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# Prevalence of NAFLD (non-alcoholic fatty liver disease) in metabolic syndrome and their correlation with various biochemical and serologic parameters for early detection and detecting patients of lean Nash (Non-alcoholic steatohepatitis)

**Dr. Priyank Jain[1], Dr. Rohit Parate[2], Dr. TN Dubey[3], Dr. RK Jain[4*]**

[1, 2] 3rd Years Medicine Resident, Gandhi Medical College, Bhopal, Madhya Pradesh, India

[3] DM Neurology, Professor and Ex-HOD, Department of Medicine, Gandhi Medical College, Bhopal, Madhya Pradesh, India

[4] DM Professor and HOD of Gastroenterology, Gandhi Medical College and Hamidiya Hopital, Bhopal, Madhya Pradesh, India

**Abstract**

**Background:** Non-alcoholic fatty liver disease (NAFLD) is a clinicopathologic entity increasingly recognized as a major health burden in developing countries. It includes a spectrum of liver damage ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and rarely, progression to cirrhosis. Various study in past have tried to establish association between serological markers and NFALD, but have not been proven to be effective in determining the further prognosis of disease.

**Aims and Objective:** To determine the prevalence of non alcoholic fatty liver disease (NAFLD) in metabolic syndrome (MS) and to establish a correlation between various serological and sociodemographic parameters in MS and NFALD grades and to establish a correlation of NAFLD and BMI to determine the presence of Lean NASH.

**Materials and methods:** Hundred patients with MS were studied at the Department of Medicine, Gandhi Medical College and associated Hamidiya Hospital, Bhopal from November 2015 to August 2017. Detailed history, sociodemographic profile and serum markers including haemoglobin, lipid profile, ALT, AST, fasting blood sugar, serum uric acid, hs CRP, fasting insulin level were estimated in each patient. Diagnosis of NAFLD was made using ultrasonography and patients were grouped in to Grade 1 (mild steatosis), Grade 2 (moderate steatosis) and Grade 3 (severe steatosis). All the groups were compared with serologic markers and waist circumference to identify the presence of NAFLD in Lean (Lean NASH).

**Results:** Prevalence of NFALD in study cohort was 64% and significantly higher in patients with age group >55 (p=0.011) years. NFALD was significantly higher in patients with WHR between 0.9-1.1 (p=0.049), WC ≥90 cm (p=0.046), SBP of ≥130 mmHg (p=0.046), DBP ≥80 mmHg (p=0.043), who were smokers (p=0.044), presence of type 2 diabetes mellitus (T2DM) (p=0.023), FBG >110 mg/dL (p=0.042), increasing SGPT (p=0.026), total cholesterol ≥200 mg/dL (p=0.042), triglycerides ≥150 mg/dL (p=0.040), LDL >130 mg/dL (p=0.027), HDL <30 mg/dL (p=0.023), fasting insulin >25 units (p=0.001) and uric acid level of ≥5.5 Units (p=0.033). In patients with lean NASH, most of them had WC >90 cm (p=0.0012), TG >150 mg/dL (p<0.049), LDL >130 mg/dL (p=0.032), HDL level <40 (p=0.048), fasting insulin level of >25 units (p=0.086) and Hb >10 (p=0.002) which were comparable to levels in overweight and obese.

**Conclusion:** Prevalence of NFALD was high among the MS patients. Most of them had direct association with WC, abdominal obesity, WHR, fasting blood sugar, TG, LDL, TC, ALT, serum uric acid, h SCRP and fasting insulin and inverse correlation with HDL. We also found significant NAFLD amongst the patients of MS and Normal BMI (Lean NASH).

**Keywords:** lean NASH, NFALD, fatty liver disease, serological markers, metabolic syndrome

## Introduction

Metabolic syndrome (MS) is increasing among the Asian population in both Urban and Rural area particularly with adaptation of modernized life style. Various studies have shown fatty liver as an accompaniment of MS and prevalence of fatty liver is found high (upto 70%) in obese, diabetic, dyslipidaemic patients [1].

The spectrum of non alcoholic fatty liver disease (NFALD) ranges from fatty liver to steatohepatitis and may progress to end stage liver disease cirrhosis and hepatocellular carcinoma. Recently there has been a growing concern over presence of fatty liver disease in patients of normal BMI (lean NASH). Compared to the west, Indians are known to develop NFALD at lower degree of adiposity and lower BMI [2, 3].

