Disease activity in inflammatory bowel disease patients is associated with increased liver fat content and liver fibrosis during follow-up

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International Journal of Colorectal Disease (2022) 37:349–356
https://doi.org/10.1007/s00384-021-04065-8

ORIGINAL ARTICLE

Disease activity in inflammatory bowel disease patients is associated with increased liver fat content and liver fibrosis during follow-up

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Accepted: 5 November 2021 / Published online: 17 November 2021

Abstract

Purpose Liver steatosis is a frequently reported condition in patients with inflammatory bowel disease (IBD). Different factors, both metabolic and IBD-associated, are believed to contribute to the pathogenesis. The aim of our study was to calculate the prevalence of liver steatosis and fibrosis in IBD patients and to evaluate which factors influence changes in steatosis and fibrosis during follow-up.

Methods From June 2017 to February 2018, demographic and biochemical data was collected at baseline and after 6–12 months. Measured by transient elastography (FibroScan), liver steatosis was defined as Controlled Attenuation Parameter (CAP) ≥248 and fibrosis as liver stiffness value (Emed) ≥7.3 kPa. IBD disease activity was defined as C-reactive protein (CRP) ≥10 mg/l and/or fecal calprotectin (FCP) ≥150 µg/g. Univariate and multivariate regression analysis was performed; a *p*-value of ≤0.05 was considered significant.

Results Eighty-two out of 112 patients were seen for follow-up; 56% were male. The mean age was 43 ± 16.0 years, and mean BMI was 25.1 ± 4.7 kg/m^2. The prevalence of liver steatosis was 40% and of fibrosis was 20%. At baseline, 26 patients (32%) had an active episode of IBD. Using a multivariate analysis, disease activity at baseline was associated with an increase in liver steatosis ($B = 37$, 95% CI 4.31–69.35, $p = 0.027$) and liver fibrosis ($B = 1.2$, 95% CI 0.27–2.14, $p = 0.016$) during follow-up.

Conclusions This study confirms the relatively high prevalence of liver steatosis and fibrosis in IBD patients. We demonstrate that active IBD at baseline is associated with both an increase in liver steatosis and fibrosis during follow-up.

Keywords Inflammatory bowel diseases · Non-alcoholic fatty liver disease · Liver steatosis · Liver fibrosis

Introduction

Non-alcoholic fatty liver disease (NAFLD), which is characterized by the presence of steatosis in >5% of the hepatocytes, is the most common cause of chronic liver disease [1, 2]. NAFLD is considered a spectrum of liver disease starting with steatosis, thus characterized by lipid accumulation in the hepatocytes, to non-alcoholic steatohepatitis (NASH), with additional hepatic inflammation and ballooning and formation of fibrosis and cirrhosis. NAFLD is associated with a group of metabolic comorbidities, including obesity, hypertension, diabetes mellitus, and hypertriglyceridemia [3]. The prevalence of NAFLD is estimated at 24% in the global adult population, and NAFLD is predicted to become one of the leading causes of liver transplantation in the upcoming years [4, 5]. Liver fibrosis seems to be the most important feature associated with increased overall and liver-related mortality, and presence of fibrosis increases the likelihood of developing liver-related complications including hepatocellular carcinoma (HCC) [6].

In patients with inflammatory bowel disease (IBD), the prevalence of NAFLD may be higher than in the general population as a prevalence up to 54% has been described [7].

IBD consists of Crohn's disease (CD) and ulcerative colitis (UC) and is a chronic inflammation disorder

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of the gastro-intestinal tract. The exact etiology of IBD is still unknown, although it seems to be an interaction between genetic and environmental factors that influence the immune response and the gut microbiome.[8]

The gut microbiome is implicated in the pathogenesis and progression of numerous chronic diseases, including NAFLD. Through the so-called gut-liver axis, the liver is exposed to gut-bacterial-derived products, including toxins (lipopolysaccharides), enzymes (methylamines), alcohol, and short-chain fatty acids (mainly acetate, propionate, and butyrate). This may lead to accumulation of triglycerides, inflammatory responses, oxidative stress, and accompanying damage to the hepatocytes [9, 10]. In IBD patients, the intestinal barrier function is disrupted [11, 12]. A disturbance in the intestinal barrier can therefore result in an increased portal influx of bacteria or their products to the liver, where they can contribute or worsen a range of hepatic metabolic diseases [9].

