Coronary artery disease and non-alcoholic fatty liver disease: Clinical correlation using computed tomography coronary calcium scans

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Abstract

Background and Aim: Non-alcoholic fatty liver disease (NAFLD) and coronary artery disease (CAD) have been explored using coronary angiography, which showed a link between severe NAFLD and cardiovascular disease risk. This study’s aim is to determine if computed tomography (CT) coronary artery calcium (CAC) scores used to determine CAD severity in asymptomatic populations can help predict the presence of NAFLD.

Methods: This was a retrospective cross-sectional study of positive CT CAC scores and liver imaging with either CT; ultrasound; magnetic resonance imaging of the abdomen; or CT of the chest, which included liver images. Drinking 7 or 14 drinks per week for a female or male, respectively, and chronic viral hepatitis diagnosis were the exclusion criteria. CT CAC scores, hepatic steatosis, age, gender, lipid and liver panels, weight, blood pressure, F-4/BARD scores, and hemoglobin A1c were correlated to CAD severity and NAFLD by logistic regression.

Results: A total of 134 patients with a mean age of 62.3 years (σ = 9.1), with 65% males, body mass index 28.5 (σ = 6.0), and 8% diabetics, were recruited. CAD severity was not associated with the presence of hepatic steatosis (odds ratio 1.96 [95% confidence interval, confidence interval 0.74–5.23] P = 0.36). Adjusted for variables, a link between hepatic steatosis, CAD severity, body mass index over 30 (odds ratio 6.77 [95% confidence interval 1.40–32.66] P = 0.02), and diabetes (odds ratio 9.60 [95% confidence interval 0.56–165.5] P = 0.01) was observed.

Conclusions: In patients with CAD detected using a positive CT CAC scan, we determined that BMI over 30 and diabetes were correlated with the presence of NAFLD. There was no direct relationship between CAD presence and hepatic steatosis presence.

Introduction

Due to the increasing prevalence of coronary artery disease (CAD) and non-alcoholic fatty liver disease (NAFLD), finding methods for secondary disease prevention is extremely important.1,2 Available screening tools for secondary disease prevention for populations with asymptomatic CAD and NAFLD are computed tomography (CT) coronary artery calcium (CAC) scan and ultrasound/CT/magnetic resonance imaging (MRI) with elastography of the liver, respectively.1,3 In coronary angiography studies, severe CAD and severe NAFLD have a clear association.4,5 However, whether this association is valid when the CAD and NAFLD are asymptomatic has not been explored.

CAD and NAFLD have well-known associations with several metabolic disorders such as type 2 diabetes mellitus, dyslipidemia, hypertension, and abdominal obesity.5 NAFLD develops according to a “multiple hit” hypothesis in which increased insulin, which would eventually lead to insulin resistance; increased low-density lipoproteins (LDL); increased cholesterol; and increased triglycerides contribute to increased fat accumulation in the liver.6,8 The metabolic disorders associated with CAD share many factors that contribute to NAFLD development.9 These metabolic disorders increase the risk of acute myocardial infarctions caused by cardiovascular disease (CVD), which will increase NAFLD risk by 2–3-fold compared to the general population.10 In previous studies on the NAFLD and CAD relationship, CT coronary angiography was used as the imaging modality that analyzes calcified and noncalcified atherosclerotic plaque in the coronary arteries.5 While CT coronary angiography can identify noncalcified plaques, the study requires iodinated contrast, which exposes the patients to a possible allergic reaction and renal injury.11 CT CAC scans have strong prognostic efficacy in asymptomatic populations. According to the
Multi-Ethnic Study of Atherosclerosis, there was a strong positive correlation between the magnitude of CAC scores and future cardiovascular events across four ethnic groups. That is why, currently, guidelines advise physicians to screen for CAD using CT CAC imaging (which does not use iodinated contrast material) as a second-line tool. NAFLD screening is not advised even in high-risk groups (type 2 diabetes and obesity) due to uncertainty in diagnostic testing results and a lack of effective medical management.

Knowing that CT CAC imaging is a tool that can screen for CAD in an asymptomatic population, the purpose of this study was to use CT CAC scans to identify a population with asymptomatic CAD and to determine whether there was an increased risk of NAFLD in this population.

