**ORIGINAL ARTICLE**

# Association between Non-Alcoholic Fatty Liver Disease (NAFLD) and Raised Carotid Intima-Media Thickness (CIMT)

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## ABSTRACT

**Aim:** To determine the association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness

**Methods:** A total of 218 i.e. 109 with non-alcoholic fatty liver disease and 109 normal subjects of age 30-45 years of either gender were included. Patients with known diabetes, k/c of hypertension, known IHD and chronic renal failure were excluded. All the subjects were undergone abdominal and carotid ultrasound in order to assess nonalcoholic fatty liver disease and carotid IMT measurement. Three readings were recorded at each site and average measurement was used.

**Results:** The mean age in cases group was 37.51±4.07 years and in control group was 37.45±4.03 years. Out of 218 patients, 136(62.39%) were males and 82(37.61%) were females with male to female ratio of 1.7:1. Frequency of raised CIMT in cases group was seen in 62(56.88%) while in control group was seen in 41(37.61%) cases with a p-value of 0.004 and odds ratio of 2.1879 which is statistically significant and shows a positive association between NAFLD and raised CIMT.

**Conclusion:** This study concluded that the frequency of raised carotid intima-media thickness is higher in patients with non-alcoholic fatty liver disease and shows the positive association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness.

**Keywords:** Liver, alcohol, fatty, carotid.

## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a highly prevalent condition characterized by excessive accumulation of fat in liver cells.[1]Nonalcoholic fatty liver disease (NAFLD) encompass a spectrum of pathological conditions, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis[2], resembling that of alcoholic liver disease but occurs in persons who do not abuse alcohol[3]. Thus, NAFLD shares many features of metabolic syndrome, a highly atherogenic condition, and its presence could signify a substantial cardiovascular risk above and beyond that conferred by individual risk factors[4]. NAFLD itself is a risk factor for increased morbidity and mortality, cardiovascular disease and malignancy[5]. Despite these facts, most patients have a good prognosis if the condition is caught in its early stages.

In published data, the mortality rate for coronary heart disease in patients with NAFLD is equal to mortality related to cirrhosis[6]. It is important to determine whether NAFLD is an independent predictor of cardiovascular morbidity and mortality and several studies have suggested that there is an association between NAFLD and cardiovascular disease[7]. NAFLD is the most common cause of abnormal liver function tests in adults. There is no data available locally regarding the role of carotid atherosclerosis in NAFLD patients. Furthermore, study of this kind was required for establishing if atherosclerosis affects vascular anatomy and physiology in NAFLD patients, independent of other risk factors. Through this study, we would be able to find the relation between nonalcoholic fatty liver disease and carotid intima-media thickness as the main predictor of cardiovascular disease, by comparing CIMT of sonographically diagnosed NAFLD patients with control group having normal liver echogenicity on ultrasound. Our study would provide baseline and current local statistics of association between NAFLD and raised CIMT. It would also help in deciding whether further recommendations, with regards to CIMT screening, should be implemented in all NAFLD patients. Therefore, this study would be of clinical importance in planning prevention and therapeutic strategies.

## MATERIAL AND METHODS

This case series study was conducted at Department of Medicine, Sahiwal Medical College, Sahiwal from January 2016 to June 2016. Total 109 patients either male or female having age from 30-45 years having nonalcoholic fatty liver disease on ultrasound and with HbsAg –ve, Anti HCV –ve were selected. One hundred and nine controls, preferably from relatives

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of these patients, having normal liver echogenicity on abdominal ultrasound, were matched for age, gender and body mass index were selected.

Patients with diabetes mellitus (having fasting serum glucose ≥126mg/dl or on treatment for diabetes), patients with hypertension (having BP ≥ 140/90 mmHg or on treatment for hypertension), having history of ischemic heart disease, history of chronic liver disease, patients with alcohol consumption ( more than 140g weekly in men and 70g weekly in women), Cigarette smoking (smoking ≥ 20 cigarettes/day for last 6 months) and having history of pregnancy in previous year or history of delivery within past six months and positive viral markers were excluded from the study. Approval of the ethical committee of the institution was sought. Written informed consent of the patients was taken.

