Original Article

Liver fibrosis, insulin resistance and cardiovascular risk scores in obese and non-obese patients with non-alcoholic fatty liver disease

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease. Obese children and adolescents, particularly those with metabolic syndrome (MetS), commonly report NAFLD, which can lead to various other problems and diseases. There are different opinions on how the liver fibrosis score, insulin resistance indices, and risk of cardiovascular disease are related in people with NAFLD who have different body mass index (BMI) levels. This study aimed to investigate the relationship between liver fibrosis score, insulin resistance indices, and cardiovascular disease risk in patients with NAFLD, specifically focusing on two groups with normal and high BMI.

Materials and Methods: This analytical cross-sectional study was conducted on patients with NAFLD referred to Taleghani Hospital (Tehran-Iran) between 2019 and 2020. Data such as age, gender, BMI, height, weight, blood sugar level, hemoglobin A1C level, lipid profile, liver fibrosis level, insulin resistance level, liver aminotransferases level, Framingham risk score, and presence of MetS were evaluated. The significance level was considered less than 0.05.

Results: We evaluated 140 patients, 14 of whom had normal BMI, and the rest had high BMI. There was a significant relationship between the homeostatic model assessment for insulin resistance (HOMA-IR) index and the liver fibrosis score. For a one-unit increase in the liver fibrosis score, the HOMA-IR score increased by 0.287 times (P-value=0.001). There was a significant relationship between MetS and the risk of cardiovascular diseases based on the Framingham risk score and liver fibrosis (P-values<0.05).

Conclusion: High BMI levels can increase the incidence of NAFLD, Framingham, and HOMA-IR indices.

Keywords: Liver fibrosis score, Insulin resistance index, Non-alcoholic fatty liver, Obesity, Body mass index

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease in developed countries, which results from the excessive accumulation of fat in the liver[1]. According to the definition of the North American Society of Gastroenterology, Hepatology, and Nutrition (NASGHAN), NAFLD is defined as chronic hepatic steatosis not secondary to genetic disorders, metabolic disorders, infections, use of steatogenic drugs, ethanol consumption, or malnutrition[2].

The natural history of NAFLD describes distinct degrees of liver tissue damage. These changes range from simple accumulation of non-alcoholic fatty liver (with lipid content in hepatocytes above 5%) to non-alcoholic steatohepatitis (NASH), characterized by liver cell damage and cell death. Collagen deposition and subsequent vascular remodeling lead to fibrosis, cirrhosis, and end-stage liver diseases[3].

NAFLD is commonly reported in obese children and adolescents, especially in those with metabolic syndrome (MetS). Its prevalence in obese youth has shown a significant increase, similar to the childhood obesity epidemic in the past years[4].

Evidence of triglyceride accumulation is based on imaging (ultrasonography most of the time) and/or liver biopsy. Although liver biopsy is the gold standard for diagnosing the disease, ultrasonography is more acceptable and comfortable for patients and physicians[5].

Many studies have reported a strong relationship between NAFLD and insulin resistance (IR), which is usually considered a common and major component of the metabolic changes characterizing the MetS. Although several definitions of metabolic syndrome have been presented, the data collected from recent reports consider central obesity, impaired glucose tolerance, dyslipidemia, and hypertension as the main features of this disease[6]. Also, some studies have pointed out the relationship between NAFLD and cardiovascular diseases[7]. Several risk factors are associated with increased cardiovascular disease risks, including age, gender, total cholesterol, smoking habits, high-density lipoprotein cholesterol (HDL), and systolic blood pressure[8]. These factors estimate the 10-year risk of coronary diseases and are known as the Framingham risk score[9]. The importance of NAFLD and the relationship between liver fibrosis score, insulin resistance indices, and cardiovascular disease risk in patients with NAFLD, with normal and high BMI, is still controversial[10]. In this study, we aimed to investigate liver fibrosis score, insulin resistance indices, and risk of cardiovascular diseases in patients with NAFLD in two groups with normal and high BMI.

Methods

The study was an analytical cross-sectional study on patients with NAFLD referred to Taleghani Hospital (Tehran-Iran) during 2020 and 2021.

The inclusion criterion was the presence of fatty liver on ultrasonography. The exclusion criteria were age below 18 years, diabetes involvement, alcohol consumption, and hepatic disorders.

