

Nonalcoholic fatty liver disease is associated with coronary artery disease in Koreans

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Abstract

AIM: To investigate whether nonalcoholic fatty liver disease (NAFLD) affects coronary artery disease (CAD) and identify candidate mediators.

METHODS: Patients who underwent coronary angiography were consecutively recruited. The patients were classified into four groups by coronary artery stenosis: A, insignificant; B, one-vessel disease; C, two-vessel disease; and D, three-vessel disease. Abdominal ultrasonography was performed to determine the presence of a fatty liver and categorize by grade: 0, no evidence; 1, mild; 2, moderate; and 3, severe. We measured not only known CAD risk factors, but also serum insulin, HOMA-index, adiponectin, interleukin-6, tumor necrosis factor- α and high-sensitivity C-reactive protein levels.

RESULTS: Of the 134 patients who met the inclusion criteria, 82 (61.2%) had ultrasonographically diagnosed NAFLD. Among the 46 patients with CAD, 37 (80.4%) had evidence of a fatty liver. The two groups (A vs B-D) were significantly different in terms of age, total cholesterol, triglycerides, low-density lipoprotein levels and fatty liver. Coronary artery stenosis was strongly associated with fatty liver in a grade-dependent manner ($P = 0.025$). In binary logistic regression, NAFLD was a significant independent predictor of CAD ($P = 0.03$, OR = 1.685; 95%CI: 1.051-2.702). Among the candidate mediators, the serum adiponectin level showed a trend toward lowering based on CAD progression ($P = 0.071$).

CONCLUSION: NAFLD is an independent risk factor for CAD in a grade-dependent manner. Moreover, adiponectin might be related to the pathogenesis of NAFLD.

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Key words: Nonalcoholic fatty liver disease; Coronary artery disease; Coronary angiography; Adiponectin; Insulin resistance

Core tip: This article shows that angiographically proven coronary artery stenosis is strongly associated with nonalcoholic fatty liver disease (NAFLD) in a grade-dependent manner. Although many recent studies used coronary artery calcification score, carotid artery intima-media thickness, or carotid artery plaque measurements as surrogate markers for coronary artery disease (CAD), we evaluated the interaction between fatty liver and cardiovascular outcomes using coronary angiograms in a prospective case-controlled study. Because the pathogenesis of NAFLD and CAD is not fully elucidated, we attempted to identify mediators of these diseases and believe that adiponectin might be related to the development and progression of CAD in patients with NAFLD.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common disorder with an increasing prevalence of approximately 34% of the adult population in the United States^[1]. Patients with NAFLD can progress to more aggressive forms of nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis, end-stage liver disease, and eventually hepatocellular carcinoma^[2]. Because NAFLD is related to metabolic syndrome and obesity, many patients with NAFLD have coronary artery disease (CAD). Several studies have reported that NAFLD is a strong independent risk factor for CAD^[3,4]. However, these studies have some clinical application limitations because of the use of indirect modalities, such as coronary artery calcification or intima-media thickness despite coronary artery imaging. Authors of these studies suggested that the presence of CAD was indicated by coronary artery calcification or intima-media thickness despite conducting coronary artery imaging^[5,6]. Many NAFLD studies conducted in Western populations have found a relationship between NAFLD and CAD in relatively obese patients, which has not been found in Asian populations^[6,7]. Therefore, the relationship between NAFLD and CAD in relatively thin Asian people must be evaluated. This study was conducted to evaluate whether NAFLD independently affects angiographically proven CAD in Asians and, if so, which mediator is responsible for this association.

MATERIALS AND METHODS

Subjects and study design

From January 2009 to June 27, 2011, 184 adult patients who underwent elective coronary angiography (CAG) at Kangwon National University Hospital were consecutively recruited. Indications for CAG included Canadian Cardiovascular Society class III or IV angina upon medical treatment, high-risk findings upon noninvasive testing, acute coronary syndrome, or a chest pain evaluation according to the American College of Cardiology/American Heart Association recommendations^[8]. Standard selective CAG was performed by three experienced cardiologists and reviewed by another cardiologist. CAD was defined as the presence of at least a 50% stenosis in at least one major coronary artery. The patients were classified into four groups according to the number of major coronary arteries affected by CAD: A, insignificant coronary artery stenosis; B, one-vessel disease; C, two-vessel disease; and D, three-vessel disease.

