The Changing Prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) in Turkey in the Last Decade

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ABSTRACT

Background: *The true prevalence of non-alcoholic fatty liver disease (NAFLD) is unknown in Turkey due to a lack of population-based studies. The aim of this study was (i) to determine the overall and region-specific prevalence of NAFLD in Turkey; (ii) to analyze the factors associated with the prevalence; and (iii) to determine the nationwide change in the prevalence of NAFLD in the last decade.*

Methods: *The 10-year data (2007-2016) of 113 239 apparently healthy subjects visiting the check-up clinics of Acibadem Hospitals Group were retrospectively analyzed. A subgroup of patients (n=8120) statistically representing the bigger cohort was selected. The prevalence was analyzed according to ultrasound findings, age, sex, body mass index (BMI), geographical region, and time periods trisected as 2007-2010, 2011-2013, and 2014-2016.*

Results: *The overall prevalence of NAFLD in Turkey was found to be 48.3%. It was highest among people >50 years of age (65.6%), male sex (64.0%), with a BMI >25 kg/m^2 (63.5%), and in Central and Eastern Anatolia regions (57.1% and 55.7%, respectively). The prevalence of NAFLD was 43.5% between 2007 and 2010, 47.6% between 2011 and 2013, and 53.1% between 2014 and 2016, and the rate of increase was 22%. Multivariate analysis showed that male sex, serum alanine aminotransferase level, older age, BMI, type-II diabetes mellitus, hypertension, and dyslipidemia were independent factors associated with NAFLD.*

Conclusion: *NAFLD is a highly prevalent disease affecting almost half of the Turkish population (48.3%). We are faced with a dramatic increase in NAFLD prevalence in the past 10 years.*

Keywords: *Fatty liver, non alcoholic fatty liver, prevalence, Turkey, obesity*

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disorder worldwide. Recent studies have reported that the global prevalence of NAFLD is currently 25%.[1] Studies from South America and the Middle East have reported the highest (31% and 32%) prevalence, followed by Asia (27%), North America (24%), Europe (23%), and Africa (27%).[1]

This wide range in the prevalence rates is mostly due to the differences in the studied populations and the methods used to detect fatty liver. The prevalence is known to be higher in males and in biopsy-based studies, increases with older age, and is affected by ethnicity and the proportion of obese and overweight persons in the studied population.[2] In a study from Korea, NAFLD was detected in 51% of the liver biopsy samples obtained from 589 consecutive potential liver transplant donors.[3] In a similar study from the United States, 20% of the donors had more than 30% of fat in their liver biopsy samples.[4] Although liver biopsy is the gold standard method for the diagnosis of fatty liver, it is not considered suitable for population-based studies due to its invasive nature. Liver ultrasound, on the other hand, is a noninvasive method and has high sensitivity and specificity (84.8% and 93.6%) and a good positive likelihood ratio (13.3) to detect moderate to severe fatty liver.[5] Thus, it is the most commonly used method to define NAFLD in population-based studies.

The prevalence of NAFLD was reported as 20% in Italy, 33.5% in Brazilian, 20% in Romanian, 17% in Indian, 30% in German, 10-42% in Chinese, and 20-46% in USA-based studies.[6,7] Meanwhile, in a Japanese-based study, the prevalence of ultrasound-defined NAFLD showed a dramatic increase from 13% to 30% in a cohort of 35 519 cases in a 10-12 years period.[8] Based on recently

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published studies and the recent APASL guideline, the prevalence of NAFLD is showing a dramatic rise in both East and West part of the world and the rates are beginning to approximate each other.[9]

The prevalence of NAFLD in Turkey has not been investigated so far in a large population-based study that included data from different parts of the country. There are only a few small-sized, single-centered studies done on specific groups that are published in the literature. In a study by Celebi et al. that included 404 patients aged between 18 and 80 years, ultrasound-based NAFLD was found in 19.8% of the population (16.5% in females, 23.7% in males) in the Elazig region.[10] Okur et al. reported the prevalence to be 10.6% in a group of 254 healthy young males and Kaya et al. found that the transient elastography defined NAFLD prevalence was 23.2% in 112 medical school students.[11,12] A ultrasound-based recent study performed on 2792 apparently healthy individual cohort from the Cappadocia region of Turkey found a 60.1% steatosis rate.[13]

The aim of this study was (i) to determine the hospital-based prevalence of NAFLD both in the general population, and in different age, sex, and body mass index (BMI) groups, (ii) to understand whether there is a geographic difference in the prevalence of NAFLD across the country, (iii) to analyze the factors associated with the prevalence, and finally (iv) to determine the change in the prevalence of the disease by analyzing the 10-year data between 2007 and 2016.

