

# Evaluation of Relationship between Nonalcoholic Fatty Liver and Coronary Artery Disease Severity by Multidetector Computed Tomography

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## Abstract

**Background:** Coronary Heart Disease (CHD) is considered to be a leading cause of morbidity and mortality worldwide, so early detection of CHD in asymptomatic individuals is required. Several metabolic risk factors contribute to development of both Nonalcoholic Fatty Liver Disease (NAFLD) and CHD.

**Aim of Study:** To evaluate the association between (NAFLD) and (CAD) severity.

**Material and Methods:** This study included thirty patients with symptoms suggestive of ischemic heart disease. All patients were subjected to clinical evaluation, coronary CT angiography and Gensini score was used to assess the coronary artery disease severity. Ultrasound examination of the liver to assess the hepatic steatosis.

**Results:** Among thirty patients enrolled in our study 13 patients had positive coronary findings 9 of them showed also hepatic steatosis. The association between NAFLD and CAD was significant as regard the age ( $p=0.010$ ), BMI ( $p=0.011$ ). And diabetes mellitus ( $p=0.011$ ). In comparison with the normal group. There was significant association between Gensini score and grading of fatty liver infiltration ( $p$ -value=0.017).

**Conclusion:** There was high prevalence of NAFLD in patients with documented CAD (69.2%) with significant association between Gensini score and grading of fatty liver infiltration.

**Key Words:** Coronary heart disease – Nonalcoholic fatty liver disease – Computed tomography (CT).

## Introduction

THE prevalence and incidence of cardiovascular disease have been known to be associated with the presence of NAFLD [1,2].

However, NAFLD was thought to be a benign condition but now studies reported that NAFLD

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may progress to cirrhosis, liver failure, and hepatocellular carcinoma [3].

NAFLD is strongly associated to the features of metabolic syndrome and insulin resistance that contribute to development of Coronary Artery Disease (CAD). Thus, it was hypothesized that NAFLD associated CAD [4].

CAD is usually symptomatic; so finding significant relationship between CAD and NAFLD may indicate that screening for NAFLD in patient with CAD has great importance in early diagnosis of the disorder and vice versa [5].

Recently Coronary Computed Tomography Angiography (CCTA) has proven to be effective in evaluation of coronary artery atherosclerosis, including the plaque characteristics and degree of stenosis. Thus, this method can be used to diagnose subclinical atherosclerosis [6,7].

## Patients and Methods

This study was performed in Radiology Department, Tanta University Educational Hospital, during the period from February 2017 to February 2018.

This study included thirty patients; 9 males and 21 females with age ranged from 33 to 78 years (mean age 58 years). All patients were suffering from symptoms suggestive of ischemic heart disease and were referred from Cardiology Department of Tanta University Hospital.

- Committee approval and informed consent were obtained. Inclusion criteria included patients who had symptoms suggestive of ischemic heart disease referred for evaluation by MDCT.

- Patients with history of Alcohol consumption, history of using agent known to induce fatty liver disease such as steroids, estrogens, aminodarone, tamoxifen, or other chemotherapeutic agents within the previous 6 months and patients who had impaired renal function (creatinine level  $\geq 1.8$  mg/dl) were excluded.

All patients were subjected to detailed history taking, clinical examination, laboratory investigations (including serum creatinine and lipid profile) and radiological examination including:

- 1- Multislice CT angiography for evaluation of the coronary arteries.
- 2- Evaluation of the liver by Ultrasound to detect the hepatic steatosis.

#### *CCTA image acquisition and analysis:*

##### *I- Patient preparation:*

- A- Detailed explanation of the procedure to all patients with reassurance was done to relieve any anxiety.

##### *B- Heart rate control:*

- Heart rate and blood pressure were recorded on arrival to set a baseline for monitoring.
- Patients with heart rate below 65 bpm not given any heart rate control medications. Patients with higher heart rate were given oral  $\beta$ -blockers provided that there was no contraindication

##### *C- At scanner room:*

- ECG electrodes were applied to chest wall, Brief explanation of the procedure to the patient and reassurance was done to relieve any anxiety.
- Breath holding instructions was given to the patients to avoid respiratory motion artifacts.

