Gaziosmanpaşa Üniversitesi Tıp Fakültesi Dergisi 2023;15 (1):1-14 Orijinal Makale

İnflamatuar Bağırsak Hastalığı Olan Hastalarda Nonalkolik Yağlı Karaciğer Hastalığının Sıklığı ve Risk Faktörleri

Frequency and Risk Factors of Nonalcoholic Fatty Liver Disease Among Patients with Inflammatory Bowel Disease

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Özet

Amaç: Bu çalışmada İnflamatuvar Barsak Hastalığında (İBH) Alkol Dışı Yağlı Karaciğer Hastalığı (ADYKH) sıklığını ve bu hastalık için risk faktörlerini araştırmayı amaçladık.

Metot: Bu retrospektif çalışmada İBH hastalarında ADYKH sıklığını ve bunu predikte eden faktörleri araştırdık. ADYK tanısı ultrasoografik temelli olarak konuldu. Sağlıklı kontrol grubu, ADYK grubu ile yaş, cinsiyet, metabolik risk faktörleri 1:1 olarak randomize eşleştirilerek oluşturuldu.

Bulgular: Çalışmaya 40 Ülseratif Kolit, 40 Crohn Hastası ve 40 sağlıklı kontrol hastası alındı. Gruplar arasında ADYKH sıklığı açısından fark yoktu. İBH'de hiperlipidemi ve Diabetes Mellitus ADYK gelişimi için risk faktörü olarak bulundu (sırasıyla; p:0.004, p:0.03).

Sonuç: İBH'de ADYKH riski artmamıştır. Diabetes Mellitus ve hiperlipidemi ADYK gelişimi için risk faktörüdür.

Anahtar kelimeler: İnflamatuvar Bağırsak Hastalığı, Ülseratif Kolit, Crohn Hastalığı, Alkol Dışı Yağlı Karaciğer Hastalığı

Abstract

Aim: The aim of this study was to investigate the frequency of Nonalcoholic Fatty Liver Disease (NAFLD) in patients with Inflammatory Bowel Disease (IBD) and asses the risk factor for developing NAFLD.

Method: We retrospectively investigated prevalence and predictors of NAFLD in patients with IBD. The diagnosis of NAFLD was based on the presence of ultrasonographic steatosis. Healthy controls with 1:1 ratio by gender, age, metabolic risk factors were matched randomly to compare of NAFLD detective rate and analyzing other risk factors.

Results: A total of 120 patients, including 40 UC, 40 CD and 40 healthy controls (HC), were included in this study. There was no difference between the groups in terms of NAFLD frequency. Hyperlipidemia and DM were found to be risk factors for NAFLD in patients with IBD (p:0.004, p:0.03, respectively).

Conclusion: The frequency of NAFLD is not increased in IBD patients. Hyperlipidemia and DM are risk factors for NAFLD.

Key Words: Fatty Liver, Inflammatory Bowel Disease, nonalcoholic fatty liver disease, Ulcerative Colitis, Crohn

Introduction

Non-alcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease in developed countries in recent years. Non-alcoholic fatty liver disease is defined as the absence of secondary causes and the presence of more than 5% of the liver steatosis. Non-alcoholic fatty liver increases liver-related morbidity and mortality and often increases the risk of other comorbidities, such as type 2 diabetes and cardiovascular disease. Metabolic syndrome and accompanying insulin resistance, genetic predisposition, hormonal disorders and lifestyle are the main pathogenic triggers that accelerate the development of NAFLD. Biochemical markers and radiological imaging, in selected cases; liver biopsy helps in diagnosis and prognosis. (1-4). Nonalcoholic fatty liver disease remains asymptomatic in a significant proportion of patients, and the diagnosis is suspected when there are abnormalities in liver function tests and other biochemical parameters, or abnormal radiological imaging findings.

Nonalcoholic fatty liver disease was found to be the most common cause of elevated transaminase levels in patients with Inflammatory Bowel Disease (IBD). The incidence of NAFLD in patients diagnosed with IBD was between 6.2% and 40%, while the rate of people with liver fibrosis was found to be between 6.2% and 10% (5-6). A concomitant NAFLD increases mortality in patients with IBD compared to the population; in these patients who were hospitalized, increased mortality was observed up to 2 times (7). At the same time, the presence of a NAFLD accompanying IBD has an effect on the choice of treatment, since the selected treatment protocols may have a negative effect on the occurrence of NAFLD. A previous study determined that the risk of NAFLD in IBD increased 3.7 times by surgery, 3.5 times by hypertension, 2 times by obesity, and 4 times by steroid treatment (8). Another study conducted with seven Crohn's Disease (CD) patients suggested that anti-TNF therapy used in the treatment of IBD is a risk factor for the formation of NAFLD (9).