Although liver biopsy is the gold standard for diagnosis of NFALD, NASH/cirrhosis, the inability to perform such invasive procedure compels us to make the development of non-invasive, readily available and easy to perform serum markers which along with the severity of grades of NAFLD on ultrasonography can give us an idea about the presence and severity of liver disease in patients of MS [1].

Several markers such as lipid profile, ALT, AST, fasting blood sugar, serum uric acid, hs CRP, fasting insulin level have been recognized to play a significant role in the

correlation. These markers will thereby help to understand the severity and prognosis and also lead to early intervention and prove to be a good substitute for liver biopsy [2, 3].

Present study is planned to find out the prevalence of NAFLD amongst patients of MS. We tried to find that in the absence of liver biopsy can these combination of various biochemical markers and radiological parameters will be able to guide us about the severity of spectrum fatty liver disease and to know which patient of NAFLD would progress to further NASH/Cirrhosis. We also tried to compare groups of lean NASH (BMI<23kg/sqm), overweight (BMI 23-25kg/sqm) and obese>25 kg/sqm) patients having NAFLD in terms of various biochemical and physical parameters.

## Material and Methods

A prospective study was performed on 100 patients of MS at the Department of Medicine, Gandhi Medical College and associated Hamidiya Hospital, Bhopal from November 2015 to August 2017.

All the subjects signed an Informed Consent before including them in to study. Institutional Ethics Committee approval was obtained before starting study.

Patients fulfilling the criteria for MS as per the American Heart Association and AHA/NHLBI which update the NCEP ATP III guidelines for MS were included. Those with history of known liver disease, ultrasonic proven liver disease other than fatty liver, consumption of alcohol, with other co morbid conditions like hypothyroidism and patients taking estrogen, amiodarone, methotrexate, pyrazinamide which are known to produce fatty liver were excluded from the present study.

Sociodemographic profile including age, gender, ethnicity, marital status and smoking status were recorded. Patients height, weight, BMI and waist circumference was also measured

Serum markers such as Haemoglobin, lipid profile, ALT, AST, fasting blood sugar, serum uric acid, hsCRP, fasting insulin level were estimated in all the subjects under study using B500 Automated Biochem Analyzer.

The diagnosis of NAFLD was made on the basis of characteristics real time ultrasonography features.All Serorologic investigations are compared to NAFLD with BMI of less than 23 kg/m 2 as lean NAFLD,23-25 kg/m as overweight and >25 kg/sqm as Obese. We also compared all the groups with above mentioned serologic markers and waist circumference to Identify the presence of NAFLD in Lean (Lean NASH) subjects compared to overweight and obese.

Fatty liver defined as the presence of an ultrasonographic pattern consistent with “bright liver”., vessel blurring and narrowing of the lumen of the hepatic veins in the absence of findings suggestive of chronic liver disease. NAFLD defined as any degree of fatty liver in the absence of alcohol intake. NAFLD is classified based on standard ultrasonographic criteria (with a 3.5 MHz probe) as Grade 1 (mild steatosis); slightly increased liver echogenicity with normal vessel and absent posterior attenuation, Grade 2 (moderate steatosis); moderately increase liver echogenicity with partial dimming of vessel and early posterial attenuation and Grade 3 (severe steatosis); diffused increased liver echogenicity with absence of visible vessels and heavy posterior attenuations.

All the data were analysis using IBM SPSS Ver. 20 software. Data is expressed as percentage and mean ± SD. Student t test and subgroup analysis was performed using ANOVA wherever applicable. Linear logistic regression was performed to confirm the effect of each parameter under study.

## Results

Out of 100 patients of MS, 64 % patients had NAFLD. Distribution of NFALD patients was significantly higher in patients with age group >55 (p=0.011) years.

**Table 1:** Comparing different parameters with NFALD grades in study cohort

| Parameters | | NAFLD | | | | Total | P value |
|---|---|---|---|---|---|---|---|
| | | Absent | Grade 1 | Grade 2 | Grade 3 | | |
| BMI (kg/m2) | Obese (25-30) | 11 | 6 | 6 | 9 | 32 | a= 0.116 |
| | Overweight (23-25) | 8 | 5 | 10 | 3 | 26 | b=0.034 |
| | Lean NASH (<23) | 14 | 11 | 15 | 2 | 42 | c=0.025 |
| WHR | 0.9-1.1 | 18 | 12 | 19 | 12 | 61 | 0.049 |
| | <0.9 | 16 | 9 | 13 | 1 | 39 | |
| WC (cm) | <90 | 5 | 5 | 6 | 6 | 22 | 0.046 |
| | ≥90 | 29 | 16 | 26 | 7 | 78 | |
| SBP (mmHg) | <130 | 5 | 3 | 4 | 6 | 18 | 0.046 |
| | ≥130 | 29 | 18 | 28 | 7 | 82 | |
| DBP (mmHg) | ≥80 | 33 | 15 | 27 | 11 | 86 | 0.043 |
| | <80 | 1 | 6 | 5 | 2 | 14 | |
| Smoking | Yes | 19 | 5 | 21 | 6 | 51 | 0.044 |
| | No | 15 | 16 | 11 | 7 | 49 | |

