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Liver Function Test Abnormalities in Patients with Inflammatory Bowel Diseases: A Hospital-based Survey

Maria Cappello, Claudia Randazzo, Ivana Bravatà, Anna Licata, Sergio Peralta, Antonio Craxì and Piero Luigi Almasio

Gastroenterology and Hepatology Section, Dipartimento Biomedico di Medicina Interna e Specialistica, Università di Palermo, Palermo, Italy.

ABSTRACT

BACKGROUND AND AIMS: Inflammatory bowel diseases (IBD) are frequently associated with altered liver function tests (LFTs). The causal relationship between abnormal LFTs and IBD is unclear. The aim of our study was to evaluate the prevalence and etiology of LFTs abnormalities and their association with clinical variables in a cohort of IBD patients followed up in a single center.

MATERIALS AND METHODS: A retrospective review was undertaken of all consecutive IBD in- and outpatients routinely followed up at a single referral center. Clinical and demographic parameters were recorded. Subjects were excluded if they had a previous diagnosis of chronic liver disease. LFT abnormality was defined as an increase in aspartate aminotransferase, (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), or total bilirubin.

RESULTS: A cohort of 335 patients (179 males, mean age 46.0 ± 15.6 years) was analyzed. Abnormal LFTs were detected in 70 patients (20.9%). In most cases, the alterations were mild and spontaneously returned to normal values in about 60% of patients. Patients with abnormal LFTs were less frequently on treatment with aminosalicylates (22.8 vs. 36.6%, $P = 0.04$). The most frequent cause for transient abnormal LFTs was drug-induced cholestasis (34.1%), whereas fatty liver was the most frequent cause of persistent liver damage (65.4%). A cholestatic pattern was found in 60.0% of patients and was mainly related to older age, longer duration of disease, and hypertension.

CONCLUSIONS: The prevalence of LFT abnormalities is relatively high in IBD patients, but the development of severe liver injury is exceptional. Moreover, most alterations of LFTs are mild and spontaneously return to normal values. Drug-induced hepatotoxicity and fatty liver are the most relevant causes of abnormal LFTs in patients with IBD.

KEY WORDS: liver function tests, inflammatory bowel disease, drug-induced hepatotoxicity, fatty liver

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CORRESPONDENCE: cmarica@tin.it

Introduction

Hepatobiliary diseases constitute some of the most common extra-intestinal problems of inflammatory bowel diseases (IBD).[1] Reported prevalence of liver and biliary tree illnesses in IBD ranges from 3% to more than 50%, depending on whether the definition of disease includes only definite conditions, persistent or also transient elevation of hepatic biochemistries.[2,3] Elevation of liver function tests (LFTs) has been observed from 11 to 49% in IBD patients in different studies.[4–6] A true estimation of the prevalence of altered LFTs in IBD patients is difficult to reach because different methods have been used for data collection, diagnostic criteria differ from one study to another, and patient selection has not been standardized.

Hepatobiliary diseases in IBD may be caused by an altered immune response and may also be linked to adverse reactions to drugs.[1,7] The most common immunological disorder is primary sclerosing cholangitis (PSC). Autoimmune

hepatitis (AIH) has also been described, and an overlap syndrome sharing features of PSC and AIH has been reported in some IBD patients.[8,9] Apart from classical immunological liver diseases, other abnormalities are more often observed. Non-specific hepatomegaly is commonly reported in IBD and is strictly related to fatty liver. Fatty liver has been described in clinical studies in more than 30% of patients, and it does not seem to be related to sex and kinds of IBD.[2] Also cholelithiasis is more frequent in IBD patients than in the general population.[7] Drug-related hepatotoxicity (drug-induced liver injury, DILI) is a relevant cause of altered LFTs, in particular in patients receiving thiopurines.[10] Methotrexate (MTX) and infliximab have also been reported to cause liver damage in IBD patients.[11,12]

In this study, we report the prevalence of LFT abnormalities in a cohort of IBD patients followed up in a single center. Furthermore, we evaluate the etiology and the risk factors associated with abnormal LFTs.

