Clinical and Metabolic Profiles of Patients with Lean Non-Alcoholic Fatty Liver Diseases (NAFLD) Attending a Tertiary Health Care Centre of North-Eastern Region

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ABSTRACT

BACKGROUND

NAFLD has become one of the most common liver conditions throughout the world which is now increasingly diagnosed in developing countries. Most of Lean NAFLD Patients are prone to Metabolic Syndrome.

METHODS

In this cross-sectional study descriptive and inferential statistical analysis has been carried out taking 75 (seventy-five) cases of lean NAFLD from January 2016 to June 2017 at Agartala Government Medical College & G.B.P. Hospital.

RESULTS

Amongst 75 (seventy-five) cases, 40% patients had systolic BP in the range of 120-139 mmHg followed by 36% below 120 mmHg and 18% had SBP >140 mmHg. Diastolic BP in the range of 80-89 mmHg was found in 64% of patients. Out of the 22 hypertensive patients, 18 were from 45-60 years age group, whereas most of the normotensive patients belongs to 30-45 years age group. Out of 20 diabetes patients, 14 were from 45-60 years age group, whereas most of the non-diabetes patients belongs to 30-45 years age group. In <30 years total cholesterol was 179.00 ± 29.70 mg/dL, 179.32 ± 24.90 mg/dL in 30-45 yrs. and in 45-60 yrs. was 194.55 ± 25.84 mg/dL. Triglyceride level was 140.00 ± 0.00 mg/dL in <30 years, 175.34 ± 43.87 mg/dL in 30-45 yrs. and 243.07 ± 79.24 mg/dL in 45-60 yrs. Waist hip ratio was raised in 61.3% patients, while 38.7% patient had normal waist-hip ratio (WHR). 20 patients from the age group 45-60 years had metabolic syndrome among 33 positive cases. It was followed by 13 patients from 30-45 years age group, whereas no patients belong to <30 years age group. 80% of the patients had low HDL level, 74.7% patients had hypertriglyceridaemia and all of them had metabolic syndrome too.

CONCLUSIONS

44% of the cases had metabolic syndrome and 80% of them had at least one component of metabolic syndrome. The lean NAFLD patients were metabolically similar to obese population.

KEYWORDS

NAFLD, MS, SBP, WHR

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BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is the condition where fat accumulates in the liver without significant ingestion of alcohol or consumption of certain drugs.[1] consists of different magnitudes of liver conditions from simple steatosis to non-alcoholic steatohepatitis (NASH), NASH related cirrhosis and hepatocellular carcinoma (HCC).[2] NAFLD has become one of the most common liver conditions throughout the world, though initially detected in greater number in industrialized countries but now increasingly diagnosed in developing countries as well.[3] The prevalence of NAFLD in the USA is 32% to 40% and in Indian population ranges from 5% to 28%.[4]

At the dawn of the history of NAFLD, it was thought that NAFLD is a disease in obese of affluent society but that concept is changing. Lean patients are increasingly detected to have NAFLD. In developed countries, 15% of NAFLD patients are non-obese but 65% and 85% are obese and morbidly obese respectively.[5] In developing countries, the reality is different. Obesity is an important risk factor for NAFLD and was thought to determine severity of NAFLD. It was always thought that hepatic steatosis is a manifestation of metabolic syndrome. Obese persons with type 2 diabetes are universally found to have NAFLD.

Although NAFLD is more common in subjects with obesity and diabetes mellitus (DM), it does occur in lean and non-diabetic subject.[2,4,5] Furthermore, compared to the West, Indians are known to develop NAFLD at lower degree of adiposity[2,6,7] In a recent population-based epidemiological study[2] in India, 75% of individuals with NAFLD were non-obese and 54% were neither overweight nor had central obesity. Another recent study[7] revealed that lean, non-alcoholic, non-diabetic, non-smoking ethnic Asian Indians in comparison to matched Caucasians, Hispanics, Black and Eastern Asians had 2- to 3-fold increase in insulin resistance (IR) and 2-fold increase in hepatic triglyceride content. Recent concepts also suggest that the magnitude of adipose tissue dysfunction may have more metabolic impact than the severity of adiposity.[8]

