Research Article

EASL JOURNAL OF HEPATOLOGY

Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: A cohort study

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Background & Aims: Non-alcoholic fatty liver disease (NAFLD) has been associated with chronic kidney disease (CKD), but cohort studies are limited. We investigated the longitudinal association of NAFLD and its severity with the development of CKD.

Methods: We performed a retrospective cohort study of 41,430 adult men and women (average age, 48.9 y) without CKD at baseline who underwent repeated health check-up examinations from January 1, 2003, through December 31, 2013. NAFLD status was assessed by ultrasonography, and NAFLD severity was assessed by the NAFLD fibrosis score (NFS).

Results: The outcome was an incident CKD, defined as an estimated glomerular filtration rate less than 60 ml/min/1.73 m^2. During 200,790 person-years of follow-up (median follow-up of 4.15 years), we identified 691 incident CKD cases. The multivariable-adjusted hazard ratio for CKD comparing participants with and without NAFLD was 1.22 (95% confidence interval [CI] 1.04–1.43). The risk of CKD increased progressively with increased NAFLD severity. The multivariable-adjusted hazard ratios for CKD comparing participants with NFS <−1.455 and those with NFS ≥−1.455 to participants without NAFLD were 1.09 (95% CI 0.91–1.32) and 1.58 (95% CI 1.30–1.92), respectively. The association was consistent across clinically relevant subgroups.

Conclusion: In a large cohort of adult men and women without CKD, NAFLD was associated with an increased risk of CKD development. NAFLD may adversely affect renal function and patients may need to be carefully monitored for an increased risk of CKD.

Lay summary: The presence of fatty liver is associated with the future decline of renal function. Thus, fatty liver patients need to be monitored regularly for renal function.

Introduction

Chronic kidney disease (CKD) is an important cause of death and loss of disability-adjusted life-years.[1,2] The burden of CKD is rising worldwide, and it has become a major public health issue.[1] Identifying causes and risk factors for CKD is of paramount importance to reduce the global burden of CKD.

Non-alcoholic fatty liver disease (NAFLD), is characterized by fat infiltration of the liver in the absence of significant alcohol intake, use of medications, or medical conditions that cause fatty liver.[3] It is a major cause of liver disease with a very high prevalence worldwide.[4] There is growing evidence that NAFLD is a multisystem disease, affecting extra-hepatic organs, including the kidney.[5–9] In a meta-analysis of 33 studies (63,902 participants), the prevalence and severity of NAFLD was associated with an increased risk of CKD,[10] but there was a paucity of longitudinal follow-up data. To date, only three cohort studies with reasonably long follow-up have assessed the risk of incident CKD according to NAFLD status,[11–13] but two of them were restricted to patients with diabetes,[11,12] and the other one was restricted to men without diabetes and hypertension.[13] Generalizability is still a concern in this respect. In this study, we assessed the longitudinal association between NAFLD and incident CKD in a large cohort of asymptomatic men and women unselected with respect to metabolic abnormalities.

Keywords: Chronic kidney disease; Cohort; Fatty liver; Liver fibrosis.
Received 22 February 2017; received in revised form 31 July 2017; accepted 16 August 2017

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Please cite this article in press as: Sinn DH et al. Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: A cohort study. J Hepatol (2017), http://dx.doi.org/10.1016/j.jhep.2017.08.024

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Materials and methods

Study population

We conducted a retrospective cohort analysis of men and women of 18 years of age or older who underwent a comprehensive health screening exam at the Samsung Medical Center Health Promotion Center in Seoul, South Korea, from January 1, 2003 to December 31, 2013 (Fig. 1). Since our objective was to evaluate the longitudinal association between NAFLD and incidence of CKD, the analysis was restricted to subjects who underwent at least two screening exams including both a renal function test and an abdominal ultrasound (US) (n = 68,181). We then excluded participants who had any of the following conditions at baseline: estimated glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2 (n = 1,037), proteinuria (n = 947), alcohol intake ≥30 g/day in men or ≥20 g/day in women (n = 15,606), history of liver cirrhosis or positive hepatitis B surface antigen or hepatitis C virus antibodies (n = 3,409), or history of cancer (n = 1,199). We also excluded participants who had missing information on alcohol intake (n = 6,334) or NAFLD fibrosis score (NFS) (n = 21). Since study participants could have more than one exclusion criteria, the final sample size was 41,430 (25,217 men and 16,213 women). The Institutional Review Board of the Samsung Medical Center approved this study and waived the requirement for informed consent as we used only de-identified data routinely collected during health screening visits.

Data collection

At each visit, demographic characteristics, smoking status, alcohol consumption, medical history, and medication use were collected through standardized, self-administered questionnaires. Smoking status was categorized into never, former, or current smoker. Current alcohol consumption was categorized into none or moderate (<30 g/day in men and <20 g/day in women). Height, weight, waist circumference and sitting blood pressure were measured by trained nurses. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medications. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Body mass index was classified according to Asian-specific criteria, and obesity was defined as a BMI ≥25 kg/m^2.

