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Observations and Research

Nonalcoholic Fatty Liver Disease Is a Risk Factor for Thiopurine Hepatotoxicity in Crohn's Disease

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Background: Patients with Crohn's disease (CD) are predisposed to nonalcoholic fatty liver disease (NAFLD). CD management often includes thiopurines which can promote hepatotoxicity. We aimed to identify the role of NAFLD on the risk of developing liver injury from thiopurines in CD.

Methods: In this prospective cohort analysis, CD patients at a single center were recruited 6/2017–5/2018. Patients with alternative liver diseases were excluded. The primary outcome was time to elevation of liver enzymes. Patients underwent MRI with assessment of proton density fat fraction (PDFF) on enrollment, where NAFLD was defined as PDFF >5.5%. Statistical analysis was performed using a Cox-proportional hazards model.

Results: Of the 311 CD patients studied, 116 (37%) were treated with thiopurines, 54 (47%) of which were found to have NAFLD. At follow-up, there were 44 total cases of elevated liver enzymes in those treated with thiopurines. Multivariable analysis demonstrated that NAFLD was a predictor of elevated liver enzymes in patients with CD treated with thiopurines (HR 3.0, 95% CI 1.2–7.3, $P = .018$) independent of age, body mass index, hypertension, and type 2 diabetes. Steatosis severity by PDFF positively correlated with peak alanine aminotransferase (ALT) at follow-up. Kaplan–Meier analysis demonstrated poorer complication-free survival (log-rank 13.1, $P < .001$).

Conclusions: NAFLD at baseline is a risk factor for thiopurine-induced hepatotoxicity in patients with CD. The degree of liver fat positively correlated with the degree of ALT elevation. These data suggest that evaluation for hepatic steatosis be considered in patients with liver enzyme elevations with thiopurine therapy.

Lay Summary

The presence of nonalcoholic fatty liver disease in patients with Crohn's disease increases the likelihood and severity of thiopurine-induced hepatotoxicity. Hepatic steatosis should be considered among the causes for liver enzyme elevation while on thiopurines.

Key Words: Crohn's disease, nonalcoholic fatty liver disease, thiopurine, hepatotoxicity, proton density fat fraction

Introduction

Crohn's disease (CD) is characterized by chronic inflammation of the gastrointestinal tract that can exhibit various extraintestinal manifestations. Specifically, patients with CD have been shown to have an increased risk of developing nonalcoholic fatty liver disease (NAFLD).[1–3] Both diseases are increasing in prevalence globally and create greater clinical and economic burden.[4,5] Importantly, liver diseases have been suggested to increase mortality in CD.[6] While both involve chronic inflammatory processes, the pathophysiologic association between these diseases is not completely understood. Several studies have suggested metabolic dysregulation, CD disease activity, gut dysbiosis, and adverse effects of CD-targeted therapeutic agents as contributing factors to NAFLD development in CD.[7,8]

Thiopurines, such as 6-mercaptopurine or its precursor azathioprine, are corticosteroid-sparing agents in CD management. However, they are known to trigger several forms of liver injury, including asymptomatic elevation in liver enzymes, hepatocellular necrosis, and/or cholestasis.[9] A systematic review of 34 retrospective studies on thiopurine-induced liver injury in inflammatory bowel disease (IBD) found its mean prevalence to be 3% and the mean annual incidence to be 1.4%.[9] There exist multiple physiologic pathways for 6-mercaptopurine, including degradation by xanthine oxidase, conversion to 6-methylmercaptopurine (6-MMP) by thiopurine *S*-methyltransferase (TPMT), or conversion to 6-thioguanine by hypoxanthine phosphoribosyltransferase (HPRT). Genetic polymorphisms resulting in increased TPMT activity increases 6-MMP concentrations and have been implicated in greater hepatotoxicity.[10]

Preliminary investigations have examined the role of hepatic steatosis determined by ultrasound in patients with IBD on various medications,[11,12] however, the performance of abdominal ultrasound for the diagnosis of NAFLD is suboptimal

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in large part due to its limited sensitivity for depicting mild steatosis.[13] Due to these prior limitations, we used proton density fat fraction (PDFF) mapping generated from baseline magnetic resonance enterography (MRE) sequences to better evaluate hepatic steatosis given its improved sensitivity and specificity.[14] In this prospective cohort analysis, we aimed to investigate the association between NAFLD and liver enzyme elevation in patients with CD on thiopurine therapy. We hypothesized that NAFLD increased the risk for liver injury in patients with CD being treated with thiopurines.

