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To compare the HOMA-IR and metabolic profile in lean and obese subjects with non-alcoholic fatty liver disease

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Abstract

Background and objective Non-alcoholic fatty liver disease (NAFLD) is primarily perceived as a condition prevalent among obese individuals. Its pathogenesis is closely intertwined with metabolic syndrome components. However, the association between insulin resistance and NAFLD in nonobese individuals remains ambiguous. Observational studies have scrutinized the prevalence of insulin resistance and metabolic syndrome in lean NAFLD patients.

Materials and methods This is an observational study, and NAFLD screening was carried out among inpatient and outpatient attendees at SRM Medical College's General Medicine Department. Out of 200 screened patients meeting inclusion and exclusion criteria, 80 were diagnosed with non-alcoholic fatty liver disease (NAFLD). The assessment of metabolic syndrome was performed using the NCEP-ATP III criteria, allowing for comparison between groups concerning insulin resistance and metabolic parameters.

Results Among NAFLD patients, those in the obese age group exhibited a higher prevalence of hypertension (57.8%; $p < 0.001$) and metabolic syndrome (75.6%; $p < 0.0001$). The lean NAFLD group showed elevated HOMA-IR levels (4.16) compared to obese NAFLD patients (2.92), with a significant statistical disparity ($p < 0.0001$). Additionally, the HSI value significantly increased in obese NAFLD patients ($p < 0.00001$).

Conclusion Insulin resistance, a key factor in metabolic syndrome, is prevalent in lean individuals with non-alcoholic fatty liver disease (NAFLD), playing a pivotal role in its development. This resistance, linked to metabolic syndrome, promotes hepatic triglyceride and fatty acid accumulation, leading to NAFLD. Moreover, insulin resistance correlates significantly with weight gain in NAFLD patients.

Keywords NAFLD, HOMA-IR, Metabolic syndrome, Fatty liver, Insulin resistance

Introduction

Non-alcoholic fatty liver disease (NAFLD) encompasses hepatic steatosis, evidenced by histology or imaging, predominantly macro-vesicular steatosis. It constitutes a significant global health concern affecting millions worldwide. Liver-related ailments contribute substantially to mortality, with approximately 2 million deaths annually, primarily due to cirrhosis and hepatocellular carcinoma [1]. Liver cancer ranks as the 6th most diagnosed cancer and third leading cause of cancer-related deaths, while cirrhosis ranks 11th in global mortality [1, 2]. The combined impact of these conditions accounts for nearly 3.5% of all global deaths [1].

Non-alcoholic fatty liver disease (NAFLD) is currently witnessing a surge in incidence, as indicated by numerous epidemiological studies across Western and Asian populations [2]. The pathogenesis of NAFLD, closely tied

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to metabolic syndrome, remains incompletely understood. Key features of NAFLD include lipid abnormalities and disrupted glucose homeostasis, particularly insulin resistance. Hepatic fat accumulation is influenced by factors such as insulin resistance and de novo lipogenesis [3, 4]. Patients with NAFLD often exhibit a distinct phenotype, marked by concurrent diabetes mellitus, hypertension, and obesity [5]. The risk of NAFLD development is positively correlated with body mass index [6].

There are indications that the incidence of non-alcoholic fatty liver disease (NAFLD) is increasing among lean populations in the Western world, a trend also observed in Asian populations [7, 8]. It has been suggested that despite similar body mass index (BMI) values, Asians exhibit a higher prevalence of central obesity compared to Westerners [9]. Therefore, comprehensive metabolic profiling of lean individuals with fatty liver is crucial. Fatty acid accumulation in the liver, leading to NAFLD, stems from complications arising from insulin resistance associated with metabolic syndrome. While obesity is the primary factor contributing to NAFLD, the condition often goes unnoticed in lean individuals due to the absence of conventional risk factors [10]. Despite conflicting findings, it is established that lean individuals with NAFLD exhibit less severe insulin resistance than their obese counterparts. This investigation aims to analyze metabolic profiles and insulin resistance levels in both lean and obese NAFLD patients. Given the low suspicion of fatty liver in lean individuals and their lack of routine evaluation, effective lifestyle changes are limited in this population. While NAFLD is an emerging condition, studies on lean NAFLD in the Indian population are relatively scarce compared to obese NAFLD. This study seeks to comprehensively understand the relationship between insulin resistance and NAFLD in both nonobese and obese individuals.