Taken together, the increased risk to develop NAFLD in IBD patients might be related to a higher number of people with obesity and metabolic comorbidities in the IBD population. But also intestinal disease-related factors, such as inflammatory activity, previous intestinal surgery, disease duration, or a prolonged use of steroids, may contribute to the pathogenesis of liver steatosis and fibrosis, for instance, via the gut-liver axis [7, 13].

The aims of our clinical study were to evaluate the prevalence of liver steatosis and fibrosis in IBD patients and to evaluate prospectively which factors influence changes in steatosis and fibrosis during follow-up.

Materials and methods

Study design and population

We conducted a single-center prospective study in consecutive adult IBD patients with a confirmed diagnosis of CD, UC, or IBD-Unclassified (IBD-U) at the outpatient IBD clinic of the Department of Gastroenterology and Hepatology at the Leiden University Medical Center (LUMC), The Netherlands. Demographical and biochemical data were collected from June 2017 to February 2018 at enrollment and after at least 6 but not more than 12 months.

Patient characteristics and diagnostic criteria

Baseline characteristics were collected, including age, sex, IBD phenotype, disease duration (cardiovascular), medical history, and previous or current used (IBD) medication. As biometric data, weight, height, Body Mass Index (BMI), waist-hip circumference, and waist-hip ratio was measured. Blood samples were drawn according to regular care, including C-reactive protein (CRP), alanine aminotransferase (ALAT), and glycated hemoglobin (HbA1c). A fecal sample was collected to determine fecal calprotectin (FCP). The degree of IBD complaints was measured by the partial MAYO-score (pMAYO-score) for UC and IBD-U patients and the Harvey Bradshaw Index (HBI) for CD patients. Disease activity was defined as CRP $\geq$10 mg/l and/or FCP $\geq$150 µg/g. The degree of liver steatosis and fibrosis was assessed by transient elastography (FibroScan) [14]. Liver steatosis was defined as a Controlled Attenuation Parameter (CAP) $\geq$248. Liver fibrosis was classified as a liver stiffness value (Emed) $\geq$7.3 kPa, further specified as F2-F3 if 7.3 kPa $<$Emed $<$10.49 kPa or $>$F3 if Emed $\geq$10.5 kPa. To determine changes in liver steatosis and fibrosis, ΔCAP and ΔEmed (follow-up minus baseline) were studied. The dietary pattern was assessed using the Mediterranean Diet Scale Score (MDSS), and during the study, there were no dietary interventions or restrictions.

Outcomes

The primary outcome was to evaluate the prevalence of liver steatosis and fibrosis in IBD patients. The secondary outcome of the study was to identify metabolic and intestinal disease-related factors associated with liver steatosis and fibrosis during follow-up.

Statistical analysis

Continuous variables were presented as mean with standard deviation (SD) or as median with interquartile range (IQR) depending on the normality of the underlying distribution. Baseline characteristics were compared using an independent sample T test; paired variables were compared using a paired sample T test or Wilcoxon signed rank test. Categorical variables were presented as a total percentage and compared by using the chi-squared test or Fisher's exact test; in case of $>$2 groups, the Friedman test was used. Multivariate binary logistic regression was used to assess the association between IBD-associated factors and liver steatosis at baseline. To assess the predictive factors associated with liver steatosis and fibrosis in IBD patients during follow-up, a univariate and multivariate linear regression analysis was performed. These variables were included: age, ALAT, BMI, CRP, disease activity at baseline, disease duration, FCP, gender, HBA1c, hip circumference, IBD-diagnosis, liver steatosis at baseline, MDSS, prior surgery because of IBD, use of anti-tumor necrosis factor α (anti TNF-α) therapy, use of prednisone, waist circumference, and waist-hip ratio. A p-value of $\leq$0.05 was considered significant for all tests. All data analysis was performed using SPSS, version 25.0.

