



Correlation between insulin resistance and liver histology in patients with nonalcoholic steatohepatitis with and without obesity

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Abstract

Introduction Insulin resistance (IR) plays a central role in pathogenesis of nonalcoholic steatohepatitis (NASH). The aim of this study was to correlate histopathological grading and IR in overweight/obese patients with NASH as compared with lean NASH.

Methods Patients with NASH who underwent liver biopsy between January 2012 and December 2012 were included. Anthropometric, clinical, and biochemical features, necro-inflammatory grades, and fibrosis stage on liver biopsies were scored according to Brunt and non-alcoholic fatty liver disease (NAFLD) activity score (NAS).

Results Of 42 patients, 33 (78.6%) had body mass index (BMI) ≥ 23 kg/m² (overweight/obese) while 9 had BMI < 23 kg/m² (lean). Mean fasting blood sugar (FBS) and HbA1c levels in overweight/obese patients with NASH were higher than in lean NASH ($p < 0.05$). The median homeostatic model assessment–estimated insulin resistance (HOMA-IR) among NASH patients with BMI ≥ 23 kg/m² was higher than among those with BMI < 23 kg/m² (3.02 [0.34–17.22] vs. 2 [0.52–5.26]; $p = 0.045$). However, fasting insulin levels were comparable among lean and overweight/obese patients with NASH. Metabolic syndrome could be predicted with 75% sensitivity and 85.3% specificity at a HOMA-IR cutoff value of 3.9. No significant difference was observed with regard to HOMA-IR levels with Brunt grades, Brunt staging, Brunt grades 1 and 2, Brunt scores < 2 and > 2 , and NAS scores, and NAS scores < 4 and > 4 .

Conclusions Although IR was significantly higher in overweight/obese patients with NASH as compared with that in lean patients with NASH, there was no difference in the correlation of HOMA-IR with histology between these groups.

Keywords Brunt score · Cirrhosis · Fatty liver · Obesity

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Bullet points of the study highlights

What is already known?

- Insulin resistance (IR) plays a central role in pathogenesis of nonalcoholic steatohepatitis (NASH).
- Recent reports indicate possibility of frequent occurrence of NASH with body mass index (BMI) <23 (lean NASH) in India.

What is new in this study?

- This study characterizes the clinical characteristics, metabolic profiles, and histopathological severity in patients with lean NASH in comparison to the overweight or obese NASH.
- Patients with lean NASH were younger and had a lower prevalence of IR but comparable levels of fasting insulin levels and higher prevalence of metabolic syndrome.

What are the future clinical and research implications of the study findings?

- Though IR was significantly higher in overweight/obese NASH as compared to lean NASH, there was no difference in the correlation of homeostatic model assessment-estimated insulin resistance (HOMA-IR) with histology between these groups.
- The role of genetic predisposition, variations in gut flora, and other metabolic abnormalities not associated with obesity in pathogenesis of lean NASH need to be studied in future.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological condition that comprises a wide spectrum of liver damage, ranging from steatosis alone to steatohepatitis, advanced fibrosis, and cirrhosis [1]. Nonalcoholic steatohepatitis (NASH) represents a stage in the spectrum of NAFLD and is defined pathologically by the presence of steatosis together with necro-inflammatory activity, mostly of lobular distribution, with or without Mallory's hyaline or fibrosis. The clinical implications of NAFLD are derived mostly from its potential to progress to end-stage liver disease. NAFLD has been reported in up to 70% of patients with type 2 diabetes indicating a strong association between NAFLD and type 2 diabetes [2]. In addition, a major proportion of patients with NAFLD develop impaired glucose tolerance (IGT) or type 2 diabetes, dyslipidemia, or hypertension in a median of 6 years after diagnosis of NAFLD [2].