Patients and Methods

A retrospective review of the clinical records of the Gastroenterology Unit, at University of Palermo was undertaken. All charts were reviewed identifying IBD inpatient and outpatient seen in the clinic between 2007 and 2009. The study was conducted after approval from the hospital ethical committee. Moreover, there was a waiver of the informed consent. The diagnosis of IBD was established according to standard clinical, endoscopic, histological, and radiological criteria.[13] Disease features were defined using the Vienna classification,[14] based on age at diagnosis, location, and behavior for Crohn's disease (CD), the ECCO (European Crohn's and Colitis Organization) criteria,[15] and the location and extension of the disease, for ulcerative colitis (UC). Patients in whom hepatic biochemistries were not obtained were excluded from the analysis. We also excluded patients with positive hepatitis B (HBV) or hepatitis C virus (HCV) markers and with previous diagnosis of chronic liver disease. Other analyses, such as hemochromatosis and Wilson's disease screening, were performed only by clinical judgment when needed. The following data were collected from each patient at the time of the last follow-up visit: demographic characteristics (age, gender, body weight, height), smoking habit, IBD type, disease duration, site of involvement and behavior, presence of extra-intestinal manifestations, past and current medications, and thorough medical history (including diabetes, hypertension, dyslipidemia, and obesity).

Abnormality of LFTs was defined as an increase in serum aminotransferases (alanine aminotransferase, ALT; aspartate aminotransferase, AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), or total bilirubin. The abnormal LFT pattern was characterized as follows: "cytolytic" type was defined as ALT/ALP ratio >5 and "cholestatic" type as ratio <2. The LFT abnormalities were considered transient if the liver enzymes returned to normal within a period of three months and follow-up repeat LFTs were normal.

Patients who had abnormal LFTs repeat LFTs every three to six months. If the LFTs did not normalize, and the values were persistently abnormal, the highest values of LFTs were taken into consideration. Patients with initial normal LFTs underwent follow-up only when they were on azathioprine (AZA), 6-mercaptopurine (MP), or MTX or when they had abnormal findings on abdominal imaging, such as hepatosplenomegaly. All patients with abnormal LFTs underwent abdominal ultrasound (US) examination, virological tests to rule out hepatitis B and C infection, and laboratory tests including autoantibodies (antinuclear autoantibodies, anti-smooth muscle autoantibodies, anti-liver/kidney autoantibodies, and anti-mitochondrial autoantibodies). Patients with transient abnormal LFTs did not have a complete imaging and immunological evaluation. DILI was diagnosed if the LFTs increased after the recent use of a hepatotoxic medication and the levels returned back to normal after the drug was stopped.

Statistical analysis. For continuous variables, the mean and standard deviation (SD) were calculated. For categorical variables, the frequency and corresponding percentages were provided. To explore univariate associations of categorical data distribution, chi-squared test or Fisher's exact test was used, as appropriate. Continuous variables were compared by Student's *t*-test. A *P* value less than 0.05 was considered statistically significant. Data statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 13.0 for Windows.

Results

A total of 376 IBD patients were identified from the database. In all, 41 patients (10.9%) were excluded from the study for the following reasons: 19 (5.05%) patients because LFT abnormalities were related with definite chronic liver diseases, either autoimmune (5 PSC, 2 AIH) or chronic viral hepatitis (11 HCV related, 1 HBV related), and 22 because of unavailable hepatic biochemistries. Subsequently, the records of 335 patients were accessible for the analysis. The study included 194 (57.9%) patients with CD and 141 (42.1%) with UC. According to Vienna classification, CD patients presented the following characteristics: age at diagnosis—A1 below 40 years, 65.5% and A2 above 40 years, 34.5%, location—L1 ileal, 25.8%; L2 colonic, 10.3%; L3 ileocolonic, 56.7%; and L4 upper, 7.2%, and behavior—B1 non-stricturing, non-penetrating, 42.8%; B2 stricturing, 35.6%; and B3 penetrating, 14.9%, 6.7% had both stricturing and penetrating disease. In all, 30 patients (15.4%) had perianal involvement. Location distribution for UC patients was as follows: proctitis/proctosigmoiditis (14.2%), left-sided colitis (52.5%), and pancolitis (33.3%). Table 1 summarizes the differences between UC and CD patients. UC patients were slightly older (50.5 ± 15.8 vs. 42.6 ± 14.6 years) and had a longer duration of disease (>5 years) than patients with CD

Table 1. Demographic and clinical features of inflammatory bowel diseases patients.

