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Dr. Saurabh Bhardwaj
Resident, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan- 303121, India

Dr. Manju Pandey
Assistant Professor, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan-303121, India

Dr. Rakesh Thakuriya
Assistant Professor, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan-303121, India

Dr. JP Rishi
Professor and HOD, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan-303121, India

Correspondence:
Dr. Saurabh Bhardwaj
Resident, Department of Medicine, NIMS Medical College & Hospital, Jaipur, Rajasthan- 303121, India

A study of prevalence of non alcoholic fatty liver disease in patients of coronary artery disease and their clinical correlation

Saurabh Bhardwaj, Manju Pandey, Rakesh Thakuriya, JP Rishi*

Abstract

Background: Currently, the importance of non alcoholic fatty liver disease (NAFLD) and its relationship with coronary artery disease (CAD) is being increasingly recognized and this has stimulated an interest in the possible role of NAFLD in the development of atherosclerosis. Recent studies have reported the association of NAFLD with multiple classical and non-classical risk factors for cardiovascular disease (CVD). Non-alcoholic fatty liver disease (NAFLD) is a distinct hepatic condition characterized by abnormal fat accumulation in liver cells; histologically resembling alcohol induced liver damage. The overall prevalence of NAFLD in western countries varies from 15-40% and in Asian countries from 9-40%. In the present study, we shall determine the occurrence of Non-Alcoholic Fatty Liver Disease in patients with Coronary Artery Disease and to establish any clinical correlation between the two. **Methods:** The study was conducted over a period of 18 months. Patients coming to the NIMS hospital OPD/IPD with clinical history and physical examination- suggestive of CAD and confirmed by ECG, ECHO, Cardiac Biomarkers and wherever possible with Coronary Angiography. Diagnosis of NAFLD was done using ultrasonography. **Results:** Our study exhibited that patients having NAFLD presented with increased severity of clinical symptoms and the prevalence of NAFLD is more in CAD patients. **Conclusions:** The results from this study demonstrate the prevalence of NAFLD in patients of CAD and their clinical correlation. This study will help clinicians in devising treatment and designing preventive strategies for the aforementioned diseases.

Keywords: Non alcoholic fatty liver disease, Coronary artery disease.

INTRODUCTION

In 1980, Ludwig & colleagues coined the term 'Non Alcoholic Steatohepatitis' to describe a form of liver disease observed in middle age patients with abnormal liver biochemical results & histologic evidence of alcoholic hepatitis but no history of alcohol abuse.[1] Non Alcoholic Steatohepatitis (NASH) is believed to be a part of the spectrum of Non Alcoholic Fatty Liver Disease (NAFLD) which includes fatty liver, NASH & NAFLD associated cirrhosis.

In NAFLD, the main pathophysiological process involves increase in factor VIII and a reduction of protein C leads to the progression from steatosis to cirrhosis.[2] This imbalance is supposed to play a major role in the risk of cardiovascular disease and liver fibrosis.[3] It is diagnosed when fatty infiltration affects more than 5% of hepatocytes in the presence of less than 20 gm of alcohol intake per day without evidence of other causes of liver disease.[4] Prevalence of NAFLD varies according to the population studied & diagnostic criteria used. [5] Asian studies have reported NASH and NAFLD to be occurring at lower body mass index (BMI).[6-8]

Most important risk factor for NAFLD is insulin resistance. Other major risk factors include obesity, metabolic syndrome, type 2 DM, dyslipidaemia, starvation, Kwashiorker & Marasmus. Minor risk factors include cytotoxic drugs, metals and inborn errors of metabolism, extensive small bowel resection, inflammatory bowel disease & severe anaemia.[5]

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease

of an epicardial coronary artery (orarteries) sufficient to cause a regional reduction in myocardial bloodflow and inadequate perfusion of the myocardium supplied by the involved coronary artery.[9]

Risk factors of IHD include non modifiable& modifiable factors. Non modifiable factors are age, sex, family history, genetic factors & type A personality. Modifiable factors are hypertension, smoking, dyslipidaemia, diabetes, obesity, sedentary lifestyle & stress.[10-13]

MATERIALS AND METHODS

It is a prospective observational study,carried out in the Department of Medicine, National Institute of Medical Sciences(NIMS) Medical College and Hospital, Shobha Nagar, Jaipur, Rajasthan from January 2015 to June 2016. Majority of subjects belonged to rural areas located near the hospital. The study was conducted on patients coming to medical OPD and IPD of the hospital. The main aim of this study was to assess the prevalence of non-alcoholic fatty liver disease in coronary artery disease patients and to study the clinical correlation between non-alcoholic fatty liver disease and coronary artery disease.

