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A study on association between non alcoholic fatty liver disease and ischemic heart disease in a tertiary care hospital

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is often an incidental finding in a large subset of Indian population, who because of their sedentary life style are more prone to ischaemic heart disease (IHD). This study was aimed at determining the association between NAFLD and IHD, with and without traditional risk factors for ischemic heart disease and to determine the relationship between the ischemic heart disease and severity of NAFLD.

Materials and methods: It was a prospective comparative study among patients who got admitted in General Medicine ward or visited OPD of our institute from February 2020 to September 2021. Patients selected were divided into two groups- Study arm included patients with clinical features and investigations suggestive of ischemic heart disease. Control arm patients were age (+/-5years) matched people coming to hospital with infections/ illness not affecting liver, and without any history of ischaemic heart disease. We did check for NAFLD in these patients and tried to determine the association with IHD.

Results: Significant number of patients (68.5%) had NAFLD in the study arm patients who were admitted for IHD in comparison to only 33.3% (p value-<0.001). Study arm had 31% patients with grade 2 or more NAFLD in comparison to 17% of control arm patients. There was significant association present between IHD and Severity of NAFLD (p value<0.05).

Conclusion: NAFLD should be considered a risk factor of IHD, and should prompt clinicians to search for other cardiovascular risk factors and intervene at earliest.

Keywords: non-alcoholic; fatty liver disease; ischaemic; heart disease

Introduction

Non-alcoholic fatty liver disease (NAFLD) includes a spectrum of disorders ranging from the simple fatty liver to non-alcoholic steatohepatitis causing fibrosis and subsequently leading to cirrhosis in patients who consume little or no alcohol [1, 2]. Ischemic heart diseases are the diseases of heart caused by Impedance or blockage of one or more arteries that supply blood to the heart.

NAFLD is often an incidental finding in a large subset of Indian population, who because of their sedentary life style are more prone to cardiovascular disease (CVD). This incidental finding of NAFLD often precedes the occurrence of traditional cardiometabolic risk factors (Diabetes Mellitus, Hypertension and Dyslipidemia). The intimate relationship between the liver and

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coronary heart disease likely stems from the central role the liver plays in glucose and lipid metabolism. Development of NAFLD is associated with increased production and secretion of large triglyceride-laden very low-density lipoprotein (VLDL) particles from the liver into circulation which leads to the formation of highly atherogenic low density lipoprotein (LDL) particles. Hepatic production of pro-inflammatory factors, vasoactive and thrombogenic molecules further contributes to ischaemic heart diseases and significant morbidity and mortality in patients with NAFLD [3-7].

Even in the absence of a significant relation with cardio vascular mortality, CVD is still undoubtedly increased in NALFD patients compared to controls, supporting the many convincing data that NAFLD independently contributes to (sub)clinical CVD [8, 9]. However, the optimal means of risk-stratifying and reducing CVD morbidity and mortality in patients with NAFLD remains unknown.

So, in this study we aimed to determine the association between non-alcoholic fatty liver disease and ischemic heart disease, with and without traditional risk factors for ischemic heart disease and to determine the relationship between the ischemic heart disease and severity of non-alcoholic fatty liver disease.

Materials and methods

It was a prospective comparative study among patients who got admitted in General Medicine ward or visited General Medicine OPD of our institute within February 2020 to September 2021.The study was initiated after getting the clearance from institutional ethical committee.

All patients admitted in ward or visiting the OPD of our institute fulfilling the diagnostic criteria for ischemic heart disease with the age18 years or above were included for study arm. Patients coming to hospital with infections/ illness not affecting liver, age (+/- 5 years) of cases and without any history of myocardial infarction or known case of liver disease were included for control arm.

We excluded the patients with significant alcohol intake (>30gm in males, >20gm in females) and patient with known acute/ chronic liver disease.

Study technique

Patients selected for the study were divided into two groups i.e., first group, study arm included patients who got admitted in our institute with clinical features and investigations suggestive of ischemic heart disease and fulfilling the inclusion criteria. Second group, control arm patients were age (+/-5years) matched people coming to hospital with infections/ illness not affecting liver, and without any history of myocardial infarction or any ischaemic heart disease.

After taking informed consent, patients were subjected to detailed clinical history, including risk factor assessment for ischemic heart disease, clinical examination and various anthropometric measurements (including height, weight, waist circumference, hip circumference, BMI). After that investigations like ECG, 2D echocardiography, blood for cardiac ischemia markers and liver function tests were done. Ultrasonography of abdomen for presence and severity of NAFLD was done. Fatty liver index was calculated for severity of NAFLD. The standard criteria accepted by the American Gastroenterology Association for NAFLD was used for diagnosis of NAFLD.

