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ORIGINAL ARTICLE

Relationship Between Liver Function Tests & Cardiovascular Risk Factors in Stage 3-5 Pre-Dialysis Chronic Kidney Disease

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ABSTRACT

Objectives: The main objective of this study was to evaluate the relation between liver function tests and biochemical cardiovascular risk factors in chronic kidney disease patients.

Methodology: this study was conducted in Khyber Teaching Hospital Peshawar, from Ist May 2022 till 31st Oct, 2022. 250 patients in total were included in this study. All the people included in this study were chronic kidney disease patients at pre dialysis stage 3 to 5. Data collected included demographic information, liver function tests and biochemical cardiovascular risk factors. CKD-EPI equation was used to calculate glomerular filtration rate.

Results: This study resulted in ALT being negatively correlated with C reactive protein and intact level of parathyroid hormone and positively correlated with glomerular filtration rate, triglyceride, calcifediol and albumin. Gamma-glutamyl transferase was negatively correlated with HDL cholesterol and positively correlated with glomerular filtration rate, triglycerides and C reactive protein. AST was negatively correlated with C reactive protein and intact level of parathyroid hormone and positively correlated with glomerular filtration rate, HDL cholesterol, albumin and calcifediol. In diabetic patients AST and ALT were positively correlated with glomerular filtration rate, additionally AST was also positively correlated with HDL cholesterol but negatively with intact parathyroid hormone. Gamma-glutamyl transferase had no correlation. In total population of the study and in diabetic group correlation analysis was run between glomerular filtration rate and biochemical cardiovascular risk factors, it resulted in GFR being negatively correlated with albuminuria, C reactive protein and intact parathyroid hormone and positively correlated with triglyceride, calcifediol and albumin. A partial correlation analysis, controlled for GFR, was also run between cardiovascular risk factors and LFTs. It resulted in no correlation between both.

Practical implication: this study could be useful when planning the treatment of CKD patients with cardiovascular risk factors. Also in predicting the risk of cardiovascular disease in CKD patients based on the LFTs. It could also help initiate further reseach on related topics like the role of LFTs in predicting cardiovascular disease in CKD patients.

Conclusion: this study concluded that relation between liver function tests and biochemical cardiovascular risk factors in chronic kidney disease patients could be the function of compromised glomerular filtration rate.

Keywords: cardiovascular risk factors, chronic kidney disease, aspartate transaminase, gamma-glutamyl transferase, alanine transaminase

INTRODUCTION

Renal function subtly and progressively decreases in patients with chronic kidney disease (CKD). Kidneys filter waste and toxic products out of the blood, they also regulate and maintain salt, water and mineral levels in our body. Along with that kidneys maintain blood pressure and acid base level of the body. At the same time, endocrinal function of kidneys is also important that includes the production of calcitriol, renin and erythropoietin among others. Having CKD means decrease in all these function of the body that eventually increases the risk of other morbidities and mortality. Hence, these patients are at increased risk of co-morbidities and mortality, especially the cardiovascular disease [1]. At stage 3 to 5 of the chronic kidney disease, the risk and occurrence of cardiovascular disease increases rapidly. At stage 3 of CKD, the occurrence of cardiovascular disease increase by almost 45 % and at stage 5 by 345 %. It is believed that uremia leads to cardiovascular related mortality in CKD patients, even though the core mechanism is not known [3]. Cardiovascular diseases have been a predicted consequence of CKD by many biomarkers associated with uremia. Nevertheless, this mode of diagnosis has limited use in CKD patients [2, 3].

In CKD, the kidneys loses their functioning units called nephrons, henceforth the decrease in kidney function. It is an irreversible loss of kidney function. This leads to waste products and toxins buildup in the body. At the late stage of this disease, glomerular filtration rate and urine output decreases resulting in uremia. Uremia is a toxic state. CKD can be caused due to diabetes, hypertension, acute kidney disease and other kidney diseases.

Liver function tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum albumin and prothrombin time. These factors have appeared as a marker of cardiovascular disease in the recent decade, not only in different researches but also in the patients of coronary artery disease. This finding is independent of any metabolic disease or non-alcoholic steatohepatitis (NASH). Hence, LFTs are associated with the risk of cardiovascular disease. This association is further related to many conditions such as atherosclerosis due GGT, pro-inflammatory actions of cytokines, imbalance between free radicals and antioxidants, calcifications in the blood vessels, compromised hemostasis and endothelial dysfunction [3, 4, 5].