Patient’s information, including age, gender, BMI, height, weight, blood sugar level, hemoglobin A1C level, lipid profile level, liver fibrosis level, insulin resistance level, liver aminotransferase level, Framingham risk score, presence of MetS were extracted from patient’s files. Patients’ data remained confidential. In terms of medication, some patients only used anti-hypertensive drugs, and others did not use any drug. Thus, we did not assess the medication use separately.

Metabolic syndrome was diagnosed as presentations of three items of the following conditions: more than 35 inches for women and more than 40 inches for men for waist circumference, an increase in triglycerides of at least 150 mg per deciliter or more, reduced levels of high-density lipoprotein cholesterol (HDL), which are less than 40 mg/dL for men and 50 mg/dL for women, an increase in fasting blood glucose of at least 100 mg/dL, and 130 mmHg or higher systolic and/or 85 mmHg or higher diastolic blood pressure[11, 12].

NAFLD fibrosis score (NFS) was assessed based on age, BMI, hyperglycemia, albumin, platelet count, aspartate aminotransferase, and alanine aminotransferase (AST/ALT) ratio[13].

HOMA-IR was calculated based on insulin level and FBS and with the following formula[14]: (fasting serum insulin (mUI/L)* fasting glucose (mg/dL)*

0.0555/22.5)^2.

According to the World Health Organization definition, a BMI between 18.5 kg/m^2 and 29.29 kg/m^2 is considered normal, and a BMI of more than 25 kg/m2 is considered high[15].

The sample size is based on the study of Denkmayr et al.[16], and based on the reported percentages, the prevalence of fibers in the normal weight group is 13% (P1) compared to the overweight group of 25% (P2). Also, the power of the test was 80%, and the error was 5%. In the following formula, P1=13%, P2=25%, power=80%, alpha=5%. This study can be generalized to patients with non-alcoholic fatty liver in the Iranian population with 80% power and 95% confidence.

$$n = \frac{\{Z_{1-\alpha/2}\sqrt{2P_2(1-P_2)} + Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\}^2}{(P_1-P_2)}$$

This study was approved by the ethical committee of the Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1399.513).

Statistical analysis: Frequency and percentage were used to describe qualitative data, and mean, standard deviation, and range were used quantitatively. After proving the normality of the distribution of the studied variables with the Kolmogorov-Smirnov test, the chi-square test or Fisher's exact test was used to check the relationship between the qualitative variables between the groups. A t-test was also used to compare quantitative variables. Logistic regression was also fitted to check the relationship between variables. Analyzes were performed using SPSS 25.0 statistical software. P-values less than 0.05 were considered statistically significant.

Results

One hundred and forty patients with liver disease Non-alcoholic fatty acids have been evaluated. Of 140 patients, 14 were in the normal BMI group, and 126 were in the high BMI group. In Table 1, we described demographic data, smoking history, and anthropometric data. The mean weight, height, and waist circumference between these two groups have a statistically significant difference (P-value < 0.05). Of all 140 participants, 130 (92.9%) had normal blood pressure, and 10 (7.1%) had high blood pressure (all in the high BMI group).

Table 1. Demographic information of patients of the plan separately between two groups based on BMI.

		BMI		P-value
		Normal	High	
Age		48.21 ± 9.27	48.02 ± 10.5	0.9*
Sex	Male	6 (42.9%)	47 (37.3%)	0.7**
	Female	8 (57.1%)	79 (62.7%)	
Smoking	No	13 (92.9%)	109 (86.5%)	0.6**
	Yes	1 (7.1%)	17 (13.5%)	
Weight (Kg)		67.63 ± 4.35	82.98 ± 12.05	<0.001*
Height (M)		1.7 ± 0.05	1.62 ± 0.13	0.02*
Waist Circumference (Cm)		92.64 ± 4.52	102.13 ± 9.77	<0.001*
Hip Circumference (Cm)		106.43 ± 9.42	110.9 ± 9.47	0.09*

*P-value based on T-test, **p-value based on chi-square

Table 2. Laboratory data of the two groups.

	BMI		P-value
	Normal	High	
Fasting blood glucose	91.5±5.9	94.05 ± 7.39	0.2
Serum insulin	14.1±3.4	15.87 ± 3.2	0.05
HbA1C	5.3 ± 0.2	5.42 ± 0.45	0.6
Total Cholesterol	185±35.4	183.7 ± 34.53	0.8
HDL	46.2±9.8	46.93 ± 9.98	0.8
PLT	214.2±69.5	244.73 ± 68.55	0.1
AST	19.2±5.9	22.6 ± 9.91	0.07
ALT	21.3±6.6	26.37 ± 14.27	0.03
Albumin	4.08±0.3	4.01 ± 0.39	0.5
Metabolic syndrome	2(1.6%)	0(0%)	0>0.9

P-value based on T-test

In Table 2, the laboratory data of patients were assessed in the two groups. There was a significant difference between the two groups in the ALT level. Patients with high BMI had higher levels of ALT than patients with normal BMI. Of 140 patients, 2 (1.4%) had metabolic syndrome.

