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The severity of coronary artery disease was not associated with non-alcoholic fatty liver disease in a series of 264 non-diabetic patients who underwent coronary angiography

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Background. It is now suggested an association between non-alcoholic fatty liver disease (NAFLD) and the occurrence of coronary artery disease even in non-diabetic patients. We will determine the rate of NAFLD and its main determinants in non-diabetic patients undergoing coronary angiography.

Methods. This cross-sectional study was accomplished on 264 patients who were candidates for coronary angiography during the year 2016. Coronary angiography has been done to depict the presence or absence of coronary involvement, and the severity of coronary artery disease by determining the number of vessels involved and also the SYNTAX score. During 48 hours after coronary angiography, the patients underwent abdominal ultrasonography for detection of NAFLD.

Results. The overall prevalence of NAFLD in the patients was 72.3%. The prevalence of NAFLD in those with and without coronary involvement was 71.9% and 73.1% respectively, with no notable difference ($p = 0.837$). The mean SYNTAX score in the patients with and without NAFLD was 22.32 ± 11.10 and 21.75 ± 10.71 respectively with no difference ($p = 0.702$). According to the multivariable regression models, the presence of NAFLD could not predict the likelihood of coronary artery disease (OR = 0.879, $p = 0.669$) or its severity assessed by the SYNTAX score (beta = 0.046, $p = 0.456$). NAFLD grade was also not a determinant for coronary artery disease (OR = 1.139, $p = 0.178$) or its severity (beta = 0.058, $p = 0.165$).

Conclusion. It seems that the presence and grade of NAFLD may not be correlated with atherosclerotic involvement of coronary arteries and its severity in non-diabetic patients. Future large studies and trials could elucidate the independent role of fatty liver in nondiabetic non-alcoholic patients.

Key words: Coronary Artery Disease; Non-alcoholic Fatty Liver Disease; Angiography; Coronary Angiography.

INTRODUCTION

Fatty liver disease consists of a variety of diseases from a single steatosis to progressive liver disease called non-alcoholic steatohepatitis or NASH that sometimes leads to fibrosis, cirrhosis, and even hepatocellular carcinoma [1]. NASH is primarily related to some metabolic disorders such as insulin resistance and even type 2 diabetes mellitus and, consequently, the risk of simultaneous cardiovascular events such as coronary heart disease as well as cerebrovascular abnormalities such as stroke also increase in such patients [2]. It has been supposed that fatty liver doubles the risk of these diseases, independently of the risk factors for cardiovascular disease. Some prospective studies have shown that patients with non-alcoholic fatty liver disease (NAFLD) with enhanced liver enzymes have a higher mortality rate of cardiovascular disease than those without any evidence of fatty liver [3]. In addition, mortality due to cardiovascular disease may be linked to an increase in the level of the ALT liver enzyme [4]. In some studies, increased GGT is a common finding in patients with fatty liver disease, and the relationship between increased GGT and the risk of cardiovascular disease has been confirmed [5]. Even in the ultrasonography evaluation for fatty liver disease, ultrasound evidence of fatty liver was predictive for coronary heart disease [6].

Numerous mechanisms for the development of coronary atherosclerosis have been proposed following NAFLD, which essentially includes genetic

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predisposition, insulin resistance and atherogenic dyslipidemia, oxidative stress, chronic inflammation, adiponectin levels decline, pre-coagulation factor impairment, and coagulation [7-10]. In this regard, NAFLD independent of its stage has been significantly associated with insulin resistance [11]. On the other hand, non-alcoholic fatty liver disease, especially in the form of NAFLD, can lead to atherogenic dyslipidemia [12]. Oxidative stress also plays a key role in this regard that induces a change in endothelial function that results in the oxidized LDL deposition in the sub-intimal space [13, 14].

Considering the close relationship between NASH and any of the metabolic risk factors such as obesity, insulin resistance and lipid disorders and also considering these indicators as risk factors for heart disease, it seems that there is a close association between coronary artery disease and the occurrence of NAFLD even in non-diabetic patients. In this study, we will determine the frequency of NAFLD and its main determinants in non-alcoholic and non-diabetic patients undergoing coronary angiography.

