

Research Article

Association of non-alcoholic fatty liver disease and coronary artery disease

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Received: 24 July 2016

Revised: 26 July 2016

Accepted: 30 August 2016

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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD), a feature of metabolic syndrome is a highly prevalent condition worldwide. Patients with NAFLD have a higher mortality when compared to general population. Many investigators have shown a close relationship between NAFLD and cardiovascular disease which contributes to the total mortality associated with NAFLD particularly in Western population. This study was therefore conducted to evaluate whether NAFLD independently affects angio-graphically proven coronary artery disease in Asians.

Methods: The severity assessment of fatty liver disease was done by ultrasonography and was graded with increased severity from 0 to 4. Coronary angiography was performed to detect the presence or absence of significant coronary artery disease and modified Gensini score, which determines the severity of coronary atherosclerotic involvement in individual patients was calculated.

Results: Statistical analysis showed that Fatty liver disease was significantly higher in patients with significant coronary artery disease than in non-significant coronary artery disease group. When analyzed on basis on severity of fatty liver disease, modified Gensini score was significantly higher in group with fatty liver grade 2-3 than in group with fatty liver grade 0 or 1. Logistic regression analysis further showed that severity of fatty liver disease had independent effect on coronary atherosclerotic involvement.

Conclusions: From our current study it can be reasonably said that NAFLD may be an independent risk factor for developing arteriosclerosis. This hypothesis should be verified with larger studies in different population groups.

Keywords: Nonalcoholic fatty liver disease, Coronary artery disease, Coronary angiography

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD), a highly prevalent condition, is a feature of metabolic syndrome and characterized by excessive accumulation of fat in the liver cells.¹⁻³

Patients with NAFLD have a higher mortality rate than the general population.⁴ Some investigations have shown a relationship between nonalcoholic fatty liver disease (NAFLD) and cardiovascular diseases (CVDs).⁵⁻⁷ With

the latter being one of the main causes of morbidity and mortality in these patients. Also prevalence of NAFLD is as high as 20%-30% in the adult population in Western countries and 12%-24% in Asian-Pacific countries.^{8,9} Its prevalence in obese or diabetic patients increases up to 70%-90%.⁸

Although fatty liver is related to factors such as dyslipidemia, central obesity, diabetes, and metabolic syndrome (MS) that may cause CVDs including coronary artery disease (CAD), there are few studies analyzing the

relationship between NAFLD and CAD, and they present controversial results. Many NAFLD studies conducted in Western populations have found a relationship between NAFLD and CAD in relatively obese patients, which has not been found in Asian populations.^{10,11}

Therefore, the relationship between NAFLD and CAD in relatively thin Asian people must be evaluated. This study was conducted to evaluate whether NAFLD independently affects angio-graphically proven CAD in Asians.

METHODS

Present study group consisted of 150 adult (more than 19 years) patients who underwent coronary angiography for various reasons such as acute coronary syndrome, high-risk findings on non-invasive testing, positive effort test, or chest pain evaluation according to the American College of Cardiology/American Heart Association recommendations.

We excluded patients with Viral hepatitis (positive for hepatitis B surface antigen and/or anti-hepatitis C virus), history of alcohol ingestion (>30 mg per day for man and >20 mg per day for woman), history of known Liver disease, congestive heart failure, severe pulmonary disease, corpulmonale, chronic renal failure, malignant disease, active infection, on drugs known to cause steatosis (corticosteroids, oestrogen, tamoxifen, amiodarone, diltiazem, valproic acid), on drugs known to improve steatosis (metformin, glitazones, and statins-more than one month) and HIV positive patients.

For obesity, body mass index (BMI) ≥ 30 mg/dl was used. For smoking, the one who smokes one or more cigarettes per day; for more than five days per week were counted as smoker. Diabetes was defined as fasting blood glucose ≥ 126 mg/dl or post prandial blood glucose ≥ 200 mg/dl or random blood glucose ≥ 200 mg/dl and/or patients on treatment for diabetes.

Metabolic syndrome was diagnosed based on NCEP/ATP III guidelines. Hypertension was diagnosed based on JNC VII guidelines. Blood samples were collected within 24 hours of being admitted to hospital for routine biochemistry, serology and lipid profile.

Abdominal ultrasonography was performed during hospital stay by a radiologist who did not have information about the patient. Right kidney echogenicity was used for determination of liver parenchyma echogenicity. With the same kidney cortex and liver parenchyma echogenicity it is evaluated as normal, no fatty liver (Grade 0).

