Risk of premature coronary atherosclerosis in patients with nonalcoholic fatty liver disease

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SUMMARY

OBJECTIVE: In the current literature, there are few studies investigating the relationship between premature coronary atherosclerosis and nonalcoholic fatty liver disease. We aimed to evaluate the relationship between nonalcoholic fatty liver disease and premature coronary atherosclerosis.
METHODS: In this cross-sectional study, female patients aged <55 years and male patients aged <50 years were enrolled. Both male and female patients underwent coronary angiography and abdomen ultrasonography between 2014 and 2019. A stepwise binary logistic regression analysis was carried out to evaluate the independent variables related to premature coronary atherosclerosis and nonalcoholic fatty liver disease. A p-value<0.05 was considered statistically significant.
RESULTS: nonalcoholic fatty liver disease was present in 44% of patients (n=377). Notably, 62% of the patients were female and the mean age was 44.5 (39–49) years. In a multivariate analysis, nonalcoholic fatty liver disease was shown to be an independent risk factor of premature coronary atherosclerosis (OR 1.438; 95%CI, 1.050–1.969; p=0.024).
CONCLUSIONS: The presence of nonalcoholic fatty liver disease is an important independent risk factor for the development of premature coronary atherosclerosis.
KEYWORDS: Atherosclerosis. Coronary artery disease. Nonalcoholic fatty liver disease.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is well known to affect one in every four adults in the developed countries, potentially emerging as a public health concern across the globe[1]. Furthermore, its prevalence is expected to increase substantially in the upcoming decades. In particular, the prevalence of NAFLD is even higher in patients with type 2 diabetes (T2D) and obesity (up to 70–80%)[2]. Interestingly, the most common cause of mortality in patients with NAFLD appears to be the cardiovascular disease (CVD) (accounting for 40–45% of deaths) rather than liver disease[3,4]. Experimental evidence clearly demonstrates that NAFLD (particularly its severe forms) might release a variety of pro-inflammatory, procoagulant, and profibrogenic mediators, potentially leading to a variety of cardiovascular complications mostly through exacerbation of systemic/hepatic insulin resistance with consequent atherogenic dyslipidemia. Based on these findings, patients with NAFLD might significantly benefit from intensive surveillance and, where necessary, earlier therapeutic interventions in an effort to reduce the risk of premature coronary atherosclerosis (PCA) and associated cardiovascular complications[5-8].

Traditionally, PCA has been defined as the presence of coronary artery disease (CAD) in females aged <65 years and males aged <55 years[9]. Clinically, PCA is strongly associated with acute myocardial infarction (AMI) that might, in turn, lead to increased risk of heart failure (HF) and mortality along with a substantial cost due to necessary therapeutic interventions, including myocardial revascularization strategies in adults. Interestingly, it has been reported that 50–66% of all NAFLDs have been encountered in patients with AMI[10]. This might also suggest the evaluation of PCA in patients with NAFLD through highly applicable and predictive methods[11,12]. In the current literature, NAFLD has been suggested to be associated with the presence and severity of CVD across different populations largely through its association with various markers of subclinical atherosclerosis (for instance, increased arterial stiffness and carotid atherosclerotic plaques)[13-15]. To the best of our knowledge, there has been no single study particularly investigating the relationship between PCA and NAFLD. Accordingly, we aimed to investigate the relationship between PCA and NAFLD.

METHODS

This is a single-center, cross-sectional study. Approval was obtained from the Institutional Ethics Committee prior to the study (TÜTF-BAEK 2018/332). Between 2014 and 2019, consecutive patients (comprising women aged 18–55 years and men aged 18–50 years) who underwent coronary angiogram (CAG) and abdominal ultrasonogram (USG) were recruited. Not to affect the results due to the COVID-19 pandemic, the records of patients after 2019 were not included. Evaluation of NAFLD by abdominal USG in patients with CAD was part of our institutional protocol based on the fact that it has been proven to be associated with traditional CAD and MI in previous studies[1-4]. Patients who did not undergo CAG and abdominal USG evaluation in the same year, cancer patients, pregnant women, and re-MI were excluded from the study. The remaining cases were recorded on case report forms (CRFs). Based on these data, basic clinical and echocardiographic (TTE) features, therapeutic strategies (including drugs), and laboratory results (total cholesterol [TC], low-density lipoprotein [LDL], triglycerides [TG], high-density lipoprotein [HDL]) were evaluated.