Materials and Methods

Patient Selection

This study was approved with a waiver of consent by our institutional review board with ID#201705093. Patients with CD undergoing MRE were prospectively and consecutively enrolled at our IBD Center between June 1, 2017 and May 31, 2018. A chart review was conducted to determine demographics, vital statistics, CD phenotype, outpatient and inpatient records, medication lists, laboratory values, endoscopic reports, and radiographic data. Baseline clinical prediction tool for nonalcoholic fatty liver disease (CPN-CD) scoring was calculated (ibdnafld.wustl.edu) as previously described.[2] Baseline endoscopy was scored using the simple endoscopic score in Crohn's disease (SES-CD).[15] All data were managed using REDCap (Research Electronic Data Capture)[16] tools hosted by Washington University in St. Louis.

Inclusion and Exclusion Criteria

Patients were included if they were diagnosed with CD by a gastroenterologist at the Washington University IBD Center and had undergone MRE examination with multi-echo sequences to generate PDFF measurements. Patients were excluded if they had a confounding IBD diagnosis (ie indeterminate colitis, ulcerative colitis, microscopic colitis) or another etiology of their liver disease. Specifically, those with greater than moderate alcohol use per AASLD[17] and EASL[18] guidelines (>3 standard drinks/day in men or >2 standard drinks/day in women), or a diagnosis of alcohol use disorder, chronic viral hepatitis, autoimmune liver disease, or other toxic-metabolic liver diseases (hemochromatosis, α-1 antitrypsin deficiency) were excluded. Patients with severe malnutrition, glucocorticoid use, methotrexate use, and baseline elevated liver enzymes were not excluded so that they could be characterized in the context of this population.

Imaging and PDFF Processing

Imaging was performed on 1.5 or 3.0 T Siemens (Erlangen, Germany) MR machines. Previous studies have reported agreement of PDFF measurements regardless of MR machine manufacturers or magnet strength.[19] Patients underwent staging MRE with assessment of PDFF, where a mean PDFF >5.5% indicated NAFLD.[20] Severity of disease activity was scored using the magnetic resonance index of activity (MaRIA) score.[21]

Measurement of Liver Enzymes and Liver Injury

Levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were collected at baseline and follow-up. Those found to have elevated liver enzymes at follow-up were defined to have AST >45 units L^{-1}, ALT >45 units L^{-1}, or ALP >130 units L^{-1}. Patients diagnosed with drug-induced liver injury (DILI) experienced an ALT >5 times the upper limit of normal and/or an ALP >2 times the upper limit of normal, consistent with updated Roussel Uclaf Causality Assessment Method criteria.[22] Persistent elevations were defined as 2 consecutive elevations in liver enzymes.

Statistical Analysis

The primary outcome included time to elevation in liver enzymes and secondary outcome was time to DILI. Categorical variables were compared using the chi-square test. Medians were compared using the independent-samples median test. Kaplan–Meier analysis was used to determine complication-free survival which referred to the time until the patient was found to have an elevated liver enzyme at follow-up. Multivariable regression was performed on variables with $P < .1$ in the univariate analysis or if biologically relevant. This was completed using a Cox-proportional hazards model and backward stepwise selection method with Bayesian information criterion (BIC) selection criteria. A 2-sided P value <.05 was considered statistically significant. All statistics were calculated using SPSS v28 (IBM Corp).

Ethical Considerations

Study was approved by the Washington University in St. Louis School of Medicine Institutional Review Board # 201705093 initially on 5/162017 and reapproved on 3/20/22 through 3/19/23.

Results

Baseline Characteristics

A total of 311 patients with CD were enrolled after the exclusion of 22 patients (Figure 1) as previously published.[1,2] The subset of the cohort analyzed here consisted of 116 patients who were initiating or maintained on a thiopurine, 54 (47%) of which had NAFLD. Baseline characteristics showed that those diagnosed with NAFLD were older with higher median body mass index (BMI) and a greater percentage with hypertension and type 2 diabetes mellitus (Table 1). Median follow-up time was 2.5 years.

