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Prevalence of non-alcoholic fatty liver disease is not increased in patients with celiac disease: a cross-sectional study

Çölyak hastalarında non-alkolik yağlı karaciğer hastalığı yaygınlığı artmıyor: Kesitsel çalışma

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Abstract

Objective: Celiac disease (CD) is associated with liver diseases and could be associated Non-alcoholic fatty liver disease (NAFLD) due both diseases have same etiopathogenetic risk factors such as altered gut microbiota and intestinal permeability. Despite this tight association of these disease, there are few studies on this subject. Therefore, we aimed to determine the prevalence of NAFLD in patients with celiac disease.
Material and Methods: This cross sectional, was carried out in a tertiary health center. The aim of the study is to determine the frequency of NAFLD in CD patients treated with a gluten-free diet (GFD) for at least 6 months. The secondary aim was to assess the relative risk of NAFLD in CD patients treated with a GFD for at least 6 months. Patients with diagnosed CD and a GFD was initiated at least 6 months before were included the study as a group A. The control group (group B) was selected from the outpatients who applied to our polyclinic with dyspepsia. Hepatosteatosis was diagnosed by ultrasonographic examination.
Results: Group A and Group B were similar in terms of age, gender frequency, body mass index (BMI) and presence of diabetes mellitus. The frequency of NAFLD was 22.7% in Group A and 28.1 in Group B (P = 0.35). Advanced age, high BMI, high blood sugar, presence of DM was a risk factor for NAFLD.
Conclusion: Individuals with celiac disease are not at increased risk of nonalcoholic fatty liver disease compared to the general population.

Keywords: Ultrasonography, non-alcoholic fatty liver disease, celiac disease.

Öz

Amaç: Çölyak Hastalığı (CH), karaciğer hastalıklarıyla ilişkilidir. Her iki hastalıkta; bağırsak mikrobiyotasında değişiklik ve bağırsak geçirgenliği gibi aynı etiyopatogenetik risk faktörlerine sahip olması nedeniyle alkolik olmayan yağlı karaciğer hastalığı (AOYKH) ile ilişkilendirilebilir. Bu hastalıkların bu yakın lişkisine rağmen, bu konuda çok az çalışma yapılmıştır. Bu nedenle, biz çalışmamızda ÇH olan hastalarda AOYKH yaygınlığını belirlemeyi amaçladık.
Gereç ve Yöntem: Kesitsel nitelikte çalışmamız; üçüncü basamak bir sağlık merkezinde gerçekleştirildi. Çalışmanın ilk amacı, en az 6 ay boyunca glutensiz diyet ile tedavi edilen ÇH AOYKH sıklığını belirlemektir. İkincil olarak da; en az 6 ay boyunca glütensiz diyet ile tedavi edilen ÇH AOYKH'nın göreceli riskini değerlendirmektir. Tanısı konulmuş ÇH ve en az 6 ay önce glutensiz diyet başlatılmış hastalar çalışmaya Grup A olarak alındı. Kontrol grubu (Grup B), polikliniğimize dispepsi ile başvuran ayaktan hastalar arasından seçildi. Hepatosteatoz, ultrasonografik inceleme ile teşhis edildi.
Bulgular: Grup A ve Grup B, yaş, cinsiyet, vücut kitle indeksi (VKİ) ve diabetes mellitus (DM) varlığı açısından benzerdi. Alkolik olmayan yağlı karaciğer hastalığı sıklığı Grup A'da %22,7 iken, Grup B'de %28,1 idi (P = 0,35). İleri yaş, yüksek VKİ, yüksek kan şekeri, DM varlığı AOYKH için bir risk faktörüydü.
Sonuç: Çölyak hastalığı olan bireyler, genel popülasyona kıyasla alkolik olmayan yağlı karaciğer hastalığı açısından artmış risk altında değildir.

