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RELATIONSHIP BETWEEN PARATHYROID HORMONE LEVEL AND HEPATIC STEATOSIS DEGREE BY FIBROSCAN AMONG PREVALENT HEMODIALYSIS PATIENTS

By
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Abstract

This study evaluated the hypothesis of a possible association between hyperparathyroidism and the presence of hepatic steatosis and fibrosis among prevalent hemodialysis (HD) patients and evaluated the possible risk factors of non-alcoholic fatty liver disease (NAFLD) among those patients. This is a case-control study that included HD patients divided into GI: (30) HD patients with NAFLD, GII: (25) HD patients without NAFLD as well as GIII: (30) healthy volunteers as a control. Viral hepatitis, Diabetes mellitus, recent hepatobiliary surgery, ascites, active infection, malignancy, alcohol, or drugs induce hepatic steatosis were excluded. Complete blood count, Iron profile, lipid profile, liver function tests, C- reactive protein (CRP) titer, intact parathyroid hormone (iPTH), and other routine chemistry tests were done. Transient elastography Fibroscan® to assess controlled attenuation parameter (CAP) to detect liver steatosis grades and liver stiffness measurement was done.

Results: Mean ±SD values of CAP of liver steatosis (263.7±52.7, 181.3±23, 210.8±33.7) (dB/m) in GI, GII & control group respectively (P <0.001). Post-Hoc analysis revealed a significant statistical difference between G I and II as regards ALT, AST, Bilirubin level and serum albumin, CRP titer, and lipid profile. In HD patients' studied groups, the CAP value of liver steatosis was significantly correlated to BMI, ALT, AST, Cholesterol, LDL, TG, & CRP Titer, but not correlated to PTH or other parameters. In GIII, there was a significant correlation between the measured CAP value of liver steatosis and BMI, iPTH, CRP titer, ALT, AST, cholesterol, LDL, and a negative correlation between HDL and CAP value. Liver stiffness/fibrosis was in 18 (60.0%), HD patients versus 8 (32%) patients in GII. Analysis showed a significant difference between GI & GII and between GI and GIII regarding the presence of liver fibrosis.

Keywords: Hyperparathyroidism, Hepatic steatosis, Hemodialysis, NAFLD

Introduction

Hepatic steatosis emerged as a growing public health concern worldwide, defined as fat accumulation (<5%) in liver cells without other liver diseases. The histologic spectrum of non-alcoholic fatty liver (NAFLD) ranges from simple liver cell steatosis to non-alcoholic steatohepatitis (NASH), liver fibrosis, & cirrhosis (Chalasani *et al,* 2012).

Liver steatosis is the hepatic manifestation of metabolic syndrome (MS) related to cardiovascular morbidity and mortality. NAFLD was associated with one or more features, such as insulin resistance, diabetes mellitus (DM), central obesity, dyslipidemia, and hypertension, known to cause MS (Dowman *et al,* 2011).

Chronic kidney disease (CKD) is a worldwide problem with a general prevalence of about 14%. CKD lies at the end of the spectrum of many diseases such as hypertension, diabetes, and obesity. It is an independent risk factor for cardiovascular disease (CVD), which results in increased morbidity and mortality rates, along with high economic costs to the healthcare system (Mikolasevic *et al,* 2014). NAFLD and CKD share many important cardio-metabolic risk factors (Bang *et al,* 2014). Studies reported a higher prevalence of CKD progression in patients with ultrasound (US)-defined NAFLD as compared to patients without liver steatosis

(Targher *et al,* 2014). Patients on hemodialysis who developed NAFLD had a faster progression of the atherosclerotic process and development of adverse CVD events as compared to those without NAFLD (Mikolasevic *et al,* 2014).

NAFLD frequencies ranged between 35%-85% among CKD patients related to obesity and DM as pathogenic factors. Patients with CKD & NAFLD met all diagnostic criteria of MS (Yoon *et al,* 2017). Egyptian hemodialysis patients showed 56.25% of non-obese, non-diabetic CKD patients with NAFLD late stages (Sherief *et al,* 2021).

Controlled attenuation parameter (CAP) as a quantitative parameter to evaluate different hepatic steatosis grades as measured by transient elastography (TE) (Fibroscan®) that simultaneously estimated liver fibrosis (Rhee *et al,* 2013), with good sensitivity & specificity (Shi *et al,* 2014).