##### *II- CT scan protocol:*

320-row multidetector CT scanner (Aquilion One, Toshiba Medical Systems, Otawara, Japan) installed at Tanta University Educational Hospital was used for scanning through these steps:

- Initial scanogram was obtained in AP and lateral projection for automatic radiation dose calculation and for planning scan range. The scan started from carina down to the apex of the heart.
- Low-dose unenhanced CT chest scans were done. The images were reviewed on a standard PACS workstation to evaluate the coronary artery calcium scoring.
- Automatic bolus tracking technique was used to detect the arrival of contrast material at descending aorta. In patients with coronary stents, the

ROI was placed at descending aorta at mid heart level with trigger threshold set at 230 repetitive low-dose monitoring examinations (120kV, 50 mAs, 0.5 second scanning time) were performed 10 seconds after contrast medium injection began. When the trigger threshold was reached, the scan started immediately after breath holding command.

Gensini score was used to determine the coronary artery disease severity, in this scoring system, reduction in the lumen diameter was evaluated. Reductions of 1%-25%, 26%-50%, 51%-75%, 76%-90%, 91%-99%, and total occlusion were scored as 1, 2, 4, 8, 16, and 32, respectively. Each principal vascular segment was assigned a multiplier that represents its functional importance in maintaining myocardial supply. Multipliers were 5 for the left main coronary artery; 2.5 for the proximal segment of the Left Anterior Descending coronary artery (LAD) and circumflex artery; 1.5 for the mid-segment of the LAD; 1 for the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery; and 0.5 for other segments.

- The severity of the disease was expressed as the sum of the scores for individual lesions. Gensini score and number of stenosed vessels were recorded. Patients with Gensini scores of 20 or more were defined as having severe CAD, which was approximately equal to one stenosed lesion of 70% or more in the proximal left anterior descending artery.

##### *Ultrasound examination:*

The liver was considered normal if it presented echogenicity equal to that of the kidney (degree 0). Fatty infiltration of the liver was described in three levels: Mild (degree 1), when there was a minimum diffuse increase in the hepatic echogenicity, contours of the diaphragm and intrahepatic vessels with normal appearance; moderate (degree 2), when there was a moderate diffuse increase in the hepatic echogenicity and a slight deterioration in the image of the vessels of the liver and diaphragm; and severe (degree 3), when there was an apparent increase in the echogenicity. The posterior segment of the right lobe of the liver was difficult to visualize, and the structure of the intrahepatic vessels and contours of the diaphragm were smeared or not viewed.

##### *Statistical analysis:*

Data were fed to the computer and analyzed using IBM SPSS software package Version 20.0. (Armonk, NY: IBM Corp) [8] Qualitative data were

described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. The used tests were:

- 1- *Chi-square test*: For categorical variables, to compare between different groups.
- 2- *Fisher's Exact or Monte Carlo correction*: Correction for chi-square when more than 20% of the cells have expected count less than 5.
- 3- *ANOVA test*: For comparison between each 2 groups was done using Post Hoc Test (Tukey).

**Results**

This study included thirty patients 9 of them were males representing 30% and 21 were females representing 70% presented by symptoms suggestive of ischemic heart disease referred for evaluation by CCTA during the period between February 2017 and February 2018.

The mean age of the patients was 58 years and ranged from 33 to 78 years.

Table (1): This table demonstrates the distribution of cases according to the finding of coronary CTA and examination of the liver (% from row).

	Liver						$\chi^2$	p
	Negative		Positive		Total			
	No.	%	No.	%	No.	%		
<i>Coronary:</i>								
Negative	10	58.8	7	41.2	17	100.0	2.330	0.127
Positive	4	30.8	9	69.2	13	100.0		
<b>Total</b>	<b>14</b>	<b>46.7</b>	<b>16</b>	<b>53.3</b>	<b>30</b>	<b>100.0</b>		

$\chi^2$ , p:  $\chi^2$  and p-values for Chi square test for comparing between the two groups.

