



Non-alcoholic fatty liver disease: A growing public health problem in Turkey

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is histologically classified as either non-alcoholic fatty liver or non-alcoholic steatohepatitis (NASH). NASH is the progressive subtype of NAFLD. Individuals with NASH are at significant risk of developing hepatic fibrosis, cirrhosis, hepatocellular carcinoma, and liver-related and all-cause mortality. NAFLD is closely associated with obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome, and cardiovascular events. Its prevalence is estimated to be above 30% in Turkey; and recent studies confirm this estimate. According to these studies, the prevalence of NAFLD in Turkey is between 48.3% and 60.1%. Currently, Turkey can be considered a risky region in terms of NAFLD burden as it is the most obese country in Europe with an obesity prevalence of 32.1% according to the 2016 World Health Organization data. Moreover, along with the increasing prevalence of obesity and T2DM in Turkey, the burden of NAFLD is estimated to increase in the upcoming decade. Despite the growing burden, we lack well-designed systemic studies that investigate NAFLD and its marked histological severity. In this review, we present studies on the burden of NAFLD and NASH, the natural history of NAFLD, and its association with other systemic diseases conducted with Turkish populations.

Keywords: Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, prevalence, Turkey

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is defined as the presence of hepatic steatosis (HS) diagnosed either by imaging or by histology after excluding the secondary causes of hepatic fat accumulation, such as significant alcohol consumption, use of steatogenic medication, and hereditary disorders (1). Histologically, NAFLD is divided into two types: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is a non-progressive subtype of NASH, whereas NASH is defined as HS with evidence of hepatocellular injury and inflammation, which carries a risk of progression to hepatic fibrosis and cirrhosis. NAFLD is frequently seen among patients with obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (MS) (1).

Non-alcoholic fatty liver disease is the most common etiology of chronic liver disease, with an estimated worldwide prevalence of 25%. NASH, the progressive subtype of NAFLD, is a major cause of cirrhosis, hepatocellular carcinoma (HCC), and liver-related deaths (2). Additionally, NASH is the second most common etiology of liver transplantation worldwide. In the last decade, NASH was the most common etiology among patients on the liver transplantation waiting list with a diagnosis of HCC (3).

According to the 2016 data released by the World Health Organization, Turkey has the highest obesity prevalence (32.1%) in Europe (4). Although few population-based studies have been conducted with Turkish populations, NAFLD prevalence in Turkey is estimated to be above 30%, in line with the high-obesity prevalence. In parallel with this estimation, Turkey is among the countries with the highest NAFLD prevalence (2). In this review, we aimed to present the available Turkish data on NAFLD prevalence, the natural history of the disease, and its association with other systemic diseases.

Prevalence of non-alcoholic fatty liver disease in Turkey

Liver biopsy is considered the reference standard for NAFLD detection. However, due to the invasiveness of the procedure, high cost, and patient discomfort, the use of liver biopsy in epidemiological studies is limited. Conventional ultrasonography, computerized tomography, magnetic resonance imaging (MRI), controlled attenuation parameter (CAP) by transient elastography (TE), and MRI-derived proton density fat fraction (PDFF-MRI) are the noninvasive methods used to detect HS. Due to the different diagnostic accuracies of these imaging methods, their use for NAFLD diagnosis can lead to over- or

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under-diagnosis of the study population (5). Here, we covered prevalence studies conducted with pediatric and adult Turkish populations in different years and using various diagnostic methods (Table 1).

Prevalence studies in Turkey conducted using imaging methods

In 2006, Celebi et al. (6) conducted a study in Elazığ, which is a rural region in Turkey, with 404 apparently healthy adults (mean age: 39.07 ± 13.8 years) using hepatobiliary ultrasonography as a diagnostic tool. In the study, NAFLD prevalence was found to be 19.8%. The low prevalence can be attributed to the fact that the study was conducted in 2006 and in a rural region. In 2010, Kasapoglu et al. (7) investigated vitamin D levels in patients with NAFLD diagnosed via ultrasonography excluding obese patients and patients with diabetes. This study was included in a meta-analysis of studies in Turkey, although it was not designed to investigate the prevalence of NAFLD. In the study, a prevalence of 55.4% was calculated by dividing patients with NAFLD by the sum of the control group and patients with NAFLD (8). Hence, the study by Kasapoglu et al. (7) is considered unsuitable for representing NAFLD prevalence in Turkey. More recently, in 2016, Okur et al. (9) conducted a study in a military hospital with 254 apparently healthy young individuals (median age: 27 years [21–41]) and found a prevalence of 10.6%. The study population consisted of male, probably non-sedentary individuals, with normal weight and normal serum aminotransferase levels, which is likely responsible for the low NAFLD prevalence. In a further study by Kaya et al. (10) published in 2016, NAFLD prevalence was reported as 23.2% in 112 apparently healthy young medical students (mean age: 20.5 ± 1.1 years) evaluated using CAP by TE (cut-off 238 dB/m). A higher prevalence was detected in the younger group due to the previously proven higher diagnostic performance of CAP in the detection of NAFLD (11,12). However, the prevalence in CAP-based studies is directly related to the cut-off value used for NAFLD detection. For instance, in a study among individuals diagnosed with NAFLD via ultrasonography, the cut-off for NAFLD was set to 222 dB/m, 238 dB/m, and 283 dB/m, resulting in a prevalence of 38.2%, 22.5%, and 4.9%, respectively (11).