Low levels of 25(OH) D and high levels of PTH were suggested as markers of metabolic syndrome and fatty liver. Severe vitamin D deficiency results in altered glucose metabolism, such as insulin resistance and glucose intolerance. NAFLD subjects have less serum 25 (OH) vitamin D levels compared to age-matched without NAFLD (Targher *et al,* 2007). Rhee *et al.* (2013) reported an association between serum 25 (OH) D. Ghoghaei and *et al.* (2015) reported that PTH but, not 25 (OH) D was significantly associated with nonalcoholic steatohepatitis in morbidly obese patients. A direct association of the PTH with metabolic syndrome was also observed in men (Lee *et al,* 2009). The biological mechanism by which 25 (OH) D and PTH influence metabolic syndrome was not reported. But, clinical and experimental studies showed that decreased vitamin D and increased PTH levels were associated with insulin resistance (Reis *et al,* 2007)

Hemodialysis (HD) patients are commonly affected by secondary hyperparathyroidism (SHPT), with 3 involved factors: hypocalcemia, hyperphosphatemia, and calcitriol deficiency. Parathyroid hormone (PTH) levels cause not only bone-associated diseases but, also a link between SHPT and systemic toxicity, with a major role in determining cardiovascular disease, including arterial calcification, endocrine disturbances, compromised immune system, neurobehavioral changes, and altered erythropoiesis (Cozzolino *et al,* 2008).

Secondary hyperparathyroidism is associated with insulin resistance and linked negatively to beta cell function, suggesting that uremic patients with elevated serum PTH were severely insulin resistant and hyperinsulinemic (Fadda *et al,* 1990). Insulin resistance is a key risk factor in NAFLD pathogenesis linked to development of oxidative stress and lipotoxicity (Park *et al,* 2004).

This study aimed to evaluate the hypothesis of a possible association between hyperparathyroidism and the presence of hepatic steatosis, and fibrosis by transient elastography among HD patients and possible risk factors of NAFLD among hemodialysis patients

Patients and Methods

This is a case-control study, was conducted at Ain Shames University Hospital over a year. Hemodialysis patients (55) were recruited from dialysis units and were divided into 2 groups: GI: 30 patients with NAFLD, GII: 25 patients without NAFLD, in addition to GIII: 30 healthy volunteers.

Adult patients, aged above 18 years, Clinically stable end-stage renal disease (ESRD) patients on regular hemodialysis>6 months, three times/week,4h duration for sessions with high flux dialyzer and bicarbonate dialysate, heparin was used as an anticoagulant. The majority of HD patients were on calcium and phosphate chelators and 1.25 (OH) cholecalciferol supplements.

Patients with hepatitis (HBV & HCV), diabetes mellitus (DM), hepatobiliary-surgery history, with BMI>30kg/m^2, drugs causing hepatic steatosis (corticosteroids, high dose estrogen, methotrexate or amiodarone within last 6 months), alcohol abuse, ascites, fever or active malignancy were excluded.

All subjects were subjected to full history and clinical examination including information on age, sex, BMI, time on HD treatment, ESRD etiology, vascular access, co-morbidities, and medications prescription.

Laboratory tests**:** CBC, iron profile (serum iron, ferritin, total iron binding capacity (TIBC), serum creatinine (Cr), calcium (Ca), phosphorus (PO_4), Intact parathyroid hormone (iPTH), ALP, γGGT, AST, ALT, albumin, total bilirubin lipid profile (total cholesterol, high-density lipoprotein cholesterol (HDL), Low-density Lipoprotein cholesterol (LDL), Triglycerides (TG), CRP titer, HBsAg, HCV Ab, Prothrombin time (PT), INR. Urea reduction ratio (URR), KT/V (K= dialyzer clearance, t: dialysis time (min.), V= distribution of urea volume (total body water) was measured as dialysis adequacy parameters in HD patients.

Transient elastography Fibroscan® to assess controlled attenuation parameter (CAP) liver steatosis degree as decibels per meter (dB/m) by Echosens FibroScan correlator; 502 F00471. Patients were measured using (71696) standard M+ probe and measurements of liver stiffness value expressed by kilo-pascals (kPa). Liver steatosis (S): Final CAP value ranged from 100 to 400 decibels/ meter/dB/m (Sasso *et al,* 2010). The liver stiffens measurement (LSM) to quantitate liver fibrosis, with the cut-off value was its stiffness (F) >7 kPa (Vergniol *et al,* 2008). LSV & CAP measurement failures were recorded when no value was obtained after at least 10 shots (valid shots= 0). The reliable LSV was defined by 3 criteria (Castéra *et al,* 2010): 1- Number of valid shots of at least 10, 2- Success rate (SR: ratio of valid shots to total shots) at least 60%, and 3- An IQR > 30% of median LSV (IQR/ M/ 30%).

Statistical analysis: Data were computerized and analyzed by IBM SPSS software package version 20.0 (Armonk, NY, IBM Corp). Qualitative data were described as numbers & percentages. The Chi-square test compared between two groups. Also, the Monte Carlo correction test was used when the expected cell counts were < 5. Continuous data were tested for normality by the Shapiro-Wilk test. Distributed data were expressed as a range (minimum & maximum), mean, standard deviation, and median Student t-test compared between groups for normally distributed quantitative variables, but ANOVA was used for comparing the four studied groups and followed by Post Hoc test (Tukey) for pairwise comparison. Mann Whitney test compared two groups for not normally distributed quantitative variables, but Kruskal Wallis test compared different groups without normally distributed quantitative variables and followed by the Post Hoc test (Dunn's for multiple comparisons test) for pairwise comparison. The significance was judged at the 5% level.

