Non-alcoholic fatty liver disease and associated risk factors among hemodialysis patients

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD), chronic kidney disease (CKD) have common pathogenic mechanisms and many important cardio-metabolic risk factors, thus diagnosis and treatment of NAFLD and related factors among CKD patients can potentially prevent CVD-related mortality, which is considered as the most common cause of death in CKD patients.

Objective: To determine the prevalence of NAFLD and related risk factors amongst hemodialysis patients.

Methods: 150 ESRD patients were included in this cross-sectional study in a 1-year period. Abdominal ultrasound was done to determine the presence of NAFLD. Risk factors and related variables including hypertension, abdominal obesity, dyslipidemia, anemia, diabetes mellitus, and qualitative C-reactive protein (CRP) were gathered.

Results: The prevalence of NAFLD was 20% (30 patients). The frequency of abdominal obesity was significantly higher in the NAFLD group (73.33%) compared to ESRD patients who did not have NAFLD (23.33%); P< 0.0001. Also, hypertension was more common in the NAFLD group (90%) than in the other group (69.16%); P= 0.021. Likewise, anemia, DM, abnormally high ALT (i.e., > 20 IU/L), dyslipidemia, and positive CRP test results all were significantly higher in the NAFLD group in comparison to the other group.

Conclusion: ESRD patients should be investigated for the presence of NAFLD, as it was present in about one-fifth of the studied sample. Established risk factors for CVD were significantly more common in ESRD + NAFLD patients compared to ESRD cases without NAFLD. This emphasizes more aggressive treatment of the risk factors in NAFLD patients.

Key words: Non-alcoholic fatty liver disease; chronic kidney disease; hemodialysis; risk factor

Introduction

Chronic kidney disease (CKD) apparently is a global health issue and its prevalence is increasing. In a recent meta-analysis of more than 100 studies, the overall prevalence of 5 stages of CKD globally was determined as 11-13%, and stage 3 was the most prevalent type (1). An important consideration in CKD patients is increased rate of cardiovascular diseases (CVD) in a way that CKD is regarded as an independent risk factor for CVD. In addition, CVD is the most common cause of morbidity and mortality in this population (2). When CKD progresses to end-stage renal disease (ESRD), replacement therapy becomes inevitable. ESRD, as well, has faced an increasing trend in most countries and its health related costs are concerning for many health-care programs.

Considering the above mentioned facts about CKD, more knowledge is required to find contributing factors in the progression of CKD, in particular focusing on CVD occurrence. The risk factors for CKD and CVD are very similar. Accumulating evidence suggests that NAFLD is associated with an increased prevalence and incidence of CKD. Non-alcoholic fatty liver disease (NAFLD) is a common liver condition and is assumed as the most prevalent liver disease at least in Western societies (3). NAFLD is characterized by accumulation of fat in the liver (i.e., hepatic steatosis) with or without evidence of inflammation (i.e., non-alcoholic steatohepatitis [NASH]) in the absence of significant cause for this fat accumulation (for instance, significant alcohol taking history). Different radiologic and laboratory methods are used to define NAFLD and its prevalence is estimated as 25.4%, depending on the definitions used to diagnose NAFLD and geographical variation depicted by higher prevalence of NAFLD in the Middle East and South America (4). Patients with NAFLD usually have components of metabolic syndrome, namely obesity, high blood pressure, dyslipidemia, insulin resistance or DM. All these factors are the same as mentioned previously for CVD and CKD. Many experts believe that NAFLD is the hepatic manifestation of metabolic syndrome (3). As stated earlier, finding contributing factors in progression of CKD to ESRD is of paramount importance with focus on decreasing the rate of CVD among CKD patients. One of these culprits is NAFLD. In fact, in recent years, much research has been done in order to determine if any possible association exits between NAFLD and CKD as well as renal function (3, 5-9). These studies have also been done in hemodialysis and renal transplant received patients. For example, in a study including hemodialysis patients, NAFLD was diagnosed in about one-quarter of patients using transient elastography (8). Furthermore, NAFLD has been proposed as a meaningful risk factor for morbidity in renal transplant recipients(10).

The objective of this study was to explore the frequency of NAFLD in patients who were receiving hemodialysis and to investigate the relevant risk factors. The authors believe that findings of this study will add to the current knowledge about the interplay between NAFLD, ESRD, metabolic syndrome and the previously known risk factors in an effort to diagnose contributing factors at earlier stages to improve the survival of ESRD patients.

