Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2021;10(1):51-5

Determination of metabolic syndrome and insulin resistance rate among adults with ultrasound diagnosed non-alcoholic fatty liver disease

Filiz Araz[1], Murat Sert[2]

[1]*Baskent University, Adana Dr. Turgut Noyan Training and Research Hospital, Gastroenterology, Adana, Turkey*
[2]*Cukurova University, Faculty of Medicine, Department of Endocrinology, Adana, Turkey*

Received 10 July 2020; Accepted 01 September 2020
Available online 20.12.2020 with doi: 10.5455/medscience.2020.07.134

Abstract

Metabolic syndrome (MS) has close association with nonalcoholic fatty liver disease (NAFLD) and is characterized by insulin insensitivity, central obesity, dyslipidemia, hypertension and high glucose levels. This study aimed to define the prevalence of MS, insulin resistance and diabetes among subjects with NAFLD. Patients and method: In a tertiary center, patients diagnosed to have fatty liver disease by ultrasound were included. Cases with drug and/or alcohol use and liver diseases were excluded. Anthropometric measures were applied. Fasting glucose, insulin, c-peptide and transaminase levels were measured. Oral glucose tolerance test was applied to all cases. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index was calculated. Insulin resistance was defined as HOMA-IR ≥2.7. ATP III criteria were applied for diagnosis of MS. 230 patients were enrolled. 141 patients (61.3%) were female. Mean age was 50.3±10 (18-95) years. Mean body-mass index (BMI) was 30.5±10.6 (18-50). Mean HOMA index was 3.3±2.6 (0.5-26.5). Impaired fasting glycemia was diagnosed in 78 (33.9%) patients, while impaired glucose tolerance and type 2 diabetes were diagnosed in 65 (28.3%) and 51 (22.1%) patients, respectively. MS prevalence among patients with NAFLD was 56.5%. MS was present in 73.2% of patients with HOMA index ≥ 2.7. Independently from BMI, insulin resistance is high in patients with NAFLD. Transaminase levels did not change with MS among NAFLD patients. NAFLD is associated with increased prevalence rate for metabolic syndrome, insulin resistance and type 2 diabetes.

Keywords: Nonalcoholic fatty liver disease, metabolic syndrome, insulin resistance, HOMA

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis in patients without other causes, drug use and heavy alcohol consumption (females >20 gr/day, males>30 gr/ day) for secondary hepatic fat accumulation [1-3]. NAFLD may potentially advance to cirrhosis and is accepted as a considerable cause for cryptogenic liver disease [4,5]. NAFLD has worldwide distribution with different prevalence rates. Prevalence of NAFLD is 10-30% in whole population in different countries [6,7]. Estimated prevalence of NAFLD in the US is 19% to 46% [7,8]. Imaging-based global NAFLD prevalence was estimated as 25.24 % by a recent meta-analysis. According to this estimation, Middle East (31.79%) and South America (30.45%) have the highest prevalence rates [9]. Age > 45, obesity (BMI ≥ 30), central obesity (defined as waist/hip ratio over 0.9 in men or over 0.85 in women, and waist ≥102 cm in men or ≥88 cm in women), presence of type 2 diabetes mellitus, family history of type 2 diabetes and dyslipidemia are major risk factors for NAFLD [10].

Components of metabolic syndrome are presence of hyperglycemia, abdominal obesity, dyslipidemia, and hypertension [11,12]. MS is related with insulin resistance, high risk of type 2 diabetes and development of atherosclerotic cardiovascular disease [13]. In order to prevent associated macrovascular complications of type 2 diabetes, it is critical to diagnose prediabetes which is defined as impaired fasting glycemia and/or impaired glucose tolerance [14,15].

NAFLD and MS have close associations. Some evidence supports common pathogenetic mechanisms for these two entities. Due to its close relationship with insulin resistance, obesity and dyslipidemia, NAFLD was referred as liver manifestation of MS [16]. Higher MS prevalence has been reported among patients with NAFLD. MS is also related with higher risk of steatohepatitis and fibrosis among NAFLD patients [17].

This study aimed to define the prevalence of MS and its components, including insulin resistance, type 2 diabetes and prediabetes,

***Coresponding Author:** Filiz Araz, Baskent University, Adana Dr. Turgut Noyan Training and Research Hospital, Gastroenterology, Adana, Turkey,
E-mail: filizaraz2@hotmail.com

among adult patients with NAFLD who were diagnosed during routine examinations and have no known systemic disease.

