DOI: 10.7860/JCDR/2021/51585.15600

Original Article

Internal Medicine Section

Metabolic Profile of Lean/Non Obese NAFLD (Non Alcoholic Fatty Liver Disease) Subjects

AKASH JAISWAL[1], KAVITA JAIN[2], NAGENDRA BABU[3]

ABSTRACT

Introduction: Non Alcoholic Fatty Liver Disease (NAFLD) in the absence of overweight and obesity has been defined as 'lean NAFLD'. Metabolic syndrome associated diseases in low and middle income countries have variable phenotypes and clinical outcomes. Hypothetically, 'Lean NAFLD' can be a part of the spectrum of classical obesity related NAFLD or separate entity with different pathophysiology.

Aim: 1) To characterise the NAFLD in lean/non obese subjects; 2) To explore how it differs from classical 'obese phenotype' of the NAFLD; 3) To explore how these lean/non obese subjects with NAFLD are different from healthy lean/non obese subjects in terms of metabolic profile.

Materials and Methods: The present study was a cross-sectional observational study conducted over a period of six months. Forty subjects were categorised into four groups (1. Lean NAFLD without Diabetes; 2. Lean NAFLD with Diabetes; 3. Obese NAFLD with Diabetes; 4. Lean healthy subjects). Clinical history, examination, anthropometry, biochemical data including insulin resistance by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were analysed.

Results: Mean Body Mass Index (BMI), Fasting Blood Glucose (FBG) and HbA1c (Glycated haemoglobin) of group 2 and group 3 were significantly higher than that of group 1 and group 4 subjects ($p<0.001$). Mean HOMA-IR of the patients of group 2 and group 3 were significantly higher than that of group 1 and group 4 ($p<0.001$). No significant difference was seen in HOMA-IR between patients of group 1 and group 4 ($p>0.05$) and also of group 2 and group 3 subjects ($p>0.05$).

Conclusion: Lean NAFLD subjects have a different metabolic profile than overweight-obese patients with NAFLD, particularly in relation to diabetes. On the basis of all metabolic parameters and insulin resistance, authors propose a spectrum of insulin resistance 'Non obese Control - Non obese NAFLD without Diabetes Mellitus (DM) - Non obese NAFLD with DM - Obese NAFLD with DM'.

Keywords: Body mass index, Diabetes mellitus, Homeostatic model of insulin resistance, Insulin resistance

INTRODUCTION

The typical paradigm of NAFLD is mostly related to variable degrees of obesity, Diabetes Mellitus type 2 (DM2), insulin resistance and other features of metabolic syndrome [1]. As BMI and Waist Circumference (WC) are described as a marker of total body and visceral adiposity respectively, these are used to describe the anthropometric phenotypes. Thus, NAFL and Non Alcoholic Steatohepatitis (NASH) in absence of overweight and obesity, defined by these anthropometric variables is being referred to as 'lean NAFLD' [2].

Pathophysiological divergences like insulin resistance, increased body fat content and abnormal adipocyte functioning are key mechanisms behind NAFLD in obese subjects [3]. Lean NAFLD was initially noted amongst Asian population and has subsequently been reported from other countries, including the west [4-7]. Normal weight subjects with NAFLD had metabolic derangements comparable to those with obesity related NAFLD [5].

A more resilient narration of the lean NAFLD, as a distinct phenotype, was reported from a community-based epidemiological study conducted in India [8]. Study described non obesity/leanness specifically using both BMI and abdominal circumference exhibiting an overall prevalence of NAFL to be 8.7%. Asian Indian men have higher Insulin resistance, with higher Triglyceride (TG) content and different adipocytokine picture in comparison to Caucasian, Black, and Hispanic population [9]. Besides, larger size of the adipocytes is demonstrated in South Asian males in comparison to Caucasians along with higher level of non esterified fatty acid, higher leptin and lower adiponectin [10]. Thus, Asian people can have higher tendency to develop NAFLD even at a lower BMI.