Ethical consideration

This research project was reviewed and approved by the Medical Ethical Committee in the LUMC, with reference number NL61647.058.17. Informed consent was obtained from all participants prior to inclusion in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Baseline characteristics

One hundred and 17 patients were enrolled in our prospective study, of which 5 patients were excluded because of a medical history with primary sclerosing cholangitis (PSC) or auto-immune hepatitis (AIH), and 82 patients were also seen for follow-up. Of these 82 patients, 40 (49%) patients were identified as having CD and 42 (51%) patients as having UC or IBD-U. Patients were predominantly male with a mean age of 43 years (16.0); the mean duration of IBD since diagnosis was 14 years (11.5).

Both at baseline and follow-up, we examined the anthropometric measurements. No differences between BMI were found: 25.1 [4.7] kg/m2 vs. 25.1 [4.5] kg/m^2 ($p=0.882$), respectively. In contrast, at baseline, there was a higher waist circumference then at follow-up, despite the fact that there was no diet intervention in between time points (88.2 [11.5] vs. 81.5 [12.0], $p=0.000$). No significant difference in waist-hip ratio was found ($p=0.186$).

At baseline 26 patients (32%) had an active episode of IBD, compared to 20 patients (26%) at follow-up ($p=0.359$). Thirteen of these 20 patients already had an active episode at baseline; 7 patients developed a disease flare during follow-up. Using transient elastography at baseline, steatosis was detected in 32 patients (40%). Liver fibrosis was found in 16 patients (20%) and was staged as grade 2 and 3 fibrosis, 11 (14%) and 5 (6%), respectively. The prevalence of liver steatosis and fibrosis was also checked for all patients ($n=112$), which was similar.

No significant difference in the prevalence of liver steatosis was found between baseline and follow-up, in contrast to the prevalence of liver fibrosis ($p=0.041$) (Table 1).

Of all 112 patients, 30 patients (26.8%) were lost to follow-up. To check if the loss of these patients led to selection bias, we compared the baseline characteristics of these 30 patients with our cohort. Between both groups, we did not find any outcomes which were clinically relevant. All outcomes are presented in Supplementary Table 1.

Factors associated with liver steatosis at baseline

In the multivariate logistic regression model age, BMI, HBA1c, the use of anti-TNF-α therapy and waist circumference were included. An increase in waist circumference was independently associated with 1.2 times higher likelihood of liver steatosis (OR 1.21, 95% CI 1.02–1.45, $p=0.029$). As shown in Table 2, no significant associations were found between liver steatosis and IBD-related factors.

To confirm our observations with liver steatosis as a continuous variable, we performed also a linear regression model. Also in this model, only waist circumference was associated with an increased risk of NAFLD development ($B=3.2$, 95% CI $1.49=4.88$, $p=0.000$), and again no intestinal disease-related factors were found (Supplementary Table 2).

Factors associated with liver fibrosis at baseline

In the univariate logistic regression model, only disease duration was associated with liver fibrosis at baseline. Again we also confirmed our observations with a multivariate linear regression model, where no IBD-related or metabolic risk factors were found to be associated with liver fibrosis (Supplementary Table 3).

Changes in liver steatosis and fibrosis during follow-up

Next, ΔCAP and ΔEmed (follow-up minus baseline) were studied to determine changes in liver steatosis and fibrosis under the influence of disease activity at baseline.