Serum creatinine was measured with the kinetic alkaline picrate method (Jaffe method) using automated chemistry analyzers, Hitachi 7600 (Hitachi, Tokyo, Japan) from 2003 to 2009 and Modular DP (Roche, Basel, Switzerland) from 2009 to 2013. Hyperlipidemia was defined according to Adult Treatment Panel III criteria, as triglyceride levels ≥150 mg/dl, high-density lipoprotein (HDL) cholesterol levels <40 mg/dl or use of medication for dyslipidemia. Serum glucose was measured by the hexokinase/glucose-6-phosphate dehydrogenase method. Hemoglobin A1c was measured by high performance liquid chromatography. Diabetes was defined as a fasting serum glucose ≥126 mg/dl or self-reported use of insulin or antidiabetic medications. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase were measured following the International Federation of Clinical Chemistry method. Urine protein was measured semi-quantitatively by urine dipstick using urine chemistry analyzers Cliniteck Atlas (Siemens, Munich, Germany) or Urisys 2400 (Roche). We defined proteinuria as protein ≥1+ on urinalysis. The Department of Laboratory Medicine and Genetics at Samsung Medical Center has participated in several proficiency testing programs operated by the Korean Association of Quality Assurance for Clinical Laboratory, the Asian Network of Clinical Laboratory Standardization and Harmonization, and the College of American Pathologists.

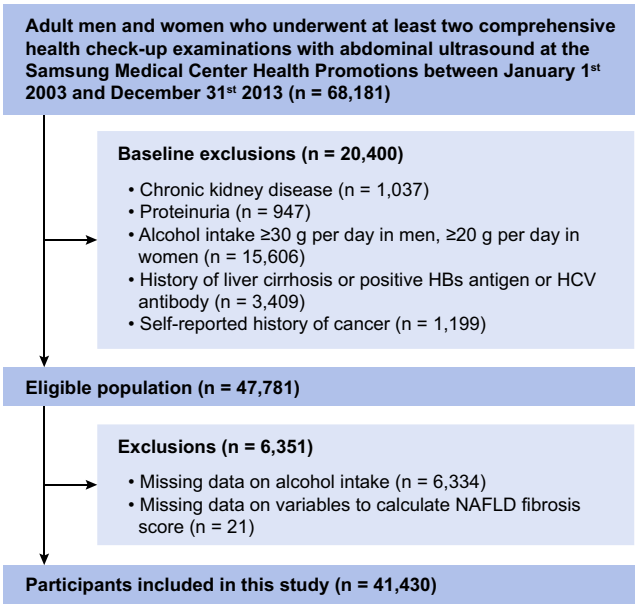

Fig. 1. Flow chart of study participants.

Abdominal ultrasound

Abdominal US were performed using LogiQ E9 (GE Healthcare, Milwaukee, Wisconsin, USA), iU22 xMatrix (Philips Medical Systems, Cleveland, Ohio, USA) or ACUSON Sequoia 512 equipments (Siemens, Issaquah, Washington, USA) by experienced radiologists unaware of the study aims. Images were captured in a standard fashion with the patient in the supine position with the right arm raised above the head. A US diagnosis of fatty liver was made based on standard criteria, including parenchymal brightness, liver-to-kidney contrast, deep beam attenuation and bright vessel walls.[14,15] Since we had already excluded participants with excessive alcohol use (≥30 g/day for men and ≥20 g/day for women), as well as other identifiable causes of fatty liver at baseline, as described in the exclusion criteria, fatty liver was considered NAFLD.

Among individuals with NAFLD, we calculated the NFS as $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ impaired fasting glucose/diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet count ($\times 10^9$/L) $- 0.66 \times$ albumin (g/dl). NFS was used to assess the severity of fibrosis[16] and to classify participants with NAFLD into two groups: high-intermediate (NFS ≥ −1.455) and low probability (NFS < −1.455) of advanced fibrosis. We also stratified NAFLD patients according to the AST to platelet ratio index (APRI) and to the fibrosis-4 score. The APRI was calculated as [(AST/normal upper limit AST)/ platelet count] × 100.[17] The fibrosis-4 score was calculated as age (years) × AST (U/L)/[platelet count (10^9/L) × ALT (U/L)$^{1/2}$]. A low APRI score (<0.5) and a low fibrosis-4 score (<1.3) are also strong predictors of the absence of liver fibrosis.

Estimated glomerular filtration rate

GFR (in ml/min/1.73 m^2) was estimated using the CKD-EPI equation.[18] For women with serum creatinine ≤0.7, GFR was calculated as $144 \times$ (serum creatinine/0.7)$^{-0.329} \times (0.993)^{age}$; for women with serum creatinine >0.7, GFR was calculated as $144 \times$ (serum creatinine/0.7)$^{-1.209} \times (0.993)^{age}$; for men with serum creatinine ≤0.9, GFR was calculated as $141 \times$ (serum creatinine/0.9)$^{-0.411} \times (0.993)^{age}$; and for men with serum creatinine >0.9, GFR was calculated as was $141 \times$ (serum creatinine/0.9)$^{-1.209} \times (0.993)^{age}$. CKD was defined as estimated GFR <60 ml/min/1.73 m^2.

Statistical analysis

The study endpoint was the development of incident CKD. Participants were followed from the baseline visit to the visit of CKD diagnosis or to the last available visit. Since incident CKD occurred at an unknown time point between the visit of diagnosis and the previous visit (interval censoring), we used a flexible parametric proportional hazards model to evaluate the association between NAFLD status at baseline and incident CKD.[19] This model used restricted cubic splines to estimate the baseline log cumulative hazards and allowed for interval censored events.

We used three models with increasing degrees of adjustment to account for potential confounding factors at baseline. Model 1 was adjusted for age, sex and year of visit. Model 2 was further adjusted for smoking (never, former, current, and missing), alcohol consumption (none, and moderate), BMI, and estimated GFR at baseline. In addition, to evaluate potential mediation of the association between NAFLD and CKD by metabolic factors, model 3 was further adjusted for systolic blood pressure, hemoglobin A1c, low-density lipoprotein (LDL) cholesterol, use of diabetes medications, use of lipid lowering medications, and use of antihypertensive medications. To evaluate if the increased risk in CKD

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