Original Article

Evaluation of the Correlation between Coronary Artery Disease and Nonalcoholic Fatty Liver Disease: Is There Any Correlation?

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Abstract

Background: *Coronary artery disease (CAD) and nonalcoholic fatty liver disease (NAFLD) are 2 common diseases around the globe. This investigation aimed to evaluate NAFLD prevalence in patients with CAD and the potential association between NAFLD and CAD.*

Methods: *This case-control study was performed between January 2017 and January 2018 at Ziaeian Hospital, Tehran, Iran. All patients aged between 35 and 5 years and referred for myocardial perfusion imaging were selected for the study. Totally, 180 participants were divided into CAD^+ and CAD^- groups. CAD was defined as stenosis of greater than 50.0% in at least 1 coronary artery. Afterward, all the patients underwent abdominal sonography and laboratory tests for NAFLD evaluation. Patients with a history of liver diseases, alcohol consumption, and drug-induced steatosis were excluded.*

Results: *The study population consisted of 122 women (67.8%) and 58 men (32.2%) at a mean age of 49.31±5.42 years. NAFLD was detected in 115 patients. NAFLD prevalence in the CAD^+ group was 78.9%. NAFLD was determined as an independent risk factor for CAD (OR, 3.9).*

Conclusion: *NAFLD prevalence was high in the CAD^+ group. The incidence of steatosis is on the rise in the general population. Hence, considering the high prevalence of abdominal obesity, all patients with NAFLD should be evaluated for CAD.*

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease the world over and is known as fat accumulation in the liver tissue as high as 5.0% to 10.0% of the total liver weight without such underlying causes as alcohol abuse, medication, and viral hepatitis. While most individuals with NAFLD ($NAFLD^+$ patients) are asymptomatic and have acute burnouts, symptomatic patients develop nonspecific signs and symptoms, complicating the diagnosis and evaluation of NAFLD severity.[1, 2]

NAFLD has an incidence rate of 35% in developed countries, with an even higher prevalence rate (70.0%-90.0%) among individuals suffering from diabetes mellitus and obesity.[3] NAFLD leads to an increased risk of several clinical conditions, such as diabetes mellitus, obesity, dyslipidemia, and most importantly, metabolic syndrome.[4] Some researchers have claimed that NAFLD is a liver manifestation of insulin resistance or metabolic syndrome.[5, 6] In some patients, NAFLD might not only result in cirrhosis, hepatocellular carcinoma, and cardiovascular disease but also lead to some extrahepatic disorders such as colorectal cancer and atherosclerosis.[7] The aforementioned NAFLD-induced liver changes are associated with dyslipidemia and increased levels of serum cholesterol and low-density lipoprotein, allied to an increased risk of cardiovascular disease and particularly, coronary artery disease (CAD) according to the criteria introduced by Framingham.[8] Therefore, there is an undeniable correlation between NAFLD and metabolic syndrome and subsequently, cardiovascular disorders.

On the other hand, CAD is one of the most common causes of mortality in that it is responsible for 14.0% of the annual total mortality rate.[9] Originating from lipid accumulation and plaque formation in the blood vessels of the heart muscle, CAD leads to the partial or complete obstruction of the heart's blood supply and reduces oxygen flow to the tissues.[10] Moreover, the huge burden and cost that CAD imposes on medical systems are preventable if the underlying risk factors of the disease, such as NAFLD, are addressed appropriately.

Numerous studies have presented data regarding the correlation between NAFLD and CAD; nonetheless, the difference in laboratory and paraclinical findings concerning NAFLD between patients with CAD (CAD^+) or without CAD (CAD^-) is still a topic of debate among experts. In the present study, we aimed to determine NAFLD prevalence among CAD^+ patients and investigate the relationship between the paraclinical findings of $NAFLD^+$ patients and CAD manifestations.

Methods

The current research was performed to evaluate the correlation between CAD and NAFLD. A case-control study was conducted on 180 patients admitted to the nuclear medicine department for stress/rest myocardial perfusion imaging (MPI), also known as "thallium scanning."

The patients recruited were aged between 35 and 55 years, and they had no prior history of alcohol consumption. Patients who had underlying conditions, such as liver diseases (eg, viral hepatitis B or C and autoimmune hepatitis), Wilson's disease, celiac disease, cardiovascular conditions (eg, valve abnormalities), a history of coronary artery bypass graft surgery, and autoimmune conditions, as well as patients who consumed drugs associated with high risks of steatosis, were excluded from the study.