Cardiovascular diseases could present with abnormal LFTs because CVD could cause liver dysfunction. Increased pressure of vena cava causes liver congestion that in turn causes elevated level of liver enzymes, direct bilirubin and indirect bilirubin. In case of cardiac anomaly and reduced cardiac output perfusion of liver tissue decreases, this could lead to necrosis of hepatic cells and marked raise in the level of aminotransferases in the serum. In acute heart failure patients, hypotension leads to acute cardiogenic hepatic injury, also known as shock liver. [7]

It is suggested that LFTS are independent marker of cardiovascular disease and mortality but this association is not thoroughly researched in chronic kidney disease patients. So, in this study the relation between liver function tests and cardiovascular risk factors in chronic kidney disease patients at stage 3 to 5 was evaluated.

METHOD

This study was conducted in Khyber Teaching Hospital Peshawar , from Ist May 2022 till 31st Oct, 2022.. 250 patients in total were included in this study. All the people included in this study were chronic kidney disease patients at stage 3 to 5, not undergoing dialysis. It was a retrospective study.

Exclusion criteria of this study was patients of hepatitis B and C diagnosed with HBsAg, anti-HBc IgM, anti-HBc IgG, anti-HBs, HCV RNA, nonalcoholic steatohepatitis patients, liver cirrhosis patients, autoimmune hepatitis patients, chronic liver disease patients, patients with present malignancy, patients with history of malignancy, autoimmune disease patients and patients of chronic kidney disease caused by dysfunction of the kidney post transplantation. Medical history, radiological and biochemical findings were used to diagnose liver diseases. Biopsy was not performed in any of the patient for diagnosis.

Liver function test of the participants included AST, GGT and ALT levels. Biochemical inflammatory mediators and cardiovascular risk factors were documented. All of the collected data was entered into a database for analysis. CKD-EPI equation was used to calculate glomerular filtration rate.

Patients of the chronic kidney disease were staged as: stage 3 patients had eGFR of 45- 59 ml/min, stage 4 patients had eGFR of 15- 29 ml/min and stage 5 patients had eGFR less than 15 ml/min.

KS test was used to determine variable distribution. Incessant variables with normal distribution of the data were marked as standard deviation. Variables with imbalanced distribution were marked as medians. Percentage and number were used to describe qualitative variable. As some variables were not equally distributed, so to determine the relationship between different variables Spearman's rank correlation coefficient was used. A partial correlation analysis with controlled GFR, was also run between variables. It was done so to remove the effect of GFR on the variables. Two-tailed P value of less than 0.05 was considered significant. SPSS was used to statically analyze all of the collected data.

RESULTS AND DISCUSSION:

In this study, we included a total of 250 patients. Clinical characteristics of all the patients are shown in Table 1. 75 patients had diabetes mellitus and 190 patients had hypertension.

Table 1: Clinical characteristics

Characteristic	Patient population
Age	70 ± 15 years
Male	45 %
Female	55 %
BMI	27.1 ± 2 kg/m^2
Diabetes mellitus	30 %
Hypertension	76 %

Stages of chronic kidney disease in the patient population is shown in Table 2. 170 patients were of stage 3 CKD, 55 of stage 4 and 25 of stage 5.

Table 2: Stages of CKD in patient population

Stage of CKD	Patient population (%)
Stage 3	68 %
Stage 4	22 %
Stage 5	10 %

Table 3 shows biochemical characteristic of the patients. This table shows reduced levels of ALT, AST, GTT, ALP, GFR and calcifediol; increased level of creatinine, uric acid, triglycerides, LDL-Cholesterol, iPTH and albuminuria . CRP, HDL-C, leucocyte and albumin had normal value.

To evaluate the relationship between liver function tests and biochemical cardiovascular risk factors correlation analysis was run. This resulted in ALT being negatively correlated with C reactive protein and normal value of parathyroid hormone and positively correlated with glomerular filtration rate, triglyceride, calcifediol and albumin. Gamma-glutamyl transferase was negatively correlated with HDL cholesterol and positively correlated with glomerular filtration rate, triglycerides and C reactive protein. AST was negatively correlated with C reactive protein and normal value of parathyroid hormone and positively correlated with glomerular filtration rate, HDL cholesterol, albumin and calcifediol.

Table 3: Biochemical characteristic

Biochemical characteristic	Patient population (%)
Hemoglobin	13 ± 1.5 g/dl
Leucocyte count	8.0 ± 2 per microliter
Creatinine	1.65 (1.32-2.35) mg/dl
eGFR	35 (22- 45) ml/min
ALT	13 (10- 22) U/l
AST	16 (13- 25) U/l
ALP	93 (72- 115) U/l
GGT	25 (18 – 35) U/l
iPTH	98 (60- 199) ng/l
Phosphorous	4 ± 0.5 mg/dl
Calcium	8.9 ± 0.4 mg/dl
Ca/P	33 (29- 38) mg/dl^2
Calcifediol	13.5 (8.5- 22.9) ng/ml
Albumin	4.2 ± 0.5 g/dl
Albuminuria	270 (37- 1200) mg/day
Ferritin	50 (25- 80) ng/ml
Uric acid	7.5 ± 1.9 mg/dl
HDL-Cholesterol	45 (32- 57) mg/dl
LDL-Cholesterol	136 (105- 170) mg/dl
Triglycerides	152 (104- 220) mg/dl
Total cholesterol	200 (165- 237) mg/dl
C- reactive protein	4 (2- 11) mg/dl

