Relationship between Non-Alcoholic Fatty Liver Disease and Cardiovascular and Metabolic Risk Indices

Non Alkolik Yağlı Karaciğer Hastalığının Kardiyovasküler ve Metabolik Risk İndeksleri ile İlişkisi

Sevin Demir[1], Huriye Ecem Subası[2]

[1]*Maltepe University, Faculty of Medicine, Department of Family Medicine, Istanbul, Turkey*
[2]*Baskent University, Istanbul Health Application and Research Center, Department of Family Medicine, Istanbul, Turkey*

Abstract

Introduction: While non-alcoholic fatty liver disease (NAFLD) is linked to other metabolic dysfunction, it may also occur alone. In our study, we investigate the factors associated with NAFLD in subjects that do not have metabolic syndrome.

Materials and Methods: The files of the patients that applied to our check-up outpatient clinic were evaluated retrospectively, and patients who met the criteria for admission to the study were divided into those with and without NAFLD (n=277 and n=280, respectively) with the age variable being adjusted. Anthropometric and biochemical values, fibrosis scores, cardiovascular and metabolic risk indices were compared between groups.

Results: Between individuals with and without NAFLD there were statistically significant differences in terms of waist circumference (WC), waist-hip ratio (WHR), body mass index (BMI), ALT, AST/ALT, uric acid, smoking status, lipid levels, Triglyceride/HDL, hemoglobin, homeostasis model assessment insulin resistance (HOMA-IR), triglyceride-glucose index (TyG), visceral adiposity index (VAI) parameters (p<0.005). When people with BMI<25 kg/m² were considered, the difference between smoking, total and LDL cholesterol, ALT, AST/ALT, and HOMA-IR values lost their significance. In the group with BMI≥25 kg/m², significant differences remained only in terms of WC, WHR and BMI. It has been observed that hepatosteatosis has a positive correlation with the values of VAI, TyG, Triglyceride/HDL and AST-platelet ratio index and a negative correlation with AST/ALT.

Conclusion: While cardiovascular and metabolic risk indicators were significantly increased in lean individuals with NAFLD, the increase in those risks in overweight individuals was independent of fatty liver.

Keywords: Non-alcoholic fatty liver disease; triglyceride glucose index; triglyceride HDL ratio; visceral adiposity index.

Özet

Amaç: Non alkolik yağlı karaciğer hastalığının (NAYKH) diğer metabolik disfonksiyonlarla birlikteliği oldukça fazla olmasına rağmen tek başına da karşımıza çıkabilmektedir. Çalışmamızda metabolik sendromu olmayan hastalarda NAYKH ile ilişkili faktörleri araştırmayı amaçladık.

Gereç ve Yöntem: Check-up polikliniğimize başvurmuş hastaların dosyaları retrospektif olarak taranarak, çalışmaya alınma kriterlerine uyan hastalar yaş değişkeni eşitlenerek 277 NAYKH olan ve 280 olmayan kişi olarak iki gruba ayrıldı. Gruplar arası antropometrik ve biyokimyasal değerler, fibrozis skorları, kardiyovasküler ve metabolik risk indeksleri karşılaştırıldı.

Bulgular: Yağlı karaciğeri olan ve olmayan bireyler arasında bel çevresi, bel kalça oranı (BKO), vücut kitle indeksi (VKİ), ALT, AST/ALT oranı, ürik asit, sigara içme durumları, lipid düzeyleri, Trigliserit/HDL oranı, hemoglobin, homeostaz modeli insülin direnci değerlendirmesi (HOMA-IR), trigliserit-glukoz indeksi (TyG), visseral adipozite indeksi (VAI) parametreleri açısından istatistiksel olarak anlamlı farklılıklar vardı (p<0.005). VKİ<25 kg/m² olan kişilere bakıldığında sigara içme, total ve LDL kolesterol, ALT, AST/ALT oranı, HOMA-IR değerleri arasındaki fark anlamlılığını yitirdi. VKİ≥25 kg/m² olan grupta ise sadece bel çevresi, BKO ve VKİ açısından anlamlı farklılıklar kaldı. Hepatosteatozisin VAI, TyG, Trigliserit/HDL ve AST-trombosit oranı indeksi değerleri ile pozitif; AST/ALT ile negatif korelasyonu olduğu gözlenmiştir.

