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Non-Alcoholicfatty Liver Diseasein Inflammatory Bowel Diseasespatients

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Abstract: *Non-alcoholic fatty liver disease has become one of the most commonly diagnosed liver diseases in patients having inflammatory bowel diseases. Studies have shown that the prevalence of NAFLD in patients with IBD ranges from 8.2% to 40%, depending on the different definitions and diagnoses used in the studies. In 12.2 % of the patients, liver fibrosis was alsoreported.Risk factors associated with NAFLD development are reported as metabolic syndrome, intestinal inflammation and dysbiosis, obesity, bowel surgery, and IBD medications in patients with IBD. Macrovascular steatosis and hepatomegaly were linked with longer duration and higher doses of glucocorticoids. Methotrexate might worsen the condition of patients already affected with NAFLD.Parenteral nutrition was also associated with complications of the liver ranging from liver steatosis to cirrhosis. Anti-TNFα was presumed to be able to protect against NASH. In contrast, in patients with underweight IBD, NAFLD was notably higher than patients with normal weight.Further studies on dose and duration of IBD medications related with NAFLD, as well as investigations of IBD patients for NAFLD and its treatment methods need to be conducted.*

Key words:*ulcerative colitis, crohn's disease, non-alcoholic fatty liver disease, metabolic syndrome, dysbiosis*

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I. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a group of diseases in the liver ranging from simple accumulation of liver fat to necroinflammation, fibrosis, cirrhosis and hepatocellular carcinoma(1).NAFLD prevalence is likely to be 10-40% among adults worldwide, and it is the most frequent liver disease in developed countries among children and adolescents(2).To some extent, NAFLD outbreak is due to increased diabetes, dyslipidemia, and obesity(3). Most NAFLD patients are asymptomatic or complaining of non-specific symptoms, such as fatigue, sleep disturbances or discomfort in the upper right quadrant. The most frequent physical finding is hepatomegaly(2).

Inflammatory bowel diseases (IBD) involve ulcerative colitis (UC) and crohn's disease (CD). Chronic, relapsing inflammation of the intestine is a common characteristic of both disorders and is supposed to result from a dysregulated and abnormal immune response to intestinal flora(4).The exact pathogenesis of NAFLD in IBD patients is not yet clearly recognized. However, numerous causes have been proposed to describe this increased NAFLD prevalence; including the presence of metabolic syndrome, chronic inflammation, dysbiosis, medications used to treat IBD, steroid use and small bowel surgery(5,6).

The purpose of this article is tosummarize and analyze the occurrence, risk factors and clinical implications with a major concentrationtargeted on the co-occurrence of NAFLD in IBD patients. To obtain these, an electronic search of PubMed, MEDLINE and EMBASE was executed using the key words “ulcerative colitis” “crohn’s disease” “non-alcoholic fatty liver disease” “non-alcoholic steatohepatitis” “metabolic syndrome” and “IBD medications” mainly in the time range of 2015 till 2019.

Epidemiology: prevalence of NAFLD in IBD

Some studies have shown that NAFLD prevalence in patients with IBD ranges from 1.5% to 40% of patients(6). Table 1 summarizes the main studies.Principi, M., et al revealed that the NAFLD prevalence in IBD patients was 28.0% higher than that of non-IBD subjects 20.1%, P=0.04(7). In NAFLD-IBD, younger age was detected than in non-IBD subjects (49.9±15.0 versus 56.2±12.1 years, P=0.02). High blood pressure, morbid abdominal circumference, and metabolic syndrome (MS) were the risk factors for NAFLD in patients with IBD. Interestingly, no association between NAFLD and corticosteroids was observed in this case-controlled study.

Saroli Palumbo, C., et al conducted a prospective one-year cross-sectional study of 384 patients at the McGill University Health Centre (MUHC) IBD Centre between October 2015 and June 2017, and NAFLD and Liver fibrosis were found in 32.8 % and 12.2% of IBD patients, respectively. The method used was transient elastography (TE)(8).The study excluded patients with hepatitis B virus (HBV), hepatitis C virus (HCV), persistent liver disease, liver transplant and alcohol intake.

