The prevalence of metabolic-associated fatty liver disease in the Turkish population: A multicenter study

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Abstract

Background and Aim: The objective of the present study was to investigate the prevalence of metabolic-associated fatty liver disease (MAFLD) in patients with dyspepsia.

Materials and Methods: A total of 909 consecutive patients who presented with dyspepsia at 8 tertiary care centers in Turkey between March 2019 and December 2019 were included.

Results: The median age was 47 years. Among them, 30.3% of the patients were obese, 18.8% had type 2 diabetes mellitus (T2DM), 35.1% had metabolic syndrome, 84.8% had dyslipidemia, and 23.9% had hypertension. The prevalence of MAFLD was 45.5%. Among the patients with MAFLD, the prevalence of obesity, T2DM, metabolic syndrome, dyslipidemia, and hypertension was 43.3%, 24.9%, 52.5%, 92.3%, and 31.9%, respectively. MAFLD was significantly associated with all of the metabolic comorbidities (p<0.001). The median Fibrosis-4 Index score of the MAFLD patients was 0.88 (range: 0.1–9.5). Of note, 53 patients with hepatic steatosis did not meet the MAFLD criteria.

Conclusion: The results of the present study indicated that there was a significantly high prevalence of MAFLD observed in daily clinical practice in Turkey. Early diagnosis and prevention efforts should be implemented to reduce disease progression, and a region-based strategy is recommended.

Keywords: Metabolic-associated fatty liver disease; non-alcoholic fatty liver disease; type 2 diabetes mellitus.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a group of clinical conditions characterized by the presence of hepatic steatosis in individuals without significant alcohol consumption; the excessive fat in the liver is the result of a secondary cause. The clinicopathological spectrum of NAFLD includes non-alcoholic fatty liver, non-alcoholic steatohepatitis, hepatic fibrosis, cirrhosis, and hepatocellular cancer. NAFLD is commonly associated with metabolic comorbidities, such as obesity, diabetes mellitus, dyslipidemia, and cardiovascular disease.[1]

Recently, some studies examined a lack of clarity in the association between NAFLD and metabolic risk factors, and a more appropriate nomenclature for the disease of metabolic (dysfunction)-associated fatty liver disease (MAFLD) has been proposed.[2,3] MAFLD is defined as evidence of hepatic steatosis with invasive or noninvasive methods and the presence of at least 1 of 3 metabolic dysfunctions, such as excess weight or obesity, type 2 diabetes mellitus (T2DM), or evidence of metabolic dysfunction (increased waist circumference and an abnormal glycemic and lipid profile).[2] MAFLD is a heterogeneous entity. Alcohol consumption, regardless of the amount, is not a reference in the diagnosis of MAFLD. Moreover, MAFLD can coexist with other liver diseases. Some studies have reported that MAFLD more accurately reflects the current knowledge of fatty liver diseases associated with metabolic disorders.[2,3] Unlike NAFLD, which requires a negative definition, i.e., a diagnosis of exclusion based on the absence of coexisting chronic liver disorders, MAFLD has a positive definition, and the focus on metabolic factors as causative drivers is expected to reduce patient confusion about disease etiology, which can in turn facilitate patient-physician communication and shared decision-making. [4,5] However, it has also been reported that the MAFLD name change is premature and requires building a wider consensus.[6]

The prevalence of NAFLD varies widely; it affects approximately 25% of individuals across the globe.[7,8] A relatively high prevalence even in apparently healthy Turkish individuals underlines the importance of early recognition of MAFLD in daily clinical practice.[9–12] Unfortunately, early diagnosis of MAFLD constitutes a major clinical challenge due to its usually asymptomatic presentation.

Dyspepsia is one of the most prevalent symptoms of gastrointestinal disorders; it affects nearly half of the general population. It is characterized by epigastric pain, burning, or abdominal discomfort.[13] The aim of the present study was to determine the prevalence of MAFLD in patients with dyspepsia in routine clinical practice.