**Methods**

**Subjects.** This was a retrospective cross-sectional study of 134 patients in the community health-care setting from 1 April 2017 to 31 January 2020 with positive CT CAC scores and liver imaging with either CT; ultrasound; MRI of the abdomen; or CT of the chest, including liver images. Patients were excluded if they had consumed more 7 drinks per week for a woman and 14 drinks per week for a man or if they had chronic viral hepatitis B, C, or D. Patients who were on chronic glucocorticoids, methotrexate, 5-fluorouracil, irinotecan, tamoxifen, amiodarone, or nucleoside reverse transcriptase inhibitor therapy were excluded from the study due to drug-induced fatty liver risk. Our study was approved by the Thomas Jefferson University Hospital institutional review board.

**Demographics.** The median age of our patient cohort was 63 years, with an interquartile range (IQR) of 57–69. The patient cohort was 65% male and 35% female. The average body mass index (BMI) was 28.5, with an IQR of 23.9–31.3. Of our patient population, 8% had a type 2 diabetes diagnosis; 19% were prediabetic with a hemoglobin A1c between 5.7 and 6.4%; And 54% had hypertension defined as blood pressure greater than 120/80 mm Hg.

**Procedures.** A list of patients with CT CAC scans was obtained. Patients qualified for the study if they had a positive CT CAC score and liver imaging, which included ultrasound, CT, MRI of the abdomen, or CT of the chest (Fig. 1). These imaging modalities have been validated for monitoring of NAFLD in previous studies. Liver imaging had to have been performed within 5 years of the CT CAC scan for inclusion in the study. For these patients, gender, coronary calcium score, triglycerides, total cholesterol, high-density lipoproteins (HDL), LDL, height, weight, platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin were obtained from patient charts in EPIC. BMI was calculated using height, weight, and a BMI calculator. FIB-4 and BARD scores were calculated from laboratory data.

**Definitions and criteria.** Data were divided into categories. CAD severity was defined as minimal if CAC the score was 1–10, mild if the CAC score was 10.01–100, moderate if the CAC score was 100.01–400, and severe if the CAC score was 400.01 and above. Steatosis was given a score of 0 for none and 1 for presence. Triglycerides were labeled as normal if the value was between 35 and 160 mg/dL, and they were labeled as high if the.

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**Figure 1** Flow of participants through the study. CT CAC, computed tomography coronary artery calcium.
value was over 160 mg/dL. Total cholesterol was labeled as normal if the value was less than 200 mg/dL, and it was labeled as high if the value was over 200 mg/dL. LDL cholesterol was normal if the value was between 35 and 80 mg/dL, low if the value was below 35 mg/dL, and high if the value was above 130 mg/dL. HDL cholesterol was normal if the value was between 20.0 and 24.9, overweight if the value was between 25.0 and 29.9, and obese if the value was above 30.0. Hypertension was defined as either blood pressure greater than 140 mm Hg systolic and 90 mm Hg diastolic or patients taking antihypertensive medication at the time of their imaging studies. Patients were considered nondiabetic if their hemoglobin A1c was less than 5.7%, prediabetic if their hemoglobin A1c was between 5.7 and 6.4%, and diabetic if their hemoglobin A1c was above 6.4% or if they were on insulin or glucose-lowering medications. AST was labeled as normal if the value was between 8 and 48 mg/dL and high if the value was over 48 mg/dL. ALT was labeled as normal if the value was between 7 and 55 mg/dL and high if the value was over 55 mg/dL. Alkaline phosphatase was labeled as normal if the value was between 40 and 129 mg/dL and low if the value was under 40 mg/dL. Total bilirubin was labeled as normal if the value was between 0.1 and 1.2 mg/dL and high if the value was over 1.2 mg/dL and high if the value was over 1.2 mg/dL.

Data collection. Proof of hepatic steatosis and CAC score is taken from radiology report findings. Triglycerides, cholesterol, HDL, LDL, AST, ALT, hemoglobin A1c, total bilirubin, height, weight, platelets, and blood pressure are obtained from clinical and laboratory reports.

Statistical tests. Data were broken into categories as described above. CAD severity was analyzed with regard to all other categories using chi-squared analysis and simple logistic regression. Hepatic steatosis was analyzed with regard to all other categories using chi-squared analysis and simple logistic regression. Categories that showed statistical significance (P-value < 0.05 and odds ratio > 3.50) for CAD severity and/or hepatic steatosis presence (BMI, triglycerides, diabetes, and AST) were analyzed with multivariate logistic regression, which took into account both CAD severity and hepatic steatosis presence. A P-value of 0.05 represents an acceptable level of statistical significance.