Sonuç: Normal kilolu bireylerde kardiyovasküler ve metabolik risk göstergeleri NAYKH ile önemli ölçüde artarken, fazla kilolularda bu risk artışı karaciğer yağlanmasından bağımsız olmaktadır.

Anahtar Kelimeler: Non alkolik yağlı karaciğer hastalığı; trigliserit glukoz indeksi; trigliserit HDL oranı; visseral adipozite indeksi.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is seen in one out of every 5 people in their fourth decade of life. Its frequency increases with age and the disease usually progresses without symptoms (1-2).

Although its prognosis is generally good, non-alcoholic steatohepatitis (NASH), a subgroup which progresses with fibrosis, has a tendency to lead to liver failure and cirrhosis (3). NAFLD is not associated with alcoholism, viral hepatitis or

hepatic accumulation and is currently termed as non-alcoholic in clinical practice has been termed metabolic associated fatty liver disease (4). Insulin resistance, dyslipidemia, abdominal obesity and fatty liver often go hand in hand, and there is an intricate relationship between them (3). While NAFLD is sometimes seen as the cause of these diseases, in some cases it can occur as a result. Considering that its frequency is quite high even at young ages, it can be considered an indicator of metabolic dysfunction (5). Although the definitive diagnosis of NAFLD is through histopathological examination, ultrasound is generally utilized for diagnosis (6). Magnetic resonance imaging proton density fat fraction is another option that shows the accumulation of fat in the liver. Correlates with biopsies, however the effectiveness of this method decreases in the presence of fibrosis (7). Another noninvasive yet rarely used method is liver elastography. It helps to recognize NASH without biopsy by identifying the presence of fibrosis as well as liposis (8). Ultrasonography is still the most commonly used method for screening because it is not invasive, easy to access and low cost (6). There have been attempts to determine fibrosis by scoring rather than imaging. Studies conducted in individuals with biopsy-detected fibrosis have shown that AST-platelet ratio index (APRI) and fibrosis-4 (FIB-4) scores are diagnostic (9). AST/ALT ratio below 1 is an indicator of fatty liver. However, as fibrosis increases, this value approaches 1 and loses its diagnostic value (10). Indices created by measurements and examinations are used to predict cardiovascular diseases, one of the most important reasons for morbidity worldwide. Of these, the visceral adiposity index (VAI) can be considered both a practical way to predict cardiovascular events in the long term and to detect cardiometabolic status (11). One of the most well-known and practical measurements of insulin resistance is the homeostasis model assessment insulin resistance (HOMA-IR). However, the measurement of insulin is not very common in clinical settings. Studies have demonstrated that the triglyceride glucose index (TyG) and triglyceride/HDL cholesterol ratio (TG/HDL), indexes that can be calculated with easily accessible measurements, have a place in the diagnosis of insulin resistance (12-13). Metabolic syndrome (MetS) is a set of disorders in which systemic disorders such as insulin resistance, glucose intolerance or diabetes mellitus, abdominal obesity, dyslipidemia, and hypertension are combined (14). It is known that the frequency of NAFLD increases with the presence of MetS

parameters and the progression of age (1). In addition to being acknowledged as the hepatic manifestation of MetS, NAFLD is also regarded to be an early indicator of metabolic disorders in those who do not have metabolic syndrome. Although ultrasonography can easily identify NAFLD, it cannot be utilized in every patient, regardless of whether they have a complaint or not. Therefore, understanding anthropometric values, biochemical parameters, and indices linked to NAFLD in patients who appear to be at low risk might help us make better clinical decisions. By adjusting for age between groups, we were able to eliminate the influence of age, which is one of the most major risk factors for NAFLD. In this study, we aimed to investigate factors that correlate with NAFLD in non-MetS individuals, by dividing them into groups according to BMI, which is another one of the most important risk factor in both NAFLD and metabolic diseases.