We assessed the relation between NAFLD and ischaemic heart diseases by statistical measures.

Statistical analysis

Data were analyzed and compared according to appropriate statistical tests using SPSSv.20 software and Microsoft word-excel. For numerical variables data were summarized as mean and standard deviation and as count and percentages for categorical variables. All tests were analyzed with a 95% confidence interval. Statistical significance was accepted at the level of $p<0.05$.

Results

108 patients were enrolled in this study, 54 patients were included in study and control arm each. Mean age (in years) of patients were 58.90 ±6.78 and 59.31±7.24 in study and control arm respectively. 63.8% patients were male with a Male:Female ratio of 1.7:1 (Table 1).

Table 1: Baseline characters of study population.

Characteristics		*Arm of the study*		*P value*
		Study arm (n=54)	*Control arm (n=54)*	
Mean age of patients (in years)		58.90±6.78	59.31±7.24	0.440
Gender	Male	37	32	0.614
	Female	17	22	
	Total	54	54	

Amongst the participants of the study, 45.37% had hypertension but study arm had more patients with hypertension than control arm (59.26% vs 31.48%).

Similarly patients with smoking habits (53.70% vs 25.93%), diabetes mellitus (62.96% vs 33.33%) and metabolic syndrome (75.93% vs 31.48%) was also higher in study arm (Table 2).

Table 2: Distribution of risk factors of IHD among study population.

Risk factors		*Study arm*		*Control arm*		*Total*	
		N(54)	*Percentage (%)*	*N(54)*	*Percentage (%)*	*N(108)*	*Percentage (%)*
Hypertension	Present	32	59.26	17	31.48	49	45.37
	Absent	22	40.74	37	68.52	59	54.63
Smoker	Yes	29	53.70	14	25.93	43	39.81
	No	25	46.30	40	74.07	65	60.19
Diabetes Mellitus	Present	34	62.96	18	33.33	52	48.15
	Absent	20	37.04	36	66.67	56	51.85
Metabolic syndrome	Present	41	75.93	17	31.48	58	53.70
	Absent	13	24.07	37	68.52	50	46.30

As per the clinical parameters concerned, study arm patients had significantly higher systolic (136.15 ± 17.95 vs 125.91 ± 9.82, p value-<0.001) and diastolic BP (82.93 ± 8.44 vs 78.93 ± 6.59, p value-0.007) than control arm. Except mean weight and hip circumference all other clinical parameters like BMI, waist circumference, waist hip ratio were significantly more in study arm (Table 3).

Table 3: Distribution of clinical parameters among study population.

Clinical parameters	*Mean±SD*		*p value*
	Study arm (N=54)	*Control arm (N=54)*	
Systolic BP (mm Hg)	136.15 ± 17.95	125.91 ± 9.82	<0.001
Diastolic BP (mm Hg)	82.93 ± 8.44	78.93 ± 6.59	0.007
Weight (Kg)	65.2 ± 5.72	63.93 ± 6.02	0.260
Height (cm)	165.35 ± 7.91	168.81 ± 6.1	0.012
BMI	23.84 ± 1.14	22.39 ± 1.19	<0.001
Waist circumference (cm)	89.26 ± 4.69	86.91 ± 5.14	0.014
Hip circumference (cm)	102.02 ± 3.14	102.74 ± 3.87	0.289
Waist hip ratio	0.87 ± 0.03	0.85 ± 0.03	<0.001

Among the blood parameters CK-MB (126.74 ± 39.7 vs 13.8 ± 4.58, p value<0.001), total cholesterol (201.85 ± 18.91 vs 187.44 ± 16.97, p value<0.001), LDL cholesterol (116.37 ± 16.52 vs 102.02 ± 16.36,p value<0.001), triglyceride profile (189.61 ± 35.79 vs 157.13 ± 27.89, p value-<0.001) was significantly worse in study arm population than control arm (Table 4).

Among the hypertensive patients of the study group, 10 (31.25%) did not have NAFLD and 22 (68.75%) had NAFLD whereas among the hypertensive patients of the control group, 11 (64.71%) did not have NAFLD and 6 (35.29%) had NAFLD. Also, there was a significant association between study arm and NAFLD among hypertensive patients (p value-0.048).