Materials and Methods

Patients

This multi-center, prospective cohort study included 932 consecutive patients with a complaint of dyspepsia who presented at 8 tertiary care centers in Turkey between March 2019 and December 2019. Dyspepsia was defined based on the clinical guidelines.[13] All of the patients underwent clinical, laboratory, and radiological examinations. The study data were collected from outpatient visit charts. This study was approved by the ethical committee of University of the Health Sciences (approval numbers: 19/127, 2019/127, approval dates: 26/03/2019, 04/09/2020). This research was funded by the Turkish Association for the Study of the Liver.

The exclusion criteria were the presence of viral hepatitis, drug-induced liver disease, significant alcohol consumption (>21 units of alcohol per week in men and >14 units of alcohol per week in women), autoimmune hepatitis, genetic liver disease, or Wilson's disease. Patients with significant transaminase levels that could be explained by liver pathologies other than MAFLD were referred for further diagnosis and excluded from the analysis. Patients with missing data for liver transaminases were also excluded.

Methods

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, fasting glucose, cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) levels, and a complete blood cell count were measured by a local laboratory at the participating centers.

All of the patients underwent abdominal ultrasonography (US) to rule out any abdominal pathology. The abdominal US was performed by an experienced radiologist who was blinded to the patient's clinical history. Hepatic steatosis was evaluated by comparing the echogenicity of the liver to that of the kidney based on standard criteria and graded as mild, moderate, or severe. Mild fatty liver was defined as slightly diffuse increased echogenicity in the hepatic parenchyma and normal visualization of the diaphragm, hepatic, and portal vein borders. Moderate fatty liver was defined as diffuse increased echogenicity in the hepatic parenchyma with slightly impaired appearance of the intrahepatic vessels and the diaphragm. Severe fatty liver was defined as marked increased echogenicity with poor or no visualization of the intrahepatic vessel borders, the diaphragm, and the posterior right lobe of the liver.[14,15]

Definitions

T2DM was defined based on the American Diabetes Association criteria[16] and metabolic syndrome was defined according to the Adult Treatment Panel III criteria.[17] Dyslipidemia was defined as elevated triglyceride and/or LDL or low HDL levels.[18] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined based on the World Health Organization

Table 1. Characteristics of the study population

Characteristics	n=909
Age, years	47 (18–91)
Gender, male/female	344 (37.8%)/565 (62.2%)
BMI, kg/m²	27.3 (15.7–58.8)
Waist circumference, cm	95 (41–137)
Systolic blood pressure, mm Hg	125 (85–189)
Diastolic blood pressure, mm Hg	79 (50–120)
Smoker, yes/no	170 (28.0%)/438 (72.0%)
Alcohol use, yes/no	50 (5.6%)/848 (94.4%)
Platelets, per µL	260 (75–731)
Type 2 DM, yes/no	171 (18.8%)/738 (81.2%)
Hypertension, yes/no	217 (23.9%)/691 (76.1%)
Dyslipidemia, yes/no	687 (84.8%)/123 (15.2%)
Metabolic syndrome, yes/no	313 (35.1%)/580 (64.9%)
Obesity, yes/no	223 (30.3%)/512 (69.7%)
MAFLD, yes/no	414 (45.5%)/495 (54.5%)
Albumin, mg/dL	4.3 (2.0–6.3)
AST, U/L	22 (8–196)
ALT, U/L	22 (2–238)
GGT, U/L	24 (6–292)
Fasting blood glucose, mg/dL	95 (52–351)
LDL, mg/dL	119 (24–410)
HDL, mg/dL	45 (10–231)
Triglycerides, mg/dL	129 (11–626)
Insulin, U/L	9.4 (2.03–142.27)

Continuous data were presented as median (minimum–maximum). BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gama glutamyl transferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; MAFLD: Metabolic-associated fatty liver disease.

criteria, with a BMI of 25–29.9 kg/m² defined as overweight, and a BMI ≥30 kg/m² defined as obese.[19]

MAFLD was defined as evidence of hepatic steatosis by sonography and the presence of at least 1 of the following 3 criteria:

- BMI ≥25 kg/m²,
- T2DM, or
- At least 2 of the metabolic dysfunction criteria for individuals with a BMI ≤25 kg/m².