Ethical considerations: The research was carried out according to the ethical standards of the Declaration of Helsinki 1964 and approved by Ain-Shams University Hospital Research Committee (Number, 000017585), Approval number FMASU MD 178/2018. Written verbal informed consent was taken from all the participants.

Results

There were no significant differences in age or gender, but a significant difference as regard BMI & blood pressure (P<0.001). There were no significant differences between GI & GII HD patients as to renal failure cause or other demographic data or laboratory parameters or dialysis adequacy by URR & Kt/V. There were significant differences between groups with regard to BMI, serum Ca, phosphorus, ALP and GGT & CRP titer, PTH &U liver function tests, lipid profile, and prothrombin time (P<0.001). Post Hoc analysis revealed a significant statistical difference between GI & GII as regards ALT, AST, Bilirubin level, serum albumin, CRP titer, GGT, ALP, & lipid profile (P<0.5). There was a significant difference among groups as to iPTH level (P<001), without significant difference by post hoc analysis between GI & GII as to PTH levels (P>0.05).

CAP of liver steatosis were (263.7±52.7, 181.3±23, & 210.8±33.7dB/m) in GI, GII, & GIII respectively (P<0.001). M±SD of kpa (6.73±6.08, 6.39±5.65, & 4.57±0.75) in GI, GII, & GIII respectively, post hoc analysis showed a significant difference between GI & GII (P=0.04) or GI & GIII (p<0.001). There was a significant difference between GI and each of GII & GIII as to Kpa (P < 0.05). Liver stiffness/fibrosis was in 18 (60%), HD patients in GI versus 8 in GII (P<0.05). GI patients without alcoholic fatty liver were S1 steatosis degree; 4 patients had S3 steatosis degree and one patient with S2 degree. GIII showed a normal kidney without a history of illness, but 11 had liver steatosis S1, and 3 with NAFLD had grade F1. In HD group, CAP of liver steatosis significantly correlated to BMI ALT (r= 0.387, P=0.004), AST (r=0.365, P= 0.006), Cholesterol (r=0.785, P<0.001), LDL (r=-0.692, P<0.001), TG (r=0.668, P<0.001), CRP (r=-0.384, P=0.004), without correlation to PTH or other parameters (P>0.05). In GIII, there was a significant correlation between CAP value of liver steatosis & BMI, PTH, CRP, ALT, AST, cholesterol, & LDL and negateve one between HDL & CAP (P<0.05).

Parathyroid hormone correlated to urea post-dialysis (r= 0.278, P=0.040), but significantly correlated to the ALP (r=0.402, P=0.002) in HD patients GI &GII. PTH level in GIII significantly correlated to LDL (r=0.782, P<0.001). Higher KT/V significantly lower liver stiffness (r=-0.393, P=-0.032). The CRP, ALT, AST, cholesterol, TG, LDL, BMI, & CRP independently correlated to CAP of liver steatosis with cholesterol significant only. Significant positivity was between liver stiffness, and ALT, AST, & bilirubin, but negative correlation with serum albumin in HD patients with NAFLD.

Details were given in tables (1, 2, 3, 4, 5 & 6) and figures (1 & 2).