	CROHN'S DISEASE (n = 194)	ULCERATIVE COLITIS (n = 141)	*P* VALUE
Gender			
Male	100 (51.5%)	79 (56.0%)	0.5
Female	94 (48.5%)	62 (44.0%)	
Mean age (yrs)	42.6 ± 14.6	50.5 ± 15.8	<0.001
Duration of disease (months)			
<1 year	24 (12.4%)	12 (8.5%)	<0.001
1–5 years	84 (43.3%)	46 (32.6%)	
>5 years	86 (44.3%)	83 (58.9%)	
Extraintestinal manifestations	54 (27.8%)	15 (10.6%)	<0.001
Previous surgery	54 (27.8%)	9 (6.4%)	0.3
Current smokers	61 (31.4%)	17 (12.0%)	<0.001
Medical treatment#			
• Only aminosalicylates*	59 (30.4%)	54 (38.3%)	0.2
• Any corticosteroids**	59 (30.4%)	55 (39.0%)	0.1
• Immunosuppressive agents***	40 (20.6%)	26 (18.4%)	0.7
• TNF-antagonists****	42 (21.6%)	9 (6.4%)	<0.001
Obesity	23 (11.8%)	3 (2.1%)	0.001
Diabetes	7 (3.6%)	17 (12.0%)	0.003
Hypertension	29 (14.9%)	18 (12.7%)	0.6
Hypercholesterolemia	13 (6.7%)	17 (12.0%)	0.09

Notes: #Some patients with more than one treatment. *Mesalazine, sulfasalazine; **Includes budesonide, prednisone, methylprednisolone; ***Azathioprine, 6-mercaptopurine, methotrexate; ****Infliximab, adalimumab.

($P < 0.001$). Significant differences were found in the proportion of smokers ($P < 0.001$), extra-intestinal manifestations ($P < 0.001$), and obesity ($P = 0.001$) between CD and UC patients. Diabetes was more frequently found in UC patients ($P = 0.003$). The use of anti-Tumor Necrosis Factor (aTNF) alpha agents was significantly higher in patients with CD ($P < 0.001$) as expected.

Abnormal LFTs were detected in 70 (20.9%) patients (44 males, mean age 48.1 ± 15.0), equally distributed among CD and UC (21.6 vs. 19.9%). A comparison of demographic and clinical features between the groups with normal and abnormal LFTs is shown in Table 2. On univariate analysis, there were no significant differences between the two cohorts as regard to gender, age, duration of disease, history of previous intestinal resection, extra-intestinal manifestation, and smoking. Patients with abnormal LFTs were less likely to be taking aminosalicylates than those with normal hepatic biochemistries (22.8 vs. 36.6%, $P = 0.04$). The use of other medications, such as corticosteroids, immunosuppressant, and TNF-antagonists, did not differ between the two groups. The increase in enzyme elevation was mild. In patients with abnormal LFTs, the median AST level was 41 U/L (interquartile range [IQR] 24 U/L, normal <35 U/L), the median ALT level was 61 U/L (IQR 33 U/L, normal <41 U/L), the median GGT level was 76 U/L (IQR 82 U/L, normal <36 U/L), the median ALP level was 120 U/L (IQR 165 U/L, normal <104 U/L), and the median of total bilirubin was 0.75 mg/dL.

Persistent two-fold LFT elevation was found in 26 (37.1%) out of 70 patients (Table 3). These data were confirmed by subsequent biochemical control after three months since first detection. In the remaining patients, the enzyme elevation was transient, lasting for not more than three months. The most common cause of persistent abnormal LFTs was fatty liver (65.4%). Among patients with persistent altered LFTs, four patients were hypertensive, three were obese, and one patient presented dyslipidemia, while none of them had diabetes. In nine patients, cause for persistent LFT abnormalities was not found. One patient had liver metastasis at abdominal US examination.