a; significant difference between BMI 25-30 and BMI-23-25, b; significant difference between BMI 25-30 and BMI < 23, c; significant difference between BMI < 23 and BMI-23-25.

NFALD was significantly high in lean patients which is comparable to that in obese and overweight. P value <0.05 is considered as significant, WHR; waist hip ratio, WC; waist circumference, SBP; systolic blood pressure, DBP; diastolic blood pressure.

NAFLD was significantly higher in subjects with DM (p=0.023). Comparing different grades of NAFLD showed that distribution of diabetes patients were higher in grade 2 (n=28) compared to grade 1 (n=16) and 3 (n=12).

**Table 2:** Comparing different serologic markers with NFALD grades in study cohort

| Parameters | | NAFLD | | | | Total | P value |
|---|---|---|---|---|---|---|---|
| | | Absent | Grade 1 | Grade 2 | Grade 3 | | |
| FBS | ≤110 | 2 | 5 | 5 | 5 | 17 | 0.042 |
| | >110 | 32 | 16 | 27 | 8 | 83 | |
| Bilirubin | ≥1.1 | 20 | 13 | 15 | 6 | 54 | NS |
| | <1.1 | 14 | 8 | 17 | 7 | 46 | |
| SGOT/SGPT | <40 | 0 | 1 | 1 | 1 | 3 | NS |
| | 40-80 | 34 | 19 | 30 | 3 | 86 | |
| | >80 | 0 | 1 | 1 | 9 | 11 | |
| TC | <200 | 10 | 8 | 14 | 7 | 39 | 0.042 |
| | ≥200 | 24 | 13 | 18 | 6 | 61 | |
| TG | ≥150 | 15 | 9 | 19 | 7 | 50 | 0.040 |
| | <150 | 9 | 12 | 13 | 6 | 50 | |
| LDL | ≥ 130 | 9 | 11 | 23 | 12 | 65 | 0.027 |
| | <130 | 15 | 10 | 9 | 1 | 35 | |
| HDL | <30 | 3 | 1 | 24 | 12 | 40 | 0.023 |
| | 30-40 | 15 | 16 | 7 | 1 | 39 | |
| | >40 | 16 | 4 | 1 | 0 | 21 | |
| hsCRP | ≤1 | 26 | 14 | 2 | 0 | 42 | a=0.011 |
| | 1.1-3 | 6 | 7 | 29 | 6 | 48 | b=0.021 |
| | >3 | 2 | 0 | 1 | 7 | 10 | c=0.89 |
| Fasting insulin | >25 | 34 | 15 | 17 | 0 | 66 | <0.001 |
| | ≤25 | 0 | 6 | 15 | 13 | 34 | |
| Uric acid | <5.5 | 4 | 6 | 8 | 10 | 28 | 0.033 |
| | ≥5.5 | 30 | 15 | 24 | 3 | 72 | |

a; significant difference between hs CRP<=1 and >3, b; significant difference between hs CRP >3 and hs CRP- 1.1-3, c; significant difference between hs CRP- 1.1-3 and hs CRP<=1, p value <0.05 is considered as significant.

## Discussion

In present study, we found higher prevalence of NAFLD in various grades of NFALD (64%) in MS which is consistence with the previous studies where the prevalence of NAFLD ranges from 56% to 82.9%. 35,8,62 In another study in which NAFLD was detected in 53.7% subjects, of whom 28.8% had mild steatosis and 17.1% had moderate-to-severe steatosis is in agreement with the present study. Many cross-sectional studies have demonstrated that NAFLD is strongly associated with MS [4]. Our study is consistence with these previous findings.

NAFLD was found to be significantly higher in Age group >55 yrs (47%) compared to lower age groups which means prevalence of NAFLD increases with increasing Age. In a previous study 54.2% identified were in the age group of ≥51 years; with highest prevalence recorded in 61-70 year age group, at 61.8% [5]. The results are consistent with previous study and reinforced the well established clinical association of NAFLD with elements of MS including dyslipidemia, hypertension and obesity. An inverse correlation between NAFLD and serum levels of adipocyte-fatty acid binding protein, an intracellular lipid transporter, has been reported in the elderly [5].

