

Original Article

From NAFLD to MASLD: Meta-analysis and systematic review of NAFLD patients in Turkey in terms of metabolic profile and MASLD potential

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Abstract

Background & Aims: Non-alcoholic Fatty Liver Disease (NAFLD) is both cause and consequence of metabolic disturbances. Therefore, the disease term was recently changed to metabolic dysfunction-associated steatotic liver disease (MASLD). Turkey is one of the leading countries with a high incidence of diseases such as diabetes, obesity, metabolic syndrome, and fatty liver. This study aims to identify the metabolic parameters and MASLD potential of NAFLD in Turkey.

Material & Methods: All NAFLD studies conducted in Turkey were systematically searched with "fatty liver disease" AND "turkey" keywords on Pubmed, Scopus, and Web of Science databases. In total, 2653 articles were scanned. A total of 120 studies were eligible for meta-analysis. The metabolic parameters were meta-analyzed from a wide perspective.

Results: According to meta-analysis results, there were significant increases in waist circumferences (Mean difference: 10.90, $p < 0.00001$), HOMA-IR (Mean difference: 2.13, $p < 0.00001$), aspartate amino transferase (AST) (Mean difference: 17.82, $p < 0.00001$), systolic blood pressure (SBP) (Mean difference: 5.86, $p < 0.00001$) and C-reactive protein (CRP) levels (Mean difference: 0.95, $p < 0.00001$). These parameters are representative biochemical findings of disturbed glucose metabolism, lipid profile, blood pressure, and acute phase response mechanisms. Furthermore, analysis of all related parameters commonly found among the articles confirmed these metabolic dysfunctions.

Conclusion: NAFLD is a metabolic disease that includes multiple pathways related to glucose and lipid metabolism, vascular function, inflammation, and acute phase responses. Also, according to our results, Turkish NAFLD patients detected in the previous studies might mostly have MASLD. This was the first meta-analysis study indicating changes in metabolism-related parameters with the cumulative meta-analysis with all Turkish NAFLD studies.

Keywords: Diabetes, fatty liver disease, hypertension, inflammation, lipid profile, metabolism

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of $\geq 5\%$ of hepatic steatosis without having a competing liver disease such as viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson's disease or alcoholic liver disease as well as without using steatosis inducing medications. Non-alcoholic steatohepatitis (1) occurs with histopathological findings that cause hepatic damage/fibrosis/cirrhosis/mortality in a smaller group of patients with NAFLD(2). On the other hand with the participation and the agreement of a total of 236 panellists from 56 countries, new medical terms were introduced to the scientific field. Metabolic dysfunction-associated steatotic liver disease (MASLD) is mentioned as a new definition for NAFLD and is defined as the detection of liver steatosis (liver histology, non-invasive biomarkers, or imaging) together with the presence of at least one of three criteria that include overweight or obesity, type 2 diabetes mellitus or clinical evidence of metabolic dysfunction such as high waist circumference and an abnormal lipid or glycemic profile. Also, similar to NAFLD, nonalcoholic steatohepatitis (NASH) term was changed to “metabolic-associated steatohepatitis (MASH) to refer steatohepatitis patients with metabolic dysfunctions (3,4). Also, diagnosis criteria was updated. In the presence of steatotic liver disease (SLD), the identification of any cardiometabolic risk factor alone would lead to a diagnosis of MASLD, provided that no other causes of hepatic steatosis are evident. If additional contributors to steatosis are discovered, it suggests a combination etiology. Specifically, in cases involving alcohol, it is referred to as MASLD with increased alcohol intake (MetALD). In situations where explicit cardiometabolic criteria are absent, other potential causes must be ruled out. If none are found, this is categorized as cryptogenic SLD. However, depending on clinical

judgment, it could also be considered as a possible MASLD, warranting periodic reassessment on a case-by-case basis (4).

NAFLD is the burden of health problems that cause chronic liver diseases around the world. A very recent meta-analysis study examined the up-to-date incidence of NAFLD with a total of 1,201,807 individuals data from 63 studies. According to this global analysis, NAFLD incidence was found to be 4,613 per 100,000 person-years, which is higher, especially in men. There was a dramatic increase in the incidence rate by more than 3-fold between 2000 and 2015 (5).

According to the regional results in 2019, NAFLD occurs in 31.29% of the Middle East, 30.45% of South America, 27.37% of Asia, 24.13% of North America, 23.71% of Europe, and 13.48% of Africa regions (6). Nearly 30% of the world's population is currently challenged with this health problem (7).

