A Prospective Study of Fatty Liver Index and Incident Hypertension: The KoGES-ARIRANG Study

Ji Hye Huh1, Song Vogue Ahn2, Sang Baek Koh2, Eunhee Choi3*, Jang Young Kim4*, Ki-Chul Sung5, Eung Ju Kim6, Jeong Bae Park7

1 Division of Endocrinology and Metabolism, Department of Internal Medicine, Wonju College of Medicine, Wonju, Korea, 2 Department of Preventive Medicine, Institute of Genomic Cohort, Wonju College of Medicine, Wonju, Korea, 3 Institute of Life Style Medicine, Wonju College of Medicine, Wonju, Korea, 4 Division of Cardiology, Department of Internal Medicine, Yonsei University, Wonju College of Medicine, Wonju, Korea, 5 Division of Cardiology, Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea, 6 Division of Cardiology, Department of Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea, 7 Division of Cardiology, Department of Medicine, Cheil General Hospital, Kwandong University College of Medicine, Seoul, Korea

* eunhee_choi@yonsei.ac.kr (EHC); kimjy@yonsei.ac.kr (JYK)

Abstract

Background

Although non-alcoholic fatty liver disease is the hepatic manifestation of metabolic syndrome, its influence on hypertension development is poorly understood. We investigated whether fatty liver disease, as assessed by the fatty liver index, could predict the development of hypertension independently of systemic insulin resistance, inflammatory status and adiponectin levels.

Methods

Prospective cohort study of 1,521 adults (484 men and 1037 women) aged 40 to 70 years without baseline hypertension examined. An equation was used to calculate fatty liver index and classify patients as follows: fatty liver index <30, no non-alcoholic fatty liver disease; fatty liver index ≥60, non-alcoholic fatty liver disease; and 30 ≤ fatty liver index <60, intermediate fatty liver index.

Results

During an average of 2.6 years of follow-up, 153 subjects (10.06%) developed hypertension. Fatty liver index was positively associated with baseline blood pressure, homeostasis model assessment of insulin resistance, urinary albumin/creatinine excretion, and high sensitivity C-reactive protein. After adjustment for confounding factors, including markers of insulin resistance, systemic inflammation and adiponectin levels, the odds ratio [95% confidence interval] for the incident hypertension increased in a graded manner with fatty liver index (<30 vs. 30–59 vs. ≥60 = 1 vs. 1.83 [1.16~2.88] vs. 2.09 [1.08~4.05], respectively).
Conclusions
Non-alcoholic fatty liver disease assessed by fatty liver index was an independent risk factor for hypertension. Our findings suggest that fatty liver index, a simple surrogate indicator of fatty liver disease, might be useful for identifying subjects at high risk for incident hypertension in clinical practice.

Introduction
Hypertension is a growing public health problem because it is closely associated with the risk for chronic kidney disease and morbidity or mortality of cerebral and cardiovascular disease, which demand substantial healthcare costs [1, 2]. Furthermore, the prevalence of hypertension has increased and remains high, as approximately 35% of individuals in East Asia are hypertensive despite significant global and regional efforts [3]. Therefore, it is important to identify adults who are at higher risk for incident hypertension. However, there is still no useful index that predicts incident hypertension.

Non-alcoholic fatty liver disease (NAFLD) is the most common metabolic liver disease, with a prevalence as high as 30% in developed countries [4]. NAFLD is the hepatic component of metabolic syndrome and is also a risk factor for various metabolic disorders including type 2 diabetes, insulin resistance, dyslipidemia, and cardiovascular events [5, 6]. NAFLD and cardiovascular disease may share common pathogeneses such as insulin resistance, aging, and obesity. In addition, altered levels of hepatokines such as fetuin-A, fibroblast growth factor 21, and selenoprotein P in NAFLD might directly affect the progression of atherosclerosis by modulating endothelial dysfunction and infiltration of inflammatory cells into vessel walls. Also, several cross-sectional studies have demonstrated that approximately 50% of subjects with hypertension are known to have NAFLD [7, 8]. However, few studies have examined whether NAFLD itself is associated with the development of hypertension in a community-dwelling cohort, independent of traditional cardiovascular disease risk factors.

Although the gold standard for NAFLD diagnosis is a liver biopsy, this test has limited diagnostic value in a population-based study due to its invasive nature [9]. Therefore, abdominal ultrasonography is the most common technique used to assess the presence of NAFLD in clinical settings. However, abdominal ultrasonography is also expensive and laborious for study participants, and is a subjective operator-dependent examination [10, 11]. Recently, Bedogni et al. developed a simple scoring system called the fatty liver index (FLI) as a predictor of fatty liver diseases [12]. Previous studies have shown that NAFLD assessed by FLI was well-correlated with hepatic steatosis using abdominal ultrasonography in a general population that included Korean patients [13, 14]. In addition, several studies reported that the FLI, as a surrogate indicator of hepatic steatosis, is associated with the development of type 2 diabetes in Asian populations [15]. However, no study has investigated the validity of the FLI for predicting incident hypertension in the general population. We aimed to determine whether NAFLD, as measured by FLI, was associated with new-onset hypertension in a relatively healthy Korean rural population. We also investigated whether fatty liver disease as assessed by FLI was an independent contributor to incident hypertension, regardless of confounding factors such as diabetes, insulin resistance, systemic inflammation status and adipokine levels.
Materials and Methods