Anahtar Kelimeler: Ultrasonografi, alkolik olmayan yağlı karaciğer hastalığı, çölyak hastalığı.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common cause of chronic liver disease in the worldwide. The worldwide prevalence of NAFLD ranges from 6.3% to 33%, with a median of 20% in the general population, based on the assessment method (1). Non-alcoholic fatty liver disease has a wide spectrum of liver pathology from simple steatosis to the necroinflammatory disorder named as nonalcoholic steatohepatitis (NASH), to cirrhosis and liver cancer. Non-alcoholic fatty liver disease is excessive fat build-up in the liver (more than %5 of the liver) without another clear cause such as alcohol use. Non-alcoholic fatty liver disease shows increased echogenicity, or 'bright liver' and blurring of vessels by hepatic ultrasound. Non-alcoholic fatty liver disease is frequently associated with metabolic disorders such as insulin resistance, obesity, type 2 diabetes mellitus. There are two types of NAFLD; non-alcoholic fatty liver (NAFL) which has just simple steatosis without ballooning degeneration and NASH which has liver inflammation (2). However, NAFL may not be considered dangerous according to NASH because mortality rate of NAFL did not increase compared to healthy society and it rarely and slowly progress to NASH or liver cirrhosis. Non-alcoholic fatty liver disease has progress to liver cirrhosis and hepatocellular carcinoma and with so many comorbid diseases such as colorectal carcinoma, polycystic over syndrome, sleep-apnea disease etc.

Most effective treatment of NAFLD is weight loss by changing of lifestyle such as dietary changes and exercise. There is no universally accepted effective pharmacological options but pioglitazone and vitamin E can be recommended in selected cases (2-4).

Celiac disease (CD) is a chronic immune disorder that primarily affects the small intestine. Gastrointestinal symptoms such as chronic diarrhea, abdominal distention, malabsorption, growth and developmental retardation are the main symptoms of celiac disease. However, originally, it was thought to have a childhood disease, now it is known that it may develop at any age (5).

Celiac disease is immune-mediated enteropathy that is precipitated by dietary gluten in genetically predisposed individuals. Gluten is the commonly used term for the complex of water-insoluble proteins from wheat, rye, and barley that is harmful to patients with celiac disease. Upon exposure to gluten, an abnormal immune response may lead to the production of several different autoantibodies that can affect number of different organs particularly small intestine. The villus atrophy of the small intestinal mucosa due to abnormal immune response causes malabsorption of nutrients. Diagnosis is typically made by a combination of blood antibody tests and intestinal biopsies by gastrointestinal endoscopy. Treatment is a gluten-free diet (GFD). After adhering to the GFD, clinical and subsequent histological improvement occurs and clinical and histologic relapse when gluten is reintroduced (6). Abnormal liver test sometimes can be single clinical sign of CD. Furthermore, Primary Biliary Cholangitis, Primary Sclerosing Cholangitis and Autoimmune Hepatitis may be associated with CD. Impaired absorption and resultant malnutrition in CD may lead to deposition of fat in the liver, related, in part, to reduced fat mobilization from hepatocytes (7). Increased intestinal permeability and dysbiosis in celiac disease may be risk factors NAFLD. Although it is known that fatty infiltration of liver in patients with CD since the early 1980s, there are few studies on this subject (8-10).

Therefore, we aimed to determine the prevalence of NAFLD in patients with celiac disease.

Material and Methods

We performed a retrospective analysis database of adult CD patients who were consecutively diagnosed at Gaziosmanpasa University Hospital which is tertiary Health center, between May 2017 and 31 April 2021. One hundred and sixty-two outpatients were enrolled and grouped as CD (Group A) and controls (Group B). Eight patients were not in accordance with gluten free diet and we could not find laboratory and radiological data of 44 patients. Finally, 110 patients with CD were enrolled as CD

group. Patients were matched for demographic characteristics (age and gender) and metabolic risk factors (overweight, diabetes mellitus, total cholesterol, and triglycerides) using a case: control 1:1 ratio.

The aim of the study is to determine the frequency of NAFLD in CD patients treated with a GFD for at least 6 months. The secondary aim was to assess the relative risk of NAFLD in CD patients treated with a GFD for at least 6 months.

Inclusion criteria were: 1, diagnosis of CD with positivity anti-transglutaminase IgA and classical sign of CD with histopathologically; 2, a GFD was initiated at least 6 months before enrolment; 3, availability of demographical data and biochemical laboratory tests including low density lipoprotein (LDL) and high-density protein (HDL) cholesterol, serum triglycerides and aminotransferases and radiological images.

