Original Article

# Non-alcoholic Fatty Liver Disease and Chronic Kidney Disease in Koreans Aged 50 Years or Older

Ah-Leum Ahn, Jae-Kyung Choi*, Mi-Na Kim, Seun-Ah Kim, Eun-Jung Oh, Hyuk-Jung Kweon, Dong-Yung Cho

Department of Family Medicine, Konkuk University School of Medicine, Seoul, Korea

**Background:** Non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) share common pathogenic mechanisms and many risk factors, and both are linked to an increased risk of cardiovascular diseases. The aim of this study was to assess the association between NAFLD and CKD according to the presence of hypertension and diabetes mellitus in Koreans aged 50 years or older.

**Methods:** A cross-sectional study of 1,706 subjects who received their routine health examination was conducted between May 2008 and April 2010 at Konkuk University medical center. Biochemical tests for liver and abdominal ultrasonography were performed. CKD was defined as either proteinuria or glomerular filtration rate ≤60 mL/min per 1.73 $m^2$.

**Results:** Among the 1,706 subjects, There were 545 (31.9%) with non-alcoholic fatty liver disease and 424 (24.9%) with chronic kidney disease. In univariate logistic regression analysis, NAFLD was significantly associated with CKD (odds ratio [OR], 1.69; 95% confidence interval [CI], 1.34 to 2.12). In multivariate logistic regression analysis adjusted for age, sex, current smoking, abdominal obesity, aspartate aminotransferases, alanine aminotransferases, γ-glutamyltransferase, hypertension, diabetes mellitus, hypertriglyceridemia, and low high-density lipoprotein cholesterol, NAFLD was associated with CKD (adjusted OR, 1.68; 95% CI, 1.27 to 2.24). This relationship remained significant after classification according to the presence of hypertension or diabetes mellitus.

**Conclusion:** NAFLD diagnosed by ultrasonography was significantly associated with CKD in Koreans aged 50 years or older.

**Keywords:** Non-alcoholic Fatty Liver Disease; Chronic Renal Insufficiency; Ultrasonography; Glomerular Filtration Rate; Proteinuria

## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as fat accumulation in the liver exceeding 5% to 10% by weight and refers to a spectrum of diseases ranging from simple steatosis to steatohepatitis and cirrhosis.[1,2] The pathological picture resembles that of alcohol-induced liver injury, but it occurs in patients who do not abuse alcohol.[3] NAFLD has emerged as a growing public health problem worldwide and is the most common cause of chronic liver disease in Western countries.[2,4]

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*Corresponding Author: Jae-Kyung Choi
Tel: +82-2-2030-7683, Fax: +82-2-2030-7748
E-mail: cjk@kuh.ac.kr

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The prevalence of NAFLD in Korea is approximately 10% to 25%.[5] NAFLD is associated with comorbidities, such as obesity, diabetes, hypertension, and atherogenic dyslipidemia, and it is now regarded as the hepatic manifestation of the metabolic syndrome.[6]

Chronic kidney disease (CKD) is defined as a sustained reduction in glomerular filtration rate (GFR) or evidence of structural or functional abnormalities of the kidneys based on urinalysis, biopsy, or imaging.[7-9] CKD is a worldwide health problem that results in high morbidity and mortality. Recent data from the Unites States population-based third National Health and Nutrition Examination Survey reported that the prevalence of CKD in the United States is approximately 13%.[8,9] CKD has many potential causes. Older age, hypertension, diabetes, obesity, and dyslipidemia are consistently associated with CKD.[7,8]

