

Hepatic steatosis and patients with inflammatory bowel disease: when transient elastography makes the difference

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Background Recent studies suggest an increased prevalence of hepatic steatosis (HS) in patients with inflammatory bowel disease (IBD). Features such as chronic inflammation, previous surgeries, drug-induced hepatotoxicity, malnutrition, and intestinal dysbiosis seem to be involved in its pathogenesis.

Aims The aim of this study was to assess the frequency of HS in patients with IBD quantified by controlled attenuation parameter (CAP) and by clinical-analytical scores: Hepatic Steatosis Index (HSI) and Fatty Liver Index (FLI). The secondary aim was to investigate risk factors associated with HS in patients with IBD.

Patients and methods A cross-sectional study was carried out including consecutive outpatients observed in our department between January and March 2017. HS was defined as HSI of at least 36 or FLI of at least 60 or CAP of greater than 248.

Results A total of 161 patients were included, with a mean age of 40.6 ± 12.8 years. There were 86 (53.4%) female patients. Overall, 62.7% had Crohn's disease and 37.1% had ulcerative colitis. Moreover, 73 (45.3%) patients had CAP greater than 248, 27 (16.8%) had FLI greater than 60, and 46 (28.6%) had HSI greater than 36. We found that patients with CAP of greater than 248 were more frequently obese (28.8 vs. 0.0% $P < 0.001$), male (57.5 vs. 37.5% $P = 0.011$), and presented more frequently with metabolic syndrome (23.9 vs. 4.5% $P < 0.001$). With regard to IBD factors, patients with HS had a higher frequency of previous surgeries (31.5 vs. 12.5% $P = 0.003$). In multivariate analysis, only male sex [odds ratio: 5.7 (95% confidence interval: 2.0–15.9); $P = 0.001$] and previous surgeries [odds ratio: 5.9 (95% confidence interval: 1.5–22.9); $P = 0.011$] were independent risk factors of HS.

Conclusion In our cohort, the frequency of HS varied between 16.8 and 45.3% defined by noninvasive methods. We found that male sex and previous history of surgery were the independent risk factors of HS when quantified by transient elastography. Eur J Gastroenterol Hepatol 00:000–000

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Introduction

Inflammatory bowel disease (IBD), mainly comprising Crohn's disease (CD) and ulcerative colitis (UC), is increasing across the globe with higher incidence and prevalence in North America and Western/Northern Europe [1].

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease around Western countries, and it is a spectrum of disorders ranging from hepatic steatosis (HS) to nonalcoholic steatohepatitis, liver fibrosis, cirrhosis, and hepatocellular carcinoma [2,3]. The pathogenesis of this health burden seems to be linked with

metabolic syndrome, and insulin resistance appears to play a central role [2,4].

Recent data suggest an increasing prevalence of NAFLD in patients with IBD ranging from 6.2 to 40% [5–7]. Although the precise etiology is unknown, some factors such as chronic inflammation, previous surgeries, drug-induced hepatotoxicity, malnutrition, and intestinal dysbiosis seem to be involved in the pathogenesis of this disease [7–10].

There are several noninvasive techniques for screening and diagnosis of HS, with significant accuracies, such as clinical-analytical scores, ultrasonography, computed tomography, and magnetic resonance [3]. Clinical-analytical scores such as Hepatic Steatosis Index (HSI) and Fatty Liver Index (FLI) are simple, easy and free from costs for screening HS and have been validated in a variety of clinical populations [11–13].

Transient elastography (TE) with controlled attenuation parameter (CAP) is a new, promising, noninvasive, fast, reliable, and reproducible technique with a good intraobserver and interobserver agreement, which may assess the presence of HS and hepatic fibrosis [14–17].

Although little is known about the role of NAFLD in disease natural history of patients with IBD, some recent connections with extrahepatic diseases have been shown,

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particularly with chronic kidney disease and cardiovascular disease [18]. Consequently, it seems extremely important to identify patients with IBD at higher risk of chronic liver disease to predict long-term adverse outcomes among asymptomatic patients and to define a risk population for screening and surveillance measures.

