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MINIREVIEWS

Co-existence of non-alcoholic fatty liver disease and inflammatory bowel disease: A review article

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Abstract

Emerging data have highlighted the co-existence of non-alcoholic fatty liver disease (NAFLD) and inflammatory bowel disease; both of which are increasingly prevalent disorders with significant complications and impact on future health burden. Cross-section observational studies have shown widely variable prevalence rates of co-existing disease, largely due to differences in disease definition and diagnostic tools utilised in the studies. Age, obesity, insulin resistance and other metabolic conditions are common risks factors in observational studies. However, other studies have also suggested a more dominant role of inflammatory bowel disease related factors such as disease activity, duration, steroid use and prior surgical intervention, in the development of NAFLD. This suggests a potentially more complex pathogenesis and relationship between the two diseases which may be contributed by factors including altered intestinal permeability, gut dysbiosis and chronic inflammatory response. Commonly used immunomodulation agents pose potential hepatic toxicity, however no definitive evidence exist linking them to the development of hepatic steatosis, nor are there any data on the impact of therapy and prognosis in patient with co-existent diseases. Further studies are required to assess the impact and establish appropriate screening and management strategies in order to allow early identification, intervention and improve patient outcomes.

Key words: Crohn's disease; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Ulcerative colitis; Metabolic syndrome

Core tip: This article reviews the current available literature on issues relating to the co-existence of non-alcoholic fatty liver disease and inflammatory bowel disease with particular focus on the prevalence, risk factors and the clinical implications.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disorders ranging from hepatic steatosis to steatohepatitis (NASH) with associated inflammation and may lead to liver fibrosis along with potential progression to cirrhosis, hepatic failure and hepatocellular carcinoma[1-3]. Currently, NASH is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States and is predicted to become the leading indication for liver transplant in the near future[4]. The epidemic of NAFLD in the general population is partly due to the increase in diabetes, dyslipidemia, and obesity. Liver biopsy has long been the gold standard to assess NAFLD and to stage liver fibrosis but this procedure is invasive, costly and not very practical for screening[5]. Other non-invasive methods to diagnose fatty liver and liver fibrosis have been used including serum biomarkers, ultrasound (US), computed tomography and magnetic resonance imaging. NAFLD is largely asymptomatic until end-stage complications occur. Hence, identification of risk factors, early diagnosis and intervention are pivotal in the management of this common disease.

Inflammatory bowel disease (IBD), consisting of ulcerative colitis (UC) and Crohn's disease (CD), is an increasingly prevalent intestinal disorder with significant co-morbidities. North America has the highest prevalence and incidence rates of IBD worldwide which translate into a significant health care related cost[6,7]. Elevated transaminases in IBD patients are frequent[8], with NAFLD being the most common cause[9]. There are some emerging data suggesting an increase in prevalence of NAFLD in IBD patients compared to the general population, although this is not yet clearly established. Some have attributed this to a general increase of metabolic syndrome (MS) or the increasingly successful IBD therapy in achieving remission and improved nutritional status. However, the pathogenesis of NAFLD in the IBD population may be more complex involving disease-specific risk factors, such as chronic inflammation, drug-induced hepatotoxicity, steroid exposure, malnutrition and gut dysbiosis[10,11]. This article examines the prevalence, risk factors and the clinical implications relating to the coexistence of NAFLD in IBD patients.

