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Evaluation of Coronary Artery Disease among Population with Fatty Liver Disease Using Multi-Slice Computed Tomography

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ABSTRACT

Background: Fatty liver disease (FLD) is a common disorder with an increasing prevalence. It is considered to be an important syndrome associated with several cardiovascular risk factors and to be a component of metabolic syndrome. Several studies found significant association of fatty liver and coronary artery disease (CAD).

Aim of the Work: was to evaluate the presence and the severity of coronary artery disease among FLD population and to evaluate the association of FLD and CAD using Multi-Slice Computed Tomography (MSCT) and the possibility of considering FLD as a predictor for CAD. **Patients and Methods:** The study was conducted in Radiological Department of Ain-Shams Hospital and other private centers. It focused on evaluating 30 patients, who were referred to perform CT coronary angiography. These patients were examined in the period between 1st of Oct. 2017 and 1st of Apr. 2018. The target sample was patients with fatty liver who underwent CT coronary angiography for recent chest pain. Fatty liver was diagnosed using non-contrast CT when calculated attenuation value of the liver is less than spleen by 10 UH. The coronary arteries were assessed using CT angiography, significant CAD was defined as a stenosis of more than 50% in at least one major coronary artery.

Results: fatty liver developed coronary atherosclerosis were 17 (56.7%) and **this was statistically significant P= 0.017**. Patients with fatty liver developed significant CAD were 9 (30.0%) and this was statistically insignificant P=0.266. **Conclusion:** Fatty liver disease may be considered as a predictor for coronary atherosclerosis and based on this, more individuals from the general population with subclinical CAD could be detected at earlier stages when fatty liver is identified. Presence of fatty liver may help in cardiovascular risk stratification and assessment. **Recommendations:** It will be worthwhile to study whether improving FLD will ultimately prevent the development of CAD.

Keywords: coronary artery disease; fatty liver disease, multi-slice CT; atherosclerosis.

INTRODUCTION

Coronary artery disease (CAD) is a complex chronic inflammatory disease, characterized by remodeling and narrowing of the coronary arteries supplying oxygen to the heart. It can have various clinical manifestations, including stable angina, acute coronary syndrome, and sudden cardiac death. It has a complex etiopathogenesis and a multifactorial origin related to environmental factors, such as diet, smoking, and physical activity, and genetic factors II that modulate risk of the disease both individually and through interaction [(1)].

Fatty liver disease (FLD) is increasingly recognized as the most common liver disorder in Western countries. It is the most common cause of liver enzyme abnormalities in clinical practice, with a prevalence of 15%–20% in the general population and increases steadily to 70%–90% in obese or type 2 diabetic patients [(2)].

Risk factors for atherosclerosis, such as obesity, diabetes, and dyslipidemia, are frequently associated with FLD [(3)].

Fatty liver is blamed to play a role in development of atherosclerosis. However, few clinical studies have examined the association between fatty liver disease and subclinical coronary atherosclerosis in patients with low to intermediate cardiovascular risk factors [(4)].

Moreover, FLD has been included among the components of metabolic syndrome, a clinical condition with a high risk of coronary artery disease (CAD) [(5)].

Recognition of a role for FLD in development of CAD will allow more individuals from the general population with subclinical CAD to be detected at earlier stages when fatty liver is identified. Presence of fatty liver may help in cardiovascular risk stratification and assessment [(6)].

The standard of reference for diagnosis of CAD is still the conventional coronary angiography, however, it is an invasive technique associated with non-negligible complication. Moreover, this procedure offers little information on coronary artery wall changes associated with the early stage of coronary artery disease [(7)].

Multislice CT coronary angiography has been proposed as a noninvasive modality to help detect coronary plaques and classify coronary artery disease (CAD) [(8)]. It has been used successfully to quantify coronary artery calcium, which helps to predict the presence of coronary artery disease [(9)].

Coronary CT angiography (CTA) can evaluate both calcified plaque and noncalcified plaque. Coronary CTA is able to show the lumen of the

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coronary arteries as well as the vessel wall, analogous to intravascular sonography [(10)].

Multiple studies have shown coronary CTA to have a high negative predictive value for the detection of coronary atherosclerosis: greater than 95% for significant stenosis and approximately 90% for any plaque [(11)].