NAFLD and CKD share common pathogenic mechanisms and many cardiometabolic risk factors, and both are linked to an increased risk of cardiovascular disease events.[2,7] It is possible that NAFLD not only is a marker of CKD but also may play a part in the pathogenesis of CKD, possibly through the systemic release of several pro-inflammatory/pro-coagulant mediators from the steatotic/inflamed liver or through the contribution of NAFLD itself to insulin resistance and atherogenic dyslipidemia. Moreover, the presence of pathophysiological inter-relationships between the liver and the kidney is well established in humans, and is supported by the presence of hepato-renal syndrome, which may occur in patients with decompensated cirrhosis, regardless of its aetiology.[4] But there are sparse data on the relationship between NAFLD and CKD risk in apparently healthy persons. Some studies suggest that ultrasound-diagnosed NAFLD is associated, independently of several confounding factors, with a higher prevalence of CKD and retinopathy in type 1 diabetic individuals.[10] Also, NAFLD was associated with an increased CKD risk among nondiabetic, nonhypertensive Korean men.[11] However, there are few studies on the relationship between NAFLD and CKD according to the presence of hypertension and diabetes mellitus. The aim of this study was to assess the association between NAFLD and CKD according to the presence of hypertension and diabetes mellitus in Koreans aged 50 years or older.

## METHODS

### 1. Study Subjects

The subjects 50 years and older were enrolled in our study because kidney diseases in older people, especially menopausal women, have generally been shown to be related with the sex hormones through the renin-angiotensin-aldosterone system.[12] A total of 3,011 subjects received their routine health examination between May 2008 and April 2010 at Konkuk University medical center. The following subjects were excluded: 1) those (n = 1,070) who had alcohol intake >30 g/d (male), >20 g/d (female);[13,14] 2) those (n = 97) who had a positive serologic finding for either hepatitis B or C virus;[15] 3) those (n = 69) who had abnormal liver ultrasound findings indicating diffuse or local liver disease;[16] 4) those (n = 26) who had aspartate aminotransferases (AST)/alanine aminotransferases (ALT) ≥ 80 IU/L;[15,17,18] 5) those (n = 43) who had missing data from information on their liver ultrasound findings or medical histories. Because some individuals were excluded for multiple reasons, the total number of subjects in our study was 1,706.

### 2. Clinical Measurements and Laboratory Procedures

The health examination included a medical history, physical examination, questionnaire on health-related behavior, and anthropometric and biochemical measurements. The medical history and history of prescription drug use were assessed by the examining physicians. Trained nurses measured the height and weight using a calibrated stadiometer. Information on history of alcohol intake and smoking status was obtained from all subjects by questionnaire. Body mass index was calculated by dividing weight in kilograms by height in meters squared. Blood pressure (BP) was measured with a standard mercury manometer. Waist circumference was measured at the umbilicus level.

Venous blood was drawn in the morning after an overnight fast. Serum levels of fasting glucose, total cholesterol, triglyceride, low density lipoprotein cholesterol, high density lipoprotein (HDL) cholesterol, γ-glutamyltransferase (GGT), AST, and ALT were measured using the TBA-200FR NEO (Toshiba, Tokyo, Japan). Insulin resistance was assessed with the homeostasis model assessment of insulin resistance: fasting blood insulin (in microunits per milliliter) × fasting blood glucose (in millimoles

per liter) / 22.5. Serum creatinine was measured by means of the alkaline picrate (Jaffe) method. We used the Modification of Diet in Renal Disease equation to calculate the estimated glomerular filtration rate from serum creatinine in mL/min/1.73 $m^2$.[8]

Urine protein was determined at each examination by the single urine dipstick semiquantitative analysis (Clinitek Atlas; Siemens Healthcare Diagnostics, Eschborn, Germany). Dipstick urinalysis was performed on fresh midstream urine samples collected in the morning. The amount of urine protein was reported on a 6-grade scale, absent, trace, 1+, 2+, 3+, and 4+, which corresponded to protein levels of approximately undetectable, 10, 30, 100, 300, and 1,000 mg/dL, respectively. CKD was defined as either proteinuria or GFR ≤ 60 mL/min per 1.73 $m^2$.[7,8]

