Association between nonalcoholic fatty liver disease and coronary artery calcification in postmenopausal women

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Abstract

Objective: Cardiovascular disease is a leading cause of death in postmenopausal women, and nonalcoholic fatty liver disease (NAFLD) has been known to be associated with cardiovascular disease. However, little information regarding the relationship between NAFLD and coronary artery calcification (CAC) in postmenopausal women is available. The aim of this study was to investigate the association between NAFLD and CAC in postmenopausal women.

Methods: Among 4,377 participants who underwent cardiac computed tomography in a health promotion center, 919 postmenopausal women were enrolled. Anthropometric profiles and multiple cardiovascular risk factors were measured. NAFLD was measured by ultrasonography, and CAC was evaluated by cardiac computed tomography. Odds ratios and 95% CI for the presence of CAC, by severity of fatty liver disease, were estimated using logistic regression.

Results: Women were stratified into three groups by severity of NAFLD. There were significant differences in cardiovascular parameters among the groups, and prevalence of CAC significantly increased with severity of NAFLD. On logistic regression analysis after adjustment for multiple risk factors, the odds ratios for the prevalence of CAC were as follows (P < 0.05): no NAFLD, 1.0; mild NAFLD, 1.34 (95% CI, 0.92-2.16); moderate to severe NAFLD, 1.83 (95% CI, 1.06-3.16). However, this association was attenuated after adjustment for insulin resistance (P = 0.16).

Conclusions: There is a significant correlation between NAFLD and prevalence of CAC, but NAFLD is not an independent factor for coronary atherosclerosis in postmenopausal women.

Key Words: Nonalcoholic fatty liver disease – Coronary artery calcification – Menopause.

Nonalcoholic fatty liver disease (NAFLD) is a condition found in people who do not consume alcohol but shares similar histological features with alcohol-induced liver injury, ranging from simple steatosis to steatohepatitis, which can progress to advanced fibrosis and cirrhosis.1 Previous studies have reported that the prevalence of NAFLD is higher in postmenopausal women2 and that postmenopause is a risk factor for NAFLD.3,4

NAFLD is closely related to several metabolic disorders4-6 and is also associated with increased risk of cardiovascular disease (CVD), including coronary artery disease.7 Recently, several studies have shown that NAFLD is associated with increased incidence of cardiovascular events.8-10 CVD is a leading cause of death in postmenopausal women.11 Coronary artery calcification (CAC), as determined by multidetector computed tomography (CT), is a sensitive measure for detecting the existence of early coronary atherosclerosis. Moreover, CAC may have prognostic value for predicting future cardiovascular events.12-14

Although several studies have investigated the relationship between NAFLD and CAC, results have been inconsistent.15-17 In addition, no study has investigated the relationship between CAC and severity of NAFLD in postmenopausal women. Therefore, we investigated the relationship between NAFLD and prevalence of CAC in postmenopausal women.

METHODS

Study population

This is a retrospective cross-sectional study. There were 4,377 participants, all of whom underwent cardiac CT in a health promotion center at Gangnam Severance Hospital (Seoul, Korea) between January 2008 and February 2013.
From 4,377 participants, we excluded men (n = 2,584) and premenopausal women (n = 748). Postmenopausal women 50 years or older with no menstrual periods for more than 12 consecutive months and women with elevated follicle-stimulating hormone levels (>30 IU/L) were included in this study (n = 1,045). Women with diabetes mellitus (n = 59), excessive alcohol consumption (n = 7), viral hepatitis (positive results for hepatitis B surface antigen or anti–hepatitis C virus; n = 19), liver cirrhosis or malignancy on ultrasonography (n = 6), and self-reported or medically verified history of CVD (n = 35) were excluded from this study. Ultimately, 919 postmenopausal women were enrolled in this study. The institutional review board of Yonsei University College of Medicine approved the study protocol. A written informed consent form was obtained from all participants.

Clinical characteristics

Height and weight were measured, and body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m²). Lifestyle, personal medical history of acute and chronic diseases, and medication history were assessed using a standard questionnaire. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured after a 5-minute rest.

