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The Relationship Between the Prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) with the Severity of Coronary Artery Disease (CAD) in Patients Undergoing Coronary Artery Angiography: A Cross- Sectional Study

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the most frequent liver diseases worldwide. There are several common risk factors between NAFLD and coronary artery disease (CAD).
Objectives: This study aims to evaluate the relationship between the prevalence of Non-alcoholic fatty liver disease (NAFLD) with severity of Coronary Artery Disease (CAD) in patients undergoing coronary artery angiography.
Methods: This study was a cross-sectional, descriptive-analysis research that included 514 patients who underwent angiography. The severity of CAD was assessed by the number of vessels involved (vessel score: vd). An ultrasound was performed for all the patients also, intensity of fatty liver involvement was graded from zero (absence of steatosis) to three (severe steatosis).
Results: Ultrasonographic examination proven NAFLD in 59.1% of patients with different grades. Patients with NAFLD had significantly higher body mass index ($P < 0.001$), waist circumference ($P = 0.03$), and age ($P < 0.001$). In addition, there were significant differences between ALT and AST within the normal group and NAFLD patients ($P < 0.001$). Moreover, coronary angiographic data indicated that the presence of NAFLD significantly correlated with the CAD severity score as so: 64% of people with 2vd and 60.5% of people with three-vessle lisense had fatty liver that was statistically significant ($df = 4$; $P = 0.014$).
Conclusions: This study showed a high prevalence of NAFLD in patients with documented CAD. It is extremely important since knowing risk factors, designing screening programs, and early treatment of fatty liver could lead to reducing the risk of cardiovascular diseases.

Keywords: Angiography, Coronary Artery Disease, Non-Alcoholic Fatty Liver Disease, Ultrasound

1. Background

NAFLD is the most common abnormality seen in the pathology of the liver, which is defined as the presence of macrovascular steatosis (increasing of fat in the liver without inflammation) and non-alcoholic steatohepatitis in the absence of significant alcohol consumption and negative virologic assessments (1). Non-alcoholic steatohepatitis may lead to fibrosis, cirrhosis, and liver failure. NAFLD is associated with visceral obesity, hypertension, dyslipidemia, insulin resistance, type 2 diabetes mellitus, and CAD (2-5). All of these factors are defined as clinical features of metabolic syndrome (MetS). There is an important clinical association between NAFLD and MetS components (6, 7). However, emerging evidence suggests that the risk of CAD in NAFLD is independent of other metabolic risk factors and cardiovascular disease is the most important cause of death in patients suffering from NAFLD (3, 8). Although the exact reason is not yet completely understood, increasing the activity of inflammatory mediators, decreasing the endothelial function, adiponectin levels, collateral circulation, vascular repair capacity, and athero-

genic lipoprotein profile are mentioned as related factors of CAD in NAFLD patients (8, 9).

2. Objectives

Presence of such an association may indicate the usefulness of screening patients with NAFLD for CAD and vice versa. So in the present study we aimed to evaluate the relationship between the prevalence of NAFLD with the severity of CAD in patients undergoing coronary artery angiography.

3. Methods

3.1. Patients

This study was a cross-sectional, descriptive-analysis research conducted in 2015 in the cardiovascular angiography department of Vali-Asr Hospital, Birjand, Iran. Ethical approval of this study was obtained by the research committee of the Birjand University of Medical Sciences (IR.bums.REC.1394.216).

The study group included a consecutive series of 514 patients who underwent an angiography during the study period of Jun-Jan 2015. They were selected using the formula

$$n = \frac{z^2 pq}{d^2} \quad (1)$$

and p = 0.58 based on the prevalence of fatty liver on the ultrasound and a < 0.05, d = 0.045. All patients entered the study with convenience sampling strategy and signed an informed consent. Inclusion criteria included patients who underwent coronary angiography and did not have any of the following items. Excluding criteria included incomplete patient documents, history of viral hepatitis or alcohol abuse, cor pulmonale, chronic kidney disease, and cardiac heart failure. A total of 462 patients were included and 52 were excluded based on the mentioned criteria.

