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Nonalcoholic Fatty Liver Disease is Associated with Coronary Artery Calcification

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is related to risk factors of coronary artery disease, such as dyslipidemia, diabetes, and metabolic syndrome, which are closely linked with visceral adiposity. The aim of this study was to investigate whether NAFLD was associated with coronary artery calcification (CAC), which is used as a surrogate marker for coronary atherosclerosis independent of computed tomography (CT)-measured visceral adiposity. Out of 5,648 subjects who visited one of health screening centers between 2003 and 2008, we enrolled 4,023 (mean age

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56.9 ± 9.4 years, 60.7% males) subjects without known liver disease or a history of ischemic heart disease. CAC score was evaluated by the Agatston method. In univariate analyses, the presence of CAC (score >0) was significantly associated with age, sex, body mass index, aspartate aminotransferase, alanine aminotransferase, high-density lipoprotein cholesterol, triglycerides and increased odds of diabetes, hypertension, smoking, and NAFLD. Increasing CAC scores (0, <10, 10-100, 100) were associated with higher prevalence of NAFLD (OR 1.84, 95% CI 1.61-2.10, $P<0.001$). Multivariate ordinal regression analysis adjusted for traditional risk factors, and CT-measured visceral adipose tissue area in a subgroup of subjects showed that the increased CAC scores were significantly associated with the presence of NAFLD (OR 1.28, 95% CI 1.04-1.59, $P=0.023$) independent of visceral adiposity.

CONCLUSIONS—Patients with NAFLD are at increased risk for coronary atherosclerosis independent of classical coronary risk factors, including visceral adiposity. These data suggest that NAFLD *per se* might be an independent risk factor for coronary artery disease.

Keywords

Coronary Artery Disease; Coronary Artery Calcium; Hepatic Steatosis; Visceral Obesity; Visceral Adipose Tissue

Introduction

With an estimated prevalence of 20-30%, nonalcoholic fatty liver disease (NAFLD) is recognized as the most prevalent liver disease in the general population.(1) Recently, a series of studies reported that NAFLD is not only a hepatic manifestation of metabolic syndrome,(2) but is also associated with an increased risk of cardiovascular disease,(3) including coronary artery disease. Similarly, subjects with NAFLD have an elevated risk of increased carotid intima media thickness,(4-6) elevated estimated ten-year risk of developing coronary artery disease,(7, 8) reduced endothelial function,(9) and increased prevalence of vulnerable coronary plaques.(10) The association between NAFLD and increased carotid intima media thickness, a marker of carotid atherosclerosis, was independent of traditional risk factors, metabolic syndrome, and insulin resistance.(4-6) Despite these results, it remains unclear whether NAFLD is merely a marker of a risk of coronary artery disease or an independent, pathogenetic mediator that promotes a systemic proatherogenic and inflammatory state.

Recently, the coronary artery calcification (CAC), which has been focused to be an indicator of subclinical coronary artery disease, strongly correlated with the extent of atherosclerosis and the risk of cardiac events.(11-13) Like carotid intima media thickness, CAC represents the atherosclerotic burden in arterial beds. Whereas carotid intima media thickness is recognized as an indicator of generalized atherosclerosis,(14) CAC is a more specific predictor of coronary artery disease,(15) including subclinical disease.(16, 17)

To date, studies investigating the relationship between NAFLD and coronary artery disease have not adequately evaluated visceral adipose tissue (VAT) as a major contributor to the metabolic syndrome, and atherosclerosis.(10, 18-20) The purpose of the present study was to evaluate the relationship between NAFLD and CAC taking into account of the risk factors for coronary artery disease, including VAT in a large apparently healthy population.

Materials and Methods

Subjects and Study Design

This cross-sectional study retrospectively enrolled a total of 5,648 adults who visited two health screening centers, the Seoul National University Hospital, Gangnam Healthcare Center (SNUH-HCS), and Bundang Hospital's Health Promotion Center (SNUBH-HPC), for a comprehensive health evaluation (including CAC) between October 2003 and December 2008. Some subjects voluntarily paid for a general health check, and others were supported by their employer. This screening program included a calcium-scoring computed tomography (CT) with or without an abdominal fat CT as well as hepatic ultrasonography on the same day.

