Original Paper

Correlation between Coronary Artery Disease and Non-Alcoholic Fatty Liver Disease Using Computed Tomography Coronary Calcium Scans

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ABSTRACT: Introduction: Concerns about how non-alcoholic fatty liver disease (NAFLD) might contribute to the development of cardiovascular disease (CVD) have grown as the importance of NAFLD and its relationship to the metabolic syndrome has grown. The purpose of this cross-sectional retrospective is to investigate potential correlations between hepatic steatosis in liver segments seen when measuring calcium score and the presence of atherosclerotic CAD (coronary artery disease). Methods: Two hundred patients (mean age, 57 years±10) who underwent coronary cardiac computed tomography (CT) scans were included. CT scans were analysed to assess the attenuation of liver parenchyma and the coronary artery calcification (CAC). Results: Age, gender, body mass index (BMI) and CAC score were significantly associated with hepatic steatosis. Among all patients, CAC score (r=-0.31, p<0.0001), and BMI (r=-0.40, p<0.0001) had a moderate negative correlation with the values of liver attenuation. BMI (OR: 1.109, p=0.001), CAC score (OR: 1.629, p<0.001), and age (OR: 1.050, p<0.001) were found to be independent predictors of hepatic steatosis through logistic regression. Conclusions: A statistically significant correlation between CAC score and the presence of NAFLD as evaluated by non-contrast-enhanced CT was demonstrated. BMI, CAC score, and age were identified as independent predictors of hepatic steatosis.

KEYWORDS: *Hepatic steatosis, computed tomography, non-alcoholic fatty liver disease, Coronary artery calcium score.*

Introduction

The most prevalent chronic liver illness, non-alcoholic fatty liver disease (NAFLD), is defined by a fat accumulation (> 5%) in the hepatocytes without evidence of excessive alcohol consumption, chronic viral hepatitis, and any other liver disorders [1].

It stands for a spectrum of liver diseases, from isolated fatty liver to fatty liver plus inflammation, non-alcoholic steatohepatitis (NASH), which could develop into cirrhosis [2].

Almost one-fourth of adults around the world deal with NAFLD, which places a heavy financial and health burden on all communities [3].

NAFLD is strongly linked to metabolic syndrome features such as insulin resistance, impaired glucose tolerance, hypertension, dyslipidaemia, and abdominal obesity [3-5].

Although it is challenging to assess the relative contributions of various causes to the onset of hepatic steatosis, one obvious outcome may be that progressively steatotic hepatocytes start to rupture or die. When combined with unmetabolized long-chain fatty acids, triglycerides released by apoptotic or ruptured hepatocytes increase hepatic injury. While NASH can develop even in the lack of apparent insulin resistance, hepatic steatosis in NAFLD is linked to insulin resistance [6].

These findings suggest that in people with NAFLD who consume excessive amounts of energy that exceed the capacity of PPARα mediated fatty acid oxidation systems to burn that energy, hepatic steatosis may simply manifest as an overaccumulation of unmetabolized energy in hepatocytes [7].

10.12865/CHSJ.49.02.14

It's important to point out that cardiovascular disease is the main cause of death of NAFLD patients [8].

Coronary microvascular dysfunction, carotid intima-media thickness, and increased arterial stiffness are all linked to NAFLD [9,10].

Reduced liver attenuation on computed tomography (CT) can be used to detect liver steatosis, the increasing fat accumulation in the liver that distinguishes NAFLD [11].

The main cause of death around the globe is CAD (coronary artery disease) [12].

Atherosclerosis is the primary cause of vascular disease, and the initial step of subclinical atherosclerosis is endothelial abnormality [13].

Acute coronary syndromes (ACS) are primarily brought on by thrombosis-induced plaque disintegration, whereas atherosclerosis is by far the most common cause of CAD [14].

Concern about the possibility that people with NAFLD may also have a higher risk of developing coronary heart disease has grown as a result of the fact that CAD is also associated to a variety of metabolic diseases [15].

Several metabolic conditions, including abdominal obesity, type 2 diabetes mellitus, hypertension, and dyslipidaemia, are known to be associated with NAFLD and CAD [16].

As compared to the general population, the risk of NAFLD is 2 to 3 times higher because these metabolic abnormalities raise the risk of acute myocardial infarctions brought on by cardiovascular disease (CVD) [17].

