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Nonalcoholic steatohepatitis and increased risk of chronic kidney disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) share common features. Both are associated with visceral obesity, type 2 diabetes mellitus, metabolic syndrome, and insulin resistance. However, the relationship between NAFLD and CKD is poorly understood. We examined the prevalence of and risk factors for CKD in patients with NAFLD. We analyzed 174 Japanese patients with liver biopsy–proven NAFLD using a cross-sectional design. Chronic kidney disease was defined as estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2 and/or overt proteinuria. Of 174 NAFLD patients, 92 (53%) exhibited histologic characteristics of nonalcoholic steatohepatitis (NASH), the progressive form of NAFLD; and 82 (47%) had non-NASH NAFLD. Chronic kidney disease was present in 24 (14%) of 174 NAFLD patients. The prevalence of CKD was significantly higher in NASH patients (19 of 92; 21%) than non-NASH patients (5 of 82; 6%). The presence of CKD was associated with a higher body mass index and the presence of hypertension and NASH. Our results demonstrated a high prevalence of CKD among patients with NASH.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease. The incidence of NAFLD continues to increase, and the prevalence of NAFLD ranges from 17% to 33% in the general population of Western countries [1]. The spectrum of NAFLD ranges from a relatively benign accumulation of lipid (simple steatosis) to progressive nonalcoholic steatohepatitis (NASH) associated with fibrosis, necrosis, and inflammation [2-4]. Nonalcoholic steatohepatitis can progress to cirrhosis and hepatocellular carcinoma.

Chronic kidney disease (CKD) encompasses a spectrum of different processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). The prevalence of CKD in American adults was estimated to be 11% (19.2 million) [5]. Chronic kidney disease is increasingly recognized as a major risk factor for not only end-stage renal failure but also cardiovascular disease [6,7].

Nonalcoholic fatty liver disease and CKD share some common features, including visceral obesity, type 2 diabetes mellitus, hypertension, and metabolic syndrome [8-11]. Both diseases are also linked to an increased risk of cardiovascular disease [6,7,11]. Common factors underlying the pathogenesis of NAFLD and CKD include insulin resistance, oxidative stress, activation of the renin-angiotensin system, and inappropriate secretion of inflammatory cytokines [12,13]. However, the relationship between NAFLD and CKD is poorly understood; and the prevalence of and risk factors for CKD in patients with NAFLD remain unknown.

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Whereas laboratory test abnormalities and ultrasound or radiographic findings may be suggestive of NAFLD, histologic evaluation remains the only means of accurately assessing the degree of steatosis and the distinct necroinflammatory lesions and fibrosis of NASH; and it remains the only means of distinguishing NASH from simple steatosis [14]. In the present study, we therefore examined the association between liver biopsy–proven NAFLD and CKD using a cross-sectional design; and we investigated the risk factors associated with CKD in patients with NAFLD.

2. Methods

2.1. Patients

The study included a total of 174 Japanese patients with NAFLD who underwent liver biopsy between 2001 and 2009 at the Hospital of Kyoto Prefectural University of Medicine (Kyoto, Japan) and Nara City Hospital (Nara, Japan). The diagnosis of NAFLD was based on a liver biopsy showing steatosis in more than 5% of hepatocytes, along with exclusion of liver diseases of other etiology. Patients had to be older than 18 years. Exclusion criteria were as follows: patients consuming more than 20 g of alcohol per day; positive for hepatitis B virus surface antigen; positive for anti–hepatitis C virus antibody; other types of liver diseases, including primary biliary cirrhosis, autoimmune hepatitis, Wilson disease, or hemochromatosis; treated with drugs known to produce hepatic steatosis, including corticosteroids, high-dose estrogen, methotrexate, or amiodarone within 6 months of enrollment; and a history of gastrointestinal bypass surgery.

The Ethics Committees of the Kyoto Prefectural University of Medicine and Nara City Hospital approved this study. Informed consent was obtained from each patient in accordance with the Declaration of Helsinki.