Out of the 5,648 subjects, we excluded 419 subjects who had a history of heart attack, coronary artery disease including acute myocardial infarction, angina, or congestive heart failure. We also excluded 1,206 subjects with at least one potential cause of chronic liver disease: 701 subjects with excessive alcohol consumption (≥ 20 g/day), 241 with positive hepatitis B surface antigen, 54 with positive hepatitis C antibody, and 42 with other history of hepatitis or liver disease (e.g., hemochromatosis, primary biliary cirrhosis, autoimmune hepatitis, Wilson's disease etc). In addition, we excluded 168 subjects who had taken medications with known hepatotoxicity, such as estrogens, tamoxifen, glucosteroids, amiodarone, methotrexate, diltiazem, and valproate during the previous year. Altogether, 4,023 subjects were enrolled in the study, and 1,854 out of whom had a CT measurement of their abdominal fat.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital.

Clinical and Laboratory Evaluations

In addition to a laboratory examination, each subject underwent a questionnaire assessment, and an anthropometric assessment. Systolic and diastolic blood pressures were measured twice on the same day, and the mean of the two values was used in the analysis. Height and body weight were measured using a digital scale. Body mass index was calculated with the following formula: body mass index = weight (kg)/height squared (m^2). The waist circumference was measured (using a tape measure to the nearest millimeter) at the midpoint between the lower costal margin and the iliac crest by a well-trained nurse. Current smokers were defined as those who had smoked at least one cigarette per day during the previous year. Physical activity was measured by self report using the questionnaire and addressed 'times (hours) of exercise per week'. Laboratory evaluations included aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total serum cholesterol, serum triglycerides (TG), serum high-density lipoprotein (HDL) cholesterol, fasting glucose, serum creatinine, C-reactive protein, hepatitis B surface antigen, and an antibody to hepatitis C virus. Venous blood samples were taken from all subjects before 10 AM after a 12-h overnight fast. All laboratory determinations were carried out using standard laboratory methods.

We have calculated estimated glomerular filtration rate according to the Modification of Diet in Renal Disease (MDRD) equation as following: glomerular filtration rate ($mL/min/1.73 m^2$) = $186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.210$ (if African American).⁽²¹⁾ Systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg and/or previous use of antihypertensive medication were used to define hypertension. Subjects with fasting plasma glucose levels ≥ 126 mg/dl and/or treatment with a hypoglycemic agent or insulin were defined as having diabetes mellitus. We divided

participants with ultrasonography diagnosed NAFLD depending on the status of ALT (elevated ALT was defined as ALT > 30 U/L for men and > 19 U/L for women).(22)

Ultrasonographic Examinations

Hepatic ultrasonographies were examined by experienced radiologists who were blinded to the laboratory and clinical details of the subjects at the time of the procedure. Hepatic ultrasonography (Acuson, Sequoia 512, Siemens, Mountain View, CA) was used to diagnose fatty liver. The diagnosis of fatty liver was made on the basis of characteristic ultrasonographic features consistent with “bright liver” and evident contrast between hepatic and renal parenchyma, vessel blurring, focal sparing, and narrowing of the lumen of the hepatic veins.(23-25)

Measurement of CAC by Multi-Detector CT

A CT scan of the coronary artery was performed using a 16-slice multi-detector CT system (Somatom Sensation 16; Siemens Medical Solutions, Forchheim, Germany) at SNUH-HCS and a 64-channel multi-detector CT system (Brilliance 64; Philips Medical Systems, Best, Netherlands) at SNUBH-HPC. CAC scans were acquired using the standard procedure of prospective ECG-triggered scan acquisition with a tube voltage of 120 kV and 110 effective mAs with a 200-mm field of view.(26) The data were reconstructed to a 3-mm-thick slice with a 400-ms acquisition window. The CAC score was calculated using a CT software program (Rapidia 2.8; INFINTT, Seoul, Korea) with the Agatston method.(27)

Measurement of Abdominal Adipose Tissue Areas

We used a previously described method for VAT area measurement in cross-sectional CT images.(28) Briefly, the subjects were examined with a 16-detector row CT scanner (Somatom Sensation 16; Siemens Medical Solutions, Forchheim, Germany) in the supine position. The area was measured with commercially available CT software (Rapidia 2.8; INFINTT, Seoul, Korea), which electronically determined the adipose tissue area by setting the attenuation values for a region of interest within a range of –250 to –50 Housefield units.