Obesity is a major risk factor of both NAFLD and type 2 diabetes, and likely provides the common link through insulin resistance (IR). In a recent population-based epidemiological study in India, 75% of individuals with NAFLD were non-obese and 54% were neither overweight nor had central obesity [3]. Another recent study revealed that lean, non-alcoholic, non-diabetic, non-smoking ethnic Asian Indians in comparison with matched Caucasians, Hispanics, Black, and Eastern Asians had 2- to 3-fold increase in IR and 2-fold increase in hepatic triglyceride content [4]. However, data on clinical characteristics, metabolic profiles, and histopathological severity in lean patients with NASH in comparison with the overweight or obese patients with NASH is scant. It is not clear what proportion of lean NASH patients in India has abdominal obesity, IR, and features of metabolic syndrome (MS). Therefore, this prospective study was undertaken to find out the association between clinical and biochemical parameters in NASH patients

(lean and overweight/obese) and to correlate histopathological grading and IR in patients with NASH.

Methods

Patients presenting with NASH satisfying inclusion criteria and undergoing liver biopsy over a period of 1 year from January 2012 to December 2012 in the Department of Gastroenterology, Amrita Institute of Medical Sciences, Kochi, Kerala, were prospectively enrolled.

To be eligible for the study, inclusion criteria included (1) persistently elevated alanine aminotransferase (ALT) levels (> 1.5 -fold of the upper limit of normal); (2) no history of significant alcohol intake (absent alcohol or less than 20 g alcohol/day); (3) fatty liver revealed by abdominal ultrasonographic examination; and (4) liver biopsy features consistent with NASH. Exclusion criteria included (1) viral hepatitis B and C; (2) primary biliary cirrhosis; (3) autoimmune hepatitis; (4) sclerosing cholangitis; (5) hemochromatosis; (6) Wilson's disease; (7) drug-induced liver injury; (8) biliary obstruction; (9) patients drinking alcohol more than 20 g/day; and (10) patients on oral hypoglycemic drugs, including insulin sensitizers.

At the first visit, patients were interviewed for demographic data such as age and sex and detailed history was obtained and findings on physical examination recorded in a structured questionnaire. Patients were subjected to anthropometric evaluation (height, weight, and body mass index [BMI], kg/m^2). Patients were categorized into different BMI groups according to Asian-Pacific cutoff points [5]. Waist circumference (at the nearest half centimeter) was measured at the midpoint between the lower border of the rib cage and the iliac crest, whereas hip circumference was similarly obtained at the maximum diameter at the buttocks. Waist hip ratio of ≥ 0.9 and ≥ 0.85 for male and female, respectively were considered as abnormal.

All the patients were subjected to hematological and biochemical evaluations including complete blood count, blood sugar (fasting and post-prandial), liver function tests, lipid profile, fasting insulin levels, serology for hepatitis (A, B, C), anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), liver/kidney microsome type 1 antibody (LKM), serum iron, total iron binding capacity, ferritin, and C-reactive protein using conventional techniques.

Ultrasonographic scan (USG) of the upper abdomen was performed in all the patients to assess the grades of fatty liver at presentation and to rule out other hepatic pathologies. The severity of hepatic steatosis was graded in these patients [6]. The fatty liver was defined by the presence of at least two of three abnormal findings on abdominal USG as follows: diffusely increased echogenicity ("bright") liver with liver echogenicity being greater than that of kidney, vascular blurring, and deep attenuation of ultrasound signal.

Sections from liver biopsy tissue were stained with hematoxylin and eosin for making a diagnosis of NASH and for grading the histologic features, necro-inflammatory grades, and fibrosis stages, which were scored according to Brunt et al., NAS score [7], and SAF (steatosis, activity, and fibrosis) score devised by Bedossa et al. [8] and based on the description of the pathology committee of the NASH Clinical Research Network [9]. All the biopsies were reported by a single pathologist who was blinded to the anthropometric data.

The 5 components of the MS were available in all the patients, and subjects having 3 or more of the following criteria were labeled as having MS: [10] (1) fasting glucose ≥ 110 mg/dL; (2) central obesity (waist circumference ≥ 90 cm [men] and ≥ 80 cm [women]) [11]; (3) arterial pressure $\geq 130/85$ mmHg or pharmacologically treated; (4) triglyceride levels > 150 mg/dL or current use of fibrates; and (5) high-density lipoprotein (HDL) cholesterol 40 mg/dL (men) and 50 mg/dL (women).