Material and Method

Subjects: This study - performed at a check-up outpatient clinic in a tertiary university hospital between January 2020 and November 2021. The patient files of 1782 patients were retrospectively analysed and the following were noted: patients' weight, height, waist circumference, hip circumference, blood pressure values, smoking status, complete blood count, AST, ALT, fasting glucose, fasting insulin, HbA1c, lipid values, uric acid and abdominal ultrasonography results. The following criteria were used to exclude patients from the study: Age <18 years, those with metabolic syndrome, malignancies, hepatitis, HIV, insulin dependent diabetes mellitus, use of parenteral nutrition, use of corticosteroids and those consuming alcohol (>20 g/day for women and >30 g/day for men). Six hundred and sixty five patients were eligible for inclusion in the study. They were divided into two groups: those with NAFLD and those without. As one of the most important factors for development of NAFLD is age, the two groups were then age matched. Following age-matching, 557 patients were included in the study. The following parameters, calculated using data obtained from patient files, were used to compare the two groups: body mass index (BMI), waist/hip ratio (WHR), HOMA-IR, TyG, TG/HDL, AST/ALT ratio, VAI, APRI and FIB-4 scores. A further analysis of the same parameters were performed to compare patients with BMI <25 kg/m² vs BMI ≥25 kg/m². The correlation of insulin resistance and fibrosis scores with the stage of

Table 1: Comparison of patients with and without NAFLD

	Non- NAFLD (n=277) (Mean ± SD)	NAFLD (n=280) (Mean ± SD)	p
Age (year)	45.56±10.61	47.04±9.29	0.082
Gender (F/M) (n)	195/82	180/100	0.124
Cigarette (pack-years)	9.79±14.02	12.855±14.84	0.020
SBP (mm Hg)	113.79±13.19	117.86±14.79	0.013
DBP (mm Hg)	73.00±9.45	76.08±10.41	0.008
WC (cm)	82.13±10.01	94.36±1.28	0.001
WC-F (cm)	78.12±7.99	92.08±13.88	0.001
WC-M (cm)	91.61±7.66	98.45±11.06	0.001
WHR	0.82±0.07	0.88±0.08	0.001
BMI (kg/m²)	23.72±2.94	28.00±4.08	0.001
AST (U/L)	19.18±9.03	20.59±10.10	0.083
ALT (U/L)	28.88±12.73	33.16±17.78	0.001
AST/ALT	0.71±0.27	0.66±0.17	0.010
APRI	0.25±0.15	0.26±0.16	0.271
FIB-4	0.73±0.45	0.73±0.27	0.987
T. Chol. (mg/dl)	215.58±43.64	225.14±46.08	0.012
TG (mg/dl)	95.92±57.42	114.39±62.12	0.001
HDL (mg/dl)	63.15±17.22	57.96±15.41	0.001
LDL (mg/dl)	133.27±38.02	144.63±40.56	0.001
TG/HDL	1.77±1.52	2.22±1.60	0.001
Uric acid (mg/dl)	4.19±1.28	4.71±1.20	0.001
HbA1c (%)	5.41±0.50	5.47±0.57	0.213
HOMA-IR	1.72±0.74	2.11±0.94	0.001
TyG	8.31±0.54	8.52±0.50	0.001
VAI	2.84±2.25	3.59±2.20	0.001
VAI-F	2.55±1.96	3.22±1.79	0.072
VAI-M	3.51±2.72	4.25±2.68	0.001
Hgb (g/dl)	13.59±1.46	13.88±1.49	0.022

Abbreviations: SD: Standard deviation, **F:** Female, **M:** Male, **SBP:** Systolic Blood Pressure, **DBP:** Diastolic Blood Pressure, **WC:** Waist circumference, **WHR:** Waist to hip ratio, **BMI:** Body mass index, **APRI:** AST-platelet ratio index, **FIB-4:** fibrosis 4 score, **T. Chol.:** Total cholesterol, **TG:** Triglyceride, **HOMA-IR:** Homeostasis model assessment insulin resistance, **TyG:** Triglyceride glucose index, **TG/HDL:** Triglyceride-HDL cholesterol ratio, **VAI:** Visceral adiposity index, **Hgb:** Hemoglobin.

hepatosteatosis was also evaluated. Local ethics committee approved the study (Maltepe University Clinical Research Ethics Committee, Approval Date: 20.10.2021, Approval Number: 2021/900/104), which was carried out in adherence to the Declaration of Helsinki II.