Statistical Analysis

The outcome variable was the CAC score in this study. We used chi-squared tests for categorical variables and Student’s t-test or the Mann-Whitney test and ANOVA or Kruskal-Wallis test for continuous variables. Because a large proportion of the subjects had a CAC score of zero, CAC scores were dichotomized as presence of CAC (score >0) vs. absence, 10 vs. <10, and 100 vs. <100 for binary logistic regression analysis. We also separated CAC into four categories: 0, 1 to 10, 11 to 100, 100 for use in ordinal logistic regression analysis to determine if NAFLD was associated with increased CAC scores. The logistic regression analysis was used to analyze the association between NAFLD and CAC while controlling for potential confounders. Covariates in the multivariable model, chosen for clinical importance as well as statistical significance included age, sex, body mass index, waist circumference, daily alcohol consumption, smoking status, physical activity, diabetes, hypertension, total cholesterol, TG, HDL cholesterol, and C-reactive protein. To investigate the associations between NAFLD and subclinical coronary atherosclerosis, the primary analysis included the entire cohort, and a secondary analysis focused on the individuals with VAT data. Analyses were conducted using SPSS 12.0 (SPSS, Inc., Chicago, IL, USA), and SAS 9.2 (SAS institute, Cary, NC, USA).

Results

There were a total of 4,023 subjects that met the inclusion criteria for the study. The majority of the subjects had no demonstrable calcification in the coronary arteries (CACS=0, n=2,737), whereas the remaining 1,286 had evidence of coronary calcification (presence of CAC), and the largest group of which were those with CACS between 10 and 100. The characteristics of the study subjects are shown in Table 1. The majority of the overall group comparisons were statistically significantly different. Some of the more noticeable differences were seen in the mean age, gender, and the prevalence of diabetes and hypertension, as well as body mass index, waist circumference, and serum levels of AST, GGT, and fasting glucose.

Of the study subjects, 1,617 had ultrasonographically-diagnosed NAFLD (40.2%). Table 2 compares individuals with and without NAFLD. The two groups were statistically significantly different in majority of the variables evaluated. The differences are in the expect direction that clinical features associated with insulin resistance is more prevalent in subjects with NAFLD.

Figure 1 illustrates the relation between CACS score and NAFLD - the proportion of patients with NAFLD progressively increased from 35% in subjects with CACS=0 to 52% in those with CACS = 100. A formal analysis for the relation between NAFLD and CAC score is shown in Table 3. In univariate analysis, NAFLD was associated with 86% increase in the risk of coronary calcification (presence of CAC versus absence of CAC). The odds ratio (OR) for NAFLD associated with one step increase was similar between severity categories, including that from the ordinal logistic regression analysis (OR 1.84, 95% confidence interval [CI] 1.61-2.10). As expected, this effect of NAFLD became attenuated in multivariable analyses, when other well established risk factors of coronary artery disease were taken into account. In those models, NAFLD remained statistically and clinically significant. The effect size of NAFLD was similar to that of diabetes (OR 1.39, 95% CI 1.13-1.72), reduced plasma concentrations of HDL-cholesterol (OR 1.26, 95% CI 1.05-2.10), and smoking (OR 1.42, 95% CI 1.18-1.72) (Supplementary Table 1).

Figure 2 illustrates that NAFLD is more associated with presence of CAC in the group without known coronary risk factors (women, younger age, normal-overweight, non-hypertensive, non smoker, non-dyslipidemic, and non-diabetes) than in the groups with risk factors.

NAFLD with elevated ALT were found to have higher risk of CAC than NAFLD with normal ALT by the trend test in age, sex adjusted model. In multivariable analysis, these associations were attenuated, but remained statistically and clinically significant with a *P* value for the test of trend of odds (Table 4).