The aim of this study was to evaluate the presence and the severity of coronary artery disease among FLD population and to evaluate the association of FLD and CAD using MSCT and the possibility of considering FLD as a predictor for CAD.

PATIENTS AND METHODS

This study included a total of 30 patients, who were referred to perform CT coronary angiography attending at Radiological Department of Ain-Shams hospital and other private centers. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between 1st of Oct. 2017 and 1st of Apr. 2018. The target sample was patients with fatty liver who underwent CT coronary angiography for recent chest pain.

- ❖ **Inclusion Criteria:** Adult patients aged between 40-70 years with fatty liver, who underwent CT coronary angiograms for cardiac problems and patients with recent chest pain.
- ❖ **Exclusion Criteria:** Many patients were excluded from this study according to the following criteria:
  1. Patients known to have cerebrovascular disease and those with evident clinical history of ischemic heart diseases are excluded.
  2. Patients with implanted coronary-artery stents or who had coronary artery bypass graft surgery are excluded.
  3. Patients who had unevaluated coronary-artery segments owing to motion artifacts or inadequate contrast medium filling are also excluded.

Clinical and laboratory data were obtained via self-administered questionnaire

- Hypertensive and Diabetic patient diagnosed from patient history of long standing elevated blood pressure, elevated blood glucose and antihypertensive and hypoglycemic drugs intake.
- Hyperlipidemic patients had elevated cholesterol and triglycerides with variable results regarding HDL and LDL levels.
- All the smokers kept smoking for long period of time at least 5 years.

➢ **Study Tools:** Multidetector computed tomography is used to get coronary angiogram for the selected patients with submillimeter collimation and gantry rotation times under 0.5 seconds. Postprocessing techniques, including multiplanar reformation (MPR), maximum intensity projection (MIP), volume rendering (VR), curved reformation, and cine imaging allow the acquisition of studies with high temporal resolution and isotropic voxels.

All patients were examined by CT coronary angiography with high technology multislice CT scanner (Dual-Source 128 Slice CT, optima GE) for the presence or absence of Coronary Artery Diseases. Non-enhanced CT was performed to evaluate coronary calcium scoring and presence or the absence of fatty liver. Then coronary arteries are evaluated by enhanced CT angiography with the following protocol:

Preparations of the patients: All the patients were prepared as following:

- The patients were asked to fast for 4-6 h prior to the examinations.
- Cannulation of the right antecubital vein.
- Beta blockers were administrated to all patients with heart rate above 75 beat per minute, 50 mg Atenolol or 5mg bisoprolol, 45minutes prior to the examination provided that contraindications to B-blockers are excluded. This increases the diastolic phase of the cardiac cycle which facilitates the acquisition process.
- No sedation was used in most cases.
- Reassurance of the patients and clear explanation of the procedure to them.
- Emergency drugs that were available at the time of the procedure includes:
- Adrenaline ampoule to control severe cases of hypotension.
- Anti-histamine ampoules to control allergic reaction to contrast media.
- The patients were imaged in the supine position.
- A bolus of 70–90 ml of Iopromide (370 mg of iodine per milliliter, Ultravist; Bayer HealthCare Pharmaceuticals, Germany) was injected intravenously at a rate of 5 mL/sec followed by a 50-mL bolus of saline via an 18-gauge catheter placed in the right antecubital vein.
- Scan delay was determined by employing an automatic bolus test in which the ROI was located on the ascending aorta. Patients were instructed to maintain an inspiratory breath hold while CT data and an electrocardiographic trace were acquired.
- A CT examination with a section thickness of 0.625 mm was obtained.
- Electrocardiographic gating was used.

- Gantry rotation of 350–500 msec.
- Temporal resolution was as low as 83 msec. Pitch and tube currents of 200–500 mA were determined by using the patient's weight.
- Plaques were classified as calcified or noncalcified plaque on a segmental basis, according to plaque features that included volume, attenuation, and calcification pattern.
- A calcified lesion was defined as a minimum of 2 pixels (area, 0.52 mm^2) with a minimum attenuation of 130 HU.
- The coronary calcifications was calculated according to Agatston calcium scoring table.

Raw image data sets from all acquisitions were analyzed. Images reconstruction was performed with 0.6-mm section thickness; 0.3 mm overlap (curved multiplaner reformat) and VRT images.

The degree of stenosis was considered significant if an occlusion of more than 50% of the arterial lumen was present [12].