In the group of patients with no disease activity at baseline, the ΔCAP declined with a mean difference of −34.9 (68.4), whereas the ΔCAP increased with a mean difference of 23.2 (78.8) in patients with a disease flare at baseline ($p=0.003$).

The same trend was seen in liver fibrosis during follow-up. The ΔEmed decreased with a mean difference of −0.88 (1.9) in patients with quiescent IBD at baseline, and an increase of the ΔEmed with a mean difference of 0.45 (2.0) was noticed in patients with active disease at baseline ($p=0.007$).

Factors associated with liver steatosis (ΔCAP) and fibrosis (ΔEmed) during follow-up

In consequence of this, a multivariate linear regression analysis was performed to identify whether disease activity was actually associated with liver steatosis and fibrosis during follow-up.

To start with liver steatosis, where IBD diagnosis (CD or UC), use of anti-TNF-α, liver steatosis at baseline and

Table 1 Patient characteristics of the cohort group ($n=82$) at baseline and follow-up

	Cohort baseline ($n=82$)	Cohort follow-up ($n=82$)	p-value
Age (y), mean (SD)	42.7 (16.0)	-	
Gender—male, *N* (%)	46 (56.1)	-	
IBD type, *N* (%)			
CD	40 (48.8)		
UC, IBD-U	42 (51.2)		
Disease duration (y), mean (SD)	14.0 (11.5)	-	
Prior surgery because of IBD, *N* (%)	26 (32.1)		
pMAYO score, *N* (%)			0.052
Remission (0–1)	31 (73.8)	38 (90.5)	
Mild (2–4)	7 (16.7)	4 (9.5)	
Moderate (5–6)	2 (4.8)	0	
Severe (7–9)	2 (4.8)	0	
HBI score, *N* (%)			0.166
Remission (< 5)	27 (69.2)	34 (85.0)	
Mild (5–7)	7 (17.9)	3 (7.5)	
Moderate (8–16)	5 (12.8)	2 (5.0)	
Severe (> 16)	0	1 (2.5)	
FCP, µg/l, median (IQR)	66.5 (25.5–230.3)	43.0 (15.0–170.0)	0.035*
CRP, mg/l, median (IQR)	3.0 (3.0–5.8)	1.8 (0.6–5.1)	0.000*
ALAT, U/l, median (IQR)	18.0 (13.5–23.0)	21.0 (17.0–25.3)	0.042*
Disease activity, *N* (%)			0.359
Active	26 (32.1)	20 (26.0)	
Remission	55 (67.9)	57 (74.0)	
BMI, kg/m^2, mean (SD)	25.1 (4.7)	25.1 (4.5)	0.882
Waist circumference (cm), mean (SD)	88.2 (11.5)	81.5 (12.0)	0.000*
Waist-hip ratio, mean (SD)	0.9 (0.1)	1.0 (0.8)	0.186
Liver steatosis, CAP, mean (SD)	234.8 (73.2)	219.5 (74.5)	0.054
Liver steatosis, *N* (%)			0.664
< 248	49 (60.5)	52 (64.2)	
> 248	32 (39.5)	29 (35.8)	
Liver fibrosis, Emed, mean (SD)	5.5 (2.9)	5.0 (2.4)	0.041*
Liver fibrosis, *N* (%)			0.317
F0-F1	65 (80.2)	71 (87.7)	
F2-F3	11 (13.6)	7 (8.6)	
F > 3	5 (6.2)	3 (3.7)	
MDSS (mean, SD)	13.1 (3.1)	13.5 (3.4)	0.239

ALAT alanine aminotransferase, *BMI* Body Mass Index, *CD* Crohn's disease, *cm* centimeters, *CRP* C-reactive protein, *FCP* fecal calprotectin, *HBI* Harvey Bradshaw Index, *IBD* inflammatory bowel disease, *IBD-U* IBD unclassified, *IQR* interquartile range, *MDSS* Mediterranean Diet Scale Score, *N* number, *pMAYO score* partial MAYO score, *SD* standard deviation, *UC* ulcerative colitis, *y* years

*$p \leq 0.05$ considered statistically significant

disease activity at baseline were included in the final model. Whereas at baseline no significant associations were found between IBD-related factors and the risk of liver steatosis, an IBD disease flare at baseline was indeed associated with an increase in liver steatosis during follow-up ($B=36.8$, 95% CI 4.31–69.35, $p=0.027$). Also liver steatosis (CAP value) at baseline was found to be associated ($B=-0.4$, 95% CI −0.6–0.2, $p=0.000$) (Table 3).

