Evaluation of Coronary Artery Disease Among Patients with Non-Alcoholic Fatty Liver Diseases Using Multislice C.T.

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Abstract

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

Aim of Study: To evaluate the presence and the severity of Coronary Artery Disease (CAD) among Non-alcoholic Fatty liver Diseases (NAFLD) patients compared to non-fatty liver population and to evaluate the association of NAFLD and CAD using MSCT and subsequently the possibility of considering NAFLD as a predictor for CAD.

Patients and Methods: The study was conducted in Radiological Department of Ain Shams Hospital. It focused on evaluating 42 patients, who were referred to perform CT coronary angiography. These patients were examined in the period between from December 2015 till December 2016. The target sample was patients with non-alcoholic 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: Non-alcoholic fatty liver patients developed coronary atherosclerosis were 16 (76.2%) and this was statistically significant $p=0.028$.

Conclusion: Non-alcoholic 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 non-alcoholic fatty liver may help in cardiovascular risk stratification and assessment.

Key Words: Coronary artery disease – Non-alcoholic fatty liver disease – Multi-slice CT – Atherosclerosis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, with prevalence above 30% in adult populations. It is strongly associated with obesity. Weight loss through diet and physical activity are considered the mainstay of its management. Weight loss can be difficult to achieve and maintain [1].

Risk factors for atherosclerosis such as obesity, diabetes and dyslipidemia are also frequently associated with NAFLD [2].

This has stimulated an interest in the possible association between NAFLD and the development of atherosclerosis. Many clinical studies have examined the association between NAFLD and subclinical coronary atherosclerosis and NAFLD was significantly associated with the development of coronary artery disease (CAD) independent of cardiovascular and metabolic risk factors. Patients with NAFLD are at a high risk of carotid atherosclerosis regardless of metabolic syndrome and classical cardiovascular risk factors. NAFLD may play a pathophysiological role in atherosclerosis development and may be useful to identify subjects with a higher risk of subclinical disease progression [3].

The detection of NAFLD should alert to the existence of an increased cardiovascular risk. Moreover, NAFLD might be an independent risk factor for cardiovascular disease [4].

Un-enhanced computed tomography (CT) is an accurate imaging modality used to detect and characterize hepatic steatosis. Ultrasound (U/S) is also widely used to detect fatty liver but may provide inconsistent results [5].

At the same time, Multi-slice CT coronary angiography has been proposed as a noninvasive modality to detect coronary plaques and classify coronary artery disease (CAD). It has been used successfully to quantify coronary artery calcium,
which helps to predict the presence of coronary artery disease [6].

Coronary CT angiography (CTA) can evaluate both calcified plaque and non-calcified plaque. Coronary CTA is able to show the lumen of the coronary arteries as well as the vessel wall, analogous to intravascular sonography [7].

The assessment of NAFLD with CT can improve the risk stratification of patients with suspected coronary artery disease; the presence of NAFLD is associated with high-risk coronary plaque independently of traditional risk factors and severity of coronary artery disease [8].

We aimed by this study to evaluate the presence and the severity of Coronary Artery Disease (CAD) among Non-alcoholic Fatty liver Diseases (NAFLD) patients compared to non-fatty liver population and to evaluate the association of NAFLD and CAD using MSCT and subsequently the possibility of considering NAFLD as a predictor for CAD.

Patients and Methods

This is retrospective Study where the data collected from Ain Shams University Hospitals, Radio-diagnosis Department in a period between December 2015 to December 2016 after approval of our ethical committee which waived the requirement for written consent. In our study the patients were (42 patients), 22 were men and 20 women. Patient age Range was 35-71 [Mean ± SD=53 ± 10.47]. Clinical and radiological records of patients coming to the Radiology Department to do Coronary CTA (angiography) and selecting 21 patients with NAFLD as the case group and 21 patients with non-fatty liver as the control group.

Inclusion criteria:

- Diabetic patients with type II diabetes mellitus for at least 3 years.
- Hypertensive patient with history of long standing elevated blood pressure and antihypertensive drugs intake.
- Hyperlipaemia patients with elevated cholesterol and triglycerides with variable results regarding HDL and LDL levels.
- All smokers with smoking history for at least 5 years.
- Obesity where BMI was calculated as weight in kilograms divided by height in meters squared.