Study population and design

We used data from the Korean Genome and Epidemiology Study on Atherosclerosis Risk of Rural Areas in the Korean General Population (KoGES-ARIRANG), a population-based prospective cohort study, to assess the prevalence, incidence, and risk factors for chronic degenerative disorders such as hypertension, diabetes, metabolic syndrome, and cardiovascular disease [16, 17]. KoGES-ARIRANG invited all adults in rural areas of Wonju and Pyengchang in South Korea, where demographic shifts are infrequent and the population can be followed long term, to participate in the study. The baseline survey, carried out from November 2005 to January 2008, included 5178 adults (2127 men and 3051 women) aged 40–70 years. All study participants were invited to the first follow-up survey (April 2008 to January 2011) and 3862 (74.6%) attended. Subjects with missing data for the FLI (N = 8) and hypertension (N = 2) were excluded. We also excluded subjects who had a history of hypertension (N = 2108) or overt cardiovascular disease (N = 26) at baseline or excessive alcohol intake (alcohol consumption >140 g/week for men and 70 g/week for women) (N = 197). Finally, 1521 participants (484 men and 1037 women) were included in the analysis (Fig 1).

Ethics Statement

Because the KoGES-ARIRANG study data are publicly available, ethical approval was not required for this study. Prior to the survey, all participants were informed that they had been randomly chosen to participate in the KoGES-ARIRANG survey with the right to refuse to be involved in further analyses, and signed informed consents were obtained. We received the data in fully anonymized form. The study was carried out in accordance with the ethical standards of the Helsinki Declaration.

Data collection

At baseline and at the follow-up examination, study participants completed a standardized medical history and lifestyle questionnaire and underwent a comprehensive health examination according to standard procedures. Body weight and height were measured while participants were wearing light indoor clothing without shoes. Blood pressure was measured in the right arm using a standard mercury sphygmomanometer after the participant had rested for at least 5 min in a quiet room (Baumanometer, Copiague, NY, USA). With participants seated, an appropriately-sized cuff was applied snugly around the upper right arm at the heart level. The appropriate cuff size was chosen for each subject according to mid-arm circumference. Two measurements were made with at least 5 min intervals in between, and the mean of the two measurements was used in the analyses. According to the Eighth Joint National Committee (JNC-8) guidelines [18], hypertension was defined as a systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg, or current use of antihypertensive agents. Diabetes mellitus was defined as fasting serum glucose of at least 126 mg/dL or current use of blood glucose-lowering agents at baseline. Baseline information on smoking status and current alcohol intake was collected with a self-reported questionnaire (yes/no). Subjects who answered yes to the question: “Do you perform physical exercise regularly enough to make you sweat?” were assigned to the regular exercise group. A venous blood sample was drawn from study participants after fasting for ≥12 h or overnight. The serum concentrations of adiponectin were measured by radioimmunoassay (RIA) (LINCO Research, Inc., USA) with intra-assay and inter-assay coefficients of variation ranging from 2.9% to 6.6% for adiponectin. Fasting glucose was determined by a glucose oxidase-based assay and fasting insulin was determined...
Fig 1. Description of the study populations.

doi:10.1371/journal.pone.0143560.g001
by a double-antibody radioimmunoassay (Biosource Europe SA, Nivelles, Belgium). Serum concentrations of total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides (TG), aspartate aminotransaminases (AST), alanine aminotransaminases (ALT), and γ-Glutamyltransferase (GGT) were determined by enzymatic methods (Advia 1650, Siemens, Tarrytown, NY, USA). High sensitivity C-reactive protein (hsCRP) was measured by the Denka Seiken (Tokyo, Japan) assay, which has been validated against the Dade Behring method. Homeostasis model assessment of insulin resistance (HOMA-IR) values were calculated using the following formula: fasting plasma glucose (milligrams per deciliter) × fasting insulin (milliinternational units per milliliter))/22.5 [19].

Definition of hepatic steatosis according to FLI

The FLI was used as a surrogate measure for fatty liver. This index was calculated according to a previously published report by Bedogni et al. [12]: FLI = [e^{0.953×\log_e (TG) + 0.139×BMI+0.718×\log_e (GGT) + 0.053×waist circumference–15.745)] / [1+e^{0.953×\log_e (TG) + 0.139×BMI+0.718×\log_e (GGT) + 0.053×waist circumference–15.745}] × 100, with triglycerides measured in mmol/l, GGT in U/l, and waist circumference in cm. The score ranges from 0 to 100. According to the previous study by Bedogni et al., FLI < 30 can be used to rule out (sensitivity = 87%; negative likelihood ratio = 0.2) and FLI ≥ 60 to rule in hepatic steatosis (specificity = 86%; positive likelihood ratio = 4.3). Thus, we classified participants into three groups according to the value of FLI: FLI < 30 was defined as not having NAFLD, and FLI ≥ 60 was defined as having NAFLD. Patients with FLI 30–59 were defined as having intermediate FLI.