None of the people in the normal group had hypertension, of whom 5 (35.7%) took antihypertensive drugs and 9 (64.3%) did not take antihypertensive drugs. In people with high BMI, 10 (7.9%) had hypertension, and 31 (24.6%) of these patients with high BMI took antihypertensive drugs. The mean HOMA-IR index in people with high BMI was 3.7±0.85, significantly higher than the normal group (P-value=0.043). The mean Framingham risk score and liver fibrosis score (NAFLD) were not significantly different between the two groups.

In the group of normal people, 7 (50%), and in the high BMI group, 88 (69.8%) patients had the MetS (P-value=0.143).

We evaluated the relationship between the severity of liver fibrosis and the risk of cardiovascular diseases based on the Framingham risk score and the HOMA-IR score. As seen, there is a weak statistical relationship between the liver fibrosis score and the risk of cardiovascular diseases. The correlation coefficient between the two factors was equal to 0.038 (correlation coefficient=0.038, P-value=0.653). However, there was a statistically significant relationship between the HOMA-IR score and the liver fibrosis score, so that for one-unit increase in the liver fibrosis score, the HOMA-IR score increases 0.287 times (Pearson Correlation=0.287, P-value=0.001) (Table 3).

In Table 4, the relationship between MetS and HOMA-IR scores, Framingham risk score, NAFLD score, liver fibrosis, and insulin level has been investigated. There was a significant relationship between the presence of MetS and the risk of cardiovascular diseases based on the Framingham risk score and liver fibrosis (NAFLD score).

Table 3. HOMA-IR, Framingham risk, and NAFLD score based on BMI groups.

	BMI		P-value
	Normal	High	
HOMA-IR	3.21 ± 0.84	3.7 ± 0.85	0.04
Framingham risk score	3.47 ± 4.66	3.22 ± 5.04	0.8
NAFLD score	-2.03 ± 1.23	-1.59 ± 1.31	0.2

P-value based on T-test

Table 4. Determining the relationship between MetS and insulin, severity of liver fibrosis, and risk of cardiovascular diseases based on Framingham risk score and H score.

	Metabolic syndrome		P-value
	No	Yes	
Serum insulin level	15.07±3.32	16±3.2	0.1
HOMA-IR	3.48±0.79	3.72±0.88	0.1
Framingham risk score	5.29±5.98	2.28±4.13	0.001
NAFLD score	-2.18±1.2	-1.38±1.27	0.001

Discussion

This study observed that among 140 patients, 126 were classified as obese, with 67% exhibiting MetS. The mean insulin resistance score was 3.21 ± 0.84 in individuals with normal BMI and 3.7 ± 0.85 in those with high BMI. Bhat et al. reported that 120 individuals (80%) of the 150 patients studied were classified as obese. Forty individuals, representing 30% of the sample, were diagnosed with MetS. The average insulin resistance was 10.9 ± 5.3. Among patients with NAFLD, 23 individuals (15.3%) exhibited a low BMI. Among the 23 individuals, 80% (18/23) exhibited insulin resistance, with a mean HOMA-IR of 1.9±3.4. Only four individuals (17%) exhibited no component of MetS. Insulin resistance, frequently linked to MetS, is prevalent and plays a significant role in lean patients with NAFLD.

The present study found no relationship between MetS and insulin resistance, contrasting with the findings of Butt et al.[17].

We assessed one hundred-forty patients; 14 patients had normal BMI, and the rest had higher BMI. This issue can be due to the increasing prevalence of obesity in the population of Iran. In fact, in a study conducted in Iran in 2016, it was found that a total of about 80% of Iranian people are overweight or obese[18]. This issue can be due to the lifestyle of Iranians, including diet habits and low levels of activity. Iranian people often have unhealthy meals, office jobs, or jobs with low activity[19].