Exclusion criteria:

- Patients known to have CAD or previous surgical coronary intervention.
- Patients with known liver disease.

Study tools, procedures and interventions:

- Equipment used:
  The examination was done using high technology Multislice-CT scanner (Dual-Source 64 Slice CT, General Electric, USA) and (TOSHIBA,80 Multislice) starting with non-contrast study for calcium scoring calculation and the presence or the absence of fatty liver, to be followed by Coronary CT angiography.

- Patients preparation:
  ° Normal recent serum creatinine level should be available.
  ° Fasting for at least 6 hours.
  ° B-blockers [10mg of Propranolol (Inderal; Astra Zeneca, Egypt)], was given orally if resting heart rate higher than 70 beats per minute.

- Patients positioning:
  ° The patients was imaged in the supine position.

- Non enhanced CT:
  ° Non enhanced CT was done from the level of arch of aorta down to the kidney level.
  ° Liver density was measured.
  ° Splenic density was measured.
  ° Fatty liver is considered when splenic-hepatic density >10 [9]. The coronary calcifications was calculated according to Agatston calcium scoring table.

- Coronary CTA:
  ° Contrast media used was include: A bolus of 70-90ml of Iopromide (370mg of iodine per milliliter, Ultravist; Bayer Health Care Pharmaceuticals, Germany) that was injected intravenously at a rate of 5ml/sec Followed by a 50-mL bolus of saline via an 18-Gauge catheter placed in the antecubital vein.
  ° Retrospective electrocardiographic gating was used, with heart rate adjusted gantry rotation of 350-500msec.

- Scan protocol:
  ° 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 was acquired.
A CT examination with a section thickness of 0.625mm was obtained.

- Temporal resolution was as low as 83msec. Pitch and tube currents of 200-500mA was determined by using the patient's weight.

- 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 volume rendering technique (VRT) images.

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

- Plaques were classified as calcified, non-calcified and mixed plaques.

**Image interpretation:**

- For every patient, we were calculating liver density as well as calcium scoring and record the incidence of coronary affection.

- Data was collected and statically analyzed.

**Statistical analysis:**

After exclusion of patients not following the inclusion criteria, patients was classified as Group A which was include patients with fatty liver and Group B which was a control group with patients free from fatty liver.

Statistical correlation between the presence of fatty liver and coronary artery atherosclerosis was done.

**Statistical package:**

The data was collected, coded and entered to the computer. The data was analyzed with the program (SPSS) Statistical Package for social science version 16.

**Results**

The previous table shows that there was 24 diabetic patients (57.1%) and 18 non diabetic patients (42.9%), while the dyslipidemic patients were 38 (90.5%) and non dyslipidemic patients were 4 (9.5%). The whole patients were hypertensive and the smoker patients were 16 (38.1%) patients while the non-smoker patients were 26 (61.9%).

The previous table shows that there was statistically significant increase in hepatic attenuation in group B than group A with \( p \)-value <0.001.

The previous table shows that there was statistically highly significant increase in the risk of stenosis and the number of stenotic lesions of involved coronary arteries in group A than group B with \( p \)-value <0.001. The table also shows a highly significant increase in the risk of stenosis among the (LAD & LCX) arteries in group A than group B with \( p \)-value <0.001 & = 0.001 respectively with no significant difference according to the (PDA & RCA).

The previous table shows that there were significant increase of the risk of significant CAD in group A than group B with \( p \)-value=0.028.