Inclusion Criteria:Patients coming to the NIMS hospital OPD/IPD with clinical history and physical examination suggestive of Coronary Artery Disease and confirmed by Electrocardiogram(ECG), 2-Dimensional Echocardiography (2-D ECHO), Cardiac Biomarkers consisting of Troponins and CreatinePhospho Kinase(CPK-MB) and wherever possible with stress electrocardiography and/or Coronary Angiography.

Exclusion Criteria:

- Patients of heart disease other than CAD like valvular heart disease, cardiomyopathies, congenital heart disease, rheumatic heart disease and others.
- Patients with Liver malignancy, Nephrotic syndrome and vasculitis.
- Patients with history of alcohol consumption of more than 20gm/day.
- History of acute/chronic liver disease likes chronic hepatitis, HBsAg+, HCV, etc.
- History of intake of any hepatotoxic drugs viz.-steroids, valproic acid, oral contraceptive pills (OCPs), antiretroviral, anti-TB drugs, etc.

The sample size was determined on the basis of i) hospital statistics, ii) exclusion criteria and iii) cooperation and non-cooperation of the patients. A total of 311 patients were enrolled.

At the time of admission, after taking informed consent, patients were subjected to detailed clinical history, including presenting complaints, risk factors, family history and clinical examination. Various anthropometric measurements (including height, weight, waist circumference, hip circumference, BMI) and 12-lead ECG were recorded.

Coronary Artery Disease (CAD) was considered on the basis of clinical assessment for recent or past coronary artery disease; any event suggestive of recent or past disease, in the lack of available medical data, CAD was diagnosed and evaluated on the basis of clinical symptoms. The severity of cardiac symptoms was assessed using New York Heart Association (NYHA) classification for chest pain, dyspnea and palpitations, considered on the basis of electrocardiogram , stress electrocardiography(Treadmill test), 2D-ECHO showing any abnormal regional wall motion. Cardaic biomarkers viz; CPK-MB and Troponin-T.

Routine Hematological & Biochemical invstigations were also done.

Diagnosis of NAFLD

All patients were investigated for NAFLD by ultrasound (USG) of the abdomen to detect fatty changes in the liver, performed under the guidance of experienced radiosonologist(who was blinded to subjects' details) using a high-resolution B-mode ultrasonography system having an electric linear transducer mid frequency of 2–5 MHz. The scanning was done for atleast 10minutes or more and images obtained were recorded and photographed.

The standard criteria accepted by the American Gastroenterology association for *NAFLD* was used [14] i.e., the diagnostic accuracy of the following parameters:

(1) Parenchymal brightness -diffuse hyperechoicechotexture.

(2) Liver-to-kidney contrast - increased liver echotexture compared with kidneys.

(3) Deep beam attenuation.

(4) Bright vessel walls- vascular blurring.

(5) Gall bladder wall definition.

GRADING:

Grade 1: Slight diffuse increase in the fine echoes. Liver appears bright as compared to the cortex of the kidney. Normal visualisation of diaphragm and intrahepatic vessel borders.

Grade 2: Moderate diffuse increase in the fine echoes. Slightly impaired visualisation of the intrahepatic vessels and diaphragm.

Grade 3: Marked increase in the fine echoes. Poor or no visualisation of intrahepatic vessels, borders, diaphragm and the vessels.

RESULTS

A total of 311 patients were enrolled, out of which 221 were males and 90 were females. Average age of the patients was 59.2 years. Patients were categorized according to their symptoms. Chest pain was present in 157(50.48%) patients, dyspnea in 99 (31.8%), 38 (12.21%) had epigastric discomfort and palpitations in 16 (5.1%) patients. Each symptom with its severity was correlated and compared to the diseases, they were statistically significant *p* value=0.001.Cardiac symptoms were assessed and severity graded according to NYHA classification (Class I-IV). Ultrasonographically, amongst 152 patients of NAFLD, 21.7% (33) had grade I Fatty Liver, grade II fatty liver-53.9% (82) and grade III fatty liver-24.3% (37).