Adipose tissues secretes adiponectin, leptin, TNF alpha and resistin, and an imbalance of these components leads to NAFLD.[9] It is believed, in one hand, that not all excessive body fats are relevant, rather visceral obesity seems to be a metabolically dangerous one, being the main source of fatty acid and pro-steatogenic, pro-inflammatory and fibrogenic mediators.[10]

Asians with lower BMI have abdominal obesity and central obesity that includes subcutaneous abdominal fat which is relatively inert metabolically does not exactly corresponds to visceral adiposity.[11] Adipose tissue of lean NAFLD may be more metabolically active.[12]

A significantly higher serum alanine transaminase (ALT) and aspartate transaminase (AST) levels were found in a study of NAFLD patients with a normal BMI compared to Overweight or obese patients.[13,14,15] The recommended body mass index (BMI) cut off values for Asians for defining overweight (23-25 Kg/m^2) and obesity (>25 Kg/m^2) are lesser than those of Western populations.[16] Patients with lean NAFLD are defined as individuals having NAFLD with Body Mass Index (BMI) <23 Kg/m^2. Most of lean NAFLD patients had one or more component of metabolic syndromes and all components of metabolic syndrome are seen in 50% to 80% of these patients.[8]

The Asians are known to develop central obesity at lower BMI. Also, lower preponderance of adiposity in Indian NAFLD is well-documented;[2,6,7] however, data on clinical characteristics, metabolic profiles[17] and histopathological severity in patients with lean NAFLD in comparison to the overweight or obese NAFLD patients is scanty. It is not clear what proportion of lean NAFLD in India has abdominal obesity, IR, and features of metabolic syndrome (MS). Therefore, this study was conducted to evaluate the magnitude and clinical profiles, metabolic profiles of patients with lean NAFLD.

METHODS

Adult male or female patient of 18-60 years age, BMI < 23 Kg/m^2 and USG evidence of fatty liver without any alcohol consumption were included. Patients with HBV, HCV positivity; Liver diseases of other known causes; Patients consuming alcohol or drugs such as oestrogen, ATT, tamoxifen, methotrexate, amiodarone; Age less than 18 years and more than 60 years; Unwilling or incapacity to provide informed consent were excluded. After obtaining an Institutional Ethical Clearance and an informed consent, 75 Patients' detailed history was collected and clinical examination was done over a period of one and half year. Diagnosed NAFLD Patients attending Agartala Government Medical College & GBP Hospital was included in the study. NAFLD was diagnosed based on ultrasound evidence of fatty liver and persistent elevation of serum alanine aminotransferase (ALT) >1.5 times the upper limit (ULN for male-30 U/L, female-19 U/L).[18] Body mass index (BMI; Kg/m^2) was calculated using Quetelet index formula (BMI=Body weight in Kg/Height in meter square (m^2)). Patients with BMI >23 Kg/m^2 defined as overweight and those with a BMI >25 Kg/m^2 was labelled as pre-obese/obese according to Asian standards.[16] As per Asian standard all those patients who were neither obese nor overweight (i.e., BMI <23 Kg/m^2) were labelled as Lean in this study. Waist circumference (WC) and hip circumference (HC) in centimeters was measured at the level of the umbilicus and at the widest portion of buttocks, respectively. Waist-hip ratio (WHR) was calculated by dividing waist circumference by hip circumference. Increased WHR is defined as >0.90 in men and > 0.85 in women.[19]

After an overnight fast, 10 mL of blood was collected for a complete blood count and biochemical investigations including a liver function profile, lipid profile and fasting blood glucose Basic viral markers, namely HBsAg and antiHCV was done by Enzyme linked immunosorbent assays (ELISA) to exclude hepatitis B and C infection.