The existence of atherosclerotic CAD is radiologically confirmed by coronary artery calcification (CAC) [18]. By using the well-known Agatston score on CT, the CAC may be evaluated, and the result is reported as a CAC score [19].

As NAFLD's importance and connection to the metabolic syndrome become more well understood, concern over how NAFLD can contribute to the development of CVD has increased. It is crucial to develop strategies for secondary disease prevention due to the rising incidence of NAFLD and coronary artery disease CAD.

The goal of this cross-sectional retrospective study is to investigate potential correlations between hepatic steatosis in liver segments seen when measuring calcium score and the presence of atherosclerotic CAD.

Material and Methods

Study population

The study involved 200 consecutive adult patients who underwent coronary cardiac CT scans at a single tertiary care institution between January 2022 and April 2022.

Individuals under the age of 18, any known pre-existing liver illness (excluding steatosis), and history of CVD were excluded. Subpar images and CT scans of which the field of view (FOV) did not partially include the superior area of the liver were excluded.

Patients' demographic information (age and gender) as well as body mass index (BMI) were recorded. BMI was calculated as previously described, expressed as the ratio of weight to height squared (kg/m^2) [20].

The patients were classified as of normal weight (18.5-24.9kg/m^2), overweight (25.0-29.9kg/m^2) and obesity (over 30.0kg/m^2).

CT Protocol and Image Analysis

A 128-slice multidetector CT (MDCT) scanner was used for all investigations (Revolution HD, GE Milwaukee, USA). 2.5mm slices were acquired using through the duration of a breathold, using a tube current of 250mA, tube voltage of 120kV, and electrocardiography (EKG), in accordance with current guidelines for calcium scoring acquisition [21].

Unenhanced CT scans were used to evaluate the liver and the CAC score. Using dedicated software (cvi42, Release 5.13.9, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada), atherosclerotic plaque deposition was quantitatively assessed, using a threshold of 130 Hounsfield unit (HU) (Figure 1).

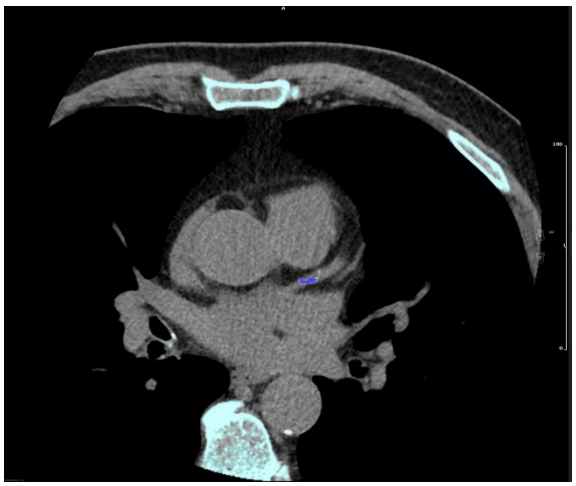

Figure 1. The quantification of CACS can be determined using multidetector computed tomography. Agatston score is used to measure the CAC score. Coronary calcification lesions are shown by the blue color area.

According to Agatston et al [19], multiple CAC scores were noted on medical charts, and each total CAC score was divided into four different stages.

A total CAC score of 0 was considered CAC stage 1, a total CAC score between 1 and 99 was considered CAC stage 2, a total CAC score between 100 and 399 was considered CAC stage 3, and a total CAC score of 400 or more was considered CAC stage 4. To diagnose hepatic steatosis on a CT scan, liver attenuation value was measured in HU. The measured liver attenuation value decreases as liver fat content gets higher [22].

The average of multiple liver density measurements was used to determine liver attenuation, this was performed by using 4 regions of interest (ROI) of 1.5cm diameter, two per slice at segments VII and VIII (Figure 2).