Measurements and Calculations: Body weight (kg) and height (m) was measured whilst subjects wore light clothing and no shoes. Waist and hip circumferences were measured with a non-stretchable tape measure, with only thin underwear left on the patients, with their feet together and arms standing upright at their sides. Waist circumference was obtained by measuring the narrowest point between the iliac crest and the subcostal region at the end of a normal expiration. Hip circumference was obtained by measuring the widest region of the hip. The body mass index (BMI; kg/m²) was calculated as weight in kilograms divided by height in square meters. Indexes, scores and ratios were calculated from the following formulas; WHR=[WC (cm) / HC (cm)], HOMA-IR=[fasting insulin (μIU/mL) × fasting glucose (mg/dl) / 405] (15), AST/ALT ratio=[AST (U/l) / ALT (U/l)], APRI=[(AST(U/l) / Upper limit of normal) / Platelet count (10³/mm³)] × 100] (16), FIB-4 index=[(AST (U/l) × Age (years)] / [Platelet count (10³ /mm³) × √ALT (U/l)] (17), VAI for male=[WC / (39.68 + (1.88 × BMI)) × (TG(mg/dL) /1.03) × (1.31/HDL(mg/dL))], VAI for female=[WC / (36.58 + (1.89 × BMI)) ×(TG(mg/dL) /0.81) ×(1.52/HDL(mg/dL))] (11), TyG=[Ln(TG (mg/dL) × fasting glucose (mg/dL) / 2)] (12), TG/HDL ratio=[TG (mg/dl) / HDL (mg/dl)]. IDF-2006 guidelines for MetS were followed for diagnosis of MetS: central obesity defined as waist circumference with ethnicity specific values (for Turkey with a WC of ≥80 cm for women and ≥94 cm for men), and any two of the following four factors: 1. TG >150mg/dl, 2. HDL-C (men <40 mg/dl, women <50mg/dl) or