NAFLD and Thiopurine-Related Liver Injury

Follow-up revealed 44 patients with elevated liver enzymes, including 2 patients meeting criteria for DILI. Specifically, one of the patients with DILI had an ALP greater than 2 times the upper limit of normal with NAFLD, while the other had an AST greater than 5 times the upper limit of normal without NAFLD. Patients on thiopurines with NAFLD were significantly more likely to experience elevated liver enzymes at follow-up compared with those without (Figure 2A, $P = .002$). Persistent elevations were also more frequent in the NAFLD group (Figure 2B, $P < .001$). While the differences remained suggestive at ALT elevations greater than 2 times the upper limit of normal (Figure 2C, $P = .051$), median peak ALT at follow-up was overall significantly greater in patients with NAFLD (Figure 2D, 43 vs 28 units L^{-1}, $P < .001$). Of the 44 patients who experienced elevations in liver enzymes at follow-up, there were 24 persistent cases, 6 of which resolved after decreasing the dose or stopping thiopurine therapy while the remaining with persistent elevation were monitored

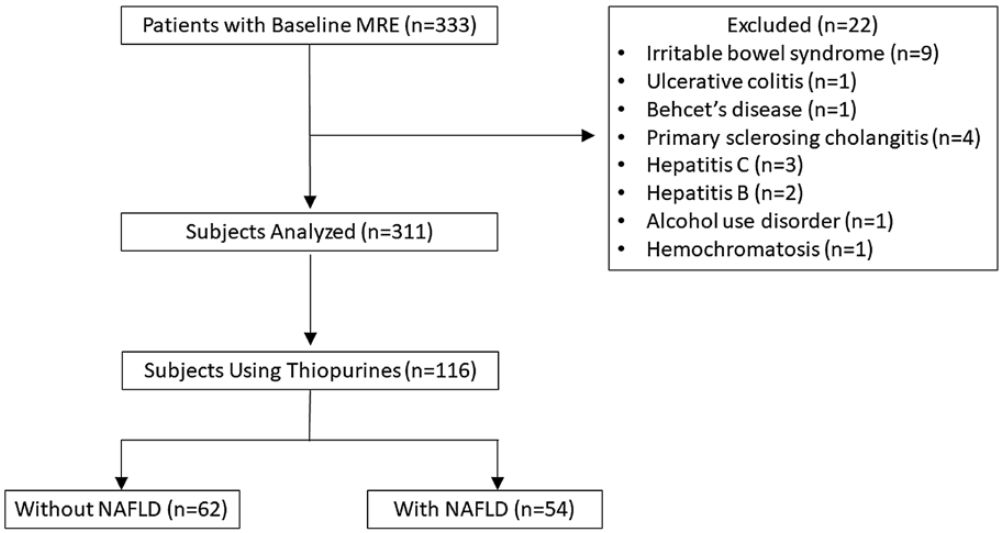

Figure 1. Patient selection. Abbreviations: MRE, magnetic resonance enterography; NAFLD, nonalcoholic fatty liver disease.

on the same dose of thiopurines. In addition, the severity of hepatic steatosis as represented by mean baseline PDFF had a direct relationship with peak ALT levels at follow-up (Figure 3A) and baseline CPN-CD scores (Figure 3B) as determined by linear regression. Of the 44 patients who experienced elevated liver enzymes at follow-up, there was no significant difference between baseline dose of azathioprine (Figure 4A, P = .711) and 6-MMP levels (Figure 4B, P = .486) among those on thiopurines regardless of the presence or absence of NAFLD. Additionally, the 44 patients with liver enzyme elevation in comparison to those without elevation (n = 72), did not demonstrate a greater odds of hospitalization, surgery or a CD flare requiring corticosteroids.

Regression Analysis

Univariate analysis found NAFLD to be a risk factor for elevated liver enzymes at follow-up (HR 3.0, 95% CI 1.6–5.5, P < .001). This persisted in the multivariable analysis which revealed NAFLD as an independent predictor of any elevation in liver enzymes from thiopurine therapy in patients with CD (Table 2, HR 3.0, 95% CI 1.2–7.3, P = .018) and not baseline age ≥40, BMI ≥30, hypertension, or type 2 diabetes. Patients treated with thiopurines for CD experienced poorer complication-free survival related to the incidence of elevated liver enzymes if they had concomitant NAFLD (Figure 5, P < .001), and this persisted the entire duration of the study.