America, which had 83 million patients of NAFLD in 2015, is expected to be the number of NAFLD patients to 100.9 million by 2030 a 21% of increase, while the prevalent of NASH cases will increase by 63% from 16.52 million to 27.00 million cases (8). The prevalence of NAFLD is estimated to be 20% -30% in the European Union, about 3% is NASH. The advanced fibrosis incidence in Non Alcoholic Steatohepatitis (NASH) patients was 67,95 in 1000 person-years. Liver-specific mortality in the pooled NAFLD versus non-NAFLD incidence rate ratio was found to be 1.94. The adjusted liver-specific mortality hazard ratio for NAFLD patients was 2.60. Although advanced fibrosis prevalence among NAFLD patients in the USA and Europe was 10-15%, fibrosis development was found to be lower in the Asia region compared to Western countries (9). In Turkey, multi-central prevalence studies are limited to showing current NAFLD status. However, it was mentioned that recent published data pointed to an alarming prevalence of 48.3%, and these results are seen as sensible when it is compared with the obesity prevalence in Turkey (10).

NAFLD is a part of metabolic syndrome hepatic outcomes and is commonly seen in obese and diabetic patients. Whether NAFLD is a cause or consequence of insulin resistance has been still debated for a long time. On the other hand, "lean-NAFLD" can be seen in non-obese subjects, especially in low-income countries or rural areas (11).

This meta-analysis aimed to evaluate all NAFLD cases, and their control data in the literature to show the metabolic profile of the disease in Turkey cumulatively for the first time. The MASLD potential of these patients were discussed according to meta-analysis results.

Material & Method

Study Design

To determine the metabolic profile of Turkish NAFLD patients, all NAFLD studies conducted in Turkey were systematically searched with "fatty liver disease" AND "turkey" keywords on Pubmed, Scopus, and Web of Science databases. All characteristics and biochemical data were screened and collected for related meta-analysis. Inclusion criteria were determined as giving the suitable data (by using international units) of biochemical parameters of NAFLD diagnosed patients and healthy control group.

The parameters of NAFLD diagnosis were generally based on ultrasound screening. Many studies confirmed ultrasound screening results with a histopathological examination after liver biopsy and used elevated liver enzyme levels as inclusion criteria. Also, exclusion criteria were generally similar between studies. Presence of viral hepatitis, hemochromatosis, Wilson disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, biliary obstruction, α 1 antitrypsin deficiency, ischemic cardiac or cerebrovascular disease, impaired renal function, or malignancies, previous abdominal surgery, medication use, and daily alcohol intake exceeding 20 g/day were excluded in almost all studies. Several studies also excluded chronic diseases such as coronary artery disease, acute chronic renal failure, hypertension, and diabetes. Some studies used 30 or 40 g alcohol intake as a limit of exclusion. Detailed

information about the inclusion and exclusion criteria of each study was given in Supplementary Table 1.

There weren't any extra restrictions for individual characteristics. The systematic search was done until July 2023. PRISMA statement guidelines were followed for this meta-analysis. Since this article is a meta-analysis article, ethics committee approval is not required.

Statistical Analysis

Cumulative data analysis was done to show metabolic comorbidities of Turkish NAFLD patients. All analysis procedure was done according to Cochrane Handbook (cochrane.org/handbook). Mean and standard deviation value of each marker that was cumulatively assessed were entered to RevMan 5.3 program. Weighted analysis was done automatically by RevMan 5.3 according to power of articles. Study power is calculated by RevMan, based on values for effect size magnitude, sample size, the number of studies, and the amount of between-study variability. The I^2 was used for measuring heterogeneity which can be seen in the bottom of each figure. I^2 values of 0–25, 25–50, 50–75, and 75–100 represent no, low, moderate, and high heterogeneity respectively. The fixed and random effect models were used according to heterogeneity τ^2 value to combine the results. If τ^2 value is found as 0, the fixed effect can be used. However, in all of our results τ^2 value was found different than 0 which led us to use random effect model for better assessment. RevMan 5.3. (Cochrane Collaboration, Copenhagen, 2014) software was used for the meta-analysis, and GraphPad Prism 6 software was used for correlation analysis and visualizing the results.

Results

In total, 2653 articles were scanned. As a result of the screening, 2533 studies were eliminated by finding not eligible for this meta-analysis. The remaining 120 studies were eligible for meta-analysis, and all data on patient and control groups from 120 studies (12-131) were evaluated (Fig 1).