Fat infiltration in liver is described in 3 ultrasonography stages. Mild (Grade 1): Minimal diffuse increase in hepatic echogenicity, diaphragm and intra hepatic vessel contours seems normal. Medium (Grade 2): Medium

grade diffuse increase in hepatic echogenicity, mild deterioration in the image of diaphragm and intra hepatic vessels. Severe (Grade 3): Apparent increase in echogenicity. Posterior segment of the right hepatic lobe is difficult to display. Intra hepatic vessel structure and diaphragm contours are vague or not seen.

All the patients enrolled in our study underwent selective right and left coronary angiography by either radial or femoral artery route using Tiger and Judkins angiographic catheter respectively using "Siemens Artis" device.

The procedure was performed and reported by a cardiologist. Another cardiologist also reviewed the angiography report in order to reduce inter-observer variation. Coronary artery disease was considered to be present when $\geq 50\%$ narrowing was present in left main coronary artery or $\geq 70\%$ narrowing in their major epicardial branches. Modified Gensini Scoring was used to determine severity of coronary atherosclerosis.

The Modified Gensini score has been described and validated previously.¹² The most severe stenosis in each of eight coronary segments was graded from 1 to 4 (1 for 1% to 49% lumen diameter reduction, 2 for 50% to 74% stenosis, 3 for 75% to 99% stenosis and 4 for 100% occlusion).

The proportion of each vessel involved by atheroma was multiplied by a factor for each vessel: left main (5), left anterior descending (20), main diagonal branch (10), first septal perforator (5), left circumflex, obtuse marginal, and posterolateral vessels (10), right coronary (20), and main posterior descending branch (10). When the major lateral wall branch was a large obtuse marginal or intermediate vessel, the factor used was 20, with a factor of 10 for the left circumflex.^{13,14}

This score therefore gives a measure of both severity and extent of coronary atherosclerosis. When a vessel was occluded and the distal vessel was not visualized, the proportion of the vessel not visualized was given the mean score of the remaining vessels. The scores for each of the vessels were summed to give a total score.

Candidates (n=150) were divided into two main groups; those with CAD (n=107) and those without CAD (n=43). All candidates underwent ultrasonography evaluation for grading of fatty liver. Modified Gensini score was calculated in all.

Statistical evaluation was performed with SPSS 20 software package for Windows (Chicago, IL, USA). Quantitative variables are given as mean \pm standard deviation, and qualitative variables are expressed as frequency and percentage. Two groups with different parameters were compared with Student's unpaired t test. When more than two groups were compared for parameters, analysis of variance (ANOVA) was used;

post hoc analysis was performed using Tukey-HSD test. Qualitative variables were compared using Chi-square. The presence of CAD and the severity of coronary atherosclerosis (modified Gensini score) were evaluated as the dependent variables. Age, gender, diabetes mellitus (DM), hypertension, smoking, blood lipids, BMI, Metabolic syndrome and fatty liver as independent variables. Logistic regression analyses were performed to determine the independent variables influencing both the presence of CAD and the severity of coronary atherosclerosis. Statistical significance was defined with p-value <0.05.

RESULTS

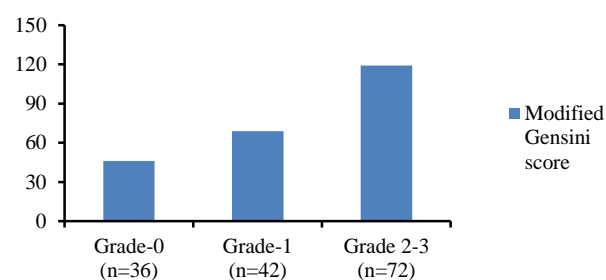
Clinical characteristics

Of the 150 patients in the study group, 45 (30%) had Myocardial infarction, 45 (30%) had chronic stable angina, 30 (20%) had Non ST elevation myocardial infarction and 18 (12%) had Unstable angina. While 12 (8%) of patients underwent coronary angiogram based on their Tread mill test results.

A total of 98 (65.5%) were males and 52 (34.7%) were females. A total of 60 (40%) were hypertensive, 59 (39%) were Diabetic, 60 (40%) were smoker, 28 (18%) were overweight or obese, 63 (42%) were having Metabolic syndrome and 114 (76%) were having fatty liver on ultrasonography. A total of 107 (71%) were having Coronary artery disease ($\geq 50\%$ narrowing in left

main coronary artery or $\geq 70\%$ narrowing in their major epicardial branches on coronary angiogram). In CAD group, prevalence of risk factors such as age, male gender, diabetes mellitus, hypertension, smoking and dyslipidemia were significantly higher ($p < 0.05$) than in non-CAD group. Fatty liver was significantly higher ($p < 0.05$) in CAD group than in non-CAD group.

In group with modified Gensini score ≥ 100 , age, male gender, dyslipidemia and fatty liver were significantly higher than that with modified genuine score < 100 , but there was no significant difference between these groups in terms of diabetes mellitus, hypertension, smoking and metabolic syndrome.



