

## ASSOCIATION OF NON ALCOHOLIC FATTY LIVER DISEASE WITH CORONARY ARTERY DISEASE

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### Contribution

MSJ, ZUZ conceived the idea and drafted the manuscript. SH collected and analyzed the data. AMJ, SBK and MI critically reviewed the manuscript. All authors contributed significantly to submitted manuscript.

### All authors declare no conflict of interest.

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## ABSTRACT

**Objective:** To determine the association between non alcoholic fatty liver disease and coronary artery disease.

**Methodology:** This cross sectional study was conducted from July to December 2016, in Cardiology Unit, Lady Reading Hospital. By using non probability consecutive sampling, patients of all age groups and either gender, presenting to cath lab for coronary angiography, indicated for angina CCS III, were included in the study. All patients fulfilling inclusion and exclusion criteria were subjected to screening for NAFLD by using ultrasonography. Patients were classified into having no, mild, moderate and sever NAFLD. Correlation between NAFLD and CAD, confirmed on cath was done using chi square test.

**Results:** Total of 370 patients with mean age of  $55.36 \pm 10.07$  years were enrolled in the study, of which 44.6% were females. Known risk factors for CAD like diabetes mellitus, hypertension, and smoking were present in 63.5%, 64.9% and 23% respectively. About 28.4% of patients had no NAFLD, 28.4% had mild, 28.4% had moderate and 14.4% had sever NAFLD, 12.2% had no CAD while mild, moderate and sever disease was present in 36.5%, 31.1% and 2.3% respectively. By using Chi square test relation between NAFLD and CAD was calculated and came out to be 285.5 ( $p < 0.000$ ). NAFLD also increased the POR of having by 2.9 times with  $p < 0.000$ .

**Conclusion:** NAFLD can be considered as an independent risk factor with CAD and increases the odds of having CAD.

**Key Words:** Non alcoholic fatty liver disease, Coronary artery disease, Canadian classification scale, Cardiac catheterization.

## INTRODUCTION

NAFLD is found in individuals consuming little or no alcohol. Most of the patients remain unaware of their disease.<sup>1</sup> Individuals between 30 to 60 years mostly suffer from NAFLD, however, frequency is increasing among adolescents and obese children.<sup>2</sup> Along with other risk factors like diabetes mellitus, hypertension, deranged lipid profile and insulin resistance, NAFLD constitutes metabolic syndrome.<sup>3,4</sup> Since its close association and potential contribution to the CAD, NAFLD gained significant importance in recent years.<sup>5,6</sup> Many studies suggest that NAFLD is associated with 2-5 fold increase in CAD risk.<sup>7,8</sup> Almost 15-30% of general population is effected from NAFLD.<sup>9</sup> Many dietary, genetic and life style factors along with obesity related ectopic fat increases the progression of NAFLD.<sup>19</sup> The exact pathogenesis of NAFLD is not completely understood. However, many factors like oxidative stress, insulin resistance, subclinical inflammation with raised CRP, fibrinogen etc, adiponectin, myocardial lipotoxicity, atherogenic dyslipidemias, post prandial lipemias, procoagulation and hypo fibrinolysin play role in the development of NAFLD and also CAD.<sup>10-18</sup> Our this study mainly focuses on the association of NAFLD and CAD.

## METHODOLOGY

This was a cross sectional observational study carried out from July to December, 2016 in Cardiology unit, Lady Reading Hospital. Patients of both sexes and ages between 20 years to 65 years who presented to cath lab for coronary angiography, indicated for angina CCS III, were enrolled in the study. Non probability consecutive sampling was used. All patients with history of alcohol consumption, history of chronic liver diseases, Hepatitis B, Hepatitis C, HIV, glycogen storage diseases, systemic diseases causing steatosis, drug use causing steatosis, pregnancy, cor pulmonale and previous cardiac diseases were excluded from the study to minimize biase. Written informed consent was taken from all patients before enrollment in the study.

All the patients were subjected to detailed history taking followed by complete physical examination. Necessary blood tests were performed to fulfill the inclusion and exclusion criteria. Patients who fulfilled the inclusion criteria were subjected to screening for NAFLD by using ultrasonography, done by senior consultants. Ultrasound abdomen was performed by using Toshiba CD70 machine and patients were classified into four sub groups i.e; no NAFLD, mild NAFLD, moderate NAFLD and severe

NAFLD. The severity of CAD was assessed in cardiac catheterization lab during angiography performed by experienced interventional cardiologist on Axiom artis Siemens 2005 machine. Again patients were classified as having no CAD, mild CAD, moderate CAD and sever CAD.

All the information was recorded in a pre designed Performa. Data was analyzed in SPSS version 20.0. Continuous variables were recorded in mean  $\pm$  SD. Categorical variables were recorded in frequencies and percentages. Correlation between NAFLD and CAD was done by using Chi square test. Odds ratios were calculated by using binary logistic regression model.

