Original Article

Association between Nonalcoholic Fatty Liver Disease Based on Ultrasonography Indices and Severity of Coronary Artery Disease: A Cross-Sectional Study

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Abstract

Background & Aims: Recent observations highlighted the importance of evaluating nonalcoholic fatty liver disease (NAFLD) in individuals with coronary artery disease (CAD) to establish strategies to prevent the evolution of the disease. However, the association between severity of CAD and NAFLD remains uncertain. The aim of this study was to investigate whether NAFLD was associated with severity of CAD assessed by coronary angiography.

Materials & Methods: This cross-sectional study was performed on 320 consecutive patients who were candidates for coronary angiography. All patients underwent coronary angiography to assess the presence and severity of coronary involvement and liver ultrasonography to assess the degree of fatty liver in the same session. The extension of CAD was measured using the Gensini score. The severity of NAFLD was measured using ultrasonography grading (Grade 0- III).

***Results*:** Regarding grade of NAFLD, 42.2% of patients had normal condition (Grade 0), 31.5% had grade I, 19.7% had grade II, and 6.6% had grade III of NAFLD. With regard to the difference in grading of NAFLD between cardiovascular risk subgroups, this difference was only observed between the patients with BMI $\geq$ 30 kg/m^2 and those with BMI < 30 kg/m^2. The mean Gensini score in patients with normal condition (Grade 0) or grade I of NAFLD was 20.6 ± 1.2, in grade II of NAFLD was 23.6 ± 4.2, and in those with grade III of NAFLD was 47.3 ± 9.6. Findings indicate that CAD severity increases with the increase in the grade of NAFLD ($p = 0.002$). Using the multivariate linear regression model and with the presence of baseline variables as the confounders, the association between the Gensini score and NAFLD grade remained significant ($p = 0.001$).

***Conclusion*:** The present study demonstrates a higher Gensini score in those patients with higher grades of NAFLD indicating a linear association between CAD severity and severity of NAFLD.

***Keywords*:** Metabolic Syndrome, Non-alcoholic fatty liver disease, Coronary artery disease, Gensini score

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease that encompasses a spectrum of conditions associated with lipid deposition in hepatocytes (1,2). This defect ranges from steatosis and nonalcoholic steatohepatitis to advanced fibrosis and cirrhosis (3,4). The disease is mostly silent and is often discovered through incidentally elevated liver enzyme levels (5,6). It is strongly associated with obesity and insulin resistance and is currently considered by many as the hepatic component of the metabolic syndrome (7-9). It has been now revealed that the metabolic syndrome and also each of its five components are strong risk factors for the presence of NAFLD (10). This has led investigators to suggest that NAFLD is a component of the metabolic syndrome, and it is frequently quoted that "NAFLD is the hepatic manifestation of metabolic syndrome" (11,12).

A close association between NAFLD and coronary artery disease has been shown (13,14). NAFLD significantly affected the development of atherosclerosis (13,14). In investigations that used MSCT to diagnose coronary artery disease, some studies analyzed the characteristics of coronary plaques and their association with NAFLD and found different results (15). While Assy et al. (16), in a small study, found an association of NAFLD with coronary artery stenosis of at least 50%, the results of Akabame et al. (17) indicated that patients with NAFLD might have a risk factor for vulnerable plaque rather than significant coronary artery stenosis. This result, therefore, suggested that NAFLD was related to the initial phase of coronary artery disease, but not with coronary artery disease severity. These observations highlighted the importance of evaluating NAFLD in individuals with subclinical coronary artery disease to establish strategies to prevent the evolution of the disease. Moreover, the association between severity of coronary artery disease and NAFLD remains uncertain. The aim of this study was to investigate whether or not NAFLD is associated with severity of coronary artery disease assessed based on coronary angiography findings.

Various studies have been conducted in this field in the world, but due to the importance of the issue and the increasing prevalence of coronary artery disease and metabolic syndrome and differences in different races, we decided to study this issue in Iranian society.