The patients were divided into 2 groups based on MPI results. The case group consisted of 90 patients with signs of CAD (CAD^+ group), and the control group comprised 90 patients with negative MPI results (CAD^- group). Subsequently, the patients were referred to a specific radiology center for sonographic liver assessments. Additionally, laboratory tests, including serum alanine transaminase, aspartate aminotransferase, high and low-density lipoproteins, surface antigens of the hepatitis B virus, hepatitis C antibodies, immunoglobulin, anti-tissue transglutaminase antibodies, total triglyceride, and total cholesterol, were performed. The study population's demographic characteristics are presented in Table 1.

Participants were considered to have diabetes mellitus if they had fasting blood glucose (FBS) levels ≥126 mg/dL or 2-hour postprandial blood glucose levels ≥200 mg/dL or if they were taking antidiabetic medications.[11] Hypertension was defined as mean systolic blood pressure ≥140 mmHg or mean diastolic blood pressure ≥90 mmHg or the use of antihypertensive medication.[12] Renal failure or chronic kidney disease was defined based on the presence of kidney damage or glomerular filtration rates <60 mL/min/1.73m^2 for ≥3 months at any time.[13] Body mass index (BMI) (calculated as weight [kg] divided by the square root of height [m]) was grouped as underweight (BMI<18.5 kg/m^2), normal (18.5≤ BMI<25 kg/m^2), overweight (25≤ BMI<30 kg/m^2), and obese (BMI ≥30 kg/m^2) according to the World Health Organization (WHO) recommendations.[14]

The methods applied in this study followed the Helsinki Declaration, and informed written consent was obtained from all the study participants. The design and conduct of the study were approved by the Ethics Committee of Tehran University of Medical Sciences (IRB code: IR.TUMS.MEDICINE.REC.1397.009).

All data regarding each patient's MPI, sonography, and laboratory results were gathered. IBM SPSS Statistics for Windows, version 25 (IBM Corp, Armonk, NY, USA, https://www.ibm.com), was used to conduct statistical analysis.

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Logistic regression analysis was utilized to assess the correlation between NAFLD and CAD risk. The data were described using frequencies, percentages, means, and standard deviations and compared between the CAD^+ group and CAD^- group using the Student t test, the χ^2 test, or the Fisher exact test.

Results

The study population was comprised of 122 women (67.8%) and 58 men (32.2%) aged between 35 and 55 years (mean= 49.11±5.32 y). The baseline demographic and clinical characteristics of the participant are presented in Table 1. The CAD^+ and CAD^- groups were matched regarding age and sex. The case group consisted of 56 women and 34 men, and the control group comprised 66 women and 24 men. Table 2 depicts the distribution of different MPI results based on sex in the study population.

Table 1. Demographic information based on case and control groups*

Variable	Control (n=90)	Case (n=90)
Sex		
Male	24 (13.3)	34 (18.8)
Female	66 (36.7)	56 (31.2)
Diabetes		
Yes	14 (15.5)	27 (30)
No	76 (84.5)	63 (70)
Dyslipidemia		
Yes	33 (36.7)	49 (54.4)
No	57 (63.3)	41 (45.6)
Hypertension		
Yes	40 (44.4)	40 (44.4)
No	50 (55.6)	50 (55.6)
Smoking		
Yes	9 (10.0)	15 (16.7)
No	81 (90.0)	75 (83.3)
BMI		
BMI≥ 25	32 (35.5)	76 (84.4)
BMI< 25	58 (64.5)	14 (15.6)

*Data are presented as n (%).
BMI, Body mass index

Table 2. MPI results based on the patients' sex*

MPI Result	Number of Cases (%)	Male (n, %)
Control		
Normal SSS<4	90 (100.0)	24 (26.6)
Case		
Mild 4≤ SSS< 8	69 (76.7)	23 (33.3)
Moderate 8≤ SSS< 13	15 (16.7)	6 (40.0)
Severe SSS≤ 13	6 (6.7)	5 (83.4)

*Data are presented as n (%).
MPI, Myocardial perfusion imaging; SSS, Summed stress score

Table 3. Association between NAFLD and MPI results*

NAFLD Grade Based on Sonographic Assessments	Study Group		Total
	MPI^+	MPI^-	
None	19 (21.1)	46 (51.1)	65 (36.1)
I	48 (53.3)	26 (28.9)	74 (41.1)
II	18 (20.0)	18 (20.0)	36 (20.0)
III	5 (5.6)	0 (0)	5 (2.8)
Total	90 (100.0)	90 (100.0)	180 (100.0)

*Data are presented as n (%).
NAFLD, Nonalcoholic fatty liver disease; MPI, Myocardial perfusion imaging