2.2. Clinical assessment and laboratory tests

Body mass index (BMI) was calculated using the following formula: weight in kilograms/(height in meters)^2. *Obesity* was defined as a BMI of at least 25 according to the criteria of the Japan Society for the Study of Obesity [15]. Diabetes was defined as a fasting plasma glucose concentration of at least 126 mg/dL or a 2-hour plasma glucose concentration of at least 200 mg/dL during an oral glucose (75 g) tolerance test or the use of insulin or oral hypoglycemic agents to control blood glucose [16,17]. Hypertension was defined as a systolic blood pressure of at least 130 mm Hg, a diastolic blood pressure of at least 85 mm Hg, or the use of antihypertensive agents [18]. Dyslipidemia was defined as serum concentrations of triglycerides of at least 150 mg/dL or high-density lipoprotein (HDL) cholesterol less than 40 mg/dL and less than 50 mg/dL for men and women, respectively, or the use of specific medication [18].

Venous blood samples were taken in the morning after a 12-hour overnight fast. The laboratory evaluation included a blood cell count and the measurement of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (γ-GTP), albumin, creatinine, total cholesterol, HDL cholesterol, triglyceride, and fasting plasma glucose. These parameters were measured using standard clinical chemistry techniques. Proteinuria was detected by dipstick examination. These clinical and laboratory data were collected at the time of liver biopsy.

Kidney function was estimated using the Japanese equation, which defines the estimated glomerular filtration rate (eGFR) as follows: eGFR = 194 × (serum creatinine$^{-1.094}$) × (age$^{-0.287}$) × 0.739 (if female) [19]. Chronic kidney disease was defined as eGFR less than 60 mL/min per 1.73 m^2 and/or overt proteinuria [20]. Both of these outcome measures had to be confirmed in a least 2 consecutive tests. Stage of CKD was defined according to the criteria proposed by the National Kidney Foundation [21].

2.3. Histopathologic examination

Liver biopsy specimens were obtained percutaneously from all patients for diagnostic purposes. The specimens were fixed in formalin, embedded in paraffin, and stained with hematoxylin and eosin, with Masson trichrome, and by silver impregnation. The sections were analyzed by experienced hepatopathologists (TO and YS) who were blinded to the laboratory parameters and clinical data. Patients with biopsy-established NAFLD were categorized as NASH or non-NASH [2,22]. Nonalcoholic steatohepatitis was defined as steatosis with lobular inflammation, hepatocellular ballooning, and Mallory hyaline (Mallory body) or fibrosis [2,14,23,24]. Patients whose liver biopsy specimens showed simple steatosis or steatosis with nonspecific inflammation were identified as having non-NASH NAFLD. The degree of fibrosis in NASH was evaluated and scored according to the criteria proposed by Brunt et al [24].

2.4. Statistical analysis

Results are presented as numbers with percentages in parenthesis for qualitative data or as the medians and ranges for quantitative data. Univariate comparisons were made using a χ^2 test for qualitative factors or a Mann-Whitney *U* test on ranks for quantitative factors with nonequal variance. Logistic regression analysis was used for multivariate analysis. *P* values < .05 from 2-sided tests were considered to be significant. Variables that achieved statistical significance on univariate analysis were entered into multiple logistic regression analysis to identify significant independent factors. All statistical analyses were performed using SPSS 15.0 software (SPSS, Chicago, IL).