Images interpretations:

All cases were interpreted depending on the followings:

1- Presence or absence of fatty liver by measuring the attenuation
By two methods as following:-
   - Liver density less than 10 HU from normal (range, 50–65 HU) denotinig fatty liver.
   - Hepatic minus splenic density less than 5 HU denoting fatty liver.

2- Presence or absence of coronary occlusion.

3- Presence or absence of significant stenosis {narrowing of coronary artery lumen > 50% is regarded as significant stenosis}.

Statistical Analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Chi-square (X2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
   - Probability (P-value)
     – P-value <0.05 was considered significant.
     – P-value <0.001 was considered as highly significant.
     – P-value >0.05 was considered insignificant.

RESULTS

Table (1) shows that the gender was male (66.7%) and female (33.3%) and ranged age was 40-61 years with mean 47.58±7.12.

Table (1): Demographic data distribution of the study group.

Demographic Data (N=30)	No.	%
Sex		
Male	20	66.7%
Female	10	33.3%
Age (years)		
Range	40-61	
Mean±SD	47.58±7.12	

Table (2) shows that the hypertensive (46.7%), hyperlipidemic (43.3%) diabetic (33.3%), and smokers (20%) of risk factors.

Table (2): Risk factors distribution of the study group.

Risk factors (N=30)	No.	%
Hypertensive	14	46.7%
Hyperlipidemic	13	43.3%
Diabetic	10	33.3%
Smokers	6	20.0%

Table (3) shows that patients with fatty liver developed coronary atherosclerosis were 17 (56.7%) and **this was statistically significant P= 0.017**, patient with fatty liver developed significant CAD were 9 (30.0%) and **this was statistically insignificant P=0.266**.

- **FLD** was found as a predictor for coronary atherosclerosis.
- **FLD** was not found as a predictor for significant CAD.

Table (3): Coronary artery disease distribution of the study group.

Coronary artery disease	No.	%	χ^2	p-value
Coronary atherosclerosis	**17**	**56.70%**	6.281	0.017*
Significant CAD	**9**	**30.00%**	2.682	0.266
Normal	**4**	**13.30%**	0.974	0.462
Total	**30**	**100.00%**	-	-

Figure (1) shows that:
A: Computed tomography (CT) image of a normal liver, showing that its attenuation (65 HU) measured using regions-of-interest (ROI) (white circles) was higher than that of the spleen (50 HU), and the CTL-S value was 15 HU, which lies within the normal reference range.
B: CT image of a steatotic liver, showing hepatic attenuation (10.5 HU) much lower than that of the spleen (51 HU), making the CTL-S value -40.5 HU, far below the normal reference range and indicating moderate-to-severe hepatic steatosis.[13]