PATIENTS AND METHODS

Patient Population and Study Design

In this cross-sectional hospital-based study, a total of 113 239 apparently healthy subjects, who had voluntarily applied to the check-up clinics of Acibadem Hospitals located in İstanbul, Kocaeli, Bursa, Eskişehir, Ankara, Adana, Bodrum, Kayseri (total of 15 centers), from February 2007 to February 2016 were enrolled in the study. The data of these patients were pulled from the electronic database system of Acibadem Health Group. First, the demographic data such as age, sex, place of birth was noted for all patients. Second, "a subgroup of patients representing the cohort was selected according to the hospital they were admitted, past medical history, presence and type of chronic diseases, alcohol intake, BMI, age, and sex" ($n=8120$). Each patient's medical records were reviewed individually and abdominal ultrasound findings, serum alanine aminotransferase (ALT) level, BMI, history of alcohol intake, presence of diabetes mellitus, dyslipidemia, hypertension, medication history, serology for viral hepatitis, and date and city of admission were noted. Patients under 18 years of age ($n=10$), patients with a history of significant alcohol intake ($n=810$), known history of chronic liver disease ($n=223$), patients whose birthplace was not in Turkey ($n=510$) were excluded from the study. The final analysis was done on 6567 patients.

The study was approved by the local ethics committee (ATADEK-2015/14-5) and was conducted according to the declaration of Helsinki.

Analysis of the Data and Definitions

NAFLD was defined as the demonstration of hepatic steatosis in the liver by ultrasound in the absence of significant alcohol use (>140 g/week for women and >210 g/week for men) and exclusion of chronic liver disease. To estimate the prevalence of NAFLD in different age groups, patients were divided into groups as <30, 30-40, 40-50, and >50 years of age. Similarly, the study group was divided into different time periods such as 2007-2010, 2011-2013, and 2014-2016 to calculate the changing prevalence of the disease over time. To calculate the prevalence of the disease in different parts of the country, patients were divided into 7 different geographical regions (Marmara, Aegean, Mediterranean region, Central Anatolia, Black Sea region, Eastern and Southeastern Anatolia) based on birthplace. Subjects were grouped into 3 categories according to their BMI on the basis of the World Health Organization criteria: "underweight" with a BMI <18.5 kg/m^2, "normal" with a BMI 18.5-24.9 kg/m^2, "overweight" with a BMI ≥25 but <29.9 kg/m^2, and "obese" with a BMI ≥30 kg/m^2.

MAIN POINTS

- *This study demonstrates that the overall prevalence of NAFLD in Turkey was found to be 48.3%.*
- *NAFLD prevalence increased from 43.5% to 53.1% in the past 10 years, parallel to the increase in obesity in Turkey.*
- *The prevalence of NAFLD showed an increase with age and BMI, was more common in male sex and showed a geographic difference in relation to the BMI patterns of the region, being highest in Central and Eastern Anatolia and lowest in Aegean and Marmara Region.*
- *A focused approach and immediate action should be put forward to reduce the rate of obesity and NAFLD in Turkey.*

The liver was characterized as fatty liver when the liver had areas of significantly increased echogenicity relative to the renal parenchyma, the ultrasound beam was attenuated with the diaphragm indistinct, or the echogenic walls of the portal veins were less visible. The severity of hepatic steatosis was graded as normal, grade I (mild), grade II (moderate), and grade III (severe).

Statistical Analyses

Categorical data were presented as number and percent and were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were expressed as mean and standard deviation (SD) unless specified otherwise and were compared using *t*-test or Mann–Whitney *U*-test. Variables that had a *P* value of <.01 on univariate analysis were entered into a Cox regression hazards model by forward logistic regression to determine the independent predictors of NAFLD. All statistical analyses were performed using IBM, SPSS, and Statistics v. 20.0.0 statistical software (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of Patients

A total of 113 239 patients were included in the study. Fifty-seven percent ($n=64$ 756) of these patients were males. The mean age of the population was 43.67 ± 11.83 years and the mean serum ALT level was 29.47 ± 23.15. The subgroup representing the study population consisted of 6567 patients and the mean age in this cohort was 43.03 ± 12.22 years and 3574 (54.4%) of them were males. The characteristics of the study population are summarized in Table 1.

The prevalence of NAFLD was found to be 48.3% ($n=3176$) in the final cohort. Fifty-nine percent ($n=1889$) of the patients had grade I, 28.6% ($n=901$) had grade II, and 12.4% ($n=386$) had grade III steatosis. Patients with NAFLD were older (46.52 ± 11.69 vs. 39.77 ± 11.80 years, $P < .001$) and had a male predominance (72.1% vs. 37.9%, $P < .001$). NAFLD group had a higher number of patients diagnosed with dyslipidemia (15.6% vs. 7.1%, $P < .001$), type 2 diabetes mellitus (13.2% vs. 3.3%, $P < .001$), and hypertension (22.6% vs. 7.0%, $P < .001$) compared to NAFLD (–) group. NAFLD (+) group had a higher mean BMI (29.38 ± 4.63 vs. 24.58 ± 3.85, $P < .001$) and a higher number of overweight (46.4% vs. 38.4, $P=.010$) and obese subjects (42.7% vs. 9.5%, $P < .001$) in total (Table 1).

The Prevalence and Grade of NAFLD According to Age, Sex, and BMI

The prevalence of NAFLD was lowest in patients <30 years of age (23.0%) and highest in patients >50 years of age (65.6%). The prevalence was 38.7% for patients between 30 and 40 years of age and 52.6% for patients between 40 and 50 years of age (Figure 1a) ($P < .001$). The severity of steatosis also showed a significant increase with age. The rate of grade I, II, and III steatoses were 68.8%, 22.2%, and 9.0% for <30 years of age, 65.3%, 24.1%, and 10.6% for 30-40 years of age, 60.3%, 26.4%, and 13.3% for 40-50 years of age, and 53.6%, 33.7%, and 12.7% for patients above 50 years of age (Figure 1b) ($P < .001$).