Methods

This cross-sectional study was performed on 320 consecutive patients who were candidates for coronary artery assessment by coronary angiography because of typical chest pain, acute coronary syndrome, or positive exercise test or perfusion scan. The exclusion criteria were history of alcohol use, history of liver disease, congestive heart failure, malignancies, Corpulmonale, acute or chronic infections, severe pulmonary diseases, chronic kidney disease, or history of using steatosis-induced drugs. The coronary artery involvement was defined as 50% or greater coronary lumen stenosis of any coronary vessel, so the patients were categorized into two groups with and without coronary artery disease. Baseline characteristics collected by reviewing the hospital record files included demographics, anthropometric indices, and coronary risk factors. All patients underwent coronary angiography to assess the presence of coronary involvement and its severity. In addition, to determine the number of diseased coronary vessels, the extension of coronary disease was measured using the Gensini score. Gensini score (18) was calculated for each patient according to coronary angiography findings. The score was computed by assigning a severity score to each coronary artery stenosis according to the degree of luminal narrowing and its anatomic importance. Reduction in the lumen

diameter, and the roentgenographic appearance of concentric lesions and eccentric plaques were evaluated. Each principal vascular segment was assigned a multiplier in accordance with the functional significance of the myocardial area supplied by that segment: the left main coronary artery × 5; the proximal segment of left anterior descending coronary artery (LAD) × 2.5; the proximal segment of the circumflex artery × 2.5; the mid-segment of the LAD × 1.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery × 1; and others × 0.5. Before discharge, all participants underwent abdominal ultrasonography by a single operator to assess the presence and grading of NAFLD. NAFLD was diagnosed based on typical ultrasonographic findings.

Conventional x-ray coronary angiography was performed with an integrated digital

Cardiac catheter imaging system (Siemens device) by a team of interventional cardiologists and then investigated by the same team. All liver ultrasounds were performed by a single radiologist by a Siemens ultrasound machine during the same hospital stay.

Liver echo pattern follows as grade 1 (mild): A slight diffuse increase in fine echoes in the hepatic parenchyma with normal visualization of the diaphragm and intrahepatic vessel borders; grade 2 (moderate): A moderate diffuse increase in fine echoes with slightly impaired visualization of the intrahepatic vessels and diaphragm; and grade 3 (marked): A marked increase in fine echoes with poor or no visualization of the intrahepatic vessel borders, diaphragm, and posterior portion of the right lobe of the liver (19).

Sample Size

Based on the calculations performed with a 95% confidence interval and 80% strength, the required sample size of 320 patients was calculated.

$$n_1 = \left[\frac{z_{1-\frac{\alpha}{2}} \times \sqrt{\overline{pq}\left(1+\frac{1}{k}\right)} + z_{1-\beta} \times \sqrt{p_1 q_1 + \frac{p_2 q_2}{k}}}{\Delta} \right]^2$$

$\alpha = 0.05 \rightarrow Z_{1-\frac{\alpha}{2}} = 1.96$

$\beta = 0.2 \rightarrow Z_{1-\beta} = 0.85$

$P_1 = 0.372$

$P_2 = 0.210$

$\Delta = P_1 - P_2 = 0.32$

Ethical Consideration:

This study was approved by our university research ethics committee. All patients gave their informed consent. Participants' information was completely confidential. Our study did not interfere with the treatment of patients.

Statistical analysis:

For statistical analysis, Kolmogorov-Smirnov test was used to check normality of data. Quantitative variables were presented as mean ± standard deviation (SD) and categorical variables were summarized by absolute frequencies and percentages. Continuous variables were compared using t-test and/or non-parametric Mann Whitney U test whenever the data did

not appear to have normal distribution or when the assumption of equal variances was violated across the three groups of TR. Categorical variables were, on the other hand, compared by the chi-square test. For the statistical analysis, the statistical software SPSS version 20.0 for windows (SPSS Inc., Chicago, IL) was used. P-value of 0.05 or less was considered statistically significant.