Table 2: Comparison of lean and obese patients with and without NAFLD

	BMI<25 kg/m²			BMI≥25 kg/m²		
	Non- NAFLD (n=189) (Mean ± SD)	NAFLD (n=65) (Mean ± SD)	p	Non- NAFLD (n=88) (Mean ± SD)	NAFLD (n=215) (Mean ± SD)	p
Age (year)	44.65±9.13	45.12±11.40	0.761	47.36±13.09	47.59±8.53	0.881
Gender (F/M) (n)	150/39	42/23	0.016	46/42	139/76	0.044
Cigarette (pack-years)	10.23±12.96	11.85±12.41	0.416	9.49±16.79	13.15±15.51	0.094
WC (cm)	77.77±7.36	82.08±8.49	0.001	91.20±8.69	97.90±12.23	0.001
WC-F (cm)	75.33±5.80	78.57±7.50	0.012	86.70±7.59	96.05±12.79	0.001
WC-M (cm)	87.08±4.83	88.48±6.20	0.325	96.14±7.02	101.25±10.40	0.005
WHR	0.80±0.06	0.83±0.06	0.001	0.88±0.06	0.90±0.08	0.034
BMI (kg/m²)	22.18±1.85	23.08±1.63	0.001	27.08±1.79	29.46±3.37	0.001
BMI-F(kg/m²)	21.96±1.90	22.85±1.64	0.007	26.91±1.71	29.97±3.61	0.001
BMI-M (kg/m²)	23.01±1.33	23.49±1.57	0.203	27.26±1.88	28.53±2.65	0.003
AST (U/L)	18.47±7.64	18.71±5.02	0.816	20.78±11.49	21.09±11.13	0.831
ALT(U/L)	27.43±12.91	29.15±11.17	0.339	32.11±12.65	34.30±19.18	0.326
AST/ALT	0.72±0.22	0.68±0.19	0.196	0.68±0.36	0.65±0.18	0.282
APRI	0.24±0.14	0.23±0.08	0.818	0.26±0.15	0.27±0.17	0.823
FIB-4	0.70±0.35	0.68±0.27	0.744	0.78±0.61	0.74±0.24	0.367
T. Chol. (mg/dl)	213.33±43.92	220.66±48.40	0.259	219.82±43.12	226.82±45.25	0.216
TG (mg/dl)	90.64±54.49	110.42±70.00	0.015	107.86±61.85	115.29±62.63	0.348
HDL (mg/dl)	65.42±17.05	58.72±16.16	0.007	57.83±15.48	57.73±15.21	0.961
LDL (mg/dl)	129.78±38.01	139.88±41.99	0.073	140.51±37.11	146.45±40.13	0.234
TG/HDL	1.63±1.52	2.14±1.72	0.025	2.09±1.49	2.23±1.57	0.454
Uric acid (mg/dl)	3.99±1.14	4.45±1.12	0.005	4.67±1.41	4.79±1.21	0.460
HbA1c (%)	5.36±0.49	5.30±0.82	0.457	5.54±0.49	5.52±0.45	0.758
HOMA-IR	1.57±0.65	1.53±0.46	0.808	2.00±0.78	2.28±0.98	0.809
TyG	8.23±0.53	8.45±0.52	0.004	8.47±0.52	8.53±0.49	0.339
VAI	2.68±2.33	3.41±0.52	0.033	3.21±2.01	3.64±2.18	0.109
VAI-F	2.43±2.04	3.20±2.21	0.036	3.00±1.60	3.22±1.63	0.440
VAI-M	3.59±3.06	3.77±2.81	0.827	3.44±2.38	4.39±2.63	0.054
Hgb (g/dl)	13.39±1.40	13.94±1.54	0.008	14.09±1.44	13.67±1.47	0.239

Abbreviations: SD: Standard deviation, **F:** Female, **M:** Male, **WC:** Waist circumference, **WHR:** Waist to hip ratio, **BMI:** Body mass index, **APRI:** AST-platelet ratio index, **FIB-4:** Fibrosis 4 score, **T. Chol.:** Total cholesterol, **TG:** Triglyceride, **HOMA-IR:** Homeostasis model assessment insulin resistance, **TyG:** Triglyceride glucose index, **TG/HDL:** Triglyceride-HDL cholesterol ratio, **VAI:** Visceral adiposity index, **Hgb:** Hemoglobin.

specific treatment for these lipid abnormalities; 3. Systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg or treatment for hypertension; 4. Fasting blood glucose ≥100mg/dl or treatment for diabetes (14).

Statistical Analyses: SPSS 25 software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) was utilized for statistical analysis. Normality of data distribution was tested with the Kolmogorov –Smirnov test. For comparison between groups: student's t-test was used in data with normal distribution and the Mann Whitney U test was used for data without normal distribution. Pearson's and Spearman's tests were used for correlation analysis in normal and non-normally

distributed data, respectively. Data are presented as mean ± standard deviation (SD). Statistically significant level was considered as 0.05 for all statistical computation.

Results

The mean age of the enrolled subjects was 46.30±9.99 years and the mean BMI was 25.88±4.15 kg/m². Three hundred and seventy five of individuals were female (67.3%) and 182 (32.7%) were male. The mean systolic and diastolic blood pressure was 115.77±14.12 mm Hg and 74.50±10.03 mm Hg, respectively. Abdominal ultrasonography showed the presence of fatty liver in 50% of patients. In those with fatty liver, 224

Table 3: The relationship between indices and grade of hepatosteatosis

	Metabolic Indices					
	VAI		TyG		TG/HDL	
	r	*p*	*r*	*p*	*r*	*p*
Grade of Hepatosteatosis	0.261	0.001	0.218	0.001	0.229	0.001
	Fibrosis Scores					
	APRI		AST/ALT		FIB-4	
	r	*p*	*r*	*p*	*r*	*p*
Grade of Hepatosteatosis	0.109	0.001	-0.125	0.003	0.067	0.117