Hence, hypothetically 'Lean NAFLD' can be a part of the spectrum of classical obesity related NAFLD or it can be a totally different entity with different pathophysiology. To the best of our knowledge, there has been no study conducted in India till date, which compared the metabolic data in lean NAFLD groups in relation to DM2 and insulin resistance status from obese NAFLD and healthy controls. Authors undertook this project to understand the entity 'Lean NAFLD' by metabolic characterisation and to understand the difference from both 'classical obese NAFLD' and healthy subjects in terms of metabolic parameters especially insulin sensitivity.

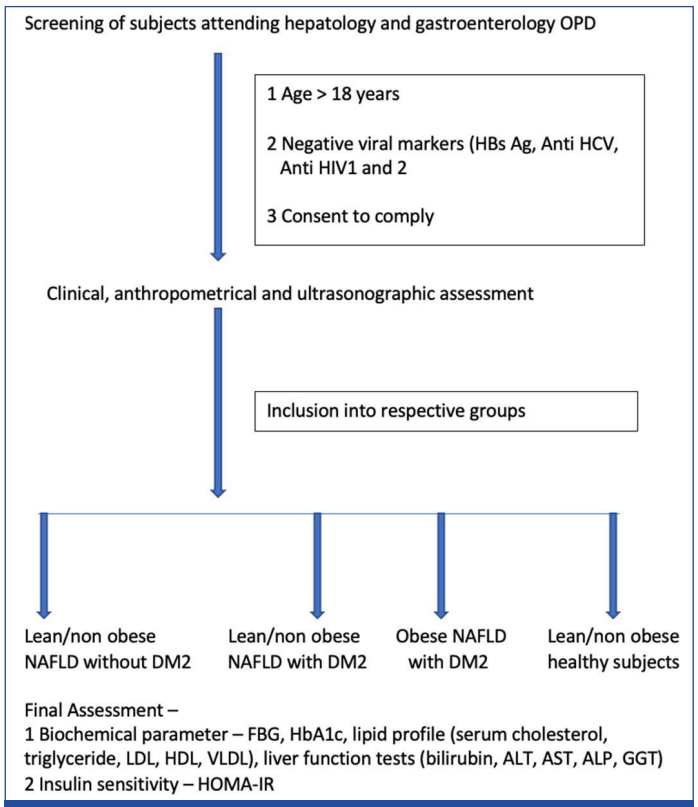
MATERIALS AND METHODS

The present study was a cross-sectional observational study conducted over a period of six months from March 2020 to August 2020. Study was conducted in Department of Hepatology and Gastroenterology of a tertiary care centre from North-east India. Sample size calculation was not possible due to lack of relevant data. However, taking this study as a 'proof of concept', a sample size arbitrarily taken as 10 subjects in each group making a total of 40 subjects. Subjects were categorised into four groups i.e., 1) Lean/Non obese NAFLD without Diabetes; 2) Lean/Non obese NAFLD with Diabetes; 3) Obese NAFLD with Diabetes; 4) Lean/Non obese Healthy subjects.

Inclusion criteria: Adults of age more than 18 years and who gave informed consent were included in study.

Exclusion criteria: HBsAg, anti-HCV, anti-HIV 1 and 2 positive candidates were excluded from study. Blood parameters- serum bilirubin (total and direct fraction), Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP), Gamma Glutamyl Transaminase (GGT), FBS, HbA1c and lipid profile

were analysed. Anthropometric measurements {weight, height, BMI, WC and skin fold thickness (SFT)} were done in each case. Insulin resistance was analysed by homeostatic model for insulin resistance (HOMA-IR). The HOMA-IR was calculated by formula- Fasting insulin (mU/L) x FBS (mg/dL)/405. [Table/Fig-1] shows the flowchart of present study.



[Table/Fig-1]: Study flowchart.