Metabolic dysfunction indicated the presence of at least 2 of the following criteria:[2,3]

1) Waist circumference ≥102/88 cm in men and women,

2) Blood pressure ≥130/85 mm Hg, or specific drug treatment,

3) Plasma triglyceride level ≥150 mg/dL or specific drug treatment,

4) Plasma HDL level <40 mg/dL for men and <50 mg/dL for women or specific drug treatment,

5) Prediabetes (i.e., fasting glucose level 100–125 mg/dL, 2-hour post-load glucose level 140–199 mg/dL, or glycated hemoglobin 5.7–6.4%,

6) Homeostasis model assessment-insulin resistance score ≥2.5, or

(7) Plasma high-sensitivity C-reactive protein level >2 mg/L.[2]

A Fibrosis-4 (FIB-4) Index score was calculated on the day abdominal

Table 2. Classification of risk for advanced fibrosis according to Fibrosis-4 Index score

	Low risk FIB-4 <1.3		Indeterminate risk FIB-4 1.3-2.67		High risk FIB-4 >2.67	
	n	%	n	%	n	%
Patients with MAFLD (n=414)	337	81.4	65	15.7	12	2.9
Patients with evidence of hepatic steatosis (n=467)	378	80.9	76	16.3	13	2.8

FIB-4: Fibrosis-4 Index; MAFLD: Metabolic-associated fatty liver disease.

Table 3. Comparison of comorbidity prevalence between patients with MAFLD and NAFLD

Comorbidity	MAFLD (n=414)	NAFLD (n=467)
Obesity	159/366 (43.4%)	159/386 (41.2%)
Type 2 diabetes mellitus	103/414 (24.9%)	103/467 (22.1%)
Metabolic syndrome	217/413 (52.5%)	217/466 (46.6%)
Dyslipidemia	360/390 (92.3%)	386/430 (89.8%)
Hypertension	132/414 (31.9%)	134/467 (28.7%)

MAFLD: Metabolic-associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease.

US was performed using the formula of age (years) x AST (U/L) / ALT (U/L)$^{1/2}$ x platelets x10^9/L.[20] The FIB-4 index yields a value between 0.2 and 10. A score of <1.3 indicates a low risk for fibrosis, while a score of >2.67 indicates a high risk for advanced fibrosis.[21,22]

Statistical Analysis

The mean and standard deviation, median and range, and frequency and percentage were used as descriptive statistics. Comparisons between 2 groups were assessed using Student's t-test or the Mann-Whitney U test, depending on the distribution of the data. Categorical variables were assessed with a chi-squared test or Fisher's exact test. The normality of distribution was analyzed with the Kolmogorov-Smirnov test. A p value of <0.05 was considered statistically significant.

Results

Of 932 consecutive patients, 9 were excluded due to a significantly elevated transaminase level and were referred for further diagnosis. Another 14 patients were excluded due to missing transaminase level data. A total of 909 patients (male/female: 344/565) with dyspepsia were included in the analysis. Most of the patients were female (62.2%). The median age was 47 years (range: 18–91 years). Of the group, 30.3% of the patients were obese, 18.8% had T2DM, 35.1% had metabolic syndrome, 84.8% had dyslipidemia, 23.9% had hypertension, 28% were active smokers, and 5.6% were social alcohol drinkers. At the time of the evaluation, the median serum AST, ALT, and GGT level was 22 U/L (range: 8–196 U/L), 22 U/L (range: 2–238 U/L), and 24 U/L (range: 6–292 U/L), respectively. The characteristics of the study population are summarized in Table 1. The association between MAFLD and comorbidities is presented in Figure 1.