Mild NAFLD was defined as patients having Increased hepatic echogenecity with visible periportal and diaphragmatic echogenecity on ultrsonography. Moderate NAFLD was defined as patients having Increased hepatic echogenecity with imperceptible periportal echogenecity without obscuration of diaphragm on ultrsonography. Severe NAFLD was defined as patients having Increased hepatic echogenecity with imperceptible periportal echogenecity and obscuration of diaphragm on ultrsonography. Mild CAD: Patients having 60% or more than 60% stenosis of a single coronary artery  $>1.5$ mm in diameter on cardiac cath studies were labeled as mild CAD. Moderate CAD: Patients having 60% or more than 60% stenosis of a two coronary artery  $>1.5$ mm in diameter on cardiac cath: studies were labeled as moderate CAD. Severe CAD: Patients having 60% or more than 60% stenosis of a three or more coronary artery  $>1.5$ mm in diameter on cardiac cath studies were labeled as sever CAD.

## RESULTS

A total of 370 were enrolled in the study with a mean age of  $55.36 \pm 10.07$  years with 44.6% of the enrolled patients were females and 55.4% were males. Baseline characteristics of all patients enrolled in the study are given in table 1.

Correlation between NAFLD and CAD was done using Chi square test and results came out to be 285.536 with a p value of  $p=0.000$ . Number of patients in each category are given in table 2.

By using logistic regression model POR were calculated and odds of havig CAD increased by 2.9 times with NAFLD (table 3). With increasing NAFLD risk of having CAD also increased.

**Table 1: Demographic Characteristics of Study Population (n=370)**

Variable	Mean	SD	Frequency (n)	Percentage (%)
<b>Age</b>	55.36	10.07	-	-
<b>Gender</b>				
Female	-	-	165	44.6%
Male	-	-	205	55.4%
<b>Diabetes Mellites</b>				
Yes	-	-	235	63.5%
No	-	-	135	36.5%
<b>Hypertension</b>				
Yes	-	-	240	64.9%
No	-	-	130	35.1%
<b>Smoking</b>				
Yes	-	-	85	23%
No	-	-	285	77%
<b>NAFLD</b>				
No	-	-	105	28.4%
Mild	-	-	105	28.4%
Moderate	-	-	105	28.4%
Sever	-	-	55	14.9%
<b>CAD</b>				
No	-	-	45	12.2%
Mild	-	-	135	36.5%
Moderate	-	-	115	31.1%
Sever	-	-	75	20.3%

CAD= Coronary artery disease, NAFLD= Non alcoholic fatty liver disease

**Table 2: Frequency of NAFLD and CAD (n=370)**

		CAD				Total
		No	Mild	Moderate	Sever	
NAFLD	No	15	65	20	5	105
	mild	15	60	30	0	105
	moderate	15	10	60	20	105
	Severe	0	0	5	50	55
Total		45	135	115	75	370

CAD= Coronary artery disease, NAFLD= Non alcoholic fatty liver disease

**Table 3: Association of CAD with NAFLD (n=370)**

NAFLD	CAD		
	POR	Exp(B)	p-value
	2.9	2.52	0.000
Mild NAFLD	0.48	1.86	0.016
Moderate NAFLD	2.25	2.21	0.000
Sever NAFLD	2.92	2.54	0.000

## DISCUSSION

NAFLD starts a pro inflammatory cascade that is highly pathogenic.<sup>20</sup> This pro inflammatory cascade sets up atherosclerosis and malignancies.<sup>21</sup> In our study NAFLD is more stronger predictor of CAD than age, sex and hypertension. NAFLD basically promotes vascular endothelial dysfunction. Studies have shown that normoglycemic, NAFLD patients have decreased brachial artery endothelial flow mediated vasodilation in comparison to healthy individuals. This decrease is directly proportional to NAFLD severity and is independent of other known cardiac risk factors.<sup>22,23</sup> In another study positive correlation is found between NAFLD and carotid artery intimal thickness, independent of known cardiac risk factors.<sup>24</sup> Patients of NAFLD have increased plasma concentrations of inflammatory and oxidative stress markers, that contribute to the severity of CAD.<sup>25</sup> However, so far it has been unclear whether, the treatment of NAFLD will prevent CAD development or not. But based on the strong association between NAFLD and CAD we suggest the important steps for the prevention of CAD in patients of NAFLD.

First, life style modification should be advised including diet modification, exercise, behavior and work environment modification. A goal of >10% weight reduction is beneficial.<sup>26</sup>

Second, progression to hepatic fibrosis from steatosis should be monitored, hepatic biopsy being the ideal tool.<sup>27</sup>

Third, cardio vascular risk factors should be performed and risk factors should be controlled.<sup>28</sup>

Fourth, NAFLD patients should be treated with metformin, pioglitazone, statins, vitamen E, omega III and vitamin D supplementation. ACEIs should be given prophylactically for CAD.<sup>29,30</sup>

## LIMITATIONS

Our study also had a few limitations like most of the participants in our study were from KPK limiting the

generalizability of our results. Second, the ultrasound sensitivity for detecting NAFLD is 70%. Third, both ultrasonography and cardiac cath: studies are operator dependent and observer bias may prevail. Further trails need to be done to see the effect whether treatment of NAFLD decreases the future risk of CAD or not.

## CONCLUSION

NAFLD is strongly associated as an independent risk factor for CAD and increases the POR of CAD be 2.9 times. The risk of CAD increases with the increase in severity of NAFLD. So for patient diagnosed with NAFLD , coronary artery disease must be ruled out.

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