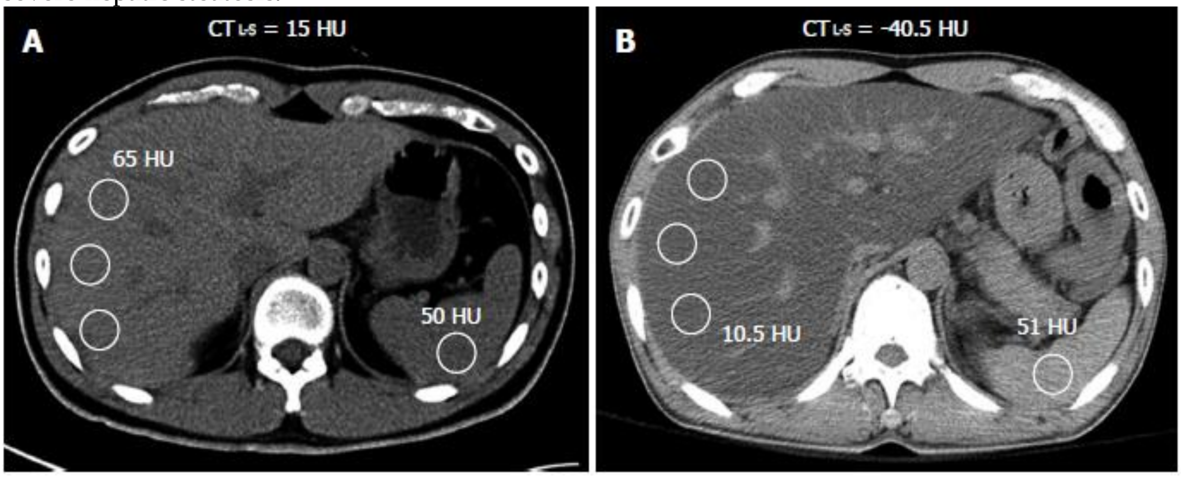


Fig. (1): Computed tomography evaluation of hepatic steatosis using computed tomographyL-S index.
Fig. (2): Male patient 61 years old with fatty liver disease, presented with Atherosclerotic non obstructive coronary artery disease. Including Proximal LAD eccentric partly calcified lesion causing about 30% stenosis and Diseased distal segment of the non dominant LCX.

Fig. (3): female patient 53 years old with fatty liver disease, presented with Significant coronary artery disease, involving Mid LCX concentric non calcified lesion causing significant stenosis.

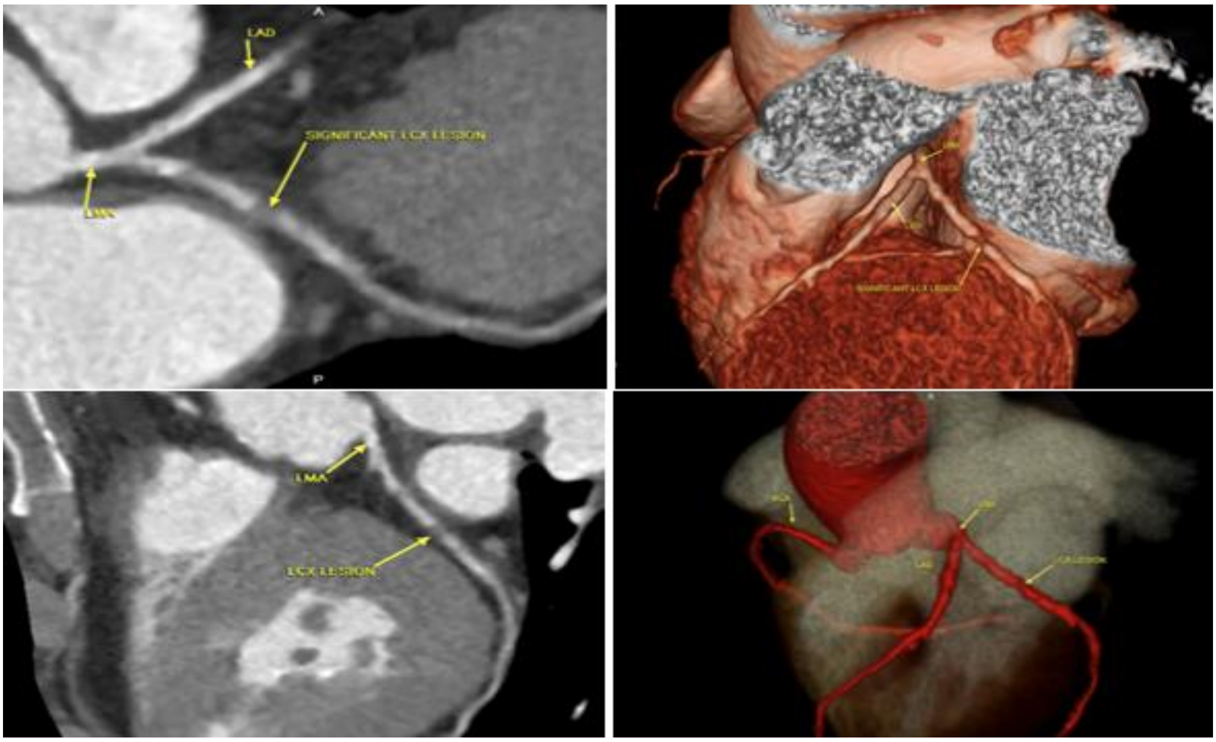


Fig. (4): male patient 43 years old with fatty liver disease, presented with Significant coronary artery disease, involving proximal LAD significant stenotic les