Patients were assessed for the presence of type 2 diabetes mellitus based on the World Health Organization (WHO) diabetic criteria. Insulin resistance was calculated by homeostasis model assessment–estimated insulin resistance (HOMA-IR) and dyslipidemia based on the National Cholesterol Education Program (NCEP) guidelines [10].

Written informed consent was obtained from all the study subjects. The study protocol conformed to the ethical guidelines of the "World Medical Association (WMA) Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004. The study was approved by the institutional ethical review committee.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, USA, version 17). Categorical data was expressed as percentages and the comparison was done using Chi-square test. Continuous data were expressed as median and range and compared by Mann–Whitney *U* test. Linear correlation between the two groups was done by calculating the Spearman rank correlation coefficient. The receiver operating characteristic (ROC) curve was used to evaluate the accuracy of HOMA-IR in predicting MS; the area under the ROC curve (AUC) was computed together with the standard error ($\text{AUC} \pm \text{SE}$) and the 95% CI. The optimal cutoff value, which best predicted MS, was calculated using maximum likelihood ratio method. Two-tailed *p*-values less than 0.05 were considered as statistically significant.

Table 1 Demographic and clinical parameters in nonalcoholic steatohepatitis patients with body mass index < 23 and ≥ 23 kg/m²

	NASH patients with BMI < 23 kg/m ² (n = 9)	NASH patients with BMI ≥ 23 kg/m ² (n = 33)	<i>p</i> value
Age (years, median, range)	28 (22–75)	40 (25–56)	<i>0.04</i>
Sex: Male	8 (88.88%)	25 (75.75%)	0.655
Right upper quadrant pain	1 (11.11%)	5 (15.15%)	0.618
Hepatomegaly	3 (33.33%)	18 (54.54%)	0.227
Hypertension	3 (33.33%)	21 (63.63%)	0.106
Diabetes mellitus	4 (44.44%)	20 (60.60%)	0.462
Metabolic syndrome	3 (33.33%)	5 (15.15%)	<i>0.002</i>

Data in italics are the *p* values

NASH nonalcoholic steatohepatitis, BMI body mass index

Results

A total of 42 biopsy-proven NASH patients (male 33) were enrolled (Table 1). The median BMI was 27.17 (23.14–43.3) kg/m² with 78.57% (33/42) of the patients meeting criteria for obesity (BMI ≥ 23 kg/m²), whereas 21 (19.22–22.98) were lean (< 23 kg/m²) patients.

Demographic and clinical parameters

The patients were predominantly middle-aged (40 ± 11.63 years). Males with BMI ≥ 23 kg/m² comprised 88.8% as compared with 75.8% (*p* = 0.655) of females with obesity. The mean age of patients with BMI < 23 kg/m² was significantly low (33.1 ± 16.4 years) compared with that of patients with BMI ≥ 23 kg/m² (41.5 ± 9.5 years) (*p* = 0.005). The median age of the NASH patients with BMI ≥ 23 kg/m² was

more than that of the NASH patients with BMI < 23 kg/m² (40 years [range 25–86 years] vs. 28 years [range 22–75 years], *p* = 0.04). Symptoms and signs were comparable in patients with BMI ≥ 23 kg/m² and in those with < 23 kg/m² (Table 1). Prevalence of diabetes and hypertension was also comparable among patients in the two groups (Table 1).