Current studies are more successful at representing the Turkish population because they use larger study populations and include recent findings. A non-published study conducted by Degertekin et al. with 113,239 apparently healthy Turkish individuals, which was published in a review as personal comment of an author currently,

showed a prevalence of 48.3% in Turkey, and the NAFLD prevalence was detected as 63.5% in overweight individuals. The highest prevalence in Turkey was in Central Anatolia (57.1%) and in East Anatolia (55.7%). Additionally, the study showed a significant increase from 43.5% to 53.1% in NAFLD prevalence in the period between 2007 and 2016 (2). Another study was conducted between 2017 and 2018 in the Cappadocia region, which is thought to best represent the Turkish population due to low amounts of immigration to the region. Abdominal ultrasonography was performed on 2797 individuals, and 60.1% of the study population showed ultrasonographic findings compatible with HS. In this study, 61% of the participants were female, and the median age was 51 years. Additionally, 45% of the individuals were obese and 35% were overweight. These characteristics of the study participants may be related to the high prevalence of NAFLD (13).

Prevalence studies in Turkey conducted using liver biopsy

Biopsy-based NAFLD studies are affected by selection bias because liver biopsy is indicated in patients with high risk of NASH. Consequently, in such studies, the ability to show NASH prevalence among patients with NAFLD is problematic. Ultrasonography is more frequently preferred as a diagnostic tool in prevalence studies, whereas liver biopsy is important in terms of prognostic value to show the presence of NASH and the degree of fibrosis as well as to define the risk of progression to liver-related morbidity and mortality (14).

In 2006, 93 patients with biopsy-proven NAFLD from five different centers in East-Southeastern Anatolia (median age 38 [19–59] years, 76% male) were recruited for a study. Among the study population, 85% were overweight and 37% were obese. The levels of median alanine transaminase (ALT) and aspartate transaminase (AST) were 104.5 [27–429] U/l and 56.3 [26–184] U/l, respectively. Increased ALT levels were seen in 97.8% of the patients and increased AST levels in 61%. However, these values were expected because patients with elevated liver enzymes were referred to liver biopsy. Furthermore, 18% of the patients had T2DM and 80.6% hyperlipidemia. None of the patients were diagnosed with simple steatosis. Fifty-five patients (59.1%) had fibrosis and 10.8% of them were classified as severe according to Brunt classification (15).

Although NAFLD is more likely to be associated with obesity, it is also present among non-obese individuals. In a study conducted with 483 patients with biopsy-proven

Table 1. Prevalence studies about non-alcoholic fatty liver disease conducted in Turkey

	Çelebi S et al. (6) (2006)	Degertekin B et al. (2) (2007-2016)	Yüksel F et al. (19) (2012)	Okur G et al. (9) (2012-2014)	Demir M et al. (30) (2015-2017)	Kaya E et al. (10) (2016)	Sezgin O et al. (13) (2017- 2018)	Tutar E et al. (20) (2018)	Yılmaz Y et al. (2009-2010 and 2017- 2018) (17)
Diagnostic Method	USG	USG	Postmortem biopsy	USG	Fibroscan	Fibroscan	USG	USG, Fibroscan, MR spectroscopy, biopsy	USG, biopsy
Study population (n)	404	113239	330	254	124	112	2797	48	468
NAFLD prevalence	19.8%	48.3%	6%	10.6%	94.3%	23.2%	60.1%	100%	100%
Age (years)	39.07±13.8	43.03±12.22	[2-20]	27 [21-41]	53±7	20.5±1.1	52	13±2.6	47 [17-71]
Gender (male%)	48.8%	54.4%	-	100%	37%	57.1%	39%	70%	47.9%
BMI (kg/m ²)	Male: 25.7±3.1 Female: 26.4±5.4	26.91±4.88	-	24 [19-25]	33.2 ± 6.6	22.4±3.1	29.6	29.5±4.8	31.72±5.12
T2DM	2.7%	8.1%	-	-	100%	-	-	-	33.5%
Metabolic syndrome	-	-	-	-	77.4%	-	-	-	63%
AST (U/l)	Male: 24.1±11.0 Female: 18.3±8.6	-	-	21 [10-34]	23 (18-32)	-	-	-	42.0 [15-302]
ALT (U/l)	Male: 23.1±19.8 Female: 15.5±9.2	29.26±22.43	-	19 [7-45]	26 (20-48)	-	-	-	66.0 [12-483]
CAP (dB/m)	-	-	-	-	317±54	205.6±43.8	-	S1: 283±42 S2: 318±54 S3: 320±35	
LSM (kPa)	-	-	-	-	7.1±3.4	4.7±0.9	-	F<2: 6.2±1.67 F≥2: 7.8±2.85	
Steatosis	-	Stage 1: 59% Stage 2: 28.6% Stage 3: 12.4%	-	-	Mild: 0 Moderate: 29 Severe: 88	-	Mild: 53.3% Moderate: 38.8% Severe: 7.9%	S1: 27.1% S2: 16.7% S3: 56.3%	Stage 1: 25% Stage 2: 55% Stage 3: 20%
Fibrosis	-	-	-	-	F≥3: 16.9% F=4: 8%	-	-	F0: 39.6% F1: 35.4% F2: 16.7% F3: 8.3%	F≥2: 35% F≥3: 17.5% F=4 3.8%
NASH	-	-	-	-	-	-	-	60.4%	90.4%