Table 1: Comparison between groups according to different parameters

Variations	GI (n = 30)	GII (n = 25)	GIII(n = 30)	significance	P
Age (years)	49.2 ± 10.9	46.3 ± 16.3	41.8 ± 13.6	H= 4.562	0.102
Median (Min. – Max.)	50 (25 – 75)	40 (22 – 78)	45.5 (22 – 67)		
Male	19 (63.3%)	14 (56.0%)	21 (70.0%)	χ^2= 1.154	0.561
Female	11 (36.7%)	11 (44.0%)	9 (30.0%)		
BMI (kg/m^2)	28.3 ± 0.93	27.5 ± 1.69	25.1 ± 1.85	F= 34.888*	<0.001*
Median (Min. – Max.)	28.5 (26- 29.5)	28 (21.5 – 29)	25.5 (21.2- 27.6)		
Sig. bet. Groups.	p_1=0.143,p_2<0.001*,p_3<0.001*				
Systolic blood pressure (mmHg)	131 ± 13.5	130.4 ± 14.6	115.5 ± 9.50	F= 14.229*	<0.001*
Median (Min. – Max.)	130 (110-150)	130 (110- 160)	115 (100-130)		
Sig. bet. Grps.	p_1=0.983,p_2<0.001*,p_3<0.001*				
Diastolic blood pressure (mmHg)	81.3 ± 9.37	81.2 ± 9.71	71.3 ± 7.54	F= 12.178*	<0.001*
Median (Min. – Max.)	80 (60- 100)	80 (70 – 100)	70 (60- 80)		
Sig. bet. Groups.	p_1=0.998,p_2<0.001*,p_3<0.001*				
Mean arterial blood pressure(MABP) (mmHg)	97.8 ± 10.4	97.14 ± 10.64	73.5 ± 8.42	F= 57.929*	<0.001*
Median (Min. – Max.)	96.6 (76.6- 116.6)	96 (83 -120)	75.5 (60- 85)		
Sig. bet. Groups.	p_1=0.967,p_2<0.001*,p_3<0.001*				
WBCS	7.30 ± 1.25	6.76 ± 1.41	6.73 ± 1.54	F= 1.537	0.221
Median (Min. – Max.)	7 (5.20 – 11.5)	7 (3.40 – 9)	7 (3.50 – 10)		
HB (g/dl)					
Mean ± SD.	10.3 ± 0.73	10.1 ± 0.93	13.7 ± 1.04	F= 141.075*	<0.001*
Median (Min. – Max.)	10.2 (8.80 – 12)	10.2 (8.50- 12)	13.9 (11.7 – 15)		
Sig. bet. Groups.	p_1=0.803,p_2<0.001*,p_3<0.001*				
PL	207.6 ± 46.3	209.6 ± 52.1	264.3 ± 66.2	F= 9.756*	<0.001*
Median (Min. – Max.)	202.5 (140 – 330)	192 (145- 340)	254 (169 – 380)		
Sig. bet. Groups.	p_1=0.991,p_2<0.001*,p_3<0.001*				
Cr	5.74 ± 1.41	5.49 ± 0.91	0.84 ± 0.11	H= 57.837*	<0.001*
Median (Min. – Max.)	5.30 (4.50- 12)	5.50 (3.80- 7.10)	0.85 (0.60- 1)		
Sig. bet. Groups.	p_1=0.771,p_2<0.001*,p_3<0.001*				

*Significant at p ≤ 0.05

Table 2: Comparison between groups according to different parameters

variations	GI (n = 30)	GII (n = 25)	GIII(n = 30)	significance	P
Ca (mg/dl)	8.37 ± 0.60	8.50 ± 0.87	8.86 ± 0.40	F=4.790*	0.011*
Sig. bet. Groups.	p_1=0.735,p_2=0.010*,p_3=0.094				
Phosphorus (mg/dl)	5.58 ± 0.76	5.16 ± 0.97	3.93 ± 0.53	F=37.679*	<0.001*
Sig. bet. Groups.	p_1=0.115,p_2<0.001*,p_3<0.001*				
Ca × po4 product	46.7 ± 6.98	43.6 ± 8.42	34.9 ± 5.22	F=23.439*	<0.001*
Sig. bet. Groups.	p_1=0.233,p_2<0.001*,p_3<0.001*				
PTH (pg/ml)	573.2 ± 242.9	489.6 ± 251.3	42.7 ± 21.6	H= 58.815*	<0.001*
Median (Min. -Max.)	535 (250 – 1200)	418 (150 – 1100)	33.5 (15 – 75)		
Sig. bet. Groups.	p_1=0.270,p_2<0.001*,p_3<0.001*				
CRP titer (mg/L)	21.63 ± 27.2	9.64 ± 7.47	5.40 ± 7.93	H= 18.903*	<0.001*
Median (Min. - Max.)	12 (2- 128)	6 (0 – 24)	0 (0- 24)		
Sig. bet. Groups.	p_1=0.050,p_2<0.001*,p_3=0.020*				
ALT (U/L)	48.6 ± 26.6	34 ± 23.9	28.5 ± 7.15	H= 14.924*	0.001*
Median (Min. – Max.)	45 (16- 120)	29 (12- 112)	27 (21- 42)		
Sig. bet. Groups.	p_1=0.003*,p_2<0.001*,p_3=0.638				
AST(U/L)	41.9 ± 22.9	28.3 ± 21.82	24 ± 7.09	H= 15.981*	<0.001*
Median (Min. – Max.)	34.5 (16- 95)	22 (12 – 110)	21 (17 – 37)		
Sig. bet. Groups.	p_1=0.001*,p_2<0.001*,p_3=0.998				
Bilirubin (mg/dl)	0.82 ± 0.26	0.84 ± 0.37	0.55 ± 0.22	H= 17.128*	<0.001*
Median (Min. – Max.)	0.90 (0.40 -1.50)	0.90 (0.30 – 2)	0.55 (0.30 – 0.90)		
Sig. bet. Groups.	p_1=0.959,p_2<0.001*,p_3=0.001*				
Serum albumin (g/dl)	3.47 ± 0.32	3.48 ± 0.47	4.35 ± 0.34	F=52.666*	<0.001*
Sig. bet. groups.	p_1=0.994,p_2<0.001*,p_3<0.001*				