Discussion

The conducted study was a hospital based study, in this study 54 patients each from study and control arms were studied. Overall, the mean age of the participants was 59.14 years. The mean age of participants in case and control group was comparable (p value-0.44) i.e., 58.98 years in study and 59.31 years in control arm. These results are similar to the study by Montemezzo et al. where mean age was 59.7 years [9]. On the other hand, study by Ajmal et al. showed the mean age of the patients was 54.73 ± 11.7 years which was lower as compared to mean age of our study group [10].

Table 4: Distribution of biomarker values among study population.

Biomarker	*Mean±SD*		*p value*
	Case	*Control*	
Haemoglobin (g/dl)	12.22 ± 2	13.11 ± 1.78	0.216
WBC (X10*3/uL)	8.79 ± 2.57	9.43 ± 3.2	0.258
Platelet count (lakhs/uL)	2.12 ± 0.67	2 ± 0.71	0.365
Total Bilirubin (mg/dl)	0.77 ± 0.27	0.82 ± 0.22	0.353
SGPT (IU/L)	46.33 ± 14.50	39.37 ± 10.54	0.006
SGOT (IU/L)	42.96 ± 10.03	38.77 ± 7.80	0.025
Alkaline phosphate (IU/L)	105.59 ± 23.85	94.13 ± 18.05	0.005
Serum albumin (g/dl)	3.88 ± 0.4	4.08 ± 0.33	0.005
GGT (U/L)	34.56 ± 6.71	26.69 ± 7.48	<0.001
CK-MB (IU/L)	126.74 ± 39.7	13.8 ± 4.58	<0.001
Total cholesterol (mg/dl)	201.85 ± 18.91	187.44 ± 16.97	<0.001
LDL cholesterol (mg/dl)	116.37 ± 16.52	102.02 ± 16.36	<0.001
HDL cholesterol (mg/dl)	47.93 ± 7.04	54.3 ± 6.76	<0.001
Triglyceride (mg/dl)	189.61 ± 35.79	157.13 ± 27.89	<0.001
Serum creatinine (mg/dl)	1.38 ± 0.42	1.18 ± 0.34	0.006
FBS (mg/dl)	130.67 ± 33.48	106.74 ± 28.18	<0.001
HbA1c (%)	6.69 ± 0.89	6.06 ± 0.73	<0.001

Majority of patients (68.5%) had NAFLD in the study arm patients who were admitted for IHD in comparison to only 33.3% patients in control arm. This difference was statistically significant (p value-<0.001) (Table 5).

Table 5: Distribution of NAFLD among study participants and association between NAFLD and IHD.

Non-alcoholic fatty liver disease	*Study(N=54)*	*Control (N=54)*	*Total(N=108)*	*p value*
Present	37(68.5%)	18(33.3%)	55(50.9%)	<0.001
Absent	17(31.5%)	36(66.7%)	53(49.1%)	

Study arm had 31% patients with grade 2 or more NAFLD in comparison to 17% of control arm patients. There was significant association present between IHD and Severity of NAFLD by USG grading (p value<0.05) (Tables 6&7).

Table 6: Association of severity of NAFLD with IHD.

NAFLD grade	*Study Arm*		*Control Arm*		*Total*		*p value*
	N(54)	*Percentage (%)*	*N(54)*	*Percentage (%)*	*N(108)*	*Percentage (%)*	
0	17	31.48	36	66.67	53	49.07	<0.05
1	20	37.04	16	29.63	36	33.33	
2	[2]	27.78	2	3.70	17	15.74	
3	2	3.70	0	0	2	1.85	

In our study, number of male patients was approximately twice as compared to number of females patients. Out of total 108 patients, 74 (68.51%) were male and 34 (31.48%) were female. In a study by Bhardwaj et al the distribution of male and female patients were similar (71% vs 39%) [11]. Ajmal et al. in their study showed that, number of male cases was slightly higher than females than our study (80.8%malesand 19.2% females) [10].

Approx three-fourth of the total number of participants were from the age group between 50-70 years (38% between 51 to 60 and 33.3% in 61 to 70 group). Approx 2 % of the study participants were below 40 years and 10.2% were above 70 years.

Table 7: Association of IHD with NAFLD in presence of risk factors for IHD.