Table 4. Associations between NAFLD and underlying conditions in CAD cases*

Underlying Condition in the CAD^+ Group	Total (n=90)	NAFLD		*P*
		Positive (n=71)	Negative (n=19)	
Smoking	15 (16.7)	9 (12.7)	6 (31.6)	0.049
Diabetes	27 (30.0)	24 (33.8)	3 (15.8)	0.128
Dyslipidemia	49 (54.4)	42 (59.2)	7 (36.8)	0.083
Hypertension	40 (44.4)	33 (46.5)	7 (36.8)	0.453
BMI ≥25	76 (84.4)	64 (90.1)	12 (63.2)	0.003

*Data are presented as n (%).
NAFLD, Nonalcoholic fatty liver disease; CAD, Coronary artery disease; BMI, Body mass index

Liver sonographic assessments revealed 65 patients with normal livers and 115 with different grades of steatosis. Among the affected cases, 74 patients (41.1%) had grade I steatosis; 36 patients (20%), had grade II steatosis; and only 5 cases (2.8%) had grade III steatosis. In total, 56% of the men and 67% of the women were diagnosed with NAFLD, showing a statistically similar sex distribution in this regard. Liver sonographic assessments in the positive MPI patients (the study group) revealed that out of 90 patients, 19 patients (21.11%) had normal livers, 48 patients (53.33%) had grade I NAFLD, 18 patients (20%) had grade II NAFLD, and 5 patients (5.5%) had grade III NAFLD. In patients with normal sonographic assessments (65 patients), 19 patients were CAD^+ and 46 patients were CAD^-. As is indicated in Table 3, the patients with positive MPI results were more prone to NAFLD incidence in the 3 different sonography grades. The statistical analysis with the Fisher exact test demonstrated a significant correlation between MPI results (the study group) and NAFLD incidence in the 3 different sonography grades (P<0.001).

The univariate analysis revealed that NAFLD independently increased the risk of CAD (OR, 3.9; 95% CI, 2.03 to 7.51). The multivariate analysis, considering sex and age besides NAFLD, showed that NAFLD was associated with a relatively increased risk of CAD incidence (OR, 4.26; 95% CI, 2.12 to 8.53). The adjustment of sex and age

among the studied patients indicated a further increased risk of CAD associated with NAFLD (OR, 4.95; 95% CI, 2.20 to 11.14).

Apropos of underlying diseases in the study population, diabetes mellitus (22.8%), dyslipidemia (45.6%), hypertension (44.4%), smoking (13.3%), and steatosis (63.9%) were the most common findings. Concerning predisposing factors for NAFLD, of the 115 affected cases, 18.8% had a history of diabetes mellitus, 33.8% had hypertension, and 60.0% had a BMI >25.

The prevalence of CAD in diabetic NAFLD$^+$ patients was 20.9%, which was lower than that among nondiabetic NAFLD+ patients. Still, the difference was shown to be nonsignificant (P=0.206), signifying no notable correlation between diabetes in NAFLD$^+$ patients and CAD incidence. Similarly, NAFLD$^+$ patients with dyslipidemia had a CAD incidence rate of 36.5%, which was statistically similar to the rate among NAFLD$^+$ patients without dyslipidemia (P=0.231). Moreover, among NAFLD$^+$ patients, no substantial correlation was detected either between hypertension and CAD (P=0.073) or between high BMI ≥25 and CAD (P=0.073).

As is shown in Table 4, NAFLD was significantly associated with smoking (P=0.049) and BMI ≥25 in patients with CAD (P=0.003). Finally, the correlations between BMI, CAD grades, and NAFLD grades were evaluated in the study population. The results indicated a positive significant correlation between BMI and NAFLD grades (correlation coefficient =0.448; P<0.001), whereas no significant correlation was revealed between BMI and MPI or its grade (P>0.05).

Comparisons of the laboratory evaluations between CAD$^+$ and CAD$^-$ in NAFLD$^+$ patients revealed no significant differences regarding total cholesterol (P=0.539), total triglyceride (P=0.542), alanine transaminase (P=0.898), high-density lipoprotein (P=0.325), and low-density lipoprotein (P=0.701), signifying no significant associations between these factors and CAD in NAFLD$^+$ patients.

Similarly, comparisons of the laboratory evaluations between CAD$^+$ and CAD$^-$ in NAFLD$^-$ patients yielded no significant differences vis-à-vis total cholesterol (P=0.268), total triglyceride (P=0.471), alanine transaminase (P=0.804), high-density lipoprotein (P=0.365), and low-density lipoprotein (P=0.260), indicating no significant associations between these factors and CAD in NAFLD$^-$ patients.