*significant at $p \leq 0.05$

Table 3: Comparison between groups according to different parameters

variations	GI (n = 30)	GII (n = 25)	GIII(n = 30)	Significance	P
Cholesterol (mg/dl)	211.9 ± 27.6	180.4 ± 11.6	184.2 ± 29.6	F= 13.778*	<0.001*
Median (Min. – Max.)	210 (170- 260)	180 (160- 205)	171.5 (154- 238)		
Sig. bet. Groups.	p_1<0.001*,p_2<0.001*,p_3=0.839				
Triglycerides(mg /dl)	180.8 ± 30	150.7 ± 23	128.1 ± 27	F= 28.648*	<0.001*
Median (Min. – Max.)	180 (140- 248)	150 (105- 195)	125 (78- 172)		
Sig. bet. Groups.	p_1<0.001*,p_2<0.001*,p_3=0.008*				
LDL (mg/dl)	135.5 ± 26.9	103.7 ± 16.6	110.9 ± 30.5	F= 11.854*	<0.001*
Median (Min. – Max.)	140 (80- 175)	102 (80- 150)	99.5 (74- 167)		
Sig. bet. Groups.	p_1<0.001*,p_2=0.001*,p_3=0.561				
HDL (mg/dl)	53.1 ± 8.03	52.6 ± 6.06	48.9 ± 6.41	F= 3.186*	0.046*
Median (Min. – Max.)	52 (40- 66)	52 (40- 65)	50 (37- 58)		
Sig. bet. Groups.	p_1=0.967,p_2=0.048*,p_3=0.126				
INR	1.26 ± 0.15	1.21 ± 0.15	0.96 ± 0.09	F= 45.959*	<0.001*
Median (Min. – Max.)	1.25 (1.08- 1.80)	1.20 (1.0- 1.60)	1.0 (0.80- 1.10)		
Sig. bet. Groups.	p_1=0.391,p_2<0.001*,p_3<0.001*				
PT (seconds)	15.60 ± 1.63	15.1 ± 1.68	11.5 ± 0.96	F= 68.932*	<0.001*
Median (Min. – Max.)	15.5 (13- 22)	15 (13- 20)	11 (10- 13.5)		
Sig. bet. Groups.	p_1=0.384,p_2<0.001*,p_3<0.001*				
Alkaline phosphatase (IU/L)	419 ± 319.5	453.5 ± 431.2	66.2 ± 38.8	H=55.570*	<0.001*
Median (Min. – Max.)	304.5 (116- 1519)	276 (150- 1890)	56 (20- 140)		
Sig. bet. Groups.	p_1=0.990,p_2<0.001*,p_3<0.001*				
GGT (IU/l)	32.8 ± 22.78	28.1 ± 16.3	15 ± 7.72	H=20.793*	<0.001*
Median (Min. – Max.)	25 (9- 110)	25 (10 -75)	12 (6- 30)		
Sig. bet. Groups	p_1=0.741,p_2<0.001*,p_3<0.001*				

*Significant at $p \leq 0.05$

Table 4: Comparison between groups as to the degree of liver stiffness and liver steatosis parameters values

variations	GI (n = 30)	GII (n = 25)	GIII(n = 30)	Significance	P
Liver stiffness value (Kpa)	6.73 ± 6.08	6.39 ± 5.65	4.57 ± 0.75	H= 9.421*	0.009*
Median (Min. – Max.)	5.80 (3.70- 38.20)	4.70 (3.30- 31.60)	4.80 (3.30- 5.40)		
Sig. bet. Groups.	p_1=0.041*,p_2=0.003*,p_3=0.418				
Liver stiffness					
Absent	12 (40.0%)	17 (68.0%)	27 (90.0%)	χ^2= 16.754*	<0.001*
Present	18 (60.0%)	8 (32.0%)	3 (10.0%)		
Cap value steatosis (dB/M)					
Mean ± SD.	263.7 ± 52.7	181.3 ± 23	210.8 ± 33.7	F= 31.589*	<0.001*
Median (Min. – Max.)	240 (214- 398)	180 (121- 217)	210 (165- 271)		
Sig. bet. Groups	p_1<0.001*,p_2<0.001*,p_3=0.019*				