USG: Ultrasonography, MR: Magnetic resonance, NAFLD: Non-alcoholic fatty liver disease, BMI: Body mass index, T2DM: Type 2 diabetes mellitus, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CAP: Controlled attenuation parameter, LSM: Liver stiffness measurement, S: Steatosis, F: Fibrosis, NASH: Non-alcoholic steatohepatitis

NAFLD, the prevalence of lean NAFLD was 7.6%. In the study, lean patients with NAFLD had higher hemoglobin levels compared to obese and overweight patients with NAFLD. Moreover, they were younger, were less likely to have MS, and had lower mean blood pressure (16).

The patient demographics from a more recent study (data collection between 2009–2010 and 2017–2018) conducted with 468 patients with biopsy-proven NAFLD was as follows. The median age was 47 [18–71] years, and the male to female ratio was 224/244. Among the 468 patients, 61% were obese and 32.6% overweight. The T2DM and MS rates were 33.5% and 63%, respectively. The median ALT (elevated in 76.9%) and AST (elevated in 61.2%) levels were 42 [15–302] U/l and 66 [12–483] U/l, respectively. According to the SAF/FLIP algorithm, 90.4% of the patients were diagnosed with NASH. Finally, according to their NASH CRN (Kleiner) scores, 66.9% could be characterized as definite NASH, 28.6% as borderline NASH, and 4.5% as simple steatosis (17).

Prevalence studies in Turkey conducted with pediatric populations

Non-alcoholic fatty liver disease is as prevalent in pediatric populations as in adults, with an estimated prevalence of 9.6%. Due to the growing epidemic of childhood obesity in Westernized countries, NAFLD has become the most common etiology for chronic liver disease in pediatric populations (18). The burden of NAFLD in the Turkish pediatric population is also not to be underestimated.

A liver biopsy study performed during the autopsy of 330 Turkish children and adolescents (age: 2–20 years) revealed a NAFLD prevalence of 6%. Among the study population, 66 were obese. NAFLD prevalence was 10.6% in the obese children and 4.9% in children with normal weight. The prevalence was significantly higher in obese children ($p < 0.001$) (19).

In recent unpublished research from Turkey, 48 children (43 of them were obese and all of them had high transaminase levels) with suspected NAFLD in ultrasonographic and laboratory examination underwent liver biopsy for confirmation of the diagnosis. According to the Kleiner classification, most of the patients had NASH, whereas only 10% had simple steatosis or non-NASH. Based on the liver biopsy results, 60.4% were diagnosed with NASH, with 35.4%, 16.7%, and 8.3% having stage 1, stage 2, and stage 3 fibrosis, respectively. It is noteworthy that over 60% of the cases had evidence of fibrosis. Even more importantly, 25.0% of the patients showed significant fibrosis (20).

As in adults, NAFLD is associated with obesity and metabolic syndrome in pediatric populations. In studies conducted with obese children, NAFLD prevalence was around 48.1%–60.8% (21–23). Moreover, a study by Boyraz et al. (21) examined the relationship between NAFLD and MS in children. In the study, the prevalence of MS, abdominal obesity, hypertension, impaired fasting glucose, hyperinsulinemia, dyslipidemia, and T2DM was 21.3%, 61.8%, 25.7%, 4.4%, 54.3%, 41%, and 2.2%, respectively. The criteria for MS are significantly associated with NAFLD presence. Additionally, the severity of hepatic steatosis is positively correlated with an increased number of MS criteria (21).