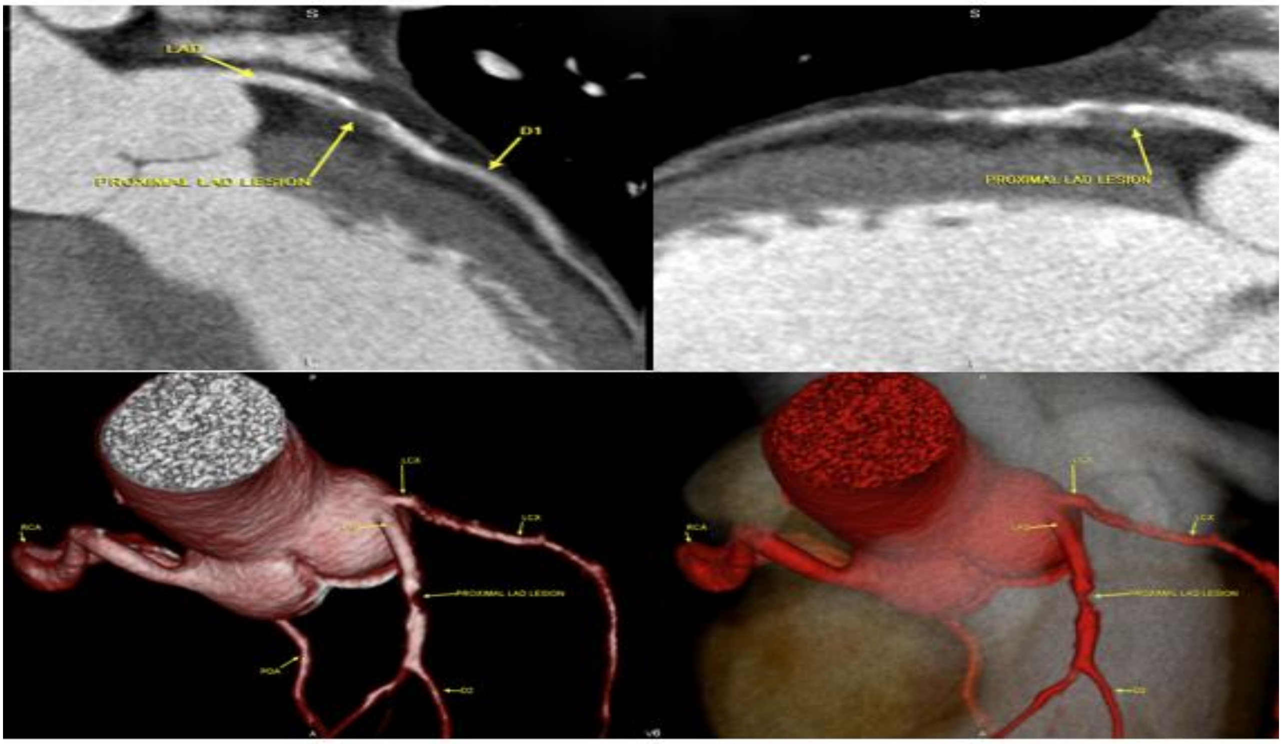
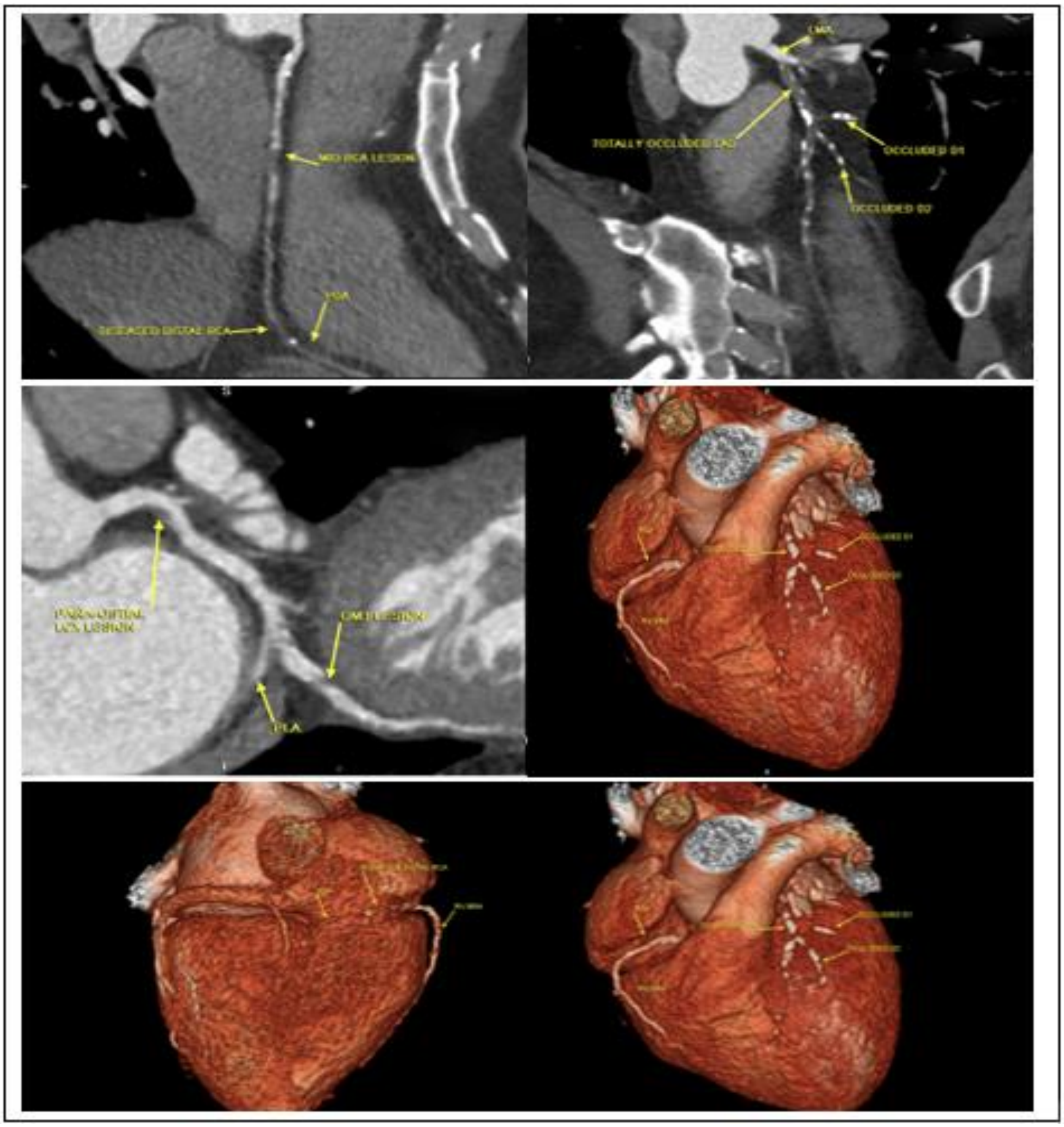