The main purpose of this retrospective study is to determine the frequency of NAFLD in patients with IBD. The secondary aim is to determine the risk factors of NAFLD by examining the clinical and metabolic features in patients with IBD.

Material Methods

This study was carried out with the approval of the ethics committee with the decision numbered 20-KAEK-288 at the 2020/16 meeting of the Tokat Gaziosmanpasa University Clinical Research Ethics Committee held on 19.11.2020.

Study design

Medical records of patients undergoing evaluation and treatment for, CD and Ulcerative Colitis (UC) at our tertiary care center between October 2015 and October 2020 were reviewed.

Inclusion criteria were the following; Patients age 18 years old and diagnosed IBD included the study.

Exclusion criteria were the following: (a) any other chronic liver disease apart form NAFLD; (b) hazardous alcohol intake, as more than 20gr/day for women, 30g/day for men (c) pregnancy at time of recruitment.

At the same time, we selected 40 healthy cases which were 2:1 ratio matched by gender, age, Body Mass Index (BMI) from patient who were admitted to our outpatient clinic due to dyspeptic symptoms.

Data collection

We performed a retrospective review of the medical records of the patients using by the ENLIL system (Enlil version v2.20.14 20200406).

Gender of the patients, age at diagnosis of IBD, biochemical parameters in hospital records; fasting blood glucose, insulin, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride (TRG), aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), albumin, hemoglobin, platelet levels were screened. Abdominal ultrasonography (USG), computerized tomography (CT), or if performed, liver biopsies in the records of our hospital were scanned for whether NAFLD was detected.

Definition

The diagnosis of IBD was based on clinical examination, endoscopic, laboratory and histopathological findings according to the European Crohn's and Colitis Organization (ECCO) (10). The diagnosis of NAFLD was made on the basis that the liver was hyperechoic compared to the kidney, ultrasonographically, in people who had no alcohol intake over 20 g/day and did not have any other liver disease that could cause steatosis (11). For the control group, patients who were diagnosed with dyspepsia according to the Rome IV criteria and had abdominal imaging in order to be able to compare NAFLD were screened; forty patients matched in terms of demographic (age, gender) and metabolic characteristics (BMI, presence of Diabetes Mellitus [DM]) were included in the study (12).

The patients were evaluated for the presence of metabolic syndrome (metS), Diabetes Mellitus or insulin resistance. The Homeostasis Model Assessment (HOMA) method, which is the most preferred formula for calculating insulin resistance, was used (HOMA: fasting glucose(mg/dl) x fasting insulin (μu/ml) / 405). If HOMA index is >2.7, it is considered as insulin resistance. Hypertension (systolic blood pressure is >130mmHg, diastolic blood pressure >85 mmHg or using antihypertensive), dyslipidemia (triglyceride level >150 mg/dl or HDL level <40 mg/dl in men, <50 mg/dl in women or using antihyperlipidemic), abdominal obesity was defined as BMI >30 kg/m2 (the patient's weight in kilograms divided by the square of the patient's height in square meters)] and was considered as metS if he had two of these risk factors.

The fibrosis 4 (FIB4) score for liver fibrosis was calculated using the following formula: FIB4 = (age × AST) / (platelet count [10.9/L] × ALT [alanine aminotransferase]). For advanced fibrosis, a FIB4 score of <1.45 had a negative predictive value of 90% (Ishak fibrosis score 4–6 includes early bridging between fibrosis and cirrhosis). In contrast, a FIB4 score of >3.25 will have a 97% specificity and a 65% positive predictive value for advanced fibrosis.