Results

A total of 320 consecutive patients were assessed. The mean age of patients was 58.6 ± 11.5 years, (Range 23 to 86 years), the mean body mass index was 26.9 ± 4.7 kg/m^2 (Range 15.19 to 43.29 kg/ m^2) and 59.7% of patients were male. Regarding cardiovascular risk factors, 19.3% were smokers, 24.7% were diabetic, 44.3% were hypertensive, and 25.0% were hyperlipidemic. Positive exercise test and positive MPI results were 10.3% and 23.8%, respectively. Also, 4.7% had reduced LVEF (Table 1). The Gensini score was zero in 26.4%, 0.5 to 10 in 31.4%, 11 to 20 in 10.4%, 21 to 40 in 11.3%, 41 to 60 in 8.5%, 61 to 100 in 6.6%, and higher than 100 in only 5.4% of patients (Figure 1). Furthermore, regarding grade of NAFLD, 42.2% had normal condition, 31.5% had grade I, 19.7% had grade II, and 6.6% had grade III of NAFLD. As shown in Table 2, with regard to the difference in grading of NAFLD between cardiovascular risk subgroups, this difference was only observed between the patients with BMI ≥ 30 kg/m^2 and those with BMI < 30 kg/m and with hyperlipidemia[2]. In this regard, there was no relationship between grading of NAFLD and other risk profiles including male gender, advanced age, hypertension, diabetes, smoking, and family history of coronary disease and waist to hip ratio (WHR). Concerning the difference in mean Gensini score between the different grades of NAFLD, the mean Gensini score in patients with normal condition or grade I of NAFLD was 20.6 ± 1.2, in grade II of NAFLD was 23.6 ± 4.2, and in those with grade III of NAFLD was 47.3 ± 9.6. In other words, CAD severity increases with the increase in the grade of NAFLD (p = 0.0025) (Table 3). Mean Gensini score of all patients was 31.06 ± 2.37. Gensini score difference was only observed between age, sex, Smoking, and WHR. Using the multivariate linear regression model and with the presence of baseline variables as the confounders, the association between the Gensini score and NAFLD grade remained significant (p = 0.001). Overall, in those patients with acute coronary syndrome, 58.6% had no evidence of NAFLD, while 13.8% had grade I, 24.1% had grade II, and 3.5% had grade III of NAFLD.

Table 1: Baseline characteristics and clinical data of study population

Age subgroups	
≤ 50 years	81 (25.3)
> 50 years	239 (74.7)
Mean age, year	58.6 ± 11.5
Male gender	191 (59.7)
History of smoking	62 (19.3)
Family history of CAD	55 (17.1)
Diabetes mellitus	79 (24.7)
Hypertension	142 (44.3)
Hyperlipidemia	80 (25.0)
Body mass index, kg/m^2	26.9 ± 4.7

Body mass index ≥ 30 kg/m^2	80 (25.0)
Waist circumference, cm	104.4 ± 10.8
Waist to hip ratio ≥ 0.85	300 (93.7)
Indications for angiography	
Chest pain	164 (51.2)
ACS	29 (9.1)
ETT	33 (10.3)
MPI	76 (23.8)
Reduced-EF	15 (4.7)
Other	3 (0.9)

Table 2: Correlation between patients' cardiovascular risk factors & staging of NAFLD

Item	Normal /grade I	Grade II	Grade III	p-value
Gender				
Male	137 (71.7)	42 (22.0)	12 (6.3)	0.45
Female	99(76.7%)	21(16.3%)	9(7.0%)	
Age subgroup				
≤ 50 years	61 (75.3)	15 (18.5)	5 (6.2)	0.93
> 50 years	175 (73.2)	48 (21.1)	16 (6.7)	
History of smoking				
Positive	46 (74.2)	11 (17.7)	5 (8.1)	0.81
Negative	190 (73.6)	52 (20.2)	16 (6.2)	
Family history of coronary disease				
Positive	41 (74.5)	9 (16.4)	5 (9.1)	0.60
Negative	195 (73.6)	54 (20.4)	16 (6.0)	
Body mass index				
< 30 kg/m2	191 (79.6)	36 (15.0)	13 (5.4)	< 0.001
≥ 30 kg/m2	45 (56.3)	27 (33.7)	8 (10.0)	
Waist to hip ratio				
< 0.85	17 (85.0)	2 910.0)	1 (5.0)	0.48
≥ 0.85	219 (73.0)	61 (20.3)	20 (6.7)	
History of diabetes				
Positive	55 (69.6)	20 (25.3)	4 (5.1)	0.32
Negative	181 (75.1)	43 (17.8)	17 (7.1)	
History of hypertension				
Positive	104 (73.2)	28 (19.7)	10 (7.1)	0.95
Negative	132 (76.2)	35 (19.6)	11 (6.2)	
History of hyperlipidemia				
Positive	53 (66.2)	18 (22.5)	9 (11.3)	0.09
Negative	183 (76.2)	45 (18.8)	12 (5.0)	