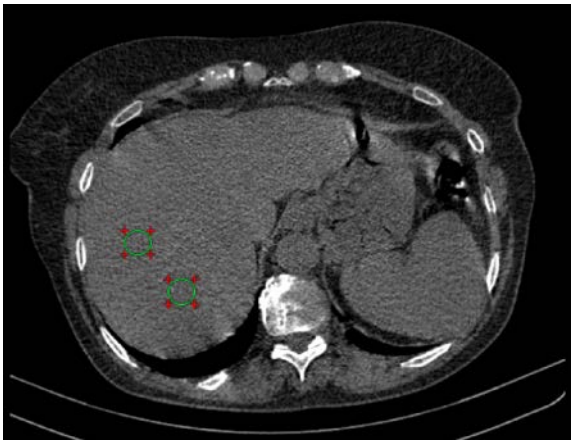

Figure 2. Representation of an axial non-contrast CT slice with the ROI positioned within hepatic segments VII and VIII.

Assessing representative areas of the liver parenchyma was performed with caution to keep any visible vessels outside the ROI. The diagnostic threshold for steatohepatitis on unenhanced CT was an absolute density of less than 48 HU in the liver parenchyma, suggested in previous studies [23,24].

Two measurements from the same radiologist were used to calculate the intraobserver variability.

Statistical Analysis

The means, standard deviations, medians, interquartile ranges, or counts and percent of parameters are shown, depending on how they are distributed. Mann-Whitney U-tests and unpaired t-tests were used to compare continuous variables. In order to compare categorical variables, the $\chi 2$ test was utilized. Spearman correlation coefficients was used to analyse the relationship between liver attenuation values and CAD severity. The correlation strengths of none (0-0.1), weak (0.1-0.3), moderate (0.3-0.5), and strong (0.5-1) were used as recognized criteria [25].

Multivariate logistic regression analysis was used to ascertain the independent predictors. A $p<0.05$ level of significance was used for the statistical tests. Graphpad Prism version 9.1 (GraphPad Software, San Diego, California) was used for statistical analysis.

Results

A total of 200 patients were enrolled in this study. The median BMI and mean age were 57±10 years (range: 33-85 years) and 29 [26-32] kg/m2, respectively. 50% of them were men and 39% of the patients were obese. Mean liver attenuation value was 51±13 HU. With an intraclass correlation value of 0.99, the intraobserver reliability for liver density measurements was excellent. 103 (51%) individuals had calcified plaque when the CAC score was evaluated, the median CAC score was 5 [0-128] AU.

Moreover, the CAC score was significant higher in individuals with NAFLD (p=0.0002). Subjects with NAFLD had a greater BMI compared to those without it (p=0.0003). In the group of patients without hepatic steatosis, we observed a higher incidence among normal-weight individuals, and a higher incidence among patients in stage 1 of CAC scoring. On the other hand, in the hepatic steatosis group, we found a higher incidence among obese patients and a higher incidence among patients in stage 4 of CAC scoring. The characteristics of the study subjects are displayed in Table 1.

Among all patients, CAC score (r=-0.31, p<0.0001), and BMI (r=-0.40, p<0.0001) had a moderate negative correlation with the values of liver attenuation (Table 2 and Figure 3).

Furthermore, age (r=-0.17, p=0.0149) had a weak negative correlation with the values of liver attenuation. A moderate significant correlation was found between calcium scoring and age (r=0.48, p<0.0001) (Table 3).

In the logistic regression analysis, we identified BMI (OR: 1.109, p=0.001), CAC score (OR: 1.629, p<0.001), and age (OR: 1.050, p<0.001) as independent predictors of hepatic steatosis (Table 4).

10.12865/CHSJ.49.02.14

Table 1 Baseline characteristics according to the presence of hepatic steatosis.

		Hepatic Steatosis		*P* Value
	Study Sample	Yes	No	
N	200	57 (28)	143 (71)	
Age	57±10	61±8	56±10	**0.02**
Gender				**0.0014**
Male	101 (50)	39 (68)	62 (43)	
Female	99 (49)	18 (32)	81 (56)	
BMI (kg/m2)	29 [26-32]	30 [27-35]	27 [24-50]	**0.0003**
BMI group				
Normal	42 (21)	5 (9)	37 (26)	**0.007**
Overweight	79 (39)	18 (32)	61 (43)	0.14
Obese	79 (39)	34 (60)	45 (31)	**0.0002**
CAC score	5 [0-128]	62 [0-296]	0 [0-81]	**0.0002**
CAC group				
1 (0AU)	97 (48)	16 (28)	81 (57)	**0.0003**
2 (1-99AU)	47 (23)	18 (32)	29 (20)	0.08
3 (100-399AU)	29 (14)	10 (18)	19 (13)	0.44
4 (≥400AU)	27 (13)	13 (23)	14 (10)	**0.015**

N, number of individuals; BMI, Body mass index; CAC, coronary artery calcification; AU, Agatston units.
Results are presented as median [interquartile range] or mean±SD for continuous variables and as n (%) for categorical variables.
Statistical significance is denoted by bold.