*Significant at $p \leq 0.05$

Table 5: Correlation between Cap value steatosis and parameters in groups

	Cap value steatosis (dB/M)			
	GI & GII		GIII	
	r	p	r	p
Age years	0.120	0.383	0.005	0.978
HD duration year	0.063	0.650	–	–
BMI (Kg/m2)	0.310	0.021*	0.407	0.026*
Systolic (BP (mmHg)	0.115	0.403	-0.023	0.905
MABP (mmHg)	0.152	0.268	-0.050	0.794
Diastolic BP (mmHg)	0.159	0.245	0.104	0.584
WBCS 10(9)/L	0.075	0.587	0.130	0.492
Hemoglobin (HB) (g/dl)	-0.054	0.696	-0.062	0.745
Platelets 10^9/L	-0.023	0.866	-0.287	0.124
Iron (ug/dl)	-0.021	0.879	–	–
Ferritin (ug/L)	0.079	0.565	–	–
TIBC	0.033	0.814	–	–
T sat	-0.094	0.493	–	–
Cr (mg /dl)	-0.145	0.290	0.197	0.297
Ca (mg/dl)	0.018	0.897	-0.362	0.051
Po4	0.212	0.121	0.228	0.225
Ca × po4 product	0.219	0.108	0.103	0.590
iPTH (pg/ml)	0.145	0.292	0.829	<0.001*
CRP titer (mg/L)	0.384	0.004*	0.459	0.011*
ALT(IU/L)	0.387	0.004*	0.516	0.003*
AST (IU/L)	0.365	0.006*	0.462	0.010*
Bilirubin (mg /dl)	0.063	0.650	-0.253	0.177
Serum Albumin(g/dl)	0.024	0.860	-0.264	0.159
Cholesterol (mg/dl)	0.785	<0.001*	0.521	0.003*
Triglycerides (mg/dl)	0.668	<0.001*	0.128	0.501
LDL (mg/dl)	0.692	<0.001*	0.584	0.001*
HDL (mg/dl)	0.024	0.860	-0.669	<0.001*
INR	0.181	0.186	0.276	0.140
PT (seconds)	0.182	0.182	0.002	0.993
Urea pre (mg/dl)	0.080	0.560	–	–
Urea post (mg/dl)	0.102	0.459	–	–
Ur reduction ratio	-0.022	0.873	–	–
KTV	0.247	0.070	–	–
Liver stiffness value Kpa	-0.066	0.634	-0.172	0.363
Alkaline phosphatase(IU/L)	-0.120	0.381	0.230	0.221
GGT(IU/L)	0.205	0.134	0.352	0.057

*Significant at $p \leq 0.05$

Table 6: Correlation between liver stiffness value (Kpa)and others in HD patients with NAFLD (G I).

Variations	Liver stiffness value (Kpa)	
	r_s	p
Age years	-0.154	0.418
HD duration year	-0.141	0.457
BMI	0.293	0.116
Systolic	0.223	0.235
MABP	0.225	0.232
Diastolic	0.156	0.409
WBCS	-0.186	0.326
HB	0.123	0.518
PL	-0.142	0.455
Iron	0.096	0.614
Ferritin	0.038	0.841
TIBC	0.049	0.799
T sat	0.028	0.884
Cr	0.097	0.609
Ca	-0.249	0.184
Po4	0.192	0.310
Ca × po4 product	0.063	0.740
CRP titre	0.223	0.237
ALT	0.474	0.008*
AST	0.435	0.016*
Bilirubin	0.429	0.018*
Serum Albumin	-0.531	0.003*
Cholesterol	-0.053	0.781
Triglecrid	0.059	0.756
LDL	0.018	0.925
HDL	0.076	0.690
INR	0.440	0.015*
PT	0.440	0.015*
Ur pre	-0.011	0.953
UR post	0.024	0.898
Ur reduction ratio	0.141	0.457
KTV	-0.393	0.032
Alkaline phosphatase	0.027	0.889
GGT	0.086	0.652

Discussion

NAFLD is a common disease in HD patients, liver steatosis and CKD hypothetically altered renin-angiotensin system (RAS) and activated protein kinase (AMPK), impaired antioxidant defense, excessive dietary fructose intake that affects renal injury via altered lipogenesis and inflammatory response causing chronic kidney disease and fibrosis among liver steatosis patients as the NAFLD complications (Marcuccilli *et al,* 2016).

In the present study, the NAFLD risk in patients compared to HD (GI) was 263.7± 52.7dB/m and HD patients (GII), without NAFLD, with CAP value 181.3±23dB/m versus controls with 210.8±33.7. In GI liver (NAFLD) patients were S1 steatosis degree & 5(16.6%) S2-S3 steatosis degrees. Among healthy individuals as controls, 11 (36%) had liver steatosis S1. Also, there was a significant difference between HD GI & G2 versus G III as mean BMI, systolic Bp, diastolic BP, and mean arterial BP (MABP) was higher among HD patients. This agreed with Adejumo *et al.* (2016), who found that median serum LDL-C was significantly higher, but mean serum HDL-C was significantly lower in CKD compared to controls. Increase BMI & hyper triglyceridemia and high LDL, low HDL defined the metabolic syndrome according to HMetS 2009 Criteria. Also, others found that metabolic syndrome was common in hemodialysis patients as a predictive of major adverse cardiovascular events (Delautre *et al,* 2020). Pouwels *et al.* (2022) reported that histologic evaluation with a liver biopsy is the gold diagnostic standard for NAFLD as the presence of hepatic steatosis, ballooning, and lobular inflammation with or without fibrosis.

