ORIGINAL ARTICLE

Medical Journal of Western Black Sea
Batı Karadeniz Tıp Dergisi

Med J West Black Sea 2021;5(2): 143-149
DOI: 10.29058/mjwbs.811398

Non-Alcoholic Fatty Liver Disease in Patients with Non-Metabolic Syndrome

Metabolik Sendromlu Olmayan Hastalarda Non-Alkolik Yağlı Karaciğer Hastalığı

Vahide Betül CANITEZ[1], İbrahim GUNEY[2], Edip ERKUŞ[2]

[1]University of Health Sciences, Konya Research and Training Hospital, Department of Internal Medicine, Konya, Turkey
[2]University of Health Sciences, Konya Research and Training Hospital, Department of Nephrology, Konya, Turkey

ORCID ID: Vahide Betul Canıtez 0000-0003-2758-0773, İbrahim Güney 0000-0002-1646-2811, Edip Erkuş 0000-0002-7821-8275

Cite this article as: Canıtez VB, et al. Non-Alcoholic Fatty Liver Disease in Patients with Non-Metabolic Syndrome. Med J West Black Sea. 2021;5(2):143-149.

Corresponding Author
Edip Erkuş

E-mail
dr.ediperkus@gmail.com

Received
16.10.2020
Revision
31.01.2021
Accepted
01.02.2021

ABSTRACT

Aim: Non-alcoholic fatty liver disease (NAFLD) is the most common type of chronic liver diseases and it is the hepatic evidence of metabolic syndrome (MetS). But patients with NAFLD have not always MetS, and all patients with MetS have not always NAFLD. In our study, we aimed to investigate the factors related to NAFLD in patients with non-MetS.

Material and Methods: Our study was made at least 400 volunteers from 10 randomly selected Family Health Centers (FHCs) in our city center. Complete blood counts, biochemical tests and hepatobiliary ultrasonography (hUSG) were performed from the individuals. Body mass index (BMI), homeostasis Model Assessment of insulin Resistance (HOMA-IR), fibrosis-4 (FIB-4) and BARD scores were calculated.

Results: The prevalence of fatty liver was detected as 33.8% with hUSG. The frequencies of stage 1, 2 and 3 fatty liver were found to be 71.6%, 25.4% and 3.0%, respectively, in those with fatty liver (n=67). In univariate analysis; there were statistically significant differences between those with and without fatty liver individuals for the parameters of age, BMI, waist circumference, diastolic blood pressure, hemoglobin, AST/ALT ratio, ALT, GGT and triglyceride levels. In multivariate logistic regression analysis, BMI (OR: 1.311, p <0.001), hemoglobin (OR: 1,311, p = 0.005), DBP (Diastolic blood pressure) (OR: 1.046, p = 0.044) were shown to be independently associated factors for fatty liver.

Conclusion: The frequency of non-alcoholic fatty liver disease is also common in patients with non-MetS. BMI, hemoglobin and DBP are independently associated parameters for NAFLD in those with non-MetS.

Keywords: Non-alcoholic fatty liver disease, Metabolic syndrome, Hemoglobin level, Obesity

ÖZ

Amaç: Non-alkolik yağlı karaciğer hastalığı (NAYKH) en yaygın kronik karaciğer hastalığı türüdür ve metabolik sendromun (MetS) hepatik kanıtıdır. Ancak NAYKH'li hastalar her zaman MetS'ye sahip değildir ve MetS'li tüm hastalar her zaman NAYKH'ye sahip değildir. Çalışmamızda MetS olmayan hastalarda NAYKH ile ilişkili faktörleri araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmamız şehir merkezimizde rastgele seçilen 10 Aile Sağlığı Merkezi'nden (ASM) en az 400 gönüllü ile yapılmıştır. Bireylerden tam kan sayımı, biyokimyasal testler ve hepatobiliyer ultrasonografi (hUSG) yapıldı. Vücut kitle indeksi (BMI), homeostaz Modeli İnsülin Direnci Değerlendirmesi (HOMA-IR), fibrozis-4 (FIB-4) ve BARD skorları hesaplandı.