From (Table 1) we found that 13 patients out of 30 (13/30) with symptoms suggesting ischemic heart disease had positive coronary atherosclerosis (43.3%) 9 of them (9/13) had positive liver affection (69.2%) and 4 cases (4/13) had normal liver (30.8%).

Also we found that 17 patients out of 30 (17/30) showing no evidence of coronary atherosclerosis 7 of them (7/17) representing 41.2% had positive liver affection and 10/17 representing 58.8% had normal liver.

By another mean we found that 16 patients out of 30 (16/30) had positive liver affection (53.3%)

and 9 of them (9/16) had coronary artery disease (56.3%) and 7 cases (7/16) with no evidence of coronary artery disease (43.8%).

According to the coronary CTA and liver examination we can classify our patients in to four groups:

- Group (A) patients with coronary positive and liver positive findings.
- Group (B) patients with coronary positive and liver negative findings.
- Group (C) patients with liver positive and coronary negative findings.
- Group (D) patients with coronary negative and liver negative findings.

The present study indicated a high prevalence of NAFLD in patients with documented CAD (69.2%) as shown in (Table 1).

Table (2): Relation between Gensini score and ultrasound finding of the liver examination (n=30).

	Gensini score				$\chi^2$	p
	Mild (n=26)		Severe (n=4)			
	No.	%	No.	%		
<i>US:</i>						
<i>Fatty:</i>						
Negative	13	50.0	1	25.0	0.871	FE <sub>p</sub> =
Positive	13	50.0	3	75.0		0.602
<i>Degree:</i>						
Normal	13	92.9	1	7.1	8.207	MC <sub>p</sub> =
Grade I	1	33.3	2	66.7		0.017*
Grade II-III	12	92.3	1	7.7		

$\chi^2$ : Chi square test for comparing between the two groups.

MC<sub>p</sub>: p-value for Monte Carlo for Chi square test for comparing between the two groups.

FE<sub>p</sub>: p-value for Fisher Exact for Chi square test for comparing between the two groups.

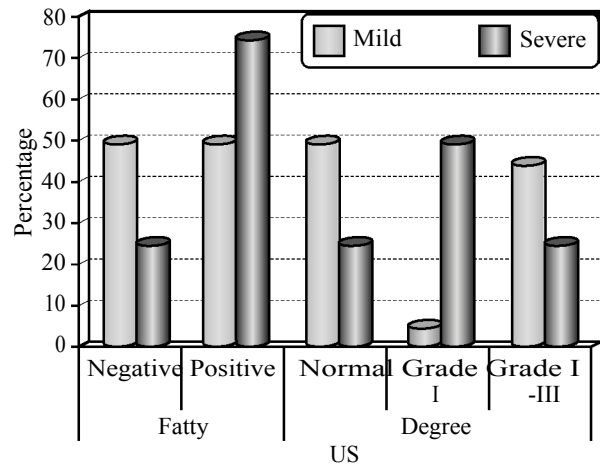


Fig. (1): Relationship between Gensini score and degree of liver affection.

From (Table 2) and Fig. (1) that demonstrates the relationship between Gensini score and degree of liver affection we found that:

Patients with Gensini score less than 20 (no or mild atherosclerosis) were 26 patients 13 (13/26) of them (representing 50%) with fatty liver infiltration 12 of them with grade II-III (representing 92.2% from patients with grade II-III).

Patients with Gensini score more than 20 (severe atherosclerosis) were 4 patients 2 (2/4) of them with mild fatty liver infiltration and 1 of them (1/4) with grade II-III.

There was significant association between Gensini score and grading of fatty liver infiltration ( $p$ -value=0.017).

Table (3): Comparison between the different studied groups according to BMI ( $\text{kg/m}^2$ ).