Then liver fibrosis, where both disease activity and liver steatosis at baseline were included in the final model. The same trend was seen, since an IBD flare at baseline was associated with an increase in liver fibrosis during follow-up ($B=1.18$, 95% CI 0.23–2.14, $p=0.016$) (Table 4).

Table 2 Predictive factors associated with the presence of liver steatosis in IBD patients at baseline

	OR*	95% CI	*p*-value
Age at baseline (y)	1.023	0.953–1.098	0.527
Waist circumference (cm)	1.217	1.020–1.452	0.029**
BMI (kg/m^2)	0.836	0.601–1.164	0.290
HBA1c (mmol/l)	1.066	0.938–1.212	0.328
Use of anti-TNF-α	0.595	0.090–3.933	0.590

ALAT alanine aminotransferase, *BMI* Body Mass Index, *CI* confidence interval, *cm* centimeters, *CRP* C-reactive protein, *FCP* fecal calprotectin, *HBA1c* glycated hemoglobin, *IBD* inflammatory bowel disease, *MDSS* Mediterranean dietary serving score, *OR* odds ratio, *TNF* tumor necrosis factor, *y* year

*Adjusted for age, ALAT, BMI, CRP, disease activity, disease duration, FCP, HBA1c, hip circumference, IBD-diagnosis, MDSS, sex, surgery because of IBD, use of anti-TNF-α,use of prednisone, waist circumference, waist hip ratio

**$p \leq 0.05$ considered statistically significant

Table 4 Predictive factors associated with liver fibrosis during follow-up (ΔEmed) in IBD patients

	Unstandardized B*	95% CI	*p*-value
Disease activity at baseline	1.183	0.266–2.140	0.016**
Liver steatosis at baseline	−0.003	−0.010–0.003	0.277

ALAT alanine aminotransferase, *BMI* Body Mass Index, *CD* Crohn's disease, *CI* confidence interval, *cm* centimeters, *CRP* C-reactive protein, *FCP* fecal calprotectin, *HBA1c* glycated hemoglobin, *IBD* inflammatory bowel disease, *OR* odds ratio, *TNF* tumor necrosis factor, *y* year

*Adjusted for age, ALAT, BMI, CRP, disease activity at baseline, disease duration, FCP, HBA1c, hip circumference, IBD-diagnosis, liver steatosis at baseline, sex, surgery because of IBD, use of anti-TNF-α,use of prednisone, waist circumference, waist hip ratio

**$p \leq 0.05$ considered statistically significant

Discussion

In this prospective study, a prevalence of liver steatosis was found in 40% of all IBD patients, whereas liver fibrosis was detected in 20%. Furthermore, an IBD disease flare at baseline was associated with an increase in liver steatosis and fibrosis during follow-up, whereas at baseline, no associations were found between IBD-related factors and the risk of liver steatosis and fibrosis.

A prevalence of 32% of NAFLD among IBD patients, with a BMI range similar to our study, was mentioned in a recent meta-analysis by Lin et al., which is comparable with the prevalence of liver steatosis in our cohort [15]. However, the real prevalence of NAFLD worldwide is still not entirely clear because of the lack of consensus in terminology and the wide range in diagnostic criteria [16].