Bulgular: Çalışmada karaciğer yağlanması prevalansı hUSG ile 33,8 % olarak tespit edildi. Karaciğer yağlanması olanlarda (n = 67) evre 1, 2 ve 3 yağlı karaciğer sıklığı sırasıyla 71,6 %, 25,4 % ve 3,0 % olarak bulundu. Tek değişkenli analizde; yağlı karaciğeri olan ve olmayan bireyler arasında yaş, vücut kitle indeksi, bel çevresi, diyastolik kan basıncı, hemoglobin, AST / ALT oranı, ALT, GGT ve trigliserit düzeyleri parametreleri açısından istatistiksel olarak anlamlı farklılıklar vardı. Çok değişkenli lojistik regresyon analizinde, BMI (OR: 1,311, p <0,001), hemoglobin (OR: 1,311, p = 0,005), DBP (OR: 1,046, p = 0,044) yağlı karaciğer için bağımsız ilişkili faktörler olarak gösterilmiştir.

Sonuç: Non-alkolik yağlı karaciğer hastalığı sıklığı, MetS olmayan hastalarda da yaygındır. BMI, hemoglobin ve DBP, MetS olmayanlarda NAYKH için bağımsız olarak ilişkili parametrelerdir.

Anahtar Sözcükler: Non-alkolik yağlı karaciğer hastalığı, Metabolik sendrom, Hemoglobin düzeyi, Obezite

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common type of chronic liver diseases (1). NAFLD is a disease characterized by immune system-mediated inflammation and progressive liver fibrosis (2,3). The prevalence of NAFLD is rapidly increasing worldwide and it is recognized as the liver manifestation of metabolic syndrome (MetS) and basically plays a role in insulin resistance (IR) (3,4).

Obesity, type 2 diabetes mellitus (DM), age, male sex, drugs and sedentary lifestyle are considered as risk factors for NAFLD (5). Only 20% - 80% of those with NAFLD have all the criteria for MetS. Therefore, MetS alone cannot exactly explain why some people have NAFLD while others do not have NAFLD (6,7). The main finding of NAFLD is fat accumulation in hepatocytes. Insulin resistance, abnormalities in cytokine regulation, oxidative stress, mitochondrial dysfunction are some of the factors thought to be responsible for the development of the disease. The most important mechanism among these is insulin resistance. The important role of insulin resistance in the development of fatty liver makes this disease closely related to MetS (8). Insulin resistance has an important role in the development of steatosis. However, steatosis itself also triggers insulin resistance (9).

In insulin resistance, there is a decrease in plasma lipoproteinlipase activity, an increase in plasma triglycerides, high sensitivity lipoprotein degradation and hepatic gluconeogenesis. Liver and muscles become susceptible to glucose intolerance. In addition, increasing plasma free fatty acid concentration is observed in insulin resistance, and free fatty acids also stimulate triglyceride accumulation in the liver (10).

In our study, we aimed to investigate the factors related to NAFLD in patients with non-MetS.

MATERIALS and METHODS

The cluster sample method was used to determine the sample size for our study. Accordingly, at least 40 volunteers in each FHCs (Family Health Centers) between the ages of 18-65 were recruited from 10 randomly selected FHCs in our city center. A total of 400 individuals were included in the study. As a result of the laboratory tests, 5 individuals who were positive for hepatitis B (HbsAg) and 197 individuals with MetS were excluded from the study. Data from 198 individuals was analyzed (Figure 1). The study was approved by the local ethics committee with decision no 2018/71 dated 21.02.2018. All patients were informed in detail about the study and signed the 'informed consent form'.