Exclusion criteria: 1, incomplete compliance to the GFD; 2, alcohol consumption; 3, diagnosed with any other liver disease; 4, pregnancy.

The control group was selected from the outpatients who applied to our polyclinic with dyspepsia. Abdominal ultrasonography evaluation is performed in all patients admitted to our clinic with dyspeptic symptoms. Data of these patients were examined and recorded. Height and weight measurements of all patients were recorded and body mass index (BMI) was calculated as weight in kg/square of height in meters. Blood glucose, triglyceride (TRG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels of all patients were recorded. Co-morbidity as diabetes mellitus was recorded.

Hepatosteatosis was diagnosed non-invasively and defined high level echoes arising of hepatic parenchyma and liver kidney difference in echo amplitude by ultrasonographic examination.

This study was approved by the XXX University Ethical Committee XXX and performed according to the Declaration of Helsinki guidelines. Because of its retrospective design, no participant was contacted and all data were anonymized prior to data analysis.

Statistical Analysis

Statistical analyses were conducted using SPSS (Version 22.0, SPSS Inc., Chicago, Illinois, United States). Continuous data were expressed as mean ± standard deviation; categorical data were presented as numbers and percentages (%). Student's t-test or the Mann–Whitney U test was used to compare the group means of the patient and control groups when the data were normally distributed. A chi-square test was used to compare the proportions between the groups. Multivariate logistic regression analysis was performed to identify independent factors of NAFLD by using Manova test. P-values less than 0.05 was considered to be statistically significant.

Results

Group A and Group B were similar in terms of age, gender frequency, body mass index (BMI) and presence of DM, p values were 0.5, 0.65, 0.2, 0.6, respectively. The frequency of NAFLD was 22.7% in Group A and 28.1 in Group B, and there was no statistically significant difference (P = 0.35) (Table 1).

Table 1. Demographic, clinical characteristic and frequency of non-alcoholic fatty liver disease (NAFLD) in all study group

	Group A (n:110)		Group B (n:110)		P
Gender (F/M)	78/32		74/36		0.5
Age (y)	42.4 ± 14.6		46.0±14.4		0.065
BMI (kg/m^2)	23.9 ± 4.1		24.5±3.4		0.2
Glucose	100.4 ± 25.6		105.4 ± 27.4		0.1
LDL (mg/dl)	109.6 ± 55.2		115.9±35.1		0.3
HDL (mg/dl)	52.3 ± 15.9		52.6±11.6		0.1
TRG (mg/dl)	111.8 ± 54.2		128.38±98.7		0.8
AST (IU/dl)	22.3 ± 10.6		19.4±7.0		0.02
ALT (IU/dl)	20.6 ± 12.3		21.1±13.4		0.8
DM (n, %)	21	19.1	24	21.8	0.6
NAFLD (n, %)	25	22.7	31	28.1	0.35

BMI = body mass index; LDL = low-density lipoproteins; HDL = high-density lipoproteins; TRG = triglyceride; AST = aspartate aminotransferase; ALT = alanine aminotransferase; DM = Diabetes Mellitus;

When the demographic data and metabolic risk factors of who diagnosed with NAFLD and whose did not in the whole study group are examined, advanced age (P = 0.002), high BMI (P = < 0.001), high blood sugar (P = < 0.001), high LDL (P = 0.01), the presence of DM (P = 0.004) were risk factors.

The mean AST and ALT levels were statistically significant higher in patients with NAFLD than those without NAFLD (P = < 0.004 and P = < 0.001, respectively) (Table 2).

