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Original Paper

Chronic Kidney Disease and Nonalcoholic Fatty Liver Disease Proven by Transient Elastography

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Key Words

Chronic kidney disease • Non-alcoholic fatty liver disease • Fibroscan®

Abstract

Background/Aim: Preliminary data suggest an association between chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NAFLD). The aim of this study was to further investigate the association between NAFLD and decreased kidney function. **Methods:** A total of 62 patients with CKD were enrolled in the study. Liver stiffness was used to detect liver fibrosis and CAP (controlled attenuation parameter) was used to detect and quantify liver steatosis (Fibroscan®). NAFLD was defined by CAP values ≥ 238 dB.m⁻¹. **Results:** CKD stage III was present in 29 patients (46.8%) and CKD stage IV in 33 patients (53.2%). Out of 62 CKD patients 53 (85.5%) had NAFLD and of these 14/53 patients (26.4%) had also liver stiffness >7 kPa. The severity of liver steatosis was positively correlated with serum creatinine ($r=0.399$; $p<0.01$) and CRP ($r=0.261$; $p<0.05$) and negatively correlated with eGFR ($r=-0.413$; $p<0.01$) and serum iron concentration ($r=-0.365$; $p<0.01$). **Conclusion:** The results suggest a high prevalence of NAFLD in CKD patients. The severity of liver steatosis is negatively correlated with kidney function. The study documents the value of ultrasonographic elastography as an effective non-invasive screening method for the diagnosis of NAFLD.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases in Western countries. It encompasses a spectrum of conditions with lipid deposition in hepatocytes, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) i.e. fatty liver with inflammation and hepatocellular injury with or without fibrosis, advanced

fibrosis and cirrhosis. Today, it is believed that NAFLD represents a hepatic manifestation of the metabolic syndrome (MS). MS and all its clinical traits are highly prevalent in patients with NAFLD. In the recent past the importance of NAFLD and its link to the metabolic syndrome has generated great interest in view of its potential role in the development of atherosclerosis [1-5].

Preliminary data suggest an association between chronic kidney disease (CKD) and NAFLD: the prevalence of CKD was significantly higher in patients with NASH compared to patients without NASH [6, 7]. Furthermore, a recent study documented moderately decreased eGFR and high frequency of microalbuminuria in patients with biopsy proven NASH; the severity of liver damage was correlated with lower eGFR [8]. In the absence of a noninvasive method the diagnosis of NAFLD/NASH was based on the gold standard of liver biopsy or less reliably - on serum liver enzymes or ultrasound imaging. But even the gold standard of liver biopsy has its limitations: apart from being an invasive procedure, connected with serious complications, it samples only 1/50 000th of the liver and is thus prone to significant sampling error. Today it is still under discussion whether liver biopsy is required to confirm a diagnosis of NAFLD [1-5, 9]

In view of this dilemma many non-invasive procedures have been intensively applied to detect hepatic steatosis and fibrosis. Recently a novel parameter has been developed, i.e. the Controlled Attenuation Parameter (CAP); it can be quantitated using transient elastography (TE) (Fibroscan®) which permits to efficiently separate different grades of severity of steatosis. CAP is based on the properties of ultrasonic signals acquired by the Fibroscan®. This diagnostic tool allows to simultaneously measure liver stiffness and CAP in the same liver volume. The volume used for the measurement by the Fibroscan® is 200 times larger than that of a liver biopsy specimen. Therefore the Fibroscan® is used more and more in clinical practice [10].

The relationship between NAFLD and CKD is still poorly understood. The aim of the present study was to evaluate how frequently NAFLD is present in patients with chronic kidney disease. In the present cross-sectional study we assessed the frequency of NAFLD in patients in different stages of CKD. To this end we used transient elastography (Fibroscan®-CAP).

Patients and Methods

Patients

Sixty-two CKD patients were recruited from the Department of Nephrology and Dialysis. CKD was defined as eGFR(MDRD formula) ≤ 60 ml/min/1.73 m² for > 3 months. CKD stages were defined according to the National Kidney Foundation. None of the involved patients had serological evidence of chronic hepatitis B and/or C virus infection, had a history of alcohol abuse of more than 20 g alcohol per day, had a history of drug treatment causing hepatic steatosis (e.g. corticosteroids, high-dose estrogen, methotrexate or amiodaron within 6 months of enrollment) or had a history of gastrointestinal bypass surgery. Other types of metabolic or autoimmune liver disease were ruled out as well.