Obesity-Glucose Metabolism Related Parameters

Data obtained from 14138 NAFLD, 15335 healthy individuals showed that BMI level is significantly higher in the NAFLD group (Mean difference: 3.48, 95% CI: [3.02, 3.94], $p < 0.00001$). A waist circumference of the NAFLD group (n:4650) was increased compared to the control group (n:7346) (Mean difference: 10.90 cm, %95 CI: [9.83, 11.96], $p < 0.00001$)(Fig 2). Data from 6769 NAFLD, 7646 healthy individuals showed that fasting blood glucose levels were found higher in the NAFLD group (Mean difference: 12.32 mg/dl, 95% CI: [9.96, 14.69], $p < 0.00001$). HbA1c% values were increased in the NAFLD group (n: 1254) than in the control ones (n: 1327) (Mean difference: 0.52, 95% CI: [0.28, 0.76], $p < 0.0001$). Insulin levels were higher in the NAFLD group (n: 3194) compared to control (n: 1881) (Mean difference: 6.73, 95% CI: [5.94, 7.53], $p < 0.00001$). The HOMA-IR values of patients also showed significant increase in the NAFLD group (n: 7341) compared to the control group (n: 8381) (Mean difference: 2.13, 95% CI: [1.95, 2.32], $p < 0.00001$)(Fig 3).

Liver Function Parameters

To examine liver function, AST, ALT, GGT, Total bilirubin, and albumin levels were analyzed. AST values of the NAFLD group (n:9357) were higher than the control group (n:11080) (mean difference: 17.82 IU/L, %95 CI: [15.47, 20.17], $p < 0.00001$) (Fig 4). Similarly, ALT levels in the NAFLD group (n:12535) were found to be increased compared to healthy ones (n:14434) (mean difference: 35.11 IU/L, %95 CI: [31.27, 38.95], $p < 0.00001$). Increased ALP levels were observed in NAFLD patients (n:2615) compared to healthy controls (n:4452) (mean difference: 12.10 IU/L, %95 CI: [8.38, 15.83], $p < 0.00001$). GGT level in NAFLD group (n:5756) was found to be higher than control (n:7634) (mean difference: :21.73, %95 CI: [19.35, 24.10], $p < 0.00001$). There wasn't any significant difference in total bilirubin levels between the NAFLD group.

(n:830) and control group (n:735) (mean difference: 0.07, %95 CI: [-0.01, 0.16], p:0.10). Similarly, albumin levels didn't show a significant difference between groups (NAFLD group n: 1994, control group n:1752) (mean difference: -0.02, %95 CI: [-0.09, -0.05], p:0.55).

Hyperlipidemia Related Parameters

Increased levels of triglyceride were found in NAFLD patients (n:9052) compared to healthy ones (n:10489) (Mean difference: 49.34 mg/dl, %95 CI: [44.24, 54.44], p<0.00001). HDL levels of the NAFLD group (n:9097) were found to be lower than the control group (n:10522) (Mean difference: -2.59 mg/dl, %95 CI: [-3.86, -1.32], p<0.0001). LDL levels of the NAFLD group (n: 8695) were higher than the control group (n:10249) (Mean difference: 13.52, %95 CI: [10.94, 16.10], p<0.00001). Total cholesterol levels of NAFLD patients (n:8823) were also increased (n:9699) (Mean difference: 22.59, %95 CI: [18.94, 26.24], p<0.00001).

Blood Pressure Parameters

Systolic blood pressure (SBP) was also higher in NAFLD patients (n:3778) than in controls (n:2987) (mean difference: 5.86 mmHg, %95 CI: [5.39, 8.14], p<0.00001)(Fig 5). Diastolic blood pressure was found increased in NAFLD patients (n:3778) compared to control (n: 2987) (mean difference: 3.83 mmHg, %95 CI: [2.55, 5.11], p<0.00001).

Acute Phase Reactants

CRP, ESR, Ferritin, Hemoglobin, and Creatinine meta-analysis was held with the data obtained from NAFLD studies in Turkey. According to our results, CRP values of the NAFLD group (n:3765) were found to be higher than the control group (n:5859) (Mean difference: 0.95 mg/L, %95 CI: [0.72, 1.19], p<0.00001)(Fig 6). ESR was prolonged in the NAFLD group (n:786) compared to the healthy group (n:482) (mean difference: 2.35 mm/hr, %95 CI: [0.47, 4.23], p<0.01). Ferritin levels of NAFLD patients (n:1921) were increased compared to the control group (n: 3812) (Mean difference: 45.63 ng/mL, %95 CI: [32.72, 58.54], p<0.00001). Hemoglobin level was also found to be higher in the NAFLD group (n:398) than in the control

group (n:780) (Mean difference: 0.28, %95 CI: [0.12, 0.43], p:0.0004). Serum Creatinine levels of NAFLD patients (n:2650) were higher than healthy controls (n:2479) (mean difference:0.07 mg/dL, %95 CI: [0.05, 0.09], p<0.00001).