Table 3: Association between severities of CAD based on Gensini Score & NAFLD

Gensini score	Fatty liver severity
20.6(±1.2)	No Fl+Grade I
23.6(±4.2)	Grade II
47.3(±9.6)	Grade III

(P-value=0.0025)

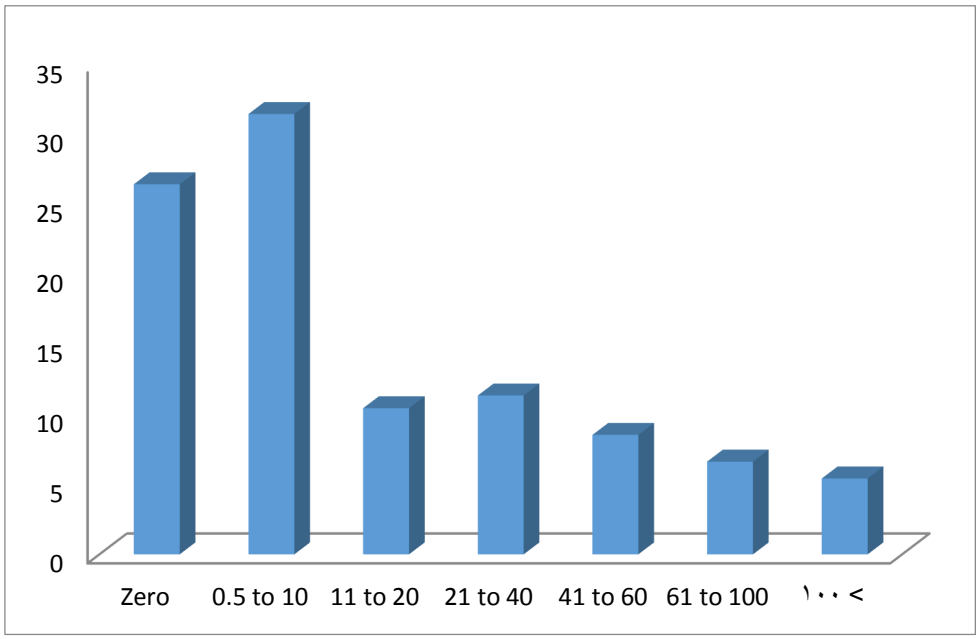

Figure 1: Frequency of Gensini score

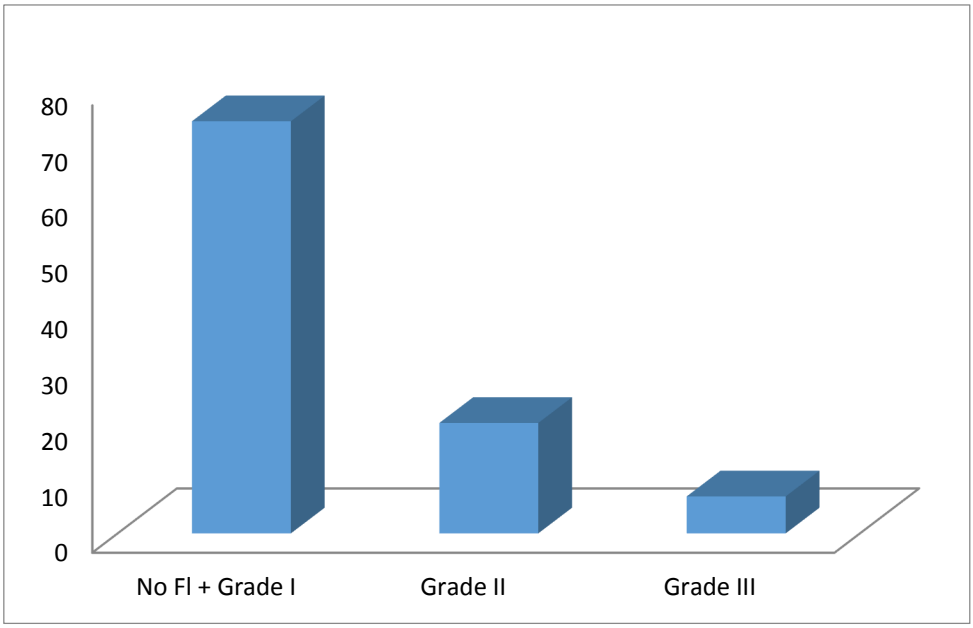

Figure 2: Grading of NAFLD

Discussion

The present study demonstrated higher Gensini score in patients with higher grades of NAFLD indicating a linear association between CAD severity and severity of NAFLD. This finding was also approved by a multivariate regression modeling adjusted for baseline variables including demographic and anthropometric indices as well as general cardiovascular risk factors. In fact, because of the confirmed association of both NAFLD and CAD with metabolic syndrome, it seems that the presence of this syndrome as an underlying factor can mediate the progression of coronary disease in patients with NAFLD. Therefore, among different risk factors of CAD, only obesity and hyperlipidemia were significantly more prevalent in higher grades of NAFLD, and the central role of obesity in mediating CAD in those with NAFLD can be specifically considered. In addition to this risk factor, some other risk factors for subclinical atherosclerosis have been identified in both NAFLD and CAD including increase of carotid intima-media thickness and vasodilation abnormality due to flow defects (20,21). Pathophysiological similarity between NAFLD and metabolic syndrome has also been described by the presence of two etiological factors of inflammation and insulin resistance that have critical role in progression of CAD (22). It has been demonstrated that the activation of fat-based hormones such as resistin, leptin, adiponectin, and various types of cytokines can induce insulin resistance (23). The insulin resistance can increase lipolysis, and the level of triglyceride, and thus accumulation of fat tissues in liver leads to simple hepatosteatosis as the first phase of NAFLD (24).

In recent years, the metabolic effects of NAFLD have gained great attention. It has been shown that NAFLD is directly associated with obesity and its complications such as insulin resistance, hypertension, and hyperlipidemia and thus can be closely associated with the presence and severity of CAD (25). As shown in our study, the patients with BMI higher than 30 had higher grades of NAFLD. It seems that NAFLD may be an important component of obesity-related metabolic syndrome which may lead to CAD.