Abbreviations: r: Spearman's correlation coefficient, **VAI:** Visceral adiposity index, **TyG:** Triglyceride glucose index, **TG/HDL:** Triglyceride-HDL cholesterol ratio, APRI= AST-platelet ratio index, **FIB-4:** Fibrosis 4 score.

had grade 1, 19 grade 1-2, 33 grade 2 and 4 of the individuals had grade 2-3. No study participant was found to have grade 3 or 4 fatty liver disease. Hemoglobin (Hgb) was the only complete blood count parameter found to correlate with the presence of fatty liver disease (p=0.022). Waist circumference, WHR, BMI, smoking status, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, LDL cholesterol, uric acid, HOMA-IR, VAI, TyG, TG/HDL, Hgb levels were significantly higher while the AST/ALT ratio and HDL levels were lower in patients with NAFLD compared to those without (p <0.05). No difference between groups was observed for APRI and Fib-4, which are indicators of fibrosis (Table 1). When lean individuals with and without NAFLD were compared, the difference between smoking, total and LDL cholesterol, ALT, AST/ALT ratio, and HOMA-IR values lost their significance (Table 2). In the group with BMI >25 kg/m², significant differences remained only in terms of waist circumference, WHR and BMI, and the statistical difference in other values lost its significance. The stage of hepatosteatosis was found to be positively correlated with VAI, TyG, TG/HDL and APRI values and a negatively correlated with AST/ALT (Table 3).

Discussion

NAFLD is thought to be an early phenotypic determinant of future metabolic dysfunction in individuals who appear metabolically healthy and its prevalence is increasing. Therefore, anthropometric values, biochemical parameters, and easily calculated indices associated with NAFLD are becoming more important, since ultrasonography cannot be performed on all individuals, whether they have a complaint or not. In a group of 28880 individuals >18 years of age, with a BMI between 18.5–24.9 kg/m², without metabolic syndrome, Yang et al. (18) compared hepatic steatosis index between patients with and without NAFLD (28698 Non-NAFLD vs 182 NAFLD). At least two interviews were performed with patients between 2009 and 2015. Subgroup analysis (910 non-NAFLD vs 182 NAFLD was performed by adjusting individuals according to age, gender, smoking status and BMI, and this analysis showed that the effect of NAFLD on the future development of MetS, Diabetes Mellitus or prediabetes, hypertension and dyslipidemia is independent of these factors. In our study, waist circumference, WHR, and BMI -which are classical measurements used in metabolic prediction as well as VAI, which is used to predict cardiovascular events, were found to be significantly higher in those with NAFLD, and it continued to be significant in the group with BMI <25 kg/m². In the current study, no difference between groups with regards to HbA1c values was detected, although HOMA-IR values were elevated in the NAFLD group. In the subset of patients according to BMI, HOMA-IR also lost its significance. This may suggest that one of the first detectable signs of metabolic dysfunction is NAFLD. Tunç et al. (19) compared the lipid values of obese children with and without fatty liver. While triglycerides were found to be significantly higher in those with fatty liver, no