We next evaluated the role of visceral adiposity assessment in the association between CAC and NAFLD. Abdominal fat CT data were available in 1,854 subjects (46.1%). Supplementary Table 2 compares individuals with and without VAT data. Those with the data were older (mean 59 years versus 55 years) and had a larger waist circumference (mean 87 versus 86 cm) and higher prevalence of hypertension (39% versus 33%) than those without. There were minor differences in other characteristics between the two groups although some of them reached statistical significance because of the large sample size.

Of the 1,854 subjects with VAT data, 770 had NAFLD (Supplementary Table 3). Compared to those without NAFLD, NAFLD patients had a significantly larger area of total abdominal adiposity (difference in means=50.4 cm²), which was mainly attributable to differences in VAT (38.5 cm²) rather than subcutaneous adiposity (11.8 cm²). Figure 3 illustrates that

VAT, not subcutaneous adiposity, is correlated with the CAC score. Finally, Table 5 repeats the multivariable analysis correlating CAC with predictors, including NAFLD, VAT, and other existing variables. Compared to subjects without NAFLD, subjects with NAFLD had a higher OR of increased CAC scores like entire cohort (OR 1.60, 95% CI 1.32-1.93). When NAFLD and VAT were jointly considered in the full multivariable models, the association between NAFLD and both the presence of CAC (OR 1.29, 95% CI 1.03-1.62) and the increased CAC scores of 0, 1 to 10, 10 to 100, 100 (OR 1.28, 95% CI 1.04-1.59) attenuated, but remained significant; however, NAFLD was not statistically significantly associated with CAC scores 100 (OR 1.30, 95% CI 0.94-1.80).

Discussion

The main finding of this large population-based study was a strong relationship between NAFLD and CAC, the latter being an established surrogate marker for coronary atherosclerosis. Importantly, this association was independent of the traditional risk factors for coronary artery disease as well as visceral adiposity.

The association of NAFLD with CAC may be indirect and due to generalized obesity or ectopic fat, including VAT. However, CT measured visceral adiposity attenuated but did not eliminate the relationship between NAFLD and CAC. This study gave us the unique opportunity to assess the relationship between NAFLD and subclinical coronary atherosclerosis above and beyond VAT. An increasing number of studies have suggested that NAFLD is an independent risk factor for coronary artery disease and mortality.(3, 5, 6, 9) This hypothesis has been supported by community-, population-, and hospital-based studies.(29-31) Recent large prospective cohort study reported that in patients with clinical indications for coronary angiogram, NAFLD is associated with coronary artery disease independently of other metabolic factors.(32) However, most of the previous studies that have suggested an independent association between NAFLD and coronary artery disease did not directly measure abdominal VAT. Most of these studies indirectly measured VAT using waist circumference, which has been shown to be more closely correlated with subcutaneous adipose tissue than with VAT.(33) Because of this, multivariable analysis adjusted for waist circumference is not sufficient to demonstrate an independent relationship between NAFLD and coronary artery disease above and beyond VAT. Recent studies have reported that the VAT is the abdominal fat that is most intimately associated with metabolic disease, myocardial infarction, stroke, and overall mortality.(34-36) The cardiovascular risk in NAFLD may be attributed in part to underlying VAT.(37) Therefore, we examined the relative contributions of hepatic fat and VAT to subclinical coronary atherosclerosis. Multivariable regression analysis proved that the relationship between NAFLD and CAC score was significant, even after adjusting for age, sex, traditional coronary risk factors, and VAT. Therefore, we suggest that NAFLD *per se* might be an independent risk factor for subclinical coronary atherosclerosis. In addition, NAFLD together with elevated ALT, which might indicate suspected nonalcoholic steatohepatitis, was more associated with CAC than NAFLD with normal ALT in a dose-dependent manner. These findings suggest that CAC is associated with both nonalcoholic steatohepatitis and NAFLD.