Table 1
Patient characteristics

Characteristic	Total (n = 174)	NASH (n = 92)	Non-NASH (n = 82)	*P*
Age (y)	54 (18-78)	62 (24-78)	49 (18-78)	<.001
Sex				.009
Male	102 (59%)	45 (49%)	57 (70%)	
Female	72 (41%)	47 (51%)	25 (30%)	
BMI (kg/m^2)	26.2 (18.6-43.4)	26.5 (19.1-39.4)	25.2 (18.6-43.4)	.02
Obesity	106 (61%)	61 (66%)	45 (55%)	.16
Diabetes	53 (31%)	33 (36%)	20 (24%)	.14
Dyslipidemia	84 (48%)	44 (48%)	40 (49%)	1.00
Hypertension	59 (34%)	39 (42%)	20 (24%)	.02
Platelet count (×10^4/μL)	21.8 (4.6-37.3)	18.9 (4.6-35.1)	24.2 (12.3-37.3)	<.001
AST (IU/L)	49 (10-447)	61 (10-447)	39 (16-151)	<.001
ALT (IU/L)	77 (12-358)	79 (16-316)	75 (12-358)	.14
γ-GTP (IU/L)	73 (19-1681)	76 (19-1681)	69 (19-568)	.59
Albumin (g/dL)	4.6 (2.9-5.5)	4.5 (2.9-5.2)	4.8 (4.0-5.5)	<.001
Fasting glucose (mg/dL)	102 (65-452)	103 (65-452)	99 (76-333)	.17
Total cholesterol (mg/dL)	202 (52-344)	192 (52-288)	217 (99-344)	.003
HDL cholesterol (mg/dL)	47 (25-79)	46 (25-79)	49 (35-77)	.12
Triglyceride (mg/dL)	136 (35-1454)	131 (42-1454)	139 (35-410)	.56
eGFR (mL/[min 1.73 m^2])	82.3 (46.5-161.8)	82.1 (46.5-161.8)	82.7 (53.8-137.9)	.18
Proteinuria	17 (10%)	12 (13%)	5 (6%)	.14
CKD	24 (14%)	19 (21%)	5 (6%)	.007
Stage[a]				.07
1	7 (4%)	6 (7%)	1 (1%)	
2	9 (5%)	5 (5%)	4 (5%)	
3	8 (5%)	8 (9%)	0 (0%)	
4	0 (0%)	0 (0%)	0 (0%)	
5	0 (0%)	0 (0%)	0 (0%)	

Values are median (range) or number (percentage). Where no other unit is specified, values refer to number of patients. All patients were of Japanese ethnicity.
[a] According to Levey et al [20].

3. Results

The characteristics of the 174 NAFLD patients included in the study are summarized in Table 1. Of these 174 NAFLD patients, 92 (53%) exhibited histologic characteristics of NASH; and 82 (47%) had non-NASH NAFLD. Five patients had liver cirrhosis (fibrosis stage 4). Patients with NASH, as compared with patients with non-NASH NAFLD, were significantly older, were more often female, had a higher BMI, more often had hypertension, had a higher AST, and had lower platelet count, albumin, and total cholesterol (Table 1).

Chronic kidney disease was present in 24 patients (14%), including 7 (4%) with stage 1, 9 (5%) with stage 2, and 8 (5%) with stage 3. The prevalence of CKD was significantly higher in patients with NASH (19 of 92; 21%) than in those with non-NASH NAFLD (5 of 82; 6%) (Table 1). Patients with NASH tended to have a more advanced stage of CKD than patients with non-NASH NAFLD, although the difference was not statistically significant (Table 1).

We evaluated the relationship between eGFR values and the histologic severity of NASH (fibrosis stage). The median (range) of eGFR values in NASH patients with fibrosis stage 1 (n = 37), 2 (n = 24), 3 (n = 26), and 4 (n = 5) was 79.4 (46.5-122.8), 82.2 (57.0-161.8), 83.8 (48.4-144.1), and 85.0 (66.5-97.6) mL/min per 1.73 m^2, respectively. The correlation between eGFR values and the fibrosis stage was not significant (P = .47).

Univariate correlations between variables and CKD are shown in Table 2. The presence of CKD was associated with a higher BMI and the presence of hypertension and NASH; but it was not associated with age, sex, the presence of diabetes or dyslipidemia, or levels of AST, ALT, or γ-GTP. Multivariate analysis revealed that the presence of hypertension correlated independently with the presence of CKD (Table 3).

Table 2
Univariate analysis of factors associated with CKD in NAFLD patients

Factor	No CKD (n = 150)	CKD (n = 24)	*P*
Age (y)	55 (18-78)	54 (31-78)	.19
Male	89 (59%)	13 (54%)	.66
BMI (kg/m^2)	25.6 (18.6-43.4)	28.3 (21.1-35.1)	.003
Diabetes	42 (28%)	11 (46%)	.10
Dyslipidemia	72 (48%)	12 (50%)	1.00
Hypertension	43 (29%)	16 (67%)	.001
AST (IU/L)	50 (10-210)	45 (21-447)	.82
ALT (IU/L)	78 (12-358)	65 (18-254)	.45
γ-GTP (IU/L)	77 (19-568)	72 (29-1681)	.87
NASH	73 (49%)	19 (79%)	.007

Values are median (range) or number (percentage). Where no other unit is specified, values refer to number of patients.