NAFLD (+) group had a higher number of overweight and obese subjects in total and this difference in the BMI ratio was significant for all age groups. The subjects with a BMI over 25 kg/m^2 was 81.2%, 86.8%, 89.3%, and 91.5% for patients <30, 30-40, 40-50, and >50 years of age in the NAFLD (+), 30.9%, 40.7%, 47.9%, and 56.0% for patients <30, 30-40, 40-50, and >50 years of age in the NAFLD (–) group, respectively ($P < .001$) (Figure 2).

The increase in the prevalence of NAFLD was more significant for men compared to women; the overall prevalence of NAFLD was 64.0% for men vs. 29.6% for women ($P < .001$). This trend was seen in all age groups; 38.0% vs. 8.9%, 59.1% vs. 15.5%, 68.7% vs. 29.4%, and 74.3% vs. 55.3% for men and women <30, 30-40, 40-50, and >50 years of age, respectively ($P < .001$) (Figure 3).

The Prevalence and Grade of NAFLD According to Year

The prevalence of NAFLD was 43.5% for 2007-2010, 47.6% for 2011-2013, and 53.1% for 2014-2016 time periods ($P < .001$) (Figure 4a). The rate of increase from 2007-2010 to 2014-2016 was 22%. Although there was an increase in the prevalence of NAFLD in the 10-year period, the severity of steatosis did not increase dramatically. The rate of grade I, II, and III steatosis were 57.1%, 29.8%, and 13.1% for 2007-2010, 55.5%, 30.1%, and 14.4% for 2011-2013, 66.1%, 25.3%, and 8.6% for 2014-2016 years, respectively ($P=.083$) (Figure 4b).

Regional Differences in the Prevalence and Severity of NAFLD

The prevalence of NAFLD was lowest in the Aegean Region (39.8%) and highest in Central Anatolia (57.1%).

Table 1. Demographics of the Study Population

	NAFLD (+)	NAFLD (–)	Total	*P* Value
No. of patients	3176 (48.3)	3391 (51.7)	6567 (100)	
Age, years	46.52 ± 11.69 (18-85)	39.77 ± 11.80 (18-93)	43.03 ± 12.22 (18-93)	<.001
Age distribution				<.001
<30	189 (6.0)	631 (18.6)	820 (12.5)	
30-40	772 (24.3)	1222 (36.0)	1994 (30.4)	
40-50	1001 (31.5)	902 (26.6)	1903 (29.0)	
>50	1214 (38.2)	636 (18.8)	1850 (28.2)	
Sex, male	2290 (72.1)	1284 (37.9)	3574 (54.4)	<.001
Dyslipidemia	496 (15.6)	239 (7.1)	735 (11.2)	<.001
Diabetes mellitus	420 (13.2)	113(3.3)	533 (8.1)	<.001
Hypertension	644 (22.6)	229 (7.0)	873 (14.3)	<.001
Serum ALT, U/L	36.4 ± 25.01	22.57 ± 19.0	29.26 ± 22.43	<.001
ALT >ULN (40 U/L)	952 (30.3)	272 (8.1)	1224 (18.7)	<.001
BMI, kg/m^2	29.38 ± 4.63	24.58 ± 3.85	26.91 ± 4.88	<.001
<18	3 (0.1)	110 (3.3)	113 (1.8)	
19-24.9	339 (10.9)	1618 (48.8)	1957 (30.4)	
25-29.9	1448 (46.4)	1273 (38.4)	2721 (42.3)	
30-34.9	953 (30.6)	266 (8.0)	1219 (18.9)	
35-44.9	345 (11.1)	48 (1.4)	393 (6.1)	
>45	31 (1.0)	3 (0.1)	34 (0.5)	
Year distribution				<.001
2007-2010	680 (21.4)	882 (26.0)	1562 (23.8)	
2011-2013	1400 (44.1)	1540 (45.4)	2940 (44.8)	
2014-2016	1096 (34.5)	969 (28.6)	2065 (31.4)	
Region				<.001
Marmara	1319 (41.5)	1662 (49.0)	2981 (45.4)	
Aegean	259 (8.2)	391 (11.5)	650 (9.9)	
Mediterranean Region	240 (7.6)	250 (7.4)	490 (7.5)	
Central Anatolia	565 (17.8)	423 (12.5)	988 (15.0)	
Black Sea Region	333 (10.5)	267 (7.9)	600 (9.1)	
Eastern Anatolia	241 (7.6)	191 (5.6)	432 (6.6)	
Southeast Anatolia	219 (6.9)	207 (6.1)	426 (6.5)	

Results expressed as number (%) or median (range) unless specified otherwise.
ALT, alanine aminotransferase; BMI, body mass index; ULN, upper limit of normal (40 U/L for both sex).