**Table 1.** General characteristics of the study participants according to nonalcoholic fatty liver disease

| Characteristic | Non-NAFLD (n = 1,161) | NAFLD (n = 545) | P-value |
|---|---|---|---|
| Male | 586 (50.5) | 352 (64.6) | <0.001 |
| Age (y) | 57.5 ± 6.8 | 58.8 ± 7.0 | 0.29 |
| Waist circumference (cm) | 81.8 ± 7.7 | 88.9 ± 7.2 | 0.03 |
| Abdominal obesity | 392 (33.8) | 333 (61.1) | <0.001 |
| Body mass index (kg/$m^2$) | 23.1 ± 2.6 | 25.4 ± 2.6 | 0.88 |
| Current smoking | 171 (15.3) | 94 (17.7) | 0.22 |
| Systolic blood pressure (mm Hg) | 121.3 ± 14.5 | 125.4 ± 12.2 | 0.02 |
| Diastolic blood pressure (mm Hg) | 79.9 ± 10.7 | 82.5 ± 10.1 | 0.08 |
| Hypertension | 380 (32.7) | 268 (49.2) | <0.001 |
| Hemoglobin A1c (%) | 5.6 ± 0.6 | 6.0 ± 1.0 | <0.001 |
| Fasting glucose (mg/dL) | 92.0 ± 18.6 | 100.9 ± 27.2 | <0.001 |
| Fasting insulin (mg/dL) | 4.9 ± 5.7 | 7.1 ± 4.1 | 0.04 |
| HOMA-IR | 1.2 ± 2.4 | 1.8 ± 1.1 | 0.33 |
| Diabetes mellitus | 67 (5.8) | 93 (17.1) | <0.001 |
| Total cholesterol (mg/dL) | 202.2 ± 33.9 | 210.2 ± 37.0 | 0.17 |
| Triglyceride (mg/dL) | 115.9 ± 70.1 | 165.5 ± 88.3 | <0.001 |
| High density lipoprotein (mg/dL) | 57.5 ± 14.0 | 51.2 ± 11.5 | <0.001 |
| Low density lipoprotein (mg/dL) | 123.7 ± 28.7 | 131.3 ± 31.0 | 0.12 |
| Hypertriglyceridemia | 245 (21.1) | 261 (47.9) | <0.001 |
| Low high density lipoprotein | 189 (16.3) | 132 (24.2) | <0.001 |
| Metabolic syndrome | 205 (17.7) | 249 (45.7) | <0.001 |
| Aspartate aminotransferase (IU/L) | 26.2 ± 7.4 | 29.5 ± 8.6 | <0.001 |
| Alanine aminotransferase (IU/L) | 23.4 ± 9.9 | 33.6 ± 14.2 | <0.001 |
| Alkaline phosphatase (IU/L) | 76.5 ± 23.5 | 77.9 ± 20.6 | 0.04 |
| γ-Glutamyltransferase (IU/L) | 31.1 ± 29.1 | 43.3 ± 32.4 | <0.001 |
| Creatinine (mg/dL) | 1.1 ± 0.2 | 1.1 ± 0.2 | 0.19 |
| Glomerular fitration rate (mL/min per 1.73 $m^2$) | 65.6 ± 7.8 | 65.1 ± 8.3 | 0.15 |
| Chronic kidney disease | 251 (21.6) | 173 (31.7) | <0.001 |

Values are presented as mean ± SD or number (%) as assessed by t-test and chi-square test.
NAFLD: nonalcoholic fatty liver disease, HOMA-IR: homeostasis model assessment of insulin resistance.

Hepatic ultrasonography scanning was performed in all subjects by an experienced radiologist, who was blinded to subject details and laboratory value, and was unaware of the aims of the study. The diagnosis of fatty liver was based on the results of abdominal ultrasound with a 3.5 MHz transducer (Logic Q700 MR; GE, Milwaukee, WI, USA). Of the 4 known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring), participants were required to have hepatorenal contrast and liver brightness in order to be diagnosed with fatty liver.

The Adult Treatment Panel III proposed the following 5 abnormalities to define metabolic syndrome:[19] 1) abdominal obesity, male ≥90 cm, female ≥80 cm; 2) high fasting glucose ≥ 100 mg/dL; 3) hypertriglyceridemia ≥150 mg/dL; 4) low HDL, male ≤40 mg/dL, female ≤50 mg/dL; 5) high BP ≥130/85 mm Hg. Subjects with 3 or more of the above 5 abnormalities were considered to have metabolic syndrome.