Statistical analyses

Data are expressed according to the properties of the variable. Continuous variables are presented as means and standard deviations. Categorical variables are presented as frequencies and percentages. In order to compare incident hypertension and FLI categories, we performed the two-sample t-test, one-way analysis of variance (ANOVA), and chi-square test (Fisher’s exact test), as appropriate. The association between the FLI and baseline metabolic parameters was evaluated using Pearson correlation analysis. Multivariate logistic regression was used to assess the independent association of baseline FLI with incident hypertension. We used three models with progressive degrees of adjustment. First, we performed an age (continuous variable) and sex adjusted analysis. Second, we further adjusted for baseline systolic and diastolic blood pressure (continuous variable), smoking (yes/no), alcohol intake (yes/no), regular exercise (yes/no) and diabetes. Finally, we further adjusted for baseline levels of hs-CRP (continuous variable), HOMA-IR (log-transformed continuous variable), ALT (log-transformed continuous variable), serum creatinine (continuous variable) and adiponectin (continuous variable). Results were expressed as odds ratios with 95% confidence intervals (CI). P values less than 0.05 were considered statistically significant and all statistical analyses were performed using SAS 9.2 Ver. (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

Baseline clinical and biochemical characteristics of participants based on the development of hypertension during 2.6 years are shown in Table 1. The overall incidence of hypertension during this period was 10.06% (N = 153). Subjects who developed hypertension had significantly higher baseline age, waist circumference, body mass index, blood pressure, total cholesterol, and serum creatinine than those who did not. The AST, ALT, total bilirubin, and GGT levels at
baseline were not different between the incident and the non-incident hypertension groups. FLI values were higher in the incident hypertension group (30.95 ± 22.16 vs. 21.69 ± 20.15, P < .0001). The baseline demographic and clinical characteristics of the subjects, who were classified into three groups according to baseline FLI values, are presented in Table 2. 1098 (72.19%), 299 (19.66%), and 124 (8.15%) subjects were classified as not having NAFLD (<30), intermediate FLI (30–59), or having NAFLD (≥60), respectively. As the FLI increased, subjects were more likely to be male, current smokers, obese, and insulin resistant. Subjects with higher FLI also had higher baseline blood pressure, fasting/postprandial plasma glucose, TG, AST, ALT, GGT, and urinary albumin/creatinine excretion. Subjects with higher FLI had lower HDL cholesterol and adiponectin than other groups. Incident hypertension gradually increased across all FLI groups.

| Table 1. Baseline characteristics according to incident hypertension. |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Incident hypertension (+) | Incident hypertension (-) | P-value |
| Age (years)                    | 57.56 ± 7.8      | 53.1 ± 8.07     | < .0001 |
| Gender (male)                  | 59 (38.56%)      | 425 (31.07%)    | 0.0591 |
| BMI (kg/m²)                    | 25.03 ± 2.87     | 23.7 ± 2.91     | < .0001 |
| Waist circumference (cm)       | 85.45 ± 7.82     | 80.25 ± 8.47    | < .0001 |
| Weight (kg)                    | 62.79 ± 9.46     | 59.37 ± 9.02    | < .0001 |
| Systolic blood pressure (mmHg) | 122.9 ± 9.99     | 116.9 ± 11.07   | < .0001 |
| Diastolic blood pressure (mmHg)| 75.78 ± 6.53     | 73.5 ± 7.45     | 0.0003 |
| HbA1c (%)                      | 5.59 ± 0.71      | 5.5 ± 0.72      | 0.1397 |
| Fasting glucose (mg/dl)        | 93.8 ± 13.12     | 92.93 ± 19.43   | 0.4599 |
| HOMA-IR                        | 2.0 ± 1.25       | 1.9 ± 1.15      | 0.2783 |
| Total cholesterol (mg/dl)      | 204 ± 34.32      | 196.3 ± 35.67   | 0.0111 |
| HDL-C (mg/dl)                  | 45.37 ± 9.89     | 46.32 ± 10.52   | 0.2891 |
| Triglycerides (mg/dl)          | 136.4 ± 76.28    | 124.4 ± 80.78   | 0.0788 |
| LDL-C (mg/dl)                  | 122.9±28.37      | 115.6±30.75     | 0.0051 |
| AST (IU/l)                     | 27.15 ± 8.74     | 26.21 ± 15.15   | 0.2514 |
| ALT (IU/l)                     | 24.51 ± 13.61    | 22.51 ± 14.86   | 0.1124 |
| GGT (IU/l)                     | 24.47 ± 20.2     | 25.17 ± 54.86   | 0.7503 |
| Total bilirubin (mg/dl)        | 0.84 ± 0.28      | 0.86 ± 0.31     | 0.456  |
| Adiponectin (μg/ml)            | 10858.2 ± 5509   | 10978.9 ± 5321  | 0.7982 |
| Fatty liver index              | 30.95 ± 22.16    | 21.69 ± 20.15   | < .0001 |
| Creatinine (mg/dl)             | 0.93 ± 0.15      | 0.91 ± 0.14     | 0.0365 |
| Urine ACR (mg/g)               | 3.26 ± 9.45      | 1.89 ± 6.49     | 0.1194 |
| hsCRP (mg/l)                   | 1.8 ± 3.51       | 1.64 ± 4.61     | 0.6043 |
| Alcohol use                    | 64 (42.38%)      | 452 (33.16%)    | 0.0233 |
| Current smoker                 | 38 (25.17%)      | 303 (22.18%)    | 0.4045 |
| Regular exercise               | 34 (22.37%)      | 409 (30.01%)    | 0.0495 |