EPIDEMIOLOGY: PREVELANCE OF NAFLD IN IBD

Cross-sectional studies reported a prevalence of NAFLD in IBD ranging between 6.2% and 40%[12-14]. A summary of the major studies are provided in Table 1. This discrepancy is largely owed to different definitions and diagnostic tools adopted for NAFLD. Liver fibrosis has been reported in 6.4%-10% of IBD patients, however limited data are available for fibrosis specifically relating to underlying NAFLD[15,16]. Several studies evaluated NAFLD in IBD using ultrasonography, which has an 85% (95%CI: 79.5%-88.9%) sensitivity and 94% (95%CI: 87.2%-97%) specificity for NAFLD[17]. A one year, single center nested case controlled study analyzed 928 IBD patients who had any abdominal imaging and found 7.2% had NAFLD[13]. All included patients did not have clinically significant alcohol consumption to minimize confounding appearance of hepatic steatosis on imaging. Mean age, age at diagnosis, body mass index (BMI) and prevalence of MS were greater in NAFLD patients. Risk factors for NAFLD in IBD were small bowel surgery (OR = 3.7, 95%CI: 1.5-9.3, P = 0.005), hypertension (OR = 3.5, 95%CI: 1.5-8.1, P = 0.004) obesity (OR = 2.1, 95%CI: 1.05-4, P = 0.035) and steroid use at imaging (OR = 3.7, 95%CI: 1.5-9.3, P = 0.005). Confounding factors such as nutrition and lifestyle factors were not accounted for in this study. In a large, single-center study of 511 IBD patients, liver steatosis was found in 40% of patients (P < 0.001 *vs* healthy controls)[14]. In this study, patients with underlying MS and obesity (BMI > 30) were excluded however assessment of nutritional status and physical activity among the cohorts were again not available. Other studies have found 13%-16% rate of hepatic echobright patterns in IBD[18,19]. Several studies have used liver enzymes derangements to detect NAFLD in IBD, which have poor predictive value to exclude NAFLD[20]. A one-year prospective analysis of 200 UC patients found 40% with abnormal liver enzymes, with liver biopsy revealing NAFLD in 11.2% of these patients[21]. A five-year prospective study of IBD (401 UC, 385 CD) showed 15.3% had abnormal liver enzymes[12]. Ultrasonography of these patients revealed 40.8% had NAFLD, representing 6.2% of all patients. These two studies are also limited by lack of evaluation on relevant confounding factors.

A study from our group using the validated hepatic steatosis index (HSI) longitudinally followed 321 IBD patients over 7 years (217 CD, 104 UC)[22]. HSI, defined as: 8 × AST/ALT + BMI (+2, if female; +2, if diabetes), was applied to diagnose hepatic steatosis if

Table 1 Prevalence of non-alcoholic fatty liver disease and fibrosis in inflammatory bowel disease reported by major studies since 1990

Ref.	Diagnostic method	No. of patients	Mean age	Gender (male)	IBD type	Mean BMI	NAFLD prevalence	Fibrosis
Gisbert *et al*[12]	Ultrasound	786	44		49% (CD) 51% (UC)		40.8%	-
Sourianarayanane *et al*[13]	Ultrasound/CT/MRI	928	44 (NAFLD) 42 (Non-NAFLD)	41%	53% (CD) 47% (UC)	30.4 (NAFLD) 27 (Non-NAFLD)	8.2%	-
Bargiggia *et al*[14]	Ultrasound	511	38 (CD) 39 (UC)	-	61% (CD) 39% (UC)	21 (CD) 21.6 (UC)	39.5% (CD) 35.5% (UC)	-
de Fazio *et al*[18]	Ultrasound	74	35 (CD) 39 (UC)	55%	32% (CD) 68% (UC)		12.0% (CD) 16.6% (UC)	-
Riegler *et al*[19]	Ultrasound	484	38 (CD) 41 (UC)	57%	35% (CD) 65% (UC)		8.9% (CD) 13.6% (UC)	-
Yamamoto-Furusho *et al*[21]	Ultrasound	200	31	53%	UC		11.2	-
Bessissow *et al*[22]	Hepatic steatosis index/Fibrosis-4 score	321	33.7	47%	68% (CD) 32% (UC)	22.2	33.6% (Incidence)	7.4%

NAFLD: Non-alcoholic fatty liver disease; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; CT: Computed tomography; MRI: Magnetic resonance imaging.

the score is ⩾ 36. We found the incidence of NAFLD was 33.6% or 9.1/100 patient-years (PY), compared with 0.029 to 3.1/100 PY in the general population. Of those with NAFLD, 7.4% developed advanced liver fibrosis (Fibrosis-4 score > 3.25). The average BMI was 22.2, similar between those who did not develop NAFLD; although we did not capture other nutritional and lifestyle data. NAFLD development was predicted by active disease (HR = 1.58, 95%CI: 1.07-2.33), longer disease duration (HR = 1.12, 95%CI: 1.03-1.23) and prior IBD-related surgery (HR = 1.34, 95%CI: 1.04-1.74). Anti-tumor necrosis factor alpha (Anti-TNFα) therapy trended toward predisposing to NAFLD (HR = 1.69, 95%CI: 0.99-2.9, P = 0.056). There was no association between the incident of NAFLD and steroids use. However, steroid use was defined as use at any point prior to a NAFLD diagnosis, which may not appropriately characterize those with repeated or prolonged steroid use.

