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NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)—A NEW CARDIOVASCULAR RISK FACTOR IN PERITONEAL DIALYSIS PATIENTS

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♦ ***Background:*** **Recent investigations indicated that nonalcoholic fatty liver disease (NAFLD), a hepatic component of metabolic syndrome (MS), is associated with an increased risk of cardiovascular disease (CVD). Accordingly, we were interested in exploring the frequency of NAFLD in peritoneal dialysis (PD) patients and analyzing factors in PD patients associated with NAFLD occurrence. In addition, we were interested in investigating whether NAFLD is associated with higher CVD risk in our PD patients.**

♦ ***Methods:*** **In the present cross-sectional study, we analyzed 58 PD patients. The controlled attenuation parameter (CAP) was used to detect and quantify liver steatosis with the help of transient elastography (TE) (FibroScan, Echosense SA, Paris, France). A carotid ultrasound was performed in all patients to measure carotid intimae media thickness (IMT) and plaque as surrogate measures of increased CVD risk, and we investigated their association with NAFLD.**

♦ ***Results:*** **Nonalcoholic fatty liver disease was present in 74.1% of PD patients. Peritoneal dialysis/nonalcoholic fatty liver disease patients had statistically greater daily (136.5 ± 62.6 vs 93.6 ± 36.1; $p = 0.02$) and monthly (4,095.3 ± 1,877.7 vs 2,806.6 ± 1,083.2; $p = 0.02$) glucose load in comparison to the non-NAFLD/PD patients. In the next step, we were interested in analyzing what demographic and clinical characteristics in our PD patients are associated with a higher NAFLD occurrence. Presence of diabetes mellitus (DM), arterial hypertension (AH), dyslipidemia, body mass index > 25 kg/m^2, and daily glucose load > 100 g were associated with NAFLD occurrence. Peritoneal dialysis patients with NAFLD showed more carotid atherosclerosis than PD patients without NAFLD. In addition, CAP values (as indicator of liver steatosis) showed strong positive association with IMT ($r = 0.801$; $p < 0.0001$). Nonalcoholic fatty liver disease was a strong predictor of carotid atherosclerosis in PD patients.**

♦ ***Conclusion:*** **Nonalcoholic fatty liver disease is highly prevalent in PD patients. Peritoneal dialysis patients with NAFLD are at high risk of atherosclerosis. Assessment of NAFLD in PD patients may be helpful for CVD risk stratification.**

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Patients with chronic kidney disease (CKD) are at high risk of developing cardiovascular disease (CVD), with contributions from both "traditional" and "nontraditional" CVD risk factors. According to the literature, traditional risk factors such as hypertension, dyslipidemia, diabetes, and obesity have a higher prevalence in CKD patients and dialysis patients compared to non-CKD patients. In recent years, it is assumed that a number of non-traditional risk factors (endothelial dysfunction, chronic inflammation, increased oxidative stress, insulin resistance, etc.) could also play an important role in increased CVD morbidity and mortality in peritoneal dialysis (PD) patients. The interplay of many pathways, traditional risk factors, uremia-specific risk factors and novel, non-traditional risk factors may be responsible for the accelerated atherosclerosis that was observed in these patients. During the last decade, PD has become an increasingly popular treatment option for patients suffering from end-stage renal disease (ESRD). Despite significant improvement in the reduction of infectious complications in the past years, CVD mortality in PD patients remains unchanged. Therefore, searching for new causes of increased CVD risk in PD patients has attracted further research interest (1,2).