Correlation Results

Correlation analysis showed that obesity and glucose metabolism parameters such as fasting blood glucose, waist circumference, insulin, and HOMA-IR levels correlated with liver function, which was examined with an increase in ALT, AST, and GGT enzyme levels. Fasting blood glucose correlated with AST (p:<0.0001, r:0.401), ALT (p: <0.0001, r:0.276), and GGT (p:0.018, r:0.245). Waist circumference levels were found to be correlated with AST(p:<0.0001, r:0.371), ALT (p:<0.0001, r:0.368) and ALP (p:0.04, r:0.50) levels. Similarly, insulin/HOMA-IR levels correlated with AST (p:0.001/p:<0.0001, r:0.342, 0.760), ALT (p:<0.0001/p:<0.0001, r:0.369/0.710) and GGT levels (p:0.017/p:<0.0001, r:0.289,0.495).

Discussion

Our meta-analysis showed that Turkish NAFLD patients have glucose metabolism disorders. As it was expected, it was found hyperlipidemia and impaired liver functions in NAFLD patients compared to the control. Blood pressure values were found elevated in NAFLD patients. Furthermore, CRP, ESR, Ferritin, Hemoglobin, and Creatinine levels which were determined as acute phase reactants, were elevated in NAFLD patients in Turkey. These results suggested that NAFLD patients in Turkey carry a high risk of metabolic dysfunction and Turkish NAFLD patients detected in the previous studies might mostly have MASLD.

In NAFLD pathogenesis, whether NAFLD precedes insulin resistance or insulin resistance causes NAFLD has been debated for a long time. Diacylglycerol is known as a key factor of lipid-induced insulin resistance in the liver. Elevated diacylglycerol activates protein kinase C, which phosphorylates and inhibits the insulin receptor. Impaired glucose metabolism in NAFLD is developed mainly by this mechanism (132).

The global prevalence of NAFLD is 30% (7) and in the meta-analysis conducted in 2016, the pooled analysis for NASH prevalence was 59.10% among biopsied NAFLD patients. According to comorbidity analysis, obesity prevalence was 51.34%/81.83%, diabetes was 22.51%/43.63%, hyperlipidemia was 69.16%/72.13%, hypertriglyceridemia was 40.74%/83.33%, hypertension was 39.34%/67.97%, and metabolic syndrome was 42.54%/70.65% among NAFLD/NASH patients around the world. These results showed that prevalence of comorbidities was risen with NASH development compared to NAFLD without steatohepatitis(8). On the other hand, the recent meta-analysis study published in 2023 showed that the NAFLD incidence is higher if those had obesity, diabetes, hyperlipidemia, and metabolic syndrome, but the difference wasn't found significantly. Only tobacco use status showed significant incidence differences among the characteristics of patients (5).

The single-center study investigating Turkey's NAFLD profile showed that 90.4% of NAFLD patients had biopsy-proven NASH, and simple steatosis was rare (9.6%). The clinical outcomes of patients indicated that significant fibrosis was seen in 6.4%, advanced fibrosis was seen in 32.6%, and cirrhosis was seen in 61% of patients. Overweight (32.6%), obesity (61%), diabetes (33.5%), and metabolic syndrome (63%) are the important comorbidities that are seen frequently in patients' disease profiles. The reason for this could be that this hospital is a tertiary referral center and Fibroscan is commonly used for biopsy indication in this center. (9). These results showed evidence that NAFLD/NASH is an epidemic in Turkey. The study conducted in 5 different centers in East-Southeastern Anatolia Regions of Turkey showed that 85% were overweight, 37% were obese, 18% had type 2 diabetes mellitus, and 80.6% had hyperlipidemia. According to the multivariate regression analysis, age, diabetes, and aspartate aminotransferase were related to the severity of the disease (24).

Is It "Non-Alcoholic Fatty Liver Disease " or "Metabolic Dysfunction Associated Steatotic Liver Disease?

Our results showed that NAFLD is not only a liver-based disease, and it is both a cause and consequence of metabolic disturbances. Insulin resistance and glucose metabolism-related parameters are good indicators for this hypothesis.. After many critical meetings, authorities agreed that MASLD was decided to be a more appropriate overarching term by integrating the current understanding of patient heterogeneity caught under the acronym of NAFLD and by offering terminology suggestions that more accurately reflect pathogenesis and can aid patient stratification for treatment. It is thought that this new term will accelerate the transition to new treatments and will open the door to sub-phenotyping efforts of the disease with the studies to be carried out (4, 133, 134).