History of alcohol intake and smoking-alcohol abuse of patients were recorded. In endoscopic examinations, the level of involvement of IBD in the gastrointestinal tract was determined. According to the location and type of involvement in terms of endoscopic findings: Crohn's disease;

ileocecal, ileocolonic, colonic involvement, if UC; it was classified as proctitis, left-sided colitis, pancolitis. The Mayo Scoring System was used to evaluate clinical activation in patients with ulcerative colitis, and the Crohn's Disease Activity Index was used for Crohn's disease. The drugs that the patients used in the past and were using were determined; corticosteroids (prednisolone, methylprednisolone, and budesonide); immunosuppressive therapy [6 mercaptopurine (6-MP), azathioprine], biological agents (different forms of anti-TNF-α), or 5 amino-salicylic acid (5-ASA).

Statistical analysis

SPSS Statistics Version 25.0 (IBM, Chicago, IL, USA) package program was used in the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and numerical measurements were summarized as mean ± standard deviation. Whether numerical measurements provided the assumption of normal distribution was tested with the Shapiro Wilk test. Parametric tests (t-test, ANOVA) were used for normally distributed numerical measurements, and non-parametric tests (Mann-Whitney U Test) were used for numerical measurements that did not show normal distribution. In general, the statistical significance level was taken as 0.05 in the tests. In the triple comparison tests performed ANOVA, the p value was accepted as 0.017 as the level of significance.

Results

A total of 123 patients diagnosed with IBD were scanned. After the exclusion, the data of 80 patients were analyzed retrospectively. Fifty percent (n=40) of the IBD group consists of UC and fifty percent (n=40) of CDs. The control group was selected from patients with functional dyspepsia. Demographic data of the patient and control groups are presented in table 1 (Table 1).

Total cholesterol and LDL levels were found to be significantly higher in the control group (p: 0.008) (Table 1).

Table 1. Demographic, clinical data and frequency of NAFLD of all study group

	IBD (n:80)	***Control (n:40)***	***p***
Gender (F/M) (n, %)	49/31 (61.3/38.8)	27/13 (67.5/32.5)	0.5
Age (year)	48.6±15.2	47.8±13.8	0.7
BMI (kg/m²)	26.5±3.9	27.9±3.8	0.051
LDL (mg/dl)	98.1±37.3	123.9±25.7	**0.02***
HDL (mg/dl)	45.0±12.2	48.7±9.7	0.1
TRG (mg/dl)	106.5±79.1	163.1±97.9	0.16
TC (mg/dl)	158.0±49.2	200.0±46.1	**0.008***
HOMA-IR	2.8±1.6	3.0±1.2	0.69
FIB-4 Score	1.0±0.6	1.5±1.5	0.3
DM (n, %)	11 (13.8)	2 (5.0)	0.2
HT (n, %)	15 (18.8)	7 (17.5)	0.8
HL (n, %)	7 (8.8)	3 (7.5)	0.8
NAFLD (n, %)	26 (32.5)	14 (35)	0.9

IBD, Inflammatory bowel disease; BMI, Body mass index; LDL, Low Density lipoprotein; HDL, High density lipoprotein; TRG, Triglyceride; TC, Total cholesterol; HOMA-IR, Homeostasis Model Assessment; FIB-4,

Fibrosis -4;DM, Diabetes Mellitus; HT, Hypertension; HL, Hyperlipidemia; NAFLD, Non-alcoholic fatty liver disease; UC, Ulcerative colitis; CH, Crohn's disease.

When subgroup analysis was performed, statistically significant differences were found between these three groups in terms of triglyceride, LDL and total cholesterol multivariate analyzes were performed on the basis of these variables (p values are respectively: 0.01; 0.01; 0.04) (Table 2).

Table 2. Demographic, clinical data, and prevalence of NAFLD in patients with ulcerative colitis, Crohn's Disease, and control group

	UC	***CH***	***Control***	***p***
Gender (F/M) (n, %)	24/16 (60/40)	25/15 (62.5/37.5)	27/13 (67.5/32.5)	0.7
Age (year)	51,0±14.3	46.2±15.9	47.8±13.8	0.3
BMI (kg/m²)	27.4±3.3	25.8±4.2	27.9±3.84	0.29
BMI>25 (%)	77.5	50	62.5	0.02
LDL (mg/dl)	103.6±39.8	88.7±33.3	123.9±25.7	**0.01***
HDL (mg/dl)	45.2±10.8	44.9±13.5	48.7±9.7	0.2
TC (mg/dl)	170.4±49.2	145.6±46.5	163.1±97.9	**0.01***
TRG (mg/dl)	127.2±101.6	85.7±38.5	200.0±46.1	**0.04***
HOMA-IR	3.4±2.0	2.2±0.8	3.0±1.2	0.6
FIB-4 Score	1.1±0.4	1.2±0.4	1.3±0.6	0.3
NAFLD %	32.5	32.5	35	0.95
DM (%, n)	15 (6)	12.5 (5)	5 (2)	0.3
HT (%, n)	12.5(5)	25 (10)	17.5 (7)	0.3
HL (%, n)	10 (4)	7.5 (3)	7.5 (3)	0.8