After the anamnesis, physical examination of all subjects was performed. Height, body weight and waist circumference were measured. Blood pressure (BP) was measured after 10 minutes of rest and recorded as systolic BP (SBP) and diastolic BP (DBP). Blood samples for complete blood count, biochemical tests (glucose, creatinine, ALT, AST, ALP, GGT, LDH, total bilirubin, cholesterol, HDL, LDL, triglyceride, insulin), HbsAg, Anti-HCV were taken for all volunteers who wanted to participate in the study. Hepatobiliary USG was performed to see if there was fatty liver, and if there was fat, the degree of fat was determined and recorded. Body mass index (BMI), homeostasis Model Assessment of insulin Resistance (HOMA-IR) (11), fibrosis-4 (FIB-4) (12) and BARD (13) scores were calculated. The diagnosis of MetS was made by meeting at least three of the five criteria according to the Adult Treatment Panel (ATP) III (14).

Exclusion Criteria;

1. Co-morbid diseases (Such as advanced stage chronic obstructive pulmonary disease, cancer, end stage renal failure, liver cirrhosis, and heart failure),
2. Chronic viral hepatitis,
3. Alcohol usage,
4. Previously known other causes of liver disease,

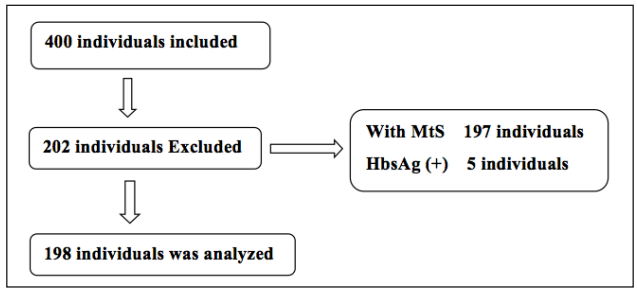

Figure 1: Individuals included in the study.

5. Determining MetS,

6. Individuals who did not agree to participate in the study.

The SPSS 22.0 package program was used for statistical data analyses Descriptive statistics were shown for normal distribution of continuous variables as mean ± standard deviation, while numerical parameters without normal distribution were shown with median (minimum-maximum). Categorical variables were represented by numbers and percentages. Continuous numerical variables were checked by the Kolmogorov-Smirnov Test to determine normality of distribution. In the comparison of the two groups, those with normal distribution were performed with the T-test, and those with abnormal distribution were performed with the Mann Whitney U test. In comparison of categorical variables, Fisher's exact test and Chi-square test were used according to their suitability. In the logistic multivariate regression analysis model, which was performed to determine the parameters related to the fatty liver in patients with non-MetS, all parameters with a p value <0.05 in the univariate analysis were included. The parameters associated with fatty liver in multivariate analyses were further evaluated with Reciever Operating Characteristic (ROC) Curve analysis to determine the optimum cut-off levels and the predictive values for predicting fatty liver. p <0.05 was considered significant in all analyses.

RESULTS

The prevalence of fatty liver was detected in hUSG as 33.8% (67 of 198 individuals) in the study. Of the 198 individuals, 94 (47.5%) were male and 104 (52.5%) were female, with a median age of 33 (18-65) years. Patients with NAFLD were older than those without (35 years (18-65), 31 years (18-63), respectively; p =0.026). BMI, waist circumference, DBP, hemoglobin and triglyceride levels were significantly higher in patients with NAFLD than those without (p< 0.05). In addition, the AST/ALT ratio was lower and the number of patients with ALT and GGT values above normal was higher in patients with NAFLD. But, we could not find any significant difference between the two groups in terms of MetS components, except waist circumference (Table 1,2).

In multivariate logistic regression analysis, the increase in BMI, hemoglobin and DBP were identified as independently associated factors for fatty liver in non-MetS patients (OR= 1.311, p< 0.001; OR= 1.311, p=0.005; OR= 1.046, p= 0.044 respectively) (Table 3). Independently associated factors for fatty liver were further evaluated with ROC curve analysis (Table 4).