Table 2 Correlation between CAC score, BMI, age and liver attenuation values.

	Liver attenuation values (HU)	
	r	*P* value
Age	-0.17	**0.0149**
BMI (kg/m2)	-0.40	**<0.0001**
CAC score (AU)	-0.31	**<0.0001**

r, Spearman correlation coefficient; BMI, Body mass index; CAC, coronary artery calcification; AU, Agatston units. Statistical significance is denoted by bold.

Table 3 Correlation between BMI, age and CAC score.

	CAC score (AU)	
	r	*P* value
Age	0.48	**<0.0001**
BMI (kg/m2)	0.1	0.15

r, Spearman correlation coefficient; BMI, Body mass index; CAC, coronary artery calcification; AU, Agatston units. Statistical significance is denoted by bold.

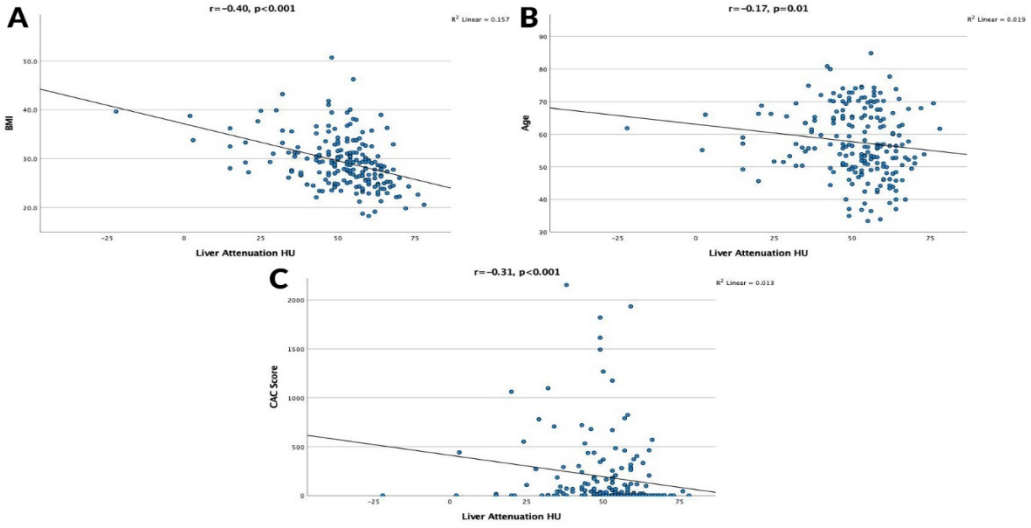

Figure 3. Plot representation of the dispersion of data of the correlation between BMI and HU density (A); correlation between age and HU density (B); correlation between CAC score and HU density (C).

Table 4 Multivariate logistic regression for NAFLD risk factors.

Variables	β	SE	Wald	df	*P* value	OR	95% CI
Age	0.049	0.016	9.318	1	**0.002**	1.050	1.018-1.083
BMI (kg/m2)	0.103	0.031	10.788	1	**0.001**	1.109	1.042-1.179
CAC score (AU)	0.488	0.144	11.498	1	**<0.001**	1.629	1.229-2.160

BMI, Body mass index; CAC, coronary artery calcification; AU, Agatston units. Statistical significance is denoted by bold.

Discussion

The aim of this retrospective cross-sectional study was to explore possible links between hepatic steatosis observed in liver segments during calcium score measurement and the occurrence of atherosclerotic CAD.

Our study showed an association between NAFLD and the presence of atherosclerotic CAD with a moderate negative correlation. Moreover, subjects with hepatic steatosis were more likely to be obese and men than those without it. The key elements of the metabolic syndrome, such as insulin resistance, obesity, dyslipidaemia, and diabetes mellitus are frequently linked to NAFLD. The conventional cardiovascular risk factors and the metabolic risk variables of hepatic steatosis are highly overlapping. It is debatable if NAFLD represents an independent risk factor for cardiovascular events despite research in this area. While some studies have not demonstrated a relationship with higher cardiovascular mortality in individuals with NAFLD [26,27], a number of cohort investigations have found NAFLD patients had an increase in cardiovascular mortality [9,28,29].