In TTE, patients were monitored by using Vivid 7 Pro (General Electric Medical System, Milwaukee, WI, USA) echocardiography device to obtain parasternal long axis, parasternal short axis, apical four spaces, and apical two spaces images obtained by a 2.5- to 3.5-MHz transducer. Left ventricular ejection fraction (EF) was measured using the Simpson method.

Abdominal USG was planned after 12 h of fasting as per our institutional protocol and was performed by radiologists using the device Toshiba Aplio 500. Right kidney echogenicity was used as a comparative marker to determine the grade of liver parenchymal echogenicity as follows:

- Grade 0 (normal): No difference in echogenicity between renal cortex and liver parenchyma (normal liver parenchyma)
- Grade 1 (mild): Mildly enhanced echogenicity defined in at least three regions of the parenchyma
- Grade 2 (moderate): Diffuse enhancement in liver echogenicity along with normal contours of intrahepatic vessels and diaphragm
- Grade 3 (severe): Slight deterioration in the appearance of the diaphragm and intrahepatic vessels along with a widespread increase in hepatic echogenicity

As per our institutional protocols, CAGs were evaluated by expert cardiologists. CAD was defined as a stenosis degree of >50% in at least one coronary artery on CAG. Subsequently, the participants were divided into two groups, namely, patients with CAD and those with normal coronary arteries. The participants were also categorized into two groups, namely, patients with NAFLD and those without NAFLD. The relationship between NAFLD and PCA was investigated between the two groups.

Statistical analysis

Shapiro-Wilk test was harnessed to analyze the normal distribution. Regarding the comparison of the groups, the Student's t-test was harnessed for variables within the normal distribution, along with the use of Mann-Whitney U test for those out of the normal distribution. Regarding multi-group comparisons, one-way analysis of variance was harnessed for those that were in accordance with the normal distribution, along with the use of Kruskal-Wallis test for those out of the normal distribution. Regarding the association between the quantitative variables, the Pearson's correlation coefficient was implemented for variables concording with the normal distribution along with the use of the Spearman's correlation coefficient for those out of the normal distribution. Pearson's χ^2 test was harnessed to assess the potential association among qualitative variables.

Stepwise binary logistic regression analysis was harnessed to uncover risk factors for PCA. Bland-Altman graphs identified the potential inter-intra observer concordance. The mean and standard deviation were harnessed for variables within the normal distribution along with the use of median and quarters for those out of the normal distribution. A p-value of <0.05 served as significant in all statistical assessments. Statistical software: Turcosa Analytics Ltd. Co., Turkey, www.turcosa.com.tr.

RESULTS

The demographic features of participants are summarized in Table 1. HDL-C levels were significantly lower and TC, TG, and LDL levels were significantly higher in the PCA group as compared with controls. In addition, the incidence of traditional risk factors, including DM, HT, smoking, obesity, hyperlipidemia, and gender, was significantly different between the two groups. Furthermore, the incidence and severity of NAFLD was found to be significantly higher in the PCA group (Table 1).

When the angiographic outcomes between those with and without NAFLD were compared, the NAFLD group was found to undergo elective CAG in a more frequent manner and have a higher incidence of PCA (Table 2). In addition, the mean LVEF value in the NAFLD group was found to be significantly higher as compared with the control group (Table 2).

Clinical factors, including HDL-C, TC, DM, HT, age, smoking, and the presence of NAFLD (potentially associated with PCA), were also evaluated in the multivariate regression analysis. NAFLD was found to serve as an independent risk factor for PCA evolution (p=0.024) (Table 3).