MATERIALS AND METHODS

This cross-sectional study was executed on 264 patients who were candidates for coronary artery angiography that were referred to one of the two general hospitals and underwent angiography according to the last ACC/AHA guidelines for coronary angiography during the year 2016. The exclusion criteria were the history of diabetes mellitus, liver disorders, alcohol consumption or history of using drugs affecting liver indices. Coronary artery angiography was done to characterize the presence or absence of coronary involvement, and the severity of coronary artery disease by determining the number of vessels involved and also the SYNTAX score. During 48 hours after coronary angiography, the patients underwent abdominal ultrasonography for detection of NAFLD. The severity of fatty liver disease was ranked semi-quantitatively in accordance with a well-known scale from 0 to 8 points, regarding liver-kidney differences (0 to 3 points), profound attenuation (0 to 1 point), haziness of diaphragm (0 to 1 point) and/or of the hepatic vein (0 to 1 point) and/or of the gallbladder wall (0 to 1 point), and detecting focal sparing (0 to 1 point) [15].

By determining the weight and height of the patients, their body mass index (BMI) was calculated. Also, the patient's blood pressure and serum lipid profile and fasting blood sugar were determined at baseline.

Results were presented as mean ± standard deviation (SD) or median ± interquartile range for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using chi-square test or Fisher's exact test when at least a cell had expected count of less than 5. Quantitative variables were also compared with t test or Mann-Whitney U test. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

RESULTS

In total, 264 patients were included with the mean age of 61.16 ± 11.34 years (ranged 31 to 91 years) and male gender rate of 70.1%. The mean BMI was also 26.07 ± 2.08 kg/m^2 indicating the presence of obesity condition in 6.0%. Regarding traditional cardiovascular risk factors, hypertension was found in 44.7%, hyperlipidemia in 23.5%, family history of cardiovascular events in 19.7%. The mean LVEF was 44.17 ± 10.57% on admission and 44.26 ± 10.65% on discharge. Based on coronary angiography results, 64.8% of the patients had coronary artery disease that single-vessel disease was revealed in 46.6%, two-vessel disease in 14.4% and three-vessel disease in 3.8%. The left main lesion was also found in 2.7%. Regarding coronary artery involvement, LAD defects were found in 40.9%, LCX defects in 20.5%, RCA defects in 18.9%, diagonal involvement in 4.5% and PDA involvement in 2.3%. The mean SYNTAX score was also shown to be 22.17 ± 10.98. The overall prevalence of NAFLD in the patients was 72.3% that was scored as 0 in 27%, 1 in 28.8%, 2 in 15.2%, 3 in 18.9%, 4 in 7.2%, and 5 in 2.3%.

As shown in Table 1, the overall prevalence of NAFLD did not depend on baseline characteristics including gender ($p = 0.064$), mean age ($p = 0.583$), mean BMI ($p = 0.695$), hypertension ($p = 0.351$), hyperlipidemia ($p = 0.211$), family history of cardiovascular disease ($p = 0.633$). Similarly, the rate of NAFLD was independent of cardiac dysfunction assessed by the mean LVEF ($p = 0.443$). The prevalence of NAFLD in those with and without coronary involvement was 71.9% and 73.1% respectively with no difference ($p = 0.837$). In this regard, the prevalence of NAFLD in the groups with healthy patients as well as those with one, two, and three vessels involvement was 73.1%, 68.0%,

81.1% and 88.9% respectively with no significant difference (p = 0.278). As shown in Table 1, the presence of NAFLD was also independent of the type of involved coronary artery. Totally, the mean SYNTAX score in the patients with and without NAFLD was 22.32 ± 11.10 and 21.75 ± 10.71 respectively with no difference (p = 0.702). In this regard, the mean NAFLD score in the groups with and without coronary artery disease was 1.49 ± 1.30 and 1.69 ± 1.50 respectively with no significant difference (p = 0.267). Also, no significant correlation was found between NAFLD grade and SYNTAX score (Kendall's tau correlation coefficient = 0.023, p = 0.624, Figure 1).