Definitions used in the study:

Lean/non obese NAFLD subject:

- BMI < 23 Kg/m^2 (as defined for south Asian population) [11].
- Absence of abdominal obesity i.e., WC ≤90 cm in men and ≤80 cm in women (as defined for south Asian population) [12].
- Alcohol consumption <20 gm per day in males and <10 gm per day in females.
- Presence of fatty liver on Ultrasound.

Obese NAFLD subject:

- BMI >27.5 Kg/m^2 (as defined for south Asian population) [11].
- Alcohol consumption <20 gm per day in males and <10 gm per day in females.
- Presence of fatty liver on ultrasound.

Lean/non-obese Healthy subject:

- BMI < 23 Kg/m^2 (as defined for south Asian population) [11].
- Absence of abdominal obesity i.e., WC ≤90 cm in men and ≤80 cm in women. (as defined for south Asian population) [12].
- Alcohol consumption <20 gm per day in males and < 10 gm per day in females.
- Negative viral markers (HBsAg, Anti-HCV and Anti-HIV 1 and 2).
- Normal Blood pressure (≤120/80 mmHg) [13].
- Normal Blood glucose value (FBG <100 mg/dL, PPBG <140 mg/dL) [14].
- Normal lipid profile (As per National Cholesterol Education Program (NCEP)/Adult Treatment Panel (ATP) III guideline) [15].
- Euthyroid.
- Normal Liver function test.
- No illness/hospitalisation within last three months.

Definition of NAFLD on Ultrasound [16]:

Increased echogenicity of liver along with the presence of any two of the three features-

a. Liver-kidney contrast (brightness of liver in contrast to Kidney parenchyma).
b. Vascular blurring (blurring of hepatic vasculature, mainly hepatic vein trunk).
c. Deep attenuation of echo-beam (attenuation of echo-beam in the deep portion of right lobe of liver).

STATISTICAL ANALYSIS

The data collected was entered in MS Excel-2010 and statistical analysis was performed with help of Epi Info (TM) 7.2.2.2 which is a trademark of the Centre for Disease Control and Prevention (CDC). Using this software, basic cross-tabulation and frequency distributions were prepared. The mean with corresponding standard deviations were calculated. Chi-square (χ^2) test was used to test the association between different study variables under study.

Corrected χ^2 test was used in case of any one of cell frequency was found less than 5 in the bivariate frequency distribution. In the cases, where one of the cell frequencies were less than 5, corrected chi-square (χ^2) was used to find the association between variables. Also, One-Way Analysis of Variance (ANOVA) followed by Post-hoc Tukey's test was performed with the help of Critical Difference (CD) or Least Significant Difference (LSD) at 5% and 1% level of significance to compare the mean values. The p-value <0.05 was taken to be statistically significant.

RESULTS

Demographic, anthropometrical, laboratory characteristics and insulin resistance of the 40 subjects of four groups were analysed.

Demographic profile: Each group comprised of 10 subjects [Table/Fig-1]. Thus, the patients in the groups were in the ratio 1:1:1:1. Mean age of four groups, lean NAFLD without DM2, lean NAFLD with DM2, obese NAFLD with DM2 and healthy control group were 41.90±13 years, 45.70±13 years, 43.90±12 years, 41.80±9 years, respectively. There was no significant difference in mean age of the patients of the four groups (p=0.877).

Male:female ratio in the four groups, were 8:2, 7:3, 4:6, 7:3, respectively. No significant association in gender was identified between the subjects of the four groups (p=0.26). Thus, the patients of the four groups were matched for age and gender.

Anthropometric profile: Mean BMI, WC, SFT, of four groups was calculated and analysed [Table/Fig-2]. There was significant difference in mean BMI, WC, SFT of the subjects of the four groups (p<0.05). Mean BMI, WC, SFT of the patients of group 3 were significantly higher than that other groups (p<0.05).