Fig. (5): male patient 44 years old with fatty liver disease, presented with Significant coronary artery (multivessel) disease, involving

- Totally occluded LAD and its diagonal branches with no significant distal filling.
- Near total occlusion distal segment of the dominant RCA.
- Significantly stenotic lesions at the mid RCA segment and at the proximal segment of the third OM artery (large branch of the LCX).
- Para-ostial LCX eccentric plaque causing moderate stenosis.
- Diseased second OM artery.



DISCUSSION

Fatty liver disease (FLD) is a common clinical condition with histological features that resemble those of alcohol-induced liver injury, but occur in patients who did not abuse alcohol [(4)].

It is increasingly recognized as the most common liver disorder in Western countries and also in other parts of the world. It is the most common cause of liver enzyme abnormalities in clinical practice, with a prevalence of 15%–20% in the general population and increases steadily to 70%–90% in obese or type 2 diabetic patients [(2)].

It may be frequently associated with risk factors for atherosclerosis, such as obesity, diabetes, and dyslipidemia [(14)].

Moreover, FLD has been included among the components of metabolic syndrome, a clinical condition with a high risk of coronary artery disease (CAD) [(5)].

Emerging evidence suggests fatty liver (FL) as an important component of metabolic syndrome (MS), a major contributor to coronary artery disease (CAD), A few studies, however, have actually evaluated whether the association between FL and CAD is solely due to the presence of MS causing both disease or there is also an independent relationship between the two [(15)].

We used multislice CT to diagnose fatty liver in patients referred to perform CT angiography study after exclusion of patients with high risk of both CAD and fatty liver.

Patient selection were non-randomized since all the selected patients were planned to undergo coronary CT angiography in a given period of time.