On the other hand, until recently, the presence of fatty liver was considered as a trivial finding. Nowadays, nonalcoholic fatty liver disease (NAFLD) has become the most common cause of alternated liver enzymes and the most common liver disease in Western countries. Currently, the importance of NAFLD and its relationship to metabolic syndrome (MS) is increasingly recognized. There is growing evidence suggesting that CVDs are the leading cause of death in patients with advanced NAFLD and that NAFLD is associated with an increased risk of CVD (3–7). In recent years, NAFLD was recognized as an important factor in CKD pathogenesis. A growing numbers of studies as well as a recent meta-analysis by Musso *et al.* have shown that the presence and severity of NAFLD are associated with an increased risk and severity of CKD (8–12). Moreover, NAFLD is now recognized as a common condition that markedly increases the risk of ESRD (13). Results from

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the United Network Organ Sharing (UNOS) database during the time period from 2002 to 2011 show that cirrhosis related to nonalcoholic steatohepatitis is an increasing indication for simultaneous liver-kidney transplantation (14). In view of these preliminary observations, we had recently investigated whether the presence of transient elastography (TE)-defined NAFLD is associated with higher CVD risk in our hemodialysis (HD) patients. We have found that HD patients with NAFLD showed more carotid atherosclerosis and higher incidence of adverse CVD events in comparison to HD patients without NAFLD and the control subjects (15). Our results were in accordance with recent studies that investigated the association of NAFLD with the risk of CVD in the general population (3–7) as well as with 2 other studies that investigated the association of NAFLD with the risk of CVD in HD patients (16,17).

We were interested in exploring the frequency of NAFLD in PD patients and analyzing what factors in PD patients are associated with NAFLD occurrence. In addition, we were interested in investigating whether NAFLD was associated with higher cardiovascular risk in our PD patients.

PATIENTS AND METHODS

In the present cross-sectional study, we analyzed 61 ESRD patients treated with PD for at least 3 months. The exclusion criteria were: serological evidence of chronic hepatitis B and/or C virus infection, alcohol abuse, presence of other autoimmune or cholestatic liver disease, malignancy, use of potentially hepato-toxic medications, uncontrolled secondary hyperparathyroidism, and technical reasons (failed transient elastography measurement). In the study group, there were no patients with infections at the time of TE measurements. Considering the above, 58 patients were enrolled in the further analysis.

Patients' demographic characteristics, medical history, and laboratory data were obtained by medical record. Co-morbid conditions included the presence of diabetes mellitus (DM), dyslipidemia, and arterial hypertension (AH), as well as obesity. This data was obtained using a standard questionnaire. Body fat (FAT) was assessed using skinfold caliper measurements. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Obesity was defined as a BMI > 25 kg/m^2. Diabetes mellitus was defined by fasting glucose ≥ 5.6 mmol/L or drug treatment, dyslipidemia by triglycerides ≥ 1.7 mmol/L (150 mg/dL) or by drug treatment as well as high-density lipoprotein (HDL) < 0.9 mmol/L (< 40 mg/dL) in men and < 1.1 mmol/L (< 50 mg/dL) in women. Blood pressure was measured with a standard mercury sphygmomanometer. The criterion used for defining AH was systolic blood pressure (SP) > 140 mmHg and diastolic pressure (DP) > 90 mmHg or the routine use of anti-hypertensive medications.

Laboratory data included hemoglobin, serum iron, ferritin, aspartate aminotransferase (AST), alanin aminotransferase (ALT), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), C-reactive protein (CRP), calcium, phosphorus, and parathyroid hormone (PTH), which were obtained by standard clinical chemistry techniques. The clinical and laboratory data were collected within 2 weeks of TE measurements.

We calculated glucose weight as the sum of the products of the volume and glucose concentration for each exchange. We calculated glucose load as the average dialysate glucose concentration:total glucose weight/total volume of PD solution prescribed (18).

Liver stiffness was selected as the parameter to quantify liver fibrosis. Furthermore, the controlled attenuation parameter (CAP) was used to detect and quantify liver steatosis with the help of TE (FibroScan, Echosense SA, Paris, France). The cut-off value for defining liver steatosis was CAP ≥ 238 dB/m and cut-off value for defining the presence of fibrosis was liver stiffness of > 7.1 kPa. The diagnosis of NAFLD was defined according to the TE findings with the CAP ≥ 238 dB/m, with or without any stage of fibrosis and after exclusion of other secondary causes of chronic liver disease. Measurements were performed using the M and XL probe on the right lobe of the liver through intercostal spaces with the patients lying in dorsal decubitus with the right arm in maximal abduction. Ten successful measurements were performed on each patient and only cases with 10 successful acquisitions were taken into account for this study. With CAP being implemented on TE, both steatosis and fibrosis could be evaluated simultaneously (19).