<table>
<thead>
<tr>
<th>Table (1): Demographic data and characteristics of the studied patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No.</strong> &amp; 42</td>
</tr>
<tr>
<td><strong>Age:</strong> &amp; 50.76±8.23</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong> &amp; 35-71</td>
</tr>
<tr>
<td><strong>Gender:</strong> &amp; 20 (47.6%)</td>
</tr>
<tr>
<td>Female &amp; 22 (52.4%)</td>
</tr>
<tr>
<td>Male &amp; 0 (0.0%)</td>
</tr>
<tr>
<td>No &amp; 42 (100.0%)</td>
</tr>
<tr>
<td>Yes &amp; 18 (42.9%)</td>
</tr>
<tr>
<td><strong>HTN:</strong> &amp; 4 (9.5%)</td>
</tr>
<tr>
<td>No &amp; 24 (57.1%)</td>
</tr>
<tr>
<td>Yes &amp; 38 (90.5%)</td>
</tr>
<tr>
<td><strong>DM:</strong> &amp; 26 (61.9%)</td>
</tr>
<tr>
<td>No &amp; 16 (38.1%)</td>
</tr>
<tr>
<td>Yes &amp; 4 (9.5%)</td>
</tr>
<tr>
<td><strong>Dyslipidemic:</strong> &amp; 30 (0-150)</td>
</tr>
<tr>
<td>No &amp; 0-2376</td>
</tr>
<tr>
<td>Yes &amp; 0.2376</td>
</tr>
<tr>
<td><strong>Smoker:</strong> &amp; 100</td>
</tr>
<tr>
<td>No &amp; 57.1</td>
</tr>
<tr>
<td>Yes &amp; 90.5</td>
</tr>
<tr>
<td><strong>Ca score:</strong> &amp; 38.1</td>
</tr>
</tbody>
</table>

**Fig. (1): Gender distribution of the studied patients.**
Table (2): Comparison between group A and group B regarding splenic-hepatic ratio.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Test value</th>
<th>p-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-significant CAD</td>
<td>Significant CAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>5</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenic att:</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>-2.163</td>
<td>0.043</td>
<td>S</td>
</tr>
<tr>
<td>Range</td>
<td>188.37±13.50</td>
<td>261.13±73.54</td>
<td>176.87-389.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic att:</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>-0.342</td>
<td>0.736</td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>13.78-19.02</td>
<td>17.47±2.53</td>
<td>14.3-22.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splenic-hepatic ratio:</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>-2.003</td>
<td>0.060</td>
<td>NS</td>
</tr>
<tr>
<td>Range</td>
<td>11.23±1.66</td>
<td>14.99±4.03</td>
<td>10.41-25.42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-value >0.05: Non significant (NS).
p-value <0.05: Significant (S).
p-value <0.01: Highly significant (HS).
*: Independent t-test.

Table (4): Comparison between group A and group B regarding percentage of patients with significant CAD.

<table>
<thead>
<tr>
<th>Significant CAD</th>
<th>Group A</th>
<th>Group B</th>
<th>Test value</th>
<th>p-value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non significant CAD</td>
<td>5 (23.8%)</td>
<td>12 (57.1%)</td>
<td>4.842</td>
<td>0.028</td>
<td>S</td>
</tr>
<tr>
<td>Significant CAD</td>
<td>16 (76.2%)</td>
<td>9 (42.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p-value >0.05: Non significant (NS).
p-value <0.05: Significant (S).
p-value <0.01: Highly significant (HS).
*: Chi-square test.

Fig. (2): Male patient 43 years old with fatty liver disease, presented with Significant coronary artery disease, involving proximal LAD significant stenotic lesion.
Fig. (3): 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.

Fig. (4): Male patient 50 years old, diabetic, hyperlipidemiaic and hypertensive. Recently he started to experience recurrent attacks of chest pain that increases with inspiration. The left main is normal, supplying LAD and LCX branches. The LAD artery is mildly atherosclerotic vessel supplying 3 normal diagonal branches. LAD had mixed plaques at its proximal segment causing mild (~30%) luminal stenosis. The LCX artery is a non-dominant, small and atherosclerotic vessel. The RCA is a dominant, large and normal vessel supplying rather normal PDA and PL branches.

Fig. (5): 52 years old male patient with controlled hypertension. He is not diabetic ,hyperlipidemaic or smoker. He has positive family history of ischemic heart disease. He performed multislice CT coronary angiography for checkup. Liver & spleen densities were calculated. Hepatic minus splenic density was - 11 denoting fatty liver. Calcium score was 126.4.