Mean WC of four groups were compared in males and females separately [Table/Fig-2]. [Table/Fig-1] similar results were seen in both males and females, as per respective cut-off defined for each group.

Biochemical profile: Individual biochemical parameters like bilirubin, (total and direct fraction), ALT, AST, ALP, GGT, serum albumin and serum globulin were compared in all four groups. No significant difference was seen in all these parameters in patients of the four groups (p>0.05).

Mean FBG and HbA1c of four groups were compared [Table/Fig-2]. Significant difference was identified in mean FBG (p<0.001) and HbA1c (0.043) of the patients of the four groups. Mean FBG and HbA1c of the patients of group 2 and group 3 were significantly higher than that of group 1 and group 4 (p<0.001). But there was no significant difference in mean FBG and HbA1c of the patients of group 1 and group 4 (p>0.05). Similarly, difference between mean FBG and HbA1c of the patients of group 2 and group 3 was non significant (p>0.001).

Demographic Parameters	Group 1 (n=10)	Group 2 (n=10)	Group 3 (n=10)	Group 4 (n=10)	Test Statistic	p-value
Age (Years)	41.90± 13.52	45.70± 13.70	43.90± 12.31	41.80± 9.17	$F_{3,36}$= 0.227	0.877 NS
Gender (Male: Female)	8:2	7:3	4:6	7:3	χ_2 =3.95	0.26 NS
BMI (kg/m^2)	18.84± 1.10	19.86± 6.55	33.74± 2.65	20.60± 1.50	$F_{3,36}$= 53.64	<0.001*
WC (cm) male	90.50± 8.45	89.10± 9.00	101.60± 8.67	89.00± 10.26	3.710	0.020*
WC (cm) female	78.85± 6.56	79.76± 6.97	97.43± 9.54	77.46± 8.67	2.310	0.030*
SFT (cm)	9.91± 1.19	9.28± 1.60	14.97± 1.56	10.61± 1.90	2.265	0.018*
Bilirubin (Total)	0.74± 0.17	0.81± 0.17	0.81± 0.11	0.82± 0.12	0.649	0.589 NS
Bilirubin (Direct)	0.31± 0.19	0.38± 0.20	0.54± 0.17	0.51± 0.26	2.661	0.059 NS
ALT (IU/L)	42.70± 25.69	37.00± 9.50	37.40± 10.39	39.50± 20.81	2.049	0.124 NS
AST (IU/L)	37.40± 8.33	37.90± 15.24	39.40± 14.25	37.50± 19.06	1.022	0.394 NS
ALP (IU/L)	167.70± 22.38	153.10± 18.89	170.90± 30.56	168.40± 31.47	0.936	0.433 NS
GGT (IU/L)	43.90± 12.76	46.00± 6.94	49.40± 11.23	43.30± 14.75	0.547	0.653 NS
Albumin (gm/dL)	4.31± 0.40	4.26± 0.41	4.22± 0.51	4.31± 0.31	0.111	0.953 NS
Globulin (gm/dL)	3.98± 0.33	4.49± 0.38	4.26± 0.31	4.51± 0.46	4.395	0.010*
FBG (mg/dL)	93.70± 12.47	190.70± 62.76	199.20± 21.48	87.70± 7.44	19.830	<0.0001*
HbA1c (%)	5.52± 0.46	6.72± 0.40	6.92± 0.29	5.61± 0.41	3.014	0.043*

[Table/Fig-2]: Comparison of demographic, anthropometric and biochemical parameters of the patients of the four groups.
*Statistically significant; NS: Statistically not significant; ANOVA test for mean values. Chi-square test for categorical data

Lipid profile was compared in all four groups [Table/Fig-3]. There was significant difference in mean level of TG, cholesterol, and Low Density Lipoprotein (LDL) of the patients of the four groups (p<0.05). Mean level of TG, cholesterol, and LDL of the patients of group 2 and group 3 were significantly higher than that of group 1 and group 4 (p<0.001), but there was no significant difference seen in the mean level of TG, cholesterol, LDL of the patients of group 1 and group 4 (p>0.05). Mean level of TG, cholesterol, LDL of the patients of group 3 was significantly higher than that of group 2 (p<0.05). There was no significant difference in mean level of VLDL (p-0.418) and HDL (p-0.27) of the patients of the four groups.