Data are expressed as mean ± standard deviation.
BMI, Body mass index; HOMA-IR, homeostasis model assessment of insulin resistance, HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; urine ACR, urine albumin/creatinine ratio

doi:10.1371/journal.pone.0143560.t001
Correlation between FLI and metabolic parameters

Table 3 presents correlation analysis between FLI and baseline major metabolic parameters. FLI values were positively correlated with systolic and diastolic blood pressure, HbA1c, fasting/postprandial plasma glucose, HOMA-IR, AST, ALT, total cholesterol, urinary albumin/creatinine ratio, and hsCRP. FLI values were significantly negatively associated with HDL cholesterol and adiponectin.

The risk for incident hypertension according to fatty liver index groups

The risk of incident hypertension according to the baseline FLI groups is shown in Table 4. After adjustment for age and gender, the odds ratios for incident hypertension increased across
This trend remained statistically significant even after further adjustment for other confounding variables, including baseline blood pressure, smoking status, regular exercise, alcohol intake, and diabetes, which are established risk factors for hypertension. In full adjusted model including insulin resistance status, liver enzyme, hsCRP, serum creatinine level and adiponectin, the odds ratios (95% CI) for developing hypertension in the FLI > 30 and FLI > 60 were 1.87 (1.2–2.91) and 2.22 (1.16–4.25) comparing to those in the FLI < 30. We also investigated FLI values at the end of the study and the change of FLI values during follow-up period in participants. As a result, we found that subjects who developed hypertension had still higher FLI values at the end of study than the other group (32.87±22.23 vs. 22.15±19.49, P < 0.001). In addition, FLI values were more frequently increased in incident hypertension group than in non-incident hypertension group during follow-up period (41.83% vs. 32.31%, P = 0.0051) (S1 Table).

Table 3. Correlation between fatty liver index (FLI) and metabolic parameters.

| Correlation coefficient | p-value |
|-------------------------|---------|
| Systolic BP mmHg        | 0.121   | < .0001 |
| Diastolic BP mmHg       | 0.114   | < .0001 |
| HbA1c* (%)              | 0.242   | < .0001 |
| Fasting glucose* (mg/dl)| 0.234   | < .0001 |
| Postprandial glucose (mg/dl)| 0.216 | < .0001 |
| Fasting insulin* (μIU/ml)| 0.294  | < .0001 |
| HOMA-IR*                | 0.337   | < .0001 |
| Total cholesterol (mg/dl)| 0.24    | < .0001 |
| HDL-C (mg/dl)           | -0.265  | < .0001 |
| LDL-C (mg/dl)           | 0.168   | < .0001 |
| AST* (IU/l)             | 0.36    | < .0001 |
| ALT* (IU/l)             | 0.511   | < .0001 |
| Urine ACR* (mg/g)       | 0.202   | < .0001 |
| Adiponectin (μg/ml)     | -0.315  | < .0001 |
| Creatinine (mg/dl)      | 0.29    | < .0001 |
| hs-CRP (mg/l)           | 0.081   | 0.0016  |

Values are Pearson correlation coefficients between variables and FLI

*Log transformed variables

doi:10.1371/journal.pone.0143560.t003

Fatty Liver Index Is Associated with Incident Hypertension

Table 4. Odds ratios (OR) and 95% confidence intervals for hypertension according to fatty liver index (FLI) categories.

| FLI  | Incident hypertension | Crude OR | Model 1 | Model 2 | Model 3 |
|------|-----------------------|----------|---------|---------|---------|
| <30  | 84 (7.65%)            | 1        | 2.31 (1.58–3.38) | 2.46 (1.46–4.14) | 2.46 (1.46–4.14) |
| 30–60| 48 (16.05%)           | 1        | 2.04 (1.38–3.02) | 2.47 (1.43–4.26) | 2.47 (1.43–4.26) |
| ≥60  | 21 (16.94%)           | 1        | 1.79 (1.19–2.68) | 2.07 (1.15–3.7)   | 2.07 (1.15–3.7)   |

Model 1: Adjusted for age, gender
Model 2: Model 1 + further adjusted for baseline systolic blood pressure, baseline diastolic blood pressure, smoking, regular exercise, alcohol intake, and diabetes
Model 3: Model 2 + further adjusted for log ALT, log HOMA-IR, hsCRP, serum creatinine, adiponectin

doi:10.1371/journal.pone.0143560.t004

Table 3. Correlation between fatty liver index (FLI) and metabolic parameters.