IBD, Inflammatory bowel disease; F, female; M, male; n, number; BMI, Body mass index; kg, kilogram; m, meter; LDL, Low Density lipoprotein; mg, milligram; dl, deciliter; HDL, High density lipoprotein; TRG, Triglyceride; TC, Total cholesterol; HOMA-IR, Homeostasis Model Assessment; FIB-4, Fibrosis -4; NAFLD, Non-alcoholic fatty liver disease; DM, Diabetes Mellitus; HT, Hypertension; HL, Hyperlipidemia.

*The corrected significance value is p=0.017.

In the multivariate analysis, it was observed that the difference between the groups in mean BMI, LDL, TC, TRG and HOMA-IR levels was between the CD and control groups. In terms of HOMA-IR levels and TRG, the differences between groups were found to be between UC and CD. There was a just single difference between UC and control groups and it was in term of HOMA-IR level (Table 3).

Table 3. Multivariate analysis of LDL, total cholesterol, triglyceride and HOMA-IR between Ulcerative Colitis, Crohn Disease and control groups

	UC	*CD*	*Control*	*P values*		
				UC - CD	UC - C	CD - C
BMI (kg/m²)	27.4±3.3	25.8±4.2	27.9±3.84	0.95	0.29	0.009
LDL (mg/dl)	103.6±39.8	88.7±33.3	123.9±25.7	0.93	0.22	0.02
TC (mg/dl)	170.4±49.2	145.6±46.5	163.1±97.9	0.07	0.05	<0.001
TG (mg/dl)	127.2±101.6	85.7±38.5	200.0±46.1	0.01	0.07	<0.001
HOMA-IR	3.4±2.0	2.2±0.8	3.0±1.2	0.001	0.04	0.01

UC, Ulcerative Colitis; CD, Crohn Disease, LDL, Low Density lipoprotein; mg, milligram; dl, deciliter; TC, Total cholesterol; TRG, Triglyceride; HOMA-IR, Homeostasis Model Assessment;

The risk factors for NAFLD in patients with IBD presents in table 4. There was a difference, demographical finding and about disease related factor, only in terms of surgical history (p:0.007). The frequency of NAFLD in the group with IBD was 63.6% in those with diabetes, 20% in those with hypertension, and 42.9% in those with hyperlipidemia (HL). While there was a significant difference in causing NAFLD between those with and without diabetes (p:0.03). No statistically significant difference was found in terms of the presence of hypertension and hyperlipidemia causing NAFLD (p values: 0.36; 0.67, respectively) (Table 4).

Table 4. The risk factors for NAFLD in patients with Inflammatory Bowel Disease

	NAFLD+ (n=26)	***NAFLD- (n=54)***	***p***
Gender F/M (n, %)	15/11 (30.6/35.5)	34/20 (69.4/64.5)	0.65
Age (y)	51.6±13.6	47.2±15.8	0.23
BMI (kg/m²)	26.9±3.4	26.4±4.0	0.59
Age at diagnosis (y)	43.5±13.0	39.3±15.7	0.25
Age of disease (y)	8.1±4.5	7.8±5.1	0.82
Remission +(n:58) n (%)	12 (41.2)	17(58.8)	0.38
Surgery + (n:13) n (%)	0 (0)	13 (100)	**0.001***
Smoking status (n:9) n (%)	2 (22.2)	7 (87.8)	0.06
LDL (mg/dl)	95.5±36.6	96.5±37.9	0.91
HDL (mg/dl)	43.7±9.2	45.7±13.4	0.49
TRG (mg/dl)	108.3±52.7	105.6±89.6	0.88
TC (mg/dl)	159.4±41.1	157.3±53.0	0.86
AST (U/L)	21.0±9.5	19.1±7.1	0.32
ALT (U/L)	20.9±20.3	14.8±6.5	0.15
HOMA-IR	2.8±1.9	2.8±1.5	0.93
FIB-4 Score	0.9±0.3	1.0±0.7	0.73
DM n (%)	7 (63.6)	4 (36.4)	**0.03***
HT n (%)	3 (20)	12 (80)	0.36
HL n (%)	3 (42.9)	4 (57.1)	0.67

