Lean NAFLD: Is their metabolic pattern unique in type 2 diabetes mellitus patients?

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Abstract

Introduction: 'Lean NAFLD' has been defined as the Non-alcoholic fatty liver disease(NAFLD)in the absence of overweight and/or obesity, defined by the anthropometric parameter, body mass index (BMI).

Aims and Objectives: To assess the prevalence of lean NAFLD in type 2 diabetes mellitus(T2DM) patients and to compare the clinical and metabolic profile among lean, overweight and obese NAFLD patients.

Materials and Method: 60 type 2 diabetes mellitus patients with NAFLD were analyzed for the demographic, anthropometric and biochemical data. The subjects were categorized into three groups according to their BMI, namely lean, overweight and obese NAFLD. One way Analysis of Variance was used to compare the means of continuous variables between groups.

Results: The prevalence of lean NAFLD was 25% in our study population. Lean NAFLD patients had lower fasting, but higher postprandial blood glucose and higher insulin resistance. They had comparable blood pressure, HDL-C, total proteins, albumin and bilirubin. Triglycerides, total cholesterol, LDL-C, AST, ALT, AST/ALT ratio, and GGT were significantly different between the three groups.

Conclusion: Lean NAFLD patients were unique in terms of their blood glucose, Insulin resistance, lipid profile and liver enzymes when compared to the overweight and obese NAFLD.

Keywords: NAFLD, Type 2 Diabetes Mellitus, Lean NAFLD, Overweight, Obese.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is highly associated with obesity and insulin resistance (IR) and represents a spectrum of liver injury ranging from simple steatosis with a more benign course to nonalcoholic steatohepatitis (NASH) which may progress to advanced fibrosis and cirrhosis.[1,2]

The prevalence of NAFLD varies depending on the study population and the diagnostic tool used to determine the condition. Fatty liver is a common finding among type 2 diabetes mellitus patients. Along with the increasing westernization of diet, physical inactivity, and the obesity epidemic,[3] the world wide prevalence of non-alcoholic fatty liver disease is increasing rapidly, affecting between 15 and 30% of adults.[4,5] In India, the prevalence of NAFLD in pre-diabetics and diabetics varies from 33 to 55%.[6] A recent study carried out in the same region as the present study, has reported a prevalence of 36% NAFLD among T2DM patients.[7] It has been clearly established that individuals with NAFLD, especially those with metabolic syndrome, have higher overall mortality, cardiovascular mortality, and liver-related mortality compared with the general population.

Although NAFLD is considered to be a disease of obesity, accumulating evidence have shown that NAFLD occurs in non-obese and non-overweight (defined as BMI < 25 kg/m^2) persons as well. Based on the third NHANES data, 7% of the lean individuals have NAFLD compared to 28% of the overweight-obese population.[8] The prevalence of NAFLD in nondiabetic, non-obese adults was 23.4% (16.1% in the normal-weight group and 34.4% in the overweight group)in the study of Kim et al.[9] Du et al had concluded that the association of NAFLD with diabetes is more pronounced in normal-weight individuals than in overweight/obese individuals among participants without metabolic at-risk.[10]

The recommended BMI cut off values for Asians for defining overweight (23-25kg/m2) and obesity (>25kg/m2) are lesser than those of western populations.[11] Few Indian studies have documented the lower preponderance of adiposity in Indian NAFLD.[12,13] Recently more attention is paid to the occurrence of NAFLD because of its associated severe complications. However, there is paucity of data on the metabolic profile of normal weight NAFLD type 2 diabetes patients in our population. Hence, the study was designed to assess whether the lean NAFLD patients differ from the overweight and obese patients.

Materials and Method

This is a hospital based cross sectional study which includes 60 type 2 diabetes mellitus patients diagnosed with NAFLD. The study was carried out in a tertiary care centre over a period of 10 months from February 2016 to November 2016. Ethical clearance was obtained from the Institutional ethical committee. Informed verbal

consent was taken from each patient after explaining the nature of study. A pre-designed pro-forma was filled in, which includes the demographic, anthropometric and clinical details of the study subjects. All the type 2 DM patients diagnosed with fatty liver by ultrasound were considered for the study. Patients with known liver diseases, hepatotoxic drug intake, and alcoholism were excluded from the study.

The height, body weight, waist circumference (WC), and hip circumference (HC) were measured. Measurement was done by the investigators themselves.