Biochemical parameters

No significant difference was noted in abnormal liver function tests between lean and overweight/obese patients with NASH. No significant difference was noted in mean total cholesterol, triglycerides, HDL, low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), serum iron, iron binding capacity, % transferrin saturation, and ferritin between overweight/obese and lean patients with NASH. The fasting blood sugar

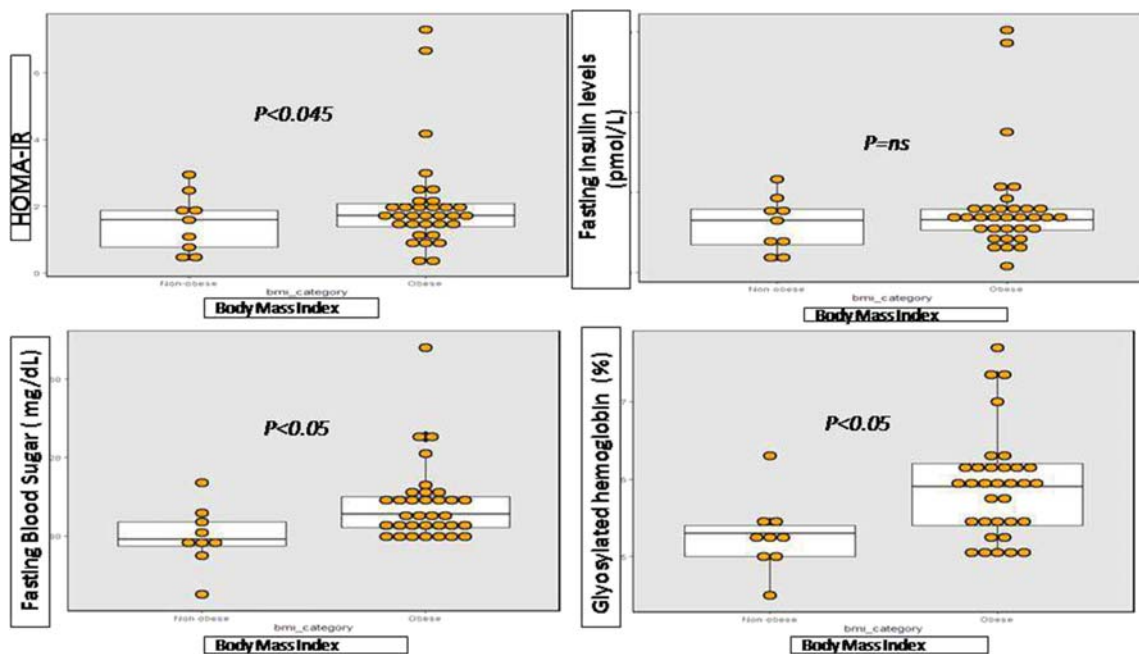


Fig. 1 Insulin resistance in nonalcoholic steatohepatitis patients with body mass index < 23 and ≥ 23 kg/m². HOMA-IR homeostasis model assessment–estimated insulin resistance

Table 2 Association between insulin resistance and body mass index (BMI) in nonalcoholic steatohepatitis (NASH) patients with BMI <23 and ≥ 23 kg/m²

Homeostatic model assessment–estimated insulin resistance	NASH patients with BMI <23 kg/m ² (n = 9)	NASH patients with BMI ≥ 23 kg/m ² (n = 33)	
> 3	2 (22.22%)	17 (51.51%)	<i>p</i> = 0.118

(FBS) and HbA1c levels among overweight/obese NASH patients were higher compared with those in lean NASH patients (Fig. 1).

Insulin resistance

HOMA-IR among NASH patients with BMI ≥ 23 was higher compared with that among NASH patients with BMI <23 though fasting insulin levels were comparable (Tables 2 and 3; Fig. 1). There was a positive correlation between insulin resistance and HbA1c levels (Fig. 2).

Metabolic syndrome

Eight of 42 patients (19%) were found to have MS. MS was commoner among lean patients with NASH than among obese patients with NASH (3/9 [33.3%] vs. 5/33 [15.15%]; *p* = 0.002) (Table 1). ROC curve to predict presence of MS in NASH patients at various HOMA-IR values is shown in Fig. 3. At a cut-off value of HOMA-IR of 3.98, presence of MS could be predicted with sensitivity of 75% (6/8) and specificity of 85.3% (29/34).

Insulin resistance and histology

Insulin resistance did not correlate with histology (Brunt grades, Brunt staging, Brunt grades 1 and 2, Brunt scores < 2 and ≥ 2 , NAS scores, and NAS scores < 4 and ≥ 4) in the two groups (Table 4).