Table 1
The prevalence of NAFLD based on patients' characteristics

Characteristics	With characteristics	Without characteristics	P value
Male gender	75.7%	64.6%	0.064
Age < 60 years	77.5%	69.1%	0.141
Hypertension	69.5%	74.7%	0.351
Hyperlipidemia	66.1%	74.3%	0.211
Family history	75.0%	71.7%	0.633
Obesity	68.8%	72.6%	0.740
Coronary artery disease	71.9%	73.1%	0.837
LAD involvement	73.1%	71.8%	0.809
LCX involvement	75.9%	71.4%	0.510
RCA involvement	76.0%	71.5%	0.521
Diagonal involvement	83.3%	71.8%	0.384
PDA involvement	66.7%	72.5%	0.753
Left main lesion	71.4%	72.4%	0.999

Abbreviations: LAD: Left anterior descending artery; LCX: Left circumflex artery; RCA: Right coronary artery; PDA: Posterior descending artery.

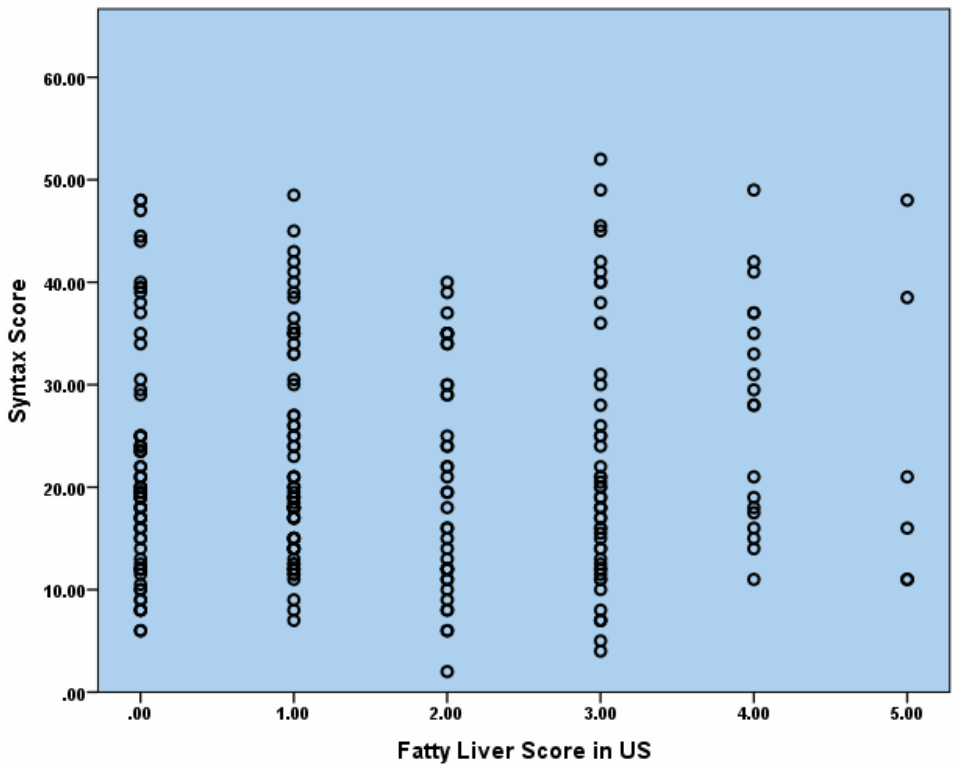

Figure 1. Correlation between fatty liver score in ultrasonography and SYNTAX score in angiography.

DISCUSSION

In various studies, the association between metabolic syndrome and fatty liver has been proved, both in obese patients [16] and lean subjects [17]. Some studies have shown association between fatty liver disease and increased risk of atherosclerotic process in coronary arteries. The key related patho-