Sonographic examination revealed hepatic steatosis in 467 patients (51.4%). Among them, 288 patients (61.7%) had mild steatosis, 151 (32.3%) had moderate steatosis, and 28 (6%) had severe steatosis.
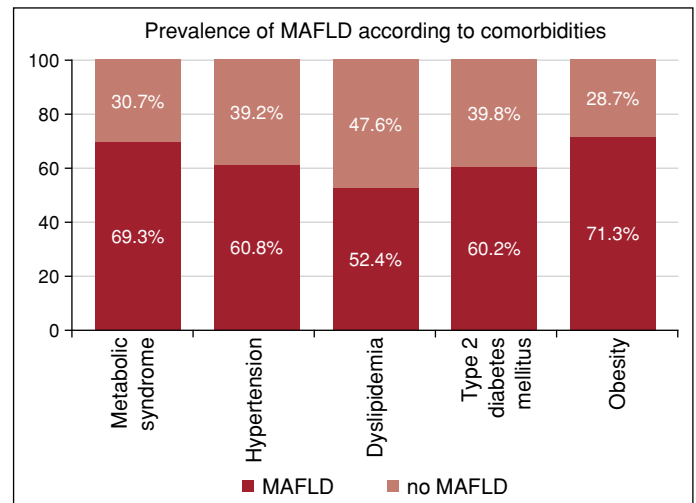
Figure 1. Metabolic-associated fatty liver disease association with co-morbidities.

MAFLD: Metabolic-associated fatty liver disease.
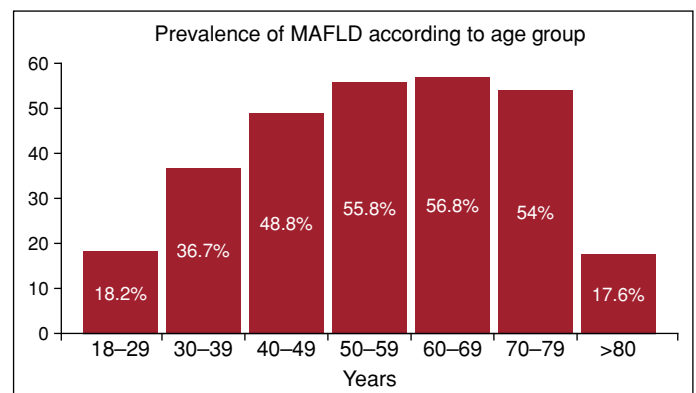
Figure 2. Prevalence of metabolic-associated fatty liver disease according to age group.

The median FIB-4 score of the patients with hepatic steatosis was 0.88 (range: 0.1–9.5). A low fibrosis score (<1.3) was observed in 81% of the patients and 2.8% presented with high risk for advanced fibrosis (FIB-4 >2.67).

MAFLD was diagnosed in 45.5% of the 909 dyspeptic patients (n=414) and 88.7% of the patients with hepatic steatosis. Most of the patients were female (56.8% vs. 43.2%, p=0.002). MAFLD was most prevalent in the fifth decade of life (p<0.001). MAFLD was diagnosed in 71.3% of the obese patients (p<0.001), 60.2% of the diabetic patients

(p<0.001), 69.3% of the patients with metabolic syndrome (p<0.001), 60.8% of the hypertensive patients (p<0.001), and 52.4% of the patients with dyslipidemia (p<0.001). The median FIB-4 score of the patients with MAFLD was 0.88 (range: 0.1–9.5). In all, 81.4% of the patients had a low fibrosis score, and 2.9% presented with high risk for advanced fibrosis according to the FIB-4 score. The distribution of MAFLD according to the FIB-4 score and age is summarized in Table 2 and Figure 2, respectively.

The prevalence of metabolic comorbidities in patients with MAFLD and NAFLD is depicted in Table 3.

Of note, 53 dyspeptic patients (5.8%) with hepatic steatosis did not meet the MAFLD criteria.

Discussion

The present study determined the prevalence of MAFLD in patients with dyspepsia at 8 tertiary care centers in Turkey. Half of the dyspeptic patients (51.4%) were diagnosed with hepatic steatosis by abdominal US. Interestingly, 38.3% had moderate and severe steatosis. There was a relatively high presence of comorbid conditions. The prevalence of obesity, T2DM, metabolic syndrome, dyslipidemia, and hypertension was 30.3%, 18.8%, 35.1%, 84.8%, and 23.9%, respectively. These findings are consistent with results reported in previous studies,[7–10] indicating that NAFLD is a growing public health problem worldwide, as well as in Turkey.