Material and methods

This observational study was conducted over 18 months, spanning from January 2021 to June 2022. A total of 200 patients were identified with ultrasound-proven fatty liver of varying grades and elevated ALT levels compared to baseline, screened within the internal medicine department of SRM Medical College, Kattankulathur, Tamil Nadu. From this cohort, 80 patients meeting the exclusion and inclusion criteria for non-alcoholic fatty liver disease (NAFLD) were included in the study (Sup. 1). Patients willing to participate provided written consent prior to enrollment. The study commenced after obtaining approval from the Ethical and Scientific Committee of SRM Medical College Hospital and Research Centre (Approval number: 2383/IEC/2021 dated 29 January 2021). Exclusion criteria comprised patients with chronic liver disease, alcoholic liver disease (with alcohol consumption exceeding 20 g/day), viral hepatitis, hemochromatosis, evidence of portal hypertension on ultrasonography, or those receiving treatment with drugs affecting liver function. Inclusion criteria for NAFLD were defined as non-alcoholic fatty liver. Tests were conducted to detect chronic liver disease. All patients were divided into two categories according to their BMI and waist circumference.

1. Obese or overweight according to Asia-Pacific criteria: BMI > 23 kg/m^2, *WC* > 90 cm in men, and *WC* > 80 cm in women
2. Lean body weight according to Asia-Pacific criteria: BMI — 18.6–22.9 kg/m^2 and *WC* < 90 cm in men and < 80 cm in women

Furthermore, plasma glucose levels, both fasting and post-prandial, were assessed using an automated analyzer employing glucose oxidase and peroxidase methods. Fasting insulin levels (mU/l) were determined via radioimmunoassay, and insulin resistance was evaluated using the homeostatic model assessment (HOMA-IR) criteria. A comprehensive lipid profile, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, very low-density lipoprotein (VLDL), and triglycerides (TGL), was obtained in the fasting state. Additionally, serum iron studies, albumin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were assessed at baseline for all patients. Screening for HBsAg and anti-HCV was performed to exclude hepatitis B and C infections, while iron studies were conducted to rule out viral hepatitis and hemochromatosis. The metabolic syndrome was evaluated using the NCEP-ATP III the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria [11]. Groups were compared based on their insulin resistance and metabolic parameters. The hepatic steatosis index was calculated for all patients. The metabolic syndrome was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated as well.

Statistical analysis

Descriptive statistics were expressed as mean ± standard deviation. Statistical comparison between the groups was made using chi-square test and paired *t*-test for categorical variables and continuous variables. *P*-value lower than 0.05 was considered statistically significant. The data were analyzed using SPSS version 20.

Table 1 Basic demographic characteristics and clinical and epidemiological parameters between obese NAFLD and lean NAFLD groups

Parameters	NAFLD group		*P*-value
	Lean NAFLD	Obese NAFLD	
Age	56.86 ± 6.45	54.56 ± 9.3	0.220
Female	20 (52.6%)	18 (47.3%)	0.128
Male	15 (35.71%)	27 (64.28%)	0.442
Non-diabetic	26 (44.8%)	32 (55.2%)	0.752
Diabetic	9 (20.94%)	13 (79.06%)	
Non-hypertension	28 (59.57%)	19 (40.43%)	0.001
Hypertension	7 (21.21%)	26 (78.79%)	
Non-metabolic syndrome	26 (74.3%)	11 (24.4%)	0.000
Metabolic syndrome	9 (25.01%)	34 (74.99%)	

Data represented as Mean ± SD for age and as count (percent) for other parameters

Results

The mean age in the lean group and in the obese group showed no significant difference in age between groups ($p > 0.05$) (Table 1).

Statistical analysis showed no significant difference in the prevalence of diabetes mellitus between the lean and obese groups (Table 1). Statistical analysis revealed a significant difference in the prevalence of hypertension and metabolic syndrome between the two groups ($p < 0.001$) (Table 1).

The mean fasting blood sugar in the lean NAFLD group was 130.06 ± 34.44, compared to 136.87 ± 35.43 in the obese group. There was no significant difference in fasting blood sugar and postprandial blood sugar between the groups (Table 2). There was a significant difference in systolic blood pressure and diastolic blood pressure between the groups ($p < 0.002$) (Table 2).