Because the CAC score indicates the presence and extent of coronary atherosclerosis, it is not surprising that many studies have reported that a high CAC score is a marker for an increased risk of coronary events.(38) Thus, a CAC score of zero is associated with a very low risk of subsequent coronary events,(38, 39) whereas an elevated CAC score is related to a stepwise increase in the risk of subsequent coronary events.(11, 38) CAC scores have been shown to be highly predictive of future cardiovascular events independent of traditional risk factors.(11, 40, 41) Thus, in this study, we utilized the CAC score as an outcome variable to predict future coronary heart disease in individuals with NAFLD.

Currently, three published papers address the relationship between NAFLD and CAC. But, these results conflict with each other. As part of the Diabetes Heart Study, McKimmie et al. (42) suggested that hepatic steatosis is less likely to be a direct mediator of cardiovascular disease and may be described as an epiphenomenon. The preponderance of diabetes (82.8%) and the nature of the Diabetes Heart Study as a family study, however, may limit the generalizability of these results. On the contrary, Chen et al.(43) reported a significant relationship between NAFLD and CAC in Taiwan, but the possibility of selection bias was raised because of the exclusion of a large number of subjects without hepatic imaging. Jung et al.(44) also suggested that hepatic steatosis and increased ALT are associated with CAC. They used less stringent criteria to define ALT elevation for women and only single cutoff point of CAC (>100). Importantly, two studies did not include VAT data in multivariate analysis.

Although the pathogeneses that relate NAFLD and coronary artery disease have not been thoroughly investigated, several possible explanations have been offered. A low-grade systemic and hepatic inflammatory milieu may link NAFLD to atherosclerosis, which increases the risk of coronary artery disease.(45, 46) In NAFLD, reactive oxygen radicals may induce the production of cytokines, such as tumor necrosis factor- α and interleukin-6,(47) and add further atherogenic stimuli to the already high oxidative and pro-inflammatory status that is closely related to metabolic syndrome.(48, 49) In addition, such conditions favor the up-regulation of hepatic C-reactive protein levels, which may link NAFLD to coronary atherosclerosis.(45, 50) Furthermore, subjects with NAFLD have shown reduced serum adiponectin levels, which are inversely related to the severity of NAFLD histology.(3, 51) Low serum adiponectin levels may also play an important role in the pathogenesis between NAFLD and subclinical coronary atherosclerosis.

The strengths of our study are the utilization of CAC scores, CT-measured VAT, with a high degree of validity and reproducibility, high-quality data collected by trained personnel with a systematic protocol, wealth of metabolic variables, and a large number of subjects. In addition, we simultaneously measured CAC, hepatic ultrasonography, and VAT on the same day. Moreover, we believe that the subjects in our study are representatives of general population, given the nature of the screening program which is tailored for healthy, asymptomatic individuals. Finally, we utilized the CAC score as an outcome variable to predict future coronary artery disease in individuals with NAFLD. The suggested relationship between CAC score and coronary artery disease is rational because the CAC score reflects the actual presence and severity of atherosclerosis, whereas risk factors, risk scores, and biomarkers reflects only likelihood of coronary artery disease.(38)

Some limitations of our study merit comment. First, the cross-sectional design makes it difficult to determine causal or temporal relationships between NAFLD and the development of subclinical coronary atherosclerosis. Second, hepatic ultrasonography was used to diagnose NAFLD, and this technique cannot identify fatty infiltration below 30% (52) and have intra- and inter-observer variability in making diagnosis. The advantages of ultrasonography, however, include its safety, low cost, repeatability, satisfied sensitivity, and specificity.(53) Based on these characteristics, ultrasonography is the first-line imaging technique for both clinical practice and epidemiological studies.(54) Third, VAT data was not available to all study subjects. Although they are likely representative of the whole study population, the anthropometric and laboratory data of subjects with VAT data may have differed in some way from subjects without VAT data. Fourth, we did not have data on fasting insulin and did not have information on insulin resistance for our cohort due to retrospective design. In addition, this study was conducted at health screening centers, which introduces the possibility of selection process.