The current study showed that the mean fasting blood sugar and insulin levels in the normal BMI group were 91.57 ± 5.96 mg/dl and 14.14 ± 3.44 mIU/L, respectively. In the high BMI group, these counts were equal to 94.05 ± 7.39 mg/dl and 15.87 ± 3.2 mIU/L, respectively, and this difference was not statistically significant. This lack of significance may be due to the lack of sample size in the present study. A study by Valle-Martos et al. conducted in 2021 showed that high BMI is associated with increased ALT, fasting blood sugar, and insulin resistance. The current study showed that high BMI is not only associated with an increase in ALT and fasting blood sugar but also causes an increase in AST. High-level BMI can increase insulin resistance (HOMA-IR) based on our findings; in this respect, these two studies were similar. Among the differences between these two studies, we can point to the population studied in the two studies. In the current study, the study population was adults, while children were studied in Valle-Martos et al.'s study. In the present study, high-level BMI causes an increase in AST, which was different from the study of Valle-Martos et al.[20].

In Gentili et al.'s study, it was seen that patients with a higher liver fibrosis or HOMA-IR score had higher vascular thickness and less vascular flow-dependent dilatation. These parameters were signs of cardiac involvement in people with a higher fibrosis score or HOMA-IR. The current study showed that the Framingham risk score was related to the liver fibrosis score. The greater level of damage and fibrosis of the liver increases cardiovascular involvement. The results of these two studies were similar. The present study showed that insulin resistance is significantly related to the liver fibrosis score[21].

Cardiovascular risk was found to be associated with the presence of MetS and BMI. Cardiovascular risk was associated with liver fibrosis score. Lee et al. concluded that a higher fatty liver index (FLI) is associated with an increased Atrial Fibrillation (AF) risk. Individuals classified as underweight and exhibiting elevated FLI levels demonstrated an increased risk for AF. In individuals with elevated BMI, a higher FLI correlated with an increased risk of AF; however, this risk remained lower compared to that of lean individuals. In obese individuals, an elevated FLI did not correlate with an increased risk of AF[22]. Obesity and MetS can affect the development of fatty liver[23]. Fatty liver is associated with obesity and the prevalence of metabolic syndrome, both of which elevate the risk of cardiovascular diseases, as noted in this study and the research conducted by Lee et al.

Chen et al. conducted a study on fatty liver disease associated with metabolic disorder (MAFLD), noting that MAFLD prevalence increased with age in women. The prevalence of this disease varied across different BMI categories (underweight, normal, overweight, and obesity) and was significantly associated with BMI levels. Our study yielded results that differ from those of Chen et al. The two studies differed in their patient populations; the current study focused on NAFLD, whereas Chen et al. studied patients with MAFLD. Chen et al. identified associations between age, BMI, waist circumference, ALT, triglycerides, fasting glucose, uric acid, and platelet count with MAFLD. The observed factors were not associated with BMI or NAFLD indices[24].

Insulin resistance was substantially correlated with elevated BMI, and a robust positive association existed between insulin resistance and the incidence of NAFLD. No correlation existed between the incidence of diabetes and NAFLD in those with normal BMI. The research conducted by Sinn et al. revealed that the presence and severity of NAFLD in adults with normal weight correlated with an increased incidence of diabetes. NAFLD in persons with normal BMI presents a greater risk for diabetes development compared to overweight or obese individuals without NAFLD. This issue must be assessed in the future with a larger statistical sample[25].

The limitation of the current study was the lack of sample size, and it is recommended that further studies be done with higher sample sizes.

Conclusion

It is concluded that a high BMI can increase NAFLD, Framingham indices, and HOMA-IR. These indices should be calculated for all the patients with high BMI in the clinical setting. The association between NAFLD score and insulin resistance index is strong, so for a one-unit increase in liver fibrosis score, the HOMA-IR score increases 0.287 times. MetS increases cardiovascular disease and NAFLD. It is suggested that studies be conducted with a larger statistical population and different genetics in the future.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

