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

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

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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: Whilecardiovascular 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.

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 analyzed 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                   | 12.85±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-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                   | 11.49±62.12               | 0.001|
| 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) / Age (years)] / [Platelet count (10³ /mm³) × Age (years)] (16), FIB-4 index=[[(AST (U/l) × Age (years)) / (Platelet count (10³ / mm³)) × VAI (U/l)] (17), VAI for male=[WC / (39.68 + (1.88 × BMI)) × (TG/mg/dL) / (1.03 × (1.31/HDLC/mg/dL))], VAI for female=[WC / (36.58 + (1.89 × BMI)) × (TG/mg/dL) / (0.81 × (1.52/HDLC/mg/dL))] (11), TyG=[ln(TG (mg/dL) × fasting glucose (mg/dl) / 2)] (12), TG/HDL ratio=[TG (mg/dl) / HDLC (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. HDLC (men <40 mg/dl, women <50mg/dl) or
Table 2: Comparison of lean and obese patients with and without NAFLD

|                   | BMI<25 kg/m² (n=189) (Mean ± SD) | BMI≥25 kg/m² (n=215) (Mean ± SD) | p     |
|-------------------|----------------------------------|----------------------------------|-------|
| **Age (year)**    | 44.65±9.13                      | 46.30±11.40                      | 0.761 |
| **Gender (F/M) (n)** | 150/39                           | 46/42                            | 0.016 |
| **Cigarette (pack-years)** | 10.23±12.96                     | 23.08±1.63                       | 0.001 |
| **WC (cm)**       | 77.77±7.36                      | 82.08±8.49                       | 0.001 |
| **WC-F (cm)**     | 61.33±5.20                      | 65.37±5.02                       | 0.012 |
| **WC-M (cm)**     | 87.08±8.43                      | 88.48±6.20                       | 0.325 |
| **WHR**           | 0.80±0.06                       | 0.83±0.06                        | 0.001 |
| **BMI (kg/m²)**   | 22.18±1.85                      | 23.08±1.63                       | 0.001 |
| **BMI-F (kg/m²)** | 21.96±1.93                      | 22.85±1.64                       | 0.007 |
| **BMI-M (kg/m²)** | 23.01±1.33                      | 23.49±1.57                       | 0.203 |
| **AST (U/L)**     | 18.47±7.64                      | 18.71±5.02                       | 0.816 |
| **ALT (U/L)**     | 27.43±12.91                     | 29.15±11.17                      | 0.339 |
| **APRI**          | 0.24±0.14                       | 0.25±0.08                        | 0.818 |
| **FIB-4**         | 0.70±0.35                       | 0.78±0.61                        | 0.744 |
| **HbA1c (%)**     | 13.39±1.40                      | 13.94±1.54                       | 0.008 |

**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.
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 |
|-----------------|------|---------|-------|
| Grade of Hepatosteatosis | $r$ | $p$ | $r$ | $p$ | $r$ | $p$ |
|                  | 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 hepatosteatosis and both values. The ratio of both TyG and TG/HDL was significantly higher in the NAFLD group compared to non-NAFLD. While these signifiants 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.

Ethics Committee Approval: The study was conducted in adherence to the Declaration of Helsinki II. The study protocol was approved by local ethics committee (Maltepe University Clinical Research Ethics Committee, Approval Date: 20.10.2021, Approval Number: 2021/900/104).

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Financial Support: The authors received no financial support for the research, authorship, and/or publication of this article.

Authorship Contributions: Concept: Ş.D., Design: Ş.D., H.E.S, Data Collection or Processing: Ş.D., Analysis or Interpretation: Ş.D., Literature Search: Ş.D., H.E.S., Writing: Ş.D., H.E.S.

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