| Correlation coefficient | p-value |
|-------------------------|---------|
| Systolic BP mmHg        | 0.121   | < .0001 |
| Diastolic BP mmHg       | 0.114   | < .0001 |
| HbA1c* (%)              | 0.242   | < .0001 |
| Fasting glucose* (mg/dl)| 0.234   | < .0001 |
| Postprandial glucose (mg/dl)| 0.216 | < .0001 |
| Fasting insulin* (μIU/ml)| 0.294  | < .0001 |
| HOMA-IR*                | 0.337   | < .0001 |
| Total cholesterol (mg/dl)| 0.24    | < .0001 |
| HDL-C (mg/dl)           | -0.265  | < .0001 |
| LDL-C (mg/dl)           | 0.168   | < .0001 |
| AST* (IU/l)             | 0.36    | < .0001 |
| ALT* (IU/l)             | 0.511   | < .0001 |
| Urine ACR* (mg/g)       | 0.202   | < .0001 |
| Adiponectin (μg/ml)     | -0.315  | < .0001 |
| Creatinine (mg/dl)      | 0.29    | < .0001 |
| hs-CRP (mg/l)           | 0.081   | 0.0016  |

Values are Pearson correlation coefficients between variables and FLI

*Log transformed variables

doi:10.1371/journal.pone.0143560.t003

Fatty Liver Index Is Associated with Incident Hypertension

Table 4. Odds ratios (OR) and 95% confidence intervals for hypertension according to fatty liver index (FLI) categories.

| FLI  | Incident hypertension | Crude OR | Model 1 | Model 2 | Model 3 |
|------|-----------------------|----------|---------|---------|---------|
| <30  | 84 (7.65%)            | 1        | 2.31 (1.58–3.38) | 2.46 (1.46–4.14) | 2.46 (1.46–4.14) |
| 30–60| 48 (16.05%)           | 1        | 2.04 (1.38–3.02) | 2.47 (1.43–4.26) | 2.47 (1.43–4.26) |
| ≥60  | 21 (16.94%)           | 1        | 1.79 (1.19–2.68) | 2.07 (1.15–3.7)   | 2.07 (1.15–3.7)   |

Model 1: Adjusted for age, gender
Model 2: Model 1 + further adjusted for baseline systolic blood pressure, baseline diastolic blood pressure, smoking, regular exercise, alcohol intake, and diabetes
Model 3: Model 2 + further adjusted for log ALT, log HOMA-IR, hsCRP, serum creatinine, adiponectin

doi:10.1371/journal.pone.0143560.t004
Discussion

In this rural cohort study, we found that NAFLD, as assessed by FLI, was significantly associated with development of hypertension during a 2.6-year period in Korean adults. Furthermore, the FLI was an independent predictor for incident hypertension, regardless of insulin resistance status, as reflected by HOMA-IR and systemic inflammatory status reflected by hsCRP. To the best of our knowledge, this is the first population-based study to reveal an association between fatty liver disease as assessed by FLI and incident hypertension. Our results suggest that fatty liver disease itself independently increases the risk of hypertension and that the FLI may be a useful clinical marker for prediction of incident hypertension.

NAFLD is an emerging risk factor for cardiovascular disease, as demonstrated by the significant association between NAFLD and fatal and nonfatal cardiovascular disease [20, 21]. Aneni et al. reported that NAFLD was associated with pre-hypertension as well as hypertension [22]. Moreover, Lopez et al. also demonstrated that NAFLD is associated with blood pressure in hypertensive and non-hypertensive individuals with normal liver enzyme levels [7]. However, because these were cross-sectional studies, they could not confirm a cause-effect relationship between NAFLD and hypertension. In one study, NAFLD assessed by ultrasonography was associated with incident hypertension in Korean men [23]; however, this study did not measure adipokines such as adiponectin, which could explain the association between fatty liver disease and incident hypertension. In addition, because this study did not consider insulin resistance and inflammatory status when analyzing the association between NAFLD and incident hypertension, they could not clarify the independent effect of NAFLD on incident hypertension. Therefore, we assessed whether NAFLD contributes to the development of hypertension independently of insulin resistance and systemic inflammation in relatively healthy Korean adults.