Discussion

Here, we demonstrate the influence of NAFLD on liver injury in patients with CD taking thiopurines. Specifically, patients with CD and NAFLD were about 3 times as likely to be found with elevated liver enzymes at follow-up independent of BMI. Linear regression also demonstrated a direct association between fat content and peak ALT concentration at follow-up.

Two prior studies have suggested an association between steatosis and elevated liver tests in patients with CD taking immunomodulators. In a retrospective study of 259 patients with IBD (170 [66%] with CD and 73 [28%] with steatosis), a greater percentage of those with IBD and steatosis compared with those without steatosis were found to have elevated liver enzymes at follow-up (44% vs 24%, P = .0095).[12] However, this study diagnosed steatosis by ultrasound which has been shown to not always correlate with histological findings,[13,20] and the risk of liver injury specifically in patients with CD taking thiopurines was not investigated. In a second study of 121 IBD patients where 39 (32.2%) had steatosis determined by ultrasound, there was a greater mean change in ALT in the NAFLD group versus those without NAFLD (+23.5 vs –4.75 U L^{-1}) in patients with an elevated 6-MMP level, though this was limited to 8 patients.[11] This study concluded that there was a positive association between 6-MMP levels and change in ALT in patients with fatty liver (P < .001) but not in those with a normal liver as determined by ultrasound imaging. In addition, in these 8 patients, patients with steatosis were associated with high 6-MMP levels despite being on lower doses of azathioprine per kilogram of body weight.

Our study is the first and largest to investigate the role of NAFLD diagnosed by a more reliable method specifically in patients with CD on thiopurines. The use of proton magnetic resonance spectroscopy to calculate mean PDFF allowed for a quantified and more reliable assessment of hepatic steatosis that has been shown to correlate well with liver biopsy results unlike other radiological modalities such as CT or ultrasound which are more subjective and generally less sensitive for small amounts of fat.[1,20] Therefore, our cohort had a more reliable diagnosis of NAFLD. In addition, we show a quantifiable association between peak ALT and increasing PDFF. Our study also collected metabolite levels on 27 subjects, a greater amount than has been reported in previous studies. We also demonstrate that patients with elevated liver enzymes at follow-up had no significant difference in the baseline dose of azathioprine and 6-MMP levels, suggesting that the mechanism for elevated ALT was independent of 6-MMP levels, contrary to what has previously been reported.

The coexistence of CD and NAFLD is being increasingly recognized.[1–3] A recent meta-analysis of 44 studies demonstrated that up to 38% of patients with IBD have NAFLD, and there was nearly double the risk of NAFLD in IBD patients compared with healthy controls (OR 1.96, 95% CI 1.13–3.41).[23] The etiology of this association is likely multifactorial, including increased intestinal permeability,

Table 1. Baseline characteristics.