	Coronary +ve & Liver +ve (n=9)		Coronary -ve & Liver +ve (n=7)		Coronary +ve & Liver -ve (n=4)		Coronary -ve & Liver -ve (n=10)	
	No.	%	No.	%	No.	%	No.	%
<b>BMI (<math>\text{kg/m}^2</math>):</b>								
Normal (18.5-24.9)	0	0.0	0	0.0	0	0.0	1	10.0
Overweight (25-29.9)	4	44.4	1	14.3	0	0.0	6	60.0
Obese (30-34.9)	3	33.3	5	71.4	4	100.0	3	30.0
Severely obese (35-39.9)	1	11.1	1	14.3	0	0.0	0	0.0
Morbidly obese (>40)	1	11.1	0	0.0	0	0.0	0	0.0
Min.-max.	28.20-44.40		29.40-36.60		31.60-34.60		23.0-32.0	
Mean $\pm$ SD.	32.61 $\pm$ 5.04		33.23 $\pm$ 2.33		32.80 $\pm$ 1.28		28.26 $\pm$ 2.75	
Median	30.50		33.90		32.50		28.25	
F (p)			4.013* (0.018*)					
Significance between the groups	$p_1=0.928, p_2=0.725, p_3=0.011^*, p_4=0.844, p_5=0.035, p_6=0.007^*$							

F, p : F and p-values for ANOVA test, pairwise comparison bet. Each 2 groups was done using Post Hoc Test (Tukey).

$p_1$  : p-value for comparing between coronary +ve & liver +ve and coronary -ve & liver +ve.

$p_2$  : p-value for comparing between coronary +ve & liver +ve and coronary +ve & liver -ve.

$p_3$  : p-value for comparing between coronary +ve & liver +ve and coronary -ve & liver -ve.

$p_4$  : p-value for comparing between coronary -ve & liver +ve and coronary +ve & liver -ve.

$p_5$  : p-value for comparing between coronary -ve & liver +ve and coronary -ve & liver -ve.

$p_6$  : p-value for comparing between coronary +ve & liver -ve and coronary -ve & liver -ve.

\* : Statistically significant at  $p \leq 0.05$ .

From (Table 3) we found that:

- The mean BMI was 30.5 and ranging from 28.2 to 44.4.
- BMI was statistically significantly in:
  - Group A showing positive coronary and liver findings compared to group D (normal group) (value=0.011).
  - Group C showing positive liver findings only compared to group D (normal group) ( $p$ -value=0.035).
  - Group B showing positive coronary findings and normal liver compared to group D ( $p$ -value=0.007).

Also we found that:

Diabetes mellitus was statistically significant in:

- Group A that had positive coronary and liver finding compared to group D (normal group) (value=0.011).
- There is no significance in comparison between the groups as regard the dyslipidemia and hypertension.

Illustrated cases:

Case (1): Diabetic female patient aged 60 years old presented by chest that increased by effort: Showing coronary vascular affection and fatty liver.

Multidetector coronary CT angiography findings:

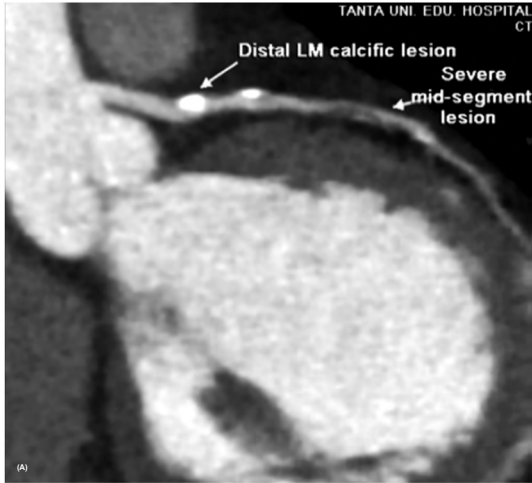


Fig. (A,B): Left anterior oblique Maximum Intensity Projection images (MIP) showing calcific lesion at the distal Left Main (LM) artery exerting mild stenosis measured about 5.5mm in length. Mixed lesion at the proximal segment of Left Anterior Descending artery (LAD) exerting 50% stenosis measured about 8mm in length. Another soft lesion seen at the distal segment of the LAD artery exerting severe stenosis measured about 10mm in length.