NAFLD, Non-alcoholic fatty liver disease; n, number; F, female; M, Male; y, year, BMI, Body mass index; kg, kilogram; LDL, Low Density lipoprotein; mg, milligram; dl, deciliter; HDL, High density lipoprotein; TRG,

Triglyceride; TC, Total cholesterol; AST, aspartate aminotransferase; U, Unite; L, liter; ALT, alanine aminotransferase; mm, millimeter; h, hour; CRP, C reactive protein; HOMA-IR, Homeostasis Model Assessment; FIB-4, Fibrosis -4; DM, Diabetes Mellitus; HT, Hypertension; HL, Hyperlipidemia.

TABLE 4

When the risk factors for NAFLD were analyzed in patients with UC and CD by subgroup analysis, no statistically significant risk factors were found except DM and HL comorbidity, DM and HL comorbidities were more common in NAFLD+UC group and NAFD+CD than without NAFLD (Table 5 and 6).

Table 5. Comparison of the data according to the presence of NAFLD in the group with ulcerative colitis

	NAFLD (+) (n:13)	***NAFLD (-) (n:27)***	***p***
Gender F/M (n, %)	7/6 (29.2/37.5)	17/10 (70.8/62.5)	0.58
Age (y)	54.2±12.3	49.5±15.2	0.34
Age at diagnosis (y)	44.6±13.3	42.3±15.9	0.66
BMI (kg/m²)	27.9±3.4	27.1±3.3	0.49
Duration of disease (y)	9.6±4.6	7.1±3.8	0.09
LDL (mg/dl)	100.1±40.9	105.4±39.9	0.70
HDL (mg/dl)	45.8±9.6	45.0±11.6	0.82
TRG (mg/dl)	117.2±61.8	132.1±116.8	0.67
TC (mg/dl)	163.4±41.2	173.7±53.1	0.54
AST (U/L)	22.3±13.0	18.0±4.7	0.27
ALT (U/L)	26.4±27.5	16.1±7.2	0.20
HOMA-IR	3.5±2,3	3,4±1,8	0,88
FIB-4 score	0,9±0,3	1,0±0,7	0,89
Smoking status (n:6) n (%)	1 (16.6)	5 (83.4)	0,06
Remission + (n:30) n (%)	12 (40)	18 (60)	0,17
Surgery + (n:6) n (%)	0/0	6 (100)	**<0,001***
DM n (%)	4 (30.7)	2 (7)	**0,001***
HT n (%)	15.3(2)	3 (11.1)	0,17
HL n (%)	3(23)	2(7)	**0,041***

NAFLD, Non-alcoholic fatty liver disease; F, female; M, Male; n, number; y, year, BMI, Body mass index; kg, kilogram; LDL, Low Density lipoprotein; mg, milligram; dl, deciliter; HDL, High density lipoprotein; TRG, Triglyceride; TC, Total cholesterol; AST, aspartate aminotransferase; U, Unite; L, liter; ALT, alanine

aminotransferase; mm, millimeter; h, hour; CRP, C reactive protein; HOMA-IR, Homeostasis Model Assessment; FIB-4, Fibrosis -4; DM, Diabetes Mellitus; HT, Hypertension; HL, Hyperlipidemia.

Table 6. Comparison of the data according to the presence of NAFLD in the group with Crohn's Disease