Grade 0- no fatty liver, Grade 1- mild fatty liver, Grade 2- moderate fatty liver, Grade 3- severe fatty liver.

Figure 1: Relation between ultrasonography fatty liver and the severity of coronary atherosclerosis (modified Gensini score).

Table 1: Clinical, laboratory and angiographic findings according to fatty liver grade.

Parameters	Ultrasonographic Fatty liver grade			F or X2	*P
	Grade-0 (n=36)	Grade-1 (n=42)	Grade-(2+3) (n=72)		
Age in years	53.8+13.8	53.7+11	56.6+15.5	0.761	0.469
Male gender, n (%)	17 (44.2)	25 (59.5)	56 (77.7)	6.870	0.005
Diabetes Mellitus, n (%)	7 (19.4)	17 (40.4)	35 (48.6)	8.364	0.014
Hypertension, n (%)	6 (16.6)	21 (50)	33 (45.8)	11.098	.004
Smoking, n (%)	10 (27.7)	18 (42.8)	32 (44.4)	3.147	0.227
Body mass index, kg/mt2	22.4+2	25.5+3	26.9+3.1	28.719	0.0001
HDL cholesterol, mg/dl	43.3+8.6	40.8+6.4	37.5+5.9	9.768	0.0001
LDL cholesterol, mg/dl	97.6+23.3	125.7+39.9	157.4+33.3	40.335	0.0001
Triglycerides, mg/dl	121.2+29.2	157.5+50.6	200.5+59.9	58.810	0.0001
Total cholesterol, mg/dl	165.3+21.9	198+43.2	235.1+39.1	44.514	0.0001
Metabolic syndrome, n (%)	3 (8.3)	18 (42.8)	42 (58.8)	26.926	0.0001
Coronary artery disease	15	23	69	42.26	0.0001
Modified Gensini score	46.9+46	69.6+45.8	119.8+34.5	43.804	0.0001
Modified Gensini score > 100, n (%)	10 (27.7)	25 (59.5)	56 (77.7)	15.999	0.0001

Values are presented as mean + SD or proportions/percentages, where appropriate; *P value for X2 test or one way ANOVA for comparison of variable across groups.

When analyzed on the basis of fatty liver there were significant differences between groups in terms of risk factors and CAD rate. Again modified Gensini score was significantly higher in grades 2-3 than in grades 0 and 1

groups (Table 1 and Figure1). Post Hoc test also showed significant difference in modified Gensini score between the different fatty liver grade groups.

Logistic regression analysis for presence of coronary artery disease

Independent variables were presented in multiple logistic regression model with CAD as dependent variable. Results showed that age, hypertension, diabetes, smoking, obesity, HLD, LDL, TG, total cholesterol and fatty liver had independent effect on presence of CAD; whereas male gender did not have independent effect for the presence of CAD. Logistic regression analysis for the severity of CAD showed that age male gender, hypertension, diabetes, smoking, BMI, HDL, LDL, TG, total cholesterol and fatty liver had independent effects on severity of coronary atherosclerosis.

DISCUSSION

In this study, we showed direct relations among both the presence and severity of CAD and NAFLD in 150 patients who underwent coronary angiography. Non-alcoholic fatty liver disease is a clinical and pathological condition associated with abdominal obesity, DM, hypertension, dyslipidemia and insulin resistance.

It is also considered the hepatic manifestation of metabolic syndrome and present in up to one-third of the general population and in the majority of patients with metabolic risk factors.⁸ Classic risk factors like age, smoking, hypertension, diabetes mellitus and dyslipidemia were higher in coronary artery disease group; which is consistent with the literature.^{15,16}

When various factors were assessed for the severity of CAD it was found that age, male gender, dyslipidemia and fatty liver were significantly higher in group with modified Gensini score more than 100 when compared to group with modified Gensini score less than 100, but there was no significant difference between these groups in terms of diabetes mellitus, hypertension, smoking and metabolic syndrome.

The reason for this may be clinical characteristic of my study group with 18% of patient with coronary artery disease who were either smoker, hypertensive, diabetic, overweight or obese were below 45 years of age. This may indicate that they have angiogram performed at earlier stage in the course of disease where atherosclerosis is severe enough to cause clinical presentation but can progress even further later in the course of disease.

In subgroup of patients divided on the basis of fatty liver grade there was substantial significance for the presence of risk factors, for the presence of CAD and its severity; which was comparable to the study performed by Acikel et al.¹⁷

Fatty liver for the presence of CAD was an independent risk factor when other factors such as gender, hypertension, smoking, diabetes mellitus, blood lipids,

metabolic syndrome, BMI were excluded; analyzed by logistic regression analysis. NAFLD an independent factor associated with coronary artery disease was also reported by Arslan et al and Acikel et al.^{17,18}

Regarding the relationship between CAD and NAFLD, Arslan et al found that the probability of detecting the presence of CAD was 6.73 times higher in patients with NAFLD than in patients without it ($p=0.035$). The presence of NAFLD was independently related to the presence and extent of CAD.