Table 3 Comparison of insulin resistance in nonalcoholic steatohepatitis patients with body mass index <23 and ≥ 23 kg/m²

	NASH patients with BMI <23 kg/m ²	NASH patients with BMI ≥ 23 kg/m ²	
Fasting insulin levels (pmol/L)	13 (2.8–23.2)	13.1 (1.6–60.4)	<i>p</i> = 0.546
HOMA-IR	2 (0.52–5.25)	3.02 (0.34–17.22)	<i>p</i> = 0.081

NASH nonalcoholic steatohepatitis, BMI body mass index, HOMA-IR homeostasis model assessment–estimated insulin resistance

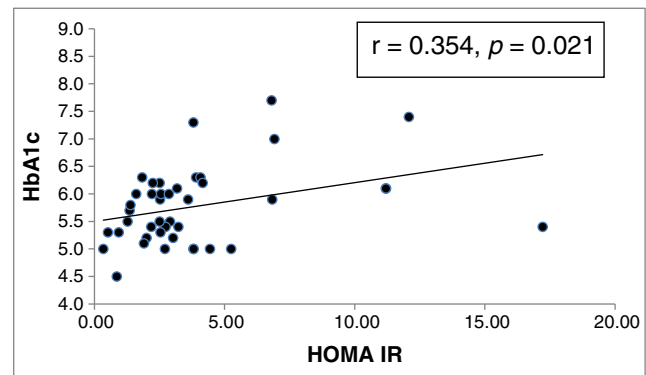


Fig. 2 Correlation between glycosylated hemoglobin (HbA1c, %) and homeostatic model assessment–estimated insulin resistance (HOMA-IR) in nonalcoholic steatohepatitis patients

Discussion

Although most patients with NAFLD do not seem to have a progressive course, the data from natural history studies suggest that patients with NASH (10% to 40%) are at risk for advanced liver disease, including hepatic fibrosis, cirrhosis and hepatocellular carcinoma. Established risk factors for advanced liver disease in patients with NAFLD include older age, obesity, and type 2 diabetes.

Although obesity is an important risk factor, NAFLD has been reported in non-obese subjects from developing as well as developed countries [12, 13]. The classifications of obesity (based on BMI) that have been used in Western studies are based on data from the Caucasian populations. These classifications are not accurate for Asian populations due to differences in body fat percentage and distribution. To avoid the under recognition of obesity among Asian populations, revised guidelines for the classification of patients into obesity groups based on BMI have been established [14]. Using Asian standards [5], we determined that 21.4% of our lean patients had NASH and 78.6% of overweight/obese had NASH. In contrast, a study by Singh et al. [15] from New Delhi reported that only 8.5% of the patients with NASH had normal BMI. The difference in the proportion of patients with normal BMI in the present study and the study by Singh et al. could be attributed to the smaller sample size of the present study.

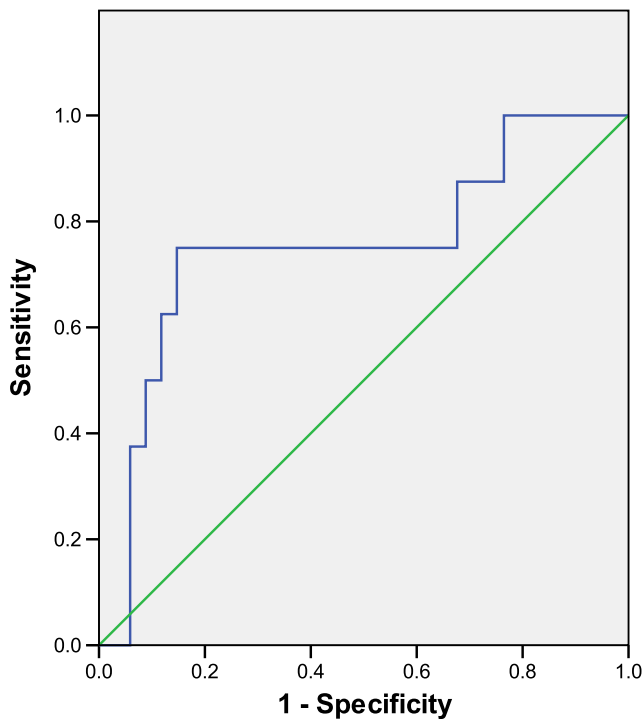


Fig. 3 Receiver operating characteristic curve to predict metabolic syndrome in nonalcoholic steatohepatitis patients at various homeostatic model assessment–estimated insulin resistance values