Table 1: Comparison of clinical and demographic characteristics of individuals with and without fatty liver in patients without MetS

Parameters	All cases (n=198)	Individuals with fatty liver (n=67)	Individuals without fatty liver (n=131)	p
Age (year)	**33.0 (18.0-65.0)**	**35.0 (18.0-65.0)**	**31.0 (18.0-63.0)**	**0.026**
Sex male	94 (47.5%)	35 (52.2%)	59 (45.0%)	0.369
DM yes	4 (2%)	3 (4.5%)	1 (0.8%)	0.113
BMI (kg/m²)	**25.5 (19.1-48.1)**	**28.5 (19.1-48.1)**	**24.3 (15.8-34.9)**	**<0.001**
Waist Circumference (cm)	**86 (60-129)**	**92 (70-129)**	**82 (60-106)**	**<0.001**
SBP (mmHg)	117 (95-185)	121 (95-185)	117 (101-165)	0.061
DBP (mmHg)	**77 (50-120)**	**78 (67-120)**	**75 (50-102)**	**0.008**
FIB-4 score	0.64 (0.18-2.25)	0.64 (0.22-1.90)	0.64 (0.18-2.25)	0.936
BARD score	2 (0-4)	2 (0-4)	2 (0-4)	0.781
Hypertension Yes No (SBP<130, DBP<85, no drug	35 (17.7%) 163 (82.3%)	17 (25.4%) 50 (74.6%)	18 (13.7%) 113 (86.3%)	0.050
Glucose (mg/dl) < 100 ≥ 100	198 (100%) 0	67 (100 %) 0	131 (100 %) 0	……..
TG (mg/dl) ≥ 150 < 150	18 (9.1%) 180 (90.1%)	6 (9%) 61 (91%)	12 (9.2 %) 119 (90.8%)	1.0
Waist circumference (cm) ≥88(for F), ≥102 (for M) <88 (for F), <102 (for M)	**85 (42.9%) 113 (57.1%)**	**46 (68.7%) 21 (31.3%)**	**39 (29.8%) 92 (70.2%)**	**<0.001**
HDL(mg/dl) <50(for F), <40(for M) >50 (for F), > 40 (for M)	129 (65.2%) 69 (34.8%)	46 (68.7%) 21 (31.3%)	83 (63.4%) 48 (36.6%)	0.529
Liver Fat Stage Stage 1 Stage 2 Stage 3	48 (71.6%) 17 (25.4%) 2 (3.0%)	48 (71.6%) 17 (25.4%) 2 (3.0%)	0 0 0	…….

DM: Diabetes Mellitus, **BMI:** Body mass index, **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure, **HDL:** High density lipoprotein, **TG:** Triglyceride, **F:** Female, **M:** Male.

Table 2: Comparison of laboratory characteristics of individuals with and without fatty liver in patients without MetS