On the other hand, 44 patients had transient abnormal LFTs. In this group, 15 patients had drug-induced cholestatic liver damage mainly because of immunosuppressants (AZA, MTX). Fatty liver, evaluated by US examination, was found only in one patient. In the remaining 28 cases, the cause of transient abnormal LFTs remained unknown. Six patients were hypertensive, three were obese, three had diabetes, and other three patients presented dyslipidemia. Seven patients had

Table 2. Univariate analysis of risk factors for any abnormal liver function tests.

	ABNORMAL LFTs (n = 70)	NORMAL LFTs (n = 265)	*P* VALUE
Gender			
Male	44 (62.9%)	135 (50.9%)	0.08
Female	26 (37.1%)	130 (49.1%)	
Mean age (yrs)	48.1 ± 15.0	45.4 ± 15.6	0.2
Duration of disease (months)			
<1 year	6 (8.6%)	30 (11.3%)	0.6
1–5 years	25 (35.7%)	105 (39.7%)	
>5 years	39 (55.7%)	130 (49.0%)	
IBD type/extent			
Crohn's disease (n = 194)			
• Ileum	10 (23.9%)	40 (26.3%)	0.8
• Colon	3 (7.1%)	17 (11.2%)	
• Ileo-colon	26 (61.9%)	84 (55.3%)	
• Upper GI	3 (7.1%)	11 (7.2%)	
Ulcerative colitis (n = 141)			
• Proctitis	3 (10.7%)	17 (15.1%)	0.04
• Left-side colitis	10 (35.7%)	64 (56.6%)	
• Pancolitis	15 (53.6%)	32 (28.3%)	
Extra intestinal manifestations	10 (14.3%)	59 (22.2%)	0.18
Previous surgery	15 (21.4%)	48 (18.1%)	0.5
Current smokers	17 (24.3%)	61 (23.0%)	0.7
Medical treatment#			
• Only aminosalicylates*	16 (22.8%)	97 (36.6%)	0.04
• Any corticosteroids**	30 (42.8%)	84 (31.7%)	0.1
• Immunosuppressive agents***	21 (30.0%)	78 (29.4%)	1
• TNF-antagonists****	13 (18.6%)	38 (14.3%)	0.5
Obesity	6 (8.6%)	20 (7.5%)	0.8
Diabetes	3 (4.3%)	21 (7.9%)	0.3
Hypertension	10 (14.3%)	37 (13.9%)	0.9
Hypercholesterolemia	4 (5.7%)	26 (9.8%)	0.3

Notes: #Some patients with more than one treatment. *Mesalazine, sulfasalazine; **Includes budesonide, prednisone, methylprednisolone; ***Azathioprine, 6-mercaptopurine, methotrexate; ****Infliximab, adalimumab.
Abbreviations: LFTs, liver function tests; IBD, inflammatory bowel diseases; GI, gastrointestinal.

also incidental abnormalities at US examination: four benign cysts, two angiomas, and one focal nodular liver hyperplasia.

Among the 70 patients with abnormal LFTs, 28 patients (40.0%) had isolated abnormal aminotransferases and were considered to have a cytolytic pattern of liver damage. In all, 42 patients had also abnormal GGT and ALP levels being classified as cholestatic liver damage. A comparison of demographic and clinical features between the groups with cytolytic and cholestatic LFT abnormalities is shown in Table 4. There were no significant differences between the two groups with regard to gender, IBD subtype, history of intestinal resection, extra-intestinal manifestation, and smoking. Patients with cholestatic pattern of LFT abnormalities were slightly older (52.0 ± 15.4 vs. 42.3 ± 14.0 years, $P = 0.01$) and had a longer duration of disease ($P = 0.005$) than patients with cytolytic pattern. The presence of co-existing hypertension was significantly higher in patients with cholestatic pattern ($P = 0.005$).