Methods

The body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Obesity was defined as a BMI of > 25 kg/m², diabetes mellitus by fasting glucose ≥ 5.6 mmol/L or drug treatment, dyslipidemia by triglycerides ≥ 1.7 mmol/L, by drug treatment or by HDL < 1 mmol/L in men and < 1.29 in women. Laboratory data included: blood cell count, serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transferase (GGT), albumin, fasting glucose, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, urea, creatinine, and C-reactive protein (CRP) by standard clinical chemistry techniques. The clinical and laboratory data were collected at the time of transient elastography.

Liver stiffness was selected as the parameter to quantitate liver fibrosis. Furthermore the CAP (controlled attenuation parameter) was used to detect and quantify liver steatosis with the help of Fibroscan® (Echosense, Paris, France). The examination was performed using an M probe (at 3 MHz) on

Table 1. Demographic characteristics of analyzed patients

Characteristic	Total (n=62)	CKD III (n=29)	CKD IV (n=33)	p
Age (y)	64.9±8.6	63.3±9.3	66.4±7.7	NS
Sex				
Male	41 (66.1%)	24 (82.8%)	17 (51.5%)	NS
Female	21 (33.9%)	5 (17.2%)	16 (48.5%)	0.04
Etiology:				
Nondiabetic nephrop.	37 (59.6%)	20 (69%)	13 (39.3%)	
Diabetic nephropathy	25 (40.3%)	12 (41.45)	13 (39.4%)	
NAFLD	53 (85.5%)	24 (45.3%)	29 (54.7%)	NS
BMI (kg/m ²)	27.19±2.6	27.8±2	26.7±2.7	NS
Hypertension	62 (100%)	29 (100%)	33 (100%)	NS
Diabetes	35 (56.5%)	13 (44.8%)	22 (66.7%)	0.04
Dyslipidemia	61(98.4%)	28(96.6%)	33(100%)	NS

*years (y); non-alcoholic fatty liver disease (NAFLD); body mass index (BMI); chronic kidney disease (CKD); non-significant (NS)

the right lobe of the liver through intercostals spaces with the patients in dorsal decubitus with the right arm in maximal abduction. Ten successful measurements were performed in each patient; only cases with 10 successful acquisitions were taken into account for this study. All scans were performed by the same investigator.

The cut-off value for the diagnosis of liver steatosis was a CAP value ≥ 238 dB.m⁻¹. The cut-off value for the diagnosis of liver fibrosis was liver stiffness >7 kPa.

According to this evaluation, NAFLD was defined by the presence of steatosis with CAP values ≥ 238 dB.m⁻¹ regardless of presence or absence of any stage of fibrosis. CAP values between 238 to 258 dB.m⁻¹ were categorized as steatosis grade 1 (S1), values between 259 to 292 dB.m⁻¹ as S2, and CAP values >292 dB.m⁻¹ as steatosis grade 3 (S3) [10].

Statistical Analysis

Data was performed using descriptive statistics (mean and standard deviation). Categorical variables were tested by chi-square test. Testing the difference of two independent groups was performed using t-test. The Pearson or Spearman correlation coefficient was used to express correlations between variables. P-value <0.05 was considered to be statistically significant. Statistical analysis was made using MedCalc statistical software package, version 10 (MedCalc, Mariakerke, Belgium).

Results

The total cohort of 62 CKD patients comprised 41 men and 21 women with an average age of 64.9±8.6 years. 29 patients (46.8%) had CKD III and 33 patients (53.2%) CKD IV ; patients with CKD V were not available. Table 1 shows the demographic characteristics of the 62 patients.

Of the 62 CKD patients 53 (85.5%) had CAP > 238 dB.m⁻¹ and had thus by definition NAFLD.