		Thiopurine use without NAFLD (n = 62)	Thiopurine use with NAFLD (n = 54)	P
Age, years, median (IQR)		36 (29–45)	48 (38–58)	.002
Female sex, n (%)		32 (52)	31 (57)	.532
Black or African American race, n (%)		8 (13)	2 (4)	.078
Current smoker, n (%)		13 (21)	11 (20)	.937
BMI, median (IQR)		24 (21–28)	31 (25–34)	<.001
CD duration, years, median (IQR)		12 (5–19)	17 (5–25)	.352
Hypertension, n (%)		7 (11)	15 (28)	.024
Type 2 diabetes, n (%)		0 (0)	6 (11)	.007
Dyslipidemia, n (%)		4 (6)	8 (15)	.140
History of TPN, n (%)		1 (2)	2 (4)	.475
Baseline AST >45 units L^{-1}, n (%)		0 (0)	0 (0)	—
Baseline ALT >45 units L^{-1}, n (%)		1 (2)	1 (2)	.947
Baseline ALP >130 units L^{-1}, n (%)		2 (3)	0 (0)	.173
SES-CD, median (IQR)		6.5 (1.5–9.0)	0 (0–2)	.164
MaRIA, median (IQR)		13 (4–23.5)	0 (0–2.5)	.002
Prior biologic use, n (%)		54 (87)	44 (81)	.405
Baseline methotrexate use, n (%)		0 (0)	0 (0)	.282
Baseline glucocorticoid use, n (%)		6 (10)	3 (6)	.408
Biologic use, n (%)	Anti-TNF	35 (56)	30 (56)	.923
	Anti-integrin	4 (6)	7 (13)	.232
	Anti-IL-12/23	9 (15)	4 (7)	.226
Montreal location, n (%)	Ileum (L1)	7 (11)	7 (13)	.783
	Colon (L2)	5 (8)	4 (7)	.895
	Ileocolonic (L3)	50 (81)	43 (80)	.891
Upper GI, n (%)		2 (3)	3 (6)	.538
Montreal age, n (%)	<17 years (A1)	9 (15)	4 (7)	.217
	17–40 years (A2)	41 (66)	39 (72)	.496
	≥40 years (A3)	8 (13)	8 (15)	.780
Montreal phenotype, n (%)	Inflammatory (B1)	6 (10)	7 (13)	.576
	Stricturing (B2)	6 (10)	4 (7)	.664
	Penetrating (B3)	50 (81)	43 (80)	.891
Perianal disease, n (%)		23 (37)	12 (22)	.082
Surgical history, n (%)	No bowel surgery	31 (50)	13 (24)	.070
	Ileocecal resection	42 (68)	26 (48)	.033
	Small bowel resection	6 (10)	5 (9)	.939
	Subtotal colectomy	5 (8)	4 (7)	.895
	Total colectomy	2 (3)	3 (6)	.538
Bowel continuity, n (%)	Normal	2 (3)	3 (6)	.820
	Ileocolonic anastomosis	19 (31)	25 (46)	.655
	Ileoanal pouch	0 (0)	1 (2)	.363
	Ileostomy	3 (5)	3 (6)	.788
	Colostomy	2 (3)	0 (0)	.110

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CD, Crohn's disease; GI, gastrointestinal; IQR, interquartile range; MaRIA, magnetic resonance index of activity; NAFLD, nonalcoholic fatty liver disease; SES-CD, simple endoscopic score in Crohn's disease; TNF, tumor necrosis factor; TPN, total parenteral nutrition.

disruption of the gut microbiome, exposure to hepatotoxic medications, and nutritional deficiencies.[3] The increased incidence of liver injury identified in our study in patients with CD and NAFLD treated with thiopurines may be consistent with a multi-hit hypothesis where the addition of this medication amplifies hepatic insult. The metabolite levels were found to be similar between patients with and without NAFLD. This may be because the mechanism of thiopurine-induced liver injury in this population is independent of detected levels of 6-MMP. Alternatively, this may be because only 27 of 44 patients had this value recorded. Patients with NAFLD often have concomitant obesity, diabetes, hyperlipidemia, and/or cardiovascular comorbidities. Notably, our data also suggest the influence of NAFLD on elevated liver enzymes was