Cut off values for fasting blood glucose -110 mg/dL, serum triglyceride - >150 mg/dL, serum HDL cholesterol <50 mg/dL for women and <40 mg/dL for men, ALT>1.5 times of normal. Metabolic syndrome was defined as per Modified Adult Treatment Panel III criteria for Asians[20] and three of the five listed criteria were considered:

Ultrasonography (USG) was performed in fasting state for grading the extent of fatty liver and to look for evidence of portal hypertension using SONO ACEX 8 Manufactured by Medison. Convex probe with frequency of 2 to 5 mHz.

Grades	USG features
Grade 0	Normal echogenicity
Grade 1	Slight, diffuse increase in fine echoes in liver parenchyma with normal visualization of diaphragm and intrahepatic vessel borders.
Grade 2	Moderate, diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm
Grade 3	Marked increase in fine echoes with poor or non-visualization of the intrahepatic vessel borders, diaphragm, and posterior right lobe of the liver.

Statistical Analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Analysis of variance (ANOVA), Chi-square/ Fisher Exact test has been used to find the significance of study parameters. The Statistical software namely SPSS 18.0, and R environment Ver.3.2.2 were used.

RESULTS

BP	Age in Years			Total (n=75)	p
	<30 Y (n=2)	30-45 Y (n=44)	45-60 Y (n=29)		
SBP (mmHg)					
• <120	2(100%)	19(43.2%)	6(20.7%)	27(36%)	0.004**
• 120-139	0(0%)	20(45.5%)	10(34.5%)	30(40%)	
• >/=140	0(0%)	5(11.4%)	13(44.8%)	18(24%)	
DBP (mmHg)					
• <80	1(50%)	15(34.1%)	8(27.6%)	24(32%)	0.227
• 80-89	1(50%)	29(65.9%)	18(62.1%)	48(64%)	
• >/=90	0(0%)	0(0%)	3(10.3%)	3(4%)	

Table 1. Association of Blood Pressure with Study Group

Variables	Age in Years			Total	p
	<30 Y	30-45 Y	45-60 Y		
No Hypertension	2(100%)	38(86.4%)	13(44.8%)	53(70.7%)	<0.001**
Hypertension	0(0%)	6(13.6%)	18(62.1%)	22(29.3%)	
No Diabetes	2(100%)	38(86.4%)	15(51.7%)	55(73.3%)	0.002**,
Diabetes	0(0%)	6(13.6%)	14(48.3%)	20(26.7%)	
Increased WHR	2(100%)	24(54.5%)	20(69%)	46(61.3%)	0.458
Normal WHR	0(0%)	20(45.5%)	9(31%)	29(38.7%)	
MS - present	0(0%)	13(29.5%)	20(69%)	33(44%)	0.001**,
MS - absent	2(100%)	31(70.5%)	9(31%)	42(56%)	
Low HDL	1(50%)	34(77.3%)	25(86.2%)	60(80%)	0.250
Normal HDL	1(50%)	10(22.7%)	4(13.8%)	15(20%)	
High TG	0(0%)	31(70.5%)	25(86.2%)	56(74.7%)	0.017*
Normal TG	2(100%)	13(29.5%)	4(13.8%)	19(25.3%)	
ALT (IU/L)	52.50 ± 0.71	56.00 ± 9.02	57.31 ± 16.50	56.41 ± 12.29	0.820
AST (IU/L)	37.50 ± 2.12	40.34 ± 10.07	41.03 ± 14.14	40.53 ± 11.62	0.906

Table 2. Association of Different Variables with Lean NAFLD Cases

In this study 40% patients had systolic BP in the range of 120-139 mmHg, followed by 36% below 120 mmHg SBP and 18% had SBP >140 mmHg. Diastolic BP in the range of 80-89 mmHg found in 64% of patients. Statistical analysis shows that there was a strong association (p value=0.004) between the patients studied and distribution of SBP, but distribution of DBP was not significant statistically.

Out of 22 hypertensive patients 18 were from 45-60 years age group, whereas most of the normotensive patients belongs to 30-45 years age group. Statistical analysis shows that there was a strong association (p value<0.001) between the patients studied and hypertension.