Table 3
Multivariate analysis of factors independently associated with CKD in NAFLD patients

Factor	Odds ratio	95% Confidence interval	*P*
BMI (kg/m^2)	1.09	0.98-1.21	.11
Hypertension	3.90	1.42-10.71	.008
NASH	2.46	0.82-7.42	.11

Data are from a total of 174 patients.

4. Discussion

Our results demonstrated a high prevalence (21%) of CKD among patients with NASH. The prevalence of CKD was significantly higher in NASH than in non-NASH NAFLD.

It is important to identify factors that increase the risk for CKD, even in individuals with normal GFR. In general, known risk factors include hypertension, diabetes, autoimmune disease, older age, African ancestry, a family history of renal disease, a previous episode of acute renal failure, or structural abnormalities of the urinary tract [25]. Our results showed that the risk factors associated with CKD in NAFLD patients include obesity (higher BMI), hypertension, and NASH. In particular, hypertension was an independent risk factor for CKD.

Nonalcoholic fatty liver disease is closely associated with obesity, hypertension, dyslipidemia, and type 2 diabetes mellitus, which are all features of the metabolic syndrome. This strongly supports the idea that NAFLD is the hepatic manifestation of the metabolic syndrome [8]. The presence of insulin resistance is recognized as the pathophysiologic hallmark of NAFLD. A recent study show that NAFLD is more prevalent in nondipper hypertensive patients than dipper hypertensive patients, and a high prevalence of NAFLD is associated with insulin resistance and low adiponectin in the nondippers [26]. Similarly, growing evidence suggests that the metabolic syndrome is an important factor in the pathogenesis of CKD [27]; and there is a positive relationship between insulin resistance and CKD [10].

Relatively few studies have evaluated NAFLD and the risk of CKD. Recent studies found that NAFLD is associated with an increasing incidence of CKD in type 2 diabetes mellitus patients [28] and in nonhypertensive and nondiabetic Korean men [29]. Although these findings are important, their interpretation is limited by the fact that the diagnosis of NAFLD was based on liver ultrasound imaging. Whereas ultrasound is the commonly used for diagnosing NAFLD in clinical practice, it cannot distinguish NASH from simple steatosis. Histologic evaluation remains the only means of diagnosing NASH. To our knowledge, our current study is the first to assess the association between NASH and CKD.

A recent report showed a positive relationship between microalbuminuria and liver fibrosis in nondiabetic patients with NAFLD [30]. In this study, however, we did not find an association between eGFR values and the degree of liver fibrosis in NASH patients. The association of liver fibrosis with low eGFR or proteinuria remains to be verified in future prospective studies using a larger number of samples.

The underlying mechanisms by which NASH increases the risk for CKD remain to be elucidated. It may simply reflect the coexistence of underlying known risk factors. Alternatively, NASH may be a stimulus for further increases in whole-body insulin resistance, leading to the development of CKD. Another possible underlying mechanism is increased oxidative stress and chronic subclinical inflammation. The possible mediators linking NASH and CKD include reactive oxygen species, tumor necrosis factor–α, and other proinflammatory cytokines [11,31].

Certain limitations should be considered in the interpretation of our findings. First, the cross-sectional study design hinders the ability to draw inferences regarding causality between NASH and CKD. Second, an eGFR was used rather than more precise measures to identify and classify kidney disease. However, equations that estimate GFR for the evaluation of renal function are recommended for epidemiological studies and for clinical practice [20]. Third, the dipstick urinalysis has a lower sensitivity and specificity in the diagnosis of proteinuria than 24-hour urine collection or measurement of the albumin-to-creatinine ratio in a random spot collection. Nevertheless, in most cases, screening with urine dipsticks is considered acceptable for detecting proteinuria [21]. Fourth, this was a hospital-based study and therefore may be influenced by selection bias. Finally, the study did not include a control group of nonsteatotic subjects.

In summary, this study shows that it is important to assess the risk of CKD in NASH/NAFLD patients. In addition, our findings suggest that preventing and treating obesity, hypertension, and NASH may help prevent NAFLD patients from developing CKD. Moreover, our results suggest that a higher BMI and the presence of hypertension and NASH are associated with an increasing prevalence of CKD in NALFD patients. Further prospective studies are warranted to establish the causal relationship between NASH and CKD.

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