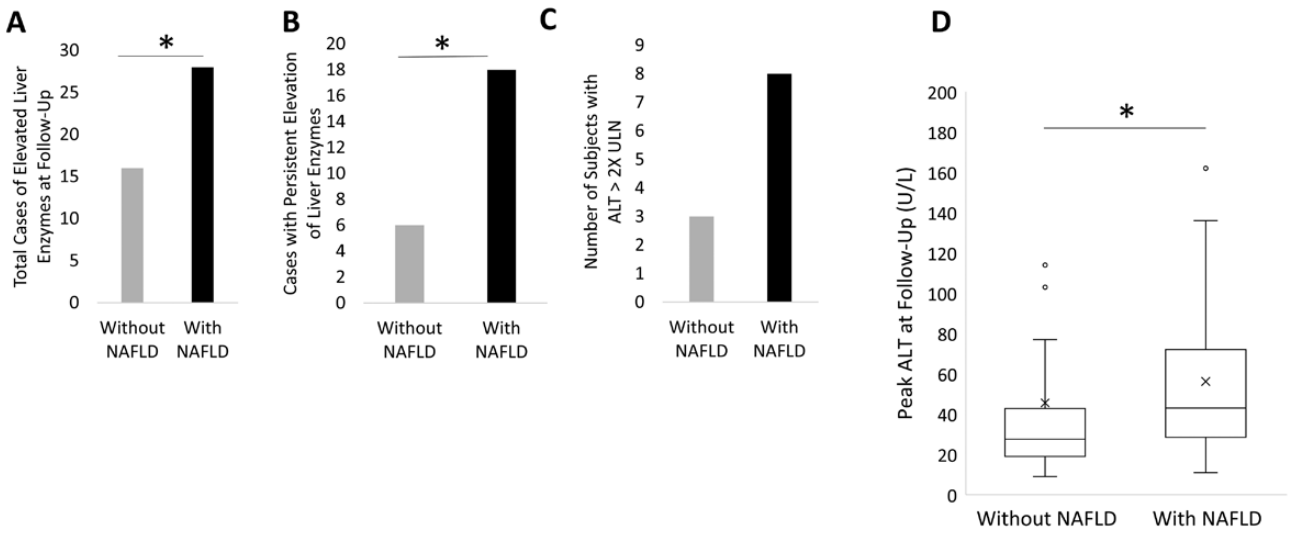

Figure 2. NAFLD and liver injury in patients taking thiopurines. NAFLD was significantly associated with elevated liver enzymes at follow-up in patients taking thiopurines (A, $P = .002$), and this remained true for those with persistent elevations (B, $P < .001$). This trend remained suggestive at greater magnitudes of ALT elevation (C, $P = .051$). The peak ALT level at follow-up was significantly greater in the NAFLD group than those without NAFLD (D, 43 vs 28 units L^{-1}, $P < .001$). * indicates $P < .05$. Abbreviations: ALT, alanine aminotransferase; NAFLD, nonalcoholic fatty liver disease; ULN, upper limit of normal.