There is a significant difference in TC between groups ($p < 0.0001$). However, there is no significant difference in TGL between groups ($p < 0.245$). Additionally, there is a significant difference in HDL between groups ($p < 0.009$), as well as in LDL between groups ($p < 0.004$). Nevertheless, there is no significant difference in VLDL between groups (Table 2). There is a significant difference in HOMA-IR between groups ($p < 0.0001$) (Table 2). There is no significant difference in AST and ALT between groups (Table 2). There is a significant difference in HSI between groups ($p < 0.0001$) (Table 2). There is no significant difference in NAFLD grade between fatty liver groups ($p < 0.382$).

In comparing HOMA-IR and NAFLD grades between groups, there is a significant difference between the HOMA-IR and NAFLD grade-1 groups ($p < 0.001$). However, there is no significant difference between groups of HOMA-IR and NAFLD grade 2 and grade 3. Nonetheless, there is a significant difference between groups of HOMA-IR and NAFLD grade 4 ($p < 0.05$) (Fig. 1).

Table 2 Blood sugar level and blood pressure level for obese NAFLD and lean NAFLD groups

Parameters	NAFLD group		*P*-value
	Lean NAFLD	Obese NAFLD	
Blood sugar level			
FBS (mg/dl)	130.06 ± 34.44	136.87 ± 35.43	0.391
PPBS (mg/dl)	174.71 ± 65.22	183.84 ± 41.39	0.448
Blood pressure level			
SBP (mmHg)	116.00 ± 17.55	133.29 ± 20.75	0.0001
DBP (mmHg)	77.09 ± 12.61	86.00 ± 12.25	0.002
Lipid profile components			
TC (mg/dl)	180.83 ± 26.84	214.73 ± 37.13	0.0001
TGL (mg/dl)	135.74 ± 44.66	148.22 ± 49.26	0.245
HDL (mg/dl)	49.91 ± 7.8	42.76 ± 10.20	0.009
LDL (mg/dl)	111.00 ± 31.56	136.49 ± 42.01	0.004
Other parameters			
AST	65.28 ± 2.46	68.80 ± 15.09	0.271
ALT	71.27 ± 8.67	68.12 ± 9.86	0.14
HSI	27.25 ± 2.46	40.85 ± 3.19	< 0.0001
HOMA	4.16 ± 1.55	2.92 ± 1.05	< 0.0001

Data represented as mean ± SD

FBS Fasting blood sugar, *PPBS* Postprandial blood sugar, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure

Lipid profile components for lean NAFLD and obese NAFLD group. *TC* Total cholesterol, *TGL* Triglycerides, *LDL* Low-density lipoprotein, *HDL* High-density lipoprotein, *VLDL* Very low density lipoprotein

Other parameters: *AST* Aspartic transaminase, *ALT* Alanine transaminase, *HIS* Hepatic steatosis index, and HOMA-IR were also measured. Data represented as Mean + SD

Discussion

The accumulation of hepatic triglycerides beyond normal limits results in non-alcoholic fatty liver disease (NAFLD), a significant contributor to chronic liver disease globally. NAFLD encompasses simple steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis. Obesity is believed to be the primary factor leading to NAFLD development, as most patients are either obese or overweight. In our study, lean NAFLD patients had a mean age of 56.86, while obese NAFLD patients had a mean age of 54.58. Jung et al. [12] reported a similar mean age range among nonobese and obese NAFLD patients. NAFLD was prominent in lean females (57.1%) and obese males (60%). The possible explanation for the higher prevalence of NAFLD in lean females could be genetic risk factors [13]. However, Alam et al. [14] observed female predominance in both obese and nonobese patient categories.

Recently, it has been widely accepted that NAFLD is a type of metabolic syndrome that manifests in the

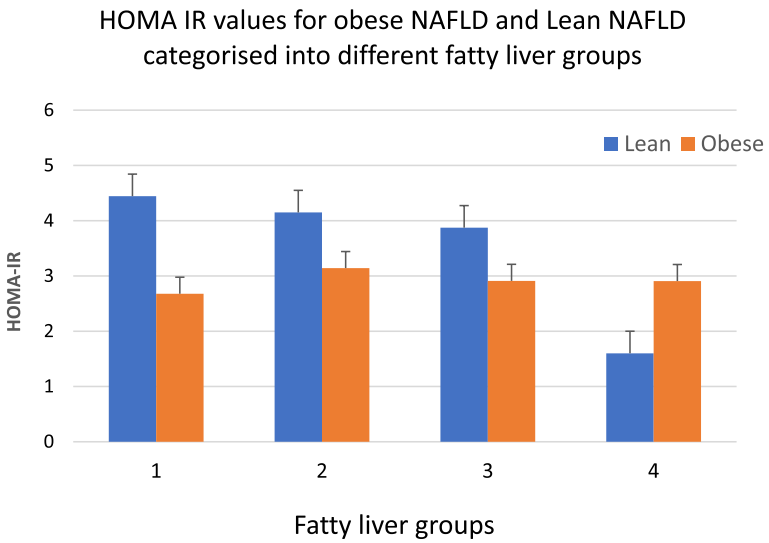

Fig. 1 HOMA-IR of lean NAFLD and obese NAFLD in different grades of fatty liver. Values are expressed as mean ± SD