### 3. Statistical Analysis

Statistical analysis was performed with the windows SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). Statistical analyses included the t-test and the chi-square test. Logistic regression analysis was used to assess the independent association of CKD with NAFLD after adjustment for potential confounders. We also performed multivariate logistic regression analysis. In the multivariate models, we included the following variables that might confound the relationship between NAFLD and CKD: age, sex, current smoking, abdominal obesity, AST, ALT, GGT, hypertension, diabetes mellitus, hypertriglyceridemia, and low HDL.[4,7] Values at $P < 0.05$ were considered to be statistically significant.

## RESULTS

Our study included 1,706 subjects aged 50 to 86 years. Among the 1,706 subjects, the frequency of NAFLD and CKD was 545 (31.9%) and 424 (24.9%), respectively. The clinical characteristics stratified by the presence of NAFLD are shown in Table 1. The subjects with NAFLD were abdominally obese, more likely to be male and had higher frequency of hypertension, diabetes mellitus, CKD, and metabolic syndrome than those without NAFLD. They also had lower HDL, higher hemoglobin A1c, fasting glucose, fasting insulin, triglyceride, and liver enzymes than those without NAFLD.

Table 2 shows the association between NAFLD and CKD in univariate and multivariate models. In univariate logistic regression analysis, NAFLD was significantly associated with CKD (odds ratio [OR], 1.69; 95% confidence interval [CI], 1.34 to 2.12). Age, abdominal obesity hypertension, and diabetes mellitus were also significantly associated with CKD. In multivariate logistic regression analysis after adjustment for age, sex, current smoking, abdominal obesity, AST, ALT, GGT, hypertension, diabetes mellitus, hypertriglyceridemia, and low HDL, NAFLD was significantly associated with CKD (OR, 1.68; 95% CI, 1.27 to 2.24). This relationship remained significant after classification according to the presence of hypertension or diabetes mellitus (Table 3).

**Table 2.** Univariate and multivariate logistic regression analyses of the presence of chronic kidney disease

| Variable | Univariate | Multivariate |
|---|---|---|
| Sex (male) | 1.12 (0.90–1.40) | 1.09 (0.83–1.44) |
| Age (y) | 1.10 (1.08–1.12) | 1.09 (1.07–1.11) |
| Current smoking | 1.19 (0.87–1.63) | 1.01 (0.78–1.43) |
| Abdominal obesity | 1.48 (1.19–1.85) | 1.03 (0.79–1.34) |
| AST (IU/L) | 1.01 (1.00–1.03) | 1.02 (1.00–1.04) |
| ALT (IU/L) | 1.00 (0.99–1.01) | 0.99 (0.97–1.00) |
| GGT (IU/L) | 1.00 (0.99–1.00) | 1.00 (1.00–1.01) |
| Hypertension | 1.70 (1.36–2.12) | 1.50 (1.17–1.92) |
| Diabetes mellitus | 1.58 (1.25–2.01) | 1.16 (0.79–1.72) |
| Hypertriglyceridemia* | 1.05 (0.83–1.33) | 0.82 (0.62–1.09) |
| Low HDL† | 1.25 (0.95–1.64) | 1.08 (0.79–1.49) |
| NAFLD | 1.69 (1.34–2.12) | 1.68 (1.27–2.24) |

Values are presented as odds ratio ± 95% confidence intervals as assessed by univariate or multivariate logistic regression analysis. Multivariatic models adjusted for age, sex, current smoking, abdominal obesity, AST, ALT, GGT, hypertension, diabetes mellitus, hypertriglyceridemia, and low HDL.
AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ-glutamyltransferase, HDL: high density lipoprotein, NAFLD: nonalcoholic fatty liver disease.
*Serum triglyceride ≥150 mg/dL. †Serum HDL: male ≤40 mg/dL, female ≤50 mg/dL.