The left main is an atherosclerotic vessel showing normal patency. The left main bifurcates into LAD and LCX. The LAD is an atherosclerotic vessel that supplies two diagonals and runs till it wraps around the left ventricular apex. The mid segment of the LAD shows a heavily calcified plaque causing severe luminal stenosis. The LAD afterwards shows good patency. Both diagonal branches of the LAD are of good caliber showing good patency. The LCX is an atherosclerotic non dominant vessel that supplies three OM branches. The LCX and its branches show some atherosclerotic irregularities with no significant luminal affection. The RCA is an atherosclerotic dominant vessel showing a mid segment mild stenosis caused by a non calcified plaque.
Discussion

Non-alcoholic fatty liver disease (NAFLD) is a common clinical condition with histological features that resemble those of alcohol-induced liver injury, but occur in patients who do not abuse alcohol [10].

It is increasingly recognized as the most common liver disorder in Western countries & 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 [11].

NAFLD represents a spectrum of disease ranging from hepatocellular steatosis through steatohepatitis to fibrosis and irreversible cirrhosis [12].

It may be frequently associated with risk factors for atherosclerosis, such as obesity, diabetes & dyslipidemia. Moreover, NAFLD has been included among the components of metabolic syndrome, a clinical condition with a high risk of coronary artery disease (CAD) [13].

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 [14].

Recent studies demonstrated that NAFLD could further predict cardiovascular diseases or even involved the pathophysiologic process of atherosclerosis. Galiero et al., [15] reported that there is an independent association between hepatic steatosis and carotid atherosclerotic plaques. They suggested that metabolic changes due to nonalcoholic fatty liver disease may explain this relationship. In our study, we evaluated the possibility of correlation between presence of non-alcoholic fatty liver and coronary atherosclerosis in Egyptian patients, moreover we tried to evaluate the presence of significant CAD in such patients.

We used multi-slice 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. We found that there is a significant correlation between presence of NAFLD and presence of coronary atherosclerosis, yet there was no significant correlation between presence of NAFLD and between presence of significant CAD.

So we suggest that NAFLD may be a predictor of presence of coronary atherosclerosis, yet we cannot inform that presence of NAFLD may indicate or predict presence of significant CAD. We agreed with Hsu et al., [16], as they demonstrated that NAFLD patients had developed subclinical atherosclerosis when compared to non-steatosis individuals.

Also, we agreed with Ismaielet al., [17] as they evaluated 355 subjected to coronary angiography for the degree of severity of coronary atherosclerosis in correlation with the degree of NAFLD (on ultrasound basis) and they reported that NAFLD rate is significantly higher in patients with medium-severe atherosclerosis. Moreover, they evaluated association between non-alcoholic fatty liver disease (NAFLD) and the presence and severity of coronary artery disease (defined as at least 50% stenosis) and obesity as well as association between CAD and NAFLD with aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyltransferase (GGT) levels. They concluded that ultrasonography fatty liver have independent effects on both the presence of CAD and severity of coronary atherosclerosis. In addition, increased serum AST and GGT levels may be independently associated with CAD.

Also our results matched with Koulaouzidis et al., [18]. That reported that there is correlation between NAFLD & coronary calcifications but he also tried to define the correlation between the extent of NAFLD (based on U/S), cardiovascular risks, and MDCT-acquired calcium score. They found that more severe fatty liver disease may serve as an independent factor even after adjustment of clinical variables and estimated cardiovascular risk scores. They also demonstrated that the presence of more severe degree fatty liver disease added incremental value beyond such traditional cardiovascular risks in the prediction of coronary artery calcification.

Hao et al., [19] attempted to prove the association between metabolic syndrome (MS), NAFLD & CAD. Ninety-two patients without known CAD, underwent elective coronary angiography, were studied. Nonalcoholic fatty liver disease (NAFLD) was diagnosed based on the results of abdominal ultrasonography. 70.7% and 46.7% of patients turned out to have FL and CAD, respectively. In binary logistic regression analysis using the presence of CAD as the outcome variable and age, sex, body mass index, smoking history, waist circumference, blood pressure (cut-off: 130/85mmHg), fasting blood sugar (FBS), total cholesterol, low-
and high-density (HDL) lipoproteins, and triglycerides as independent variables, NAFLD significantly correlated with the presence of CAD. Next, Hao considered a patient with MS as an independent variable in logistic regression. NAFLD turned out to be a significant predictor of CAD & 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.