Material and Methods

Patient characteristics

This prospective study was conducted at outpatient clinic of Internal Medicine department in Çukurova University. Adult subjects who were diagnosed as NAFLD by ultrasonography and had no known diabetes and/or liver disease were included into the study.

Patients were excluded if they had any one of following criteria;

1. Diagnosis of type 2 diabetes, chronic hepatitis B, chronic hepatitis C, cirrhosis, congestive cardiac failure or renal failure.
2. Heavy alcohol consumption (females >20 gr/day, males>30 gr/ day)
3. Drug use (including amiodarone, corticosteroid, methotrexate, tamoxifen and oral contraceptives)
4. Jejunoileal by-pass or wide small intestinal resection, 5. Malignancy
5. Total parenteral nutrition
6. Hypo or hyperthyroidism
7. Pregnancy

Laboratory analysis and measurements

Height, weight and waist circumference of all patients were recorded. Basal laboratory examination including fasting blood glucose, insulin, c-peptide, transaminases, albumin, lipid profile, thyroid stimulating hormone, HbA1C, C-reactive protein and Apo-B were performed. Oral glucose tolerance test (OGTT) with 75 gr glucose load was applied to all subjects. Formula was used to calculate Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index for each subject.

Definitions

ADA criteria was used to diagnose type 2 diabetes [18]. Subjects with fasting glucose level ≥ 126 mg/ dL or 2-hour plasma glucose level ≥ 200 mg/ dL during OGTT using glucose load of 75 gr or random plasma glucose level ≥ 200 mg/ dL were diagnosed as type 2 diabetes. Impaired fasting glycemia was defined as plasma glucose level of 100-125 mg/dL. Plasma glucose level of 140-199 mg/ dL 120 minutes after glucose load was defined as impaired glucose tolerance. Systolic blood pressure of 120-139 mm Hg and diastolic blood pressure of 80-89 mm Hg were accepted as prehypertension [19].

The formula using fasting glucose and fasting insulin levels was used to calculate HOMA-IR. HOMA-IR ≥2.7 was accepted as cut off to define insulin resistance [20,21].

HOMA-IR=[Fasting glucose (mmol/L)x Fasting insulin (mU/ml)]/22.5 ATP III criteria defines the metabolic syndrome as having three of the following five criteria [11].

- Central obesity (waist circumference ≥102 cm in male and ≥88 cm in female)
- Serum triglycerides ≥150 mg/dL or drug treatment for hypertriglyceridemia.
- Serum high-density lipoprotein (HDL) cholesterol <40 mg/dL in male and <50 mg/dL in female
- Blood pressure equal or higher 130/85 mmHg or taking antihypertensive medication
- Fasting plasma glucose (FPG) ≥110 mg/dL or taking anti-diabetic medication.

Çukurova University Institutional Review Board approved this study.

Statistical analysis

SPSS 15.0 software was used to perform statistical analyses. Parameters were expressed as Mean ± SD or n (%). Continuous variables were compared by Student's t-test. For comparison of categorical variables, Pearson Chi-squared test was used. For comparing variables of more than two groups, ANOVA test was applied. For Spearman's coefficient, $p < 0.05$ was accepted as significant.

Results

Two hundred and thirty adult subjects who were diagnosed as AFLD by ultrasonography and had no history of diabetes and/or liver disease were enrolled into the study. Mean age of whole cohort was 50.3±10.6 (18-95) years. One-hundred and forty-one (61.3%) of all patients were female. Mean level for fasting glucose was 101.39±27.9 (69-364). Mean HOMA-IR index was 3.3±2.6 (0.5-26.5). Demographic and laboratory parameters of patients are shown in Table 1.

Fasting blood glucose level was normal in 138 (60%) subjects, while 78 (33.9%) and 14 (6.1%) of patients were diagnosed as impaired fasting glycemia (IFG) and type 2 diabetes, respectively. After OGTT, impaired glucose tolerance (IGT) was present in 65 (28.3%) subjects, while type 2 diabetes was diagnosed in 51 (22.1%) of all subjects.

Among 75 (32.6%) subjects with family history of type 2 DM, IFG was present in 22 (29.3%) and type 2 DM was present in 20 (26.2%) subjects. Among 155 (67.4%) patients with no family history of type 2 DM, IFG and type 2 DM were present in 43 (27.7%) and 31(20%) subjects, respectively. For NAFLD, having family history of type 2 DM did not significantly affect the diagnosis rate of type 2 DM or IFG.