Results

A total of 134 patients met the inclusion criteria of this study. Mean age of the patient cohort was 62.3 years (σ = 9.1). The cohort was 65% male. The average BMI of the cohort was 28.5 (σ = 6.0). The cohort had 8% diabetic patients with a mean hemoglobin A1c of 7.2 (σ = 1.3). The cohort had a rate of hypertension of 54%, and 21 patients or 15.7% of our cohort had hepatic steatosis. CAD severity was not associated with the presence of hepatic steatosis (odds ratio [OR] 1.96 [95% confidence interval, CI 0.74–5.23] and P = 0.36). There were associations between hepatic steatosis and triglycerides over 160 (OR 3.60 [95% CI 1.05–12.29] and P = 0.03), BMI over 25 (OR 4.26 [95% CI 0.94–19.31] and P = 0.02), and diabetes (OR 8.64 [95% CI 2.35–31.83] and P < 0.001) and between CAD severity and AST over 48 (OR 3.50 [95% CI 0.35–34.64] and P = 0.02) (Fig. 2). CAD severity and hepatic steatosis analyses are shown

![Percentage of Patients with Abnormal Clinical Parameters](image)
in Table 1. No AST or ALT values were greater than 1.5 times the upper limit of normal.

Both FIB-4 and BARD scores in our cohort had a positive correlation with hepatic steatosis presence as seen in Table 2. Neither score had any association with CAD severity (Table 2). Multivariate analysis of these scores, CAD severity, and hepatic steatosis indicated that these findings were associated and statistically significant (Table 2).

Statistically significant findings between hepatic steatosis, CAD severity, BMI over 30, and diabetes history were determined by multivariate logistic regression (Table 1). Insignificant findings from multivariate logistic regression include associations between hepatic steatosis, CAD severity, AST, BMI between 25 and 29.9, and triglycerides (Table 1).

**Discussion**

We found that there was no association between CAD severity and hepatic steatosis in this patient population that has asymptomatic CAD and NAFLD. However, we found that obesity, defined as BMI over 30.0, and diabetes, defined as hemoglobin A1c 6.5% and over or as patients who are on diabetic medication, had significant relationships with CAD severity and hepatic steatosis when analyzed by logistic regression. We also found that FIB-4 and BARD scores which indicated a higher risk of hepatic fibrosis were associated with greater rates of combined hepatic steatosis and CAD.

Obesity and a history of diabetes were the only factors that were significant in the appearance of both CAD and NAFLD. Abnormally high lipid (triglycerides, total cholesterol, LDL, HDL) or liver panels (AST, ALT, alkaline phosphatase, total bilirubin) had no effect on the presence of CAD and NAFLD. In fact, in our asymptomatic CAD population, there were very few patients with increased liver labs (3.3% of patients for ALT, and 5.0% of patients for AST, and 3.3% of patients for total bilirubin). We could conclude that severely increased weight and an insulin resistance were early signs of asymptomatic CAD and NAFLD.

Our cohort’s overall health was inconsistent, with a subpopulation of patients with increased rates of NAFLD and CAD.3,5,19