PATHOGENESIS

Although the pathogenesis for IBD and NAFLD are both poorly understood, these disorders are likely to have arisen from complex interaction of polygenic predisposition with multiple environmental factors. For NAFLD, it is postulated that hepatic steatosis may have developed from insulin resistance and the associated metabolic disturbances leading to fatty infiltration in the liver[23]. Oxidative damage, immune activation, dysregulated cytokine and apoptosis pathways, are among other processes, further contribute to hepatic insult and fibrogenesis leading to NASH; the so called multi-hit hypothesis. IBD is characterised by dysregulated immune activation through host microbiota dysbiosis and environmental triggers in a genetically predisposed individual[24]. More than 200 genetic polymorphisms have been linked to the development of IBD. Similarly several single nucleotide polymorphisms have been found through genome wide association studies that may contribute to the development of NAFLD. There does not however appear to be any definite overlap of genetic predisposition in these two populations, albeit this has not been directly evaluated. Other factors, such as MS, microbial dysbiosis, immune activation, and medications on the other hand may be exert more influence in the coexistence of these two disorder and these topics will be discussed in the following sections.

MS

An overlap of the metabolic risk factors for type 2 diabetes and for atherosclerotic cardiovascular disease, such as abdominal obesity, hyperglycemia, dyslipidemia and hypertension have led to the concept of the MS. Its cardinal pathophysiology is insulin resistance due to obesity. NAFLD is thought to be the hepatic manifestation of MS. A recent study demonstrated the prevalence of MS in IBD patients was comparable to that of the general population (18.6%)[25]. Potential confounding factors, including exercise, sleeping, alcohol intake and smoking did not differ significantly between IBD patients with or without MS; nutritional factors were not assessed by the study. In addition, a trend toward a higher prevalence of MS was found in UC (23%) patients compared to CD (7.1%) patient and in male IBD patients (21.1%) compared to female patients (12.9%). Another study found the prevalence of MS was 10.3% under 45 years of age and 55% over 45 years of age[26]. Furthermore, they found that it was more prevalent in patients with UC (29.5%) than in patients with CD (17.7%). This study however did not account for potential confounding lifestyle characteristics. A North American study found that the prevalence of MS was lower among their IBD patients both with and without NAFLD compared