BMI was normal (18.5-25) in 26 (11.3%) subjects. For 91 (39.6%) and 70 (30.4%) subjects BMI was between 25-29.9 and 30-35, respectively. For 43 (18.7%) patients BMI was over 35. Table 2 shows characteristics of patients by BMI. Diagnosis of IGT and type 2 DM did not significantly differ by BMI (p: 0.10).

Fifty-nine (27.5%) of 230 subjects had normal blood pressure. Prehypertension was present in 41 (17.8%) of all subjects. 130 (56.5%) subjects had hypertension or were treated for hypertension.

Metabolic syndrome by ATP-III criteria was present in 56.5% of

patients with ultrasound diagnosed NAFLD. MS was present in 57.9% of females, while it was present in 54.4% of males (p: 0.610). Among subjects with MS, mean HOMA-IR was 2.5±16 (0.5-14.2), while for subjects without MS, mean HOMAIR was 3.9 ±2.4 (1.2-16.5) (p: 0.0001). Table 1 shows patient characteristics according to the presence of metabolic syndrome. Metabolic syndrome was detected in 93 (73.2%) out of 127 subjects whom HOMA-IR was ≥2.7 (Table 3). HOMA-IR was positively correlated with increasing component of ATP III criteria (r=0.409, p=0.0001).

Insulin resistance was not affected significantly by BMI in this study. Mean HOMA-IR was 2.79 ±2.33 for subjects with BMI < 25. For subjects with BMI of 25-29.9 and 30-35, mean HOMA-IR were 2.94 ±1.81 and 3.92± 3.51, respectively. Mean HOMA-IR was 3.6 ±2.0 for subjects with BMI > 35 (p: 0.059). HOMA-IR did not show any correlation with BMI (p: 0.061, r: 0.124).

Mean ALT level was 33.2 ± 22.1 (6-143) U/L. In 53.5% of all subjects, ALT level was ≥ 25 U/L. In 48.7% of all subjects ALT level was ≥30 U/L. Among our patients with NAFLD, presence of metabolic syndrome was not related with significant elevation in transaminase levels (p>0.05).

Table 1. Demographic and biochemical parameters of patients

	All patients (n:230)	MS (n: 130)	No-MS (n: 100)	p
Female n (%)	141(61.3)	81 (57.9)	60 (42.1)	.610
Age (years)*	50.3±10.6	51.4 ± 10.5	49 ± 10.6	.096
Body-mass index (kg/m²)*	30.5± 4.9	31.4±4.9	29.4±4.8	.002
Waist circumference*	104.8±10.0	107.8±9.2	100.8± 9.8	.0001
Fasting blood glucose (mg/dl)*	101.39±27.9	108.7±34.8	91.9±8.5	.0001
OGTT 2h blood glucose (mg/dl)*	142.8±52.7	157.7± 58.7	124.3±36.8	.0001
Fasting insulin (mU/ml)*	13.2± 8.1	15.1±9.1	10.7±5.7	.0001
C-peptide (ng/ml)*	3.1±1.1	3.5±1.2	2.6±0.8	.0001
HOMA-IR*	3.3 ±2.3	3.9±2.4	2.5±1.6	.0001
HbA1C (%)*	5.8±0.8	6.0±0.8	5.5±0.5	.0001
AST (U/L)*	28.0 ±15.4	28.8±16.1	27± 14.6	.388
ALT (U/L)*	33.2±22.1	33.2±21.4	33.2± 23.2	.988
Total cholesterol (mg/dl)*	200.5±53.8	204.9±54.3	196.3±49.8	.218
HDL (mg/dl)*	48.3±13.9	43±10.6	55.1±13.8	.0001
LDL (mg/dl)*	120.7±42.2	122.8±44.8	118.1±38.6	.406
Triglyceride (mg/dl)*	163.8±92.8	194.0±101.8	124.7±60.8	.0001
APO-B (mg/dl)*	95.8±28.5	101.2±27.3	88.8±28.6	.001
CRP (mg/L)*	7.1± 9.2	7.7±9.2	6.4±9.2	.268

Assessment-Insulin Resistance, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine Aspartate aminotransferase, Apo-A: Apolipoprotein-A, Apo-B: Apolipoprotein -B, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride * Mean ± Standard Deviation

Table 2. Characteristics of patients by Body-Mass Index.