The prevalence rates for Marmara, Mediterranean Region, Black Sea Region, Eastern, and Southeastern Anatolia were 44.2%, 49.9%, 55.5%, 55.7%, and 51.4%, respectively (*P* < .001) (Figure 5a). The rate of grade 1 steatosis ranged from 47.5% in Mediterranean Region to 64.4% in Central Anatolia, grade II steatosis ranged from 24.8% in Central Anatolia to 35.4% in Mediterranean Region and the rate of grade III steatosis ranged from 9.3% in Aegean to 17.1% in Mediterranean Region (Figure 5b) (*P* = .032).

Factors Affecting the Prevalence of NAFLD

Univariate analysis showed that the presence of NAFLD was significantly higher among male sex (*P* < .001), elderly patients (*P* < .001), patients with type 2 diabetes mellitus

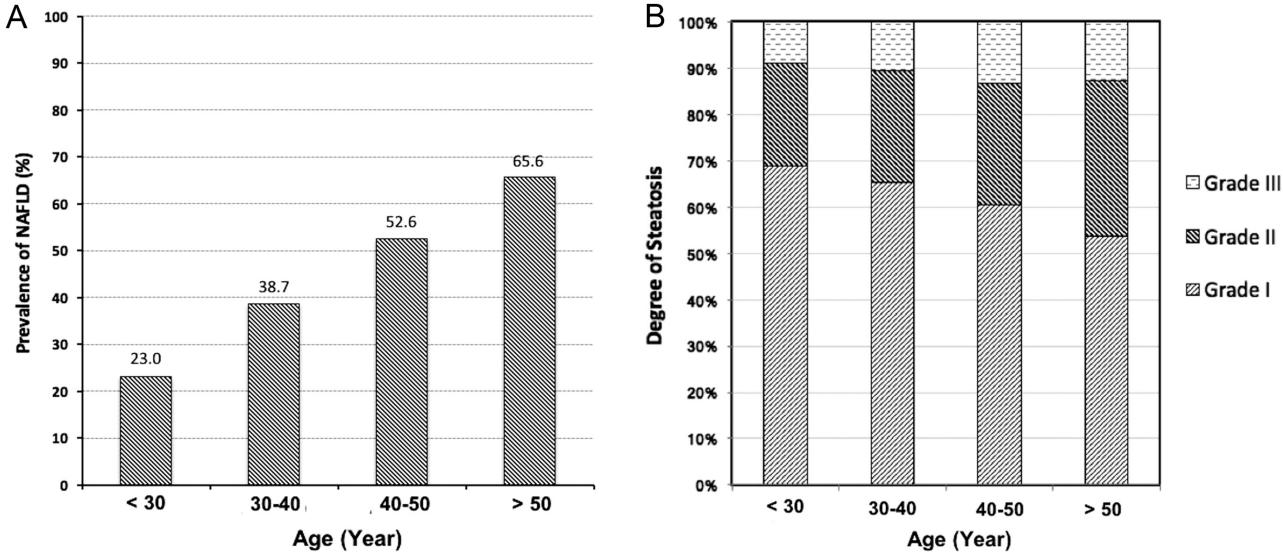

Figure 1. The prevalence of NAFLD and degree of steatosis according to age. (a) The prevalence of NAFLD increased with advancing age groups ($P < .001$ for age groups <30 years vs. 30-40 years vs. 40-50 years vs. >50 years). (b) Grade I steatosis decreased and grade II and III steatosis increased with aging ($P < .001$).