The aim of this study is to assess the frequency of HS in patients with IBD quantified by CAP and by clinical-analytical scores: HSI and FLI. A secondary aim is to investigate risk factors associated with HS in patients with IBD.

Patients and methods

Population

We undertook a cross-sectional study to assess the presence of HS in 191 consecutive IBD outpatients that were observed in the Gastroenterology Department of Hospital da Senhora da Oliveira between January and March 2017. Eligible patients were older than 18 years with IBD diagnosis and with serum parameters within 2 weeks from our observation. Patients with known liver disease (metabolic, autoimmune, viral, or alcoholic) or with alcohol habits (>20 g/day for women or >30 g/day for men) [3] or on steroids or methotrexate were excluded. Patients with unreliable TE measures or with missing data on medical records were also excluded. Patients agreed to participate in the study, and during data collection and statistical analysis, anonymity was ensured.

Study variables

The following variables were extracted from medical records: age, sex, IBD type, IBD extension, age at diagnosis, IBD duration, use of azathioprine or anti-tumor necrosis factor- α agents, previous cycles of corticosteroids, IBD-related surgeries, laboratory measures and comorbidities (obesity, hypertension, diabetes, dyslipidemia, and metabolic syndrome). The previous use of corticosteroids was considered as a variable when it was performed more than 2 weeks in a dose superior to 20 mg/day.

Anthropometric data and serum parameters

The BMI (kg/m²) was calculated using body weight (kg) and height (m). Waist circumference was measured at a level midway between the lowest rib and the iliac crest in centimeters (cm).

Metabolic syndrome was present, according to guidelines of the American Heart Association, when a patient has at least three of the following five conditions: fasting glucose of at least 100 mg/dl (or receiving drug therapy for hyperglycemia), blood pressure of at least 130/85 mmHg (or receiving drug therapy for hypertension), triglycerides of at least 150 mg/dl (or receiving drug therapy for hypertriglyceridemia), high-density lipoprotein-cholesterol less than 40 mg/dl in men or less than 50 mg/dl in women (or receiving drug therapy for reduced high-density lipoprotein-cholesterol), and waist circumference of at least 102 cm (40 in) in men or at least 88 cm (35 in) in women [19].

All serum parameters such as hemoglobin (g/dl) aspartate aminotransferase (U/l), alanine aminotransferase (U/l), γ -glutamyltransferase (G-GT) (U/l), triglycerides (mg/dl),

C-reactive protein (CRP) (mg/l), and erythrocyte sedimentation rate (mm) were obtained after 12-h overnight fasting, within the past 2 weeks.

Stool samples of calprotectin (g/g) were collected from the first bowel movement of the day.

Clinical-analytical scores

Two scores validated in a variety of clinical populations were used to assess HS. HSI was defined as follows: $8 \times \text{aspartate aminotransferase/alanine aminotransferase} + \text{BMI} (+2, \text{ if female; } +2 \text{ if diabetes})$ [12]. FLI was defined as follows [11]: $e^{0.953 \times \log e(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \log e(\text{G-GT}) + 0.053 \times \text{waist circumference} - 15.745} / 1 + e^{0.953 \times \log e(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \log e(\text{G-GT}) + 0.053 \times \text{waist circumference} - 15.745}$.

Standard cutoff values were applied to measure HS, defined as HSI of at least 36 and FLI of at least 60 [11,12].

Transient elastography

Transient elastography (FibroScan; Echosens, Paris, France) was performed in patients with a minimum fasting of 2 h [20,21]. Measurements were performed using the M probe on the right lobe of the liver through 9–11th intercostal space on the middle axillary line with the patient lying in a dorsal position with the right arm in maximal abduction. Ten or more successful acquisitions were performed [14]. To be a valid examination, the interquartile range had to be inferior to 30% [14]. The operator was experienced, had undergone formal training and performed at least 500 examinations before this study. Although the exact cutoff values remained to be explored, a recent pooled analysis of data from 19 studies, comparing with histology, verified that CAP data defined the presence of HS with the optimal cutoffs of 248, 268, and 280 dB/m for identifying steatosis grades greater than S0, S1, and S2, respectively [16].