In the present study, although there was a non-significant difference between HD patients with NAFLD and HD patients without NAFLD as regards BMI, there was a significant positive correlation between the CAP value of liver steatosis and BMI among HD patients (r=0.310, P=0.021). There was a significant correlation between CAP value and BMI in controls (r= 0.407, 0.026). This agreed with Loomis *et al.* (2015), who found that NAFLD/NASH increased linearly with increased BMI. Sapmaz *et al.* (2016) found that NAFLD was strongly associated with central obesity and significantly higher BMI values. Lipid profile among HD patients with NAFLD showed a significantly higher value of serum cholesterol, TG, & LDL than those without NAFLD, without a significant difference as to HDL levels. Univariate linear regression analysis showed highly significant correlations between CAP degree liver steatosis and serum cholesterol, TG, LDL, & HDL among total HD patients. Multivariate analysis showed that serum cholesterol was an independent factor affecting CAP value of liver steatosis P=0.001, B=1.982(0.908-3.057) 95%CI. This agreed with Orlić *et al.* (2014), who reported that one of the main features of NAFLD was the atherogenic dyslipidemia characterized by an increased number of small, dense LDL cholesterol particles, low levels of HDL cholesterol, and increased plasma triglyceride concentrations. Also, Julián *et al.* (2021) that dyslipidemia in HD patients was due to moderately increased apoB and significantly increased apoC-III. Triglyceride-rich apoB-contained lipoproteins (VLDL & IDL) were elevated by decreased activities of lipoprotein lipase and hepatic lipase in HD patients, resulting in hypertriglyceridemia.

In the present study, dyslipidemia among non-diabetic hemodialysis patients was significantly correlated to the NAFLD degree assessed by CAP Fibroscan value. So, atherogenic dyslipidemia management among hemodialysis patients as a possible reversible risk factor of NAFLD must be considered. Tsimihodimos *et al.* (2011) reported found that HDL levels increased by using high-flux membranes compared with low-flux membranes can increase HDL levels, Besides, using bicarbonate dialysate results in elevated HDL more often than the use of acetate dialysate.

In this study, there was a non-significant difference between HD patients with or without NAFLD as to MABP (P>0.05). Nigam *et al.* (2013) reported that the pathogenesis of NAFLD and NASH involved a two-hit hypothesis; first, hepatic insulin resistance causes steatosis, and second, pathogenic stimulus causes oxidative stress and cytokines production led to hepatic inflammation, CRP is an acute-phase reactant synthesized in hepatocytes. Oikonomou *et al.* (2018) reported that NAFLD association with increased blood pressure was the possible progression to liver fibrosis, but there were no significant differences between HD patients with and without the NAFLD regarding age, gender, HD start duration, or adequacy parameters of dialysis KT/V or URR. There was a significant correlation between PTH and post dialysis Urea level (P<0.01), So, adequate dialysis was valuable to control hyperparathyroidism in dialysis patients, but without statistical correlation detected as regard liver steatosis degree to parameters of the adequacy of dialysis parameters URR, KT/v or post-dialysis urea might be due to relatively small sample size in a study that needed further large cohort ones. Julián *et al.* (2021) reported that atherogenic dyslipidemia was associated with moderate-to-advanced liver fibrosis in type 2 diabetic patients with NAFLD, but not in the non-diabetic ones.

In the present study, the mean value of the CRP in HD patients with NAFLD was significantly higher than in those without the NAFLD, and Univariate linear regression analysis showed a significant correlation of CRP titer to liver steatosis among HD patients and controls (r =0.384, P=0.004,& r= 0.459, P=0.011), respectively. This agreed with Mikolasevic *et al.* (2014), who found that NAFLD positive correlation with hs-CRP values (r=0.659; P<0.0001) among elderly hemodialysis patients. Yeniova *et al.* (2014) included that non-CKD patients with NAFLD had hs-CRP levels higher in the NAFLD patients as compared to control (0.68mg/ dl vs. 0.34 mg/dl, respectively; P < 0.05), hs-CRP, which was considered a predictor for NAFLD by logistic regression analysis.

In the present study, there was a significant difference between HD patients with or without NAFLD as regards the mean of ALT & AST levels, but without significant differences between those without NAFLD and control. Total bilirubin level was significantly higher in HD patients with NAFLD compared to control but without significance as to mean bilirubin between HD with or without NAFLD. There were significantly higher AlP, GGT levels, PT, INR levels, and lower serum albumin levels in HD patients compared to control, however no statistical differences between HD patients with or without NAFLD as to albumin level, PT, INR levels as synthetic function tests of liver and no differences of the mean levels of GGT or Alkaline phosphatase between those two groups.

In the present study, ALT& AST significantly correlated with CAP of liver steatosis degree in HD patients (r=0.387, P=0.004), (r=0.365, p=0.006) respectively. Also, ALT and AST correlated significantly to the degree of liver steatosis among control, without significance between CAP value and serum albumin, GGT, AIP, or bilirubin among HD patients.

This agreed with Stolic *et al.* (2016) reported that HD patients without NAFLD showed significantly lower AST, & ALT. Also, this agreed with Yoon *et al.* (2017), they didn't find a correlation between the degree of liver steatosis and S. albumin and S. bilirubin. But, this disagreed with Mikolasevic *et al.* (2014), who found that CAP value negatively correlated to S. albumin with poor outcomes and malnutrition in HD patients.