Lipid profile	Group 1 (n=10)	Group 2 (n=10)	Group 3 (n=10)	Group 4 (n=10)	$F_{3,36\text{-value}}$	p-value
Triglyceride level (mg/dL)	122.30± 26.23	164.20± 26.31	230.80± 27.52	97.60± 13.70	4.697	0.007*
Cholesterol level (mg/dL)	121.70± 26.75	264.30± 40.13	309.40± 52.59	141.50± 9.85	7.434	0.001*
HDL (mg/dL)	40.50± 9.18	39.60± 5.85	34.40± 6.74	44.70± 6.67	3.436	0.27 NS
LDL (mg/dL)	132.00± 30.55	163.70± 32.50	191.20± 46.00	63.40± 14.14	15.038	<0.0001*
VLDL (mg/dL)	25.90± 5.57	29.80± 6.75	26.70± 5.79	25.30± 7.44	0.968	0.418 NS

[Table/Fig-3]: Comparison of lipid profile of the patients of the four groups.
*Statistically Significant; NS: Statistically not Significant; ANOVA test for mean values; Chi-square test for categorical data

Insulin resistance: Insulin resistance was analysed by HOMA-IR. Mean values of HOMA-IR of four groups are shown in [Table/Fig-4]. There was significant difference in mean values for HOMA-IR of the subjects of the four groups (p<0.001). Mean HOMA-IR of the subjects of group 2 and group 3 were significantly higher than that of group 1 and group 4 (p<0.001). But there was no significant difference in HOMA-IR of the patients of group 1 and group 4 (p>0.05) and also mean HOMA-IR of the patients of group 2 and group 3 (p>0.05).

Insulin resistance	Group 1 (n=10)	Group 2 (n=10)	Group 3 (n=10)	Group 4 (n=10)	$F_{3,36\text{-value}}$	p-value
HOMA-IR	8.71± 2.17	11.57± 2.23	13.75± 2.32	6.10± 2.34	21.658	0.001*

[Table/Fig-4]: Comparison of insulin resistance of the patients of the four groups.
*Statistically Significant

DISCUSSION

In the present study done from northeast India, author aimed to characterise the metabolic profile of lean NAFLD subjects, with or without DM2 and compared them with healthy (normal BMI) controls and obese subjects with NAFLD. With regards to most anthropometric and metabolic parameters such as WC, SFT, BMI, lipid profile, FBG and HbA1C, lean NAFLD subjects were in between lean control and obese NAFLD in this study. This finding was supported by Younossi ZM et al., which showed significant metabolic and anthropometric abnormalities in both lean and obese NAFLD in comparison to their controls, along with moderately deranged parameters in lean. Younossi ZM et al., also showed lesser prevalence of insulin resistance, diabetes and hypercholesterolemia in lean NAFLD, in comparison to obese NAFLD. According to their study, obese candidates were more likely to have components of metabolic syndrome [17].

In current study, lipid profile of lean NAFLD with DM2 subjects and obese subjects were significantly deranged in comparison to lean NAFLD without DM2 and healthy controls. Marchesini G et al., reported higher dyslipidemic changes in NAFLD with high BMI in comparison to normal weight NAFLD [1]. Prevalence of higher BMI was seen in 67% of obese NAFLD, while it was seen only in 18% of lean NAFLD subjects. Till date, at best of our knowledge, no previous data is available which analyse the comparison of lipid profile of lean NAFLD without diabetes with healthy controls. Author reported no significant difference in lipid profile of lean NAFLD without DM2 subjects and healthy controls, whereas lipid profile of obese NAFLD subjects was significantly higher than that of lean NAFLD with DM2. It suggests a lesser degree of systemic metabolic derangements in lean NAFLD subjects in comparison to those who are additionally obese. It is important to understand that a different picture arises from a comparison of lipid profile from lean NAFLD subjects to overweight-obese NAFLD patients. Infact lean NAFLD subjects are less likely to have altered parameters of metabolic syndrome. It indicates that lean NAFLD patients may have other metabolic abnormalities which may lead to NAFLD in the setting of less severe metabolic conditions.