difference was observed in other lipid values. In our study, we observed that the non-HDL lipid values of the NAFLD group were significantly higher than those of the non-NAFLD group, while the HDL cholesterol levels were lower. In the comparison carried out in the non-obese group, LDL cholesterol lost its significance, while the difference between triglyceride, HDL cholesterol, TG/HDL and NAFLD continued. The difference in LDL cholesterol levels between with and without NAFLD in the whole group may be due to the weight difference of groups. All of them lost their significance in the evaluation of the obese group within itself. Li et al. (20) reported that uric acid levels in individuals with NAFLD are significantly higher compared to non-NAFLD individuals, and that an increased level of uric acid is an independent risk factor for NAFLD. In our study, we were also observed that uric acid levels were significantly higher in people with NAFLD in both the entire sample and the group with BMI <25 kg/m² but not in obese group. Uric acid, like other risk markers, was found to be similar between NAFLD and non-NAFLD in the obese group. In a report by Jiang et al. (21), NAFLD and non-NAFLD groups were compared, and a significant difference was reported between hemoglobin values. In the same study, a significant positive correlation was observed between Fatty Liver Index and Hgb value. In our study, as in this study, there was a significant elevation in the Hgb value of NAFLD patients. In a study of check-up patients, Xu et al. (22) evaluated the VAI values by dividing patients into 4 separate groups and found that the incidence of NAFLD increases as the VAI value increases. VAI was also reported as an independent risk factor for NAFLD. In our study, a positive correlation was detected between the stage of hepatosteatosis and VAI values. When we look at the whole study group, the relationship between NAFLD and VAI in females was not as significant as in males, because females tend to have more subcutaneous fat than males. Having more visceral fat causes the risk of NAFLD to be higher in males. The VAI values in lean individuals with NAFLD were found to be close to those who were overweight, and the correlation between VAI and NAFLD in normal-weight group was found to be significant (3.41 vs 2.68). However, VAI values with or without NAFLD were found to be high and close to each other in overweight individuals, and the relationship between VAI and NAFLD lost significance (3.64 vs 3.21). Therefore, it could be suggested that obesity increases cardiovascular risk regardless of

fatty liver, while fatty liver increases this risk in individuals with normal weight. When females and males were evaluated separately, it was seen that the be due to there was no statistical difference between the BMI and WC of lean men with and without NAFLD. In a study conducted by Zhang et al. (23), two groups with and without NAFLD were established by evaluating at 10761 employees with abdominal ultrasound, and it was found that the TyG values of the group with NAFLD were significantly higher. In addition, when four subgroups were analysed according to TyG values, it was observed that the frequency of NAFLD and TyG level were correlated. In a study with 44767 participants conducted in Taiwan, patients were divided into 4 groups: no fatty liver, mild NAFLD, moderate NAFLD and severe NAFLD as staged by ultrasound. When the TG/HDL ratios of these groups were compared, a significant difference was found that increased as the stage increased (24). In our study, a significant positive correlation was shown between the stages of hepatosteosis and both values. The ratio of both TyG and TG/HDL was significantly higher in the NAFLD group compared to non-NAFLD. While these significants are preserved in normal-weight individuals, they lose their meaning in the overweight and obese group just as they are in the VAI. In a study conducted by Sapmaz et al. (25) with 276 (non-NAFLD: 90, Grade 1: 67, Grade 2: 86, Grade 3: 23) patients, there was a statistically significant difference in APRI values between patients with and without NAFLD, but no statistically significant difference was observed for FIB-4 score. In our study, unlike this study, no difference was observed in APRI values between patients with and without NAFLD but, as this study no statistically significant difference was observed for FIB-4 score. This may be due to there were more advanced grade NAFLD patients in this study than our study. In this study, as in our study, a significant correlation was found between the hepatosteatosis grades and APRI values, but not with FIB-4.

Limitations: The use of ultrasonography for diagnosis of NAFLD and not liver biopsy which is the gold standard is the major limitation of this study. A further limitation is that it the study does not include patients with advanced stage NAFLD because it was conducted amongst check-up patients. However, our aim was to find the parameters associated with NAFLD in individuals appearing to be healthy with fatty liver but no metabolic syndrome and to ensure that they guide us in our clinical practice. Since advanced NAFLD is usually accompanied by additional pathologies,

we believe that excluding them will not change the outcome of the study.

Conclusion

NAFLD, which is considered a liver marker of MetS, is also common in non-MetS patients, and this is important because it can be an early indicator of metabolic diseases. While VAI, indicating cardiovascular risk as well as TyG and TG/HDL ratios - indicating insulin resistance, increased significantly in lean individuals with NAFLD when compared to the non-NAFLD group, cardiovascular and metabolic risk increased independently of fatty liver in overweight individuals. If NAFLD can be detected prior to development of MetS, we may be able to protect these individuals from future cardiovascular diseases and other metabolic conditions.