Statistical analysis

Statistical analysis was performed with SPSS, version 22.0 (IBM, Armonk, New York, USA). The categorical variables are presented as frequencies and percentages, and continuous variables as means and SDs. All reported *P* values are two tailed, with a *P* value inferior to 0.05 indicating statistical significance. The distribution of categorical variables between groups was evaluated by χ^2 -analysis and continuous variables by independent samples Student's *t*-test. Multivariate analysis was performed using binomial regression to identify potential independent predictive factors of HS.

Results

After applying exclusion criteria, 161 patients were included (Fig. 1). The main demographic and clinical characteristics of the study population are summarized in Table 1.

The mean age was 40.6 ± 12.8 years, and 86 patients were females (53.4%). CD affected 101 (62.7%) patients and 60 (37.1%) patients had UC. With regard to CD location, 53.5% of the patients were classified as ileal (L1), 36.6% as ileocolic (L3), and 9.9% as a colic disease (L2). The disease behavior of patients with CD was B1

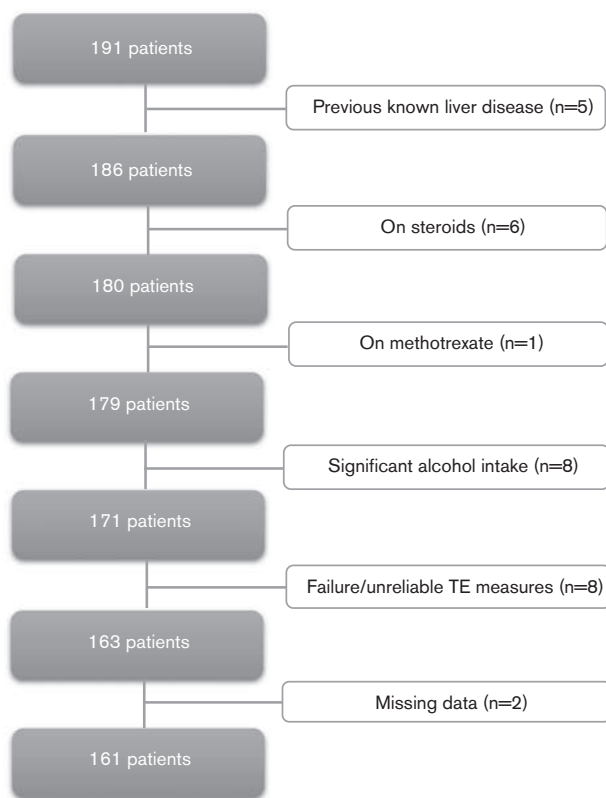


Fig. 1. Flow chart displaying the selection of patients in the study cohort.

Table 1. Demographic and clinical characteristics of the population

Variables	
N	161
Female [n (%)]	86 (53.4)
Age (mean ± SD) (years)	40.6 ± 12.8
Age at diagnosis (mean ± SD) (years)	33.2 ± 11.9
Duration of IBD (mean ± SD) (months)	91.5 ± 77.4
BMI (mean ± SD) (kg/m ²)	25.1 ± 3.9
Weight (mean ± SD) (kg,)	69.1 ± 12.6
Height (mean ± SD) (m)	1.7 ± 0.1
Waist circumference (mean ± SD) (cm)	87.4 ± 11.4
Obesity [n (%)]	21 (13)
Diabetes [n (%)]	10 (6.2)
Arterial hypertension [n (%)]	18 (11.2)
Dyslipidemia [n (%)]	50 (31.1)
Metabolic syndrome [n (%)]	21 (13.2)
Previous cycles of steroids [n (%)]	85 (52.8)
Azathioprine [n (%)]	77 (47.8)
Biological Therapy [n (%)]	63 (39.1)
IBD-related surgeries [n (%)]	34 (21.1)
Follow-up after surgery (mean ± SD) (months)	110 ± 62.5
Hgb (mean ± SD) (g/dl)	14.0 ± 1.3
AST (mean ± SD) (U/l)	20.8 ± 13.2
ALT (mean ± SD) (U/l)	30.8 ± 18.7
G-GT (mean ± SD) (U/l)	29.9 ± 23.2
TG (mean ± SD) (mg/dl)	117.2 ± 61.5
Albumin (mean ± SD) (g/dl)	3.8 ± 0.5
ESR (mean ± SD) (mm)	13.4 ± 12.8
CRP (mean ± SD) (mg/l)	6.4 ± 12.1
Calprotectin (mean ± SD) (g/g)	429.5 ± 494.4
HSI (mean ± SD)	33.4 ± 5.2
FLI (mean ± SD)	33.5 ± 26.2
CAP (mean ± SD) (dB/m)	248.4 ± 55.7