We excluded patients with viral hepatitis (positive for

hepatitis B surface antigen and anti-hepatitis C virus), history of alcohol ingestion (> 30 g/d for men and > 20 g/d for women), history of drug use reported to cause steatosis (steroids, estrogens, tamoxifen, amiodarone, valproic acid, diltiazem, or methotrexate), improved steatosis (metformin, statins, or glitazones) within 3 mo of enrollment, or other history of chronic liver disease. Hypertension was defined as systolic blood pressure \geq 140 mmHg, diastolic blood pressure \geq 90 mmHg or using antihypertensive medications. Diabetes was defined as fasting blood sugar \geq 126 mg/dL or using glucose-lowering medications (oral agents or insulin). Of the 184 patients, we excluded 50 with at least one potential cause for chronic liver disease. Altogether, 134 patients were enrolled and underwent abdominal ultrasonography within 2 d after CAG by a single experienced physician to determine the presence of four fatty liver grades: 0, no evidence of fatty liver; 1, mild; 2, moderate; and 3, severe degree. The presence of a fatty liver was identified by characteristic echo patterns such as a diffuse increase in the echogenicity of the liver compared with that of the kidney according to conventional criteria^[9]. We measured not only known risk factors (*i.e.*, age, male gender, high low-density lipoprotein, low high-density lipoprotein, triglyceride, body mass index, diabetes, and hypertension) for CAD but also serum insulin, HOMA index, adiponectin, interleukin (IL)-6, tumor necrosis factor (TNF)- α and high-sensitivity C-reactive protein (hs-CRP) levels. This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Kangwon National University Hospital.

Statistical analysis

Clinical and biochemical variables were compared between the two groups (A vs B-D). Continuous variables were assessed with the unpaired Student's *t*-test, and nominal variables were compared with the chi-square test. Variables that were significantly different between the two groups were extracted and included as covariates in a binary logistic regression with CAD as the dependent and NAFLD as the independent variable. Correlations between CAD severity and NAFLD degree were analyzed using Pearson's correlation analysis. A *P*-value < 0.05 was considered significant. All analyses were conducted using the SPSS for Windows 12.0.1 statistical software (SPSS, Inc., Chicago, IL, United States).

RESULTS

A total of 134 (37 males and 97 females) patients met the inclusion criteria for the study. Table 1 demonstrates the demographic, clinical and laboratory data of the subjects without CAD (A) and those with CAD (B-D). The two groups were significantly different in terms of age, total cholesterol, triglycerides, low-density lipoprotein levels and presence of NAFLD. In addition, there tended to be more clinical features associated with metabolic syndrome in the CAD group, but the difference was not significant. In each

Table 1 Comparison of clinical characteristics and laboratory data between subjects with and without coronary artery disease