Parameters	All cases (n=198)	Individuals with fatty liver (n=67)	Individuals without fatty liver (n=131)	p
WBC (10^3/mm^3)	6.90 (4.07-15.86)	7.23 (4.07-13.24)	6.68 (4.27-15.86)	0.147
Hemoglobin (g/dl)	**14.5±1.9**	**14.9±1.8**	**14.3±1.9**	**0.042**
RDW (fL)	40.1 (32.1-56.49	39.8 (35.3-49.5)	40.1 (32.1-56.4)	0.431
Platelet (10^3/μL	270.1±63.2	272.9±60.9	268.6±64.5	0.653
MPV (fL	10.5±0.8	10.5±0.8	10.5±0.8	0.875
NLR	1.75 (0.65-13.98)	1.75 (0.86-10.15)	1.76 (0.65-13.98)	0.569
PLR	117.76 (32.65-386.52)	110.3 (59.1-386.5)	118.8 (32.7-302.7)	0.291
Glucose (mg/dL)	85.4±7.1	86.4 ±7.1	84.9±7.1	0.160
Creatinine (mg/dl)	0.80 (0.53-1.46)	0.8 (0.59-1.28)	0.8 (0.53-1.46)	0.353
APRI	0.08 (0.01-0.31)	0.79 (0.03-0.31)	0.09 (0.01-0.21)	0.114
AST/ALT	**1.24 (0.15-4.67)**	**1.0 (0.15-4.67)**	**1.31 (0.57-4.13)**	**<0.001**
ALT (U/L) (0-50) (≥ 50)	**18.0 (3.0-98.0)**	**63 (94%) 4 (6%)**	**130 (99.2%) 1 (0.8%)**	**0.046**
AST (U/L) (0-50) (≥ 50)	21.0 (3.0-98.0)	64 (100%) 0 (0%)	130 (99.2%) 1 (0.8%)	0.662
ALP (U/L) (0-120) (≥ 120)	73.0 (8.0-212.0)	64 (95.5%) 3 (4.5%)	129 (98.5%) 2 (1.5%)	0.215
GGT (U/L) (0-55) ≥ 55)	**20.0 (5.0-352.0)**	**62 (92.5%) 5 (7.5%)**	**129 (98.5%) 2 (1.5%)**	**0.045**
T. chol (mg/dL)	179.7±37.8	185.8±38.5	176.6±37.1	0.104
HDL (mg/dL)	43.0 (24.0-83.0)	43.0 (30.0-76.0)	46.0 (24.0-83.0)	0.303
TG (mg/dL)	**121.0 (29.0-830.0)**	**102.0 (30.0-226.0)**	**89.0 (40.0-830.0)**	**0.024**
LDL (mg/dL)	113.2±32.1	118.5±32.4	110.5±31.8	0.099
Insulin (μU/mL)	7.83 (2.0-89.5)	8.44 (2.0-89.5)	7.11 (2.0-43.5)	0.179
HOMA-IR	1.62 (0.35-150.16)	1.86 (0.39-21.44)	1.44 (0.35-9.99)	0.137

WBC: White blood cell, **RBC:** Red blood cell, **MPV:** Mean plathelet volume, **RDW:** Erythrocyte distribution width, **NLR:** Neutrophil lymphocyte ratio, **PLR:** Plathelet lymphocyte ratio, **ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase, **ALP:** Alkalen phosphatase, **GGT:** Gamma glutamyl transferase, **T.chol:** Total cholesterol, **LDL:** Low density lipoprotein, **HDL:** High density lipoprotein, **TG:** Triglyceride, **HOMA-IR:** Homeostasis Model Assessment of Insulin Resistance.

Table 3: Multivariate regression analysis of the factors associated with fatty liver in patients with non-MetS

	Step1 (Forward Conditional) R^2=0.221			Step2 (Forward Conditional) R^2=0.253			Step3 (Forward Conditional) R^2=0.270		
	OR	%95 GA	*p*	OR	%95 GA	*p*	OR	%95 GA	*p*
BMI	1.289	1.183-1.404	<0.001	1.321	1.204-1.450	<0.001	1.311	1.193-1.440	<0.001
Hb				1.309	1.085-1.580	0.005	1.311	1.084-1.586	0.005
DBP							1.046	1.001-1.092	0.044

Parameters included in the logistic regression model; Age, DBP (diastolic blood pressure), triglyceride, GGT group, ALT group, ALT / AST ratio, hemoglobin (Hb), waist circumference group and BMI (body mass index)

Table 4: ROC curve analysis results of the parameters those independently associated with fatty liver in patients with non-MetS

Parameters	Cut-off	AUC	Sensitivity %	Specificity %	p value
BMI, kg/m^2	>24.45	0.788	91.04	53.44	<0.001
Hemoglobin (g/dl)	>13.9	0.596	74.63	45.80	0.022
DBP (mmHg)	>74	0.615	76.12	45.80	0.005

BMI: Body mass index, **DBP:** Diastolic blood pressure. ROC curve analysis was conducted by MedCalc program. Youden index was used for detecting cut-off levels (DeLong method).