liver [15]. The obese group exhibited a predominance of hypertension and metabolic syndrome, as reported by Kumar et al. [16] in NAFLD patients. Lean NAFLD patients, compared to their obese counterparts, were more likely to be male, younger, and have lower fasting glucose, glycated hemoglobin, and blood pressure readings [17]. The association of lean NAFLD with age, gender, and decreased risk of IR and hypercholesterolemia has been widely explored in existing research. In particular, previous studies have indicated a small male prevalence of lean NAFLD, falling within the range of 19 to 56 [18]. Furthermore, both groups exhibited higher blood glucose levels independent of BMI. This emphasizes the importance of recognizing DM as a major risk factor for NAFLD, which has been shown to increase mortality rates [19]. Total cholesterol (TC), HDL, and LDL levels varied significantly among the groups. In a previous study, it was observed that 20 to 80% of patients afflicted with NAFLD had dyslipidemia, characterized by high cholesterol levels (hypercholesterolemia), high triglyceride levels (hypertriglyceridemia), or both. NAFLD dyslipidemia was often characterized by elevated blood TG levels, tiny, dense LDL particles, and reduced HDL cholesterol [19] According to research conducted among lean patients, TCG levels were notably linked to the onset and remission of NAFLD [20].

A recent study has revealed that the LDL/HDL ratio is significantly linked to the degree of hepatocellular ballooning and liver fibrosis in individuals with non-alcoholic fatty liver disease (NAFLD) and a low body mass index. This ratio may play a crucial role in distinguishing between moderate and severe NAFLD conditions [21].

Notably, the lean NAFLD group has shown higher levels of HOMA-IR compared to obese NAFLD patients. It is important to note that insulin resistance plays a crucial role in the onset of NAFLD [22]. In fact, Bugianesi et al. [23] have documented a significant percentage of slim NAFLD patients without metabolic risk factors having insulin resistance, indicating a strong link between insulin resistance and NAFLD regardless of BMI. The resultant biochemical outcomes, characterized by elevated transaminases, along with slight elevations of ALP and AST, and normal liver synthetic function, are due to the stored glycogen in the hepatocytes. The increased activity of liver enzymes serves as an indication of hepatic damage. As not every patient can undergo a liver biopsy, noninvasive markers such as detecting ALT and AST levels in the liver may be employed instead. Our study found that the mean levels of ALT and AST did not differ significantly between nonobese and obese individuals. As reported by Kumar et al. [16], there is likely a statistical insignificance in correlating AST and ALT levels among obese and nonobese NAFLD patients. Insulin resistance (IR), diabetes mellitus (DM), and metabolic syndrome are all associated with increased activity of these markers. Appropriate glycemic management has been shown to provide a cure for the increased transaminases and hepatomegaly.

HSI is a quick and effective screening technique for NAFLD that may be used to select individuals for liver ultrasound and assess whether lifestyle changes are necessary. In our current study, the HSI value was high in NAFLD patients who were obese. In a similar study by Sviklāne et al. [24], waist size and C-reactive protein were associated with HSI. Correlations between $HSI > 36$

and nephropathy and metabolic syndrome were found. A correlation analysis between NAFLD severity grade and obesity denoted a greater number of patients in the obese group < grade 2. The lean group had more patients belonging to grade 1. The prevalence of NAFLD/NASH parallels the degree of obesity reported by several studies [23]. The hepatic steatosis index (HSI) is a prompt and efficacious screening technique used to identify non-alcoholic fatty liver disease (NAFLD) and select candidates for liver ultrasound, evaluating the necessity of lifestyle modifications. Our current study revealed that NAFLD patients with obesity exhibited high HSI values. In a comparable study by Sviklāne et al. [24], waist size and C-reactive protein were associated with HSI, and correlations between *HSI* > 36 and nephropathy and metabolic syndrome were identified. A correlation analysis between NAFLD severity grade and obesity showed a greater number of patients in the obese group with grade < 2, while the lean group had more patients in grade 1. The prevalence of NAFLD/NASH is observed to be proportional to the degree of obesity, as reported by several studies [24].