	Group A Insignificant stenosis (n = 88)	Group B-D Significant stenosis (n = 46)	P value
Age (yr)	62.5 ± 10.8	65.2 ± 9.2	0.010
Sex (male)	20 (22.7)	17 (37.0)	0.104
DM	11 (12.5)	10 (21.7)	0.211
HTN	49 (55.7)	33 (71.7)	0.093
Height (cm)	155.0 ± 7.4	156.4 ± 8.4	0.333
Weight (kg)	61.9 ± 8.2	62.5 ± 10.0	0.734
BMI (kg/m ²)	25.8 ± 3.3	25.6 ± 3.4	0.697
Waist circumference (cm)	86.8 ± 13.4	89.7 ± 6.9	0.169
Hip circumference (cm)	97.6 ± 13.8	98.7 ± 8.3	0.607
WHR	0.89 ± 0.9	0.91 ± 0.8	0.238
Total cholesterol (mg/dL)	177.1 ± 30.8	195.6 ± 39.1	0.009
HDL cholesterol (mg/dL)	41.2 ± 12.2	38.4 ± 12.1	0.227
Triglyceride (mg/dL)	134.9 ± 72.4	177.4 ± 94.4	0.012
Measured-LDL cholesterol (mg/dL)	102.3 ± 26.1	115.5 ± 33.3	0.015
Calculated-LDL cholesterol (mg/dL)	108.6 ± 28.3	121.7 ± 33.7	0.033
Creatinine (mg/dL)	0.8 ± 0.3	1.1 ± 0.4	0.068
Uric acid (mg/dL)	4.6 ± 1.4	4.9 ± 1.6	0.399
Hemoglobin (g/dL)	13.4 ± 1.8	13.0 ± 1.5	0.356
HbA1c (%)	5.7 ± 0.7	6.3 ± 1.2	0.072
Systolic BP (mmHg)	123.3 ± 16.6	125.6 ± 15.6	0.409
Diastolic BP (mmHg)	73.8 ± 10.7	75.9 ± 9.6	0.250
FBS (mg/dL)	104.2 ± 21.2	115.3 ± 37.3	0.082
Total bilirubin (mg/dL)	1.0 ± 0.5	1.1 ± 0.6	0.432
Albumin (g/dL)	3.9 ± 0.3	3.9 ± 0.4	0.465
AST (U/L)	34.1 ± 55.0	27.1 ± 11.0	0.394
ALT (U/L)	30.7 ± 53.4	22.8 ± 9.7	0.321
PT INR	0.9 ± 0.3	0.8 ± 0.1	0.182
HOMA-index	6.29 ± 9.16	5.99 ± 5.39	0.838
NAFLD	44 (51.2)	36 (78.3)	0.002

Data are expressed as mean ± SD or n (%). DM: Diabetes mellitus; HTN: Hypertension; BMI: Body mass index; WHR: Waist-hip ratio; HDL: High density lipoprotein; LDL: Low density lipoprotein; BP: Blood pressure; FBS: Fasting blood sugar; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; PT: Prothrombin time; HOMA-index: Homeostatic model assessment of insulin resistance, fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5; NAFLD: Nonalcoholic fatty liver disease.

group, women were predominant, and all subjects were post-menopausal except for one person in the CAD group.

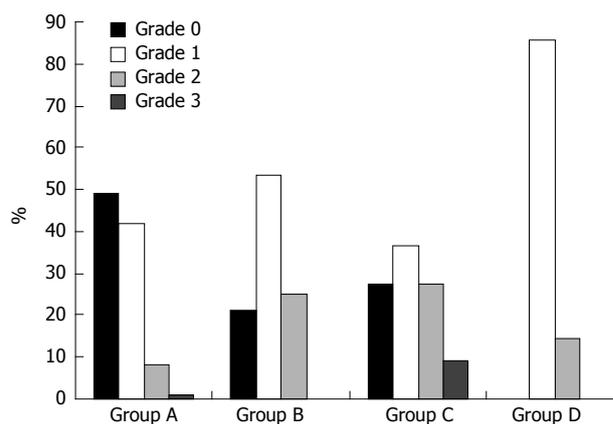
An analysis of the relationship between NAFLD and the presence of CAD is shown in Table 2. In addition to the significantly different variables between the two groups in Table 1, well-known established risk factors for CAD, such as age, gender, glucose, HbA1c and body mass index, were considered as covariates in conducting the multivariate analysis. In those models, as shown in Table 2, NAFLD was the significant independent predictor for CAD ($P = 0.03$, OR = 1.685; 95%CI: 1.051-2.702).