Biochemical parameters

Blood samples were obtained from all participants after 12 hours of fasting. Fasting plasma glucose (FPG), aspartate aminotransferase, alanine aminotransferase, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and C-reactive protein (CRP) levels were determined by enzymatic methods using a Hitachi 7600-120 automated chemistry analyzer (Hitachi, Tokyo, Japan). Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald equation. Hepatitis B surface antigen levels and antibodies to hepatitis C virus were measured with a Roche E-170 device (Roche Diagnostics, Mannheim, Germany). Fasting serum insulin was determined by chemiluminescence (radioimmunoassay kit; Daiichi, Kyoto, Japan), and insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) index calculated from the following formula: HOMA-IR = fasting insulin (µU/mL) × FPG (mmol/L) / 22.5.

CAC measurement with multidetector CT

CAC was determined with a multidetector CT scanner (Philips Brilliance 64; Philips Medical System, Best, the Netherlands). We used a standard prospective electrocardiogram gating protocol with a step-and-shoot technique. The scanning protocol included a slice section collimation of 64 × 0.625 mm, rotation time of 420 milliseconds, tube voltage of 120 kV, and tube current of 210 mAs. Quantitative CAC score (CACS) was calculated with dedicated software and expressed as Agatston score. Presence of CAC was defined as CACS higher than 0.

| TABLE 1. Clinical characteristics of participants, by severity of fatty liver disease |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Group I (no NAFLD; n = 625) | Group II (mild NAFLD; n = 165) | Group III (moderate to severe NAFLD; n = 129) | P               |
| Age, y          | 57.06 (7.08)    | 58.10 (5.97)    | 59.52 (6.52)    | <0.01           |
| BMI, kg/m²      | 22.11 (2.62)    | 24.18 (2.85)    | 25.70 (3.72)    | <0.01           |
| SBP, mm Hg      | 122.27 (18.31)  | 127.32 (18.75)  | 134.24 (19.43)  | <0.01           |
| DBP, mm Hg      | 74.96 (10.41)   | 78.38 (10.48)   | 81.06 (10.38)   | <0.01           |
| FPG, mg/dL      | 90.29 (10.01)   | 95.96 (9.69)    | 99.36 (11.78)   | <0.01           |
| TC, mg/dL       | 201.16 (33.79)  | 204.65 (34.84)  | 204.31 (38.73)  | 0.39            |
| TG, mg/dL       | 114.70 (59.40)  | 143.39 (85.37)  | 143.39 (85.37)  | <0.01           |
| HDL-C, mg/dL    | 56.98 (12.90)   | 51.90 (11.61)   | 47.67 (9.35)    | <0.01           |
| LDL-C, mg/dL    | 123.23 (30.46)  | 128.05 (32.37)  | 127.96 (35.95)  | 0.10            |
| AST, IU/L       | 22.56 (8.55)    | 24.10 (9.30)    | 26.77 (10.49)   | <0.01           |
| ALT, IU/L       | 19.93 (11.23)   | 25.32 (16.28)   | 31.48 (17.99)   | <0.01           |
| CRP, median (interquartile range), mg/L | 0.5 (0.3-1.2)  | 1.0 (0.5-1.7)  | 1.3 (0.7-2.2)  | <0.01           |
| HOMA-IR, median (interquartile range) | 0.78 (0.53-1.14) | 1.12 (0.88-1.50) | 1.56 (0.97-2.44) | <0.01           |

Data are presented as mean (SD) unless otherwise stated. Intergroup comparisons were performed using analysis of variance.

NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance.
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### TABLE 2. Prevalence of CAC and mean of ln(CACS+1), by severity of fatty liver disease

|                        | Group I (no NAFLD; n = 625) | Group II (mild NAFLD; n = 165) | Group III (moderate to severe NAFLD; n = 129) | P       |
|------------------------|-----------------------------|-------------------------------|---------------------------------------------|---------|
| ln(CACS + 1), mean (SD)| 0.59 (1.47)                 | 0.78 (1.53)                  | 1.03 (1.66)                                 | <0.01   |
| CACS >0 (%), n (%)     | 101 (16.1)                  | 38 (23.0)                    | 43 (33.3)                                   | <0.01   |

Intergroup comparisons were performed using analysis of variance. \( \chi^2 \) tests were used to compare categorical variables with percentages. CAC, coronary artery calcification; CACS, CAC score; NAFLD, nonalcoholic fatty liver disease.