Risk factors	*Patient type*	*NAFLD*				*p value*
		Yes		*No*		
		N	*Percentage (%)*	*N*	*Percentage*	
Hypertension	Case	22	68.75	10	31.25	0.048
	Control	6	35.29	11	64.71	
Smoking	Case	18	62.07	11	37.93	1
	Control	8	57.14	6	42.86	
Diabetes	Case	29	85.29	5	14.71	0.290
	Control	13	72.22	5	27.78	
Metabolic syndrome	Case	34	82.90	7	17.10	1
	Control	14	82.40	3	17.60	
Abdominal obesity (Waist/ Hip ratio)	Case	23	100	0	0	0.017
	Control	3	75	1	25	
Abdominal obesity (Waist circumference)	Case	37	75.50	12	24.50	0.593
	Control	17	60.70	11	39.30	
LDL	Case	12	100	0	0	0.073
	Control	3	60	2	40	
HDL	Case	14	93.30	1	6.70	0.201
	Control	1	100	0	0	
Triglycerides	Case	20	90.90	2	9.10	1
	Control	4	100	0	0	

In our study, out of the total 108 patients, 50.93 % had fatty liver, as detected by USG. This is similar to the study from coastal south India which reported the overall NAFLD prevalence rate of 49.8% [12-14]. Prospective Urban Rural Epidemiology (PURE) cohort study in north India reported similar prevalence of NAFLD (53.7%) in urban communities [15]. Overall one third of patients (33.33%) had fatty liver Grade 1, 15.74% had Grade 2 and 1. 85% had Grade 3 fatty liver.

In the study by Agaç et al. 43% had fatty liver Grade 1, 32.5% had Grade 2 and 5% had Grade 3 fatty liver, similar to our study[16]. Montemezzo et al. in their study showed, 55.2% participants had NAFLD including 23.6%with grade III fatty liver, which is not consistent with our study [9].

More than twice patients in the control arm did not have fatty liver (66.67%) as compared to cases (31.48%). Higher grades of fatty liver were found more in study arm as compared to control group. In the case group, 37.04% had USG Grade 1, 27.78% had USG Grade 2 and 3.70% had USG Grade 3, while in the control group, 29.63% had USG Grade1 and 3.70% had USG Grade 2.

This difference between cases and control is consistent with the study by Montemezzo et al, which reported that in severe CAD, 60.5% were associated with NAFLD, and 83.3% of these patients had severe CAD and NAFLD grade III [9].

Amongst the 108 patients, 45.37% were hypertensive, 39.81% were smoker, 48.15% had diabetes mellitus and 53.70% had metabolic syndrome. This proportion was significantly higher in study group as compared to control group. 59.26% in study arm vs 31.48% in control arm were hypertensives; 53.7% in study arm were smoker as compared to 25.93% in control, 62.9% in study group had diabetes mellitus vs 33.33% in control group.

Agaç et al. reported higher prevalence of metabolic syndrome (64.6%) in NAFLD patients and lower (33.3%) in non-NAFLD patients [16]. According to current data, the prevalence of hypertension in Indian adults is 29.8% (urban areas 33.8%). Another study conducted among residents of urban areas of east Delhi-The Delhi Urban Diabetes Survey (DUDS) demonstrated a strikingly high prevalence of diabetes (18.3%).

This difference between our study and others could be because of small sample size, and higher prevalence of risk factors amongst the study group i.e. IHD and also because of admission bias.

As per the clinical parameters concerned, study arm patients had significantly higher systolic (136.15 ± 17.95 vs 125.91 ± 9.82, p value-<0.001) and diastolic BP (82.93 ± 8.44 vs 78.93 ± 6.59, p value-0.007) than control arm. Except mean weight and hip circumference all other clinical parameters like BMI, waist circumference, waist hip ratio were significantly more in study arm (Table 3).

Bhardwaj et al showed Mean systolic blood pressure (SBP) in the study group was 139.15±17.54 mm Hg and mean diastolic blood (DBP) pressure was 89.11 ± 10.17 mm Hg [11].

This variation could be due to small sample size, presence of multiple cardiovascular risk factors, treatment for risk factors and component of metabolic syndrome more in cases as compared to control.

The difference in mean values was statistically significant (p value less than 0.05) among the two groups, i.e., study and controls for all clinical parameters, except weight and hip circumference.

The mean (±SD) values of platelet count, SGPT, SGOT, alkaline phosphate, GGT, CK-MB, total cholesterol, LDL cholesterol, triglyceride, creatinine, FBS, HbA1c were higher in study as compared to control, while for haemoglobin, WBC, total bilirubin, S. albumin, HDL and cholesterol, mean and SD values in control were higher.

In our study, the mean values of SGPT was 46.33±14.50 IU/L in cases and 39.37 ± 10.54 IU/L in control (p value = 0.006); while the mean values of SGOT was 42.96 ± 10.03 IU/L in cases and 38.77 ± 7.80 IU/L in control (p value =0.025).