The diagnostic approach used for MAFLD plays a significant role in the prediction of prevalence. The diagnostic method chosen can lead to over- or underestimation of the disease. Abdominal US, computerized tomography, magnetic resonance imaging (MRI), controlled attenuation parameter by transient elastography (TE), and MRI-derived proton density fat fraction are noninvasive imaging methods to predict hepatic steatosis.[22–24] Although abdominal US has low sensitivity, it is still routinely and widely used in daily clinical practice due to its availability and cost-effectiveness.[25] In the present study, we found that around half of the dyspeptic patients were diagnosed with MAFLD using abdominal US. Most of the MAFLD patients were female. There was a relationship between the patient's age and the prevalence of MAFLD (p<0.001). The highest prevalence of MAFLD was observed in the fifth decade of life. MAFLD was associated with metabolic disorders. Our findings indicated that more than half of the obese patients, diabetic patients, patients with metabolic syndrome, hypertensive patients, and those with dyslipidemia had a diagnosis of MAFLD.

The increasing prevalence of MAFLD is associated with the increasing prevalence of obesity and T2DM worldwide.[2,3,26] In the present study, the prevalence of obesity and T2DM in dyspeptic patients was 30.3% and 18.8%, respectively. The obesity rate was not significantly different from 2016 data reported by the World Health Organization of 32.1%.[19] Epidemiological studies, such as the Turkish Diabetes Epidemiological Study 1 (TURDEP I)[27] and TURDEP II,[28] have found that the prevalence of T2DM increased 90% over the course of 12 years, impacting 16.5% of the Turkish population.[27,28] Therefore, we believe the effects of comorbidities have minimized the reported population-based prevalence.

Recent estimation models applied in various countries suggest that in the next decade, the prevalence and the severity of MAFLD will increase worldwide with the increasing rate of comorbidities, such as T2DM, obesity, and metabolic syndrome.[29–31] Region-specific guidelines to effectively manage MAFLD are advisable given the evidence of high rates of these comorbidities in Turkey.

Several noninvasive biochemical-based biomarkers, including the FIB-4 score and imaging methods, such as TE and magnetic resonance elastography are widely used to assess liver fibrosis in routine clinical practice.[32] We calculated a FIB-4 score for the patients with MAFLD to stratify the risk for advanced fibrosis as recommended in the guidelines of European Association for the Study of the Liver and the American Association for the Study of the Liver Diseases.[1,31] The FIB-4 was an appropriate tool to assess the risk of advanced liver fibrosis in our study population since both the FIB-4 and NAFLD Fibrosis Score (NFS) have been shown to perform satisfactorily in different clinical settings, including among diabetic and non-diabetic patients as well as patients with elevated and normal transaminase levels.[33,34] However, previous studies also advise that there may be some diagnostic inaccuracies in lean and morbidly obese patients, and patients younger than 35 years or older than 65 years.[35,36] In our study, we chose to calculate a FIB-4 score rather than the NFS. It has been reported that the FIB-4 demonstrated slightly better diagnostic performance compared with the NFS and was clinically more practical since it includes fewer parameters.[34] The diagnostic utility of these tests lies in their ability to exclude patients without advanced fibrosis due to the high negative predictive value.[31,37] In our study, more than 80% of the study population was classified as low risk for advanced fibrosis. This indicates a need for referral of those remaining 20% to secondary or tertiary care centers for further diagnostics.[38–40]

The primary strength of this study lies in the large cohort sample provided by 8 tertiary care centers in Turkey. We believe our patient selection sufficiently reflects the general population due to the fact that the majority of the patients presented at gastroenterology outpatient clinics with a complaint of dyspepsia without any known liver disease. Moreover, we used a heterogeneous group in terms of comorbidities. Consequently, this study also highlighted the general characteristics of the patient profile of daily routine clinical practice. However, our study must be evaluated in light of its limitations. First, since the dyspeptic patients did not have any symptoms and/or liver test abnormalities, we did not perform a liver biopsy. The severity of liver disease was assessed based on the FIB-4 test. Second, abdominal US examinations were performed by different radiologists at the respective centers. This might have led to some heterogeneity in the sonography findings.

In conclusion, the results of the present study highlight the high prevalence of MAFLD in daily clinical practice. It is expected that the disease burden of MAFLD on the Turkish healthcare system may increase in the future. We recommend the implementation of region-specific guidelines to effectively manage MAFLD.

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