In present study 62 % patients of WC (>90 cm) have NAFLD. Soler *et al* did the abdominal ultrasound examinations on 69 patients and reported that waist circumference was significantly ($p<0.001$) higher in patients with NFALD [6], which is in agreement with the present study.

In our study 70% of patients of WHR >0.9 have NAFLD. In a previous study 75 % patients of NAFLD have a WHR >0.9 whereas only 17.9 % patients were having WHR >0.9 amongst Non NAFLD group [7]. In another study high WHR was found in 84.6% of patients of NAFLD [8]. Agrawal *et al* found that mean WHR was 0.97 and 0.93 in NAFLD and NON NAFLD population in T2DM respectively [9]. These findings are consistent with our report and hence WHR is an important anthropometric measurement in patients of MS for suspicion of NAFLD.

In our study we found 88% NAFLD in patients having T2DM and 19% were Grade 3 NAFLD. Also 61% patients have NAFLD who are having Impaired Fasting Glucose (>110 mg/dl). Suez *et al* found prevalence of NAFLD as 57.2% in T2DM patients with mean of FBS as 161.3 mg/dl and 168.8 mg/dl in Non NAFLD and NAFLD [10]. Mohan *et al* found prevalence of NAFLD (54.5 %) was significantly higher in patients with T2DM compared to those with Pre Diabetes (IGT or IFG) (33%), isolated IGT (32.4%), isolated IFG (27.3%) and normal glucose tolerance [11]. Our findings are consistence suggesting a association between high blood sugar levels and development of NAFLD in MS.

We found 64.63 % patients of SBP > 130 and 61.62 % patients of DBP >80 mmHg were having NAFLD. In a previous study the incidence rate of hypertension increased according to the degree of NAFLD (normal: 14.4%, mild: 21.8%, moderate to severe: 30.1%, $P < 0.001$) [12]. In another study the odds ratio for NAFLD with the normal group, was 1.476 (95% confidence interval, 1.166–2.551). This showed that NAFLD increases with the increasing hypertension in MS patients.

Generally, hypertriglyceridemia and low HDL are the lipid fraction disorders most often associated with the presence of steatosis [13]. Boza *et al* observed significantly lower mean HDL levels in class III obese individuals with NAFLD, when compared with the group without the disease, which is the only lipid fraction which evaluated lipid fraction with more advanced stages of the disease [14]. However, a weak negative correlation was observed between levels of HDL and the degree of simple steatosis, graded according to the lobular parenchyma involvement. The authors suggest that dyslipidemia may have a greater impact on the disease in class I or class II obesity and a lower influence in class III. Kantartzis *et al* demonstrated that fatty liver is significantly and independently associated with lower levels of high density lipoprotein 2 cholesterol, which is more potently antiatherogenic [15]. Our study also showed a association of NAFLD with TC, Triglyceride, LDL and inverse with HDL. But these cannot be helpful to ascertain the severity of fatty liver disease spectrum.

Similar to present study Uchil *et al* reported that SGPT level was significantly higher in NFALD group (38.74 ± 17.96) compared to control (31.62 ± 13.49) ($p<0.05$) [16]. Manopriya *et al* also found similar results [17]. This was in consistence with our finding that SGPT was found to be raised in only certain patients of NAFLD. Therefore it cannot be regarded as a good marker for identification of spectrum of fatty liver.

Sertoglu *et al* studied 242 male patients with NAFLD (102 with NASH and 140 with simple steatosis), reported that the prevalence of hyperuricemia was 33.4%. Serum uric acid levels in patients with NASH were significantly higher than those of simple steatosis ($p=0.035$). Univariate and

multivariate analyses both demonstrated that hyperuricemia had a significant association with younger age [OR (95%CI), 0.930 (0.884–0.979), p = 0.005], higher body mass index [OR (95%CI), 1.173 (1.059–1.301), p = 0.002] and hepatocellular ballooning [OR (95%CI), 1.678 (1.041–2.702), p = 0.033] [18]. Which is in agreement with the present study data where NFALD (n=72) was significantly higher in patients with uric acid level of >=5.5 Units (p=0.033). Similar results were depicted by Adams *et al*. 63Although their increasing value prove does not to prove to be predictive of grades of NAFLD [5].