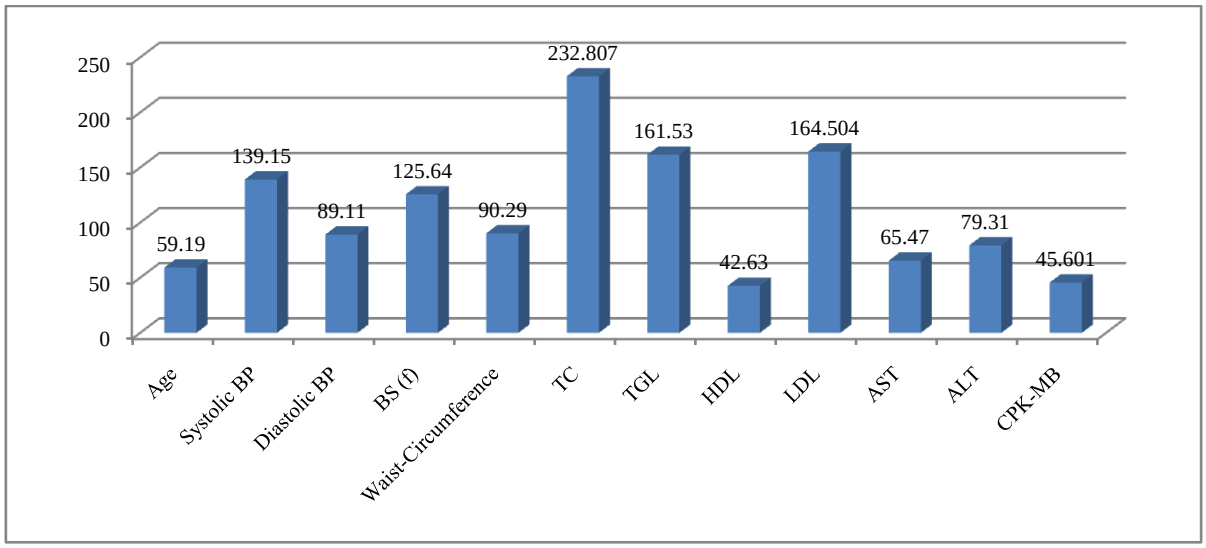
190 (61.1%) patients had ST elevation myocardial infarction (STEMI), 63 (20.25%) had non STEMI (NSTEMI) and 21 (6.7%) patients had normal ECG, 37(11.9%) of the patients had sinus tachycardia, LBBB, RBBB, etc. 2-D ECHO and cardic biomarkers (Troponins) were done. Of the total patients, 297 (95.5%) patients had regional wall motion abnormalities in 2-D ECHO. Troponin test was positive in 285 (91.6%) patients.

Mean systolic blood pressure (SBP) in the study was 139.15±17.54mm Hg and mean diastolic blood (DBP) pressure was 89.11±10.17 mm Hg, Mean Fasting blood glucose was 125.64±31.06 mg/dl. Average waist circumference was 90.29cms with standard deviation of 8.38 cms.

Table 1: demographic data of the study group N (%)

Gender	
Female	90 (28.9)
Male	221 (71.1)
USG (w/a)	
Fatty liver I	33 (10.6)
Fatty liver II	82 (26.4)
Fatty liver III	37 (11.9)
Normal	159 (51.1)
2-d echo	
LVH	14 (4.5)
RWMA+	297 (95.5)
Troponins	
-	26 (8.4)
+	285 (91.6)
Angiography	
*	278 (89.4)
Dvd	11 (3.5)
Svd	15 (4.8)
Tvd	7 (2.3)
Diagnosis	
Controls	159 (51.1)
NAFLD	152 (48.9)
TOTAL	**311**

Abbreviations: USG-ultrasonography, LVH-left ventricular hypertrophy, RWMA-resting wall motion abnormality, S/D/TVD-single/double/triple vessel disease, NAFLD-non alcoholic fatty liver disease; +/- present/absent



TC-total cholesterol, TGL-triglycerides, H/LDL-high/low density lipoprotein, AST/ALT-aspartate transaminase/alanine transaminase, CPK-creatinine phosphokinase

Figure 1: Descriptive data of study. Means of variables

Table 2: Comparison between USG (w/a) and diagnosis

		USG				**Total**
Diagnosis		fatty liver I	fatty liver II	fatty liver III	Normal	
Controls	N	0	0	0	159	159
	%	0.0%	0.0%	0.0%	51.1%	51.1%
NAFLD	N	33	82	37	0	152
	%	10.6%	26.4%	11.9%	0.0%	48.9%
Total	N	33	82	37	159	311

chi square test: Df=3 p<0.001(S)