References

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease- meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64(1): 73-84.
2. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. Gastroenterology 1994; 107: 1103-1109.
3. Gaggini M, Morelli M, Buzzigoli E, DeFronzo RA, Bugianesi E, Gastaldelli A. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 2013; 5(5): 1544-1560.
4. Eslam M. Sanyal AJ, George J. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020; 158(7): 1999-2014.
5. Mashek DG. Hepatic lipid droplets: a balancing act between energy storage and metabolic dysfunction in NAFLD. Mol Metab 2021; 50: 101115.
6. Charatcharoenwitthaya P, Lindor KD. Role of radiologic modalities in the management of non-alcoholic steatohepatitis. Clin Liver Dis 2007; 11(1): 37-54.
7. İdilman İS, Karçaaltıncaba M. Karaciğer yağlanması tanısında ve yağlanma miktarının belirlenmesinde radyolojik tanı yöntemleri. Güncel Gastroenteroloji 2014; 18(1): 112-118.
8. Sassoa M, Miettea V, Sandrina L, Beaugrand M. The controlled attenuation parameter (CAP): a novel tool for the non-invasive evaluation of steatosis using Fibroscan®. Clin Res Hepatol Gas 2012; 36(1): 13-20.
9. Biberci Keskin E, Coban G. Evaluation of liver biopsy findings and comparison with noninvasive fibrosis scores in patients with non-alcoholic steatohepatitis. Medeniyet Med J 2019; 34(4): 354-359.
10. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology 1999; 30(6): 1356-1362.
11. Amato MC, Giordan C, Massimo G, Criscimanna A, Vitabile S, Midiri M, et al. Visceral adiposity index a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care 2010; 33(4): 920-922.
12. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat D 2008; 6(4): 299-304.
13. Marotta T, Russo BF, Ferrara LA. Triglyceride-to-HDL-cholesterol ratio and metabolic syndrome as contributors to cardiovascular risk in overweight patients. Obesity 2010; 18(8): 1608-1613.
14. International Diabetes Federation. The IDF Consensus Worldwide Definition of the Metabolic Syndrome. Brussels; 2016. p. 10-11.
15. Matthews DR, Hosker JR, 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.

16. Kruger F, Daniels C, Kidd M, Swart G, Brundyn K, van Rensburg C, et al. APRI: a simple bedside marker for advanced fibrosis that can avoid liver biopsy in patients with NAFLD/NASH. S Afr Med J 2011; 101(7): 477-480.

17. Sterling RK, Lissen E, Clumerk N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006; 43(6): 1317-1325.

18. 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.

19. Tunç S, Demiral M. Obez çocuk ve ergenlerde D vitamini ve tiroid fonksiyonlarının yağlı karaciğer hastalığı ile ilişkisinin değerlendirilmesi. Güncel Pediatri 2020;18 (3): 421-433.

20. Li Y, Xu C, Yu C, Xu L, Miao M. Association of serum uric acid level with non-alcoholic fatty liver disease: a cross-sectional study. J Hepatol 2009; 50(5): 1029-1034.

21. Jiang Y, Zeng J, Chen B. Hemoglobin combined with triglyceride and ferritin in predicting non-alcoholic fatty liver. J Gastroen Hepatol 2014; 29(7): 1508-1514.

22. Xu C, Ma Z, Wang Y, Liu X, Tao L, Zheng D, et al. Visceral adiposity index as a predictor of NAFLD: A prospective study with 4-year follow-up. Liver Int 2018; 38(12): 2294-2300.

23. Zhang S, Du T, Zhang J, Lu H, Lin X, Xie J, et al. The triglyceride and glucose index (TyG) is an effective biomarker to identify nonalcoholic fatty liver disease. Lipids Health Dis 2017; 16(1): 15.

24. Wu KT, Kuo PL, Su SB, Chen YY, Yeh ML, Huang CI, et al. Nonalcoholic fatty liver disease severity is associated with the ratios of total cholesterol and triglycerides to high-density lipoprotein cholesterol. J Clin Lipidol 2016; 10(2): 420-425.

25. Sapmaz F, Uzman M, Basyigit S, Ozkan S, Yavuz B, Yeniova A, et al. Steatosis Grade is the Most Important Risk Factor for Development of Endothelial Dysfunction in NAFLD. Medicine (Baltimore) 2016; 95(14): e3280.