In this largest study conducted to date, patients with NAFLD are at high risk for coronary atherosclerosis regardless of classical cardiovascular risk factors, especially visceral adiposity. Detection of NAFLD should signal the existence of an increased coronary artery disease risk independent of visceral adiposity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Lists of Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
CAC	coronary artery calcification
CI	confidence interval
CT	computed tomography
GGT	gamma-glutamyl transpeptidase
HDL	high-density lipoprotein
NAFLD	nonalcoholic fatty liver disease
OR	odds ratio
SAT	subcutaneous adipose tissue
TAT	total adipose tissue
TG	triglycerides
VAT	visceral adipose tissue

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Fig. 1.
Prevalence of nonalcoholic fatty liver disease by coronary artery calcification score cutoff.

Fig. 2.

Forest plot shows the ORs of the association between NAFLD and presence of CAC in different subgroups of participants: men versus women, older (age ≥ 55 years) versus younger (age < 55), obese (BMI ≥ 25) versus nonobese (BMI < 25), hypertensive versus nonhypertensive, smokers versus nonsmokers, dyslipidemic (total cholesterol ≥ 240) versus nondyslipidemic (total cholesterol < 240). ORs are represented by black circles; 95% CIs are denoted by horizontal whiskers.

Fig. 3. Visceral adipose tissue area and subcutaneous adipose tissue area between coronary artery calcification score cutoff. (A) As coronary artery calcification score increases, visceral adipose tissue area increases dose-dependently. (B) Associations between CAC score and subcutaneous adipose area were not statistically significant. The horizontal line in each box represents the median. The top and bottom of each box represent the 25th and 75th percentiles (interquartile range).

Table 1

Comparison of Baseline Characteristics Between Coronary Artery Calcification Score Cut-off.

	CACS=0 (n=2,737)	0-10 (n=251)	10-100 (n=601)	100 (n=434)	P-value
Age (years)	54.5 ± 9.0	59.2 ± 8.1	60.9 ± 7.8	64.7 ± 8.2	<0.001
Male (%)	1,465 (53.5)	161 (64.1)	461 (76.7)	355 (81.8)	<0.001
Smoking (%)	507 (18.5)	59 (23.5)	154 (25.6)	106 (24.4)	<0.001
Diabetes mellitus (%)	265 (9.7)	28 (11.2)	122 (20.3)	103 (23.7)	<0.001
Diabetes medication (%)	200 (7.3)	22 (8.8)	94 (15.6)	80 (18.4)	<0.001
Hypertension (%)	775 (28.3)	114 (45.4)	279 (46.4)	262 (60.4)	<0.001
Systolic blood pressure	117.8 ± 15.6	123.2 ± 15.9	123.4 ± 16.3	126.0 ± 17.4	<0.001
Diastolic blood pressure	76.3 ± 11.8	79.7 ± 11.4	79.2 ± 11.5	79.6 ± 11.7	<0.001
Hypertension medication (%)	530 (19.4)	83 (33.1)	223 (37.1)	214 (49.3)	<0.001
Lipid-lowering medication (%)	249 (9.1)	30 (12.0)	69 (11.5)	62 (14.3)	0.004
Body mass index (kg/m ²)	23.80 ± 2.83	24.40 ± 2.60	24.49 ± 2.61	24.61 ± 2.82	<0.001
Waist circumference (cm)	85.31 ± 8.05	87.60 ± 7.13	88.07 ± 7.26	88.97 ± 7.88	<0.001
AST (IU/L)	23.0 (20.0-28.0)	24.0 (20.0-29.0)	25.0 (20.0-29.0)	25.0 (21.0-31.0)	<0.001
ALT (IU/L)	23.0 (17.0-33.0)	24.0 (17.0-37.0)	26.0 (19.0-34.0)	25.5 (18.0-36.0)	<0.001
GGT (IU/L)	23.0 (16.0-37.0)	25.0 (16.0-38.0)	28.0 (19.0-44.0)	29.0 (20.0-44.0)	<0.001
Cholesterol (mg/dL)	202.0 ± 33.2	200.7 ± 34.8	202.5 ± 34.0	198.1 ± 37.4	0.146
Triglycerides (mg/dL)	98.0 (70.3-141.0)	112.0 (78.0-170.0)	108.0 (78.0-158.0)	114.0 (81.0-156.0)	<0.001
HDL cholesterol (mg/dL)	56.3 ± 14.3	52.4 ± 14.1	51.3 ± 12.5	52.3 ± 13.3	<0.001
Fasting glucose (mg/dL)	98.1 ± 18.7	101.9 ± 19.6	105.9 ± 25.9	110.6 ± 30.2	<0.001
C-reactive protein (mg/L)	0.01 (0.01-0.15)	0.04 (0.01-0.18)	0.05 (0.01-0.16)	0.05 (0.01-0.15)	<0.001
Creatinine (mg/dL)	1.00 (0.90-1.20)	1.10 (0.90-1.20)	1.10 (1.00-1.20)	1.10 (1.00-1.20)	<0.001
Glomerular filtration rate (mL/min/1.73m ²)	71.0 ± 10.1	69.3 ± 10.6	69.0 ± 11.2	68.4 ± 12.0	<0.001
Physical activity (hr/wk)	2.55 ± 2.85	2.86 ± 2.75	2.70 ± 2.86	2.92 ± 3.18	0.033
Daily alcohol consumption (gram)	3.64 ± 5.82	3.81 ± 6.14	4.78 ± 6.79	5.54 ± 7.10	<0.001
NAFLD (%)	968 (35.4)	119 (47.4)	305 (50.7)	225 (51.8)	<0.001