NAFLD has been linked to dyslipidaemia and insulin resistance as factors for accelerated atherosclerosis [30].

Additionally, the development from steatosis to steatohepatitis and cirrhosis may be brought on by persistent subclinical inflammation and an increase in oxidative stress. The production of reactive oxygen species by steatosis promotes the oxidation of fatty acids, which results in hepatocyte damage and the release of cytokines. The resulting proinflammatory environment is likely to prolong the liver damage caused by NAFLD and increase the already high levels of oxidative stress that the metabolic syndrome confers [30,31].

Plasmatic markers of inflammation and oxidative stress are more prevalent in NAFLD patients compared to control group [32].

Independent from conventional CAD risk factors, these indicators are linked to the histopathological severity of NAFLD [33].

Enhanced atherosclerosis may also be caused by decreased levels of adiponectin, an antiatherogenic cytokine released by adipocytes. Compared to patients without NAFLD, patients with NAFLD had significantly lower plasma adiponectin levels. Independent from metabolic syndrome, this decline is linked to the histopathological severity of NAFLD [34].

Given the uncertainty in the diagnosis process and a lack of effective treatment options, the American Association for the Study of Liver Diseases discourages routine NAFLD screening, even within populations at higher risk [35].

Despite the little effect in outcomes, the European Association for the Study of the Liver advises screening individuals with metabolic syndrome and high CVD-risk for NAFLD using liver enzymes and/or ultrasonography due to its prognostic impacts [36].

Atherosclerosis is a chronic and inflammatory disease that develops early in life and has a prolonged asymptomatic course as it progresses gradually. The CAC score is a helpful tool for customized risk stratification since it clinically represents the existence and severity of coronary atherosclerosis. The amount of calcium that has been formed in the coronary tree is frequently measured by the Agatston score. The role of calcium in the individual's coronary atherosclerotic load is significant from a prognostic and epidemiological standpoint. The Multi-Ethnic Study of Atherosclerosis study has shown that models that take into account age, gender, and race in relation to the absolute calcium score value are predictors of negative outcomes [37].

Hypercoagulability and NAFLD have been associated, according to recent studies [15].

This procoagulant dysregulation in NAFLD may serve as a causal connection between CVD and NAFLD. Increased oxidative stress may potentially be the cause of the elevated CV risk linked to NAFLD [9].

Due to the liver's aundance of immune cells and macrophages, cytokines released by the damaged liver have been suggested as one of the main pathogenic pathways causing systemic inflammation and CVD [15,30].

Our study has certain limitations that should be acknowledged. The laboratory data were conducted at a different medical institution, which limited our ability to study other laboratory variables due to lack of access to them. Additionally, the study design was retrospective cross-sectional, and it was conducted at a single tertiary care institution. By addressing these limitations, it is essential to interpret the study findings with caution and acknowledge that further research with larger and more diverse cohorts is necessary to validate and expand upon the results.

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Conclusion

BMI, CAC score, and age were identified as independent predictors of hepatic steatosis.

We found a statistically significant correlation between CAC score and the presence of NAFLD as evaluated by non-contrast-enhanced CT.

It may be beneficial to include the assessment of hepatic steatosis in cardiovascular risk evaluation because patients with hepatic steatosis are at a higher risk of developing atherosclerosis, as part of a metabolic syndrome.

Taking into account that this data is accessible during the routine acquisition of coronary artery computed tomography, it does not increase examination acquisition time or ionizing radiation exposure.

The Agatston CAC score is useful in assessing a patient's cardiovascular risk, and screening for fatty liver adds additional data regarding cardiovascular prognosis to the CT investigation.

Even though the pathophysiological processes underlying the link between NAFLD and CVD are not yet fully investigated, therapies that target these pathways are being developed.

Further investigation is required.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Emergency Institute for Cardiovascular Diseases and Heart Transplant of Targu Mures (no. 8920 from 07 December 2022).

Conflict of interests

None to declare

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