Table 2. Risk factors for non-alcoholic fatty liver disease (NAFLD) in all study groups

	With NAFDL (n = 63)		**Without NAFDL (n = 157)**		**P**
Gender (F, M)	19/44		46/111		0.89
Age (y)	51.9 ± 10.8		41.6 ± 14.8		0.002
BMI (kg/m^2)	28.9 ± 3.9		24.0 ± 4.1		0.00
Underweight (n, %)	0	0	17	10.1	
Normal weight (n, %)	13	23.2	104	63.4	0.00
Overweight (n, %)	31	55.3	34	20.7	
Obesity (n, %)	12	21.4	9	5.4	
Glucose	115.8 ± 36.1		100.0 ± 24.6		0.00
Normal Glucose (n, %)	24	15,3	42	66.3	0.01
High Glucose (n, %)	134	84,7	21	33.7	
LDL (mg/dl)	127.2 ± 35.6		108.5 ± 50.3		0.01
Normal LDL (n, %)	111	70.4	36	55.3	
High LDL (n, %)	46	44.7	27	29.6	0.03
HDL (mg/dl) (n, %)	49.3 ± 12.3		50.2 ± 13.2		0.9
TRG (mg/dl)	144.1 ± 85.4		113.7 ± 86.7		0.07
Normal TRG (n, %)	51	80.9	142	90.2	0.5
High TRG (n, %)	12	19.1	15	9.2	
AST (IU/dl)	23.7 ± 12.3		20.2 ± 7.2		0.004
Normal AST (n, %)	58	92	152	96.8	0.04
High AST (n, %)	5	8	5	3.2	
ALT (IU/dl)	27.6 ± 16.0		18.5 ± 9.8		0.000
Normal ALT (n, %)	48	76.1	148	94.2	0.01
High ALT (n, %)	15	23.9	9	5.8	
DM (n, %)	21	33.9	24	15.8	0.004

BMI = body mass index; LDL = low-density lipoproteins; HDL = high density lipoproteins; TRG = triglyceride; AST = aspartate aminotransferase; ALT = alanine aminotransferase; DM = Diabetes Mellitus.

When we performed the subgroup analysis, there was no underweight patient in the fatty liver group and 76% of the NAFLD groups were overweight or obese. In the non-NAFLD group, overweight and obese individuals comprised only 25% of the entire group. Again, when subgroup analysis was performed, the number of patients with high glucose level, high LDL level, high AST and high ALT levels in the NAFLD group were statistically significantly higher than the control group (Table 2). When multivariate analysis was performed for NAFLD in the whole study group, age, BMI, LDL, ALT and AST were found to be significantly higher, DM comorbidity was significantly higher in NAFLD group (Table 3).

Table 3. Univariate-multivariate analysis of risk factors for non-alcoholic fatty liver diseases (NAFLD) in all study groups

	Univariate (P)	**Multivariate (P)**
Age	0.002	< 0.001
BMI	< 0.001	< 0.001
Glucose	< 0.001	0.001
LDL	0.01	0.02
AST	0.004	0.033
ALT	< 0.001	< 0.001
DM	0.004	0.02

BMI = body mass index; LDL = low-density lipoproteins; AST = aspartate aminotransferase; ALT = alanine aminotransferase; DM = Diabetes Mellitus.

When the demographic data and metabolic risk factors of the patients with and without NAFLD diagnosis in the CD group were examined, advanced age, high BMI, high blood sugar, presence of DM was a risk factor, p values were 0.025, 0.007, 0.04, 0.04, respectively. Mean AST level was significantly higher in patients with NAFLD than those without (P = 0.02) (Table 4).

Table 4. Risk factors for Non-Alcoholic Fatty Liver Diseases (NAFLD) in Celiac Disease (CD) groups