Simultaneously, diabetes have a contributory role in pathogenesis of NAFLD, which may lead to more severe derangement of metabolic parameters in lean NAFLD with DM2 in comparison to those without DM2. Other postulated causes of lean NAFLD could include mutations, altered gastrointestinal motility, and other metabolic derangements not associated with weight gain.

Besides lipid profile, author found that other metabolic parameters also follow a characteristic pattern in lean NAFLD subjects. Significant difference was found in mean FBG of the candidates of the four groups. As expected, mean FBG of the patients of lean NAFLD with DM2 and obese NAFLD were significantly higher than that of obese NAFLD without DM2. Although glycaemic status of the subjects of lean NAFLD without DM2 and healthy control group were similar. Similarly mean FBG of obese NAFLD with DM2 subjects and obese NAFLD subjects was comparable. Similar results were identified from western data, where prevalence of diabetes was shown to be higher in obese NAFLD subjects in comparison to lean NAFLD

[17]. In addition, Younossi ZM et al., noted that the prevalence of diabetes was more in obese controls as compared to healthy controls [17]. Mean HbA1c of the patients of lean NAFLD with DM2 and obese NAFLD was significantly higher than that lean NAFLD without DM2. Mean HbA1c of the patients of lean NAFLD without DM2 and healthy controls were similar. Also the mean HbA1c of the patients of lean NAFLD with DM2 and obese NAFLD were comparable. Findings in current study were in concordance with previous data, which showed similar higher HbA1c in obese NAFLD subjects in comparison to lean NAFLD [17].

In other studies also, similar altered metabolic profile was observed in lean NAFLD patients in comparison to obese NAFLD. Kumar R et al., reported lesser prevalence of diabetes and milder degree of dyslipidaemia in lean NAFLD in comparison to obese NAFLD [18]. Although, in their study similar lipid profile derangements were reported in all BMI categories. In current study, mean insulin resistance of lean NAFLD with DM2 and obese NAFLD subjects were significantly higher than that of lean NAFLD without DM2 and healthy controls. But no significant difference in mean insulin resistance was found between lean NAFLD with DM2 and obese NAFLD subjects, and mean insulin resistance of the patients of lean NAFLD without DM2 and healthy controls. Comparable results were reported in previous studies [18-20]. Kumar R et al., mentioned lesser prevalence of insulin resistance in lean NAFLD, in comparison to obese NAFLD measured by fasting hyperinsulinemia, HOMA-IR, irrespective of lipid profile [18]. Yun J et al., analysed insulin resistance indirectly by Oral Glucose Tolerance Test (OGTT) and found that prevalence of abnormal OGTT is directly proportional to BMI in NAFLD subjects [20]. Another study from Hongkong showed higher prevalence of insulin resistance in NAFLD subjects by indicating higher postchallenge hyperglycaemia in non diabetic NAFLD Chinese subjects [21]. Their study concluded that isolated postchallenge hyperglycaemia is prevalent in NAFLD candidates, even in absence of diabetes. Hence, glucose homeostasis appears to be particularly affected in subjects with NAFLD in the absence of obesity, suggesting that the accumulation of liver fat may be of particular importance to the development of insulin resistance and diabetes even in the absence of obesity [19,22]. Park S et al., reported a correlation between developing NAFLD and higher FBG, HOMA-IR, TG and decreased HDL. Although, this study didn't show any contributory role of liver fat in development of insulin resistance, but an association was established [19]. Sinn D et al., conducted an ultrasonography based study, which reported that NAFLD is an independent predictor of insulin resistance, measured by HOMA-IR, regardless of other components of metabolic syndrome in lean/non obese subjects in absence of diabetes [22].