	NAFLD (+) ***N:13***	***NAFLD (-)*** ***N:27***	***p***
Gender (F/M) (n, %)	8/5 (32,0/33.3)	17/10 (68.0/66.7)	0.93
Age (year)	49.0±14.9	44.9±16.4	0.45
BMI (kg/m²)	42.3±13.2	36.4±15.2	0.23
Age at diagnosis (y)	25.9±3.2	25.7±4.6	0.88
Age of disease (y)	6.6±4.1	8.5±6.1	0.31
Remission+ (n:28) (n, %)	8/28,6	20/71,4	0,87
Surgery+ (n:7) (n, %)	0/0	7/100	**<0,001***
Smoking status (n:2) n(%)	1(%50)	1(%50)	1
LDL (mg/dl)	90,9±32,6	87,6±34,2	0,77
HDL (mg/dl)	41,6±8,7	46,4±15,2	0,20
TRG (mg/dl)	99,3±42,2	79,1±35,5	0,12
TC (mg/dl)	155,3±42,3	140,9±48,4	0,36
AST (U/L)	19,7±4,2	20,2±8,8	0,84
ALT (U/L)	15,3±6,0	13,5±5,6	0,37
HOMA-IR	33.3/28.6	66.7/71.4	0.87
FIB-4 Score	0.9±0.4	0.8±0.6	0.056
DM n (%)	4 (30.7)	1 (3)	**0.001***
HT n (%)	3 (23)	4 (14.8)	0.07
HL n (%)	4 (30.7)	2 (7.4)	**0.037***

NAFLD, Non-alcoholic fatty liver disease; n, number; F, female; M, Male; y, year, BMI, Body mass index; kg, kilogram; LDL, Low Density lipoprotein; mg, milligram; dl, deciliter; HDL, High density lipoprotein; TRG, Triglyceride; TC, Total cholesterol; AST, aspartate aminotransferase; U, Unite; L, liter; ALT, alanine aminotransferase; mm, millimeter; h, hour; CRP, C reactive protein; HOMA-IR, Homeostasis Model Assessment; FIB-4, Fibrosis -4; DM, Diabetes Mellitus; HT, Hypertension; HL, Hyperlipidemia.

According to the gastrointestinal tract involvement sides, the involvement in CD was 55% ileocolic, 25% ileum and 20% colonic, respectively; in UC, it is seen as left-sided colitis in 47.5%, pancolitis in 32.5%, and proctitis in 20%, respectively. According to the site of GIS involvement, proctitis is the most common in patients with UC 37.5%, left-sided colitis with 36.8% and pancolitis with 23.1%,

respectively, accompanying NAFLD. However, there is no significant difference in the occurrence of NAFLD in UC according to the GIS involvement site (p:0.694). In patients with CD, ileum involvement with 40% accompanies NAFLD, followed by colonic involvement with 37.5% and ileocolonic involvement with 27.3%, respectively. There was no statistically significant difference in the occurrence of NAFLD in Crohn's Disease according to the GIS involvement site (p:0.733) (Table 7).

Table 7. The occurrence of NAFLD in IBD patients according to the GIS involvement site

	Side of disease	*NALFD + % (n)*	*NAFLD - % (n)*	*p*
UC	Left side	%36,8 (7)	%63,2 (12)	0,694
	Pancolitis	%23,1 (3)	%76,9 (10)	
	Proctitis	%37,5 (3)	%62,5 (5)	
CD	Ileum	%40 (4)	%60 (4)	0,733
	Ileocolonic	%27,3 (6)	%72,7 (16)	
	Colonic	%37,5 (3)	%62,5 (5)	

NAFLD, Non-alcoholic fatty liver disease; UC, Ulcerative Colitis; CD, Crohn’s Disease; n, number.

Discussion

Previous studies showed that the frequency of NAFLD is increased in patients with IBD. Although many etiological reasons have been put forward to explain this, the underlying causes have not yet been fully elucidated (6). Sourianarayanane et al. and Glassner et al. showed that lowest rates of NAFLD in patients with IBD as 8.2% and 13.3%, respectively, but frequency rates of up to 40% were reported in the literature (13-15). In our study, the frequency of ultrasound-based NAFLD was 32.5%, and it was found to be equally common in groups with and without IBD, and this rate is higher than the average prevalence of NAFLD in the world, supporting the idea that the prevalence suggested by the studies will gradually increase.

The prevalence of NAFLD is also increasing globally due to the increasing prevalence of obesity and metS. The frequency of NAFLD is higher in patients those with metabolic diseases than in the general population (16). Non-alcoholic fatty liver disease is detected in 75-80% of those with obesity, 56-70% of patients with DM, approximately 70% of patients with metS, and 70% of those with dyslipidemia (17). In our study, the frequency of NAFLD was found to be 63.6% in the presence of DM accompanying IBD, 20% in the presence of HT, 42.9% in the presence of HL, and 33.3% in those with BMI>25. In our study showed, similar to the literature, frequency of NAFLD increased in the presence of DM and HL accompanying IBD compared to the normal population (13).