After 8 - 12 hours of overnight fast, 5ml of venous blood samples were collected from all the study subjects and serum was separated, stored at -20^{0}C for insulin measurements. Insulin assay was done using the ELISA. The remaining sample was used for the analysis of blood glucose, lipid profile, total bilirubin, AST, ALT, GGT, total proteins, albumin and globulin by standard methods. All the biochemical parameters were analyzed by using the Randox fully automated analyzer. The Homeostasis Model Assessment of IR (HOMA-IR) has proved to be a robust tool for the surrogate assessment of Insulin Resistance. IR was calculated by the HOMA-IR.[14]

Body mass index and Waist hip ratio(WHR) were calculated with the anthropometric data. BMI was calculated using the Quetelet's index. Based upon the BMI, the subjects were categorized into three groups namely, lean NAFLD(BMI 18.5 – 23 kg/m^2), overweight NAFLD(BMI 23 – 25kg/m^2) and obese NAFLD(BMI > 25kg/m^2). This was done according to the classification of adult body weight by BMI in Asian populations.[11] WHR of > 0.9 in men and > 0.8 in women was defined as central obesity.

Statistical analysis: All quantitative data are presented as mean ± SD and qualitative data are presented as percentages. Statistical analysis was done by using SPSS software. One way Analysis of Variance was used to analyze the differences among group means. p- value less than 0.05 was considered statistically significant.

Results

Table 1 depicts the baseline characteristics of all the study subjects categorized into three groups. Table 2 shows the metabolic profile of the three study group subjects compared with each other.

Table 1: Baseline demographic characteristics of study subjects

Variables	Lean NAFLD (A)	Overweight NAFLD (B)	Obese NAFLD (C)	p-value
Participants (n)	15	33	12	-
Age (Yrs)	52.87±8.17	51.10±7.62	49.88±8.61	NS
Male/Female	5/10	14/19	5/7	-
Diabetes duration (Yrs)	6.31±5.51*#	4.85±3.31	3.81±3.29	<0.05 (A&B) (A&C)
BMI	21.92±1.01*#	24.20±0.56	31.23±2.12	< 0.05
WHR	0.93 ± 0.03	0.94 ± 0.04	0.97 ±0.08	NS
Systolic pressure(mm/Hg)	127.73 ±16.18	127.23 ±17.49	124.75 ±12.46	NS
Diastolic pressure(mm/Hg)	79.87 ±8.25	79.61 ±9.44	78.75 ±8.94	NS

NS – Not significant; *Significance between A and C; # Significance between A and B

Table 2: Biochemical characteristics of study subjects

Variables	Lean NAFLD (A)	Overweight NAFLD (B)	Obese NAFLD (C)	p-value
Fasting blood Glucose (mg/dl)	142.07±53.71*	148.45±41.01	156.00±39.33	<0.05 (A&C)
PPBG(mg/dl)	287.60±60.24*	270.77±42.39	239.13±64.45	<0.05 (A&C)
Insulin(µIU/ml)	57.03±27.67*	59.16±22.79	44.92±8.91	<0.05 (A&C)
Insulin resistance	22.70±13.60*	22.1±12.08	17.14±4.8	<0.05 (A&C)
Total cholesterol(mg/dl)	270.53±48.24#	256.81±43.92	276.25±41.71	<0.05 (A&B)
Triglycerides(mg/dl)	254.67±54.71#	268.65±59.30	264.75±33.93	<0.05 (A&B)
HDL(mg/dl)	42.40±8.78	42.42±9.68	41.75±10.52	NS
LDL(mg/dl)	179.20±44.09#	170.66±41.56	181.55±38.24	<0.05 (A&B)
Total bilirubin(mg/dl)	0.69±0.37	0.59±0.21	0.50±0.21	NS
AST(U/L)	39.27±18.67#	31.58±16.93	42.88±14.18	<0.05 (A&B)
ALT(U/L)	44±23.37#	34.10±21.56	46.50±18.36	<0.05 (A&B)
AST/ALT ratio	0.94±0.19#	1.01±0.23	0.99±0.25	<0.05 (A&B)

GGT (U/L)	29.07±12.48*	29.35±15.08	23.88±15.23	<0.05 (A&C)
Total proteins(gm/dl)	7.47±0.56	7.74±0.54	8.01±0.48	NS
Albumin (gm/dl)	4.26±0.31	4.35±0.31	4.33±0.28	NS
Globulin (gm/dl)	3.20±0.52*	3.45±0.41	3.60±0.34	<0.05 (A&C)

NS – Not significant; *Significance between A and C; # Significance between A and B

Discussion

NAFLD is a common finding observed in overweight or obese individuals and is highly prevalent in Type 2 diabetes mellitus. However recent studies have reported the occurrence of fatty liver in non-obese individuals. The present study analysed the characteristics of type 2 diabetes patients with NAFLD with different BMI.