In Bhardwaj et al. study mean SGPT value was 79.31 IU/L and mean SGOT 65.47 IU/L [11]. In Ajmal et al. study mean SGPT value was 20.29±11.9 IU/L and mean SGOT 21.17±10.8IU/L [10].

The mean values of SGPT and SGOT in our study lie between those of above two studies. The variation could be because of laboratory and reagent variation.

In our study, total cholesterol (201.85 ± 18.91 vs 187.44 ± 16.97, p value<0.001), LDL cholesterol (116.37 ± 16.52 vs 102.02 ± 16.36, p value<0.001), tri-glyceride profile (189.61 ± 35.79 vs 157.13 ± 27.89, p value-<0.001) was significantly worse in study arm population than control arm (Table 4).

In Bhardwaj et al**.** study Mean values of total cholesterol was 232.80 mg/dl, LDL cholesterol was 164.50 mg/dl, HDL cholesterol was 42.63 mg/dl and triglyceride was 161.53mg/dl [11].

In Ajmal et al. study, the Mean values of HDL cholesterol was 38.19 ±9.6 mg/dl and triglyceride was 151.50±63.4mg/dl [10].

This variation could be because of small sample size, patients already on treatment for dyslipidemia and confounding effect of metabolic syndrome.

Association between NAFLD and IHD

Among the study group two-thirds patients (68.52%) had fatty liver, similar finding was noted In Ajmal et al. study where NAFLD was identified in 69.2% patients [10].

NAFLD was present in more than two times in patients of study group as compared to control group (68.52% vs 33.33%). A significant association was found to be present between NAFLD and IHD (p value <0.001).

This finding was consistent with the results and conclusions of a number of studies done earlier [17, 18].

Association of severity of NAFLD by USG grading with IHD

Study arm had 31% patients with Grade 2 or more NAFLD in comparison to 17% of control arm patients. There was significant association present between IHD and severity of NAFLD by USG Grading (p value<0.05) (Table 6).

Association of severity of NAFLD by USG Grading with IHD was found to be significant (p value<0.05). Similar association was found in Alper et al and Acikel et al study according to Vilar et al [19-21].

Association of IHD with NAFLD in presence of risk factors for IHD

Among the hypertensive patients of the study group, 68.75% had NAFLD whereas among the hypertensive patients of the control group, 35.29% had NAFLD. A significant association was among study arm population and NAFLD in hypertensive patients (p value =0.048).

Among the patients with abdominal obesity (W/H ratio) in the study group, 100% had NAFLD, whereas among

the abdominal obese patients of the control group, 75% had NAFLD. Also, there was significant association among study arm patients and NAFLD presence among abdominal obese patients by (W/H Ratio) (p value =0.017).

Overall, a significant association (p value <0.05) was found between IHD and NAFLD in hypertensive patients and patients with abdominal obesity by Waist-Hip ratio, while our study failed to determine any significant association between IHD and NAFLD in presence of other risk factors for IHD such as smoking, diabetes mellitus, metabolic syndrome, abdominal obesity (waist circumference), obesity by BMI, high LDL, low HDL and high triglyceride level (Table 7).

These results are consistent with Alexander et al. study where they concluded that the diagnosis of NAFLD appears not to be associated with AMI after adjustment for established cardiovascular risk factors [22].

However, these result are in contrast to Arslan et al study where on logistic regression analysis, the presence of NAFLD independently increased the risk for CAD, [odds ratio (OR), 95% confidence interval (CI): 6.73 (1.14-39.61); P=0.035]; despite factoring in the other risk factors for CAD and the components of metabolic syndrome [17].

Limitations: The study has been done in a single tertiary care hospital and sample size was small. Study and controls were taken from hospital, so increased chances for admission rate bias. Fatty liver diagnoses by ultrasonography have limited sensitivity and specificity. Fatty liver diagnosis was not confirmed by gold standard liver biopsy. There is a possibility that patients in both study and control were on treatment for cardiovascular risk factors before this study. That can modify the clinical and laboratory findings.

Conclusion

The presence of NAFLD is associated with the presence of ischemic heart disease. Increasing severity of NAFLD as determined by USG grading and fatty liver index (FLI) is associated with increased risk for IHD. NAFLD should be considered a risk factor of IHD, and presence of NAFLD should prompt clinicians to search for other cardiovascular risk factors and intervene at earliest.

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Conflicts of interest

Authors declare no conflicts of interest.

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