The same analysis was performed on the diabetic patients, n= 75. In diabetic patients AST and ALT were positively correlated with glomerular filtration rate, additionally AST was also positively correlated with HDL cholesterol but negatively with intact parathyroid hormone. Gamma-glutamyl transferase had no correlation. Spearman's rank correlation analysis between ALT and biochemical cardiovascular disease risk factors in total study population and in the diabetic group is shown in table 4.

Table 4: Spearman's rank correlation analysis between ALT and biochemical cardiovascular disease risk factors in total study population and in the diabetic group

Parameters	ALT			
	Overall population (n= 250)		Diabetic population (n= 75)	
	r_s	P	r_s	P
BMI	0.050	0.560	-0.015	0.923
GFR	0.300	<0.001	0.356	0.004
C-reactive protein	-0.234	0.005	-0.258	-0.148
Creatinine	−0.138	0.009	−0.158	0.133
Albumin	0.234	0.003	0.154	0.165
Albuminuria	-0.065	0.583	0.089	0.735
HDL-Cholesterol	-0.073	0.725	-0.064	0.725
LDL-Cholesterol	0.037	0.492	-0.037	0.482
Triglycerides	0.145	0.009	0.072	0.736
Total cholesterol	0.064	0.479	-0.185	0.395
iPTH	-0.294	<0.001	-0.186	0.408
Uric acid	-0.040	0.472	0.067	0.836
Ca/P	-0.028	0.528	-0.193	0.374
Calcifediol	0.183	0.012	0.028	0.836

Spearman's rank correlation analysis between AST and biochemical cardiovascular disease risk factors in total study population and in the diabetic group is shown in table 5.

Spearman's rank correlation analysis between GTT and biochemical cardiovascular disease risk factors in total study population and in the diabetic group is shown in table 6.

Table 5: Spearman's rank correlation analysis between AST and biochemical cardiovascular disease risk factors in total study population and in the diabetic group

Parameters	AST			
	Overall population (n= 250)		Diabetic population (n= 75)	
	r_s	P	r_s	P
BMI	0.034	0.369	−0.059	0.849
GFR	0.345	<0.001	0.284	0.049
C-reactive protein	−0.133	0.049	−0.233	0.020
Creatinine	−0.248	<0.001	−0.175	0.193
Albumin	0.275	<0.001	0.175	0.195
Albuminuria	−0.136	0.097	−0.193	0.485
HDL-Cholesterol	0.295	0.001	0.385	0.006
LDL-Cholesterol	0.184	0.188	0.164	0.385
Triglycerides	0.009	0.974	−0.095	0.453
Total cholesterol	0.188	0.085	0.193	0.394
iPTH	−0.245	<0.001	−0.277	0.068
Uric acid	−0.035	0.635	0.093	0.823
Ca/P	−0.047	0.573	0.253	0.086
Calcifediol	0.238	<0.001	0.182	0.364

Table 6: Spearman's rank correlation analysis between GTT and biochemical cardiovascular disease risk factors in total study population and in the diabetic group

Parameters	GTT			
	Overall population (n= 250)		Diabetic population (n= 75)	
	r_s	P	r_s	P
BMI	−0.158	0.148	−0.136	0.327
GFR	0.135	0.039	0.136	0.249
C-reactive protein	0.284	0.004	0.173	0.294
Creatinine	-0.174	0.193	-0.076	0.502
Albumin	0.002	0.983	0.020	0.983
Albuminuria	0.085	0.639	0.946	0.129
HDL-Cholesterol	−0.238	0.004	−0.129	0.430
LDL-Cholesterol	−0.039	0.535	−0.049	0.972
Triglycerides	0.102	0.032	0.173	0.232
Total cholesterol	−0.138	0.136	0.092	0.764
iPTH	-0.183	0.046	-0.162	0.482
Uric acid	0.102	0.145	-0.029	0.726
Ca/P	0.028	0.839	−0.263	0.194
Calcifediol	0.030	0.882	−0.184	0.474

The results mentioned in Table 4, 5 and 6 shows that in overall population ALT, AST and GTT were all positively correlated with glomerular filtration rate. Cardiovascular disease risk factors which correlated with LFTs, were then analyzed to see GFRs effect on them. This correlation analysis resulted in GFR being negatively correlated with iPTH, C- reactive protein and albuminuria in both the overall population and the diabetic patients. The results also showed that the GFR was positively correlated with albumin, calcifediol and triglyceride in both the overall population and the diabetic patients. A partial correlation analysis, controlled for GFR, was also run between cardiovascular risk factors and LFTs. It eliminated the effect of GFR on both the variables. Its results showed no correlation between liver function tests and cardiovascular disease risk factors. In the same way, partial correlation analysis, controlled for GFR, diabetes and BMI, showed no correlation between liver function tests and cardiovascular disease risk factors. This is shown in Table 7.