	BMI<25 n=26	BMI: 25-29,9 n=91	BMI: 30-35 n=70	BMI>35 n=43	p
Age (years)	51.47 ± 10.9	49.8 ± 11.8	51.3 ± 9.3	49 ± 9.7	.619
Systolic blood pressure (mm-Hg)*	121.5 ± 18	129 ± 20.2	136 ± 18.7	139.7 ± 19,4	.0001
Diastolic blood pressure (mm-Hg)*	70.7 ± 12.3	77.6 ± 13.4	83.5 ± 12.8	85.6 ± 13.9	.0001
Fasting glucose (mg/dl)*	110 ± 57.5	100.9 ± 24.5	101 ± 21.4	97.9 ± 14.4	.366
OGTT 2h glucose (mg/dl)*	136.9 ± 36.1	133.5± 57.0	152.7 ± 49.6	149.4 ± 53.8	.103
Insulin (mU/L)*	11.1 ± 9.6	11.8 ± 6.3	14.9 ± 9.96	14.4 ± 6.6	.030
C-peptide (ng/ml)*	2.84 ± 1.43	2.93 ± 0.97	3.37 ± 1.25	3.2 ± 1.0	.068
HOMA-IR*	2.79 ± 2.33	2.94 ± 1.81	3,92 ± 3.51	3.6 ± 2.0	.059
HDL (mg/dl)*	48.1 ± 20.8	48.71 ± 12.9	49.4 ± 13.9	46.0 ± 10.2	.646
LDL (mg/dl)*	124.2 ± 60.6	127.7 ± 4.5	111.8 ± 35.3	118.3 ± 31.2	.112
TG (mg/dl)*	158.4 ± 71.3	157.0 ± 103.4	182.4 ± 94.7	151.6 ± 74.3	.247
APO-B (mg/dl)*	92.2 ± 29.3	100.1 ± 33.2	94.4 ± 24.3	91.1 ± 22.5	.286
CRP (mg/L)*	7.9 ± 11.6	7.3 ± 11.4	5.5 ± 3.7	9.03 ± 8.5	.240

OGTT: Oral glucose tolerance test, HOMA-IR: Homeostasis Model Assessment-Insulin Resistance, CRP: C-reactive protein, HDL: High density lipoprotein, LDL: Low density lipoprotein, TG: Triglyceride. * Mean ± Standard Deviation.

Table 3. Prevalence of metabolic syndrome by HOMA-IR groups

	MS n (%)	Non-MS n (%)	All patients n (%)
HOMA-IR< 2.7 n (%)	37 (35.9)	66 (64.1)	103 (44.8)
HOMA-IR≥ 2.7 n (%)	93 (73.2)	44 (26.8)	127 (55.2)
Total n (%)	130 (56.5)	100 (43.5)	230 (100)

p: 0.0001. MS: Metabolic syndrome, HOMA-IR: Homeostasis Model Assessment-Insulin Resistance

Discussion

NAFLD has worldwide and increasing prevalence. It has been reported in 10-30% of general population in different countries [6,7]. It has wide disease range from simple steatosis to steatohepatitis and severe fibrosis. NAFLD has the potential for progressing to liver cirrhosis [4,6,22]. Although the pathogenesis of NAFLD has not been fully clarified, insulin resistance has been accepted to play key role in disease pathogenesis [23,24]. A robust relationship between metabolic syndrome and the risk for future diagnosis of type 2 diabetes has been demonstrated [25,26]. Metabolic syndrome also designates high cardiovascular disease risk. Patients with NAFLD frequently have one or more components of metabolic syndrome [17].

As reported in NHANES III, MS is present in 22% of general population in USA [27]. But prevalence is higher among patients with NAFLD. Hamaguchi et al. reported the MS to be present among 194 (41%) of 478 males and 33 (29%) of 113 females with ultrasound diagnosed NAFLD [28]. In a study by Marchesini et al., MS was reported in 88% of patients with biopsy-proven steatohepatitis, while 53% of patients with simple steatosis had MS. In that study, presence of MS in NAFLD was found to be associated with steatohepatitis and severe fibrosis [17]. In our study, MS by ATP III criteria was detected in 56.5% of all patients with NAFLD. Study populations, histological or radiological diagnosis of NAFLD or the criteria used to define MS may cause differences in reported prevalence rates. We used ultrasonography for diagnosis of NAFLD in our study. Ultrasonography was found to be 89% sensitive and 93% specific for diagnosis of steatosis, especially moderate to severe steatosis [29].