A carotid ultrasound with a 9-MHz multifrequency transducer was performed in all patients to measure carotid intimae media thickness (IMT) and plaque as surrogate measures of increased CVD risk. The present analysis used the average of 10 electronic caliper IMT measurements from the far wall of the distal 10 mm of left and right common carotid arteries at a site free from any discrete plaque. A plaque was defined as a focal thickening of ≥ 1.2 mm in any of 12 carotid segments (near and far walls of right and left common carotid artery, bifurcation and internal carotid artery). These results were obtained at the time of TE measurements and were correlated with the presence of NAFLD.

In this explorative analysis we tried to explore the frequency of NAFLD in PD patients. In addition, we analyzed which factors in PD patients are associated with NAFLD occurrence. Also, we tried to investigate whether NAFLD is associated with higher cardiovascular risk in our PD patients.

Patients were informed of the purpose and methods of the research, and the study was done in accordance with the Declaration of Helsinki.

Statistical analysis of data was performed using descriptive statistics (mean and standard deviation). Categorical variables were tested by chi-square test or Fisher's exact test. Testing the importance of the difference of 2 independent groups was performed using *t*-test or ANOVA. The Pearson or Spearman correlation coefficient was used to express correlations between variables. Variables found significantly predicting NAFLD and carotid atherosclerosis were assessed by logistic regression analysis. *P* values < 0.05 were considered statistically significant. Statistical analysis was performed using the MedCalc statistical software package, version 10 (MedCalc, Mariakerke, Belgium).

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RESULTS

Demographic and clinical characteristics of the remaining 58 PD patients are shown in Table 1A. The average age of our patients (37 male and 21 female) was 59.9 ± 12.5 (range 23 to 83 years) years and the average duration of renal replacement therapy (RRT) was 14.4 ± 16.3 months. The most common primary kidney diseases that led to the development of ESRD were non-diabetic nephropathy of vascular origin (22.4%), diabetic nephropathy (22.4%), and chronic glomerulonephritis (22.4%).

We analyzed the prevalence of NAFLD in PD patients and found that NAFLD is highly prevalent in our PD patients. According to the TE findings, NAFLD was present in 43 of 58 patients (74.1%). Twenty (34.5%) patients with CAP ≥ 238 dB/m had liver stiffness of more than 7.1 kPa.

Therefore, for further analysis, PD patients were stratified into 2 subgroups according to the TE finding, i.e. the presence or absence of NAFLD.

The most common cause of ESRD in the PD/NAFLD subgroup was diabetic nephropathy (30.2%), while chronic glomerulonephritis was the most common cause of CKD in non-NAFLD/PD patients (46.7%). There was no significant difference in duration of RRT or PD modality between the 2 subgroups of patients. On the other hand, the daily number of 2.26% glucose solutions was higher in the PD/NAFLD subgroup of patients, while there was no significant difference in the use of other PD solutions (1.36% glucose solution, Extraneal and Nutrineal; Baxter Healthcare Corporation, Deerfield, IL, USA).

When analyzing comorbid conditions, we found all components of MS (DM, AH, dyslipidemia, and obesity) highly present in PD/NAFLD patients. We found a statistically significant difference between the PD/NAFLD patients and non-NAFLD/PD patients when comparing BMI values ($p = 0.03$) and the presence of DM ($p = 0.01$), hypertension ($p = 0.01$), and dyslipidemia ($p = 0.04$). Additionally, PD/NAFLD patients had a higher percentage of fat mass obtained by caliper in comparison to the non-NAFLD/PD patients ($p = 0.05$), table 1A.

Also, PD/NAFLD patients had statistically greater daily (136.5 ± 62.6 vs 93.6 ± 36.1; $p = 0.02$) and monthly (4,095.3 ± 1,877.7 vs 2,806.6 ± 1,083.2; $p = 0.02$) glucose load in comparison to the non-NAFLD/PD patients.

