Research Article

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Development of new fatty liver, or resolution of existing fatty liver, over five years of follow-up, and risk of incident hypertension

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Background & Aims: Approximately 50% of hypertensive patients have non-alcoholic fatty liver disease (NAFLD), but whether change in fatty liver status over time modifies risk of developing hypertension is uncertain. Our aim was to determine whether a change in fatty liver status (either development of new fatty liver, or resolution of existing fatty liver) over five years modified risk of incident hypertension at five year follow-up.

Methods: 11,448 patients without hypertension were examined at baseline and at five year follow-up, using a retrospective cohort study design. Fatty liver status (absent or present) was assessed at baseline and follow-up using standard ultrasound criteria. Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) for incident hypertension at follow-up were estimated controlling for potential confounders, compared to the reference group (patients who did not have fatty liver at either baseline or follow-up).

Results: 911 patients developed incident hypertension. Incident fatty liver developed during follow-up in 1418 patients and fatty liver at baseline resolved during follow-up in 684 patients. Developing incident fatty liver was associated with incident hypertension, even after adjustment for multiple confounders (aOR = 1.60 (95% CI 1.30, 1.96; p <0.001). Further adjustment for change in body mass index between baseline and follow-up only slightly attenuated this association (aOR = 1.36 (95% CI 1.10, 1.67; p = 0.004). With resolution of fatty liver at follow-up, risk of incident hypertension was not different from the reference group (aOR = 1.21 (95% CI 0.90, 1.63; p = 0.21).

Conclusions: Development of incident fatty liver is associated with increased risk of hypertension.

Keywords: Non-alcoholic fatty liver disease; Hypertension; Type 2 diabetes; Obesity; Insulin resistance; Metabolic syndrome.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransaminases; GGT, γ-Glutamyltransferase; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; BMI, body mass index.

Introduction

Approximately 50% of hypertensive patients have non-alcoholic fatty liver disease (NAFLD) [1,2] and in cross sectional studies increased blood pressure is associated with NAFLD in patients with increased alanine transaminase concentrations [3]. Although the mechanism explaining the association between NAFLD and increased blood pressure is uncertain, it has recently been demonstrated that there is general thickening of the left ventricular wall in NAFLD, independent of changes in left ventricular mass [4]. Increased wall thickness is associated with reduced longitudinal fiber shortening, which is indicative of left ventricular hypertrophy [5]. Hypertrophy of the cardiac wall may lead to the increased ventricular strain seen in NAFLD, both affecting the endocardium and entire wall, as a result of the altered geometry (reduced radius).

Although it is presently not known whether such changes underpin the association between increased blood pressure and NAFLD, it is also plausible that increased renin angiotensin system activity mediated by increased adipose tissue mass or altered renal function [6] could explain the increased prevalence of hypertension. For example many patients with NAFLD are overweight or obese and increasing evidence suggests that NAFLD is associated with chronic kidney disease (CKD) not only in a general population [7] but also in patients with both type 1 [8] and type 2 diabetes [9]. It is possible that common risk factors contribute to development of NAFLD, hypertension and to CVD. Since it is not known whether resolution of fatty liver, or development of new fatty liver, modifies risk of hypertension; the aim of our study was to determine whether a change in fatty liver status (either development of new fatty liver, or resolution of existing fatty liver over a five year period), were associated with incident hypertension at five year follow-up.

Patients and methods

Study subjects

The study population consisted of individuals who had a comprehensive health examination at baseline (in 2003) and were re-examined five years later (in 2008) at Kangbuk Samsung Hospital, College of Medicine, Sungkyunkwan University, South Korea. In South Korea, employees are required to participate in annual or biennial health examinations by the Industrial Safety and Health Law. Health checks include blood tests, anthropometry, and abdominal ultrasound examination without any selection of high risk individuals for differential testing. The Institutional review board at Kangbuk Samsung Hospital has approved the secondary analysis of anonymized data from the cohort for this study. Informed consent was not required because personal identifying information was not used. Blood pressure was determined between 08.00 h and 10.00 h, after the subject had been sitting upright. In the absence of any anti-hypertensive medication, the subject was classified as being normotensive if the systolic blood pressure was <140 mmHg and the diastolic blood pressure was <90 mmHg. If the systolic or diastolic blood pressure exceeded (or was equal to) 140 mmHg or 90 mmHg, the blood pressure was re-measured two more times after a rest and the two measurements were averaged. Incident hypertension at 5 year follow-up was defined if the average of these two measurements showed either a SBP $\geqslant$140 mmHg or a DBP $\geqslant$90 mmHg, and/or the subject was taking antihypertensive medication. Estimated GFR was calculated according to the formula GFR (ml/min per 1.73 m^2) _ 186 $*$ (SCr) $^{-1.154}$ $\times$ (Age) $^{-0.203}$ $\times$ (0.742 if female) $\times$ (1.210 if African-American) [10].

Initially 15,627 participants were identified with measurements of liver fat and blood pressure and 2387 were excluded for having hypertension (SBP $\geqslant$140 mmHg or a DBP $\geqslant$90 mmHg and/or hypertensive medication use (based on self-report or medical history). Individuals with data missing at baseline for the following variables were also excluded: plasma glucose (n = 1), serum insulin (n = 1174), BMI (n = 13), alcohol consumption (n = 336), smoking (n = 319), exercise (n = 253). Participants were excluded from the analyses of the relationship between change in fatty liver status and hypertension if data on these variables were missing at five year follow-up. N.B. some patients were excluded for more than one reason. After exclusions, 11,448 participants were eligible for this analysis at follow-up and of these 911 subjects had developed incident hypertension by the time of the follow-up examination.