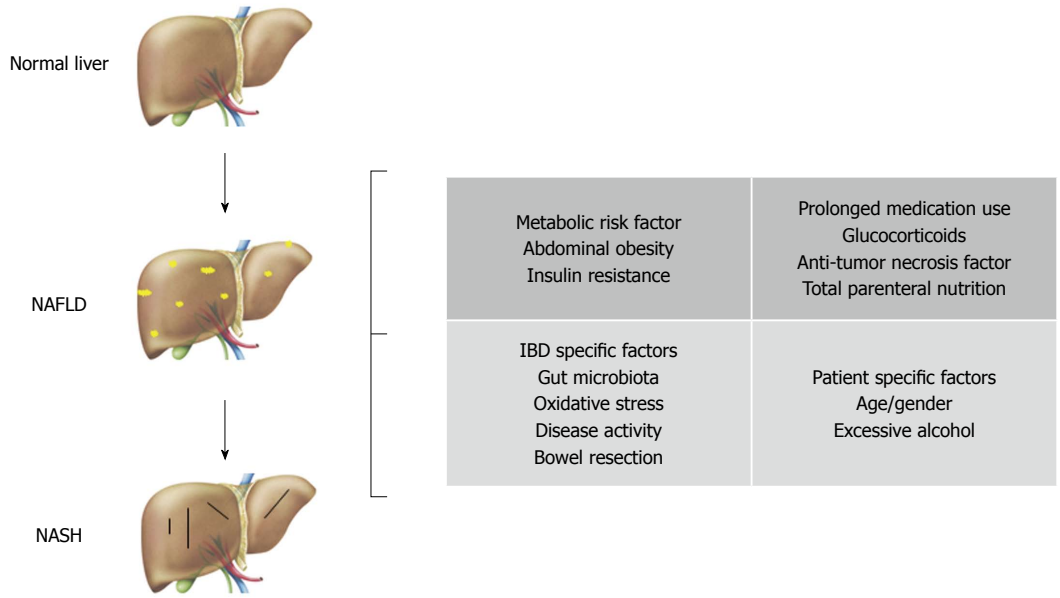

Figure 1 Potential pathogenic factors contributing to the coexistence of non-alcoholic fatty liver disease and inflammatory bowel disease. NAFLD: Non-alcoholic fatty liver disease; IBD: Inflammatory bowel disease.

Table 2 Reported risk factors of non-alcoholic fatty liver disease in inflammatory bowel disease patients

Risk factors	OR/HR (95%CI)	*P* value
Small bowel surgery[13]	OR = 3.7 (1.5-9.3)	0.005
Hypertension[13]	OR = 3.5 (1.5-8.1)	0.004
Obesity[13]	OR = 2.1 (1.05-4.0)	0.035
Steroid use[13]	OR = 3.7 (1.5-9.3)	0.005
Active disease[22]	HR = 1.58 (1.07-2.33)	0.020
Duration of IBD[22]	HR = 1.12 (1.03-1.23)	0.010
Prior IBD surgery[22]	HR = 1.34 (1.04-1.74)	0.020
Anti-TNFα use[22]	HR = 1.69 (0.99-2.90)	0.056 (Trend to significance)

IBD: Inflammatory bowel disease; TNFα: Tumor necrosis factor α.

to the general United States population[13]. MS thus may not be the only dominant factor contributing the coexistence of NAFLD in IBD patients. Nevertheless, early identification and intervention of these metabolic factors may reduce the development of complications associated with NAFLD.

IBD disease factors: Inflammation and dysbiosis

NAFLD in IBD patients was predicted by disease-specific factors in the aforementioned studies which included disease activity and duration, along with prior IBD related or small bowel surgery, steroid and possibly anti-TNFα use. The etiology of IBD and factors provoking exacerbation are still partially understood. Intestinal microbiota have emerged as a key player in the pathogenesis of IBD. Alteration of gut microbiota has been associated with disease activity[27]. On the same line, NAFLD is associated with increased intestine permeability, and this abnormality is related to the increased prevalence of small bowel bacterial overgrowth in these patients. As such, alteration of gut microbiota may act as a pathogenic link between IBD and NAFLD. This makes one suspect that an active inflammatory process could drive fatty infiltration of the liver. Similar association have been made between psoriasis and NAFLD[28]. Duration of IBD was another independent predictor of development of NAFLD in the aforementioned Bessissow *et al*[22] study. Longer disease duration exposes patients to multiple risk factors for NAFLD, including chronic relapsing inflammation, alteration of gut microbiota and hepatotoxic drugs. In particular, oxidative stress from reactive oxygen species may also be the common pathogenic factor contributing the consistence of NAFLD and IBD. Along the same lines, prior surgery was also independently associated with incident NAFLD. This is most likely a surrogate marker of the severity of the disease with a more active inflammatory condition. Those patients will also tend to be exposed to hepatotoxic medications repeatedly. NASH development following extensive small bowel resection in non-IBD patients has also been previously described and may be related to nutritional deficiencies akin to those patients with bariatric bypass procedures[29]. Table 2 summarises the reported risk factors for NAFLD in IBD and Figure 1 depicts the hypothesized pathogenic factors of NAFLD in IBD.