DISCUSSION

In our study, we found that one-third of individuals without MetS had NAFLD. Risk factors for NAFLD in individuals without MetS have not yet been fully established. Our study is one of the rare studies in the literature investigating the risk factors of NAFLD in patients without MetS. In our study, we determined that individuals without MetS had BMI > 24.45 kg/m2, hemoglobin value > 13.9 g/dl and DBP > 74 mmHg as risk factors for NAFLD.

Obesity, MetS and diabetes mellitus are closely related to NAFLD. In addition, the NAFLD prevalence (15% in 2005 and 25% in 2010) increases in parallel with obesity prevalence (15). Only 20% - 80% of those with NAFLD have all the criteria for MetS. Therefore, MetS alone can not fully explain why some have NAFLD while others do not have NAFLD (6,7). Moon et al. studied the clinical status and stage of liver fibrosis in patients with NAFLD; they reported that only 14 of 25 (56%) NAFLD patients had metabolic syndrome (16). Similarly, Kang et al. reported that 31 of 91 (31%) NAFLD patients had MetS (17).

While 15% of NAFLD patients have not obesity in developed countries (18), this rate has been reported to be 75% in non-developed countries (19). Yang et al. followed 28880 individuals without obesity and MetS between 2009 and 2015 years and included a total of 1092 individuals (NAFLD group n = 182, non-NAFLD group n = 910) in the final analysis. As a result, they reported that MetS was seen more in NAFLD group than in non-NAFLD group during the follow-up. Similarly, they reported that prediabetes / type 2 diabetes, hypertension and dsilipidemia developed more in NAFLD group than in non-NAFLD group during follow-up as secondary outcome. As a result, they reported that NAFLD is an early phenotypic predictor of MetS in metabolically healthy individuals (20).

In another study, Makker et al. (21) reported that non-MetS and NAFLD patients were associated with preclinical cardiac disease, independent of traditional risk factors such as diabetes and hypertension according to echocardiographic findings. So; if NAFLD can be detected before the MetS develops, individuals will be able to be protected from future cardiovascular diseases and poor metabolic status.

It has been reported that the presence of MetS in patients with NAFLD may lead to increased progression of the disease and serious liver diseases (such as NAFLD) (22,23). The study with the largest biopsy-proven patient population (357 patients) was performed by Yilmaz et al. In this study; patients with NAFLD and MetS were found to have more NAFLD than those without MetS, but no difference was reported in patients with and without MetS in terms of fibrosis prevalence. In this study, they found that BMI, ALT, hemoglobin, ferritin and CRP were associated with fibrosis in patients with non-MetS and NAFLD. Also, interestingly, the increase in hemoglobin level was found to be significantly associated with NAFLD and fibrosis in patients with non-MetS (22).

The first study to report a relationship between hemoglobin and NAFLD is made by Trak-Smayra et al.; they reported that there was a positive correlation between free hemoglobin subunits and liver lesions in patients with NAFLD (24). Xu et al. examined 8985 cases for NAFLD and showed that hemoglobin value was significantly higher in patients with NAFLD compared to control (143.3 g / L, 136.4 G / l, respectively). Also in the same study, when they divide the hemoglobin value into 4 quartiles; showed that the number of patients with NAFLD increased with the increase in hemoglobin value (25). In another study, Yilmaz et al. examined 357 patients with the biopsy-proven; found that the optimal hemoglobin cut-off value was 144 g/L for NAFLD diagnosis in patients with non-MetS and NAFLD (22). In our study, when we analyzed 198 individuals without MetS; NAFLD diagnosis was made with hUSG in 67 individuals and the hemoglobin values of these 67 individuals with NAFLD were significantly higher than individuals without NAFLD. In our next analysis; we determined that the increase in hemoglobin value in individuals without MetS is an independent risk factor for NAFLD (OR = 1,311 p = 0.005) and the cut-off hemoglobin value for the diagnosis of NAFLD in individuals without MetS was 13.9 g/dl (UAC = 0.596 p = 0.022).