The health examination included full medical histories, physical examinations and blood samples. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Questionnaires were used to ascertain information regarding alcohol consumption (g/day), smoking (never, ex, current) and frequency of exercise (none, less than once a week, at least once a week). Blood samples were collected after at least 10 h of fasting and analyzed in the same core clinical laboratory. The core clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. Fasting plasma glucose, GGT, AST, ALT, total cholesterol, triglyceride and high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) concentrations were measured using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). LDL-C was calculated using the Friedewald equation. Intra- and interassay coefficients of variation for all biochemical measurements were <5%. Insulin concentration was measured with an immunoradiometric assay (Biosource, Nivelle, Belgium) with an intra- and interassay coefficient of variation of 2.1–4.5% and 4.7–12.2%, respectively. Abdominal ultrasonography (Logic Q700 MR; GE, Milwaukee, WI, USA) using a 3.5 MHz probe was performed in all subjects at baseline and at 5 year follow-up by experienced clinical radiologists. The following images were undertaken: sagittal view of the right lobe of the liver and right kidney, transverse view of the left lateral segment of the liver and spleen and transverse view of the liver for altered echotexture. Fatty infiltration of the liver (fatty liver) was identified where there was an increase in echogenicity of the liver compared with the echogenicity of the renal cortex where the diaphragm and intrahepatic vessels appeared normal [11].

Statistical analysis

Continuous variables were expressed as mean ± SD for normally distributed variables or median (interquartile range) if not normally distributed. Continuous variables were compared using independent *t* tests and ANOVA, non-normally distributed variables were compared using Mann Whitney U and Kruskal Wallis tests. Categorical variables were expressed as percentages and compared between groups using the χ^2 test. Characteristics for individuals who did and who did not develop hypertension at follow-up were compared at baseline. We used logistic regression to determine odds ratios (OR) for developing incident hypertension at follow-up: (a) in patients in whom there was resolution of fatty liver over 5 years, i.e., fatty liver that had been present at baseline, but was not present at follow-up examination; (b) in patients in whom there was development of new (incident) fatty liver, between baseline and follow-up examinations and (c) in patients in whom fatty liver was present at both baseline and at follow-up. Analyses were undertaken with the following adjustments. Model 1 was adjusted for age and sex. Model 2 was adjusted for the same risk factors as Model 1 plus alcohol consumption, smoking status, exercise and systolic blood pressure. Model 3 was adjusted for the same risk factors as Model 2 plus BMI diabetes status, GGT, HOMA-IR. Model 4 was adjusted for the same risk factors as Model 3 and eGFR. Model 5 was adjusted for the same factors as Model 4 plus change in BMI between baseline and follow-up.

All data analysis was performed using SPSS, version 15.0 (SPSS, Chicago, IL, USA). The statistical significance of *p* values in this report was set at <0.05.

Results

Table 1 shows the baseline characteristics of the whole cohort stratified by the presence of incident hypertension (n = 911) at follow-up. Of these 911 subjects, at follow-up, only 70/911 (7.7%) subjects were treated with antihypertensive medication (54/769 men and 16/142 women). Features of the MetS [12], including glucose, triglyceride and HDL-C concentration were all adversely affected in subjects with incident hypertension compared to the group that did not develop hypertension. AST, ALT, and GGT concentrations were also increased in subjects with incident hypertension. Prevalence of fatty liver at baseline was 24.7% among patients who did not develop hypertension during follow-up and 39.5% among patients who did develop hypertension at follow-up. Table 2 shows the baseline characteristics stratified by fatty liver status at baseline and follow-up (no fatty liver at baseline and at follow-up, no fatty liver at baseline and fatty liver at follow-up, i.e., incident fatty liver, fatty liver at baseline and no fatty liver at follow-up, i.e., resolution of fatty liver, and fatty liver at both baseline and at follow-up, i.e., prevalent fatty liver).

We then examined the number and proportion of patients with or without fatty liver at baseline and follow-up to identify subjects developing incident fatty liver during follow-up and to identify subjects in whom fatty liver resolved during the follow-up period (Table 3A). These data showed that, during follow-up, incident fatty liver developed in 1418 patients and fatty liver resolved in 684 patients. We examined the proportions of patients with incident hypertension according to the presence (or absence) of fatty liver at baseline and at follow-up (Table 3B). Incident hypertension only occurred in 385/7071 (5.4%) of patients with no evidence of fatty liver at both baseline and follow-up. In contrast, incident hypertension developed in 166/1418 (11.7%) of patients with incident fatty liver at follow-up, (p <0.001), and in 65/684 (9.5%) of patients in whom fatty liver had resolved in the follow-up examination.

Since change in body mass index (BMI) has an important impact on blood pressure, we examined the relationship between change in BMI and incident hypertension in subjects with no fatty liver at baseline and at follow-up, with incident fatty liver at follow-up, in patients with resolution of fatty liver at follow-up, and in subjects with fatty liver that was present at both baseline and at follow-up (see on line Supplementary Table 1). Change in BMI was characterized according to tertiles of increase in BMI between baseline and follow-up, (tertile 1 $\leqslant$0.26 kg/m^2; tertile 2 = 0.26 kg/m^2–0.59 kg/m^2 and tertile 3 $\geqslant$0.59 kg/m^2). These