Discussion

In the current prospective study, NAFLD exhibited a strong association with CAD and abnormal findings during MPI, regardless of the role of other demographic, clinical, or paraclinical findings. The prevalence of CAD was higher in NAFLD$^+$ patients who also suffered from diabetes mellitus and dyslipidemia. Older NAFLD$^+$ patients were more susceptible to CAD than their younger counterparts. Nevertheless, we observed no relationships between MPI findings and lipid profile and steatosis severity.

Considering the silent and asymptomatic nature of both CAD and NAFLD, it is vital to find factors with an impact on the course of the disease. Currently, NAFLD prevalence in the healthy population is on the rise, with the latest studies estimating it at 61.0%.[3] The increasing prevalence of NAFLD could be a corollary of changes in lifestyles, such as the overconsumption of fat and alcohol, as well as smoking.[15] Furthermore, NAFLD prevalence among patients with CAD is reported to have exceeded 60.0%.[16] In light of our results, indicating that 79.0% of the CAD$^+$ group had NAFLD, we can posit an apparent association between the 2 diseases.

Many studies have highlighted a higher prevalence of NAFLD among patients whose CAD is confirmed through angiographic evaluations of the coronary arteries. Rust et al[17] examined the liver by ultrasonography in patients who underwent coronary artery angiography as a diagnostic approach. They reported a prevalence rate of 71.5% for NAFLD in the study group and severe steatosis and NAFLD in patients with more than 75% coronary obstruction. Similarly, Adibi et al[18] compared NAFLD prevalence among patients who underwent coronary artery angiography and found that the rate was noticeably high among individuals with abnormal angiographic findings by comparison with those with normal findings. Through MPI, we detected prevalence rates of 61.7% and 29.2% for NAFLD in the CAD$^+$ and CAD$^-$ groups, respectively, indicating a significantly increased risk of CAD in NAFLD$^+$ patients (risk ratio=3.90; OR, 2.11). However, despite the relationship between coronary artery angiographic findings and NAFLD liver manifestations, we were unable to establish a correlation between MPI results and NAFLD severity. In contrast, Alper et al[19] claimed that severe CAD was associated with the clinical manifestations of steatosis; nonetheless, given the invasive nature of coronary artery angiography, they suggested that better screening approaches were required to assess patients who suffer from NAFLD and CAD.

Rabiee et al[20] reported that NAFLD$^+$ patients were 3.7 times at a higher risk of diabetes mellitus than NAFLD$^-$ individuals. Moghaddasifar et al[21] observed a high prevalence of obesity, metabolic syndrome, hypertension, and hypertriglyceridemia among NAFLD$^+$ patients compared with NAFLD$^-$ individuals. We observed that despite a strong correlation between diabetes mellitus and NAFLD, NAFLD$^+$ patients with diabetes mellitus had no significantly higher risk of CAD. Our findings chime in with those reported by Ahmadi et al,[22] who reported no statistically significant differences regarding the prevalence

of chronic diseases, such as hypertension, diabetes mellitus, and dyslipidemia, in their comparison of CAD+ patients with and without NAFLD. Wong et al[23] confirmed the association between NAFLD and CAD, irrespective of other metabolic factors. We believe that patients who develop diabetes mellitus as a consequence of NAFLD are at the early stages of their chronic disease, where the severity of diabetes mellitus is still too low to predispose to subsequent cardiovascular disease. Accordingly, the coexistence of NAFLD with other chronic diseases does not seem to exert a significant influence on CAD.

On the other hand, whereas some studies have proved a correlation between data regarding the presence of NAFLD in patients with pathologic coronary arteries and laboratory findings, such as the serum lipid profile, we detected no correlation between laboratory test results and MPI findings.[24, 25] The difference might be explained by the enrollment of patients with 1 or more underlying diseases, altering the serum lipid profile.

The current investigation has some limitations, which should be considered when interpreting the results. Firstly, MPI might yield false-negative or false-positive results; however, we did our utmost to avoid misdiagnosis. Secondly, we evaluated a narrow age range, which led to a lower number of patients enrolled. Thirdly, we were unable to follow up and gather data on patients referred for coronary artery angiography.

Conclusion

NAFLD was shown to correlate with CAD and should be considered a crucial predisposing factor for CAD; nonetheless, laboratory findings in NAFLD+ patients fail to constitute a good indicator of the severity of coronary artery obstruction. NAFLD was significantly associated with BMI and smoking. CAD was shown to have a higher prevalence in NAFLD+ patients with diabetes mellitus and hyperlipidemia. No significant relations were observed between MPI findings and lipid profile and steatosis severity. In addition, no significant correlations were found between BMI, CAD grades, and NAFLD grades.

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