### Statistical analysis

Continuous variables with normal distribution were expressed as mean (SD), whereas continuous variables with skewed distribution were presented as median (interquartile range) and log-transformed for analysis. Intergroup comparisons were performed using analysis of variance. \( \chi^2 \) tests were used to compare categorical variables with percentages. Logistic regression analysis was used to analyze the association between NAFLD and presence of CAC while controlling for potential confounders. Covariates in the multivariable model, such as age, BMI, SBP, DBP, FPG, TC, LDL-C, TG, HDL-C, CRP, and HOMA-IR, were chosen for clinical importance and statistical significance. SPSS statistical package version 20.0 (SPSS Inc, Chicago, IL) was used for all statistical analyses. \( P < 0.05 \) was considered statistically significant.

### RESULTS

A total of 919 postmenopausal women were included in this study. Of these, 738 women had no CAC (CACS = 0), whereas the remaining 181 women exhibited some evidence of CAC (CACS > 0; 19.7%). Among women in this study, 294 women (31.9%) were diagnosed as having NAFLD on ultrasonography.

Women were stratified into three groups by the presence and severity of fatty liver disease. Table 1 shows the demographic, clinical, and laboratory characteristics of the groups. Significant between-group differences in several metabolic parameters were observed. Age, BMI, SBP, DBP, FPG, TG, aspartate aminotransferase, alanine aminotransferase, CRP, and HOMA-IR increased according to the severity of fatty liver disease, whereas HDL-C decreased.

The prevalence of CAC and the mean CAC score significantly increased with the severity of fatty liver disease (Table 2).

The association between fatty liver disease and presence of CAC (CACS > 0) was further explored by categorizing the severity of NAFLD into three groups and by using the first group as reference (Table 3). These relationships remained significant even after adjusting for well-established cardiovascular risk factors, including age, BMI, SBP, DBP, FPG, TC, LDL-C, TG, HDL-C, and CRP (model 2). However, this association was attenuated after additional adjustment for insulin resistance (model 3).

### DISCUSSION

In this study, we investigated the relationship between NAFLD and prevalence of CAC in postmenopausal women. We found that the prevalence of CAC was significantly associated with NAFLD after adjustment for conventional cardiovascular risk factors, but this association was attenuated after adjustment for insulin resistance. To the best of our knowledge, this is the first study to investigate the correlation between NAFLD and presence of early coronary artery atherosclerosis in postmenopausal women.

In this study, the prevalence of NAFLD in postmenopausal women was 31.9%. This prevalence was higher than that in premenopausal women (19.7%), which was determined by analyzing the subgroup of premenopausal women among 4,377 participants. Hamaguchi et al. reported that the prevalence of NAFLD in Japanese postmenopausal women was higher than that in premenopausal women and concluded that postmenopause was a risk factor for NAFLD. Although it remains unclear how estrogen deficiency increases the prevalence of NAFLD after menopause, several reports have suggested that estrogen deficiency affects body fat distribution, which increases accumulation of glucosefemoral fat and central fat. Hepatic estrogen receptors mediate estrogen action in the liver, and estradiol has been shown to play a

### TABLE 3. Odds ratios (95% CI) for developing CAC (CACS >0), by severity of fatty liver disease

| Group I (no NAFLD) | Group II (mild NAFLD) | Group III (moderate to severe NAFLD) | P for trend |
|-------------------|----------------------|-------------------------------------|------------|
| Unadjusted        | 1.00                 | 1.56 (1.02-2.37)                    | <0.01      |
| Model 1           | 1.00                 | 1.45 (0.91-2.29)                    | <0.01      |
| Model 2           | 1.00                 | 1.34 (0.92-2.16)                    | <0.05      |
| Model 3           | 1.00                 | 1.27 (0.63-2.66)                    | 0.16       |

Model 1: adjusted for age and body mass index.
Model 2: model 1 with additional adjustment for systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, low-density lipoprotein cholesterol, triglycerides, high-density lipoprotein cholesterol, and C-reactive protein.
Model 3: model 2 with additional adjustment for homeostasis model assessment of insulin resistance.