DISCUSSION

In the present study, we were able to demonstrate an increased frequency (and severity) of NAFLD along with a male gender predominance in patients with PCA as compared with controls. Specifically, we have also demonstrated characteristic biochemical findings of metabolic syndrome, including changes in specific lipoproteins (decreased HDL, increased TG) in patients with NAFLD. NAFLD is associated with cardiovascular risk factors, such as insulin resistance, diabetes, obesity, and dyslipidemia[16]. These conditions are well known to serve as components of metabolic syndrome. Therefore, NAFLD might be construed as a hepatic manifestation of metabolic syndrome. Interestingly, we have also demonstrated an increased mean LVEF value in patients with NAFLD in comparison to those without NAFLD. Even though the exact mechanism of this finding remains obscure, HT, being an important component of metabolic syndrome, might have elicited a relatively hyperdynamic ventricle (potentially due to left ventricular hypertrophy) in patients with NAFLD.

Importantly, NAFLD was found to serve as an independent risk factor for the evolution of PCA. We demonstrated this result by performing a stepwise binary logistic regression analysis (Table 3). In particular, this is the first study in which NAFLD was identified as an independent risk factor for the development of PCA, possibly due to its adverse effects on insulin resistance. The potential association between NAFLD and CAD was also demonstrated in previous studies[17-19]. Assy et al. demonstrated the relationship between coronary plaques and NAFLD through CT angiography (a noninvasive test)[17]. In contrast, we have confirmed the presence of PCA with CAG, which is accepted as the gold standard for the diagnosis of CAD[17]. Similarly, NAFLD, on top of genetic and environmental factors, was also reported to be a risk factor for the evolution of CAD in other studies[18-19]. In addition, it has been reported that nonalcoholic steatohepatitis (NAS), an advanced stage of

Table 1. Baseline demographic parameters of the study population.

	PCA group (n=408)	Control group (n=448)	p
Age	45 (40–50)	44.5 (39–49)	0.146
Gender (%)			
Female	211 (51.71)	319 (71.20)	<0.001
Male	197 (48.28)	129 (28.79)	
HT (%)	288 (70.58)	227 (50.66)	<0.001
DM (%)			
Tip 1	30 (7.37)	18 (4.01)	<0.001
Tip 2	143 (35.13)	77 (17.18)	
Smoking (%)	181 (44.36)	91 (20.53)	<0.001
Hyperlipidemia (%)	176 (43.13)	130 (29.01)	<0.001
Obesity (%)	28 (6.86)	17 (3.79)	0.045
NAFLD (%)	204(50)	173(38.61)	<0.001
NAFLD grade (%)			
0	204 (50)	275 (61.38)	0.001
1	115 (28.18)	116 (25.89)	
2	76 (18.62%)	48 (10.71%)	
3	13 (3.18%)	9 (2.00%)	
LVEF (%)	55 (50–60)	60 (55–63)	<0.001
LDL (mg/dL)	155 (129–188)	146 (119–175)	0.002
Triglycerides (mg/dL)	220 (148–343)	168 (123–260)	<0.001
Total cholesterol (mg/dL)	231 (197–270)	218 (185–259)	0.002
HDL (mg/dL)	49 (42–58)	54 (44–64)	<0.001

PCA: premature coronary atherosclerosis; HT: hypertension; DM: diabetes mellitus; n: patient number; NAFLD: nonalcoholic fatty liver disease; LVEF: left ventricular ejection fraction; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

NAFLD, is also of greater risk for the development of CAD[20]. However, previous studies did not specifically focus on PCA[18-19]. Inci et al. reported through USG that moderate-to-severe NAFLD might have the potential to predict CAD, but not its severity[21]. In our study, we found a significant relationship between NAFLD and PCA, particularly due to the increased frequency of PCA in moderate-to-severe (grades 2–3) NAFLD patients. This might also indicate that patients with moderate-to-severe NAFLD might be particularly prone to the evolution of PCA and should be under close supervision in terms of adverse cardiovascular events. In other words, detection of NAFLD on USG, which is a safe and noninvasive imaging

Table 2. Angiographic parameters of the study population.