Table 3: Comparison of risk/severity CAD

	NAFLD N=152(48.9%)	**Controls** N=159(51.1%)
ECG(STEMI)	83(54.6%)	107(67.3%)
2-D ECHO (RWMA+)	142(93.4%)	155(51.1%)
ENZYMES/ BIOMARKERS	140(92.1%)	145(91.3%)

DISCUSSION

In our study, of 311 CAD patients, the prevalence of NAFLD was seen in 152(48.9%) cases. This is similar to the studies conducted by Zafar KS *et al* (46%), Chan WK *et al* (24.7%), Ling Sun and Shuzeng Lu (45.8%), Mohan *et al* (32%), Ling YC *et al* (29.5%).[15-19]

Table 4: Comparing prevalence of NAFLD in various other recent studies

Study	**Year**	**% of NAFLD in CAD**
Zafar KS *et al*	2016	46%
Chan WK *et al*	2014	24.7%
Ling Sun and Shuzeng Lu	2011	45.8%
Mohan *et al*	2009	32%
Ling YC *et al*	2005	29.5%
Our study	2016	48.9%

NAFLD can occur at all ages including childhood, though the highest prevalence is described in those between 40– 50 years of age.[20] In our study, mean age of NAFLD was 48.84±6.73yrs, with minimum age of 35 years and maximum of 77years, which is in accordance to a study by Duseja A and Singh SP *et al*. (mean age 39.08 +/- 12.3 years).[20,21] This was statistically significant (p=0.001).

In the present study, NAFLD was seen in 24.1% males and 11.3% females. These finding were similar to Duseja A and Singh SP *et al*. [males (26.9%) than in females (13.8%)].[20,21] Many authors such as Bahceciologlu *et al*. and Weston *et al*. have reported that non alcoholic fatty liver has increased chances in males compared to females.[22,23] However, Malnick SD *et al.*, NAFLD were more common in females.[24]

An ultrasound based study was conducted by Majumdar B *et al.* to find out association of NAFLD and CAD, findings of which were consistent with that in our study.[25] There were 10.6% cases of Grade I fatty liver, 26.4% cases of Grade II fatty liver and 11.9% patients of Grade III fatty liver.

Clinically, we correlated the patients of NAFLD with symptoms of CAD and severity of clinical picture was evaluated with help of history, physical examination, Electrocardiogram (ECG), 2-D Echocardiography (2D ECHO) and cardiac biomarkers. Severity of symptoms was assessed using New York Heart Association (NYHA) classification for chest pain, dyspnea and palpitations.

Table 5: Comparison of clinical severity of CAD with NAFLD

	Chest Pain	**Dyspnea**	**Palpitaions**	**p Value**
NAFLD	76(48.5%)	40 (40.4%)	8(50%)	0.001 (S)
Controls	81(51.5%)	59 (59.6%)	8(50%)	0.001 (S)
Total	157	99	16	

Table 6: Comparing investigative findings of CAD with NAFLD

	NAFLD	**Controls**
ECG (STEMI)	83(54.6%)	107(67.3%)
2-DECHO (RWMA+)	142(93.4%)	155(51.1%)
BIOMARKERS	140(92.1%)	145(91.3%)

Our study showed that patients who had NAFLD presented with severe symptoms. 48.5% patients had Class IV angina, 54.6% patients had acute STEMI on ECG, 92.1% had raised cardiac biomarkers and 93.4% had positive 2D ECHO findings of regional wall motion abnormalities. These results were statistically significant. 28 patients with NAFLD also presented with epigastric discomfort. 49.5% of NAFLD patients had class I-II NYHA grade of symptoms, 28 patients also had epigastric discomfort. These findings were also statically significant (p=0.001).

Tagher G *et al.* in his landmark paper in 2007 tried to establish the link between cardiovascular disease and non alcolic fatty liver with metabolic syndrome. In this findings were suggestive of more complex picture of intertwined relationships between NAFLD, MS and CAD because of common molecular mediators.[26]

In a cross sectional study, Ioannou *et al.* compared the 10 year risk of cardiovascular events based on the Framingham risk score in patients with fatty liver disease & found that NAFLD is an independent risk factor for CAD.[27]

CONCLUSION

The presence of NAFLD is associated with more severe CAD, requiring that patients with NAFLD be investigated for the presence of CAD.

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