3.2. Demographic and Laboratory Measurements

Studied clinical variables included sex, age, body mass index (BMI), waist circumference, smoking status, (hypertension) HTN, CAD severity, and systolic and diastolic blood pressure. Blood pressure $\geq$ 140/90 mmHg defined as hypertension. Anthropometric parameters were obtained using similar scales and then BMI (kg/m^2) was calculated. Based on this parameter, patients were categorized into three groups (underweight: BMI $\leq$ 18, normal: 18 < BMI < 25 and overweight: BMI $\geq$ 25). Waist circumference was measured at the midpoint between the bottom of the rib cage and the top of the iliac crest during breath holding after full expiration and abnormal waist circumference defined as > 90 cm in men and > 80 cm in women.

Systolic and diastolic blood pressure was measured by a person with calibrated pressure gauge gamma G5 made in Germany. Patients' biochemical variables, including (aspartate aminotransferase) AST, (alanine aminotransferase) ALT, Cholesterol, (triglycerides) TG, (high-density lipoprotein) HDL, and (low-density lipoprotein) LDL were measured with a calibrated Tokyo Boeki, Japan autoanalyzer. Patients' family histories were asked in terms of (cardiovascular disease) CVD, HTN, (hyperlipoproteinemia) HLP, and (diabetes mellitus) DM in first-degree relatives. Consumption history of anti-hypertension and anti-hyperlipidemia drugs were recorded.

3.3. Coronary Angiography

For all patients, the intensity of coronary artery involvement was recorded after angiography by calibrated Siemens, Germany. Selective coronary angiography was performed via femoral artery by Judkins catheter. Visualization of the right coronary artery in two views left anterior descending and left circumflex coronary in at least four views was done.

3.4. Ultrasonographic Examination

Then ultrasound examination was performed using one fixed Radiologist with a calibrated ultrasound device GE Voluson E6 ultrasound machine and with a 3.5- to 5-MHz convex probe made in USA to determine the intensity of fatty liver involvement.

3.5. Statistical Analysis

Statistical analysis was performed using the SPSS Statistics for Windows, software version 16.0 (SPSS Inc., Chicago, ILL., USA). Quantitative variables are given as mean standard deviation. Chi-square, ANOVA, and t-test were done to assay the distribution of study parameters including qualitative variables, means comparison and multi-group variables, respectively. Furthermore, non-parametric tests including median and IQR were done in case of violation of the normalization assumption. However, as the sample size in each group was enough, according to the central limit theory, we were allowed to use the parametric test. In addition, there was no missing data in this study and the significance was defined with P < 0.05.

4. Results

A total of 514 patients participated in this study. Ultrasonography examination proved NAFLD in 59.1% of patients with different grades including 46.2% Grade I and

12.1% grade II. Our data showed that normal group and patients with different grades of NAFLD had significant differences in terms of anthropometric parameters including BMI ($P < 0.001$*), waist circumference ($P = 0.03$*), as well as age groups ($P < 0.001$*). However, there were no significant differences between patients with and without NAFLD with regard to sex and HTN.

Moreover, according to our data, there were significant differences between ALT and AST within the normal group and NAFLD patients ($P < 0.001$*), however, observed differences in other biochemical parameters (total cholesterol, HDL, LDL, and TG) were not significant. Distribution of fatty liver grades by all of the mentioned parameters were shown in Tables 1 and 2.

Furthermore, according to Table 1 coronary angiographic data indicated that the presence of NAFLD significantly correlated with the CAD severity score.

As shown in Figure 1, according to fatty liver there were obvious relations between groups in terms of severity of coronary atherosclerosis.

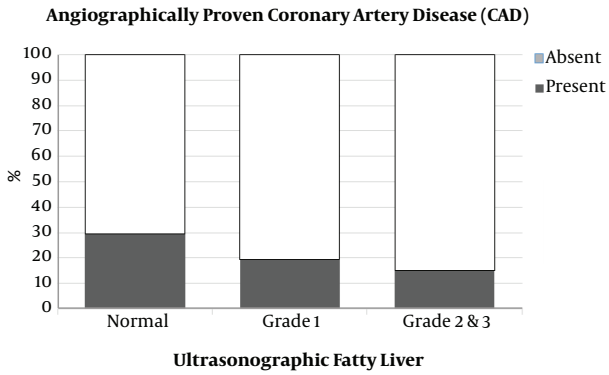

Figure 1. Angiographic Proven CAD in the Present and Absent of Ultrasonographic Fatty Liver

Moreover, Figure 2 indicated that patients with NAFLD had a higher grade of CAD as so: 64% of people with 2vd and 60.5% of people with 3vd had fatty liver, which was statistically significant ($df = 4$; $P = 0.014$).