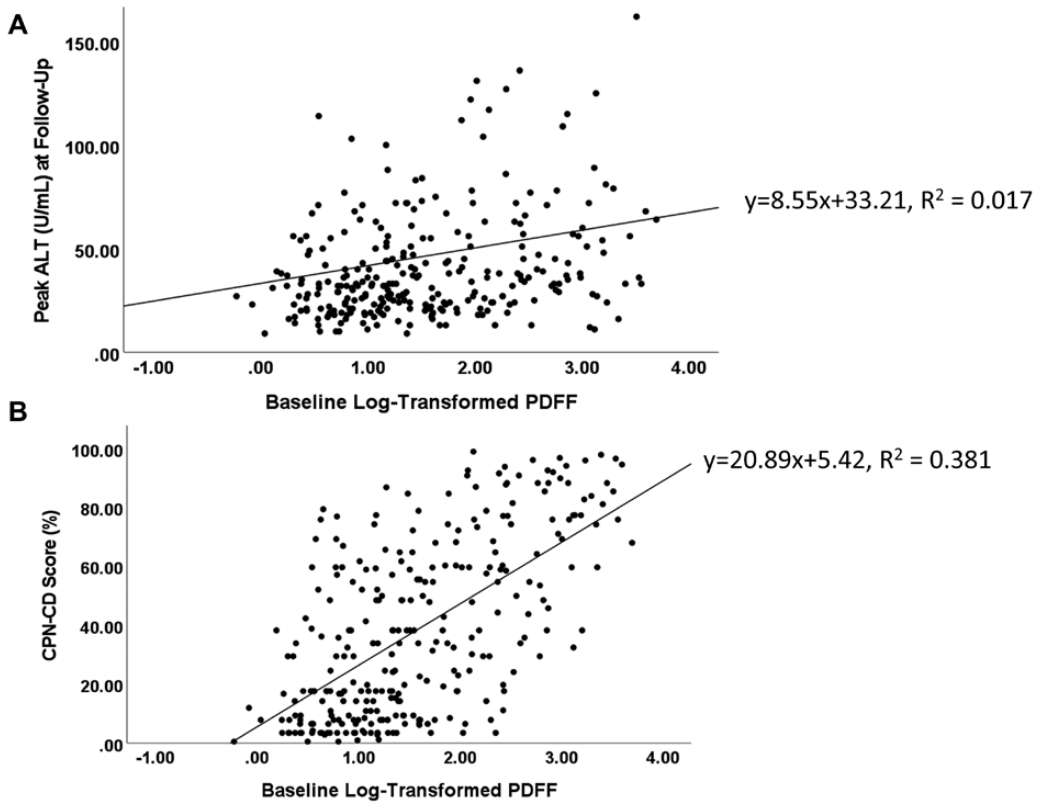

Figure 3. Peak ALT at follow-up or baseline CPN-CD as a function of baseline severity of hepatic steatosis in patients with Crohn's disease. There was a direct association between peak ALT at follow-up (A) or baseline CPN-CD score (B) with baseline severity of hepatic steatosis. Abbreviations: ALT, alanine aminotransferase; CPN-CD, clinical prediction tool for nonalcoholic fatty liver disease in Crohn's disease; PDFF, proton density fat fraction.

independent of that of obesity. NAFLD has been reported to increase drug cytotoxicity as its altered metabolic environment promotes increased baseline reactive oxygen species[24–26] which results in liver injury. Alternative management strategies to consider include decreasing thiopurine dosing, using methotrexate to attenuate anti-TNF immunogenicity,[27] or using less immunogenic biologics such as vedolizumab (4.1% incidence)[28] or ustekinumab (2.3% incidence).[29] Baseline transient or MR elastography can be considered in patients with CD and NAFLD treated with thiopurines as is

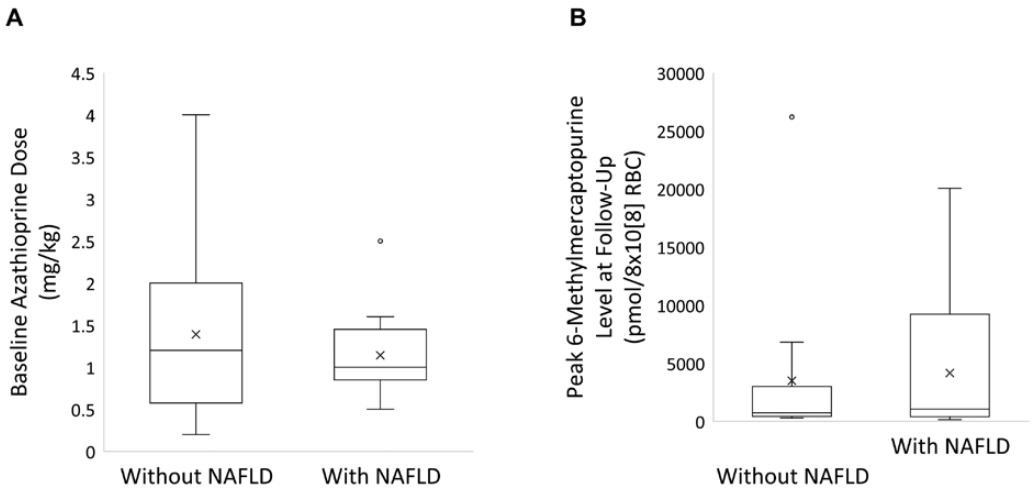

Figure 4. Baseline azathioprine dose and peak 6-methylmercaptopurine levels in patients with elevated liver enzymes at follow-up. Patients with elevated liver enzymes at follow-up were found to have similar baseline doses of azathioprine (A, $P = .711$) and peak 6-methylmercaptopurine (B, $P = .486$) levels. Mean denoted as "X." Abbreviation: NAFLD, nonalcoholic fatty liver disease.

Table 2. Univariate and multivariate analysis on the risk of liver injury due to thiopurine therapy in patients with CD.

	Univariate, HR (95% CI)	*P*	Multivariate, HR (95% CI)	*P*
Female sex	1.3 (0.7–2.3)	.461		
Baseline age ≥40	1.2 (0.7–2.2)	.486	0.9 (0.4–2.2)	.863
Black or African American race	0.7 (0.2–2.2)	.506		
Smoker	1.3 (0.7–2.7)	.429		
BMI ≥30	1.8 (1.0–3.2)	.060	1.6 (0.7–4.0)	.279
Hypertension	1.3 (0.6–2.8)	.423	1.1 (0.3–3.4)	.918
Type 2 diabetes	1.3 (0.4–4.3)	.628	0.7 (0.1–4.5)	.699
Perianal disease	0.6 (0.3–1.2)	.129		
History of ileocolonic resection	1.5 (0.9–2.8)	.155		
History of total colectomy	1.6 (0.5–5.3)	.416		
NAFLD	3.0 (1.6–5.5)	<.001	3.0 (1.2–7.3)	.018

Abbreviations: BMI, body mass index; CD, Crohn's disease; NAFLD, nonalcoholic fatty liver disease.