Regarding diagnostic tools, the EASL guideline advises to identify liver steatosis by imaging, preferably ultrasound (US), because it is widely available and rather cheap. The golden standard for diagnosing liver fibrosis is still liver biopsy, even though the procedure is invasive [2]. Although the EASL suggests that more data is needed to define the role of CAP compared with US, we have assessed the degree of both steatosis and fibrosis by transient elastography (FibroScan). Decisive factors for us to use the FibroScan were the fact that the procedure is non-invasive and could take place at the outpatient clinic.

Whether the relatively high level of NAFLD in IBD populations can solely be explained by the high prevalence of obesity and metabolic comorbidities or whether IBD-related factors also play a role is uncertain. Magri et al. demonstrates retrospectively that male sex, obesity (BMI), and a high lipidic diet were associated with the development of NAFLD in IBD patients [13]. Also Carr et al. found a higher association between NAFLD and the presence of MetS in their IBD population [17]. In our study, waist circumference was independently associated with the presence of liver steatosis at baseline,

Table 3 Predictive factors associated with liver steatosis during follow-up (ΔCAP) in IBD patients

	Unstandardized B*	95% CI	*p*-value
IBD-diagnosis (CD)	−11.301	−42.920–20.318	0.479
Disease activity at baseline	36.833	4.315–69.352	0.027**
Liver steatosis at baseline	−0.425	−0.638 to −0.213	0.000**
Use of anti-TNF-α	15.323	−16.559–47.205	0.341

ALAT alanine aminotransferase, *BMI* Body Mass Index, *CD* Crohn's disease, *CI* confidence interval, *cm* centimeters, *CRP* C-reactive protein, *FCP* fecal calprotectin, *HBA1c* glycated hemoglobin, *IBD* inflammatory bowel disease, *OR* odds ratio, *TNF* tumor necrosis factor, *y* year

*Adjusted for age, ALAT, BMI, CRP, disease activity at baseline, disease duration, FCP, HBA1c, hip circumference, IBD-diagnosis, liver steatosis at baseline, MDSS, sex, surgery because of IBD, use of anti-TNF-α,use of prednisone, waist circumference, waist hip ratio

**$p \leq 0.05$ considered statistically significant

whereas we found no association between BMI and liver steatosis.

Several studies suggested that specific IBD-related factors may contribute to the pathogenesis of NAFLD. Glassner et al. found that IBD patients with a longer duration of disease are more likely to develop NAFLD because of a potential longer exposure to multiple risk factors [18]. Bessissow et al. documented that also prior surgery and IBD disease activity were risk factors for NAFLD development in IBD patients [19]. In our cohort, the mean IBD duration was 14.2 years (11.4), and 32% had surgery because of IBD. Both factors were not associated with a higher risk of liver steatosis, and disease duration was only associated with liver fibrosis at baseline in a univariate logistic regression model.

Several studies also describe the influence of IBD medication on the development of liver steatosis. Underlying liver diseases such as NAFLD are an important cofactor for MTX-induced liver toxicity [20], whereas corticosteroids can cause an increased deposition of lipids in the liver [21]. On the other hand, anti-TNF-a therapy reduces liver steatosis in animal studies, although clinical studies are lacking [22–24]. In our study, the use of corticosteroids was no risk factor to develop liver steatosis or fibrosis; however, further research in the medication field is needed.

As earlier mentioned, prior studies found that intestinal permeability is increased both in patients with NAFLD and in patients with IBD, presumably caused by alterations in tight junctions [25]. Although there is more and more attention for the unraveling of the cause-effect relationship of the pathophysiology [26], there is no valid biomarker so far which is specific enough to determine a dysfunctional gut barrier in the gut and liver tissue. In NAFLD patients, the disturbance correlates with the severity of steatosis [27], whereas hypertransaminasemia in patients with celiac disease is related to the severity of the duodenal lesion and malabsorption [28]. The other way around, in newly diagnosed Crohn's disease, the presence of liver test abnormalities was an independent risk factor for the development of complicated disease behavior [29]. In contrast with this data, we found no significant association between IBD disease activity and liver steatosis or fibrosis at baseline.