NAFLD and the interactions with IBD therapeutic agents

Glucocorticoids: Glucocorticoid analogues (GC) are commonly used as induction agents for the management of IBD and a subset of patients with poorly controlled disease may have repeated or prolonged exposure. They have profound metabolic effects on carbohydrate and lipid metabolism which

may result in the development of MS and potentially NAFLD. *In vitro* studies have demonstrated that GC may induce lipogenesis and steatosis in hepatocytes *via* several mechanisms including up-regulation of fatty acid synthase and acetyl-CoA carboxylases 1 and 2[30]. GC and high fat diet in rodent models also can synergistically exacerbate the development of NAFLD and hepatic fibrosis[31]. However evidence linking GC and NAFLD in human studies are less direct. No prospective clinical study has shown GC use as an independent risk factor for NAFLD. Only 20% of patients with Cushing's syndrome, associated with GC use, have radiological evidence of NAFLD[32]. Similarly plasma cortisol concentrations do not differ significantly in NAFLD or obese patients as compared to controls[33]. The retrospective study by Sourianarayanane *et al*[13] found steroid use at the time of US imaging was an independent risk factor for NAFLD (OR = 3.7, 95%CI: 1.5-9.3) in the IBD population, however this was not consistently found in other observational studies. Even though no clear guidelines have been established, corticosteroid should be cautiously used in patients with existing metabolic risk factors.

Methotrexate: Methotrexate (MTX) is a folate antagonist which competitively inhibits dihydrofolate reductase and interferes with purine and pyrimidine synthesis, resulting in anti-inflammatory and other effects. It can be used as an induction and maintenance monotherapy for the treatment of IBD, or as combination therapy with anti-TNFα agents[34]. 15%-50% of patients on methotrexate may develop changes in liver enzymes, although most are self-limiting and the underlying mechanism is presumed relating to oxidative stress[35]. A retrospective analysis has reported around 24% of IBD patients on MTX have liver enzyme elevations. Significant hepatic fibrosis or cirrhosis, however are uncommon, accounting only for 5% of patients on long term low dose MTX. Association between MTX and NAFLD is less definitive. MTX use has not been shown to result in NAFLD in IBD patients. There is one report in rheumatoid arthritis patients, where average weekly dose of 13.1 mg MTX was shown to be an independent predictor of NAFLD on multivariate analysis[36]. Despite the lack of associations, there are rodent studies showing increased susceptibility to MTX induced hepatic toxicity in established NAFLD; therefore it may not be entirely appropriate in patients with NAFLD[37].

Anti-TNFα: TNFα and its participation in pro-inflammatory pathways may play an important role in the development of hepatic inflammation and NASH in NAFLD patients. Significantly elevated serum TNF level as well as messenger RNA expression in hepatocytes have been demonstrated in NASH patients compared to healthy controls[38,39]. Anti-TNFα agents are widely used in various inflammatory diseases and are by far the most effective induction and maintenance agents for IBD. It has been postulated that anti-TNFα may protect against NASH. Infliximab has been shown to reduce steatosis and increase insulin signal transduction in rodents on high fat diet[40]. Furthermore infliximab also reduced hepatic inflammation, necrosis and fibrosis in NASH rodents induced by methionine and choline deficient diet[41]. Similar effects were also shown with the use of adalimumab[42]. Finally pentoxifylline, a nonselective phosphodiesterase inhibitor that reduced TNF production, has also been reported to induce biochemical liver enzymes improvement in NASH patients[43]. On the other hand there are case series reporting the development of biopsy-proven NAFLD in patients receiving anti-TNFα despite no changes in metabolic profiles from improved disease control and enhanced nutrition. In one of the aforementioned NAFLD prevalence studies, there was a trend to significance with the use of anti-TNFα as a risk factor, whereas others did not show any statistically significant associations and one study showed that it may have a protective effect. No clear conclusions thus could be reached on the effect of anti-TNFα in NAFLD/NASH due to the conflicting evidence.