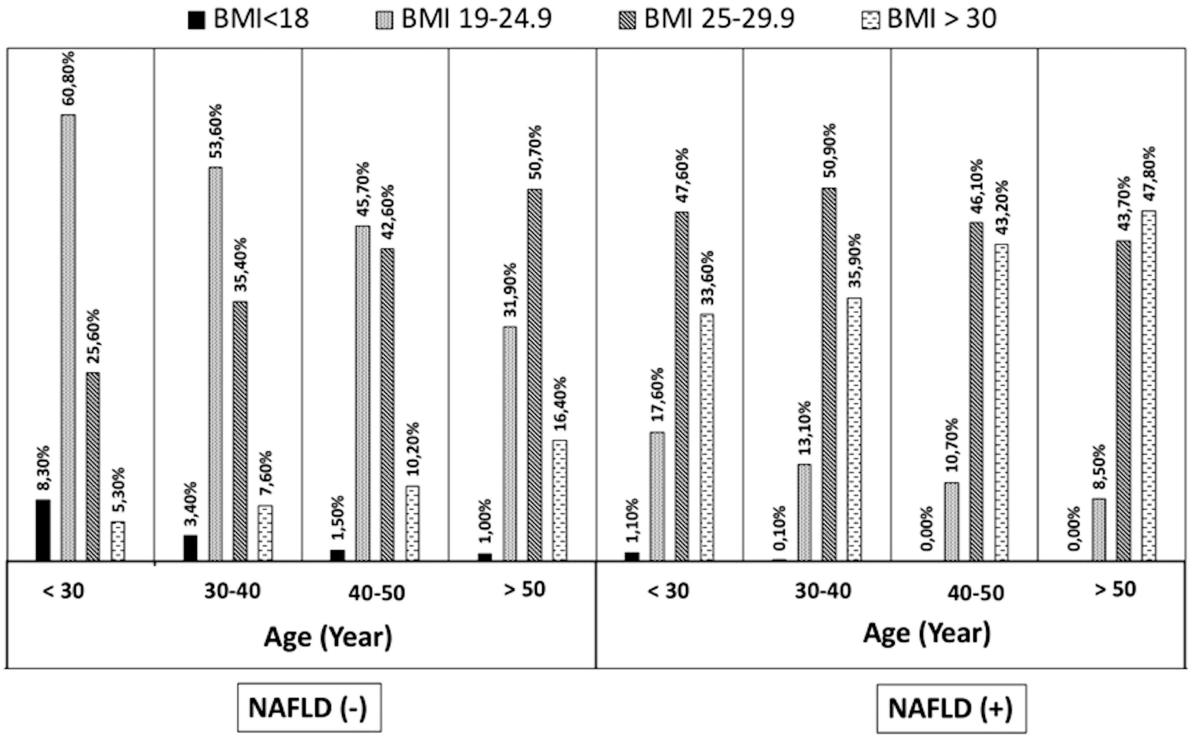

Figure 2. The distribution of BMI's according to age in NAFLD (+) and NAFLD (–) patients. BMI increases with age in both NAFLD (+) and (–) groups and NAFLD (+) patients had higher BMI in all age groups ($P < .001$).

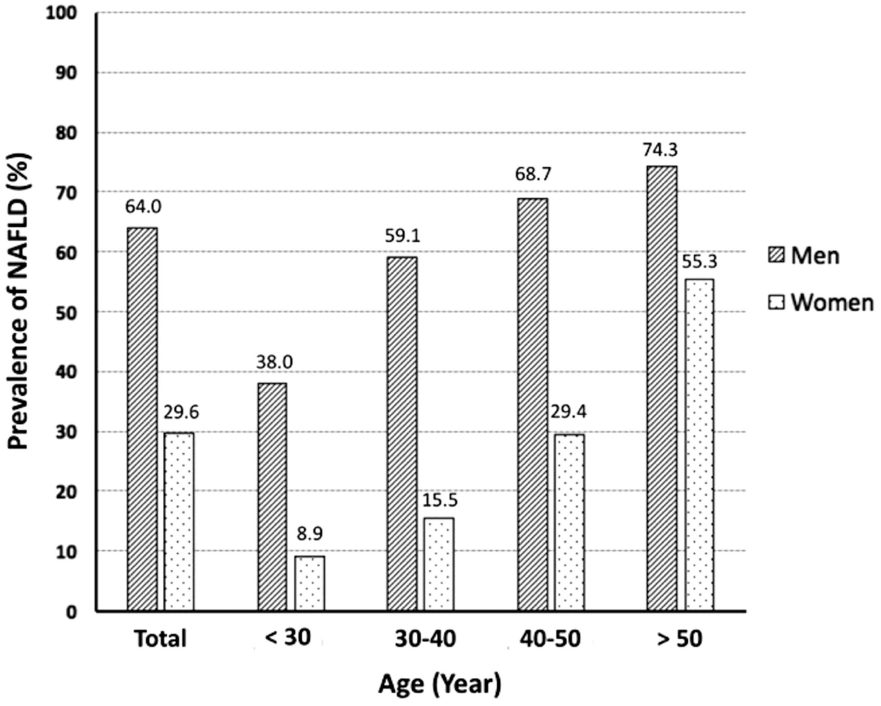

Figure 3. The prevalence of NAFLD according to sex and age groups. NAFLD was more prevalent in men overall and when both sexes were stratified according to different age groups. (*P* < .001 for overall and age groups <30 years vs. 30-40 years vs. 40-50 years vs. >50 years)