CACS, coronary artery calcification score; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease.

Data are shown as the mean $\pm$ SD or median (IQR).

Table 2

Comparison of Baseline Characteristics between Subjects With and Without NAFLD.

	NAFLD (n=1,617)	Control (n=2,406)	P-value
Age (years)	57.5 ± 9.0	56.4 ± 9.6	<0.001
Male (%)	1,180 (73.0)	1,262 (52.5)	<0.001
Smoking (%)	380 (23.5)	446 (18.5)	<0.001
Diabetes mellitus (%)	276 (17.1)	242 (10.1)	<0.001
Diabetes medication (%)	198 (12.2)	198 (8.2)	<0.001
Hypertension (%)	706 (43.7)	724 (30.1)	<0.001
Systolic blood pressure (mmHg)	122.7 ± 15.5	118.0 ± 16.4	<0.001
Diastolic blood pressure (mmHg)	79.8 ± 11.5	75.6 ± 11.7	<0.001
Hypertension medication (%)	531 (32.8)	519 (21.6)	<0.001
Lipid-lowering medication (%)	179 (11.1)	231 (9.6)	0.131
Body mass index (kg/m ²)	25.09 ± 2.70	23.31 ± 2.64	<0.001
Waist circumference (cm)	89.23 ± 7.43	84.26 ± 7.73	<0.001
AST (IU/L)	27.0 (23.0-34.0)	22.0 (19.0-26.0)	<0.001
ALT (IU/L)	33.0 (27.0-43.0)	19.0 (15.8-24.0)	<0.001
GGT (IU/L)	33.0 (23.0-50.0)	20.0 (15.0-30.0)	<0.001
Cholesterol (mg/dL)	203.9 ± 35.4	200.0 ± 32.8	<0.001
Triglycerides (mg/dL)	122.0 (86.0-175.0)	91.0 (67.0-128.0)	<0.001
HDL cholesterol (mg/dL)	51.1 ± 13.0	57.3 ± 14.3	<0.001
Fasting glucose (mg/dL)	105.6 ± 24.7	97.6 ± 19.1	<0.001
C-reactive protein (mg/L)	0.08 (0.01-0.18)	0.01 (0.01-0.13)	<0.001
Creatinine (mg/dL)	1.10 (1.00-1.20)	1.00 (0.90-1.20)	<0.001
Glomerular filtration rate (mL/min/1.73m ²)	70.2 ± 10.3	70.4 ± 10.7	0.595
Physical activity (hr/wk)	2.69 ± 2.93	2.60 ± 2.90	0.359
Daily alcohol consumption (gram)	4.81 ± 6.76	3.49 ± 5.69	<0.001
CAC score	71.88 ± 266.10	43.32 ± 198.90	<0.001

NAFLD, nonalcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; CAC, coronary artery calcification.

Data are shown as the mean ± SD or median (IQR).