We observed a significant association between NAFLD as assessed through FLI and the development of hypertension. The observed link between fatty liver disease and hypertension could be explained by multiple mechanisms. First, renin–angiotensin system (RAS) dysregulation in NAFLD might lead to the development of hypertension, as RAS dysregulation may play a key role in hepatic inflammation and fibrosis [24, 25]. RAS inhibition in experimental animal models downregulates pro-inflammatory/pro-fibrotic cytokines, reduces activation of hepatic stellate cells, attenuates oxidative stress, and inhibits hepatic inflammation and fibrosis [26, 27]. We also observed that subjects with NAFLD assessed by FLI had higher urinary albumin excretion, and FLI was positively associated with urinary albumin excretion. These findings suggest that NAFLD is associated with RAS dysregulation, and that this RAS dysregulation may play a substantial role in the development of hypertension. Second, insulin resistance and systemic inflammation in NAFLD may lead to the development of hypertension. Chronic inflammation of the liver, secondary to the storage of free fatty acids in the form of triglycerides, could cause systemic insulin resistance by inducing proinflammatory cytokines via activation of NF-κB [28, 29] [30]. In addition, insulin resistance induced by chronic systemic inflammation is a known risk factor in the development and the progression of NAFLD. We found that that both HOMA-IR (as a marker of insulin resistance) and hsCRP (as a marker of systemic chronic inflammation) were higher in subjects with NAFLD. Insulin resistance is also an important risk factor for cardiovascular disease, as this results in increased secretion of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6 [31]. Moreover, elevated vascular sympathetic activation induced by insulin resistance might result in the development of hypertension [32]. However, in our study, the strong relationship between NAFLD and incident hypertension remained even after adjustment for HOMA-IR and hsCRP. Therefore, we hypothesize that fatty liver disease itself contributes to the development of hypertension, independently of systemic inflammation and insulin resistance. Third, altered secretion
of adipokines in fatty liver disease might lead to the development of hypertension. Leptin-mediated sympatho-activation is a well-known mechanism of obesity-induced hypertension \[33, 34\]. Furthermore, adiponectin also regulates vascular homeostasis by affecting signaling pathways in endothelial cells and modulating inflammatory responses in the subendothelial space \[35\]. Given the known pathogenic role of leptin/adiponectin in hypertension development, lower adiponectin and higher leptin in subjects with NAFLD may contribute to increase of blood pressure. But, we also observed the association between FLI and incident hypertension remained statistically significant even after adjustment for adiponectin level in our study. Finally, hepatokines from a fatty liver can modulate inflammatory processes that in turn mediate vascular disease \[36\]. This mechanism might also explain the independent role of NAFLD in the progression of hypertension.

We observed significant effectiveness of FLI (\(\geq 30\)) for predicting incident hypertension. As fatty liver disease is rapidly increasing in prevalence, it is important to identify high-risk subjects early to select subjects who need further imaging study such as ultrasonography and magnetic resonance spectroscopy. Radiological modalities which are widely used for detecting fatty liver disease are rather inaccurate because milder degrees of steatosis (<33% of fat in hepatocytes) cannot be fully detected \[37\]. However, FLI is a simple and easily accessible index in clinical practice, as it only requires measurements of BMI, waist circumference, GGT, and TG. The FLI can detect fatty liver disease assessed by ultrasonography with considerable accuracy \[12\] and it has been well validated in a Korean population \[13\]. Therefore, FLI is simple and useful clinical marker for predicting the presence of hepatic steatosis as well as the risk of metabolic disorders like diabetes and hypertension. Considering that hypertension is the most important risk factor for cardiovascular disease, the FLI also can be applied to predict and prevent further cardiovascular disease.

The major strength of our study is that the data were obtained from a rural cohort study that included a large number of subjects. Moreover, this is the first population-based prospective study that extensively investigated the potential role of hepatic steatosis in the pathogenesis of hypertension. However, this study has some limitations. First, our study used FLI as a surrogate marker for NAFLD, because this cohort study did not include imaging studies such as ultrasounds or magnetic resonance spectroscopy with liver biopsy, which is a gold standard for diagnosing NAFLD. However, other recent studies also showed some important findings using these validated NAFLD predictive models to overcome the limitation of abdominal sonography based diagnosis \[38, 39\]. Second, because each component of FLI such as waist circumference, BMI, TG, and GGT is a risk factor for hypertension by itself, NAFLD may not be an independent predictor for incident hypertension. Third, because the follow-up period of our cohort was too short (2.6 years) and about 25% of the sample did not complete the follow-up visit, we could not analyze data in a large sample. Fourth, we could not measure hepatokines such as fetuin-A, fibroblast growth factor 21, and selenoprotein P and levels of renin, angiotensin II and aldosterone which could explain the mechanism for an independent role of NAFLD in incident hypertension. Finally, because our study participants were Korean rural adults, it is unclear whether our results could be applied to other regional populations and other ethnic groups.

In conclusion, our study is the largest longitudinal cohort study to examine the association between fatty liver disease and incident hypertension in a relatively healthy rural population. Our results demonstrated that the FLI, a simple surrogate indicator of hepatic steatosis, is a valuable and easily accessible tool for identifying subjects at high risk for hypertension. In addition, fatty liver disease itself contributes to the development of hypertension, independently of systemic insulin resistance, inflammatory status and adiponectin levels. Considering the worldwide increase in fatty liver disease and hypertension, further studies are warranted to elucidate
the mechanism for the independent role of fatty liver disease in incident hypertension. In addition, a larger study is needed to validate the FLI for the prediction of incident hypertension.

Supporting Information

S1 Dataset.
(XLSX)

S1 Table. Fatty liver index changes according to incident hypertension
(DOCX)

Acknowledgments

Epidemiologic data used in this study were from the Korean Genome and Epidemiology Study (KoGES) of the Korea Centers for Disease Control & Prevention, Republic of Korea.

Author Contributions

Conceived and designed the experiments: JHH JYK. Performed the experiments: JHH EHC. Analyzed the data: JHH EHC. Contributed reagents/materials/analysis tools: SVA SBK. Wrote the paper: KCS EJK JBP.