### Table 1  Analysis of computed tomography coronary artery calcium-positive patients

|                         | Total patients | % of patients with abnormal lab values | Coronary artery disease (CAD) severity P-value | OR (95% CI) |
|-------------------------|----------------|---------------------------------------|-----------------------------------------------|------------|
| **CAD Severity**        |                |                                       |                                               |            |
| Gender                  | Men: 88; Female: 46 | n/a                                   |                                               |            |
| Triglycerides           | 114            | (>160): 14.0                          | 0.13                                          | 0.56 (0.27–1.16) |
| Total cholesterol       | 115            | (>200): 40.0                          | 0.64                                          | 0.88 (0.30–2.55) |
| HDL                     | 115            | (<35): 4.3; (>80): 15.7               | 0.054                                         | 0.39 (0.18–0.86) |
| LDL                     | 115            | (>130): 28.7                          | 0.15                                          | 1.74 (0.28–10.80) |
| BMI                     | 133            | (25–29.9): 40.6; (>30): 32.3          | 0.64                                          | 1.06 (0.51–2.21) |
| Hemoglobin A1c          | 134            | (5.7–6.4): 20.1; (>6.5): 8.2          | 0.91                                          | 0.96 (0.28–3.33) |
| Hypertension            | 134            | (>120>80): 53.7                       | 0.72                                          | 1.46 (0.74–2.90) |
| AST                     | 121            | (>48): 3.3                            | **0.02**                                      | **3.50 (0.35–34.64)** |
| ALT                     | 121            | (>55): 5.0                            | 0.88                                          | 0.55 (0.10–3.10) |
| Alkaline phosphatase    | 121            | (<40): 6.6                            | 0.71                                          | 0.88 (0.21–3.71) |
| Total bilirubin         | 121            | (>1.2): 3.3                           | 0.18                                          | 1.13 (0.15–8.27) |
| **Hepatic steatosis**   |                |                                       |                                               |            |
| Gender                  | Men: 88; Female: 46 | n/a                                   |                                               |            |
| Triglycerides           | 114            | (>160): 14.0                          | **0.03**                                      | **3.60 (1.05–12.29)** |
| Total cholesterol       | 115            | (>200): 40.0                          | 0.42                                          | 0.63 (0.20–1.96) |
| HDL                     | 115            | (<35): 4.3; (>80): 15.7               | 0.42                                          | 0.60 (0.06–6.17) |
| LDL                     | 115            | (>130): 28.7                          | 0.35                                          | 0.54 (0.14–2.03) |
| BMI                     | 133            | (25–29.9): 40.6; (>30): 32.3          | **0.02**                                      | **4.26 (0.94–19.31)** |
| Hemoglobin A1c          | 134            | (5.7–6.4): 20.1; (>6.5): 8.2          | **0.00044**                                   | **8.64 (2.35–31.83)** |
| Hypertension            | 134            | (>120>80): 53.7                       | 0.75                                          | 1.19 (0.41–3.43) |
| AST                     | 121            | (>48): 3.3                            | 0.65                                          | 1.70 (0.17–17.25) |
| ALT                     | 121            | (>55): 5.0                            | 1                                             | 1.00 (0.11–9.05) |
| Alkaline phosphatase    | 121            | (<40): 6.6                            | 0.19                                          | 0.88 (0.17–4.46) |
| Total bilirubin         | 121            | (>1.2): 3.3                           | 0.36                                          | 1.18 (0.12–11.20) |
| **CAD severity and hepatic steatosis** | | | | |
| Triglycerides           | 114            | (>160): 14.0                          | 0.15                                          | 0.58 (0.05–6.47) |
| BMI > 25.0              | 133            | (25–29.9): 40.6; (>30): 32.3          | 0.47                                          | 0.63 (0.06–7.05) |
| BMI > 30.0              | 133            | (>30): 32.3                           | 0.02                                          | **6.77 (1.40–32.66)** |
| Hemoglobin A1c >6.5     | 134            | (>6.5): 8.2                           | 0.01                                          | **9.60 (0.56–165.5)** |
| AST                     | 121            | (>48): 3.3                            | 0.07                                          | 0.97 (0.01–5.80) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; HDL, high-density lipoproteins; LDL, low-density lipoproteins. The bolded values were deemed statistically significant.
CAD and NAFLD correlation using CAC scores

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Table 2  Fibrosis-4 and BARD scores

|                  | Number of patients with BARD score | Number of patients with score 1.45–3.25 | Number of patients with score > 3.25 |
|------------------|-----------------------------------|----------------------------------------|-------------------------------------|
| **FIB-4 score**  | Number of patients with score < 1.45 | Number of patients with score 1.45–3.25 | Number of patients with score > 3.25 |
| **1 (0.98%)**    | 30 (29.4%)                        | 71 (69.6%)                             | 40 (33.6%)                          |
| **P-value**      | 0.23 (OR 1.53 [95% CI 0.65–3.63])  | 0.58 (OR 1.04 [95% CI 0.50–2.20])      | < 0.001 (OR 6.29 [95% CI 1.71–18.75]) |
| **Hepatic steatosis** | < 0.01 (OR 2.38 [95% CI 0.80–5.81]) | 0.01 (OR 2.16 [95% CI 0.50–2.20])      | < 0.01 (OR 5.66 [95% CI 1.71–18.75]) |

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