Out of 20 diabetes patients 14 were from 45-60 years age group, whereas most of the non-diabetes patients belongs to 30-45 years age group. Statistical analysis shows that there was a strong association (p value<0.001) between the patients studied and diabetes. It was observed that waist hip ratio was raised in 61.3% patients, while 38.7% patient had normal waist-hip ratio (WHR). P value calculated was 0.458 which was statistically not significant.

20 patients from the age group 45-60 years had metabolic syndrome among 33 positive cases. It was followed by 13 patients from 30-45 years age group, whereas no patients belong to <30 years age group. Statistical analysis shows that there was strong association between the patients studied and metabolic syndrome.

Though 80% of the patients had low HDL level, statistical analysis did not find any significance in relation to age. 74.7% patients had hypertriglyceridaemia and all of them had metabolic syndrome too. Statistical analysis shows that there was significant association between the patients studied and occurrence of Hypertriglyceridemia.

The mean ALT and AST levels were 56.41 ± 12.29 and 40.53 ± 11.62 respectively. These values were not significant statistically. Statistical analysis shows that there was no association between the patients studied and ALT/AST level.

Variable	Age in Years			Total	p
	<30 Y	30-45 Y	45-60 Y		
Tot. Chol.	179.00 ± 29.70	179.32 ± 24.90	194.55 ± 25.84	185.20 ± 26.09	0.046*
Tgl	140.00 ± 0.00	175.34 ± 43.87	243.07 ± 79.24	200.59 ± 68.41	<0.001**
LDL	113.00 ± 41.01	110.19 ± 20.73	111.88 ± 18.72	110.91 ± 20.15	0.932
HDL	38.00 ± 11.31	35.34 ± 8.74	34.06 ± 5.83	34.92 ± 7.72	0.674

Table 3. Comparison of Lipid Parameters (in mg/dL) in Relation to Age

In this study among the lipid parameters, Total Cholesterol and triglyceride level were statistically significant, (p values were 0.046 and <0.001 respectively) when comparison done in relation to different age group. P value was not significant for both HDL and LDL.

DISCUSSION

NAFLD in India had been reported to develop at lower BMI. In a population-based study from rural India, 52% of individuals with NAFLD were lean (BMI<23). Mean BMI in this study was 21.88 ± 0.75. So affected patients still had BMI towards higher side which was also found by Kumar ET al.[19] In their study also, the mean BMI of lean NAFLD

patients were higher than 131 non-selected healthy lean subjects without fatty liver.

Previous studies support the fact that in lean subjects, those with higher BMI levels are at greater risk of developing NAFLD. It may also suggest the epidemic proportion of the metabolic syndrome in India, wherein the population which is fast acquiring western lifestyle gets exposed to the detrimental effects of high calorie diet and physical inactivity at an earlier age. In fact, Indians have been shown to have higher body fat percentage and adverse pattern of body fat distribution including abdominal adiposity even when the BMI is within limits considered as normal for Caucasians.[21]

Out of 75 patients of lean NAFLD, triglyceride level was raised in 74.7% patients with a significant p value (P = 0.017). Low HDL was found in 80% (n=60) of studied patients which was highest prevailing component of metabolic syndrome in the study group. These findings were consistent with the findings of Alam S et al.[22] In their study they found Hypertriglyceridemia was prevailing in 73.2% patients followed by Low level of HDL (65.2%). At least 3 or more than 3 component of metabolic syndrome were identified in 44% (n=33) of studied Lean NAFLD patients in the present study. The most prevailing component being the low HDL which is present in 80% of patient. A study by Kumar R ET al[19] from India with 205 NAFLD patients elucidated that at least one criterion of metabolic syndrome was seen in 89% of lean NAFLD patients. The profiles of lean and overweight NAFLD were similar in terms of the metabolic variables such lipid profiles, levels of fasting blood glucose, and insulin.[19] A similar association of NAFLD and metabolic syndrome was seen among Caucasians, Americans, and Indians. Present study found only 29.3% of lean patients had waist circumference above the normal range. Kumar R ET al[19] in his study found that WC was smaller in non-obese population than that of obese (p= 0.000), and WC was above normal in 44.6% and 78.9% in non-obese and obese patients, respectively. BMI and abdominal obesity correlated with each other. But smaller WC in non-obese/lean NAFLD may be explained by the fact that central obesity includes subcutaneous fat that is relatively inert metabolically, which may not always exactly correspond to visceral adiposity. Visceral adipose tissues of lean NAFLD may be metabolically more active conferring metabolic risks leading to NAFLD. Another study has also found a poor association of abdominal adiposity with NAFLD in Asians.