Along with metabolic risk factors, age, gender and ethnicity are significantly affect the development of NAFLD. Non-alcoholic fatty liver disease is more

common in men, older people, and Hispanics. Patients are often diagnosed at the age of 40-50, and the prevalence of the disease increases with age (18). In our study, similar to the literature, it was observed that the frequency of NAFLD increased in men and in older ages, but no statistically significant difference was found.

Some data suggest that there are differences between UC and CD when it comes to metS risk: UC patients have been reported to have higher BMI, waist circumference, systolic and diastolic blood pressures, and insulin resistance than CD patients, who tend to be leaner (15). Similar results were obtained in our study, and patients with UC had a higher BMI, HOMA-IR levels, higher prevalence of having hyperlipidemia, DM and HL comorbidities compared to patients with CD.

A retrospective study comparing 78 IBD patients with NAFLD and 148 IBD patients without NAFLD found that patients with IBD and NAFLD were younger and had a lower BMI, and less metS than patients with NAFLD without IBD (19). In a study conducted in 2018, IBD patients with NAFLD had an older population with higher BMI, LDL, blood pressures and were more likely to have metS, compared with those with IBD alone (20). In our study, patients with IBD and NAFLD were more likely to have advanced age, higher BMI, LDL, TG, total cholesterol levels, and higher metS than those with only IBD.

Approximately 20% of those with IBD have changes in liver function tests, often due to NAFLD (21). It was also seen in our study that liver function tests were higher in patients with IBD and NAFLD than those without NAFLD.

Principi et al. reported that disease activity and IBD localization were not associated with NAFLD (13). Similarly, our study showed that disease activity and IBD localization did not have a significant relationship with NAFLD.

In a meta-analysis by Lin et al., age, BMI, duration of IBD disease, diabetes, and history of surgery were found to be significant among the risk factors for NAFLD in patients with IBD (22). In particular, it has been shown that intestinal resection has a positive effect on liver fattening. In our study, no significant difference was found in patients with IBD in terms of age, BMI and IBD disease duration. A significant difference was found in patients with a history of diabetes and surgery. Non-alcoholic fatty liver disease was observed in 63.6% of those with IBD and diabetes. A significant difference was found in terms of the effect of diabetes on NAFLD (p:0.033). A total of 13 patients had a history of resection, and none of these patients developed NAFLD. A total of 67 patients were without a history of resection, and 38.8% (n=26) of them had NAFLD (p:0.007). Our study showed the opposite effect of intestinal resection on liver disease and reached a different conclusion from other studies in this respect. This may be due to weight loss due to resection. However, to say this, the number of patients with resection is small and it is not known how long it takes after resection. Further studies are needed to determine whether there is a possible fat metabolism disorder that may lead to fatty liver through

intestinal surgery in these patients or whether the time to be deprived of the ileal FXR gene expression effect has passed.

Advantages of our work; firstly, the control group and the patient group could be compared for NAFLD in terms of frequency and affecting factors. Second, patients with a history of diseases that may cause NAFLD and liver damage, other than IBD, such as alcohol consumption, liver cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis and viral hepatitis, were excluded from the study. Third, the versatile evaluation of IBD patients, their metabolic, demographic and laboratory examinations, the type of disease involvement, whether they are in remission and their surgical history are among the features that make the study valuable.

Finally, the limitations of this study are mostly related to the fact that this is a cross-sectional study without a prospective evaluation, which would be ideal for better case identification. However, it was a retrospective study, the data presented highlight the importance of NAFLD detection in IBD and determining of risk factors. Second one; the reason is that there is not enough information about the patients' nutrition and exercise status. However, all NAFLD patients followed in our clinic are included in the same diet and exercise program. Third, liver biopsies are another shortcoming; however, biopsy is not required for the diagnosis of NAFLD, and the fact that NAFLD is defined more radiologically makes this deficiency negligible.

In conclusion, in our study, it was found that NAFLD incidence in IBD patients affected disease-related factors and metabolic risk factors. Non-alcohol fatty liver disease has terrible consequences such as cardiovascular associated mortality and increase in HCC risk. Therefore, the treatment of IBD patients should not be limited to gastrointestinal tract treatment; NAFLD development and complications related to NAFLD should be tried to be prevented by encouraging healthy lifestyle and accurate diet intake.

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