Next, we evaluated the correlation between the NAFLD degree and CAD severity. The proportion of patients with NAFLD increased from 51.1% in group A to 100% in group D. In group A, most of the fatty livers were grade 1. However, in the higher grade CAD group, the proportion of patients with more severe fatty livers was increased. No subject in group D (three-vessel

Table 2 Multivariate analysis of coronary artery disease with age, nonalcoholic fatty liver disease and metabolic risk factors

	OR (95%CI)	P value
NAFLD	1.685 (1.051-2.702)	0.030
Age	1.056 (1.010-1.104)	0.057
Total cholesterol (mg/dL)	1.012 (0.982-1.043)	0.427
TG (mg/dL)	1.004 (0.998-1.010)	0.873
Measured-LDL cholesterol (mg/dL)	1.003 (0.970-1.036)	0.225

NAFLD: Nonalcoholic fatty liver disease; TG: Triglycerides; LDL: Low density lipoprotein.

**Figure 1** Relationship between the grade of nonalcoholic fatty liver disease and severity of coronary artery disease.

disease) had a normal liver. Figure 1 shows that angiographically proven coronary artery stenosis was strongly associated with NAFLD in a grade-dependent manner by Pearson's correlation analysis ($P = 0.002$).

In addition, we measured the serum level of candidate mediators of metabolic syndrome, such as insulin, the HOMA index, IL-6, TNF- α , and hs-CRP (Table 3). In our results, none of the factors assessed were found to be related to CAD. However, serum adiponectin level demonstrated a trend toward lowering based on CAD progression ($P = 0.071$).

DISCUSSION

Our findings demonstrate that NAFLD is strongly associated with coronary artery stenosis in a grade-dependent manner. Our results also demonstrate that NAFLD is a significant predictor of CAD independent of traditional risk factors in Asians. Furthermore, we suggest that adiponectin might have a potential pathogenic role in the development and progression of CAD in patients with NAFLD.

Because NAFLD is a hepatic manifestation of metabolic syndrome, many studies have suggested that NAFLD results in increased cardiovascular risk and mortality^[7,10]. The risk for developing cardiovascular morbidity and mortality is thought to be higher than the risk for developing hepatic disease because of its slow progression. Therefore, many studies have investigated the association between NAFLD and cardiovascular diseases. As a result,

Table 3 Comparison of candidate mediators between subjects with and without coronary artery disease (mean \pm SD)

	Group A Insignificant stenosis (n = 88)	Group B-D Significant stenosis (n = 46)	P value
Adiponectin (μ g/mL)	8.40 \pm 5.97	6.95 \pm 5.85	0.071
IL-6 (pg/mL)	4.55 \pm 7.75	4.71 \pm 7.41	0.894
TNF- α (ng/mL)	4.00 \pm 3.95	4.85 \pm 4.73	0.273
hs-CRP(mg/dL)	0.45 \pm 1.70	0.74 \pm 1.18	0.366

IL: Interleukin; TNF: Tumor necrosis factor; hs-CRP: High sensitive C-reactive protein.

a number of studies have demonstrated that NAFLD is an independent risk factor for CAD^[4,5,11-13]. However, most studies used coronary artery calcification score, carotid artery intima-media thickness, carotid artery plaque measurements, or circulatory endothelial dysfunction as surrogate markers for CAD^[5,6,14]. Despite the fact that the coronary calcification score is a well-known marker for an increased risk of coronary events, the direct relationship between the presence of NAFLD and clinical CAD must be evaluated for use in the clinical setting^[3]. Recently, Wong *et al*^[15] evaluated the interaction between fatty liver and cardiovascular outcomes using coronary angiograms in a prospective cohort study and demonstrated that fatty liver is associated with CAD independently of other metabolic factors, which is consistent with our results. In contrast, our study was different from that study because we demonstrated that angiographically proven coronary artery stenosis was strongly associated with fatty liver in a grade-dependent manner.