Materials and Methods

Study population and research design

In this cross-sectional study conducted from March to February 2016 in two university hospitals, the study population consisted of all ESRD patients who were receiving hemodialysis. Exclusion criteria were history of alcohol intake, inherited liver diseases, and taking tamoxifen.

Sample size

The sample size was calculated based on a former study which reported the prevalence of NAFLD among hemodialysis patients as 40% (9), at confidence level of 95% and power of 90%, the estimated sample size was calculated as 150 patients.

Data collection

A checklist was designed to gather the required data. The demographic data gathered included age, gender, blood pressure (BP), and waist circumference. Hypertension was defined as systolic BP (SBP) of ≥140 mmHg and/or diastolic BP (DBP) of ≥90 mmHg. Abdominal obesity was defined as waist circumference of more than 102 cm in males and 88 cm in females.

Five CC venous blood sample was obtained from the brachial vein and sent to the laboratory. The laboratory markers assayed were lipid profile, CBC, qualitative C-reactive protein (CRP), random plasma glucose, and alanine aminotransferase (ALT). Dyslipidemia was defined as triglyceride > 150 mg/dL, high-density lipoprotein (HDL) < 40 mg/dL, and low-density lipoprotein (LDL) > 150 mg/dL. DM was defined as random plasma glucose > 140 mg/dL. The presence of CVD was assessed using medical records of the patients.

In order to determine the presence of NAFLD, abdominal ultrasound was done. Based on the observation of increased hepatic echogenicity, the diagnosis of NAFLD was made. The severity of steatosis was graded as grades I, II, and III (11).

Statistical analyses

Descriptive indices such as frequency, percentage, mean, and its standard deviation (SD) were used to express data. In order to compare the frequency of the evaluated categorical variables between patients with NAFLD and those without NAFLD, the chi-squared test was applied. Age was compared using the Student t test. The data were gathered and entered into the SPSS software for Windows (version 21.0) (IBM Corp., Armonk, NY, USA). Significance level for all analyses was set at 0.05.

Ethics

The study protocol was approved by the Ethics Committee of our medical university. The study objectives were explained for the patients before participation, and if agreed, written informed consent was obtained from them.

Results

There were 94 male (62.7%) and 56 female (37.3%) patients. Mean (±SD) age of the sample was 63.68 (±15.66) years.

Thirty patients (20%) had NAFLD. The severity of steatosis in 49 patients was determined. Grades I, II, and III NAFLD were recorded respectively in 15, 32, and 2 patients.

Table 1: Comparison of gender, age, cardiovascular disease, hypertension, and abdominal obesity between end-stage renal disease (ESRD) patients with non-alcoholic fatty liver disease (NAFLD) and ESRD cases without NAFLD

		NAFLD (N= 30)	No NAFLD (N= 120)	P value
Age, year		66.5 (±11.36)	62.98 (±16.52)	0.272
Gender	Male	15 (50%)	79 (65.83%)	0.109
	Female	15 (50%)	41 (34.17%)	
CVD		21 (70%)	70 (58.33%)	0.242
Hypertension		27 (90%)	83 (69.16%)	0.021
Abdominal obesity		22 (73.33%)	28 (23.33%)	< 0.0001

Table 1 presents comparison of gender, age, CVD, hypertension, and abdominal obesity between 30 ESRD patients with NAFLD and 120 ESRD cases without NAFLD. As observed, the frequency of abdominal obesity was significantly higher in the NAFLD group (73.33%) compared to ESRD patients who did not have NAFLD (23.33%); P< 0.0001. Also, hypertension was more common in the NAFLD group (90%) than in the other group (69.16%); P= 0.021.

Anemia, DM, abnormally high ALT (i.e., > 20 IU/L), dyslipidemia, and positive CRP test results all were significantly higher in the NAFLD group in comparison to the other group (Table 2).