	With NAFDL (n = 9)		**Without NAFDL (n = 101)**		**P**
Gender (F, M)	4/5		73/28		0.08
Age (y)	50.7 ± 12.6		39.0 ± 15.1		0.025
BMI (kg/m^2)	23.3 ± 1.8		21.5 ± 1.8		0.007
Underweight	0	0	15	14.8	0.03
Normal weight (n, %)	8	88.8	85	84.7	
Overweight (n, %)	1	11.2	1	0.9	
Obesity (n, %)	0	0	0	0	
Glucose	117 ± 36.2		98.7 ± 24.5		0.04
Normal Glucose	3	33.3		88.1	
High Glucose	6	66.6		11.9	
LDL (mg/dl)	133.8 ± 45.1		102.1 ± 53.7		0.1
Normal LDL (n, %)	4	44.4	19	18.8	0.03
High LDL (n, %)	5	55.5	82	81.2	
HDL (mg/dl) (n, %)	46.1 ± 16.9		50.9 ± 12.9		0.9
TRG (mg/dl)	134.4 ± 62.9		114.7 ± 100.9		0.6
Normal TRG (n, %)	5	55.5	97	96	0.5
High TRG (n, %)	4	44.4	4	3.9	
AST (IU/dl)	28.3 ± 12.3		20.4 ± 7.7		0.02
Normal AST (n, %)	8	88.8	98	97	0.2
High AST (n, %)	1	11.1	3	2.9	
ALT (IU/dl)	23.3 ± 9.1		18.4 ± 10.6		0.1
Normal ALT	8	88.8	94	93	0.64
High ALT	1	11.1	7	6.9	
DM (n, %)	4	44.4	17	16.8	0.04

BMI = body mass index; LDL = low-density lipoproteins; HDL = high density lipoproteins; TRG = triglyceride; AST = aspartate aminotransferase; ALT = alanine aminotransferase; DM = Diabetes Mellitus.

When multivariate analysis was performed for NAFLD in the CD group, BMI, glucose, AST were found to be significantly higher, and DM association was significantly higher (Table 5). When the demographic data and metabolic risk factors of patients with and without NAFLD, in the control group were examined, advanced age, high BMI, high blood sugar, high LDL, DM comorbidity were risk factors, p values were 0.08, < 0.001, < 0.001, 0.045, 0.004, respectively. The mean of AST and ALT levels in patients with NAFLD were significantly higher than those without (P = 0.006 and P = < 0.001, respectively) (Table 6).

Table 5. Univariate-multivariate analysis of patients with and without non-alcoholic fatty liver diseases (NAFLD) in the celiac disease (CD) group

	Univariate (P)	**Multivariate (P)**
Age	0.002	0.25
BMI	0.007	0.007
Glucose	0.04	0.04
AST	0.004	0.023
DM	0.04	0.044

BMI = Body Mass Index; AST = aspartate aminotransferase; DM = Diabetes Mellitus.

Table 6. Multivariate analysis of risk factors for non-alcoholic fatty liver diseases (NAFLD) in the control group

	With NAFDL (n = 31)		**Without NAFDL (n = 79)**		**P**
Gender (F, M)	21/10		56/23		0.89
Age (y)	52.5 ± 10.8		45.4 ± 14.1		0.08
BMI (kg/m^2)	29.3 ± 3.9		25.5 ± 4.6		0.00
Underweight	0	0	4	5	0.00
Normal weight (n, %)	5	16	34	43	
Overweight (n, %)	16	51	23	29	
Obesity (n, %)	10	32	18	22	
Glucose	123.1 ± 41.5		101 ± 22.3		0.00
Normal Glucose	21	67	65	82	0.02
High Glucose	10	32	14	17	
LDL (mg/dl)	129.0 ± 38.6		113.3 ± 50.3		0.045
Normal LDL (n, %)	18	58	42	53	0.07
High LDL (n, %)	15	42	37	46	
HDL (mg/dl) (n, %)	51.3 ± 12.3		52.2±13.2		0.8
TRG (mg/dl)	156 ± 107		140 ± 109		0.05
Normal TRG (n, %)	23	74	71	89	0.5
High TRG (n, %)	8	25	8	10	
AST (IU/dl)	22.7 ± 9.7		18.7±5.1		0.006
Normal AST (n, %)	29	93	79	100	0.04
High AST (n, %)	2	6	0	0	
ALT (IU/dl)	27.6 ± 17.0		18.3 ± 8.5		0.000
Normal ALT	21	67	76	96	000
High ALT	10	32	3	3	
DM (n, %)	11	35	19	24	0.001

BMI = body mass index; LDL = low density lipoproteins; HDL = high density lipoproteins; TRG = triglyceride; AST = aspartate aminotransferase; ALT = alanine aminotransferase; DM = Diabetes Mellitus.