In our study, we evaluated the prevalence of coronary artery diseases in the fatty live patients. statistics revealed that the prevalence of atherosclerotic coronary artery disease was higher than the significant CAD and the normal coronaries. Analytic statistics showed significant relationship between coronary atherosclerosis and fatty liver disease since (p value =0.017*). In addition certain risk factors were included and these were (Diabetes, Hypertension, Hyperlipidemia and smoking), and other risk factors were not included within the study. The incidence of coronary atherosclerosis was high (56.7%) while the significant CAD was low (30%) in the studied population because the selected patients for the study had been undergoing their first CT angiography and we excluded the clinically evident patients having high susceptibility of having significant CAD.

We have found that there is a significant association between FLD and presence of coronary atherosclerosis, yet there was no significant association between FLD and the presence of significant CAD.

So we suggest that FLD may be a predictor of presence of coronary atherosclerosis, yet we cannot inform that presence of FLD may indicate or predict presence of significant CAD.

We agreed with ***Targher and Arcaro*** **[16]**, as they demonstrated that FLD patients had developed subclinical atherosclerosis when compared to non-steatosis individuals.

Also we agreed with ***Açıkel et al.*** **[17]**, as they evaluated 355 subjected to coronary angiography for the degree of severity of coronary atherosclerosis in correlation with the degree of FLD (on ultrasound basis) and they reported that FLD rate is significantly higher in patients with medium to severe atherosclerosis. Moreover, they evaluated association between fatty liver disease (FLD) and the presence and severity of coronary artery disease (defined as at least 50% stenosis) They concluded that ultrasonographic fatty liver have independent effects on both the presence of CAD and severity of coronary atherosclerosis.

Arslan et al. **[18]** attempted to prove the association between metabolic syndromes (MS), FLD and CAD. Arslan considered a patient with MS as an independent variable in logistic regression. FLD turned out to be a significant predictor of CAD and it was concluded that there is a relationship between fatty liver and CAD independent of MS. His study was limited by the exclusion of patients known to have dyslipidemia.

Mirbagheri et al. **[19]** stated in their study that the fatty liver was a strong independent predictor of CAD When ATP-III-defined MS was used instead of its components, both MS and fatty liver were significantly correlated to CAD.

Choi et al. **[20]** reported that angiographically proven coronary artery stenosis was strongly associated with fatty liver and regarded FLD is as a significant predictor of CAD independent of traditional risk factors in Asians.

Alper et al. **[21]** they concluded that the presence of FLD is associated with more severe CAD, requiring that patients with MS be investigated for the presence of FLD and those with FLD be attentively followed-up for the presence and severity of CAD.

The previous studies evaluated the presence and the severity of fatty liver by US. Although ultrasonography has a relatively high sensitivity (82%-94%) and specificity (66%-95%) in detecting fatty liver, it may give an incorrect diagnosis in 10%-30% of cases **[22]**.

We used non enhanced CT for evaluation of fatty liver using the splenic density as a reference. This method has a high sensitivity (88%–95%) and specificity (90%–99%). In the other hand when the liver density decreased by 10 HU or more, the condition was diagnosed as fatty liver **[23]**.

Assy et al. **[6]** used the non-enhanced CT for diagnosis of fatty liver as used coronary CTA for evaluation of presence of coronary plaques, they concluded that patients with FLD have higher prevalence of non-calcified coronary plaques and this was matching with our results regarding association of FLD and coronary atherosclerosis.

Our and other's studies proved that the presence of FLD is a predictor for coronary atherosclerosis. Whether fatty liver, per se, increases the risk of cardiovascular disease or its associated metabolic abnormalities have the actual hidden role.

Other potential mechanisms by which fatty liver may increase cardiovascular risk beyond that imposed by metabolic syndrome are lipotoxicity and increased circulating insulin-like growth factors IGF-1 and IGFBP-3 **[24]**.

Lipotoxicity may account for the increased risk of coronary plaque by means of a rise in serum-oxidized fatty acid which has been associated with enlarged intima media thickness **[25]**.

CONCLUSION

1- Fatty liver disease may be considered as a predictor for coronary atherosclerosis and based on this, more individuals from the general population with subclinical CAD could be detected at earlier stages when fatty liver is identified.
2- Presence of fatty liver may help in cardiovascular risk stratification and assessment.
3- It will be worthwhile to study whether improving FLD will ultimately prevent the development of CAD.

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