Table 2: Comparison of the frequency of anemia, diabetes mellitus, increased ALT, dyslipidemia, and CRP between end-stage renal disease (ESRD) patients with non-alcoholic fatty liver disease (NAFLD) and ESRD cases without NAFLD

	NAFLD (N= 30)	No NAFLD (N= 120)	P value
Anemia	19 (63.33%)	33 (27.5%)	< 0.0001
DM	20 (66.66%)	49 (40.83%)	0.011
ALT > 20 IU/L	6 (20%)	7 (5.83%)	0.014
Dyslipidemia	20 (66.66%)	21 (17.5%)	< 0.0001
CRP, positive	25 (83.33%)	64 (53.33%)	0.003

Discussion

There is a complex interplay between metabolic syndrome, NAFLD, CVD, and CKD. In fact, all these conditions share similar risk factors (12). In recent years, extensive studies have focused on the existence of a link between NAFLD, CKD and CVD. Epidemiologic findings show that in NAFLD patients, the prevalence of CKD and CVD is significantly higher than the general population (13). The prevalence of CKD among NAFLD patients has a wide range from 4% to 40% (12). Therefore, many experts suggest that it is useful to explore the presence of NAFLD in CKD patients. In fact, NAFLD which is the hepatic manifestation of metabolic syndrome promotes inflammation and via this mechanism may have a role in worsening CKD and reduced renal function. The severity of NAFLD has been shown to have association with CKD stage (14). This evidence supports the possible shared pathogenic mechanisms between CKD and NAFLD.

The prevalence we observed here (20%) is lower than a previous report which noted the prevalence of NAFLD in hemodialysis patients as 58% (7). However, the mentioned study included only elderly patients older than 65 years. Plus, the definition of NAFLD was based on controlled attenuation parameter (CAP) obtained by transient elastography. In the current study, we applied ultrasound to diagnose NAFLD. The previous studies have used both ultrasound and elevated hepatic transaminases in the diagnosis of NAFLD. However, more than half of NAFLD patients may have normal hepatic transaminases (3). The most definite method to diagnose NAFLD is liver biopsy. However, we did not find any study to use biopsy-confirmed NAFLD among CKD patients. Most former studies have followed NAFLD patients to discover what percentage develop decreased kidney function over time. For instance, diabetic patients with ultrasound-defined NAFLD had higher prevalence of CKD than patients without evidence of steatosis (13). Higher prevalence of

microalbuminuria has also been reported in patients with impaired glucose tolerance and NAFLD diagnosed by ultrasound (15).

One of the important issues regarding NAFLD is the inflammatory state present in such patients. As observed here, a significantly higher number of patients in the NAFLD group had positive CRP test results. Inflammation plays an important role in morbidity and mortality of CKD patients and several physiologic, metabolic, and immunologic components contribute to the development of inflammation (7). It has been proposed that in NAFLD patients, inflammatory biomarkers are released more frequently, although production of inflammatory cytokines is more pronounced in NASH (7, 16).

According to the obtained findings, hypertension, abdominal (central) obesity, dyslipidemia, DM, and anemia were more common in the NAFLD group. Hypertension and DM are the two most highly suspected culprits indicated in the high prevalence of both CKD and metabolic syndrome. In the Framingham study, the prevalence of hypertension was reported as 65% in NAFLD, 60% in metabolic syndrome, 50% among diabetics, and 40% in obese patients (17). Insulin resistance precedes overt DM and is the cornerstone of metabolic syndrome. It has been shown that insulin resistance has a direct role in progression of fatty liver to NASH (18). Abdominal obesity was also another important finding which was significantly more common in NAFLD patients. Both insulin resistance and visceral obesity are in particular common among NAFLD and CKD patients (5). Our results demonstrate that in the presence of NAFLD, in addition to CKD, the frequencies of these conditions increase more dramatically.

Limitations

We faced some limitations in this study. Firstly, we used ultrasound to diagnose NAFLD and its severity. Ultrasound has been shown to be associated with considerable between and inter-observer variability to diagnose steatosis (19). Secondly, due to the nature of cross-sectional studies, it is not clear whether patients developed NAFLD after starting hemodialysis or not. We were not able to follow the patients to determine prognosis of patients with NAFLD and the role of abnormal laboratory derangements. Also, alcohol consumption was only determined subjectively and we did not have access to objective methods to determine alcohol intake by the studied patients.

Conclusion

NAFLD was observed in about one-fifth of ESRD patients who were receiving hemodialysis. The frequency of hypertension, abdominal obesity, and metabolic derangements were more common in NAFLD patients. More studies are required to examine the therapeutic effects of available modalities in managing NAFLD and to explore the effect of such interventions in the prognosis of CKD patients.

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