Discussion

Several series described altered LFTs in IBD patients.[3–6,16–24] The reported prevalence is variable depending on practice settings and the criteria used to define abnormal LFTs, making a comparison between different studies difficult. Most studies are retrospective and lack matched control groups. Laboratory tests and US have not been used

Table 3. Comparison of clinical and demographic characteristics of IBD patients with persistent vs transient abnormal LFTs.

	PERSISTENT ABNORMAL LFTs (n = 26)	TRANSIENT ABNORMAL LFTs (n = 44)	*P* VALUE
Gender			
Male	16 (60%)	28 (63.6%)	1.0
Female	10 (40%)	16 (36.4%)	
Mean Age (yrs)	47.5 ± 17.4	49.1 ± 15.3	0.5
Type of IBD (%)			
CD	10 (38.5%)	18 (40.9%)	1.0
UC	16 (61.5%)	26 (59.1%)	
Duration of disease (months)			
<1 year	5 (19.2%)	1 (2.3%)	<0.001
1–5 years	14 (53.8%)	11 (25.0%)	
>5 years	7 (27.0%)	32 (72.7%)	
Medical treatment#			
• Only aminosalicylates*	8 (30.7%)	8 (18.2%)	**0.2**
• Any corticosteroids**	13 (50.0%)	17 (38.6%)	
• Immunosuppressive agents***	2 (7.7%)	9 (20.5%)	
• TNF-antagonists****	3 (11.6%)	10 (22.7)	
Cause of liver injury			
• Fatty liver	17 (65.4%)	1 (2.3%)	<0.001
• Drug-induced cholestasis	0	15 (34.1%)	
• Unknown	9 (34.6%)	28 (63.6%)	
Obesity	3 (11.5%)	3 (6.8%)	0.6
Diabetes	0	3 (6.8%)	0.3
Hypertension	4 (15.4%)	6 (13.6%)	1.0
Dyslipidemia	1 (3.9%)	3 (6.8%)	1.0

systematically in the diagnostic work-up. The significance of either cytolytic or cholestatic pattern elevation in LFTs has not been well addressed.

The prevalence of abnormal LFTs in our cohort was 20.9% in asymptomatic patients, with no previous known liver disease or viral-related hepatic damage. This rate is similar to that reported in the literature. An epidemiologic study conducted in the county of Stockholm, enrolling more than 1,000 UC patients followed up for 15 years, reported an 11% prevalence of altered LFTs;[18] the screening procedure included only biochemical testing. Persistent alterations, confirmed by liver morphology, were found by Schrumpf et al[21] in 3–15% of IBD patients. More recently, Gisbert et al[3] observed abnormalities in 15% of IBD patients at some time during the five years of the study.

Our study did not show any associations of LFT abnormalities with clinical and demographic parameters. Our patients with LFT alteration were less likely to be on aminosalicylates. We do not have an explanation for this finding. On the other hand, there are reports of hepatotoxicity related to aminosalicylates use.[25,26]

Transient elevations in LFTs returning to normal levels within three months were seen in 62.9% of our patients. Similar observations were reported in a large Swedish follow-up study.[18] The most frequent cause of transient LFT alteration was DILI (34.1%), possibly linked to an increased and earlier use of immunosuppressive agents in the attempt to reduce the use of corticosteroids. The incidence of thiopurine-induced hepatotoxicity has been variously reported among different case series, and the data are sometimes conflicting. Overall, the incidence of hepatotoxicity in IBD patients on AZA/6-MP calculated from previous (mainly retrospective) studies seems to be only 1–2% per patient and year of treatment, with no difference between AZA and 6-MP.[10] A favorable evolution of LFTs after withdrawal of AZA/6-MP, with liver enzymes returning to normal after stopping the medication, has been reported.[27,28] In our study, all patients in whom AZA/6-MP was withdrawn because of hepatotoxicity normalized LFTs after treatment was discontinued. Moreover, most of the cases of DILI in our IBD patients were mild.

The cause of transient abnormal LFTs was not clear in more than half of the patients. Some patients were on antibiotics; the

Table 4. Univariate analysis of risk factors for cytolytic versus cholestatic pattern of abnormal LFTs.