According to the literature the grades of liver steatosis were defined by CAP values: 10 (18.9%) patients had grade 1, 14 (26.4%) had grade 2, 29 (54.7%) had grade 3. Among the patients with NAFLD 14 patients (26.4%) had in addition liver stiffness > 7 kPa. The number of NAFLD positive patients was not significantly different between CKD stage III and CKD stage IV. The severity of liver steatosis was positively correlated with the serum creatinine concentration, the systolic blood pressure and the CRP concentration; it was negatively correlated with eGFR and serum iron levels (Table 2. and Figure 1.).

The presence of liver fibrosis (defined by liver stiffness > 7 kPa) in the patients with CAP ≥ 238 dBm⁻¹ was not significantly correlated with the eGFR.

Table 2. Correlation of CAP values (liver steatosis) with laboratory and clinical data

	Mean±SD	r	p
Hemoglobin (g/L)	123.3±16.6	0,001	NS
Iron (µmol/L)	13.5±3.3	-0.365	<0.01
RDW (%)	14.8±1.3	0.120	NS
Urea (mmol/L)	14.7±6.4	0.121	NS
Creatinine (µmol/L)	198.7±67.5	0.399	<0.01
eGFR (ml/min per 1,73 m ²)	32.8±13.6	-0.413	<0.01
Total cholesterol (mmol/L)	4.5±1.1	0.239	NS
Triglycerides (mmol/L)	1.9±0.8	0.229	NS
AST (IU/L)	20.7±8.5	0.022	NS
ALT (IU/L)	21.3±10	0.016	NS
ALP (IU/L)	90.8±30.1	0.111	NS
γGT (IU/L)	31.8±36.2	0.189	NS
CRP (mg/L)	4.2±5.1	0.261	<0.05
Age (y)	64.9±8.6	-0.108	NS
BMI (kg/m ²)	27.2±2.6	0.133	NS

*red blood cell distribution (RDW); estimated glomerular filtration rate (eGFR); aspartate aminotransferase (AST); alanin aminotransferase (ALT); γ-glutamyltransferase (GGT); C-reactive protein (CRP); systolic blood pressure (SP); diastolic blood pressure (DP); years (y); body mass index (BMI)

Discussion

To our knowledge, this is the first study using transient elastography as a noninvasive approach for the detection of NAFLD in CKD patients. Our results demonstrate that CKD patients have a high prevalence of NAFLD (85.5%) defined by transient elastography. In our study a significant number of patients had the metabolic syndrome. These results in agreement with past observations that diabetes mellitus type 2, dyslipidemia and obesity all contribute to the development of NAFLD. It is believed that approximately 90% of patients with NAFLD have more than one component of the metabolic syndrome: in our study 35-75% of patients met all diagnostic criteria of the metabolic syndrome [1-5]. We found that the severity of liver steatosis, defined by CAP values, was positively correlated with serum creatinine levels and negatively correlated with eGFR. The frequency of NAFLD between CKD stages III and IV was not significantly different, probably a result of the relatively small number of patients and because NAFLD positive patients were included regardless of the severity of liver steatosis. These findings are in accordance with recent work by Targher et al. [6] which showed that patients with biopsy

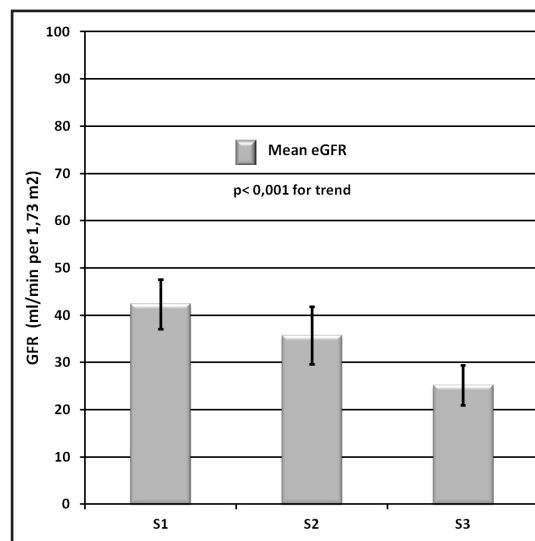


Fig. 1. Adjusted means (±SD) of eGFR in relation to the severity of liver steatosis (NAFLD). Steatosis grade increasing from S1 to S3 in CKD patients with Fibroscan®-CAP proven NAFLD. P value for the trend is assessed by analysis of covariance.