The hyperparathyroidism in HD patients was an independent cardiovascular risk factor, and was associated with markers of preclinical atherosclerosis (Richart *et al,* 2011). The hepatic steatosis/NAFLD contributed to many factors related to the MS, atherogenic

dyslipidemia, insulin resistance, adipose tissue hormones, adipokines, and other factors, these factors contributed in the pathogenesis of NAFLD also may be correlated to hype-rparathyroidism in previous studies on non-CKD individuals. Reis *et al.* (2008) reported that the PTH level, but not the vitamin D level, was an independent predictor of MS in treatment-seeking morbidly obese Caucasian women and men. Also, the patients with primary hyperparathyroidism were associated with insulin resistance which was the main risk factor for serious metabolic disorders (Bibik *et al,* 2023).

In the present study, the mean serum PTH was higher among HD patients with NAFLD in comparison to HD group without NAFLD and the control group, however, it was statistically insignificant, and there was no significant correlation between the serum iPTH level and CAP value of the degree of liver steatosis or Kpa value of the liver stiffness among HD patients may be due to a relatively small sample size of patients in this study and confounders related to secondary hyperparathyroidism in HD as patients on treatment supplement of active vitamin D, calcium supplements and different pathogenesis related to secondary hyperparathyroidism and bone mineral disease among HD patients. But, in the present study, there was a significant correlation between CAP value and mean of PTH levels among the healthy individuals in the control group, which may be explained by the hypothesis of PTH level association with insulin resistance.

The relation between hyperparathyroidism and NAFLD/ NASH was evaluated in (Ghoghaei *et al,* 2015) study which found that Elevated serum PTH level was a predictive factor for NASH in morbidly obese patients. McCarty et al. (2003) reported a relationship between PTH elevation and metabolic syndrome and added that excess PTH may promote weight gain with increasing intra-adipocytes free calcium with blunting lipolytic response to catecholamines.

In the present study, there was no significant correlation between PTH level to BMI or lipid profile as risk factors for NAFLD among HD patients, but significant correlations in control between PTH level and cholesterol (r=0.709, P=<0.001), LDL (r=0.782, p=<0.001) and significant negative correlation with HDL level p<0.01, in contrast to Chiu *et al.* (2000), who could not verify any correlations between PTH and insulin resistance, blood glucose or blood lipids. This was also the results with Reis *et al.* (2007; 2008). Moreover, Rueda *et al.* (2008) reported negative results regarding the association of the elevated PTH level metabolic syndrome. But, in comparison with Ellam *et al.* (2014), who included the ESRD in peritoneal dialysis patients, reported that higher PTH in this cohort was independently associated with lower odds of meeting the metabolic syndrome criteria for fasting blood glucose and HDL cholesterol.

In the present study, there was no significant difference between the HD patients with NAFLD or without NAFLD regarding mean values of serum calcium, phosphate, or calcium phosphate products, as well as no significant correlation between the degree CAP value of liver steatosis to calcium or phosphate (P>0.05).

In contrast to these studies on the general population, Shin *et al.* (2015) found that the NAFLD was assessed based on ultrasonographic imaging prevalence of NAFLD/NASH increased according to quartiles of serum calcium, phosphorus, and calcium-phosphorus products (P< 0.001) that was explained by that the serum calcium levels were closely related to hypertension, abnormal glucose metabolism, dyslipidemia, and metabolic syndrome (Yamaguchi *et al,* 2011). But the association between the serum phosphorus and metabolic parameters was inconsistent with Shin *et al.* (2015)'*s* report, which was also agreed with Park *et al.* (2009), they suggested that serum phosphorus was directly implicated in the pathogenesis of NAFLD rather than acting indirectly through the metabolic disorders.

In the present study, the liver stiffness value (Kpa) mean ±SD was significantly higher in HD patients with NAFLD as compared to the HD without NAFLD or control without significant difference between GII patients without NAFLD, and control by the post hoc analysis. This clarified that among HD patients with NAFLD (GI) a significant correlation between Kpa value of liver stiffness ALT (P =0.008), AST (P=0.016), Bilirubin (P=0.018), Serum Albumin (P=0.003), INR and PT (P=0.015). There was no significant correlation between the degree of liver stiffness and serum PTH, calcium, phosphate, alkaline phosphatase, or GGT among the HD patients with NAFLD.

Limitations of the study, a relatively small number of patients, no vitamin D level assay of the bone profile, insulin resistant tests as no fund was received.

Conclusions

Non-alcoholic liver disease in prevalent HD patients significantly correlated to high cholesterol, LDL, triglycerides, low HDL, increased body mass index, and CRP titer as a marker of inflammation, but not significantly correlated to elevated PTH level. Hepatic steatosis is a risk for liver stiffness/ fibrosis among chronic HD patients.

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Explanation of figures

Fig. 1: Comparison between groups according to PTH (P <0.001)

Fig. 2: Comparison between groups according to patients number with liver stiffness (P<0.001)