Chaudhary NS ET al[10] found one fourth of patients with NAFLD had BMI <23 Kg/m^2 in their study. Though adipose tissue volumes were higher in those with overweight or obesity, when the adipose tissue volumes were adjusted for the BMI, there was no difference in the VATV/BMI in two groups. Hence, in spite of having low BMI, these patients had visceral fat volume comparable to those with overweight and obesity. Results from the present study are thus in concordance with Das K ET al[17] and Chaudhary NS et al. Further it suggest that even if some of the NAFLD patients do not have overweight or obesity, they do have a higher visceral adipose tissue volume.

Hypertension, diabetes mellitus, increased total Cholesterol, Triglyceride, LDL and low HDL, all were statistically significant in relation to metabolic syndrome in the present study. These Lean NAFLD patients seem to have an equal frequency compared to obese NAFLD patients as found in other studies, since the prevalence of hypertension, diabetes, glucose levels, and high triglycerides levels was all found to be statistically significant. It indicate that though these patients were non-obese by BMI grading, but they were metabolically similar, and components of metabolic syndrome are the basic culprit behind the development of NAFLD even the patients had not developed obesity yet.

Under normal condition, adipose tissues are the primary source (70%) of free fatty acids for hepatic triglyceride. Thus, adipose tissue IR may trigger excess release of fatty acids leading to development of hepatic "lipotoxicity" in NAFLD.

A study has reported that patients with NASH have severe adipose tissue IR independent of the degree of obesity, and amelioration of adipose tissue IR by pioglitazone is closely related to histological improvement.[23] the lean NASH may have accelerated lipolysis due to IR, mainly at adipose tissues. More recent studies propose that although dyslipidaemia and dysglycaemia are two components of fatty liver disease, this condition is independent of fat deposits, including visceral adipose tissue. In light of the current findings regardless of the role of visceral adipose tissue in development of fatty liver, hypertriglyceridemia per se should be considered a marker of NAFLD in lean subjects.

Central obesity can be assessed by measuring the visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), and is directly associated with metabolic and cardiovascular diseases. VAT and SAT are different in terms of anatomical location, endocrine activity, saturation status, and their effect on disturbing glucose and lipid metabolism as well as serum triglyceride level. In a longitudinal study of 288 patients with NAFLD, Kim ET al[24] showed that an increase in VAT area at baseline is an independent predictor of NAFLD development, while increases in the SAT area are associated with regression of NAFLD in an apparently healthy general population. The causes of NAFLD development in patients with normal BMI and no metabolic risk factor have not been completely clarified. Given the multi-factorial pathogenesis of this disease, genetic factors and/or specific dietary habits might be responsible for the development of NAFLD in lean individuals, even in the absence of metabolic disorders.

CONCLUSIONS

Male middle aged populations were affected more with lean NAFLD. Among the study group, 44% patients had metabolic syndrome and 80% of them had at least one component of metabolic syndrome. Dyslipidaemia, hypertension and diabetes mellitus all were found to be associated with the development of metabolic syndrome and NAFLD. Though all

the patients in the study were nonobese by BMI grade, they were metabolically similar to the obese population. Further studies are required with larger sample size at community level for better interpretation of clinical and metabolic profile of patients with lean NAFLD.

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