CHARACTERISTICS	CYTOLYTIC PATTERN (n = 28)	CHOLESTATIC PATTERN (n = 42)	*P* VALUE
Gender			
Male	17 (60.7%)	27 (64.3%)	0.8
Female	11 (39.3%)	15 (35.7%)	
Mean age (yrs)	42.3 ± 14.0	52.0 ± 15.4	0.01
Duration of disease (months)			
<1 year	6 (21.4%)	0	0.005
1–5 years	7 (25.0%)	18 (42.9%)	
>5 years	15 (53.6%)	24 (57.1%)	
IBD type			
Crohn's disease	18 (64.3%)	24 (57.1%)	0.5
Ulcerative colitis	19 (35.7%)	18 (42.9%)	
Extra intestinal manifestations	5 (17.9%)	5 (11.9%)	0.7
Previous surgery	4 (14.3%)	11 (26.2%)	0.2
Current smoker	7 (25.0%)	10 (23.8%)	0.8
Obesity	2 (7.1%)	4 (9.5%)	0.7
Diabetes	0	3 (7.1%)	0.1
Hypertension	0	10 (23.8%)	0.005
Hypercholesterolemia	1 (3.6%)	3 (7.1%)	0.5

Abbreviation: IBD, inflammatory bowel diseses.

possibility of antibiotics causing transient elevation could not be completely ruled out. However, in most patients antibiotics were continued for several months and the LFTs normalized when the patients were still on antibiotics. It should be stressed that the short period of observation is a potential drawback of our results because the percentage of the established diagnosis may have changed as the time passed.

Fatty liver, diagnosed on abdominal US findings, was the most frequent cause of persistent altered LFTs in our cohort. Bargiggia et al[29] evaluated the prevalence of liver enlargement and steatosis in a large IBD population and found these abnormalities in >39% of CD and >35% of UC patients, a higher prevalence than among healthy controls. Other studies have also confirmed that more IBD patients than controls have liver steatosis, with percentages ranging from 13% to almost 100%.[19,20] However, US changes including hepatomegaly or a dysechoic liver echo pattern have also been observed in the absence of any LFT abnormalities in about 60% of IBD patients.[19] The rate of fatty liver in our study is similar to that described in the above-mentioned study, but this finding was not related to the presence of obesity or dyslipidemia.

Cholelithiasis was frequently found in our series of patients with persistent LFT abnormalities, especially in CD patients. Comparable findings have also been reported from Italian and Swedish studies.[29,30] Abnormal bile salt absorption is proposed to result in an increased incidence of gallbladder stones in CD patients ranging from 13 to 34%.[29] On the other hand, the association between cholelithiasis and UC is controversial. Only Lorusso et al[31] have reported that the prevalence of cholelithiasis is higher in UC patients than in the general population.

The most frequent pattern of liver damage was cholestatic. Univariate analysis suggested a correlation between older age, longer duration of disease, co-existing hypertension, and the prevalence of this pattern of LFT elevation.

In conclusion our data suggest that even in the absence of symptoms, hepatobiliary function should be monitored in IBD patients, given the high incidence of LFT abnormalities. Patients on immunosuppressive treatment should be more closely monitored. We did not found any risk factor related to cytolytic alteration, whereas cholestatic alterations seem to increase in presence of co-existent hypertension, older age, and longer duration of disease. Moreover, most of the cases of abnormal LFTs in IBD patients are mild and spontaneously return to normal values in close to 60% of patients. These data need to be further explored in larger prospective series.

Author Contributions

Conceived and designed the experiments: MC, CR, AL, SP, PLA. Analyzed the data: MC, AL, PLA. Wrote the first draft of the manuscript: MC, CR, IB. Contributed to the writing of the manuscript: MC, CR, AL, PLA. Agree with manuscript results and conclusions: MC, CR, IB, AL, SP, AC, PLA.

Jointly developed the structure and arguments for the paper: MC, PLA. Made critical revisions and approved final version: MC, AL, AC, PLA. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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