When analyzing biochemical parameters, we found statistically significant differences between the PD/NAFLD and non-NAFLD/PD patients in hemoglobin, serum iron, ferritin, and hs-CRP values. Peritoneal dialysis/nonalcoholic fatty liver

TABLE 1A
Demographic and Clinical Data of Analyzed PD Patients

Characteristic	All PD patients (*n*=58)	PD/NAFLD (*n*=43)	Non-NAFLD/PD (*n*=15)	*p**
Gender (M:F)	37:21	26:17	11:4	NS
Age (years)	59.9±12.5	63.2±11.1	50.1±16.4	0.001
Etiology of CKD				
Diabetic nephropathy, *n* (%)	13 (22.4%)	13 (30.2%)	0 (0%)	—
Nondiabetic nephropathy, *n* (%)	13 (22.4%)	12 (27.9%)	1 (6.7%)	—
Chronic GN, *n* (%)	13 (22.4%)	6 (14%)	7 (46.7%)	—
Polycystic kidney disease, n (%)	6 (10.3%)	4 (9.3%)	2 (13.3%)	—
Unknown, *n* (%)	7 (12.1%)	5 (11.6%)	2 (13.3%)	
Other, *n* (%)	6 (10.3%)	3 (7%)	3 (13.3%)	—
Duration of RRT (months)	14.4 ± 16.3	14.2±18.5	14.9±7.5	NS
Arterial hypertension, *n* (%)	54 (92%)	42 (97.7%)	11 (73.3%)	0.01
DM, *n* (%)	16 (27.6%)	16 (37.2%)	0 (0%)	0.01
Dyslipidemia, *n* (%)	26 (52%)	25 (58.1%)	4 (26.7%)	0.04
Body mass index (kg/m^2)	26.9±4.3	27.6±4.5	24.9±2.7	0.03
FAT (%)	25.7±6.4	26.9±6	23.1±6.5	0.05
CAPD:APD	37:21	26:17	11:4	NS
Total daily exchange volume (mL)	8,153.6±2,695.4	8,417.1±2,782.7	7,433.3±2,379	NS
PD solutions (daily number), mean±SD				
1.36% glucose solution	2.8±1.1	2.8±1.1	3±0.9	NS
2.26% glucose solution	0.4±0.8	0.5±0.8	0.1±0.3	0.03
Extraneal	0.4±0.5	0.4±0.5	0.3±0.5	NS
Nutrineal	0.1±0.2	0.1±0.2	0	—
Glucose weight (g/day)	116.9±56	136.5±62.6	93.6±36.1	0.02
Glucose weight (g/month)	3,762±1,791.7	4,095.3±1,877.7	2,806.6±1,083.2	0.02

PD = peritoneal dialysis; NAFLD = nonalcoholic fatty liver disease; M = male; F = female; NS = not significant; CKD = chronic kidney disease; GN = glomerulonephritis; RRT = renal replacement therapy; DM = diabetes mellitus; FAT = body fat; CAPD = continuous ambulatory PD; APD = automated PD; SD = standard deviation.

* PD patients with NAFLD vs PD patients without NAFLD.

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TABLE 1B
Laboratory Characteristics of Analyzed Groups of Patients