physiology in both fatty liver disease and coronary artery disease is the activation of oxidative stress, endothelial dysfunction and the presence of some common risk factors, such as hyperlipidemia and insulin resistance. In this regard, some studies have not been able to find a meaningful relationship between the occurrence of fatty liver disorder and coronary artery disease. The purpose of this study was to assess the relationship between the incidence of NAFLD and its severity with coronary artery disease, and its severity and also risk factors associated with cardiovascular disease. In this study, we did not find a consequential relationship between the occurrences of NAFLD or its score with coronary artery disease and its severity. Also, no significant relationship was found between fatty liver and its score with risk factors for cardiovascular disease. This finding contrasted with several studies and was consistent with some others. In Wu *et al*. study [18], NAFLD was significantly correlated with the value of coronary artery calcification score, although this relationship was observed only in women. In the study by Baharvand *et al*. [19], there was no difference between the two groups with and without NAFLD in terms of sex, diabetes mellitus, hyperlipidemia, and hypertension. Also, there was no relationship between LAD involvement and the presence of steatosis which was completely consistent with our study. It should be noted that our study and the study of Baharvand both took place in an Iran community. In the study by Sun *et al*. [20], in the logistic regression model, there was a relation between NAFLD and the severity of coronary involvement which was in contrast with our study. In the study of Choi *et al.* [21], the severity of coronary involvement was strongly associated with the severity of fatty liver disease. In the study by Arslan *et al*. [22], the presence of fatty liver disease in the regression model was a predictive factor for coronary artery disease intensity that could increase its risk by 6.7 times. What can be a factor for explaining the disparities in the findings of various studies are several factors such as the variations in inclusion criteria of each community, various sample sizes, and therefore the different power of studies, a variety of methods of assessing the presence of NAFLD or its grading (due to the low sensitivity and precision of ultrasound in contrary to CT scan in the diagnosis of NAFLD) as well as differences in the methods for evaluating the severity and extent of coronary artery disease (using various scores). On the other hand, due to the significant dissimilarity in the relationship between NAFLD and coronary artery disease in different societies, it is indispensable to consider the genetic susceptibility and predisposition in NAFLD and atherosclerotic involvement of coronary artery disease in further molecular and epigenetic assessments.

It should be emphasized as an imperative point that we included non-alcoholic and non-diabetic patients in our study, and accordingly eliminated the significant effect of diabetes in the NAFLD and coronary artery disease process. By the mentioned exclusion, we intended to evaluate the net role of fatty liver disease in coronary artery involvement. As an interesting point, our study population was not an obese one which was so helpful for us in assessment of the correlation between fatty liver disease and coronary artery disease.

Our current single center study, with moderate sample size, cannot answer all questions and controversies about the association between NAFLD and coronary artery disease; however, it may be helpful in elucidating the net association of NFALD with coronary artery disease in the absence of diabetes and obvious obesity as known interfering factors in fatty liver disease and coronary artery disease. Future multi-center investigations with large population will illuminate the various aspects of the correlation between NFALD and coronary artery disease.

CONCLUSION

It seems that the presence and grade of NAFLD may not be correlated with atherosclerotic involvement of coronary arteries and its severity in non-diabetic patients. Future large studies and trials will explain the independent role of fatty liver in nondiabetic-non-alcoholic patients.

Conflict of interest: The authors declare that there is no conflict of interest.

Introducere. *În acest moment este sugerată o legătură strânsă între steatoza hepatică non-alcoolică (NAFLD) şi boala coronariană chiar şi la pacienții fără diabet zaharat. Scopul studiului este de a determina prevalența NAFLD şi a factorilor determinanți la pacienții fără diabet zaharat.*

Materiale şi metode. *Pe parcursul anului 2016 a fost realizat un studiu transversal pe 264 pacienți cu indicație de coronarografie. Coronarografia a fost utilă pentru a evalua afectarea coronară iar scorul SYNTAX a fost calculat. În maxim 48 de ore de la realizarea coronarografiei pacienții au fost evaluați şi ecografic pentru prezența NAFLD.*

Rezultate. *Prevalența NAFLD a fost de 72.3%. Prevalența NAFLD la pacienții cu afectare coronariană față de cei fără afecare coronariană a fost de 71.9% versus 73.1%, diferența nefiind semnificativă statistic (p = 0.837). Scorul mediu SYNTAX la pacienții cu şi fără NAFLD a fost de 22.32 ± 11.10 respectiv 21.75 ± 10.71, nefiind înregistrată nicio diferență semnificativă statistic (p = 0.702). În analiza multivariată prezența NAFLD nu a putut prezice boala coronariană (OR = 0.879, p = 0.669) şi nici severitatea acesteia evaluate prin scorul SYNTAX (beta = 0.046, p = 0.456). Gradul steatozei hepatice nu a fost determinant al bolii coronariene (OR = 1.139, p = 0.178) şi nici al servității acesteia ((beta = 0.058, p = 0.165).*

Concluzii. *Se pare că prezența şi gradul steatozei nu se asociază cu afectarea aterosclerotică coronariană la pacienții non-diabetici însă studii mai extinse ar trebui să elucideze implicațiile steatozei hepatice la pacienții nediabetici.*

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