Tantawy et al., [20] evaluated 420 adult patients undergoing elective coronary angiogram. A cutoff of 30% stenosis in at least one major coronary artery was used to define clinically significant CAD. A liver ultrasonography was performed on the same day as CAG. 28.1% of patients were found to have CAD. In multivariate analysis, fatty liver was a strong independent predictor of CAD. When ATP-III-defined MS was used instead of its components, both MS & fatty liver were significantly correlated to CAD.

Saydam et al., [21] carried out a prospective observational study for apparently healthy men and women who were recruited from a health check-up program. NAFLD was diagnosed by abdominal ultrasonography. Multivariate analyses indicated that NAFLD was a predictor of cardiovascular disease independent of conventional risk factors and metabolic syndrome.

Ichikawa et al., [22] evaluated the interaction between fatty liver and cardiovascular outcomes using coronary angiograms in a prospective cohort study and demonstrated that fatty liver is associated with CAD, which is consistent with our results.

Yu et al., [23] proved that angiographically proven coronary artery stenosis was strongly associated with fatty liver in a grade-dependent manner & NAFLD is a significant predictor of CAD independent of traditional risk factors in Asians.

Mantovani et al., [24] reported in a prospective nested case-control study that NAFLD is a strong predictor of future cardiovascular events among type 2 diabetic patients, but a limitation of his study was that the subjects of their study were all patients with type 2 diabetes, which constitute a very high-risk population for cardiovascular disease. Therefore, it was uncertain whether the study could be extrapolated to the general population.

Radaelli et al., [25] included 80 patients with a diagnosis of MS. All patients underwent abdominal ultrasonography to detect NAFLD. Coronary angiography was performed. They concluded that the presence of NAFLD is associated with more severe CAD, requiring that patients with MS be investigated for the presence of NAFLD and those with NAFLD be attentively followed-up for the presence and severity of CAD.

**Conclusion:**
Non-alcoholic 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 non-alcoholic fatty liver may help in cardiovascular risk stratification and assessment.

**References**


تقييم أمراض الشريان التاجى بين المرضى الذين يعانون من أمراض الكبد الدهنية غير الكحولية

بالاستخدام الأشعة المقطعية متعددة الكواشف

المقدمة: يعتبر قصور الشريان التاجي سبباً رئيسياً في إنتشار نسبة المرضى والوفيات في جميع أنحاء العالم. لذلك يلزم الكشف المبكر عن أمراض الشريان التاجي لدى الأفراد الذين لا تظهر عليهم أعراض. تساهم العديد من عوامل الأيضية في حدوث كل من مرض الكبد الدهني غير الكحولي وقصور الشريان التاجي.

الأهداف: الدراسة تهدف إلى تقييم وجود وشدة قصور الشريان التاجي في مرضى الكبد الدهني غير الكحولي مقارنة بالمرضى الذين لا يعانون من الكبد الدهني. وتحديد العلاقة بين مرض الكبد الدهني غير الكحولي وقصور الشريان التاجي باستخدام الأشعة المقطعية.


وقد أجريت هذه الدراسة على 12 مريض كان 16 مريضاً (76.2%) وكان هذا نسبته إحصائيًا 28.

النتائج: أظهرت هذه الدراسة أن عدد مرضى الكبد الدهني غير الكحولي كان 16 مريضاً (76.2%) وكان هذا نسبته إحصائيًا 28.

الخلاصة: يمكن مرض الكبد الدهني غير الكحولي مؤشرًا لقصور الشريان التاجي وبناءً على ذلك، يمكن اكتشاف المزيد من الأفراد من عامة السكان المصابين بأمراض القلب التاجية تحت الإكليتيا في مراحل مبكرة عند تحديد الكبد الدهني قد يساعد وجوه الكبد الدهني غير الكحولي في تصنيف مخاطر أمراض القلب والأوعية الدموية وتقييمها.