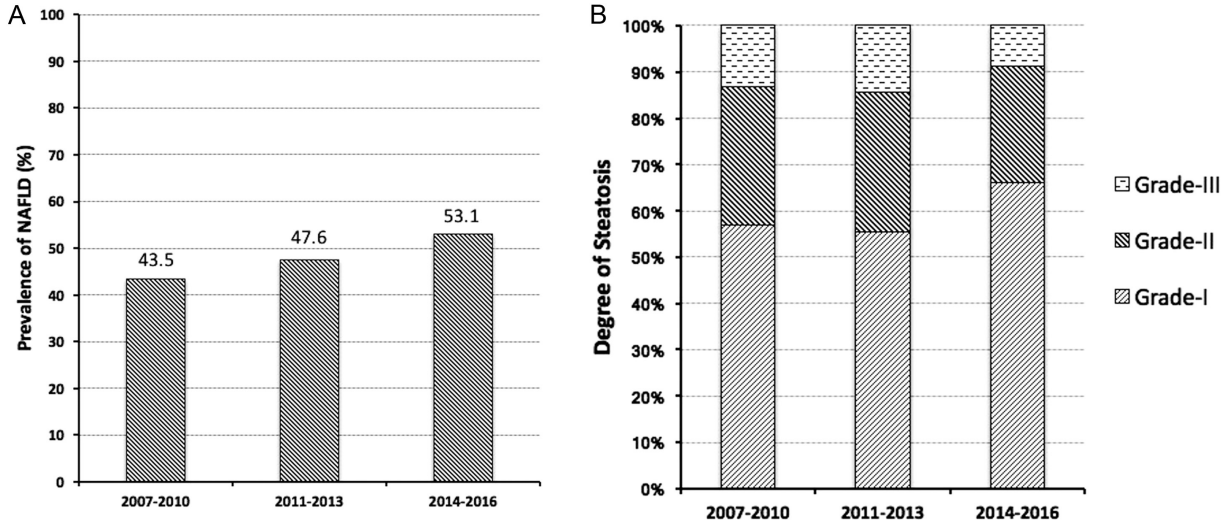

Figure 4 . The prevalence of NAFLD and degree of steatosis according to time. (a) The prevalence of NAFLD increased with time [(*P* < .001 for (2007-2010) vs. (2011-2013) vs. (2014-2016)]. (b) Grade I steatosis increased and grade III steatosis decreased in NAFLD (+) group (*P* > .05).

(*P* < .001), patients with dyslipidemia (*P* < .001), patients with hypertension (*P* < .001), higher serum ALT (*P* < .001), and higher BMI (*P* < .001) groups and showed regional differences (*P* < .001). Logistic regression analysis found that male sex [odds ratio (OR): 3.41, 95% CI (2.95-3.94), *P* < .001], serum ALT level [OR: 1.02, 95% CI (1.02-1.03), *P* < .001], older age [OR: 1.03, 95% CI (1.02-1.04), *P* = .002], high BMI [OR: 1.28, 95% CI (1.26-1.31), *P* < .001], presence of type 2 diabetes mellitus [OR: 1.65, 95% CI (1.26-2.16), *P* < .001], hypertension [OR: 1.35, 95% CI (1.09-1.67),

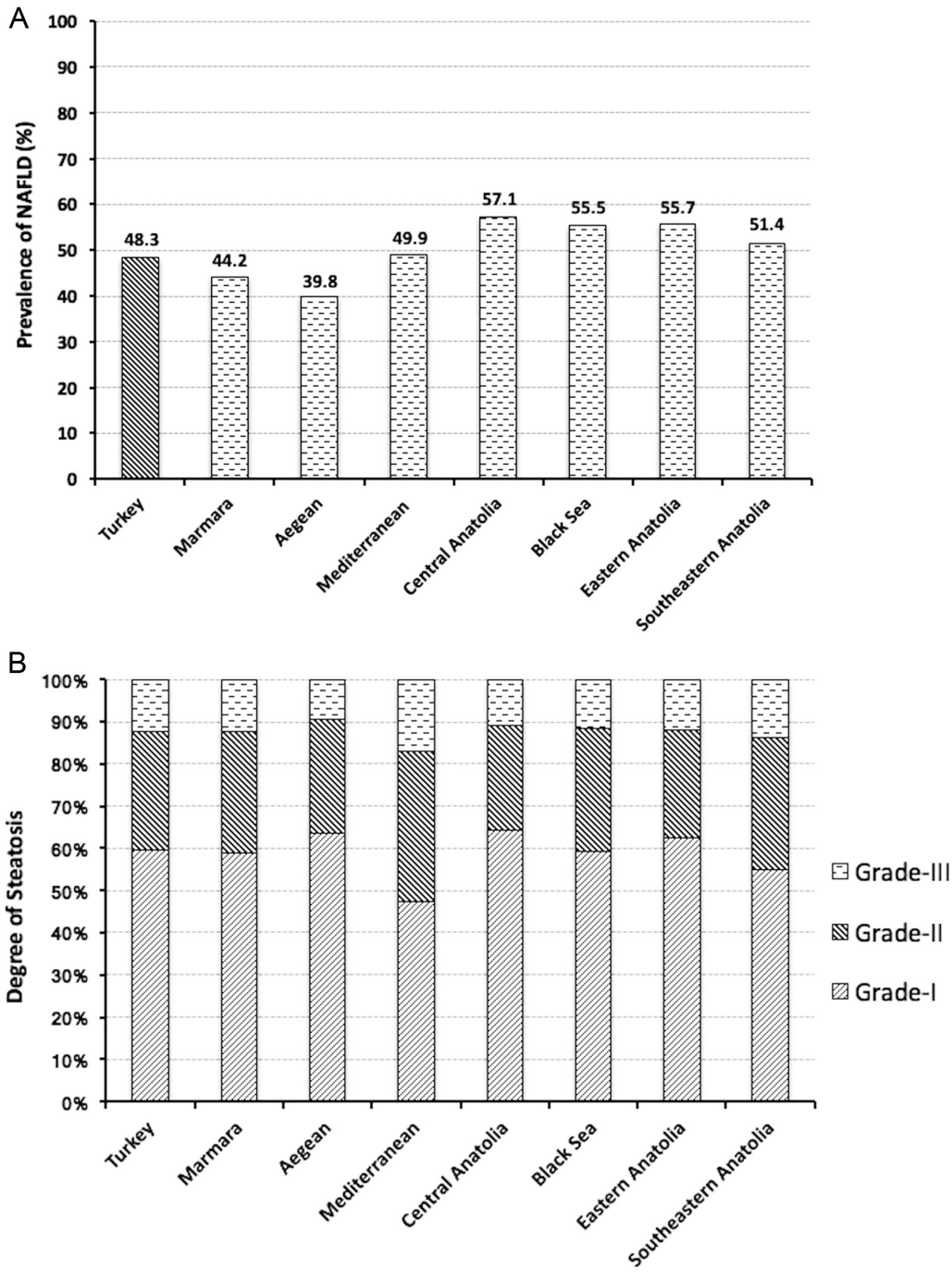

Figure 5. The distribution of NAFLD prevalence (a) and the degree of steatosis in NAFLD (+) patients (b) in different regions of the country [$P < .001$ for (a) and $P < 0.05$ for (b)].