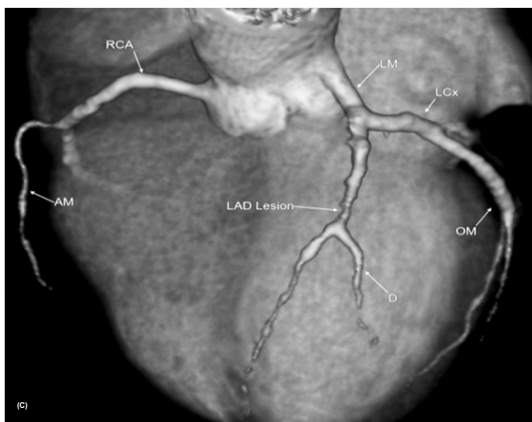


Fig. (C): 3D Volume Rendering (VR) showing severe stenosis of the distal LAD artery.

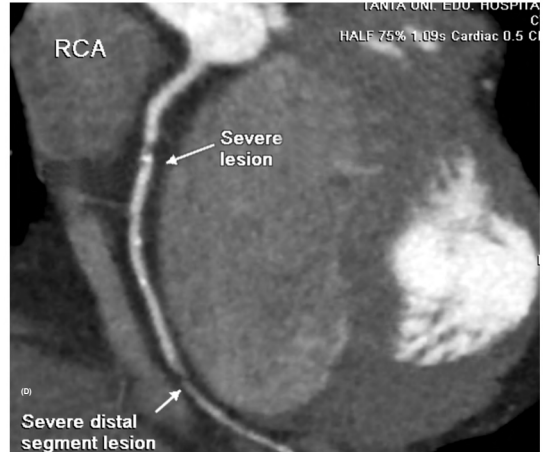


Fig. (D): Curved Multiplanar Reformation (MPR) image showing mixed lesion at the proximal segment of the Right Coronary Artery (RCA) exerting severe stenosis about 70%, another mixed lesion at the mid segment exerting moderate stenosis about 50% measured about 3.5mm in length.

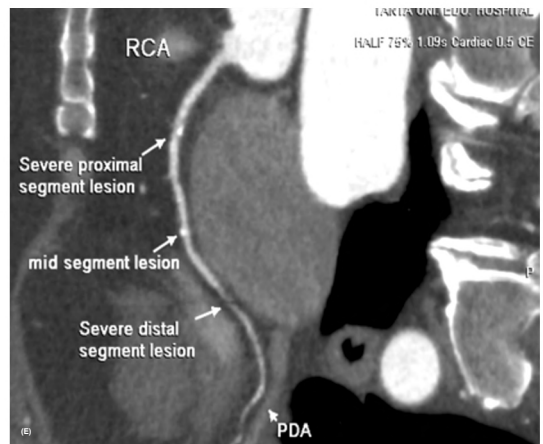


Fig. (E): Curved MPR reformatting image soft lesion seen at the distal segment of RCA exerting severe stenosis and measured about 7.5mm in length.



Fig. (F): 3D (VR) showing severe stenosis of the distal RCA artery.

Gensini score:

29 which means severe atherosclerosis.

Ultrasound flinging:



Sagittal image on the liver showing minimum diffuse increase in the hepatic echogenicity compared to the right kidney, the contours of the diaphragm and intrahepatic vessels with normal appearance...grade I fatty liver (mild hepatic steatosis).

Case (2): Hypertensive male patient aged 78 years old presented by atypical chest pain showing: Coronary vascular affection and hepatic steatosis.