Non-alcoholic fatty liver disease and its association with other systemic diseases conducted with Turkish adults

Type 2 diabetes mellitus

The close association of NAFLD with T2DM and insulin resistance is well known. Additionally, patients with T2DM have an increased risk of liver-related morbidity like fibrosis, cirrhosis, hepatocellular carcinoma, and liver-related death. Similarly, patients with NAFLD have a higher risk of developing T2DM (24–26).

Since 1980, there has been a nearly two-fold increase in the prevalence of T2DM. In the East Mediterranean region, where Turkey stands, the prevalence of T2DM is significantly higher than in other regions (27). According to the TURDEP I (28) and TURDEP II (29) studies conducted to detect T2DM prevalence in Turkey, the prevalence of DM increased from 7.2% to 16.5% in 12 years, showing a 90% increase.

In a CAP study conducted using Fibroscan with 124 patients with T2DM (mean age 53 ± 7 years) in Turkey, 94.3% of the patients were diagnosed with NAFLD. In the study population, 64.5% was obese, 28.2% overweight, and 77.4% had MS (30). Likewise, in prediabetics, there is a tendency to develop NAFLD as frequently as in diabetics. The rate of T2DM in 280 patients with biopsy-proven NAFLD was 32.8%, whereas that of prediabetes was 36.4%. Liver histology showed increased fibrosis and portal inflammation in both groups (31).

Metabolic syndrome

Non-alcoholic fatty liver disease is known as a hepatic manifestation of MS due to its frequent co-existence with MS. However, not all patients with NAFLD fulfill the criteria of MS, nor do all patients with MS have NAFLD (32). A study conducted with 81 patients with biop-

sy-proven NAFLD showed a non-significant difference of progression to NASH in a comparison of two groups with and without MS. In other words, NASH can develop independently from the presence of MS (33).

A further study involving 357 consecutive patients with biopsy-proven NAFLD demonstrated that NASH development is more frequent among patients with NAFLD with MS. However, the prevalence of fibrosis was not significantly different between patients with and without MS. In the study, increased hemoglobin levels were significantly associated with the presence of NASH and liver fibrosis in the group without MS. Therefore, the authors concluded that increased hemoglobin levels in patients with NAFLD without MS could be an indicator of a probability to progress to NASH; and liver fibrosis and further histological assessment must be considered in these patients (34).

Cardiovascular disorders

Cardiovascular disorders are the main etiology of mortality among patients with NAFLD (35). In addition, there is a strong association between the presence of NAFLD and endothelial dysfunction, which occurs during the early stages of atherosclerosis (36).

Previous Turkish studies have shown that NAFLD is associated with endothelial dysfunction (37), which is worse if the patients have NASH (38) and negatively correlates with the degree of steatosis (39). Additionally, a study conducted with young men demonstrated that NAFLD is associated with worsened endothelial function and increased risk of developing atherosclerosis independent from MS (40).

Furthermore, NAFLD leads to significant changes in vessel functionality. A study by Oguz et al. (41) showed that patients with NAFLD had a significantly lower aortic flow propagation velocity. Another study demonstrated that coronary flow velocity reserve is significantly impaired in patients with NAFLD (42,43). NAFLD also has significant effects on the heart itself. The heart rate recovery index is deteriorated in patients with NAFLD, and this might be related to cardiovascular death (44). Right ventricular function is also found to be impaired in patients with NAFLD. In those patients, NASH score plays role in predicting right ventricular function (45).

Natural history of non-alcoholic fatty liver disease in Turkey

There is no published data from Turkey regarding the natural history of NAFLD. However, there are a couple of unpublished studies.

Idilman et al. conducted a study involving 53 patients with NAFLD with paired liver biopsies. The median follow-up time was 33 [11–114] months. Fibrosis stages at the beginning were as follows: F0: 62.3%, F1: 24.5%, F2: 7.5%, F3: 5.6%, and F4: 0%. During the follow-up period, 24.5% of the liver biopsies showed progression, 13.2% regression, and 62.3% stayed stable (IR 2019). However, the median follow-up time was not enough to show the natural history of NAFLD in this research.

In unpublished research by Yılmaz et al. including nine patients with NASH with paired liver biopsies, the median follow-up time was 96 [84–99] months. In the study, 44.4% of the patients showed progression in their fibrosis scores, whereas 55.5% of the patients had no changes (YY 2019).

CONCLUSION

In line with the growing obesity epidemic and increasing prevalence of T2DM, NAFLD represents a major public health issue in Turkey due to its higher obesity rates compared to the world in general. The growing burden of NAFLD is underscored by its marked histological severity in terms of NASH and fibrosis. Well-designed systemic studies are needed to mitigate the growing burden of NASH. Finally, national health policies must be developed against NAFLD and its complications.

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