The findings of this study indicate that NASH either in lean or in overweight/obese patients was not associated with gender, but lean NASH was more commonly young in age. These findings have mirrored similar findings in other studies like that by Younossi et al. [16] and Fassio et al. [17]. There are scanty data on the age and sex predilection among the lean and overweight/obese patients with NASH. The younger age of presentation with NASH may be explained by an increasingly westernized lifestyle being followed by the younger generation in our country. It is postulated that lifestyle with a high caloric/fat intake and lower physical activity predisposes to various metabolic derangements including obesity, which is one of the most important underlying factors in the etiology of NASH.

Biochemical markers including iron stores, liver function tests, C-reactive protein (CRP), uric acid, and lipids were found to be comparable in lean and overweight/obese patients with NASH. In a study by Kumar et al. [14], the median levels of serum transaminases, gamma-glutamyl transpeptidase, and

alkaline phosphatase were similar between all three BMI categories while the lean compared with overweight/obese NAFLD patients had lower levels of serum uric acid.

Polymorphisms in genes affecting lipid metabolism, oxidative stress, IR, and immune regulation have been identified as predisposing factors for the development of NAFLD. IR plays a central role in the pathogenesis of NAFLD, especially in obese patients with diabetes and related components of MS. The clinical picture of NASH in lean patients is a wide departure from the widely studied phenotype of that in obese patients. They are younger and are less likely to have components of MS. Cruz et al. [18] reported increased overall mortality in lean patients than overweight or overweight/obese patients with NAFLD. Other studies have shown more metabolic derangements in lean individuals with NAFLD without long-term survival data [19].

There may be some differences in pathogenesis of NASH in lean patients as compared with that in obese patients [20]. Postulated mechanisms could include genetic predisposition, diet, variations in gut microbiota, and other metabolic abnormalities not associated with weight gain. Peripheral IR (adipose tissues and skeletal muscles) might contribute to steatosis by increasing lipolysis and delivery of free fatty acids to the liver. It is likely that multiple hits, acting together on genetically predisposed lean subjects, induce NAFLD.

In the present study, FBS (91.2 [78–176] vs. 78.4 [50.3–107], $p=0.015$) and HbA1c levels (5.9% [5–7.7] vs. 5.3% [4.5–6.3], $p=0.016$) in overweight/obese patients with NASH were found to be higher as compared with those in NASH patients with BMI < 23 kg/m². The HOMA-IR among patients with BMI ≥ 23 kg/m² was found to be significantly high (3.02 [0.34–17.22] vs. 1.91 [0.52–5.25], $p=0.045$) suggesting higher prevalence of insulin resistance in overweight/obese patients with NASH. However, fasting insulin levels were comparable among lean and overweight/obese patients with NASH. In contrast, in a study by Bhat et al. [21] from New Delhi, the majority of lean, NAFLD patients had insulin resistance.

Our results suggested that insulin resistance plays a significant role in the pathogenesis of NASH in overweight/obese patients as compared with lean patients, which contradict the study by Peterson et al. [22]. In a previous study from India, Kumar et al. [14] found that HOMA-IR > 2 was present in

Table 4 Comparison of insulin resistance, Brunt grade, and non-alcoholic fatty liver disease activity score in nonalcoholic steatohepatitis patients with body mass index < 23 and ≥ 23 kg/m²