When multivariate analysis was performed for NAFLD in the control group, age, BMI, glucose, ALT and AST were found to be significantly higher, and DM association was significantly higher (Table 7). When all individuals with normal weight and underweight were evaluated, the frequency of NAFLD was 5.6% in the patient group, while it was 11.6% in the control group, there was no statistically significant difference (P = 0.25) (Table 8).

Table 7. Univariate -multivariate analysis of patients with and without NAFLD in the control group

	Univariate (P)	**Multivariate (P)**
Age	0,008	0.063
BMI	< 0.001	0.02
Glucose	< 0.001	0.02
AST	0.006	0.035
ALT	0.003	0.003
DM	0.001	0.04

BMI = Body Mass Index; LDL = Low Density Lipoprotein; AST = aspartate aminotransferase; ALT = alanine aminotransferase; DM = Diabetes Mellitus.

Table 8. Frequency of non-alcoholic fatty liver disease (NAFLD) in the normal and underweight patients in all study groups

Groups	**With NAFLD**		**Without NAFLD**		**Total**
	n	%	n	%	
CD	4	5,6	67	94,3	71
Control	5	11,6	38	88,3	43
Total	9	7,8	105	92,1	114
					P = 0.25

CD = Celiac Disease.

Discussion

Celiac disease has many metabolic risk factors therefore it was thought that the risk of NAFLD may be increased in CD. To date, few studies investigated this subject have been published, and the results of these studies are contradictory (11-14). In this controlled study to shed light on this subject, it has been shown that the risk of NAFLD is not increased in CD. In addition, while age was not a risk factor for NAFLD in CD, age was found to be a risk factor for NAFLD in all study group. Metabolic risk factors such as high blood sugar, LDL, presence of DM and increased BMI were associated with NAFLD in both groups.

The pathogenetic pathway that may cause NAFLD in celiac disease is not clear; it has been suggested that the frequency of NAFLD may be increased in CD due to the fact that they have similar etiopathogenic factors. Cellular stress, especially seen in CD, may cause NAFLD (15). In addition, NAFLD has been associated with increased intestinal permeability, dysbiosis, increased cytokines (which is common in both diseases) (16,17) and risk factors which are associated with NAFLD play a major role in the etiopathogenesis of CD (18). Increased intestinal permeability, which plays the most important role in the clinical

reflection of CD, has also been accepted as an important risk factor for non-alcoholic steatohepatitis (NASH) in NAFLD. It has been shown that TNFα, which causes damage in celiac disease, is also increased in patients with NASH. It has even been thought to be a risk factor for NASH in NAFLD (19).

Bringing into the open of the relationship between NAFLD and CD is important to identify a potentially preventable and treatable cause of liver disease in patients with CD. Some of the studies on this subject, one of which is the population-based study of Reilly et al. (11), found an increased frequency of NAFLD in CD. Another study, showing an increased risk, is the study which conducted by Tovoli et al (12). Although the study by Reilly et al (11)., which found an increased risk for NAFLD in CD, seemed to involve a large number of patients, the diagnosis of CD was made only by biopsy and not confirmed by serology. Alcohol use had been defined by ICD code scanning; if there is no alcohol-related disease, no alcohol use was accepted, and the presence of NAFLD was defined only through the ICD code. However, if these patients with CD have never had a sonographic examination, they may not have been diagnosed with NAFLD even though they are NAFLD. Moreover, even if NAFLD is detected sonographically, they may not be defined in the system as an ICD code. In addition, alcohol use may not always cause alcohol-related disease, and even if it does, it may not be recorded in the system. However, patients with CD have a higher rate of being under close follow-up and sonographic examination compared to individuals who do not have this disease, and they are more likely to be undiagnosed even though they have NAFLD (11). Thus, such limitations reduce the value of the data of the Reilly et al. study. The study of Tovoli et al. (12), which was published after this study and the design of the studies is similar to our study, also shows that the frequency of NAFLD increases in CD. Their study showed that the raw prevalence of NAFLD was 34.7% and 21.8% in the CD and the control group, respectively (P = 0.006). We showed that, the raw prevalence of NAFLD was 22.7% and 28.1% in the CD and the control group, respectively (P = 0.35). Tovoli et al. showed that, unlike our study, the frequency of NAFLD increased in the CD compared to the control group. Looking at the subgroup analysis of the study of Tovoli et al., it is seen that they found a 6-fold increased risk in lean celiac patients compared to the lean control group, there is no difference in the overweight and obese patient and control groups. They explained this result with the view that risk factors that have already increased in obesity may mask the risk (12). However, when we compared underweight and normal weight patients in our study, we did not find a difference in terms of NAFLD frequency (P = 0.25).

