

^A: one way ANOVA was performed and post hoc Tukey test were used (dialysis vs. normal, CKD vs. normal, and dialysis vs. CKD all p value<0.001)
^B: Kruskal Wallis test used, (Mann Whitney test between all 2 pairs and all p value <0.001)
^C: independent t test used
SD: standard deviation, CKD: chronic kidney disease

Total calcium significantly was more elevated to normal subjects compared to both dialysis and CKD, while PO₄ was significantly more elevated to dialysis patients than the other groups. As shown in table 4. Potassium was significantly more elevated to dialysis patients than the other groups, while sodium was significantly more elevated to normal subjects compared to both dialysis and CKD. As shown in table 4. The CKD stage was stage 5 for all patients in group A, while in group B 6% was stage 2, 44% stage 3, 34% stage 4 and 16% stage 5 as shown in table 5.

Table 4: mean and SD of Ca, PO₄, K, and Na for all subject in the study

Variables		Mean	SD	P values (2 tailed)
Total calcium	Dialysis	8.5400	0.91451	<0.001
	CKD	8.6600	0.97478	
	Normal	9.1520	0.41366	
PO ₄	Dialysis	7.2600	1.56570	<0.001
	CKD	4.7960	1.15634	
	Normal	4.0200	0.33987	
K	Dialysis	5.5500	0.76191	<0.001
	CKD	4.9780	0.72542	
	Normal	4.1460	0.37808	
Na	Dialysis	140.8000	4.74234	0.011
	CKD	138.6600	4.84288	
	Normal	141.1800	3.67390	

One way ANOVA test were preformed

Table 5: CKD stage for patients

Stage	Dialysis	CKD	P values	
2	No	0	<0.001	
	%	0.0%		6.0%
3	No	0		44.0%
	%	0.0%		
4	No	0		34.0%
	%	0.0%		
5	No	50		16.0%
	%	100.0%		

Chi square analysis

The statistical analysis of serum liver enzymes and liver function test for all three groups are shown in table 6.

Table 6: mean value of variables divided according to groups (normal subjects, CKD with or without dialysis subjects)

	Variables	Mean	SD	P values
TSB	Dialysis	0.7000	0.19588	0.006 ^A
	CKD	0.5900	0.26592	
	Normal	0.5574	0.21643	
ALT	Dialysis	16.7800	7.54963	<0.001 ^B
	CKD	16.6788	6.41162	
	Normal	33.5250	15.11720	
AST	Dialysis	17.4800	5.08796	<0.001 ^C
	CKD	23	6.899	
	Normal	30.3025	12.90043	
TSP	Dialysis	7.3360	0.51220	0.158
	CKD	7.2140	0.67280	
	Normal	7.4280	0.45716	
Albumin	Dialysis	3.7280	0.46557	<0.001 ^D
	CKD	3.4120	0.54084	
	Normal	4.0680	0.39042	
PT	Dialysis	12.4600	0.73429	0.858
	CKD	12.4000	0.69985	
	Normal	12.4800	0.81416	
INR	Dialysis	0.9440	0.07602	0.322
	CKD	0.9220	0.15022	
	Normal	1.1700	1.56482	

One way ANOVA used
^A Post hoc TSB p value: dialysis vs. CKD = 0.045, dialysis vs. normal = 0.006, CKD vs. normal = 0.755
^B Post hoc TSB p value: dialysis vs. CKD = 0.999, dialysis vs. normal <0.001, CKD vs. normal <0.001
^C Post hoc TSB p value: dialysis vs. CKD <0.001, dialysis vs. normal <0.001, CKD vs. normal = 0.007
^D Post hoc TSB p value: dialysis vs. CKD = 0.003, dialysis vs. normal = 0.001, CKD vs. normal <0.001

ALT level was significantly lower in both group A (hemodialysis) (16.78 ± 7.54) and group B (CKD) (16.67 ± 6.41) as compared to group C (normal population) (33.52 ± 15.11), (p value < 0.001); but there was no significant difference between group A and B. AST level was also significantly lower in both group A (17.48 ± 5.08) and group B (23 ± 6.89) as compared to group C (30.30 ± 12.90), (p value < 0.001); also there was a significant lower level of serum AST in group A when compared to group B. TSP, PT, and INR: there was no significant differences between all groups. TSB: despite that dialysis patients had significantly more elevated TSB compared to normal subjects and CKD groups, however; mean value of TSB was below 1 (ULN). Albumin was significantly more elevated in group C when compared to the other groups (A & B).

	DM		Not DM	
	No	%	No	%
CKD	31	62	19	38
Dialysis	23	46	27	54

Table 7 shows the descriptive data onto diabetes mellitus in dialysis and CKD patients, which show 62 % of CKD & 46% of dialysis patients were diabetic.

	DM	No DM	P value
ALT	16.35 ± 9.55	17.15 ± 9.64	0.771
AST	17.91 ± 4.79	17.11 ± 5.39	0.584

T test used
P value significant if <0.05

	OR	95%CI	P value
ALT	0.991	0.934 – 1.052	0.766
AST	1.032	0.932 – 1.154	0.576

Binary logistic regression

There was no significant difference in ALT and AST between DM and non DM patient was found in both dialysis and CKD patients (see table 8 & 9), also no relationship found between liver enzymes and DM in dialysis patients and CKD patients (see table 10 & 11).