Present study serves as a pioneer study for the comparative assessment of insulin resistance in lean NAFLD subjects particularly in relation to diabetes. Authors have reported that lean individuals with NAFLD have a different metabolic profile than overweight-obese patients with NAFLD. In lean NAFLD subjects, difference in metabolic profile between diabetic and non diabetic subjects, and similarity of lean NAFLD with diabetes subjects with obese NAFLD, shows that both lean and obese NAFLD can share same pathogenesis with difference in origin of insulin resistance. On the basis of present study analysis, authors propose a spectrum of insulin resistance 'Non obese Control-Non obese NAFLD without DM-Non obese NAFLD with DM-Obese NAFLD with DM'.

To summarise, findings of current study suggests that dysfunction of adipose tissue plays a role in lean NAFLD subjects, with different severity in subjects with or without DM2. From this study, authors conclude that insulin sensitivity differs in lean NAFLD subjects in comparison to obese NAFLD subjects. Authors did not found any significant difference in insulin sensitivity between lean NAFLD with DM2 and obese NAFLD, but difference was significant in comparison to lean NAFLD without DM2.

Limitation(s)

There were several limitations in present study. First, authors could not establish a temporal association between insulin resistance and NAFLD. Another major limitation of the current study was the limited accuracy of the ultrasound used to establish the diagnosis of NAFLD. This is especially true for patients who have less than moderate-severe hepatic steatosis (as determined by ultrasound). In these cases, other modalities, such as Magnetic Resonance Imaging (MRI) or proton Magnetic Resonance Spectroscopy (MRS), may be more accurate to detect smaller amounts of hepatic steatosis. Beside all these limitations, sample size of present study was quite small. Acknowledging these limitations, the data presented herein mandate the need for larger study.

CONCLUSION(S)

Lean NAFLD is a liver disorder that can be associated with insulin resistance and type 2 diabetes. With increasing prevalence of lean NAFLD, it is important to understand the underlying pathophysiology of disease. The mechanisms underlying the development of NAFLD is not completely clear, however, present study provided an insight and helps in understanding the development and pattern of developing insulin resistance in lean NAFLD subjects. Future research should focus on clarifying the relationship between hepatic and peripheral insulin resistance and the development of hepatic steatosis. Lean NAFLD subjects may be or may not be dyslipidemic, but those who develop diabetes, are mostly dyslipidemic and metabolically behave more similar to obese NAFLD subjects. Compared to obese NAFLD, patients with lean NAFLD have minor or no insulin resistance, particularly those who do not have diabetes.