Table 3

Univariate and Multivariable Binary and Ordinal Analyses of the Risk for Coronary Artery Calcification in subjects with versus without NAFLD

CAC Score	Univariate analysis		Multivariable model 1		Multivariable model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
0 (reference)						
>0	1.86 (1.63-2.13)	<0.001	1.35 (1.15-1.59)	<0.001	1.34 (1.14-1.58)	<0.001
<10 (reference)						
10	1.84 (1.59-2.12)	<0.001	1.33 (1.12-1.58)	0.001	1.32 (1.12-1.57)	0.001
<100 (reference)						
100	1.70 (1.39-2.08)	<0.001	1.26 (1.002-1.59)	0.048	1.25 (0.99-1.57)	0.065
0						
0-10						
10-100	1.84 (1.61-2.10)	<0.001	1.34 (1.15-1.56)	<0.001	1.33 (1.14-1.54)	<0.001
100						

NAFLD, nonalcoholic fatty liver disease; CAC, coronary artery calcification; OR, odds ratio; CI, confidence interval.

The multivariable model 1 was adjusted for age, sex, body mass index, waist circumference, daily alcohol consumption, smoking status, physical activity, diabetes, hypertension, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol.

The multivariable model 2 includes C-reactive protein in addition to the variables addressed in model 1.

Table 4

Age, Sex-adjusted and Multivariable Analyses of the Risk for Coronary Artery Calcification in NAFLD with or without Elevated ALT versus Control.

CAC Score	Age, sex-adjusted analysis		Multivariable analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
0, >0				
Control	1	<0.001 *	1	0.001 *
NAFLD with Normal ALT	1.47 (1.17-1.84)	0.001	1.32 (1.05-1.67)	0.019
NAFLD with Elevated ALT	1.65 (1.38-1.97)	<0.001	1.37 (1.13-1.67)	0.001
<10, 10				
Control	1	<0.001 *	1	0.002 *
NAFLD with Normal ALT	1.39 (1.10-1.76)	0.006	1.26 (0.99-1.61)	0.060
NAFLD with Elevated ALT	1.62 (1.34-1.95)	<0.001	1.37 (1.12-1.68)	0.003
<100, 100				
Control	1	0.001 *	1	0.056 *
NAFLD with Normal ALT	1.20 (0.88-1.64)	0.255	1.09 (0.78-1.50)	0.621
NAFLD with Elevated ALT	1.53 (1.19-1.96)	0.001	1.31 (1.00-1.71)	0.054
0, >0-10, 10-100, 100				
Control	1	<0.001 *	1	0.001 *
NAFLD with Normal ALT	1.38 (1.12-1.70)	<0.001	1.24 (1.00-1.54)	0.055
NAFLD with Elevated ALT	1.65 (1.40-1.95)	<0.001	1.39 (1.16-1.67)	<0.001

NAFLD, nonalcoholic fatty liver disease; ALT, alanine aminotransferase; CAC, coronary artery calcification; OR, odds ratio; CI, confidence interval.

*
P-value for test of trend of odds

The multivariable model was adjusted for age, sex, body mass index, waist circumference, daily alcohol consumption, smoking status, physical activity, diabetes, hypertension, total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol.

Table 5

Multivariable Logistic Regression Analyses for Association Between Coronary Artery Calcification and NAFLD among subjects with VAT data.

CAC Score	Model 1		Model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value
0 (reference)				
>0	1.32 (1.07-1.66)	0.015	1.29 (1.03-1.62)	0.027
<10 (reference)				
10	1.27 (1.001-1.61)	0.049	1.25 (0.99-1.59)	0.066
<100 (reference)				
100	1.30 (0.94-1.79)	0.114	1.30 (0.94-1.80)	0.116
0-10	1.30 (1.05-1.60)	0.016	1.28 (1.04-1.59)	0.023
10-100				
100				

NAFLD, nonalcoholic fatty liver disease; VAT, visceral adipose tissue area; CAC, coronary artery calcification; OR, odds ratio; CI, confidence interval.

Model 1 was adjusted for age, sex, smoking status, diabetes, hypertension, and visceral adipose tissue area.

Model 2 includes total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol in addition to the variables addressed in model 1.