We found a significant association amongst patients having hsCRP >3 to be having NAFLD grade 3. Total 10 patients having hsCRP had NAFLD. The risk for NAFLD increased as the hsCRP level increased (p< 0.011). Lee *et al* found 28.8% of patients having hsCRP within high normal range initially developed NAFLD during the follow-up period. The conclusion made by Lee *et al* is in agreement with the present study findings where risk of NFALD was significantly increased with increasing hsCRP [19]. In another case-control study, inflammatory markers such as TNF-α, IL-6 and hsCRP levels were higher in the NAFLD group than in healthy controls [14].

Total 66 patients out of 100 MS patients had fasting insulin >25, amongst them 48% patients have NAFLD. This signifies hyperinsulinaemia is significantly correlated with the presence of NFALD. Singh *et al* studied 68 NAFLD patients and reported that patients with NAFLD had higher HOMA-IR than those with MS alone. Presence of NAFLD can detect insulin resistance with a sensitivity of 78.0% and specificity of 86.3 % with an odds ratio of 25.55 (95%CI: 11.51-56.70) which is better than that of MS diagnosed by ATP-III criteria. Multivariate logistic regression analysis showed that fatty liver was an independent predictor for insulin resistance and MS [20].

We found fatty liver is 66.66% in lean, 69.23% in overweight and 65.63 % in obese which was almost comparable. We found high prevalence of Lean NASH in our population. These studies were similar to previous studies like where Lean NASH was in the range between13% to 52 % [1-3, 21]. The lower preponderance of lean NAFLD (13.2%) in our hospital-based cohort suggests that many of lean NAFLD patients do not seek medical advice. Interestingly, Das *et al*. also found that individuals with normal BMI (18.5-24.9 Kg/m 2) had two-fold increases in risk for NAFLD than those with a BMI < 18.5 Kg/m [1, 2]. Thus, although obesity is clearly a risk factor for NAFLD, this appears to be modified strongly by ethnicity, genetic predisposition, or environmental factors, which may explain risk of NAFLD in lean subjects. The substantial variability of hepatic fat content varies among individuals with equivalent adiposity supports this view. A study revealed that lean, non-alcoholic, non-diabetic, non-smoking Asian Indians in comparison to similar age, sex, BMI-matched Caucasians, Hispanics, Black and Eastern Asians had 2- to 3-fold increase in IR and 2-fold increase in hepatic steatosis [22, 23]

All other factors like fasting blood sugar (p=0.013), dyslipidaemia (p=0.032), hyperinsulinaemia (p=0.002) were almost comparable amongst all the three groups of BMI. This means these serologic markers are equivalently raised in an otherwise lean individual as they are increased in obese and overweight patients of MS. We found haemoglobin was higher in Lean NASH (p=0.002) patients compared to obese and overweight. This significance was in consistency with the previous studies [1].

Waist circumference was significantly higher and comparable in lean NASH (p=0.0012) subjects suggesting the possibility of importance of abdominal obesity even in an otherwise lean individual. This is in consistence with previous studies on lean patients which showed that the accumulation of body fat in the abdominal region, regardless of the individual's total body fat content, is an independent predictive factor for fat accumulation in hepatocytes and, therefore, crucial in the pathogenesis of NAFLD [23].

The present study had few limitations; small sample size and control group was not taken. These combinations of serologic markers cannot be of help in determining the severity nor could they be helpful in determining which of the patients of Fatty Liver will progress to NAFLD or NASH. Liver biopsy which is the definitive diagnostic for NASH could not be done in our Hospital because of ethical and medical considerations. We would like to Include Healthy (Control group) people without MS for comparing them with Lean NASH in patients of MS. A large randomized clinical trial is required to strengthen the present study findings.

## Conclusion

Patients of MS have a high prevalence of fatty liver disease. Majority of these NAFLD patients were having a direct association with waist circumference, abdominal obesity, waist hip ratio, fasting blood sugar, serum triglyceride levels, LDL, total cholesterol, ALT, serum uric acid, hSCRP and fasting Insulin and inverse correlation with HDL. These serologic biomarkers could be helpful in early identification of fatty liver and early intervention so as to prevent their further progression to end stage liver disease. These combinations of serologic markers cannot be of help in determining the severity nor could they be helpful in determining which of the patients of fatty liver will progress to NAFLD or NASH. We also found significant NAFLD amongst the patients of MS and Normal BMI (Lean NASH). Presence of NALFD was comparable amongst those with BMI < 23 (lean NASH) and BMI 23-25(Overweight) and BMI > 25(Obese).That means BMI cannot be the criteria to determine development of complications of MS like fatty liver or cardiovascular risk.

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