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAP, controlled attenuation parameter; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FLI, Fatty Liver Index; G-GT, γ-glutamyl transferase; HSI, Hepatic Steatosis Index; IBD, inflammatory bowel disease; TG, triglycerides.

(nonstricturing/nonpenetrating) in 44.6%, stricturing (B2) in 33.7%, and penetrating (B3) in 21.8%. The perianal disease was present in 30.7% of the patients.

Patients who had UC presented with pancolitis in 43.3%, left sided-colitis in 30% and proctitis in 26.7%.

The mean BMI was 25.1 ± 3.9 kg/m², and 21 (13.0%) were obese (BMI > 30 kg/m²). Mean age at IBD diagnosis was 32.2 ± 11.9 years, and the mean duration was 91.5 ± 77.4 months. Thirty-four (21.1%) patients had a previous history of surgery, and the mean follow-up after surgery was 110 ± 62.5 months. Patients with a past history of IBD-related surgery were more frequently obese (26.5 vs. 9.4%; $P=0.009$). No patient had received par-enteral nutrition during hospitalizations.

Presence of hepatic steatosis defined by clinical-analytical scores

In our cohort, 46 (28.6%) patients had an HSI greater than 36 and 27 (16.8%) had an FLI greater than 60.

There were no differences in the mean HSI (33.4 ± 5.2) and FLI (33.5 ± 26.2) among patients with CD and UC and therefore no differences in the presence of steatosis defined by the two clinical-analytical scores between patients with CD and UC.

Patients with HSI greater than 36 had more frequent diabetes (13.0 vs. 3.5%; $P=0.023$) and metabolic syndrome (28.9 vs. 7.0%; $P<0.001$) and were more frequently obese (45.7 vs. 0.0%; $P<0.001$).

Patients with FLI greater than 60 experienced, more frequently, diabetes (14.8 vs. 4.5%; $P=0.042$), dyslipidemia (55.6 vs. 26.1%; $P=0.003$), hypertension (22.2 vs. 9.0%; $P=0.046$), and metabolic syndrome (51.9 vs. 5.3%; $P<0.001$); were more commonly obese (63.0 vs. 3.0%; $P<0.001$); and more frequently had IBD-related surgeries (48.1 vs. 15.7%; $P<0.001$).

There were no differences between the groups with or without HS in terms of sex, the frequency of previous use of corticosteroids, and biological therapy.

Presence of hepatic steatosis defined by controlled attenuation parameter: transient elastography

In our cohort, 73 (45.3%) patients presented with CAP greater than 248, 10 (13.7%) of them had CAP between 268 and 280 and 45 (61.6%) had CAP greater than 280, representing steatosis grades greater than S0, S1, and S2, respectively.

We found that patients with CAP greater than 248 were older (37.8 vs. 29.3 years; $P<0.001$), with older age at IBD diagnosis (45.7 vs. 36.4; $P<0.001$), were more frequently obese (28.8 vs. 0.0% $P<0.001$), were males (57.5 vs. 37.5% $P=0.011$), and presented more often with diabetes (11.0 vs. 2.3%; $P=0.023$), hypertension (21.9 vs. 2.3%; $P<0.001$), dyslipidemia (43.8 vs. 20.5%; $P=0.001$), and metabolic syndrome (23.9 vs. 4.5% $P<0.001$). With regard to IBD factors, patients with HS had a higher frequency of previous surgeries (31.5 vs. 12.5%; $P=0.003$).