Another reason why the frequency of NAFLD did not increase in the celiac disease group compared to the control group in our study may be the high frequency of NAFLD in the control group. Unfortunately, Turkey is one of the countries with a very high prevalence of NAFLD all over the world. As a result of the studies of public health experts, it was determined that the Cappadocia region is the region that best exemplifies Turkey, and Sezgin et al. completed the NAFLD prevalence study there. The frequency of NAFLD detected by abdominal ultrasonography in approximately three thousand (2797) healthy volunteers was found to be 60.1%. This frightening value can be explained by some other features of the study. The median age of the individuals in the study is 52 years and 45% are obese and 35% are overweight, which does not reflect Turkey (20). However, Kaya et al. found that the transient elastography defined NAFLD prevalence was 23.2% in 112 healthy medical school students (21). A study which was published in 2021, hospital-based cross-sectional study, the data of a sample from 113 239 apparently healthy subjects, demonstrated that the overall prevalence of NAFLD in Turkey was found to be 48.3%. This result was higher than results reported from other countries to date (22).

In the subgroup analysis, which was performed to prevent the effect of risk factors such as obesity, there was no difference in the frequency of NAFLD between normal weight and low weight individuals, patients and the control group in our study. Tovoli et al. interpreted this result as a finding supporting that the relationship between CD and NAFLD may be stronger, and they interpreted the possible reasons for this as increased gastrointestinal permeability in CD and gluten-free diet restriction may pose a risk for NAFLD by causing hyperphagia (12). However, we did not detect any difference in subgroup analysis in our study.

The newly published study by Agarwal et al., similar to our study, found the frequency of NAFLD in CD patients under 1 year of GFD to be similar to the population. In this study, the diagnosis of fatty liver was made with Fibroscan, but the control group was not included. The authors, who found an increase in the frequency of NAFLD in the 1st year of adherence to a gluten-free diet according to the time of diagnosis, suggest that patients should be followed closely for NAFLD and warned for high calorie intake (14).

Limitations of the study

This study has some limitations; firstly, our study has retrospective design, this could affect our results, even if the consecutive inclusion of all diagnosed CD patients (with both relative blood samples and tissue samples) probably reduce such a bias. Second, the diagnosis of steatosis was primarily based on ultrasonographic approach, not on histology (for ethical reasons). However, a recent meta-analysis showed that ultrasonography is an accurate imaging technique in detecting fatty liver compared to histology, with a sensitivity of 84.8% and a specificity of 93.6% for detecting ≥20%-30% steatosis (23). Ultrasonography is relatively inexpensive and accessible, compared to other diagnostic techniques, and is the imaging technique of choice for the screening of fatty liver in clinical settings and population studies. On the other hand, in histological examination, every sample may not be sufficient for diagnosis, it samples only the area of the liver where the biopsy was taken (each biopsy corresponds to the liver1/50,000). Differences in interpretation between pathologists are also reported. A liver biopsy from every fatty liver patient is also not cost-effective. Moreover, a liver biopsy is an invasive method that can have serious complications, including serious bleeding or even death, although not very often. For this reason, liver biopsy is not recommended for the diagnosis of NAFLD in every patient (2-5). Thirdly, the assessment of compliance to diet and caloric intake was made based on clinical features, compliance questionnaires (24). Defining the compliance to diet CD patients is always challenging for physicians, therefore, we decided to use these simple and validated approaches.

In conclusion, contrary to the previous belief, this study showed that prevalence of NAFLD in patients with CD is not increased. But NAFLD is the most common cause of liver disease and is no less common in patients with CD than in society. It should be kept in mind that hypertransaminasemia in patients with CD may be largely dependent on NAFLD, and that it may also be NAFLD without hypertransaminasemia.

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