The objective of the study was to establish a correlation between the significance of HOMA-IR and NAFLD grades. As the severity of NAFLD increased, lean NAFLD patients experienced a decline in HOMA-IR values that were initially higher. Additionally, inconsistencies in HOMA-IR levels were observed among obese NAFLD patients. Current evidence does not strongly support the notion that peripheral IR plays a critical role in the pathophysiology of lean NAFLD [25]. A study conducted by Gastaldelli et al. [25] revealed that NASH patients display marked adipose tissue IR irrespective of their level of obesity. In another study, Feldman et al. [26] demonstrated that insulin resistance and faulty adipose tissues are present in thin individuals with NAFLD. However, more research is necessary to fully comprehend this relationship.

The insulin resistance linked to metabolic syndrome leads to an increase in the synthesis and storage of hepatic triglycerides and fatty acids, ultimately resulting in the development of non-alcoholic fatty liver disease (NAFLD). Although there is significant evidence linking insulin resistance to obesity in individuals with NAFLD, the relevance of insulin resistance in non-obese patients with NAFLD remains uncertain. This observational study aims to investigate the presence of metabolic syndrome elements and insulin resistance in nonobese patients with NAFLD.

Insulin resistance (IR) is known to increase de novo lipogenesis, which subsequently leads to a direct increase in non-alcoholic fatty liver disease (NAFLD) and an indirect increase in free fatty acid (FFA) flow to the liver through the reduction of lipolysis inhibition. It is widely acknowledged that IR plays a critical role in the initiation of NAFLD [22]. Interestingly, a significant proportion of slim NAFLD patients without additional metabolic risk factors have also been observed to exhibit IR, which further supports the link between NAFLD and IR, irrespective of body mass index [23].

The investigation further aimed to establish a correlation between the significance of HOMA-IR and the grades of NAFLD. HOMA-IR values were observed to be higher in patients with lean NAFLD and exhibited a declining trend with an increase in severity. Furthermore, disparities in HOMA-IR levels were identified among obese NAFLD patients. There is a lack of robust evidence to substantiate the notion that peripheral insulin resistance plays a critical role in the pathophysiology of lean NAFLD. Notably, NASH patients demonstrate pronounced adipose tissue insulin resistance, independent of their level of obesity. Additionally, research has demonstrated that even thin individuals with NAFLD exhibit insulin resistance and faulty adipose tissue [26]. To gain a more comprehensive understanding of this association, further research is imperative.

The metabolic syndrome-related insulin resistance results in the accumulation of hepatic triglycerides and fatty acids, leading to non-alcoholic fatty liver disease (NAFLD). Despite the strong correlation between insulin resistance and obesity in individuals with NAFLD, it remains unclear whether insulin resistance is applicable to nonobese NAFLD patients.

Conclusion

Insulin resistance, the primary cause of metabolic syndrome, is prevalent among lean individuals with non-alcoholic fatty liver disease and plays a crucial role in their condition. The association between insulin resistance and metabolic syndrome leads to a rise in the generation and storage of hepatic triglycerides and fatty acids, ultimately resulting in non-alcoholic fatty liver disease (NAFLD). Furthermore, there is a significant correlation between insulin resistance and weight gain in individuals with NAFLD. However, the relevance of insulin resistance in nonobese individuals is not fully established. Therefore, future research should focus on developing an integrated model that incorporates dietary, lifestyle, genetic, gut microbiota, and environmental factors, which could potentially lead to the development of a scoring system for predicting the onset of non-alcoholic fatty liver disease (NAFLD).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43066-024-00341-8.

Supplementary Material 1: Sup. 1. Distribution of lean NAFLD and obese NAFLD patients graded into different fatty liver groups classified on the basis of Ultrasonography.

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Authors' contributions
MCN, conceptualization, methodology, data curation, writing — original draft, visualization, and investigation. LS, supervision, project administration, and validation. JSK, supervision, project administration, and validation. GS, data curation, writing — reviewing and editing, visualization, and software.

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Availability of data and materials
Due to privacy and ethical concerns, neither the data nor the source of the data can be made available.

Declarations

Ethics approval and consent to participate
Ethical and Scientific Committee of SRM Medical College Hospital and Research Centre, number 2383/IEC/2021 dated 29 January 2021. Written statement of consent from patient taken before start of study.

Competing interests
The authors declare that they have no competing interests.

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