REFERENCES

[1] Marchesini G, Bugianesi E, Forlani G. Non-alcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology. 2003;37:917-23.
[2] Das K, Chowdhury A. Lean NASH: Distinctiveness and clinical implication. Hepatol Int. 2013;7(Suppl 2):S806–S813/ DOI 10.1007/s12072-013-9477-5 .
[3] Gökhan S. Hotamisligil, Inflammation and metabolic disorders. Nature. 2006;444|14 December |doi:10.1038/nature05485
[4] Chen C, Huang M, Yang J. Prevalence and risk factors of non-alcoholic fatty liver disease in an adult population of Taiwan: Metabolic significance of non-alcoholic fatty liver disease in non obese adults. J Clin Gastroenterol. 2006;40:745-52.
[5] Kim H, Kim H, Lee K. Metabolic significance of non-alcoholic fatty liver disease in non obese, non diabetic adults. Arch Intern Med. 2004;164:2169-75.
[6] Arshad T, Golabi P, Henry L, Younossi Z. Epidemiology of non-alcoholic fatty liver disease in North America. Journal Name: Current Pharmaceutical Design. 2020;26(10)
[7] Margariti E, Deutsch M, Manolakopoulos S. Non-alcoholic fatty liver disease may develop in individuals with normal body mass index. Annals of Gastroenterology. 2012;25:45-51.
[8] Das K, Das K, Mukherjee P. Non obese population in a developing country: A high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology. 2010;51:1593-602.
[9] Petersen K, Dufour D, Feng J. Increased prevalence of insulin resistance and nonalcoholic fatty liver disease in Asian-Indian men. PNAS. 2006;103(48):18273-77.
[10] Chandalia M, Lin P, Seenivasan T, Livingston EH, Snell PG, et al. Insulin resistance and body fat distribution in south Asian men compared to Caucasian men. PLoS ONE. 2007;2(8):e812. doi:10.1371/journal.pone.0000812
[11] Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome- A new worldwide definition. Lancet. 2005;366(9491):1059.
[12] Misra A. Ethnic-Specific Criteria for Classification of Body Mass Index: A Perspective for Asian Indians and American Diabetes Association Position Statement. Diabetes Technology & Therapeutics. 2015;17(9):667-69.
[13] Chobanian A, Bakris G, Black H, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report, the National High Blood Pressure Education Program Coordinating committee. JAMA. 2003;289:2560-72.
[14] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;32(1).
[15] National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), NIH Publication No. 02-5215 September 2002

[16] Yojima Y, Ohta K. Ultrasonographical diagnosis of fatty liver: Significance of liver kidney contrast . Tohuku J Exp Med. 1983;139:43-50.
[17] Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, Srishord M. Non-alcoholic fatty liver disease in lean individuals in the United States. Medicine. 2012;91(6):319-327.
[18] Kumar R, Rastogi A, Sharma M. Clinicopathological characteristics and metabolic profiles of non-alcoholic fatty liver disease in Indian patients with normal body mass index: Do they differ from obese or overweight non-alcoholic fatty liver disease? Indian Journal of Endocrinology and Metabolism. 2013;17(4):665-71.
[19] Park S, Kim B,Yun J. Insulin resistance and C-reactive protein as independent risk factors for non-alcoholic fatty liver disease in non-obese Asian men. Journal of Gastroenterology and Hepatology. 2004;19:694-98.
[20] Yun J, Cho Y, Park J. Abnormal glucose tolerance in young male patients with non-alcoholic fatty liver disease. Liver International. 2009; DOI:10.1111/j.1478-3231.2008.01920.x
[21] Wong V, Hui A, Tsang S. Prevalence of undiagnosed diabetes and postchallenge hyperglycaemia in Chinese patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 24:1215-22.
[22] Sinn D, Gwak G, Park H. Ultrasonographically detected non-alcoholic fatty liver disease is an independent predictor for identifying patients with insulin resistance in non-obese, non-diabetic middle-aged Asian adults. Am J Gastroenterol. 2012;107:561-67; doi: 10.1038/ajg.2011.400; published online 22 November 2011

PARTICULARS OF CONTRIBUTORS:
1. Consultant, Department of Gastroenterology and Hepatology, ILS Hospital, Agartala, Tripura, India.
2. Consultant, Department of Pathology, ILS Hospital, Agartala, Tripura, India.
3. Consultant, Department of Surgery, ILS Hospital, Agartala, Tripura, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Akash Jaiswal,
Quarter No 4, ILS Hospital Premises, Kunjawan, Agartala, Tripura, India.
E-mail: akashjaiswal19@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 28, 2021
- Manual Googling: Sep 28, 2021
- iThenticate Software: Oct 05, 2021 (23%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Jul 26, 2021**
Date of Peer Review: **Sep 07, 2021**
Date of Acceptance: **Sep 28, 2021**
Date of Publishing: **Nov 01, 2021**