References

1. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage: implications for therapy. Hypertension. 2004; 44(5):595–601. doi: 10.1161/01.HYP.0000145180.38707.84 PMID: 15452024.

2. Blood Pressure Lowering Treatment Trialists C, Turnbull F, Neal B, Ninomiya, Algert, Arima H, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. Bmj. 2008; 336(7653):1121–3. doi: 10.1136/bmj.39548.739368.BE PMID: 18480116; PubMed Central PMCID: PMC2386598.

3. Harrison W, Marshall T. The epidemiology of blood pressure in East Asia. Journal of human hypertension. 2006; 20(2):97–9. doi: 10.1038/sj.jhh.1001958 PMID: 16251999.

4. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology. 2005; 42(1):44–52. doi: 10.1002/hep.20734 PMID: 15895401.

5. Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. Journal of hepatology. 2008; 49(4):608–12. doi: 10.1016/j.jhep.2008.06.018 PMID: 18682312.

6. Souza MR, Diniz Mde F, Medeiros-Filho JE, Araujo MS. Metabolic syndrome and risk factors for non-alcoholic fatty liver disease. Arquivos de gastroenterologia. 2012; 49(1):89–96. PMID: 22481692.

7. Lopez-Suarez A, Guerrero JM, Elvira-Gonzalez J, Beltran-Robles M, Canas-Hormigo F, Bascunana-Quirell A. Nonalcoholic fatty liver disease is associated with blood pressure in hypertensive and nonhypertensive individuals from the general population with normal levels of alanine aminotransferase. European journal of gastroenterology & hepatology. 2011; 23(11):1011–7. doi: 10.1097/MEG.0b013e32834b8d52 PMID: 21915061.

8. Lau K, Lorbeer R, Haring R, Schmidt CO, Wallaschofski H, Nauck M, et al. The association between fatty liver disease and blood pressure in a population-based prospective longitudinal study. Journal of hypertension. 2010; 28(9):1829–35. doi: 10.1097/HJH.0b013e32833c211b PMID: 20577126.

9. Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. Gut. 1995; 36(3):437–41. PMID: 7698705; PubMed Central PMCID: PMC1382461.

10. Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. British medical journal. 1986; 292(6512):13–5. PMID: 3080046; PubMed Central PMCID: PMC1338970.

11. Osaka H, Mori Y. Sonographic diagnosis of fatty liver using a histogram technique that compares liver and renal cortical echo amplitudes. Journal of clinical ultrasound: JCU. 1996; 24(1):25–9. doi: 10.1002/ (SICI)1097-0096(199601)24:1<25::AID-JCU4>3.0.CO;2-N PMID: 8655863.
12. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC gastroenterology. 2006; 6:33. doi: 10.1186/1471-230X-6-33 PMID: 17081293; PubMed Central PMCID: PMC1636651.
13. Kim JH, Kwon SY, Lee SW, Lee CH. Validation of fatty liver index and lipid accumulation product for predicting fatty liver in Korean population. Liver international: official journal of the International Association for the Study of the Liver. 2011; 31(10):1600–1. doi: 10.1111/j.1478-3231.2011.02580.x PMID: 22093336.
14. Zelber-Sagi S, Webb M, Assay N, Blendis L, Yeshua H, Leshno M, et al. Comparison of fatty liver index with noninvasive methods for steatosis detection and quantification. World journal of gastroenterology: WJG. 2013; 19(1):57–64. doi: 10.3748/wjg.v19.i1.57 PMID: 23326163; PubMed Central PMCID: PMC3542754.
15. Jung CH, Lee WJ, Hwang JY, Yu JH, Shin MS, Lee MJ, et al. Assessment of the fatty liver index as an indicator of hepatic steatosis for predicting incident diabetes independently of insulin resistance in a Korean population. Diabetic medicine: a journal of the British Diabetic Association. 2013; 30(4):426–35. doi: 10.1111/dme.12104 PMID: 23278918.
16. Kim JY, Ahn SV, Yoon JH, Koh SB, Yoon J, Yoo BS, et al. Prospective study of serum adiponectin and incident metabolic syndrome: the ARIRANG study. Diabetes care. 2013; 36(6):1547–53. doi: 10.2337/dc12-0223 PMID: 23275369; PubMed Central PMCID: PMC3661834.
17. Jung DH, Kim JY, Kim JK, Koh SB, Park JK, Ahn SV. Relative contribution of obesity and serum adiponectin to the development of hypertension. Diabetes research and clinical practice. 2014; 103(1):51–6. doi: 10.1016/j.diabres.2013.09.018 PMID: 24398319.
18. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). Jama. 2013; 311(5):507–20. doi: 10.1001/jama.2013.284427 PMID: 24352797.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28(7):412–9. PMID: 3899825.
20. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. The New England journal of medicine. 2010; 363(14):1341–50. doi: 10.1056/NEJMoa0912063 PMID: 20879883.
21. Oni ET, Agatston AS, Blaha MJ, Fialkow J, Curry R, Sposito A, et al. A systematic review: burden and severity of subclinical cardiovascular disease among those with nonalcoholic fatty liver; should we care? Atherosclerosis. 2013; 230(2):258–67. doi: 10.1016/j.atherosclerosis.2013.07.052 PMID: 24075754.
22. Aneni EC, Oni ET, Martin SS, Blaha MJ, Agatston AS, Feldman T, et al. Blood pressure is associated with the presence and severity of nonalcoholic fatty liver disease across the spectrum of cardiometabolic risk. Journal of hypertension. 2015; 33(6):1207–14. doi: 10.1097/HJH.0000000000000532 PMID: 25693058.
23. Ryoo JH, Suh YJ, Shin HC, Cho YK, Choi JM, Park SK. Clinical association between non-alcoholic fatty liver disease and the development of hypertension. Journal of gastroenterology and hepatology. 2014; 29(11):1926–31. doi: 10.1111/jgh.12643 PMID: 24910023.
24. Munshi MK, Uddin MN, Glaser SS. The role of the renin-angiotensin system in liver fibrosis. Experimental biology and medicine. 2011; 236(5):557–66. doi: 10.1258/ebm.2011.010375 PMID: 21508249.
25. Paschos P, Tzimalos K. Nonalcoholic fatty liver disease and the renin-angiotensin system: Implications for treatment. World journal of hepatology. 2012; 4(12):327–31. doi: 10.4254/wjh.v4.i12.327 PMID: 23355909; PubMed Central PMCID: PMC3554795.
26. Kato J, Koda M, Kishina M, Tokunaga S, Matono T, Sugihara T, et al. Therapeutic effects of angiotensin II type 1 receptor blocker, irbesartan, on non-alcoholic steatohepatitis using FLS-ob/ob male mice. International journal of molecular medicine. 2012; 30(1):107–13. doi: 10.3892/ijmm.2012.958 PMID: 22469867.
27. Hidose A, Ono M, Saibara T, Nozaki Y, Masuda K, Yoshioka A, et al. Angiotensin II type 1 receptor blocker inhibits fibrosis in rat nonalcoholic steatohepatitis. Hepatology. 2007; 45(6):1375–81. doi: 10.1002/hep.21638 PMID: 17518368.
28. Fan JG, Li F, Cai XB, Peng YD, Ao QH, Gao Y. Effects of nonalcoholic fatty liver disease on the development of metabolic disorders. Journal of gastroenterology and hepatology. 2007; 22(7):1086–91. doi: 10.1111/j.1440-1746.2006.04781.x PMID: 17608855.
29. Persenghi G, Petersen K, Shulman GI. Cellular mechanism of insulin resistance: potential links with inflammation. International journal of obesity and related metabolic disorders: journal of the
30. Cai D, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. Nature medicine. 2005; 11(2):183–90. doi: 10.1038/nm1166 PMID: 15685173; PubMed Central PMCID: PMC1440292.