The most important abnormality in NAFLD is elevation in liver enzymes, but this is not seen in the majority of patients. In NAFLD, the ratio of AST/ALT to less than 1 and increase in GGT are associated with increased mortality (26). In our study; we found that individuals with NAFLD had a lower AST/ALT ratio and higher pecentanges of individuals with ALT and GGT values above normal values than without NAFLD individuals. We also found that the percentage of individuals with a waist circumference above normal values (≥ 88 cm in women, ≥ 102 cm in men) was higher in individuals with NAFLD than those without NAFLD. For this reason, waist circumference alone may be sufficient as one of the diagnostic criteria of MetS to show the association of MetS and NAFLD . Studies involving a large number of patients are needed for this subject.

The most important limitation of our study is that liver biopsy was not performed on the patients. However, biopsy is a very difficult situation in epidemiological studies. Another limitation is the insufficient number of our study population. Our study population was relatively little, because we determined MetS approximately half of the study population at the beginning of the study.

As a result; NAFLD disease is an important public health problem because of the increased risk of MetS and cardiovascular disease. But, it can be also seen without MetS.

Therefore, early diagnosis of patients with non-MetS and NAFLD is important for preventive medicine. So; if NAFLD can be detected before the MetS develops, individuals will be able to be protected from future cardiovascular diseases and poor metabolic status.

Acknowledgment

None declared

Author Contributions

Concept, Design, Supervision: **İbrahim Güney,** Materials, Data Collection: **Vahide Betül Canıtez,** Analysis or Interpretation, Literature Search, Writing Manuscript: **Edip Erkuş, İbrahim Güney,** Critical Review: **İbrahim Güney.**

Conflicts of Interest

The authors declare that they have no conflict of interest.

Financial Support

None.

Ethical Approval

Approval was obtained with the decisions of the Selçuk University non-invasive clinical research ethics committee. Date: 21.02.2018 issue: 2018/71.

Review Process

This article is published with blind-review process and extremely review.