	All PD patients (*n*=58) mean±SD	PD/NAFLD (*n*=43) mean±SD	Non-NAFLD/PD (*n*=15) mean±SD	*p**
Hemoglobin (g/L)	117.5±17.2	113.6±13.8	127.5±21.3	0.007
Serum iron (μmol/L)	13.3±5.5	11.8±4.1	16.9±7	0.002
Ferritin (mmol/L)	249±159.5	286.1±157.4	146.2±118	0.005
AST (IU/L)	16±6	15.6±6.3	16.7±5.4	NS
ALT (IU/L)	17.9±8.6	19±9.6	16.7±7.3	NS
GGT (IU/L)	23.5±17.9	24.9±17.9	22.9±18.2	NS
ALP (IU/L)	85.7±34.9	87±37.7	82.9±28.8	NS
Triglycerides (mmol/L)	2±0.9	1.8±0.7	2.3±1.2	NS
Cholesterol (mmol/L)	4.3±1.1	4.9±1.3	5±0.8	NS
CRP (mg/L)	6.1±7.2	7.6±7.9	2.2±1.7	0.02
Albumins (g/L)	40.1±4	39.5±4	41.6±3.6	NS
Ca (mmol/L)	2.2±0.2	2.2±0.2	2.4±0.2	NS
Phosphorus (mmol/L)	1.4±0.4	1.4±0.3	1.2±0.3	NS
PTH (pmol/L)	32.5±23.7	32.7±24.3	31.9±23.1	NS

PD = peritoneal dialysis; NAFLD = nonalcoholic fatty liver disease; SD = standard deviation; AST = aspartate aminotransferase; ALT = alanin aminotransferase; GGT = γ-glutamyltransferase; ALP = alkaline phosphatase; CRP = C-reactive protein; Ca = calcium; PTH = parathyroid hormone.
* PD patients with NAFLD vs PD patients without NAFLD.

disease patients had significantly lower hemoglobin and serum iron values in comparison to the non-NAFLD/PD patients. Furthermore, PD/NAFLD patients had significantly higher values of hs-CRP and ferritin than PD patients without NAFLD. On the other hand, we found no significant difference in liver tests, markers of bone metabolism and serum albumin levels between the 2 subgroups of patients (Table 1B).

We were interested in exploring the association between liver tests and the presence of NAFLD. We did not find any significant correlation between CAP values and values of investigated liver tests: AST, ALT, GGT, and ALP (p = NS), (Table 1B).

In the next step, we were interested in analyzing what demographic and clinical characteristics in our PD patients are associated with a higher NAFLD occurrence. The presence of DM, AH, dyslipidemia, BMI > 25 kg/m^2, and daily glucose load > 110 (g/day) were associated with NAFLD occurrence (Table 2). Moreover, there was a significant positive correlation between CAP and BMI values (r = 0.491; p = 0.0001). In addition, when analyzing the association between caliper measurements and the presence of NAFLD, we found that FAT showed a significant positive correlation with CAP values (r = 0.353; p = 0.01).

Next, we were interested in exploring if NAFLD in our PD patients is associated with advanced carotid atherosclerosis. As it is shown in Table 3, our PD patients with NAFLD show more carotid atherosclerosis compared to non-NAFLD/PD patients. In the next step, we investigated the association between CAP and IMT measurements. There was a highly significant positive correlation between CAP and IMT measurements (r = 0.801; p < 0.0001) (Figure 1).

Finally, we were interested in exploring which demographic and clinical characteristics are associated with advanced carotid atherosclerosis in our PD patients. Presence of NAFLD, DM, and dyslipidemia were found to be significantly associated with higher IMT. Additionally, presence of NAFLD and DM were factors that contribute to plaque occurrence. Nonalcoholic fatty liver disease was the strongest predictor of carotid atherosclerosis (Table 4).

TABLE 2
Predictors of NAFLD Occurrence in PD Patients

Parameter	*p*	OR (95% Cl)
Dyslipidemia	0.04	3.819 (1.0463–13.9431)
Diabetes mellitus	0.05	18.600 (1.0424–331.8729)
Arterial hypertension	0.05	10.500 (0.999–110.3618)
BMI >25 kg/m^2	0.04	3.733 (1.0768–12.9436)
BMI >28 kg/m^2	0.03	11.083 (1.3354–91.9856)
Glucose weight >110 (g/day)	0.02	6.809 (1.3689–33.874)

NAFLD = nonalcoholic fatty liver disease; PD = peritoneal dialysis; OR = odds ratio; CI = confidence interval; BMI = body mass index.