Multidetector coronary CT angiography findings:

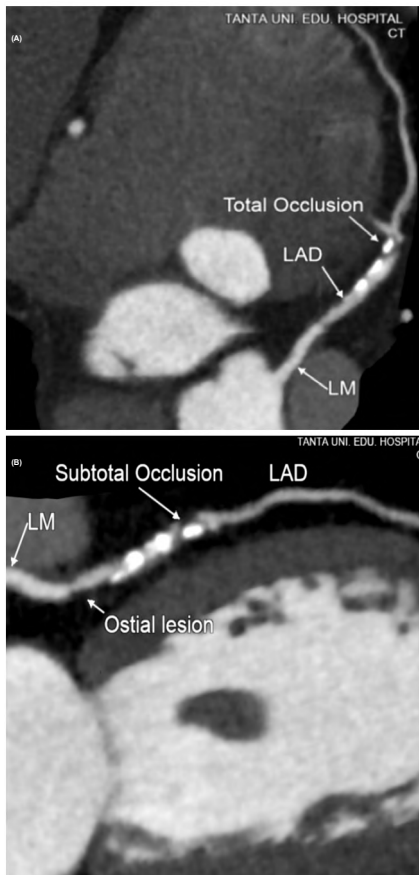


Fig. (A,B): Curved MPR images showing calcific lesion at the proximal segment of (LAD) artery exerting moderate stenosis measured about 7mm in length.

Another mixed lesion seen at the mid segment of the LAD artery exerting subtotal occlusion measured about 12mm in length.

(B): Left anterior oblique MIP image showing ostial soft lesion at the LAD artery exerting moderate stenosis measured about 4mm.



Fig. (C): Curved MPR image showing mixed lesion seen at the distal segment of the RCA artery exerting moderate stenosis about 60%.



Fig. (D): 3D (VR) showing ectasia of the RCA artery.

Gensini score:

42 which means severe atherosclerosis.

Ultra sound flinging:



Sagittal image on the liver showing minimum diffuse increase in the hepatic echogenicity compared to the right kidney, the contours of the diaphragm and intrahepatic vessels with normal appearance...grade I fatty liver (mild hepatic steatosis).

## Discussion

*In this study, we focused on the association between NAFLD and coronary artery disease severity and our main findings were as follow:*

- 1- There was high prevalence of NAFLD in patients with documented CAD (69.2%).
- 2- The association between NAFLD and CAD was significant as regard the age, BMI and diabetes mellitus in comparison with the normal group.
- 3- There is significant association between Gensini score and grading of fatty liver infiltration ( $p$ -value=0.017).

We found fatty liver disease in 69.2% of the patients with documented CAD that came in agreement with Baharvandi et al., [4] whose study showed that NAFLD can be detected in high percentage of patients with documented CAD (47%), also Adibi A et al., [5] found that the prevalence of NAFLD in CAD patients was higher than the control group. Indicating that Increase in the prevalence of NAFLD can lead to the increase in cardiovascular diseases. Wong et al., [9] showed that fatty liver was associated with CAD (64.7% of the patient with documented CAD), also that was in concurrent to the study performed by Sun and Lu [10]. That showed that fatty liver was associated with CAD (64.7%).

- We also found that there was significant association between Gensini score and grading of fatty liver infiltration ( $p$ -value=0.017). That agreed with Alper et al., [11] who observed that patients with NAFLD had significantly higher scores for the severity of CAD as evaluated by the Gensini score than patients without NAFLD ( $p$ <0.001). The presence of NAFLD and the degree of NAFLD were significantly correlated with the severity score of CAD. Also Kim et al., [12] who found that the prevalence of CAC significantly increased with severity of NAFLD and Açıkel et al., [13] who concluded that the presence of steatosis in the US and its severity may represent an independent effect in both the presence and severity of CAD.