Although the pathogenesis of NAFLD and CAD has not been fully elucidated, several explanations are present for the relationship between NAFLD and CAD. One widely accepted hypothesis implicates low-grade inflammatory conditions as key factors leading to hepatic steatosis and atherosclerosis^[16,17]. Moreover, oxidative stress is presumed to play a role in NASH pathogenesis. Many investigators have studied additional mechanisms that might be associated with NAFLD, which are supported by the levels of various biomarkers, such as reactive oxygen species, adipocytokines (leptin and adiponectin), CRP, and caspase-generated cytokeratin-18^[18-21]. In this study, we also tried to find candidate mediators of the mechanism of this relationship. We investigated several mediators, including adiponectin, IL-6, TNF- α , and hs-CRP. Among these candidate mediators, adiponectin may have been related to the development and progression of CAD in patients with NAFLD in our study. Adiponectin is the most abundant adipose-specific adipokine, and decreases hepatic insulin resistance and attenuates liver inflammation^[22]. Low levels of serum adiponectin might play an important role in the pathogenesis of clinical CAD and NAFLD. In contrast, NAFLD is also characterized by increased insulin resistance^[23]. We measured fasting serum insulin levels and calculated the HOMA index to confirm this relationship in our study. Because we included obese Asians, which in contrast with previous

Asian-Pacific NAFLD studies that included non-obese subjects, our study subjects had relatively high insulin resistance^[24]. However, fasting serum insulin levels and HOMA-IR were not different between our two groups (with/-without CAD and with/-without a fatty liver).

Some limitations of our study merit comment. First, our results were not based on a biopsy-proven NAFLD. There is no histology or staging of fibrosis by use of elastography to determine the liver fibrosis. We diagnosed NAFLD using hepatic ultrasonography. This technique does not identify fatty infiltration < 30% although it is a safe and confirmed reliable noninvasive method^[25]. This technique also has additional weak points, which are intra- and interobserver differences when making a diagnosis. However, to overcome these limitations, ultrasonography was performed by a single experienced physician to determine the presence of the four fatty liver grades. In addition, standard selective CAG was performed to diagnose and measure CAD severity by three experienced cardiologists in our study. To reduce interobserver variability for CAG, another cardiologist also reviewed all of the data. Second, this study was conducted at a single center in a rural area, which increased the chance for selection bias. Women were predominant in the included subject. A possible explanation for this gender imbalance is that men in this area had a high prevalence of alcohol intake and were excluded based on a history of alcohol ingestion.

Because NAFLD is considered a hepatic manifestation of metabolic syndrome, many studies have investigated the association between NAFLD and cardiovascular diseases. As a result, our study demonstrates that NAFLD is an independent risk factor for angiographically proven CAD in a grade-dependent manner. Because the pathogenesis of NAFLD and CAD are not fully elucidated, we also attempted to identify mediators and believe that adiponectin might be related to the development and progression of CAD in patients with NAFLD. Therefore, future large-scale studies are needed to elucidate the precise mechanism of this relationship.

COMMENTS

Background

Although recent many studies used coronary artery calcification score, carotid artery intima-media thickness, or carotid artery plaque measurements as surrogate markers for coronary artery disease (CAD), this study evaluated the interaction between fatty liver and cardiovascular outcomes using coronary angiograms in a prospective case-control study of Asians.

Research frontiers

The relationship between nonalcoholic fatty liver disease (NAFLD) and CAD in relatively thin Asian people must be evaluated. Moreover, because the pathogenesis of NAFLD and CAD are not fully elucidated, the authors attempted to identify candidate mediators.

Innovations and breakthroughs

This article show that angiographically proven coronary artery stenosis was strongly associated with NAFLD in a grade-dependent manner. In addition, the authors attempted to identify mediators and believe that adiponectin might be related to the development and progression of CAD in patients with NAFLD.

Applications

By understanding the association between NAFLD and CAD, patients with a se-

vere degree of fatty liver disease have to be concerned about CAD to improve their prognosis.

Peer review

This is a prospective single center study, which investigate the relationship between NAFLD and CAD and seeks candidate mediators. Future large-scale studies are needed to elucidate the precise mechanism of this relationship.

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