There were no differences in terms of duration of IBD (97.5 vs. 86.5; $P=0.84$), the presence of perianal disease (51.6 vs. 45.1%; $P=0.543$), previous use of corticosteroids (49.3 vs. 55.7%; $P=0.42$), and biological therapy (32.9 vs. 44.3%; $P=0.139$).

Table 2. Predictive factors of hepatic steatosis in patients with inflammatory bowel disease

	Univariate analysis			Multivariate analysis
	HS (CAP > 248)	No HS (CAP < 248)	P value	OR (95% CI); P value
Male [n (%)]	42 (57.5)	33 (37.5)	0.011*	5.7 (2.0–15.9); $P=0.001^*$
Age (years)	37.8	29.3	<0.001*	NS
Age at diagnosis	45.7	36.4	<0.001*	NS
BMI (kg/m ²)	27.7	22.9	0.005*	NS
Obese (%)	28.8	0.0	<0.001*	NS
Diabetes [n (%)]	8 (11.0)	2 (2.3)	0.023*	NS
Hypertension [n (%)]	16 (21.9)	2 (2.3)	0.000*	NS
Dyslipidemia [n (%)]	32 (43.8)	18 (20.5)	0.001*	NS
Metabolic syndrome [n (%)]	17 (23.9)	4 (4.5)	0.000*	NS
IBD-related surgery [n (%)]	23 (31.5)	11 (12.5)	0.003*	5.9 (1.5–22.9); $P=0.011^*$
CRP (mg/l)	4.5	8.1	0.002*	NS
Calprotectin (g/g)	353.3	491.7	0.039*	NS

CAP, controlled attenuation parameter; CI, confidence interval; CRP, C-reactive protein; HS, hepatic steatosis; IBD, inflammatory bowel disease; OR, odds ratio.

*Statistically significant; the P values refer to t -test or χ^2 -test between patients with the outcome (CAP > 248) and those without the outcome.

With regard to inflammatory biomarkers, we found lower levels of CRP (4.46 vs. 8.09; $P=0.002$) and calprotectin (353 vs. 492; $P=0.039$) in patients with HS.

Table 2 shows the results of multivariate analyses for predictors of HS. After adjustments, male sex [odds ratio: 5.7 (95% confidence interval: 2.0–15.9); $P=0.001$] and previous related IBD surgery [odds ratio: 5.9 (95% confidence interval: 1.5–22.9); $P=0.011$] were the independent predictive factors of HS.

Discussion

Our study reveals several important findings, namely, the high frequency of HS and the identification of independent predictive factors for HS in an IBD population. To our knowledge, there are few studies reporting the screening of NAFLD in patients with IBD [8,18,22,23]. NAFLD is the most common chronic liver disease in the world, and it is globally rising as a result of increasingly sedentary lifestyles [24]. Recently, in the IBD population, HS is increasingly being diagnosed with prevalence ranging from 6.2 to 40% depending on definition and diagnostic tool [5–8,18,22,23]. Indeed, most previous studies were either of a retrospective nature or small sample size [7,8,25,26]. Autopsy series reported a prevalence of HS in 15–88% of patients with IBD, representing the most common extra-intestinal pathologic abnormality [6,27–31].

In our cohort, we found a frequency of HS that ranges between 16.8 and 45.3%, which is in accordance with recent studies [7,8,18]. This broad range depends on the diagnostic tool used, lower frequencies correspond to clinical-analytical scores (lower sensitivity) and higher to TE.

CAP is a new modality on TE that is an easy and fast examination with high accuracy for detecting steatosis providing a numerical value [32,33]. It grades the severity of fat infiltration which correlates with the histological degree of steatosis and has been validated in a variety of clinical populations [16,32–34]. When compared with liver biopsy, TE measures a 100 times larger region than the volume of the cylinder obtained by liver biopsy [14].

The discrepancy between the frequencies of HS (16.8% defined by FLI and 45.3% defined by CAP) observed in our cohort may be owing to higher sensitivity of CAP when compared with clinical-analytical scores in the detection of early-stage steatosis, as we used a lower cutoff

of 248, reported as optimal in a recent meta-analysis, corresponding to less than 5–10% of steatosis [16]. Two recent studies that screened NAFLD in an IBD population based on TE presented a prevalence of 32–71%; the last reported prevalence was very high owing to the lower cutoff of CAP employed (219 dB/m) [18,35].