A recent meta-analysis study involving 6 cohorts from the USA, Japan, and Turkey revealed negative implications of type 2 diabetes in relation to NAFLD. The study found that participants with type 2 diabetes had a significantly elevated risk of hepatic decompensation at 1 year, 3 years, and 5 years compared to those without type 2 diabetes. After considering various confounding factors, it was determined that type 2 diabetes and glycosylated hemoglobin were independent predictors of hepatic decompensation. Furthermore, even after adjusting for baseline liver stiffness assessed by magnetic resonance elastography, the association between type 2 diabetes and hepatic decompensation remained consistent. Notably, type 2 diabetes emerged as an independent predictor of hepatocellular carcinoma development (135).

Another recent meta-analysis aimed to explore the relationship between the triglyceride and glucose (TyG) index, calculated as $\text{fasting triglyceride} / \text{fasting glucose}$, and the risk of NAFLD with a total of 4 cohorts and 8 cross-sectional studies. The results revealed a positive and linear association between the TyG index and the risk of NAFLD. Each additional unit of the TyG index was associated with a higher risk of NAFLD, with a summary odds ratio (OR) of 2.84 (136).

The findings of our meta-analysis, combined with the results from other studies, emphasize the importance of assessing metabolic parameters in understanding the development and prognosis of NAFLD. This highlights the need for countries with a high incidence of NAFLD, such as Turkey, to focus on developing metabolic approaches for the treatment and monitoring of these conditions. By paying attention to metabolic factors, healthcare professionals can better manage and address the challenges posed by NAFLD.

Our meta-analysis results indicated the overall metabolic profile and MASLD potential of NAFLD patients in Turkey for the first time. Based on the quality of the studies and data in the literature, we accept the limits of our work. Some of the limitations of our current meta-analysis are due to the characteristics of fatty liver patients, the design of the studies, and the procedures of the centers where they were performed, stemming from the determination of the disease or patients' states and heterogeneity. Statistical heterogeneity of the data was high. Also, we did not include the comorbidity or disease severity status (in terms of liver fibrosis) in our analysis due to the study amount and the heterogeneity among these studies. Our main goal was to analyse metabolic profile of the patients cumulatively and we agree that further studies and meta-analysis regarding analysis of disease stages effects on the metabolic profile. It is also beneficial to be evaluated in further due to the changes in the terminology and disease diagnosis.

Also, we are aware that there are bias risks among studies in terms of using the same cohort among studies done by the same group in the close time period. Also, all inclusion and exclusion criteria were collected and given in the supplementary table. It has resulted that although inclusion and exclusion criteria are mainly similar among studies, some studies excluded particular chronic diseases that may affect the biochemical profiles of selected patients. We accepted this heterogeneity as a limitation of our meta-analysis. However, we also believe that our meta-analysis provides a comprehensive aspect with a high amount of data, specifically

from Turkey. Those bias risks and limitations might have a more minor impact on this high amount of data.

Due to the MASLD terminology being very new and there are not many studies searching for exact MASLD patients according to the specific diagnosis criteria for the MASLD, our study couldn't show the MSFLD and NAFLD difference or MASLD profile of Turkey. We also accept these limitations on this debate (137), however, our results support that many of the patients that we included in our meta-analysis might have MASLD according to our cumulative results.

Conclusion

NAFLD is a metabolic disease that includes multi-pathways related to glucose and lipid metabolism, vascular function, inflammation, and acute phase responses. It was indicated with the cumulative meta-analysis with all Turkish NAFLD studies up to date. These cumulative results have importance to occur metabolic profile of NAFLD patients in Turkey and might be a good reference for many countries in Europe, Asia, and the Middle East. Also, the new term for this disease, MASLD, could be more suitable according to related metabolic outcomes, which are cumulatively assessed in our meta-analysis.

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Figure Legends

Fig. 1. Flow diagram of study selection.

Fig. 2. The random effect model of cumulative meta-analysis for waist circumference data obtained from NAFLD and control individuals.

Fig 3. The random effect model of cumulative meta-analysis for HOMA-IR data obtained from NAFLD and control individuals.

Fig. 4. The random effect model of cumulative meta-analysis for AST data obtained from NAFLD and control individuals.

Fig. 5. The random effect model of cumulative meta-analysis for Systolic Blood Pressure (SBP) data obtained from NAFLD and control individuals.

Fig. 6. The random effect model of cumulative meta-analysis for CRP data obtained from NAFLD and control individuals.

Supplementary Table 1. Inclusion and exclusion criteria of studies.