	NAFLD group (n=377)	Control group (n=479)	p
Indications for angiography Generally (%)			
Elective	241 (63.9)	271 (56.78)	
ACS	136 (36.07)	207 (43.21)	
CCS angina	93 (24.66)	114 (23.79)	
MPS positivity	76 (20.15)	74 (15.44)	
Exercise test positivity	72 (19.09)	82 (16.70)	
Low LVEF	3 (0.79)	6 (1.25)	0.034
Anterior MI	19 (5.03)	27 (5.63)	
Inferior MI	14 (3.71)	22 (4.59)	
Lateral MI	1 (0.26)	3 (0.62)	
NSTEMI	36 (9.54)	46 (9.60)	
USAP	42 (11.14)	47 (9.81)	
Premature CAD (%)	204 (54.11)	204 (42.58)	<0.001
Coronary artery lesions (%)			
LMCA	17 (4.50)	25 (5.21)	
LAD	185 (49.07)	212 (44.25)	
CX	126 (33.42)	144 (30.06)	0.822
RCA	125 (33.10)	156 (32.56)	
SB	95 (25.19)	126 (26.30)	
Coronary collateral flow (%)			
0–1	349 (92.57)	439 (91.64)	
2	27 (7.16)	39 (8.14)	0.856
3	1 (0.26)	1 (0.20)	
Coronary ectasia (%)	8 (2.12)	7 (1.46)	0.465
Coronary calcification (%)	2 (0.53)	2 (0.41)	0.810
Coronary anomaly (%)	4 (1.06)	5 (1.04)	0.983
Coronary slow flow (%)			
0–1	4 (1.06)	5 (1.04)	
2	18 (4.77)	23 (4.80)	0.825
3	355 (94.16)	451 (94.15)	
LVEF (%)	59 (54.5–61.5)	57 (51–61)	0.036

NAFLD: nonalcoholic fatty liver disease; ACS: acute coronary syndrome; CCS: Canadian Cardiovascular Society; MPS: myocardial perfusion scintigraphy; LVEF: ejection fraction; MI: myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; USAP: unstable angina pectoris; CAD: coronary artery disease; LMCA: left main coronary artery; LAD: left anterior descending coronary artery; CX: circumflex coronary artery; RCA: right coronary artery; SB: side branch coronary artery.

Table 3. Stepwise binary logistic regression analysis of risk factors on premature coronary atherosclerosis.

Variable	OR	95%CI	p
Gender			
Male	–	–	<0.001
Female	0.334	0.223–0.500	
Age	1.058	1.034–1.083	<0.001
DM			
Type 1	2.387	1.222–4.665	0.011
Type 2	2.206	1.521–3.201	<0.001
HT	2.01	1.436–2.837	<0.001
Smoking	3.179	2.192–4.610	<0.001
Total cholesterol	1.005	1.002–1.008	<0.001
HDL	0.978	0.967–0.991	<0.001
NAFLD	1.438	1.050–1.969	0.024

DM: diabetes mellitus; HT: hypertension; HDL: high-density lipoprotein; NAFLD: nonalcoholic fatty liver disease; OR: odds ratio; CI: confidence interval.

modality, might allow further cardiovascular risk prediction[22]. Taken together, there exists a significant gap in the early diagnosis and management strategies of PCA. To date, most studies have generally focused on traditional cardiovascular risk factors and their management in an effort to combat this inauspicious phenomenon. However, an existing NAFLD (as demonstrated with USG) might possibly be taken into consideration when evaluating relatively young patients with a high cardiovascular risk for the early diagnosis of PCA.

Study limitations

This is a single-center study and has a retrospective design. Additional detection methods (e.g., magnetic resonance imaging and biopsy) are not evaluated in USG for NAFLD. Finally, we were not able to evaluate other inflammation markers that might also have important implications in this setting.

CONCLUSIONS

These data suggest the strong and independent association of NAFLD with PCA, regardless of atherosclerotic risk factors and components of metabolic syndrome. Therefore, an existing NAFLD might serve as an adjunct to cardiovascular diagnostic tests in the early diagnosis of PCA. However, further studies are still warranted to suggest NAFLD as a routine test in the setting of PCA diagnosis.

AUTHORS' CONTRIBUTIONS

GT: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **ME:** Data curation, Methodology, Validation, Writing – review & editing. **SS:** Data curation, Software, Validation, Writing – original draft. **ÇK:** Data curation, Methodology, Software, Writing – review & editing. **KY:** Data curation, Methodology, Writing – original draft, Writing – review & editing.

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