**Table 3.** Odds ratios of nonalcoholic fatty liver disease for chronic kidney disease according to hypertension and DM

| | Total (n = 1,706) | No hypertension and no DM (n = 987) | Hypertension or DM (n = 719) |
|---|---|---|---|
| Crude | 1.69 (0.34–2.12) | 1.41 (1.00–2.01) | 1.60 (1.16–2.19) |
| Age and sex-adjusted | 1.59 (1.25–2.02) | 1.29 (0.89–1.87) | 1.64 (1.18–2.27) |
| Multivariate adjusted* | 1.68 (1.27–2.24) | 1.59 (1.03–2.44) | 1.72 (1.17–2.53) |

Values are presented as odds ratio ± 95% confidence intervals as assessed by multivariate logistic regression analysis.
DM: diabetes mellitus.
*Adjusted for age, sex, current smoking, abdominal obesity, aspartate aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, hypertriglyceridemia, and low high density lipoprotein.

## DISCUSSION

The major finding of our study was that NAFLD is significantly associated with CKD in Koreans aged 50 years or older. After adjusting for confounding risk factors and potential confounders, such as age, sex, current smoking, abdominal obesity, AST, ALT, GGT, hypertension, diabetes mellitus, hypertriglyceridemia, and low HDL, the association between NAFLD and CKD remained statistically significant.

Recent large observational studies reported that the presence of NAFLD as detected by serum liver enzyme is strongly associated with an increased prevalence and incidence of CKD.[20-22] Several studies showed that NAFLD diagnosed by liver ultrasonography was associated with an increased prevalence of CKD in both nondiabetic and diabetic individuals.[10,23,24] A previous study showed that NAFLD was associated with an increased CKD risk in nonhypertensive and nondiabetic Korean men.[11] However, the population in this study included only nonhypertensive and nondiabetic young men whose mean age was 36.7 years.

Understanding the mechanisms that link NAFLD and CKD is important not only because of the societal health burden of both diseases but also because novel insights into the underlying mechanisms may lead to new strategies to prevent or treat CKD and its associated co-morbidities. However, the underlying mechanisms putatively responsible for the association between NAFLD and CKD are not fully understood. The putative underlying mechanisms that link NAFLD and CKD might originate from expanded and inflamed visceral adipose tissue. Expanded and inflamed visceral adipose tissue releases multiple molecules that are potentially involved in the development of insulin resistance and kidney damage.[25] Insulin resistance is a key factor in the pathogenesis of NAFLD[2,26] and also plays a role in the development of CKD.[27] There is evidence to suggesting that NAFLD may be involved in its pathogenesis, possibly through the systemic release of pathogenic mediators from the steatotic and inflamed liver, including increased reactive oxygen species, advanced glycation end products, C-reactive protein, plasminogen activator inhibitor-1, tumor necrosis factor-alpha, transforming growth factor-beta, and other proinflammatory cytokines,[28] Notably, several case control studies have shown that these plasma inflammatory, pro-coagulant, and oxidative stress factors are remarkably higher in patients with NAFLD than in those without those conditions.[29,30]

Our study has several limitations. First, the cross-sectional study design precludes the establishment of a causal relationship between NAFLD and CKD. Prospective studies will be required to sort out the time sequence of events. Second, the diagnosis of NAFLD was based on ultrasound imaging and the exclusion of other secondary causes of chronic liver disease, but was not confirmed by liver biopsy. It is known that none of the radiological features can distinguish between nonalcoholic steatohepatitis and other forms of NAFLD, and that only liver biopsy can assess the severity of damage and the prognosis.[1,2] However, liver biopsy would be impossible to perform in routine health examinations. Moreover, liver ultrasound is the most widely used non-invasive technique to detect fatty infiltration of the liver in clinical practice.[1,2] Third, patients with a positive result on a disptick test for proteinuria (1+ or greater) were recommended to undergo confirmation of proteinuria by measuring the albumin creatinine ratio by an untimed urine sample within 3 months,[7,8] however, our study subjects with a positive proteinuria result had no further testing, which could have resulted in misclassification. Finally, our study subjects were selected from a population undergoing general health examination at a university medical center. Thus,

our study may have potential selection bias and it should be noted that the results may not truly represent the general population.

In conclusion, our findings showed that NAFLD diagnosed by ultrasonography was significantly associated with CKD in Koreans aged 50 years or older. These findings are sufficiently provocative to warrant further study. Further experimental studies are needed to define the mechanisms that link NAFLD and CKD. Moreover, prospective studies could determine whether NAFLD actually predicts the development or progression of CKD.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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