- We found that BMI was statistically significantly in Group A showing positive coronary and liver findings compared to Group D (normal group) ( $p$ -value=0.011) and in Group C showing positive liver findings only compared to Group D (normal group) ( $p$ -value=0.035) this was in agree with Baharvand et al., [4]. Who found that mean BMI was significantly higher in patients with fatty liver disease compared to those without liver affection ( $p$ =0.005), but not in agree with Sun and Lu [10]

and Açıkel et al., [13] as they didn't found significant relation to the BMI.

- Also we found that 26.7% of the cases were diabetic and 62.5% of the diabetic cases had association between the NAFLD and CHD with significant relationship compared to the normal group (value=0.011). This was in line with Kwak et al., [14] and Targher et al., [15]. As they found that presence of NAFLD is associated with CHD in subjects with DM, whereas Baharvand et al., [4] and Mc Kimmie et al., [16] did not found the relationship between fatty liver disease and CHD in diabetic patients.

### Conclusion:

In this study, we focused on the association between NAFLD and coronary artery disease severity and our main findings were as follow:

- 1- There was high prevalence of NAFLD in patients with documented CAD (69.2%).
- 2- The association between NAFLD and CAD was significant as regard the age, BMI and diabetes mellitus in comparison with the normal group.
- 3- There was significant association between Gensini score and grading of fatty liver infiltration ( $p$ -value=0.017).
- 4- The present study along with previous reports may indicate the importance of screening for NAFLD in patient with CAD and vice versa.

### Competing interests:

The authors declare that they have no competing interests.

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## تقييم العلاقة بين الكبد الدهني غير الكحولي وشدة الإصابة بمرض شرايين القلب التاجية عن طريق الأشعة المقطعية متعددة الكواشف

كان يعتقد أيضا أن مرض الكبد الدهني غير الكحولي أمرا حميدا ولكنه الآن يعتبر سببا رئيسا من الأسباب المرتبطة بالمخاطر وحالات الوفيات المتعلقة بالكبد حيث أن الدراسات أقرت أن الكبد الدهني قد يتطور إلى تليف كبدي أو فشل في وظائف الكبد أو قد يتطور إلى حدوث سرطان الخلايا الكبدية.

قد أقرت سلسلة من الدراسات السابقة أن مرض الكبد الدهني غير الكحولي مرتبط بمرض شرايين القلب التاجية بغض النظر عن العوامل العامة والعوامل المرتبطة بعملية التمثيل الغذائي ولذلك يمكن الافتراض أن مرض الكبد الدهني غير الكحولي مرتبط بتصلب الشرايين الغير مشخص إكلينيكيا.

تهدف الدراسة التي نقوم بها على تقييم العلاقة بين مرض الكبد الدهني غير الكحولي وشدة الإصابة بمرض شرايين القلب التاجية.

وبعد دراسة الموضوع تبين أن الكبد الدهني غير الكحولي يمثل ٩٦.٢٪ من الحالات التي وجد أنها مصابة بمرض تصلب شرايين القلب التاجية وأن نسبة الإصابة بمرض الكبد الدهني غير الكحولي ٥٣.٣٪ من إجمالي عدد الحالات التي تم فحصها.

وجدنا أن ٧٢.٧٪ من الحالات التي نسبة وجود الكالسيوم في شرايين القلب التاجية أكثر من صفر ( $CACS > 0$ ) كانت مصابة أيضا بمرض الكبد الدهني غير الكحولي، كما أننا وجدنا علاقة ذات أهمية بين شدة الإصابة بمرض شرايين القلب التاجية باستخدام (Gensini Score) ودرجة ترسب الدهون في الكبد.

وقد أشارت النتائج التي توصلنا إليها أن نسبة كبيرة من المرضى المصابون بمرض تصلب شرايين القلب التاجية مصابون أيضا بمرض الكبد الدهني غير الكحولي مع وجود ارتباط وثيقا بين درجة شدة مرض الشريان التاجي وتصنيف الكبد الدهني وتشير الدراسات الحالية إلى أهمية فحص الكبد في المرضى الذين يعانون من مرض تصلب شرايين القلب التاجية وبالعكس أيضا.