**Operational definitions:**

**NAFLD:** was defined by the presence of at least 2 of 3 abnormal findings on abdominal ultrasound: diffusely increased echogenicity (bright) liver with liver echogenicity greater than kidney or spleen, vascular blurring and deep attenuation of ultrasound signal, after exclusion of significant alcohol intake

**Carotid intima-media thickness:** Maximal IMT was measured bilaterally at posterior wall of common carotid artery, 2cm before the bifurcation as the distance between first (lumen-intima interface) and second (media-adventitia interface) echogenic lines of anterior and posterior arterial walls. Three measurements were taken at each site and average measurement used. The cut-off value for CIMT was set at 0.8mm (CIMT≥0.8mm was considered raised).

All the subjects were undergone abdominal and carotid ultrasound in order to assess nonalcoholic fatty liver disease and carotid IMT measurement. All investigations were performed by two consultant sonologists (one performing abdominal ultrasound and the other doing carotid ultrasound) at radiology department, using standardized ultrasound equipment and blinded to each other regarding respective ultrasound measurements and unaware of patients' clinical data. Nonalcoholic fatty liver disease was defined according to operational definition.

For carotid ultrasound, patients were examined in a supine position neck extended and chin facing contralateral side. Maximum CIMT was measured bilaterally at posterior wall of common carotid artery, 2cm before the bifurcation. Thickness of intima media was measured vertical to arterial wall. Three readings were recorded at each site and average measurement was used. The cut-off value for CIMT was set at 0.8mm (CIMT ≥ 0.8mm was considered raised).

All the collected data was entered in pre-designed proforma along with demographic profile of all the patients. Data was entered and analyzed using SPSS-11. Descriptive statistics were applied to calculate mean and standard deviation for quantitative variables like age and BMI. Frequencies and percentages were calculated for qualitative variables like gender and raised CIMT. Chi-square test was used to determine the association between NAFLD and raised CIMT. p-value less than or equal to 0.05 ($p \leq 0.05$) was considered as significant and odds ratio was also calculated. Effect modifiers like age, gender and BMI were controlled by stratification. Post stratification chi-square test was also applied and odds ratio was also calculated.

## RESULTS

Fig. I: Percentage of patients according to Gender (n=218).

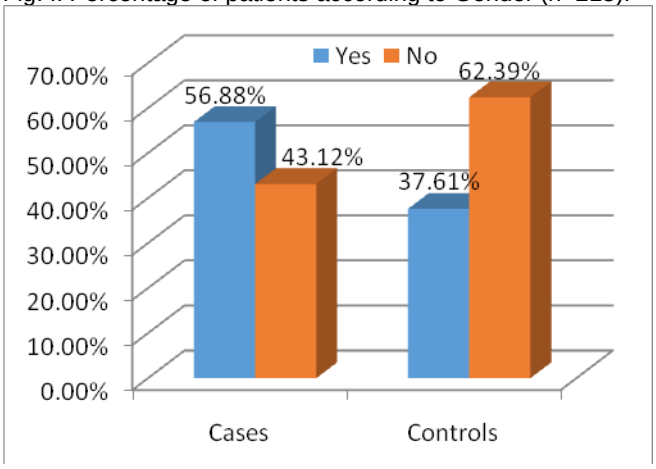
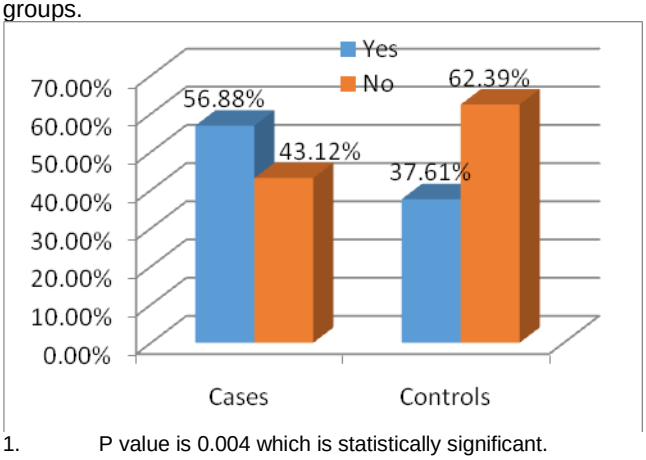



Fig. II: %age of pts according to raised CIMT between both groups.