References

1. Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: position paper of the ESPGHAN Hepatology Committee. Journal of pediatric gastroenterology and nutrition. 2012;54(5):700-13.
2. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). Journal of pediatric gastroenterology and nutrition. 2017;64(2):319.
3. Neuschwander-Tetri BA. Non-alcoholic fatty liver disease. BMC medicine. 2017;15(1):1-6.
4. Kumar S, Kelly AS, editors. Review of childhood obesity: from epidemiology, etiology, and comorbidities to clinical assessment and treatment. Mayo Clinic Proceedings; 2017: Elsevier.
5. Dumitrascu DL, Neuman MG. Non-alcoholic fatty liver disease: an update on diagnosis. Clujul medical. 2018;91(2):147.
6. Weiss R, Dziura J, Burgert TS, Tamborlane WV, Taksali SE, Yeckel CW, et al. Obesity and the metabolic syndrome in children and adolescents. New England journal of medicine. 2004;350(23):2362-74.
7. Sookoian S, Pirola CJ. Non-alcoholic fatty liver disease is strongly associated with carotid atherosclerosis: a systematic review. Journal of hepatology. 2008;49(4):600-7.
8. Burrage E, Marshall KL, Santanam N, Chantler PD. Cerebrovascular dysfunction with stress and depression. Brain circulation. 2018;4(2):43-53.
9. Lloyd-Jones DM, Wilson PW, Larson MG, Beiser A, Leip EP, D'Agostino RB, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. The American journal of cardiology. 2004;94(1):20-4.
10. Nogueira JP, Cusi K. Role of insulin resistance in the development of nonalcoholic fatty liver disease in people with type 2 diabetes: from bench to patient care. Diabetes Spectrum. 2024;37(1):20-8.
11. Burrage E, Marshall KL, Santanam N, Chantler PD. Cerebrovascular dysfunction with stress and depression. Brain circulation. 2018;4(2):43.
12. van der Pal KC, Koopman AD, Lakerveld J, van der Heijden AA, Elders PJ, Beulens JW, et al. The association between multiple sleep-related characteristics and the metabolic syndrome in the general population: the New Hoorn study. Sleep Medicine. 2018;52:51-7.
13. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846-54.
14. Diniz MdFHS, Beleigoli AMR, Schmidt MI, Duncan BB, Ribeiro ALP, Vidigal PG, et al. Homeostasis model assessment of insulin resistance (HOMA-IR) and metabolic syndrome at baseline of a multicentric Brazilian cohort: ELSA-Brasil study. Cadernos de saude publica. 2020;36:e00072120.
15. Weir C, Jan A. BMI classification percentile and cut off points.[Updated 2021 Jun 29]. StatPearls [Internet] Treasure Island (FL): StatPearls Publishing; Available from https://www ncbi nlm nih gov/books/NBK541070. 2022.
16. Denkmayr L, Feldman A, Stechemesser L, Eder SK, Zandanell S, Schranz M, et al. Lean patients with non-alcoholic fatty liver disease have a severe histological phenotype similar to obese patients. Journal of Clinical Medicine. 2018;7(12):562.
17. Bhat G, Baba CS, Pandey A, Kumari N, Choudhuri G. Insulin resistance and metabolic syndrome in non-obese Indian patients with non-alcoholic fatty liver. Tropical Gastroenterology. 2013;34(1):18-24.
18. Djalalinia S, Saeedi Moghaddam S, Sheidaei A, Rezaei N, Naghibi Iravani SS, Modirian M, et al. Patterns of obesity and overweight in the iranian population: findings of steps 2016. Frontiers in endocrinology. 2020;11:42.
19. Abdi F, Atarodi Z, Mirmiran P, Esteki T. Review of nutritional status in Iranian population. Focus Sci. 2016;2(3):1-10.
20. Valle-Martos R, Valle M, Martos R, Cañete R, Jiménez-Reina L, Cañete MD. Liver enzymes correlate with metabolic syndrome, inflammation, and endothelial dysfunction in prepubertal children with obesity. Frontiers in Pediatrics. 2021;9:629346.
21. Gentili A, Daviddi G, De Vuono S, Ricci MA, Di Filippo F, Alaeddin A, et al. Non-alcoholic fatty liver disease fibrosis score and preclinical vascular damage in morbidly obese patients. Digestive and Liver Disease. 2016;48(8):904-8.
22. Lee S-R, Han K-D, Choi E-K, Oh S, Lip GY. Nonalcoholic fatty liver disease and the risk of atrial fibrillation stratified by body mass index: a nationwide population-based study. Scientific reports. 2021;11(1):1-9.
23. Godoy-Matos AF, Silva Júnior WS, Valerio CM. NAFLD as a continuum: from obesity to metabolic syndrome and diabetes. Diabetology & metabolic syndrome. 2020;12(1):1-20.
24. Chen Y-l, Li H, Li S, Xu Z, Tian S, Wu J, et al. Prevalence of and risk factors for metabolic associated fatty liver disease in an urban population in China: a cross-sectional comparative study. BMC gastroenterology. 2021;21(1):1-12.
25. Sinn DH, Kang D, Cho SJ, Paik SW, Guallar E, Cho J, et al. Lean non-alcoholic fatty liver disease and development of diabetes: a cohort study. European journal of endocrinology. 2019;181(2):185-92.