Table 10: Mean value of ALT and AST for CKD patients

	DM	No DM	P value
ALT	15.79 ± 7.37	18.11 ± 7.45	0.287
AST	31.96 ± 10.11	34.39 ± 9.53	0.404
T test			

Table 11: relationship between liver enzymes and DM in CKD patients

	OR	95%CI	P value
ALT	0.958	0.885 – 1.037	0.289
AST	0.975	0.92 – 1.034	0.398
Binary logistic regression			

IV. Discussion

Among patients with chronic kidney disease, there is a significant number of patients had chronic co-morbidities, either that coexisting or develop later in the course of the disease. So those patients require regular laboratory investigation to exclude these diseases.

One of the important co-morbidities is hepatic disease, particularly hepatitis B and C which is frequent in patients with chronic kidney disease [1], also non alcoholic fatty liver disease is important as both diseases share same risk factors. [25-28]

For that, liver enzymes and other liver functions test to play an important role in the diagnosis and monitoring of liver damage in these patients.

Therefore we carried out the current study to assess liver enzymes AST and ALT among 3 groups: end stage renal disease patients on hemodialysis, chronic kidney disease patients not on hemodialysis, and healthy control, and to see if there are any differences in liver enzymes between these 3 groups.

So as a result, we need new reference ranges from liver enzymes for accurate diagnosis and assessment of the progression of liver disease in chronic kidney disease patients.

During our survey on Iraqi data onto Scientific Council of Internal Medicine in the Iraqi Board for Medical Specialization concerning this subject we did not come across any similar data, so the current study is the first study in regarding this subject in Iraqi population.

The current study showed that chronic kidney disease patients with or without renal replacement therapy had lower serum aminotransferases when compared to normal population; and AST level was lower in hemodialysis patients (17.48 ± 5.08) than chronic kidney disease patients not on hemodialysis (23 ± 6.89); while ALT levels were not significantly differed from both groups, (16.78 ± 7.54) in hemodialysis patients and (16.67 ± 6.41) in chronic kidney disease patients not on hemodialysis.

Several studies previously and recently discuss the relationship between liver enzymes and chronic kidney disease. In 2015 Ray et al. found that AST was (10.08 ± 3.49) in hemodialysis patients and (18.48 ± 4.14) in CKD patients; ALT was (8.3 ± 3.58) in hemodialysis patients and (18.82 ± 4.38) in CKD patients; so he concludes that the level of serum aminotransferase was low in chronic kidney disease with and without end stage renal disease and the levels become lower as the severity of CKD increase.[31]

In 2015 Sette et al. concludes that aspartate aminotransferase and alanine aminotransferase serum levels of patients with predialysis chronic kidney disease decreased in proportion to the progression of the disease; they were negatively correlated with creatinine levels and directly correlated with glomerular filtration rate.[36]

In 2014 Brazilian study shows the serum aminotransferase levels were lower in the patients with chronic kidney disease on hemodialysis (with or without viral hepatitis) than in the patients with normal renal function; this reduction has a multifactorial origin [37].

In 2012 Liberato et al. conclude that the aminotransferase levels in the patients that were undergoing peritoneal dialysis were slightly higher compared with the samples collected before the hemodialysis session, whereas the aminotransferase levels were slightly lower compared with the samples collected after the session. The hematocrits and the aminotransferase and gamma-glutamyltransferase levels of the samples collected after the hemodialysis session were significantly higher than the samples collected before the session. Taken together, the present data suggest that hemodilution could alter the serum levels of liver enzymes [29].

At 2004 Gouvei et al. suggest that ULN of ALT could be reduced for 60% from conventional limit, when we are evaluating patients with chronic renal failure of hemodialysis[38]. At 2001 Fabrizi et al. conclude that decrease serum aminotransferase activity in patients with chronic renal failure: impacts on the detection of viral hepatitis. [39]

At 1995 Yasuda et al. conclude that Serum AST and ALT levels in patients undergoing dialysis are very low, and the upper normal limits of AST and ALT levels in patients undergoing dialysis should be reduced considerably, and these levels should be interpreted with caution in the diagnosis of liver disease [40]. At 1972 Wolf et al. support low AST activity in serum of patients undergoing chronic hemodialysis [41].

It was hypothesized that this reduction in aminotransferase could be caused by factors as:

1. Low level of serum pyridoxine (B6), Ono et al. support this hypothesis,[96]but Jung et al. and Gressner et al. found no effect of B6 level on aminotransferase.[42, 30]
2. Hemodilution . Yasuda et al., Liberato et al., Sombolos et al., and Lopes et al. [40, 29, 43]
3. High homocysteine level supported by Huang et al. [44]
4. Uremic toxin, or UV-absorbing components in the blood that could alter the transaminase detection[8, 45].
5. Intermittent increases in the serum ALT concentration [39].

V. Conclusion

A normal level of serum aminotransferases in chronic kidney disease patient does not exclude liver disease in those patients. We need new normal reference ranges of liver enzymes in chronic kidney disease patients for accurate diagnosis, assessment, monitoring, treatment, and follow up of any liver disease

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