Logistic regression analysis was used to analyze the association between NAFLD and presence of CAC. CAC, coronary artery calcification; CACS, CAC score; NAFLD, nonalcoholic fatty liver disease.
favorable role in chronic liver disease.\textsuperscript{19} Thus, estrogen seems to exert a protective effect against NAFLD in women.\textsuperscript{20,21}

In this study, we showed that most metabolic risk factors increased or decreased with the severity of NAFLD. These findings are similar to those of other studies.\textsuperscript{22-24} CAC has been shown to be an independent predictor of future cardiovascular events.\textsuperscript{22,25} Moreover, the importance of CAC and its association with CVD is becoming increasingly recognized.\textsuperscript{4} Several recent studies have reported the association between NAFLD and CAC, but results have been inconsistent. As part of the Diabetes Heart Study, McKinnie et al\textsuperscript{13} reported that coronary arterial calcium did not correlate with hepatic steatosis in women with type 2 diabetes. Another study of 398 white and black participants by Ding et al\textsuperscript{26} did not find associations of liver fat attenuation with calcified coronary plaque. Recently, VanWagner et al\textsuperscript{27} showed that obesity attenuates the relationship between NAFLD and CAC. In contrast, some studies have suggested that NAFLD might be an independent risk factor for CAC, after accounting for conventional risk factors.\textsuperscript{16,17,23,28} However, these studies did not evaluate the impact of insulin resistance. Only a few studies have investigated the association between NAFLD and carotid intima-media thickness, which is another marker for subclinical atherosclerosis, after adjusting for insulin resistance and other traditional risk factors. However, whether NAFLD is an independent risk factor for increased intima-media thickness remains controversial.\textsuperscript{22,29,30}

In the present study, similar to a previous study of healthy women, we found that the presence of CAC increased with the severity of NAFLD in postmenopausal women.\textsuperscript{17} However, this association was attenuated after adjusting for insulin resistance, and insulin resistance was independently associated with CAC in these adjusted models. This suggests that insulin resistance may act as a mediator of the relationship between NAFLD and CAC. Although the pathogenesis of NAFLD and CAC has not been fully elucidated, there are several explanations for the relationship between NAFLD and CAC.\textsuperscript{31} One of the accepted hypotheses implicates insulin resistance as a major factor leading to NAFLD and CAC.\textsuperscript{32-34} Menopause affects body fat distribution, and the resultant increases in body weight and body fat lead to insulin resistance, which might play an important role in the pathogenesis of clinical NAFLD and CAC. Recently, Rodrigues et al\textsuperscript{35} reported that insulin resistance, metabolic syndrome, and abdominal obesity were risk markers for the development of NAFLD in postmenopausal women. Therefore, although the mechanism underlying the relationship between NAFLD and CAC in postmenopausal women is not completely understood, insulin resistance might provide a link between them.

There are some limitations to our study. First, this is a cross-sectional study that cannot definitively establish causality. Thus, the precise causal relationship between NAFLD and CAC remains controversial. Second, this study lacked direct measures of body fat, which affects insulin resistance. Third, our results were not based on biopsy-proven NAFLD. Fatty liver disease was assessed by liver ultrasonography—a technique that cannot detect fatty infiltration below 30%.\textsuperscript{36} However, ultrasonography is nonetheless a very useful non-invasive technique that is often used as the first-line imaging technique in clinical practice and epidemiological studies.\textsuperscript{37} Finally, because participants in the current study were enrolled in the same health promotion center, generalizability may be limited.

**CONCLUSIONS**

Increased severity of NAFLD is significantly associated with CAC, a marker of subclinical atherosclerosis. However, this association is attenuated after additional adjustment for insulin resistance; thus, NAFLD is not an independent factor for coronary atherosclerosis in postmenopausal women. Further prospective large-scale studies are required to explore these findings and to elucidate the mechanism for this association.

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