Insulin resistance is closely associated with NAFLD. Marchesini et al reported mean HOMA-IR as 1.8 ±0.6 in controls, while it was 3.3 ±1.0 in patients with NAFLD [24]. Another study with histologically proven 64 NAFLD patients with mean BMI of 28 ±3.5 reported mean HOMA-IR as 2.7± 1.7. But mean HOMA-IR among those with MS was 3.6 ±2.1 [20]. In our study, for 127 (55.2%) of all patients, HOMA-IR was ≥2.7. Among patients with MS, 73.3% had HOMA-IR ≥2.7.

The association between NAFLD and MS is bidirectional. Features of MS are common in NAFLD and on the other hand presence of MS components increase the risk of developing NAFLD [2]. NASH was reported to be more progressive as the components of metabolic syndrome increase in number. In that study by Ampuero et al, NASH was found to be more frequent in both obese and non-obese metabolically unhealthy patients than metabolically healthy patients (both obese and non-obese). Thus, they pointed to greater impact of metabolic status than obesity on NAFLD-related liver histology [30]. Independent of obesity, insulin resistance was reported to be associated with NASH [23]. Similarly, HOMA-IR did not show any correlation with BMI in our study.

As compatible with our study, Saely et al. reported increase in HOMA-IR score with increasing components of MS, namely number of ATP III criteria. They concluded that HOMA-IR and MS were predictive for increased incidence of vascular outcomes [31]. Increased diabetes risk, higher MS prevalence and insulin resistance in NAFLD associate this entity with increased cardiovascular risk.

According to TURDEP study in Turkey, 15% of subjects between age 40 and 60 years were newly diagnosed with IGT and/or type 2 diabetes [32]. This ratio has been reported as 44% among NAFLD patients in Turkey [33]. In an extensive cohort including 3091 patients with NAFLD, IFG was reported in 44.1% of patients [34]. Another prevalence study reported IGT in 42.3% of 661 patients with NAFLD [35]. Presence of NAFLD has been reported to be associated with 2-fold increased risk for type 2 diabetes even though age, gender, BMI and ethnicity were similar [36]. In our study, 50.4% of NAFLD patients had IGT and/or type II diabetes.

Apo-B was shown to be a better predictive than LDL for coronary events [37]. In our study, patients with MS had significantly higher mean Apo-B levels. Similar association was also reported by Sattar et al. In that study, patients having normal HDL and high Apo-B levels had higher BMI, waist circumference, fasting insulin and lower insulin resistance compared to patients having normal Apo-B and high non-HDL cholesterol level in whole cohort. Among patients with MS according to NCEP criteria, waist circumference and fasting insulin were higher in normal HDL/ hyper Apo-B group. They associated the increased Apo-B levels with higher cardiovascular disease risk for patients with hypertriglyceridemia [38].

Conclusion

In conclusion, prevalence rates of insulin resistance, type 2 diabetes and metabolic syndrome were increased among patients with NAFLD. Due to the increased cardiovascular risk, diagnosis and early treatment of these comorbidities has critical importance.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was approved by Çukurova University Institutional Review Board.

References

1. Younossi ZM, Diehl AM, Ong JP. Nonalcoholic fatty liver disease: An Agenda for clinical research. Hepatology. 2002; 35:746-52.
2. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American association for the study of liver diseases. Hepatology, 2018;1:328-57.
3. Naga Chalasani N, Younossi ZM, Lavine JE, et al. The diagnosis and management of non alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55:2005-23.

4. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015;148:547–55.

5. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274-85.

6. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med. 2002;16:1221-31.

7. Williams CD, Stengel J, Asike MI et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middleaged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011;140:124–31.

8. Lazo M, Hernaez R, Eberhardt MS, et al. Prevalence of non- alcoholic fatty liver disease in the United States: The Third National Health and Nutrition Examination Survey, 1998-1994. Am J Epidemiyol. 2013;178:38-45.

9. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73-84.

10. Farrell GC. Nonalcoholic steatohepatitis: What is it, and why is it important in the Asia- Pasific region? J Gastroenterol Hepatol. 2003;18:124-38.

11. Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final Report [no authors listed]. Circulation 2003;106:3143–420.

12. Kim D, Touros A, Kim WR. Nonalcoholic fatty liver disease and metabolic syndrome. Clin Liver Dis. 2018;22:133-40.

13. Fulop T, Tessier D, Carpentier A. The metabolic syndrome. Pathologie Biologie. 2006;54:375-86.

14. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American heart association /national heart, lung and blood insitute scientific statement. Circulation. 2005;112:2735-52.