TABLE 3
Carotid IMT and Plaque in PD Patients With and Without NAFLD

Criterion	PD/NAFLD (*n*=43)	Non-NAFLD/PD (*n*=15)	*p**
Carotid IMT (mm), mean±SD	1.1±0.1	0.8±0.1	<0.0001
Carotid plaque, *n* (%)	27 (62.8%)	2 (13.3%)	0.001

IMT = intimae media thickness; PD = peritoneal dialysis; NAFLD = nonalcoholic fatty liver disease; SD = standard deviation.
* PD patients with NAFLD vs PD patients without NAFLD.

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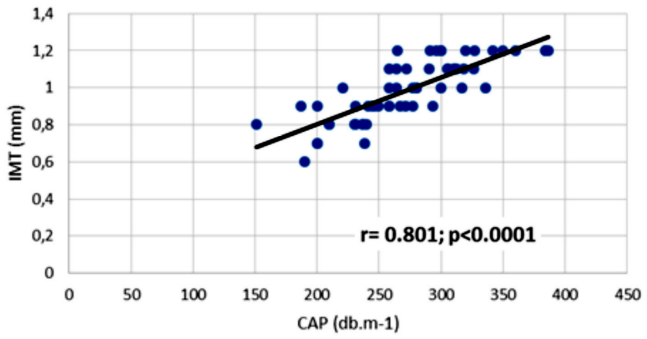

Figure 1 — The correlation between CAP values and carotid IMT in PD patients. IMT = intimae media thickness; CAP = controlled attenuation parameter; PD = peritoneal dialysis.

TABLE 4
Predictors of Carotid Atherosclerosis in PD Patients

Variable	*p*	OR (95% CI)
IMT >0.9 mm		
DM	0.008	8.473 (1.7084–42.0284)
NAFLD	0.0007	40.727 (4.7854–346.619)
AH	0.214	4.363 (0.4257–44.7328)
Dyslipidemia	0.004	5.142 (1.6546–15.9852)
Carotid plaque (%)		
DM	0.006	5.8 (1.4301–23.3425)
NAFLD	0.001	13.5 (2.6656–68.0106)
AH	0.265	3.75 (0.3663–38.3882)
Dyslipidemia	0.190	2.014 (0.7062–5.7437)

PD = peritoneal dialysis; OR = odds ratio; CI = confidence interval; IMT = intimae media thickness; DM = diabetes mellitus; NAFLD = nonalcoholic fatty liver disease; AH = arterial hypertension.

DISCUSSION

While the incidence of infectious complications in PD patients has decreased, CVD mortality remains unchanged or has even slightly increased (20). According to the European Renal Association-European Dialysis and Transplantation Association Registry, at least half of all deaths in this population of patients are attributable to CVD (21). The interplay of many pathways, traditional risk factors, uremia-specific risk factors and novel non-traditional risk factors are responsible for the accelerated atherosclerosis seen in PD patients (1,2). Searching for new causes of CVD in PD patients has attracted further research interest.

To the best of our knowledge, this is the first study investigating the association between NAFLD and CVD risk in PD patients. Our results demonstrate that NAFLD is highly prevalent in PD patients. These results can be explained by the fact that the main risk factors responsible for development of NAFLD such as diabetes, hypertension, dyslipidemia and obesity are highly present in PD patients. It is believed that almost all NAFLD patients have more than 1 component of MS and 35 – 75% of patients meet all of the diagnostic criteria. These components of MS were highly present in our PD patients with NAFLD. Moreover, in our study, the daily number of glucose solutions, obesity, and presence of AH, DM, and dyslipidemia were found to be predictors of NAFLD occurrence. In addition, fat mass showed a significant positive correlation with the severity of liver steatosis. Also, PD/NAFLD patients had statistically greater daily and monthly glucose load in comparison to the non-NAFLD/PD patients. Therefore, it could be expected that PD patients have a high prevalence of NAFLD which was confirmed in our study. Insulin resistance is recognized as the pathophysiological hallmark of NAFLD. According to the literature, insulin resistance is prevalent in CKD patients. Glucose is the most commonly utilized osmotic agent in PD patients. On the other hand, absorption of glucose in PD patients can also lead to several cardiometabolic complications, such as hyperinsulinemia, hyperglycemia, hyperlipidemia and weight gain. Some authors have postulated that glucose loading in PD patients is associated with deterioration in insulin sensitivity (22). These observations can explain the association of NAFLD and applied glucose solutions in our PD patients, as well as a high prevalence of NAFLD in our PD patients, but further studies are needed.