REFERENCES

1. Preiss D, Sattar N. Non-alcoholic fatty liver disease: An overview of prevalence, diagnosis, pathogenesis and treatment considerations. Clin Sci (Lond) 2008;115:141-150.
2. Shukla V, Fatima J, Chaudhary S, Ali M, Mishra I. A study of endothelial dysfunction in patients of non-alcoholic fatty liver disease. J Assoc Physicians India 2017;65(9):18-22.
3. Miyaoka Y, Jin D , Tashiro K, Masubuchi S, Ozeki M, Hirokawa F, Hayashi M, Takai S, Uchiyama K. A novel hamster nonalcoholic steatohepatitis model induced by a high-fat and high-cholesterol diet. Exp Anim 2018;67(2):239-247.
4. Neuschwander-Tetri BA. Non-alcoholic fatty liver disease. BMC Med 2017;15(1):45.
5. Streba LA, Vere CC, Rogoveanu I, Streba CT. Nonalcoholic fatty liver disease, metabolic risk factors, and hepatocellular carcinoma: An open question. World J Gastroenterol 2015; 21(14):4103-4110.
6. Vanni E, Bugianesi E, Kotronen A, De Minicis S, Yki-Järvinen H, Svegliati-Baroni G. From the metabolic syndrome to NAFLD or vice versa? Dig Liver Dis 2010;42:320-330.
7. Green RM. NASH-hepatic metabolism and not simply the metabolic syndrome. Hepatology 2003;38:14-17.
8. Cobbina E, Akhlaghi F. Non-alcoholic fatty liver disease (NAFLD) - pathogenesis, classification, and effect on drug metabolizing enzymes and transporters. Drug Metab Rev 2017;49(2): 197-211.
9. Lomonaco R, Ortiz-Lopez C, Orsak B, Webb A, Hardies J, Celia Darland, Finch J, Gastaldelli A, Harrison S, Tio F, Cusi K. Effect of adipose tissue insulin resistance on metabolic parameters and liver histology in obese patients with nonalcoholic fatty liver disease. Hepatology 2012;55(5):1389-1397.
10. Mykkanen L, Zaccaro DJ, Wagenknecht LE, Robbins DC, Gabriel M, Haffner SM. Microalbuminuria is associated with insulin resistance in nondiabetic subjects: The insulin resistance atherosclerosis study. Diabetes 1998;47(5):793-800.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7): 412-419.
12. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, Sulkowski MS, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M, APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006. 43(6): 1317-1325.
13. Harrison SA, D Oliver D, H L Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut 2008;57(10): 1441-1447.
14. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith Jr SC, Spertus JA, Costa F, American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: An American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112(17): 2735-2752.
15. Salva-Pastor N, Chávez-Tapia NC, Misael Uribe M, Nuño-Lámbarri N. The diagnostic and initial approach of the patient with non-alcoholic fatty liver disease: Role of the primary care provider. Gasroenterol Hepatol Bed Bench 2019;12(4):267-277.
16. Monn K, Leem JM, Bae SS, Lee KM, Kim SH, Chae HB, Park SM, Youn SJ. The prevalence of metabolic syndrome in patients with nonalcoholic fatty liver disease. Korean J Hepatol 2004;10;197-206.
17. Kang H, Greenson JK, Omo JT, Chao C, Peterman D, Anderson L, Foess-Wood L, Sherbondy MA, Conjeevaram HS. Metabolic syndrome is associated with greater histologic severity, higher carbohydrate, and lower fat diet in patients with NAFLD. Am J Gastroenterol 2006; 101:2247-2253.
18. Younossi Z, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clin Gastroenterol Hepatol 2004;2(3):262-265.
19. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, Baijal R, Lala S, Chaudhary D, Deshpande A. Prevalence of nonalcoholic fatty liver disease: Population based study. Ann Hepatol 2007;6:161-163.
20. Yang S, Kwak S, Lee JH, Kang S, Lee SP. Nonalcoholic fatty liver disease is an early predictor of metabolic diseases in a metabolically healthy population. Plos One 2019;14(11): e0224626.

21. Makker J, Tariq H , Bella JN, Kumar K, Chime C, Patel H, Kamal MU, Shaikh D, Vootla V, Bajantri B, Gomceli U, Alshelleh M, Peralta R, Zhang A, Chilimuri S. Preclinical cardiac disease in nonalcoholic fatty liver disease with and wtihout metabolic syndrome. Am J Cardiovasc Dis 2019;9(5):65-77.
22. Yilmaz Y, Senates E, Ayyildiz T, Colak Y, Tuncer İ, Kurdas Ovunc AO, Dolar E, Kalayci C. Characterization of nonalcoholic fatty liver disease unrelated to the metabolic syndrome. Eur j Clin Invest 2012;42 (4):411-418.
23. Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M. Nonalcoholic fatty liver disease, steatohepatitis, and the metabolic syndrome. Hepatology 2003;37:917-923.
24. Trak-Smayra V, Dargere D, Noun R, Albuquerque M, Yaghi C, Gannagé-Yared MH, Bedossa P, Paradis V. Serum proteomic profiling of obese patients: Correlation with liver pathology and evoluation after bariatric surgery. Gut 2009;58:825-832.
25. Xu L, Xu CF, Yu CH, Miao M, Li YM. Haemoglobin and non-alcoholic fatty liver disease: Further evidence from a population-based study. Gut 2009;58:1706-1707.
26. Brunt EM, Tiniakos DG. Histopathology of nonalcoholic fatty liver disease. World J Gastroenterol 2010;16(42): 5286-5296.