Recent studies have mainly focused on the association between NAFLD and CAD. In a recent study by VanWagner et al. (26), NAFLD remained associated with echocardiography indicators of subclinical myocardial remodeling and dysfunction e' velocity, E/e' ratio, and absolute peak global longitudinal strain. In another study by Kwak et al. (27), NAFLD was associated with high coronary artery calcium score in the group with uncontrolled diabetes. In this regard, association between NAFLD and severity of CAD has also been shown in some recent studies. In a study on Korean people, having fatty liver determined by ultrasonographic evaluation was associated with coronary artery calcification and this association was independent of the conventional risk factors (28). In another Korean study, the authors found that NAFLD was independently associated with coronary artery calcification, and interestingly a higher score of coronary calcification was associated with a higher prevalence of NAFLD (29). In a study evaluating patients consecutively referred to elective coronary angiography, NAFLD was independently associated with more severe coronary artery disease (30). A community-based cohort of male Taiwanese workers showed that the diagnosis of NAFLD by ultrasonography was independently associated with the presence of ischemic changes in electrocardiography (31). Another study from Taiwan through multivariate analysis showed that the prevalence of NAFLD in asymptomatic patients was associated with the severity of the coronary artery calcification score (32).

Study Limitation:

We have some limitations in our research. First, this was a single center experience (Imam Khomeini hospital of Tehran). Second, the diagnosis of NAFLD was based on ultrasonography but was not confirmed by liver biopsy or magnetic resonance imaging for ethical reasons. This could have resulted in underestimation of the findings and the stage of liver fibrosis.

Conclusion

Thus the association between CAD severity and higher grades of NAFLD can be strongly considered.

We suggest another study that patients with NAFLD in this research but have normal angiography be evaluated for future coronary heart disease. We also recommend that patients with a diagnosis of NAFLD be screened for coronary artery disease by physicians.

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