Alper et al observed that patients with NAFLD had significantly higher scores for affected vessels (2.5 ± 0.9 vs. 1.0 ± 1.0) and for the severity of CAD as evaluated by the Gensini score (90.2 ± 40.0 vs. 36.4 ± 28.9) than patients without NAFLD ($p<0.001$).¹⁹ The presence of NAFLD, the degree of NAFLD and the patient's age were significantly correlated with the severity score of CAD.

Acikel et al found a prevalence of NAFLD of 32.4% (115/355), while CAD was present in 70.4% (250/355) of the patients.¹⁷ They concluded that the presence of steatosis in USG and its severity may represent an independent effect in both the presence and severity of CAD. Sun and Lu showed that the prevalence of CAD was 95.6% (518/542) and significant CAD was 70.5% (382/542), while that of NAFLD was 45.7% (248/542).²⁰

Patients with NAFLD had significantly higher vessel scores (1.5 ± 0.6 vs. 1.4 ± 0.8 , $p=0.001$) and more severe CAD scores. Wong et al found fatty liver prevalence of 58.2% (356/612) while significant CAD was observed in 76.0% (465/612) of subjects.²¹ Their study concluded that fatty liver is associated with CAD independently of other metabolic factors. However, fatty liver cannot predict cardiovascular mortality and morbidity in patients with established CAD.

Although the pathogenesis of NAFLD and CAD has not been fully elucidated, several explanations are present for the relationship between NAFLD and CAD. One widely accepted hypothesis implicates low-grade inflammatory conditions as key factors leading to hepatic steatosis and atherosclerosis.^{10,22}

Moreover, oxidative stress is presumed to play a role in NASH pathogenesis. Many investigators have studied additional mechanisms that might be associated with NAFLD, which are supported by the levels of various biomarkers, such as reactive oxygen species, adipocytokines (leptin and adiponectin), CRP and caspase generated cytokeratin.²³⁻²⁶ Present study demonstrates that NAFLD is an independent risk factor for angiographically proven CAD in a grade-dependent manner. Because the pathogenesis of NAFLD and CAD are not fully elucidated, future large-scale studies are needed to elucidate the precise mechanism of this relationship, to identify the mediators involved and to identify the measures which can be taken in order to

prevent occurrence of coronary artery disease in patients with NAFLD.

CONCLUSION

In this study the presence of ultrasonographic fatty liver and its severity had an independent effect on both the presence of CAD and its severity; and was not just one aspect of obesity and metabolic syndrome. NAFLD is recognized as part of metabolic syndrome and increased cardiovascular risk. Therefore a multidisciplinary approach is needed for the patients in order to control the related risk factors and monitoring for cardiovascular and liver complications. Lifestyle modification like increased physical activity or exercise, dietary control and weight reduction are the basic steps for all patients. The combination of lifestyle modification with pharmacologic treatment tailored to each individual risk factors needs to be considered.

From our current study it can be reasonably said that NAFLD may be an independent risk factor for developing arteriosclerosis. This hypothesis should be verified with larger studies in different population groups. Because the pathogenesis of NAFLD and CAD are not fully elucidated, large-scale studies are needed to elucidate the precise mechanism related to the development and progression of CAD in patients with NAFLD. Further research on primary prevention for coronary artery disease in NAFLD is needed.

Limitations of study

The first limitation was the lack of a histological confirmation of fatty liver. It is known that ultrasonography has good sensitivity and specificity in diagnosing fatty liver, but its sensitivity is reduced when hepatic fat infiltration on biopsy is <33%.

Secondly, although coronary angiography remains the widely used technique to assess severity of coronary artery disease, but coronary angiography is not able to identify the atherosclerotic plaques which are not causing luminal narrowing. Next is the inter-observer variation while reporting percentage narrowing of coronaries on angiogram. In order to reduce this inter-observer variability, another cardiologist also reviewed the angiogram. Lastly our study was a small study (n=150) and further large studies are required to verify the hypothesis. Moreover the prevalence of fatty liver and its degree of association may vary amongst different ethnic/population groups which further need to be studied.

ACKNOWLEDGEMENTS

Authors would like to acknowledge the immense support from the hospital staff and radiology technicians during the study.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Majumder B, Tandel V, Ghosh S, Chatterjee S. Association of non-alcoholic fatty liver disease and coronary artery disease. *Int J Res Med Sci* 2016;4:4359-64.