5. Discussion

In this study, intensity role of ultrasound diagnosed fatty liver, as a predictor risk catching to cardiovascular disease and intensity involvement of angiography proven CAD, were surveyed. It is very important due to the fact that there are several reports that showed that the presence of NAFLD causes more severe CAD and on the other hand cardiovascular disease is the most important cause of death

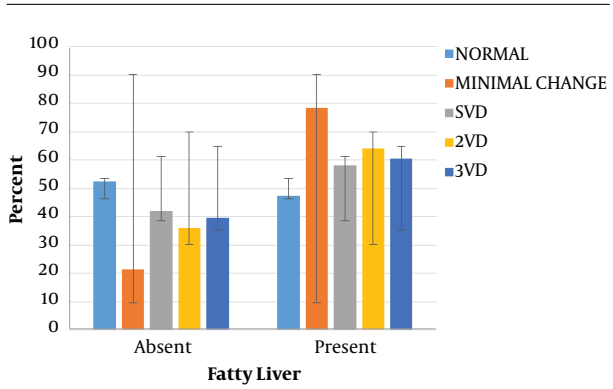

Figure 2. Severity of CAD in the Present and Absent of NAFLD

in NAFLD patients. Therefore, knowing risk factors, designing screening programs, and early treatment of fatty liver could lead to reducing the risk of cardiovascular diseases (10).

Our data revealed that the intensity of fatty liver involvement on an ultrasound had a significant relationship with the severity of coronary artery involvement.

Wong et al. in 2011, assessed the intensity of fatty liver involvement in 612 patients referred to coronary artery angiography part. Their data showed that CAD occurred in 84.6% of patients with a fatty liver and 64.1% of those without a fatty liver ($P < 0.001$) (11). However, they stated that fatty liver is associated with CAD independently of other metabolic factors, however, it cannot predict cardiovascular mortality and morbidity in patients with established CAD (11). In addition, Perera et al. in 2016, showed that NAFLD increases the mortality of acute coronary syndrome (ACS) and it would be an important novel risk factor for stratifying patients with ACS (9).

Consistent with our results, Boddi et al., in 2013, evaluated the association between NAFLD and ACS in 95 consecutive non-diabetic patients. The prevalence of NAFLD was 87% and their data showed that fatty liver increased the risk of CAD with multi independently and without communication with other proven risk factors ($P < 0.01$) (12). Another study in 2015 indicated a 47% prevalence of NAFLD in 170 patients with documented CAD; there was a significant association between NAFLD and CAD ($P < 0.001$) (13). Bhardwaj et al. in 2017, evaluated the prevalence of NAFLD in 311 patients with CAD and their clinical correlation. The prevalence of NAFLD was seen in 152 (48.9%) cases (14). This is similar to the studies performed by Zafar KS et al. (46%) (15), Chan WK et al. (24.7%) (16), Ling Sun and Shuzeng Lu (45.8%) (17), Mohan et al. (32%) (18), and Ling YC et al. (29.5%) (19).

There are several mechanistic explanations for the ob-

Table 1. Distribution of Fatty Liver Grades by Different Study Parameters, (n = 412)

Parameters	Fatty Liver Grades, %			P Value	Test
	Normal	Grade I	Grade II and III		
Sex				0.58	Chi-square
Male	39.8	46.2	14		
Female	42.5	46.5	11		
Age groups, y				< 0.001*	Chi-square
35 - 49	38.4	42.4	19.2		
50 - 59	27.4	61.1	11.5		
60 - 69	53.3	34.7	12		
> 70	44	46.2	9.9		
BMI, kg/m^2				< 0.001*	Chi-square
Underweight	71.2	25.4	3.4		
Normal	4.1	47.2	11.7		
Overweight	33.9	48.2	17.9		
Obese	23.1	64.1	12.8		
WC				0.03*	Chi-square
Normal	43	47.7	9.3		
Abnormal	38.3	44.7	17		
HTN				0.31	Chi-square
Normal	36.5	52.9	10.6		
Abnormal	42	44.6	13.4		
ALT	23.4 ± 11.1	28.2 ± 13.4	37.5 ± 16.8	< 0.001	ANOVA
AST	24.1 ± 12	36.2 ± 14.4	30.3: ± 8.1	< 0.001	ANOVA
Total cholesterol, mg/dL	1.91E2 ± 47.95	1.87E2 ± 46.9	1.83E2 ± 44.57	0.45	ANOVA
LDL cholesterol, mg/dL	1.12E2 ± 43.06	1.08E3 ± 38.69	1.09E2 ± 39.05	0.48	ANOVA
HDL cholesterol, mg/dL	43.91 ± 12.02	42.61 ± 9.7	41.81 ± 11.87	0.28	ANOVA
Triglycerides, mg/dL	1.6E2 ± 75.34	1.55E2 ± 58.36	1.75E2 ± 76.1	0.11	ANOVA
CAD severity				0.03*	Chi-square
Normal	52.5	39	8.5		
Minimal CAD	21.4	71.4	7.1		
SVD	41.9	41.9	16.1		
2VD	36	51.1	12.9		
3VD	39.5	44.9	15.6		

Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BMI, Body Mass Index; CAD, Coronary Artery Disease; HDL, High-Density Lipoprotein; HTN, Hypertension; LDL, Low-Density Lipoprotein; WC, Waist Circumference.

served correlation between NAFLD and CAD. Visceral adipose tissue inflammation, insulin resistance, and atherogenic dyslipidemia could be the main proposed pathogenesis mechanisms that led to the intensification of lipolysis, coronary endothelial vasodilation and cardiac toxic effects (10, 20, 21). In addition, increased oxidative stress may influence the progression from hepatic steatosis to steatohepatitis, fibrosis, and cirrhosis (22).

Moreover, increase abdominal circumference and body mass index that are important risk factors of MetS may serve as risk factors for fatty liver and cardiovascular disease as well (23). On the other hand, several studies have been reported the effect of NAFLD on subclinical atherosclerosis (24). The results of a recent meta-analysis,

Table 2. Medians and Interquartile Range (IQR) of the Biochemical Variables

Variables	ALT	AST	HDL	LDL	TG	Total Cholesterol
Normal						
Median	20	21	42	103.5	149.5	190
IQR	9.25	9	12.25	57.25	97	60
Grade I						
Median	26	24	41.5	98	147	182
IQR	14	8	13	56.75	77.75	57.5
Grade II and III						
Median	37	30	40	104	159	182
IQR	15.5	10	11.75	65.5	116.75	76.5
Kruskal-Wallis P value	< 0.001	< 0.001	0.17	0.63	0.14	0.56

including ten studies, proved this relationship (25).

On the molecular point of view, genetic factors may have an important role in trigging the mentioned phenomenon (10). As an example, up-regulation of the nuclear factor kappa-B (NF-κB) activates the transcription of several pro-inflammatory genes and led to production of pro-inflammatory cytokines (TNF-α, IL-6 and IL-8) or common genetic variants are known to influence on the risk of NAFLD. The gene polymorphisms of adiponectin-encoding gene (ADIPOQ), leptin receptor (LEPR), and so on have been reported to be related to NAFLD and CAD (26).

5.1. Limitations of the Study

This study was conducted by ultrasound examination. Although ultrasonography has a favorable sensitivity and specificity in detecting NAFLD, it is not a gold standard approach. However, since fibro scan was not accessible and assessing liver biopsy served as an invasive method and has ethical complications, we rely on ultrasonography to confirm NAFLD.

5.2. Conclusion

Our study is the first one to report the relationship between NAFLD and CAD in east Iran. As some ethnic and cultural factors can be considered as predictive factors of liver diseases, such regional studies could be more beneficial. According to the results of this research, the intensity of fatty liver involvement on the ultrasound has a significant relation with the intensity of coronary artery involvement on angiography. Therefore, based on our results and due to high prevalence of cardiovascular disease in the research area, screening of patients with NAFLD for cardiovascular diseases and vice versa could be beneficial for our region.

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Footnotes

Authors' Contribution: Study design, Tahmineh Tavakoli and Toba Kazemi; study performance, Toba kazemi, Samira Saghafi, Ensiah Sadat Mousavi, and Mahyar Mohamadifard; statistical analysis and interpretation of data, Fatemeh Salmani and Gholamreza Sharifzadeh; drafting of the manuscript, Homa Mollaei.

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