1. P value is 0.004 which is statistically significant.
2. Odds ratio is 2.1879 which is significant.

Age range in this study was from 30 to 45 years with mean age of 37.48±4.04 years. The mean age in cases group was 37.51±4.07 years and in control group was 37.45±4.03 years. Majority of patients were 96 (44.04%) was between 36-40 years of age as shown in Table I. The mean BMI in cases group was 29.64±4.19kg/$m^2$ and in control group was

29.62±4.53 as shown in Table II. Out of 218 patients, 136 (62.39%) were males and 82(37.61%) were females with male to female ratio of 1.7:1 (Fig. I). Frequency of raised CIMT in cases group was seen in 62(56.88%) while in control group was seen in 41 (37.61%) cases as shown in Figure II which has shown p-value of 0.004 and odds ratio of 2.1879 which is statistically significant and shows a positive association between NAFLD and raised CIMT.

Table-I: Age distribution for both groups (n=218).

| Age(yrs) | Case | Controls | Total |
|---|---|---|---|
| 30-35 | 33(30.27%) | 33(30.27%) | 66(30.27%) |
| 36-40 | 48(44.04%) | 48(44.04%) | 96(44.04%) |
| 41-45 | 28(25.69%) | 28(25.69%) | 56(25.69%) |
| Mean±SD | 37.51±4.07 | 37.45±4.03 | 37.48±4.04 |

Table-II: %age of pts according to BMI in both groups.

| BMI(kg/m$^2$) | Cases | Controls | Total |
|---|---|---|---|
| ≤ 30 | 61(55.96%) | 61(55.96%) | 122(55.96%) |
| >30 | 48(44.04%) | 48(44.04%) | 96(44.04%) |
| Mean±SD | 29.64 ± 4.19 | 29.62± 4.53 | 29.63 ± 4.35 |

Stratification of raised CIMT with respect to age groups has shown in Table III which showed statistically significant association between NAFLD and raised CIMT in age group 41-45 years. Table IV has shown the stratification of raised CIMT with respect to BMI and showed statistically significant association between NAFLD and raised CIMT in BMI >30 kg/m$^2$. Stratification of raised CIMT with respect to gender is shown in Table V which showed statistically significant association between NAFLD and raised CIMT in male gender.

Table III: Stratification of Raised CIMT with respect to age groups.

| Age (years) | Cases (n=109) | | Controls (n=109) | | P-value | OR |
|---|---|---|---|---|---|---|
| | Raised CIMT | | Raised CIMT | | | |
| | Yes | No | Yes | No | | |
| 30-35 | 19 (57.58%) | 14 (42.42%) | 14 (42.42%) | 19 (57.58%) | 0.220 | 1.84 |
| 36-40 | 27 (56.25%) | 21 (43.75%) | 21 (43.75%) | 27 (56.25%) | 0.221 | 1.65 |
| 41-45 | 16 (57.14%) | 12 (42.86%) | 07 (25.0%) | 21 (75.0%) | 0.017 | 4.00 |

Table IV: Stratification of Raised CIMT with respect to BMI.

| BMI (kg/m$^2$) | Cases (n=109) | | Controls (n=109) | | P-value | OR |
|---|---|---|---|---|---|---|
| | Raised CIMT | | Raised CIMT | | | |
| | Yes | No | Yes | No | | |
| ≤ 30 | 34 (55.74%) | 27 (44.26%) | 25 (40.98%) | 36 (59.02%) | 0.104 | 1.81 |
| >30 | 28 (58.33%) | 20 (41.67%) | 16 (33.33%) | 32 (66.67%) | 0.015 | 2.80 |