Table 7: Partial correlation analysis between LFT and CRF, controlled for GFR, diabetes and BMI.

Parameters	AST		GGT		ALT	
	r_s	P	r_s	P	r_s	P
C- reactive protein	−0.045	0.964	0.093	0.573	0.178	0.182
Albumin	−0.023	0.927	0.037	0.429	−0.062	0.840
Calcifediol	0.036	0.394	0.127	0.036	−0.072	0.446
Triglycerides	−0.037	0.529	−0.183	0.027	0.138	0.128
HDL-C	0.036	0.848	0.058	0.337	−0.127	0.248
Albuminuria	−0.047	0.738	−0.029	0.447	0.020	0.738
iPTH	0.137	0.148	−0.020	0.747	0.028	0.630

In the previous studies, patients having dialysis for the long time were found to have transaminases level in the serum close to the normal ranges [8]. Transaminases levels were found to be reduced in pre-dialysis patients of chronic kidney disease, the level of AST was investigated [9]. The results of our study showed reduced levels of AST and ALT in stage 3-5 pre-dialysis chronic kidney disease patients.

In case of chronic kidney disease, uremic toxins increases in the blood. This causes decreased production of transaminases from the hepatocytes [8, 9]. GGT resulted in being independent foretelling indicator of cardiovascular disease. In addition to that, GGT also occurred as an independent and strong indicator for cardiovascular related mortality in patients undergoing dialysis [10]. On the other hand, only a few studies are found related to the association of GGT with the risk of cardiovascular disease in pre-dialysis chronic kidney disease patients. One of these study resulted in GGT being independently associated with mortality. Levels of GTT did not affect the value of GFR [11]. In another study, GGT level and GFR were inversely related [12]. On the other hand, in our study as the severity of chronic kidney disease increased, GGT levels decreased.

In our study, all the cardiovascular risk factors correlated with LFTs also showed correlation with glomerular filtration rate. This is an already know fact as most risk factors usually increase with renal insufficiency. This includes risk factors such as inflammation, endothelial disorders, malnutrition, calcifications of the vessels, vitamin D deficiency, oxidative stress and many more. Albuminuria is also associated with renal dysfunction [13]. We eliminated the effect of GFR in partial correlation analysis, this resulted in LFTs being no longer associated with cardiovascular risk factors. This indicates that LFTs may not directly affect the cardiovascular risk in CKD patients but this effect could be secondary to the effect of reduced glomerular filtration rate.

In the general population, non-alcoholic steatohepatitis, diabetes mellitus and BMI were associated with increased level of ALT, GGT and increased cardiovascular disease risk [14]. This relation could be associated with the results of our study. This study's CKD patients with NASH may have more increased liver enzyme levels than CKD patients without NASH, and this difference may have had an impact on our findings. As a result, patients with NASH were excluded in an effort to lessen this effect. Additionally, all correlation studies were carried out separately for our diabetic participants, and the outcomes were comparable to those shown across the board. Intriguingly, in the participants in our study, there was no correlation between BMI and liver enzymes. Despite the fact that this result seems unexpected, we think that this is the study's uniqueness. That instance, it has long been known that the risk factors for CVD, diabetes, NASH, and BMI are related in the general population. However, the renal function has a direct role in these correlations, but as kidney function gradually declines, the associations become less clear.

Although there were just a few patients included in the current study for analysis, the distribution of the patient population was typical for the various stages of CKD. Additionally, patients with stage 3-5 pre-dialysis CKD represent a relatively homogenous CKD population for potentially increased CVD risk factors. Because these patients typically had a significantly higher risk for CVD than patients with stage 1-2 CKD and patients on hemodialysis are affected by many other factors for CVD risk that arise from hemodialysis treatment itself. As a result, even though our results were based on a limited sample size of patients, they nonetheless offer important information that may be applied to the stage 3-5 population of people who are waiting to start dialysis for CKD. We require prospective investigations with bigger sample sizes to corroborate our findings because the retrospective cross-sectional design of our study did not allow us to investigate the relationship between CRFs, LFTs, and GFR over time.

CONCLUSION

This study concluded that relation between liver function tests and biochemical cardiovascular risk factors in chronic kidney disease patients could be the function of compromised glomerular filtration rate.

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