15. Grundy SM, Cleeman JI, Daniels SR. et al. Diagnosis and management of the metabolic syndrome: an American heart association/national heart, lung, and blood institute scientific statement: executive summary. Crit Pathw Cardiol, 2005;4:198-203.

16. Wainwright P, Byrne CD. Bidirectional relationships and disconnects between NAFLD and features of the metabolic syndrome. Int J Mol Sci. 2016;17:367.

17. Marchesini G, Forlani G, Bugianesi E, et al. Nonalcoholic fatty liver, steatohepatitis and metabolic syndrome. Hepatology. 2003;37:917-23.

18. AMERICAN DIABETES ASSOCIATION. Standards of Medical Care in Diabetes—2011. Diabetes Care 2011; 34 (supplement): 11-61.

19. Chobanian AV, Bakris GL, Black HR,et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. JAMA. 2003;289:2560-72.

20. Siqueira ACG, Cotrim HP, Rocha R, et al. Nonalcoholic fatty liver disease and insulin resistance: importance of risk factors and histological spectrum. Eur J Gastroenterol Hepatol. 2005;17:837-841.

21. Bonora E, Kiehl S, Willeit J, et al. Prevalance of insulin resistance in metabolic disorders. Diabetes. 1998;47:1643-9.Med Science 2021;10(1):25-30.

22. Matteoni CA,Younossi ZM, Gramlich T, et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116:1413-9.

23. Chitturi S, Abeygunasekera S, Farrell GC, et al. NASH and insulin resistance: Insulin hypersecretion and specific association with the insulin resistance syndrome. Hepatology. 2002;35:373-9.

24. Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease with insulin resistance. Am J Med. 1999;107:450-5.

25. Hanson RL, Imperatore G, Bennett PH, et al. Components of the "Metabolic Syndrome" and incidence of type 2 diabetes. Diabetes. 2002;51:3120-7.

26. Klein BE, Klein R, Lee KE. Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. Diabetes Care. 2002;25:1790-4.

27. Ford ES, Giles WH, Dietz WH. Prevalence of metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002;287:356-59.

28. Hamaguchi M, Kojima T, Takeda N, et al. The metabolic syndrome as predictor of nonalcoholic fatty liver disease. Ann of Int Med. 2005;143:722-8.

29. Joseph AE, Saverymuttu SH, al-Sam S, et al. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. Clin Radiol. 1991;43:26-31.

30. Ampuero J, Aller R, Gallego-Durán R, et al. The effects of metabolic status on non-alcoholic fatty liver disease-related outcomes, beyond the presence of obesity. Aliment Pharmacol Ther. 2018;48:1260-70.

31. Saely CH, Aczel S, Marte T, The metabolic syndrome, insulin resistance and cardiovascular risk in diabetic and nondiabetic patients. J Clin Endocrinol Metabolism. 2005;90:5698-703.

32. Satman I, Yılmaz T, Sengül A, et al. Population-based study of diabetes and risk characteristics in Turkey; the results of Turkish Diabetes Epidemiology Study (TURDEP). Diabetes Care. 2002:4:1551-6.

33. Sargin M, Bayramiçli UO, Sargin H, et al. Association of nonalcoholic fatty liver disease with insulin resistance. Is OGGT indicated in nonalcoholic fatty liver disease? J Clin Gastroenterol. 2003;37:399-402.

34. Oh SY, Cho YK, Kang MS, et al. The association between increased alanine aminotransferase activity and metabolic factors in in nonalcoholic fatty liver disease. Metabolism Clin Experimental. 2006;5:1604-9.

35. Fan JG, Zhu J, Li XJ, et al. Fatty liver and the metabolic syndrome among Shanghai adults. J Gastroenterol Hepatol. 2005;20:1825-32.

36. Seppala Lindroos A, Vehkavaara S, Hakinken AM, et al. Fat accumulation in the liver is associated with defects in insulin suppression of glucose production and serum free fatty acids independent of obesity in normal men. J Clin Endocrinol Metabolism. 2002;87:3023-8.

37. Sniderman AD, Furberg CD, Keech A. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin therapy. Lancet, 2003;361:777-80.

38. Sattar N, Williams K, Sniderman AD, et al. Comparison of the associations of apolipoprotein B and non-high-density lipoprotein cholesterol with factors in patients with the metabolic syndrome in the insulin resistance atherosclerosis study. Circulation. 2004;110:2687-93.