	NASH patients with BMI < 23 kg/m ²	NASH patients with BMI ≥ 23 kg/m ²	
Brunt grade 1	2 (0.93–2.9)	2.55 (1.27–17.22)	$p=0.230$
Brunt grade 2	2.33 (0.52–5.25)	3.22 (0.34–12.08)	$p=0.469$
NAS < 4	3.05 (0.93–2.73)	3.9 (1.6–17.22)	$p=0.190$
NAS 4 or more	2.9 (0.52–5.25)	2.94 (0.34–12.08)	$p=0.542$

NASH nonalcoholic steatohepatitis, BMI body mass index, NAS NAFLD activity score

only 7.4% patients of lean, NAFLD patients, and they had lower degree of fasting hyperinsulinemia and HOMA-IR compared with overweight/obese, NAFLD patients. Ethnicity and genetic factors could be modulating factors other than IR especially in lean NASH patients. Furthermore, no significant difference was observed with regard to HOMA-IR levels in patients with different Brunt grades, Brunt stages, Brunt grades 1 and 2, Brunt scores < 2 and ≥ 2 , NAS scores, and NAS scores < 4 and ≥ 4 . A study on the effect of vitamin E in patients with NAFLD showed a significant improvement in liver histology without any change in the degree of IR [23].

Furthermore, various genetic factors are known to confer susceptibility to NAFLD in individuals without increasing the level of IR. Patients with mutations in either adipose triglyceride lipase (ATGL) or comparative gene identification-58 (CGI58) had severe steatosis but no IR [24]. Individuals with activating mutations in apolipoprotein B (APO B) gene had increased levels of hepatic triglyceride yet no IR. A study [25] showed that Asian-Indian males with two single-nucleotide polymorphisms (C-482T, T-455C, or both) in the gene encoding apolipoprotein C3 (APOC3) had increased prevalence of NAFLD and IR. Interestingly, in a recent study [26], loss-of-function variant in HSD17B13 was found to be associated with a reduced risk of chronic liver disease. In a genome-wide association scan, the rs738409 C>G single-nucleotide polymorphism (SNP) in patatin-like phospholipase 3 gene (PNPLA3) was strongly associated with increased liver fat but not with IR estimated from fasting values [27].

We estimated IR by HOMA, which is an indirect method and has limitation as it reflects only hepatic insulin sensitivity. In lean NAFLD, peripheral (adipose tissues and skeletal muscles), IR may be more important than hepatic IR. Regarding environmental factors, an increased intake of dietary fat has been suggested to lead to an increased accumulation of lipids in the liver in lean subjects [14].

Pancreatic steatosis has been correlated with liver steatosis, obesity, MS, and insulin resistance. Non-alcoholic fatty pancreatic disease (NAFPD) may progress to non-alcoholic steatopancreatitis (NASP) in a manner similar to NASH. We have reported a case series of patients with recurrent and chronic pancreatitis in setting of MS. [28]. The role of pancreatic exocrine insufficiency (PEI) in pathogenesis of NAFLD/NASH in some situations has been reported recently [29]. De novo NAFLD has been reported after pancreaticoduodenectomy and is associated with PEI [29]. However, the association between PEI with lean NASH has never been examined.

In conclusion, the present study showed that although most patients with NASH fitted conventional BMI criteria, there was a considerable proportion of patients with lean NASH. IR plays a significant role in the pathogenesis of NASH in overweight/obese patients as compared with that in lean patients; however, there was no significant difference in regard to HOMA-IR levels in patients with Brunt grades, Brunt

staging, Brunt grades 1 and 2, Brunt scores < 2 and ≥ 2 , NAS scores, and NAS scores < 4 and ≥ 4 . There is need for further studies to delineate differences in pathophysiology as well as the histopathology of NASH in lean and overweight/obese patients as this could potentially impact the prognosis and management.

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Compliance with ethical standards

Conflict of interest MVL, ME, HRN, IS, and RG declare that they have no conflict of interest.

Ethics statement Written informed consent was obtained from all the study subjects. The study protocol conforms to the ethical guidelines of the “World Medical Association (WMA) Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects” adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as revised in Tokyo 2004. The study was approved by the institutional ethical review committee.

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