Out of the 60 patients, 15(25%) of patients were having the normal BMI. The results were similar to Alam S et al who have reported 25.6% non-obese NAFLD among 465 patients.[15] The prevalence in the present study is higher than that of Ramesh Kumar et al(13.2%) and PK Biswas et al(20%).[16,17] The proportion of NAFLD varies from 11% to 31.7% among various studies conducted in India.[16] The higher percentage of NAFLD could be due to the fact that all the study subjects included in the present study are T2DM patients, who show a higher incidence of fatty liver than other patients. And also, there is significant heterogeneity in the results of lean NAFLD because of the arbitrary use of BMI cut off for labelling lean NASH.[18]

WHR is used as an indicator of central obesity. In the present study, WHR ratio in non-obese patients didnot differ from the overweight group, but lower than the obese group which was not statistically significant. 11(73%) of the non-obese NAFLD patients had shown abdominal obesity as indicated by the increased WHR. However, other studies have observed a lower WHR in patients with normal BMI.[16,19] The results in our study support the fact that Asians have abdominal obesity at lower BMI. A study has revealed that WHR is a critical anthropometric indicator for the prediction of NAFLD.[20] The present study also reveals that WHR is a risk factor of NAFLD indicating central obesity is closely associated with the occurrence of NAFLD.

Fasting blood glucose values were significantly low in the lean subjects when compared to the obese patients, but the postprandial values in them were significantly high when compared to the obese individuals.

Hyperinsulinemia was seen in 12(80%) of the 15 lean NAFLD patients and all of them had insulin resistance (HOMA-IR > 2). HOMA-IR values in them were similar to the overweight group, whereas it was significantly high when compared to the obese group. As established by many other studies, IR is believed to be an important trigger for the initiation of NAFLD. Marchesini et al[21] showed that insulin resistance was the laboratory finding most closely associated with the presence of NAFLD in a large series of patients, irrespective of BMI, fat distribution, or glucose tolerance.

Total cholesterol, triglycerides and LDL-c values of lean NAFLD subjects were significantly different from that of the overweight group, but similar to the obese patients. These findings contradict the results of R Kumar et al where they have shown similar levels of total cholesterol, triglycerides, LDL-c and HDL-c.[16] However, the present study observed similar HDL-c levels in all the three groups. All the lean NAFLD patients were dyslipidemic.

The mean values of serum transaminases and the AST/ALT ratio were significantly different between the lean and overweight categories. The lean when compared to obese had higher levels of GGT and lower levels of Globulin. GGT is an enzyme responsible for extracellular catabolism and may be linked to greater oxidative stress, which is implicated in IR.[22] Total proteins and albumin were similar between all 3 BMI categories.

NAFLD is usually considered an incidental pathologic finding especially in lean patients as they often seek less health care. Hence, it becomes difficult to prevent, diagnose and treat them at the earliest. It has been proven to be an unrecognized clinicopathological entity and a frequent cause of cryptogenic liver disease.[23] More efforts should be made to halt or reverse the progress of NAFLD in non-obese individuals.[24] The present comparative study of lean T2DM patients and their overweight or obese counterparts emphasizes that the risk factors for this type of NAFLD extend beyond a person's body weight. NAFLD should not be neglected in normal weight subjects with altered liver enzymes. It could indicate a higher risk for metabolic disturbances and/or cardiovascular morbidity, or it could unravel a different entity of non-metabolic, non-alcoholic fatty liver disease.[25]

Conclusion

The prevalence of lean NAFLD was 25% in our study population and all of them were dyslipidemic and 80% had Insulin resistance. Most of them had abdominal obesity(73%). Blood glucose, Triglycerides, total cholesterol, LDL-C, AST, ALT, AST/ALT ratio, and GGT were significantly different between the three groups.

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