The results of our study are important for 2 reasons. Nonalcoholic fatty liver disease patients have a higher risk of CVD due to the underlying metabolic disorders mentioned above, even without MS, as has been shown in recent studies (3–7). According to the literature, there is a strong association between the severity of liver histopathology in NAFLD patients and greater carotid IMT and plaque, and lower endothelial flow-mediated vasodilatation (as markers of subclinical atherosclerosis) even independently of MS (3,7,23). Recently, Targher found that NAFLD is not merely a marker of CVD, but it may be actively involved in its pathogenesis (24). Nonalcoholic fatty liver disease *per se* contributes to higher adverse CVD events due to subchronic inflammation and endothelial dysfunction, as has been observed in recent investigations (3–7,23,24). Our study showed that PD patients with NAFLD show more carotid atherosclerosis than PD patients without NAFLD. In addition, CAP values (as an indicator of liver steatosis) showed strong positive association with IMT. Nonalcoholic fatty liver disease was an independent predictor of carotid atherosclerosis in our PD patients. Our results in the present study are in accordance with recent studies investigating the association between NAFLD and the risk of CVD in the general population (3–7) and with our previous study (15) as well as 2 recent studies (16,17) regarding the association between NAFLD and CVD in HD patients. The exact mechanism linking NAFLD and increased CVD risk is not fully understood, but there is growing evidence supporting the idea that hepatic steatosis is associated with atherogenic dyslipidemia, inflammation, and endothelial dysfunction. In the last few years, many investigations have shown an increased production and release of various proinflammatory cytokines in patients with NAFLD. Accordingly, enhanced oxidation and inflammation with the release of inflammatory cytokines may account for the proatherogenic effect of NAFLD (3–7,23,24). We believe that the presence of NAFLD in PD patients could

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be a new risk factor or a new marker of increased CVD risk in this population of patients. Due to our relatively small number of patients, we can only speculate about these observations. Further, prospective, and randomized trials are needed.

In our study, none of the investigated liver tests showed any significant association with the presence of NAFLD in PD patients. We have observed similar results in our HD patients (15). On the other hand, NAFLD is the most common cause of liver enzyme abnormalities in the general population. These data indicate that standard reference liver test values cannot be used as markers of NAFLD in PD patients. These results can be explained by previous findings, which have shown that ESRD patients have decreased serum aminotransferase activity compared to the general population (25). To this day, there is still no clear recommendation that liver biopsy is required to confirm a diagnosis of NAFLD (26). Therefore, the evaluation of NAFLD using non-invasive methods such as TE-CAP may represent a potential future approach in the assessment of NAFLD in PD patients.

Our study has several limitations. The design is cross-sectional and the number of patients is relatively small. The cross-sectional format of our study does not allow conclusions as to whether the link between the NAFLD and greater CVD risk in PD patients is causal. In other words, due to the cross-sectional design it is not possible to conclude whether NAFLD is simply a reflection of MS or whether NAFLD adds additional risk. Therefore, further prospective investigations should be conducted to answer this question. In addition, the observational nature of our study makes it impossible to assess the impact of PD *per se* on the prevalence of NAFLD because there was no control group. On the other hand, our study has several strengths. It shows, for the first time, that PD patients with NAFLD show advanced carotid atherosclerosis. Therefore, we assume that NAFLD should be considered a new important risk factor or a new marker of increased CVD risk in PD patients. Further studies are needed that will investigate and confirm these observations. The clinical implication of this finding is that the presence of NAFLD in PD patients may help in cardiovascular risk stratification and assessment. The use of CAP as a screening method for NAFLD detection in PD patients could be beneficial since it is a non-invasive and quick method that is easy to perform and may be repeated.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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