$P=.006$], and dyslipidemia [OR: 1.37, 95% CI (1.12-1.67), $P < .001$] were factors associated with the presence of NAFLD. Regional differences, on the other hand, were not independently associated with NAFLD [OR: 1.02, 95% CI (0.99-1.05), $P=.151$] (Table 2).

DISCUSSION

In this hospital-based cross-sectional study, the data of a sample from 113 239 apparently healthy subjects from 15 different centers—located in 8 different cities—distributed across Turkey were analyzed and the prevalence of

Table 2. Analyses of Predictors for NAFLD Prevalence

	Univariate Analysis	Multivariate Analysis	
	P Value	Odds Ratio (95% CI)	*P* Value
Sex, male	<.001	3.41 (2.95-3.94)	<.001
Age	<.001	1.03 (1.02-1.04)	.002
Dyslipidemia	<.001	1.37 (1.12-1.67)	<.001
Diabetes mellitus	<.001	1.65 (1.26-2.16)	<.001
Hypertension	<.001	1.35 (1.09-1.67)	.006
BMI, kg/m^2	<.001	1.28 (1.26-1.31)	<.001
Serum ALT Level	<.001	1.02 (1.02-1.03)	<.001
Regions	<.001	1.02 (0.99-1.05)	.151

ALT, alanine aminotransferase; BMI, body mass index.

NAFLD in Turkey was found to be 48.3%. We also found that the prevalence increased with age and BMI was more common in male sex and showed a dramatic increase from 2007 to 2016. To the best of our knowledge, this is the first study to define the prevalence of NAFLD in a large cohort in Turkey.

There are 2 epidemiologic studies aiming to find the prevalence of diabetes mellitus (TURDEP-I and TURDEP II) and 3 nationwide studies on metabolic syndrome (TARF, METSAR, and PURETURKEY) in Turkey.[14-16] The mean age (43.03 ± 12.22), sex distribution (54.4% male to 45.6% female), rate of hypertension (14.3%), and over-weighted patient (67.8%) in our study were similar to the aforementioned studies, and the rates of the general population in Turkey. Although our study design is hospital-based and the subjects were collected from check-up units we believe our cohort is close to representing the general population in Turkey and thus the results of this study can be generalized to the general population in Turkey.

In our study, male patients had significantly higher rates of NAFLD in all age groups. We believe this was mostly due to the higher BMI rates that we saw in men (27.76 ± 4.05 for men vs. 25.8.3 ± 5.52 for women, $P < .001$), but despite the fact that men were more obese and overweight, the multivariate analysis still showed that male sex was an independent risk factor for NAFLD [OR: 3.41, 95% CI (2.95-3.94), $P < .001$]. These results are consistent with many previous studies in the literature.[17,18] In a large cohort study by Chen et al., data of 26 527 subjects were reviewed and the subjects taking medicine for high blood pressure, diabetes, and hyperlipidemia were excluded from the study. Although in our study we did not exclude these types of subjects the result of the aforementioned study were similar to our results (30.9% in men vs. 15.6% in women) and this difference again was independent of BMI level.[19] Similarly, in a study from Spain a total of 766 subjects from 25 primary healthcare centers were screened with liver ultrasound and NAFLD was found more common in men compared to women (33.4% vs. 20.3%). In this study, the authors also reported that male sex was an independent factor associated with NAFLD [OR: 2.34, 95% CI (1.57-3.49)] for NAFLD (17). Although most of the recent studies have reported that male sex is a risk factor for NAFLD, there are also some studies, especially from western countries, where a female predisposition for non-alcoholic steatohepatitis (NASH) (60-83%) has been reported.[20] It is interesting to know that the men and women groups in those studies had similar risk factors for NAFLD, which might suggest that there may be sex-specific pathophysiological factors playing role in the development of NAFLD and NASH. Some studies have shown that sex steroid hormone metabolism may be the reason for this difference.[7,17]

We also found that the prevalence and the severity of NAFLD increased dramatically with age. Many studies from different parts of the world have shown that increasing age is a risk factor for NAFLD.[21,22] In a study from Japan, age was found to be an independent risk factor for NAFLD in Japanese women.[23] In the United States, data from the NHANES-III showed that the peak prevalence of NAFLD was in the 4th decade for women and 6th decade for men.[24] Since many predisposing risk factors such as obesity, metabolic syndrome, and diabetes mellitus also increase with age, it is hard to comment on the independent effect of aging on NAFLD prevalence. We believe that the significant impact of age in our results might be related to the increase in BMI in older age groups. As shown in Figure 2 older NAFLD (+) subjects had a higher rate of BMI's over 25 kg/m^2 according to age (81.2%, 86.8%, 89.3%, and 91.5% for patients <30, 30-40, 40-50, and >50 years of age, respectively), but despite this fact in this study, older age was found to be an independent predictive factor for NAFLD as well [OR=1.089, 95% CI (1.008-1.177), $P=.002$]. Our results are also in accordance with another study from Turkey by Celebi et al performed in 2006, which found that the prevalence of NAFLD in the Elazıg-Turkey was 36.4% for people >50 years of age and 7.9% for people between 18 and 29 years of age.[10]