31. Kern PA, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. American journal of physiology Endocrinology and metabolism. 2001; 280(5):E745–51. PMID: 11287357.

32. Bhagat B, Burke WJ, Dhalla NS. Insulin-induced enhancement of uptake of noradrenaline in atrial strips. British journal of pharmacology. 1981; 74(2):325–32. PMID: 6274461; PubMed Central PMCID: PMC2071738.

33. Aizawa-Abe M, Ogawa Y, Masuzaki H, Ebihara K, Satoh N, Iwai H, et al. Pathophysiological role of leptin in obesity-related hypertension. The Journal of clinical investigation. 2000; 105(9):1243–52. doi: 10.1172/JCI38341 PMID: 10791999; PubMed Central PMCID: PMC315441.

34. Beltowski J. Role of leptin in blood pressure regulation and arterial hypertension. Journal of hypertension. 2006; 24(5):789–801. doi: 10.1097/01.hjh.0000222743.06584.66 PMID: 16612235.

35. Rojas E, Rodríguez-Molina D, Bolli P, Israeli ZH, Faria J, Fidilio E, et al. The role of adiponectin in endothelial dysfunction and hypertension. Current hypertension reports. 2014; 16(8):463. doi: 10.1007/s11906-014-0463-7 PMID: 24924994.

36. Yoo HJ, Choi KM. Hepatokines as a Link between Obesity and Cardiovascular Diseases. Diabetes & metabolism journal. 2015; 39(1):10–5. doi: 10.4093/dmj.2015.39.1.10 PMID: 25729707; PubMed Central PMCID: PMC4342531.

37. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology. 2002; 123(3):745–50. PMID: 12198701.

38. Lee YH, Jung KS, Kim SU, Yoon JJ, Yun YJ, Lee BW, et al. Sarcopenia is associated with NAFLD independently of obesity and insulin resistance: Nationwide surveys (KNHANES 2008–2011). Journal of hepatology. 2015; 63(2):486–93. doi: 10.1016/j.jhep.2015.02.051 PMID: 25772036.

39. Kozakova M, Palombo C, Eng MP, Dekker J, Flyvbjerg A, Mitrakou A, et al. Fatty liver index, gamma-glutamyltransferase, and early carotid plaques. Hepatology. 2012; 55(5):1406–15. doi: 10.1002/hep.25555 PMID: 22334565.