proven NASH have a moderately decreased eGFR and that the severity of NASH histology is associated with decreased kidney function. Our results are also corroborated by recent observational studies which showed that the presence of NAFLD is strongly associated with an increased prevalence of CKD [7, 11-12]. Furthermore, Yilmaz et al. [13] showed a positive correlation between microalbuminuria and liver fibrosis in nondiabetic patients with NAFLD. In our study, we didn't find any association between eGFR levels and the severity of liver stiffness. In all of these studies NAFLD was detected by either liver enzymes, liver ultrasound or by a liver biopsy. But it is important to note that the aminotransferase levels that are used as a marker of liver damage are normal in approximately half of all patients with NAFLD; therefore normal values do not exclude NAFLD and liver fibrosis. In our study none of the analyzed liver tests showed a significant correlation with the presence of NAFLD. The sensitivity of the ultrasonography for detection of hepatic steatosis is between 93% and 100% if the fat content in hepatic parenchyma is > 33%. But it is a relatively subjective method and is therefore prone to sampling error. Liver biopsy remains the gold standard in the diagnosis of NAFLD, but it is an invasive procedure and there is still no consensus whether the diagnosis of NAFLD should routinely be confirmed by liver biopsy [1-5].

It is important to identify factors that increase the risk of progression of CKD. Today, there is growing evidence that suggests that the metabolic syndrome (MS) is an important and potentially pathogenetically relevant factor for the genesis and progression of chronic kidney disease. In our study a majority of patients had MS and presumably this is the reason why so many patients had NAFLD. It has been well documented in the literature that there is a positive relationship between insulin resistance and CKD [14, 15]. Insulin resistance is a key pathophysiological mechanism in the metabolic syndrome; it presumably also plays a crucial role in the pathogenesis of NAFLD [16]. As mentioned, NAFLD is closely related to the metabolic syndrome and its manifestations, i.e. obesity, diabetes mellitus type 2, dyslipidemia and hypertension. NAFLD represents a liver manifestation of the metabolic syndrome and is an independent predictor of cardiovascular disease. It is believed that subchronic liver inflammation in NAFLD/NASH contributes to enhanced oxidative stress; numerous studies documented a strong link between the severity of NAFLD and the degree of oxidative stress [1-5]. Those studies showed an increase in serum oxidative markers and a decrease in antioxidant molecules in patients with NAFLD. The levels of these markers correlate with the severity of liver disease and insulin resistance [16]. In recent studies serum iron levels were negatively correlated with CAP values pointing to a potential role of chronic inflammation. In the present study, the inflammation marker CRP was positively correlated with CAP values. This correlation might be relevant to explain the inverse correlation between eGFR and liver steatosis. One cannot exclude the possibility that an inflammatory state in NAFLD aggravates CKD progression.

For now, we can only speculate about the implications of these observations and further prospective and randomized trials are needed.

The underlying mechanism by which NAFLD might promote chronic kidney disease remains unknown. It may simply reflect the fact that NAFLD and CKD share some important metabolic risk factors (diabetes mellitus, obesity, dyslipidemia and hypertension); on the other hand, NAFLD might further promote insulin resistance, thus aggravating CKD progression. Finally inflammation and oxidative stress associated with NAFLD may further promote progression, thus establishing a fatal link between liver and kidney.

Our study has certain limitations. The cross-sectional format of our study does not allow conclusions whether the link between CKD and NAFLD is causal. Secondly, we do not have a control group of nonsteatotic patients. Thirdly, we did not use liver biopsy to prove the diagnosis of NAFLD and compare the histological features of liver biopsy samples with the findings by Fibroscan®-CAP.

In conclusion, our results suggest that NAFLD is highly prevalent in CKD patients. The severity of liver steatosis is negatively correlated with the kidney function. Whether interventions to interfere with the fatal frequent connection of CKD with obesity, hypertension, diabetes and dyslipidemia would reduce the risk of NAFLD is not known. The main finding of

our study is the finding that ultrasonographic elastography (FibroScan®-CAP) provides the opportunity of non-invasive screening for NAFLD in CKD patients.

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