Table V: Stratification of Raised CIMT with respect to Gender.

| Gender | Cases (n=109) | | Controls (n=109) | | P-value | OR |
|---|---|---|---|---|---|---|
| | Raised CIMT | | Raised CIMT | | | |
| | Yes | No | Yes | No | | |
| Male | 45 (55.74%) | 23 (44.26%) | 25 (40.98%) | 43 (59.02%) | **0.0007** | **3.36** |
| Female | 17 (58.33%) | 24 (41.67%) | 16 (33.33%) | 25 (66.67%) | **0.8219** | **1.12** |

## DISCUSSION

We have conducted this case-control study to determine the association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness. Age range in our study was from 30 to 45 years with mean age of 37.48 ± 4.04 years. The mean age in cases group was 37.51±4.07 years and in control group was 37.45 ± 4.03 years. Majority of patients, 96 (44.04%) were between 36-40 years of age. These results are very much comparable to the studies of Guleria A et al[8]and Zayed BE et al[9] who had reported mean age of 37 and 39 years respectively. On the other hand, many previous studies have shown much larger mean age i.e. greater than 50 years, as compared to our study.[10-11]In initial studies of NAFLD, the percentage of female patients was reported to be as high as 75%; however, in subsequent studies, the percentage fell to roughly 50%. In our study, 62.39% were males and 37.61% were females with male to female ratio of 1.7:1. This male predominance is also found in many previous studies.[10-11]

In our study, frequency of raised CIMT in cases group was seen in 62 (56.88%) while in control group was seen in 41 (37.61%) subjects which has shown p-value of 0.004 and odds ratio of 2.1879 which is statistically significant and shows a positive association between NAFLD and raised CIMT. In one study, CIMT was increased in 52.5% of patients with NAFLD compared to 35.8% of controls.[12]Fracanzani et al[13] concluded (in a series of normal and NAFLD subjects) that independent risk predictors of increased intima-media thickness were the presence of hepatic steatosis (odds ratio (OR) = 6.9), age (OR 6.0), and increased systolic blood pressure (OR 2.3).

Zayed BE et al[9] in his study has shown a significant increase in carotid IMT in patients of NAFLD (0.8±0.1) mm than normal control persons (0.6±0.03) mm which was highly significant (p=0.0001), which means that the patients with NAFLD may be at risk of early generalized atherosclerosis. Algarem NH et al[10] also found a significant increase in carotid IMT in patients with NAFLD (0.73±0.1mm) than normal control persons (0.50±0.08mm) which was highly significant (*p* value <0.001). Similarly, Guleria A et al[8] had found the mean CIMT of both the right and left side significantly higher (0.70±0.11 mm vs. 0.61±0.08 mm) (p=0.007) and FMD% significantly lower in patients with NAFLD (9.79±3.81%) in comparison to controls (17.02±3.39%) (p<0.0001).

Despite the fact that several previous studies demonstrated the association between NAFLD and carotid IMT and/or carotid plaque, no general consensus exists on the systematic screening of carotid atherosclerosis in patients with fatty liver disease. However, patients with NAFLD having increased carotid IMT could be candidates not only for aggressive treatment of the liver disease, but also for cholesterol lowering and aggressive treatment of underlying CVD risk factors; this would help to modify and potentially decrease the global CVD risk of these patients.

## CONCLUSION

This studyconcluded that that the frequency of raised carotid intima-media thickness is higher in patients with non-alcoholic fatty liver disease and shows the positive association between nonalcoholic fatty liver disease (NAFLD) and raised carotid intima-media thickness. So, we recommend that CIMT screening should be implemented in all NAFLD patients and patients with increased carotid IMT could be aggressively treated not only for liver disease but also for underlying CVD risk factors which will ultimately reduces the morbidity and mortality of these high risk patients.

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