Whereas at baseline no significant associations were found between IBD-related factors and the risk of NAFLD, an IBD disease flare at baseline was indeed associated with increases in liver steatosis and fibrosis during follow-up. We do not have a conclusive explanation for this finding during follow-up, and also the course of steatosis and fibrosis in IBD patients over time is not entirely elucidated yet, but we have some suggestions.

First, IBD is characterized by a relapsing and remitting course which can cause structural damage in the gut and extra-intestinal organs over time [30, 31]. We think the influence of disease activity during follow-up is of greater value than just a measurement at one time point such as baseline. It could be that steatosis also disappear when the IBD flare stabilizes, like the findings of Bardella et al. about the effect of gluten-free diet (GFD) in adult celiac patients with hypertransaminasemia. After 1 year, a highly significant improvement in intestinal histology was observed and transaminase levels normalized in 95% of the patients [32].

The second is the influence of the dietary pattern during follow-up, which we checked for half of the group over time with the Mediterranean Diet Serving Score (MDSS). The MDSS is an updated and validated questionnaire to assess the Mediterranean diet (MD) adherence. The higher the MDSS, with an optimal cutoff point of 13.50, the more adherence to the MD which can be translated to a more healthy dietary pattern [33, 34]. In our cohort with no diet intervention in between time points, the mean MDSS at baseline was 12.8 points (3.1); at follow-up, it was 13.4 points (2.9), which was not a statistically significant difference ($p = 0.257$) and thereby no explanation for the follow-up outcomes.

The limitations of our study are that thirty patients were loss to follow-up, but the baseline data of this group did not differ significantly compared to our cohort with follow-up and was thus considered of having no impact on the analyses. We have chosen for the FibroScan as diagnostic device instead of ultrasound to detect liver steatosis and a biopsy to assess fibrosis, which are still the golden standards. In our study, we were particularly interested in the degree of CAP, where it seems that there is no effect from a recent meal on this value so far [35]. However, there are studies that suggest that the degree of liver stiffness could be influenced by a meal consumed 120–180 min before performing the FibroScan [36]. Therefore, performing a FibroScan under standardized fasting status should be considered in future studies. Furthermore, the only blood tests performed were those in the context of regular care, and no data is available on lipid metabolism. We therefore do not have any data on specific risk factors related to the metabolic syndrome and NAFLD. At last we only included patients from a single tertiary center in the Netherlands, so caution is needed when interpreting these data. The strength of our study lies in the fact that this is the first prospective study which analyzes steatosis and fibrosis among IBD patients during a follow-up period, which we think is a great addition in the field of a chronic relapsing disease.

In conclusion, our study reveals a relatively high prevalence of liver steatosis and fibrosis in IBD patients. This raises the question whether IBD, like celiac disease, also needs to be considered one of the secondary causes of liver steatosis and should be taken into account before diagnosing NAFLD. Furthermore, we found that an IBD disease

flare at baseline was indeed associated with a higher risk of liver steatosis and fibrosis during follow-up, showing the importance of collecting data over time in an inflammatory disease characterized by a relapsing and remitting course. However, further studies are still needed.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00384-021-04065-8.

Author contribution All authors have read and agreed to the published version of the manuscript. Conceptualization and methodology: S.M. and P.M. Investigation, data curation, project administration, and formal analysis: E.L., M.S., T.D., J.M., D.M., and P.M. Writing—original draft preparation: E.L., M.T., and P.M. Writing—review and editing: E.L., M.T., A.M., I.M., S.M., and P.M. Visualization: E.L. and P.M.

Declarations

Ethics approval This research project was reviewed and approved by the Medical Ethical Committee in the LUMC, with reference number NL61647.058.17.

Consent to participate Informed consent was obtained from all participants prior to inclusion in the study.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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