Indeed, TE results seem to outperform simple serum biomarkers and ultrasound [34,36,37], and it is why we focus on independent predictor factors based on TE.

The pathogenesis of NAFLD in IBD is not completely understood, although several factors had been pointed to be involved [7–10].

In our cohort, we verify that patients with HS defined as CAP greater than 248 had more frequently the traditional metabolic risk factors for NAFLD, namely, male sex, diabetes, hypertension, dyslipidemia, obesity, and metabolic syndrome, underlying the relevance of metabolic conditions.

Over the years, we have been assisting the change of phenotype of patients with IBD from underweight and undernourished to overweight and even obese [38]. It is estimated, as with the general population, that almost 20–30% of patients with IBD are overweight and obese [38–40]. Consequently, these patients are at risk of developing NAFLD [38,41,42]. In our cohort, the frequency of obesity was 13.0%, and these patients presented more frequently with HS (28.8 vs. 0.0%; $P<0.001$).

Even though, in multivariate analysis, we found that male sex and history of related IBD surgeries were the independent predictive factors for HS. A patient with previous IBD surgery presents a risk of HS of almost six times higher than patients without a history of previous surgeries.

In accordance with our findings, Sourianarayanan *et al.* [7] reported that patients who had small bowel surgery were 3.7 times more likely to have NAFLD. The same was verified by Bessissow *et al.* [8] when HS was assessed by serum biomarkers.

In the aforementioned study by Bessissow and colleagues, they argued that history of surgery is a risk factor for NAFLD because it represents the severity of the disease with a more active inflammatory condition, exposing patients to multiple risks factors for NAFLD including chronic relapsing inflammation, alteration of gut microbiome, hepatotoxic drugs, and even nutritional deficiencies [8,43].

However, in our study, these aforementioned mechanisms do not seem to explain our findings as we present patients with a mean follow-up of 9 years after surgery. Instead, we can hypothesize that our findings may reflect the clinical improvement after surgery, indicating a better nutritional status [25]. After the stabilization of the inflammatory activity, patients will have an improvement in appetite, promoting weight gain [25]. An excess intake of dietary triglycerides and carbohydrates is transformed into free fatty acids and triggers the development of insulin resistance through a number of mechanisms [44]. Insulin resistance plays a central role in the development of steatosis, which results in hepatic de novo lipogenesis and subsequent reduction of adipose tissue lipolysis, with a consequent increase and deposition of fatty acids in the liver [44]. Supporting this hypothesis, we verified that patients submitted to surgery were more frequently obese (26.5 vs. 9.4%; $P=0.009$).

Finally, we found that patients with HS had lower values of inflammatory biomarkers – CRP (4.5 vs. 8.1; $P=0.002$) and calprotectin (353.0 vs. 492.0; $P=0.039$); however, it was not statistically significant in multivariate analysis. These findings may be explained once again by the control of inflammatory activity and better nutritional status, turning those patients more predisposed to develop metabolic risk factors. Two studies have found that obesity and NAFLD in patients with IBD are markers of a less severe disease course in IBD which may support our results [25,45].

Conclusion

This study showed that the prevalence of HS in an IBD population is high. Optimization of metabolic risk factors, including an emphasis on weight loss promoting physical activity and healthy lifestyles, should continue to be important priorities in the management of patients with IBD.

This study advocates the routine screening of high-risk IBD individuals for hepatic disorders, including males with the previous history of IBD-related surgery. ET seems an easy, noninvasive, fast and convenient screening method. More prospective studies are needed to support our results and to evaluate the effect of HS in the follow-up of patients with IBD.

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Authors' contributions: Cátia Arieira, Francisca Dias de Castro, and Joana Magalhães designed the study, interpreted the data, and drafted the manuscript. Cátia Arieira, Sara Monteiro, and Sofia Xavier participated in the acquisition of data and performed the statistical analysis. Maria João Moreira and Carla Marinho critically revised the manuscript. José Cotter critically revised and approved the final version of the manuscript.

Conflicts of interest

There are no conflicts of interest.

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