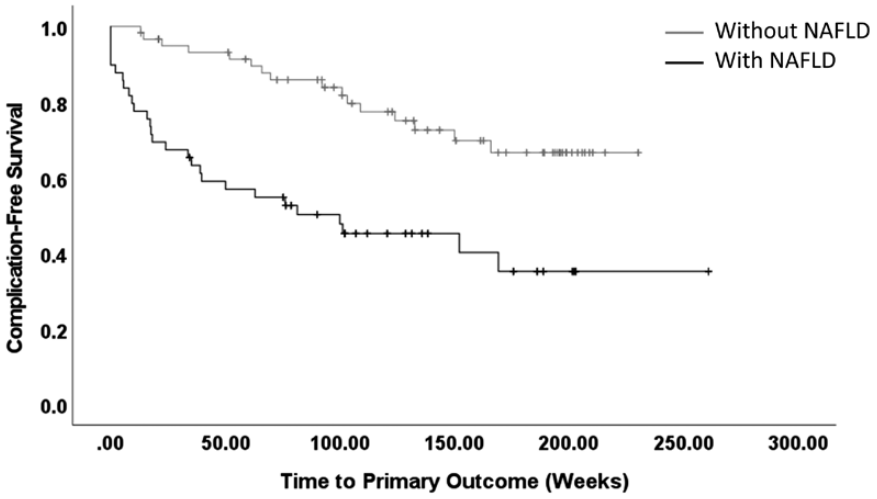

Figure 5. Complication-free survival on thiopurine therapy in patients with CD as a function of NAFLD ($P < .001$). Abbreviations: CD, Crohn's disease; NAFLD, nonalcoholic fatty liver disease.

recommended in certain scenarios of patients with psoriasis treated with methotrexate.[30]

Nevertheless, this study has several limitations. This study was completed at a single tertiary care center which may limit generalizability. The presence of NAFLD itself may increase transaminases and may confound the results irrespective of thiopurine use. The definition of liver injury included any elevation of liver enzymes above the upper limit of normal, and the clinical significance of mild asymptomatic elevations in liver enzymes, especially those that are transient, is unclear. Clinical endpoints such as hospitalizations, glucocorticoid use, and mortality were not investigated. Further evaluation of long-term clinical outcomes in larger, prospective studies is warranted.

Conclusion

The presence of NAFLD in patients with CD treated with thiopurines is significantly associated with elevation in liver enzymes compared with those without NAFLD, and complication-free survival in those with NAFLD on thiopurines was significantly worse. While patients with CD on thiopurine therapy undergo routine monitoring of their liver enzymes, screening for NAFLD among those with elevation in liver enzymes, especially among those with a normal 6-MMP level, is recommended.

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Authors' Contributions

M.G., S.M., M.A.C., and P.D. conceived idea. A.T.G., M.G., M.Z., D.R.L., and S.M. assisted with data collection. A.T.G. and P.D. performed data analysis and interpretation, drafted manuscript. All authors discussed the results and reviewed and revised the final manuscript.

Conflicts of Interest

A.T.G., M.G., Q.A., M.Z., D.R.L., and S.M.: nothing to disclose. M.A.C. participated in consulting, advisory board, or speaker's bureau for AbbVie, Pfizer, Bristol Myers Squibb, and Theravance, and received funding under a sponsored research agreement unrelated to the data in the paper from Incyte, Pfizer, Janssen, and the Crohn's and Colitis Foundation. P.D. holds the position of Associate Editor for Crohn's & Colitis 360 and has been recused from reviewing or making decisions for the manuscript. Research support under a sponsored research agreement unrelated to the data in the paper and/or consulting from AbbVie, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Pfizer, Prometheus Biosciences, Takeda Pharmaceuticals, Scipher Medicine, and CorEvitas, LLC. Writing assistance: none.

Data Availability

Data available on reasonable request.

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