Other common IBD therapeutic agents: Thiopurine analogues, azathioprine and 6-mercaptopurine, remain a corner stone therapy for the maintenance of remission in IBD. They however can be associated with liver function derangement, cholestatic and hepatocellular hepatitis, in addition to veno-occlusive disease, peliosis hepatis and nodular regenerative hyperplasia[44]. There are no clear evidence linking NAFLD to these agents, nor are there any data suggesting higher risk of thiopurine liver injury in patients with existing NAFLD. Similarly, multiple other therapeutic agents using monoclonal antibodies targeting various inflammatory pathways have been recently approved or being developed for use in IBD, such as vedolizumab and ustekinumab. Currently there are not enough published data to comment on their interactions with NAFLD.

Parenteral nutrition

A small proportion of IBD patients may develop intestinal failure secondary to extensive surgical resection or refractory disease thus requiring parenteral nutrition (PN). Hepatic steatosis is a known common complication and can occur as early as 5 d post PN commencement[45]. Progressive inflammatory response and fibrosis may also ensue with prolonged exposure. These events may be promoted through excessive caloric and carbohydrate administration. In addition, deficiencies of amino acids such as carnitine and choline as well as essentially fatty acids are also implicated. There are limited evidence suggesting the use of lipid emulsions and optimization of caloric content may help to minimize these complications[46].

CLINICAL IMPLICATIONS

Screening

According to the American association for the study of liver disease guideline, universal screening in asymptomatic general or high risk populations is not currently recommended due to uncertainties with diagnostic tests, cost-effectiveness and long term benefits[47].

US is commonly used for the screening and evaluation in patients suspected of NAFLD. Several non-invasive serum biomarker scores, such as the NAFLD liver fat score and fatty liver index have been validated for the assessment of hepatic steatosis[48]. Cytokeratin 18, another serum test, has a sensitivity of 78%, specificity of 87%, and an area under the receiver operating curve of 0.82 (95%CI: 0.78-0.88) for diagnosing steatohepatitis. Similarly, presence of fibrosis may also be detected with the use of markers including the fibrosis 4 calculator, NAFLD fibrosis score and the elevated fibrosis tests.

There has also been some promisingly development of alternative imaging methods for the detection of liver fibrosis; the most studied being transient elastography (TE) which may assess the presence of advanced fibrosis. The adjunct use of controlled attenuation parameter function of the TE has also been used to diagnosis hepatic steatosis; this however has not been robustly validated in IBD.

No specific guidelines for the assessment of NAFLD in the IBD population have been established. Evaluation may be helpful in IBD patients with high risks or those with imaging features of hepatic steatosis; although the optimal approach and benefits are yet to be studied.

Treatment

The current focus of NAFLD therapy in general is dietary and lifestyle modifications with the aim of weight reduction but no treatment has been assessed in the IBD population specifically. Weight loss > 7% has been associated with biochemical and histological improvement in patients with NASH[49]. Prevention or reversal of hepatic fibrosis ultimately should lead to reduction of NAFLD related complications. This approach may not be entirely suitable for some IBD patients with existing nutritional deficits in the setting of poorly controlled disease activity. No pharmacological agents have received formal regulatory approval as NASH therapy. Pioglitazone, a peroxisome proliferator-activated receptor agonist, vitamin E and synthetic farnesoid X receptor agonist, obeticholic acid, have all been shown to improve histological markers in NASH[50,51]. Several anti-inflammatory and anti-fibrosis agents are also being actively investigated. Bariatric surgery also could lead to improved NASH status in morbidly obese patients[52]. Once again NAFLD treatments have not been specifically studied in the IBD population and the management of these patients should be individualized and guided by existing protocols for non-IBD patients. The use of IBD treatment agents in the setting of NAFLD has been discussed in the previous paragraphs.

CONCLUSION

The co-existence of NAFLD in IBD is becoming increasingly recognized. This is partly related to an increase in MS as well as complex IBD disease associated factors. Current literature on this matter has left many issues unanswered. Long term outcomes and prognosis for co-existent patients must be characterised. The true impact of IBD therapies on co-existing NAFLD also needs to be further assessed. Furthermore, guidance on the appropriate screening tool and strategies for the management of co-existent disease in IBD patients is lacking. Clarification of these issues may enhance early intervention and improve patient outcomes.

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