It is well known that diabetes and insulin resistance are closely linked to NAFLD through many pathophysiological pathways causing increased lipolysis of adipose tissue, which leads to excessive amounts of free fatty acid rushing to the liver and causing steatosis. In accordance with many other studies showing close associations with diabetes and dyslipidemia, we also found that type 2 diabetes mellitus (13.2% vs. 3.3%) and dyslipidemia (15.6% vs. 7.1%) were more common in NAFLD (+) group.[25,26]

Obesity is known to be the major risk factor for NAFLD and it is an increasing health problem in Turkey.[15] The prevalence of NAFLD in this study was 16.5% in non-obese individuals, 53.2% in those with a BMI between 25 and 30 kg/m^2, and 80.7% in those with a BMI over 30 kg/m^2. These results are in accordance with other studies where the prevalence of NAFLD was reported to be in the range of 57-98% in non-diabetic obese patients.[27,28] Even higher rates of NAFLD have been reported in obese patients with diabetes. In a recently published study, Demir et al. from Turkey investigated the prevalence of NAFLD using fibroscan in 124 diabetic patients (65% had obesity) and reported the prevalence of NAFLD as 94%.[29] TURDEP-I and TURDEP-II, performed in 2001 and 2012, are the biggest population-based studies done in Turkey on the prevalence of obesity and diabetes.[15,16] The latest TURDEP-II study showed that 45% of the general population in Turkey had a BMI above 30 and 75% had a BMI above 25 kg/m^2. This follow-up study clearly showed that the rate of increase for obesity was 40% and for diabetes mellitus was 90% in Turkey.[15] Our results are in accordance with this rising prevalence of obesity and diabetes in our country since we not only found a high prevalence rate of NAFLD in the general population but also found a significant increase in the rate of NAFLD from 43.5% to 53.1% from 2007-2010 to 2014-2016 time periods.

As expected, mean serum ALT levels were higher in the NAFLD group (22.57 ± 19.0 vs. 36.4 ± 25.01). Thirty percent of the patients in the NAFLD group had a serum ALT above the upper limit of normal while this was significantly lower in the NAFLD (–) group (8.1%). The upper limit of normal for serum ALT has been a topic of debate in recent years and studies have shown that factors such as gender and BMI have an impact on serum ALT levels. According to a very recent study, the upper limit of normal for serum ALT was determined as 32 U/L for men, 23 U/L for women in a healthy Turkish population.[30] If we take these values into account, 58 % of the patients with NAFLD would have ALT levels above the upper limit of normal. Although we do not have liver biopsy samples, based on previous literature data, we can assume that about 10% of the patients with simple steatosis will progress to NASH; which puts about 4.8% of the general population of Turkey at risk for NASH development.

The prevalence of NAFLD showed significant geographic differences ($P < .001$) in our study. However, it was not an independent risk factor for NAFLD in the regression analysis [OR: 1.02, 95%CI (0.99-1.05), $P=.151$]. The prevalence of NAFLD was highest in Central and Eastern Anatolia (57.1% and 55.5%) and lowest in the Aegean and Marmara Region (39.8% and 44.2%). Dietary and exercise habits and the rate of obesity in that specific region might be among the many potential explanations for this difference. Unfortunately, we do not have any data on the dietary habits and amount of exercise for each patient. However, when the mean BMI and the rate of obese and overweight population in these 7 different regions were analyzed, we could see that the rate of obesity showed a positive correlation with the prevalence of NAFLD. In parallel with the NAFLD prevalence, the rates of people with a BMI of >25 kg/m^2 were higher in Central Anatolia (69.4%) compared to the Aegean Region (61.1%). Based on these results, we believe that this geographical difference in NAFLD may be related to the rate of obesity in that region.

This study has some limitations. First, some of the patients were classified based on patient and physician reports as having diabetes mellitus, dyslipidemia, and no drug use since this was a retrospective study and data were collected from hospital medical check-up standard examination. Second, the diagnosis of NAFLD was based on ultrasound findings, which was performed by different radiologist at different time points, which might have led to observer bias. Thirdly, although we had patients from almost all parts of the country and the cohort' demographic data was similar to the general population, the study population may not be full representative of the general population, and lastly because it was impossible to collect data on where and how long they lived and regional differences were based on birthplace rather than the city they have lived.

In conclusion, we showed that NAFLD is a prevalent disease affecting almost half of the population in Turkey (48.3%); NAFLD prevalence increased from 43.5% to

53.1% (22% increase) in the past 10 years, parallel to the increase in obesity in Turkey. The prevalence shows geographic differences in relation to the BMI patterns of the region, being highest in Central and Eastern Anatolia and lowest in the Aegean and Marmara Region. A focused approach and immediate action should be put forward to reduce the rate of obesity and NAFLD in Turkey.

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