A study using magnetic resonance imaging (MRI) was conducted to test whether low weight is associated with NAFLD in patients with IBD. In underweight patients with IBD, the prevalence of NAFLD/liver steatosis (defined as a measured intrahepatic fat content of at least 5%) was significantly higher than patients with normal weight (87.6% vs. 21.5%, $p<0.001$)(9).

Bargiggia, S., et al led a large one-center study of 511 IBD patients, 39.5 % of patients had liver steatosis(10). In this study, 52 patients with hepatitis B and C, metabolic syndrome and higher (BMI>30) were eliminated.

In another study, it was obtained that the incidence of NAFLD in IBD patients was 8.2%(11).This was a large case-controlled study in which variousimaging methods were used in 928 patients with the exclusion.

Total of 13 various studies containing 1471 UC patients for the approximate prevalence of fatty liver disease in UC patients, techniques of diagnosis including ultrasound, biopsy and necropsy. Mean prevalence of fatty liver in UC patients was 23% (range, 1.5–55%). An ultrasound method was used to find the incidence of fatty liver in 604 Crohn's patients from four different studies and the prevalence obtainedwas 1.5% to 39.5%(12).

A large nationwide inpatient study (NIS) was conducted between the year 1996 to 2004 and the reported prevalence of NAFLD in UC patients was 12.7% and in CD patients was 20.3%(13).From the Eastern ethnicity standpoint, a study on 303 patients who were diagnosed with CD was performedbetween November 2008 and October 2014 at Hiroshima University Hospital (Hiroshima, Japan). The occurrence of NAFLD in CD patients was noticed in21.8%(14). In this study, it was discovered that patients who had a CD with NAFLD were older and accompanied with lengthier disease duration, higher BMI, higher incidence of inflammation restricted to the ileum and had a longer surgery free interval compared to patients without NAFLD.

Lannone, A., et al carried out astudy on 378 IBD patients between December 2014 to July 2016 to find the prevalence of NAFLD and to measure liver stiffness (LE) using ultrasound and transient elastography (TE). NAFLD was identifiedin 28% of patients and the mean LS was higher than non- NAFLD patients(15).

Table1 Non-alcoholic fatty liver diseases and fibrosis prevalence in IBD patients

Source	Investigative technique	Number of subjects	Mean age	% male	IBD form	Mean BMI	NAFLD prevalence	Fibrosis prevalence
Principi, M., et al (7)	ultrasound	465	50.0	53.80%	UC,CD	26.1	28%	-
Saroli Palumbo, C., et al (8)	transient elastography (TE) with associated controlled attenuation parameter (CAP)	384	51.0	51.60%	CD	28.1	32.80%	12.20%
Bargiggia, S., et al (10)	ultrasound	511	38.4	-	UC,CD	21.3	37.70%	-
Sourianarayanane, A., et al(11)	ultrasound, CT scans, MRI	928	44.1	41.30%	UC,CD	30.4	8.20%	-
Sagami, S., et al (14)	ultrasound	303	42.0	-	CD	21.7	21.80%	-
Iannone, A., et al(15)	ultrasound,TE	378	52.6	68.80%	CD	28	28%	-

Pathogenesis

The exact pathogenesis of IBD and NAFLD is elusive and yet to be discovered. Pathogenesis of NAFLD includes multiple interactions among environmental factors, obesity, insulin resistance, dyslipidemia, inflammation and apoptosis. However, oxidative stress is more and more appearing as the most vital pathological associated event during NAFLD development. Vitamin D has an immune-regulating effect on adipose tissue and the increasing epidemiological data show that hypovitaminosis D is also associated with both obesity and NAFLD(16–18).

The most widely recognized IBD pathogenesis hypothesis is that complex interactions between genetics, environmental factors, and the host immune system result in abnormal immune responses, chronic inflammation of the intestine, and changes in the composition and function of the gut microbiota(19).

Multiple factors have been linked to the occurrence of NAFLD in IBD patients , such as metabolic syndrome (MS), intestinal inflammation and dysbiosis, the medication used to treat IBD, obese patients and bowel surgery. However, the exact association between NAFLD and IBD is yet to be determined(9).

Metabolic syndrome(MS)

MS is a group of 3 or more risk factors, including abdominal obesity, high triglycerides, low and high-density lipoprotein cholesterol, high blood pressure, and high-fasting blood glucose(20).NAFLD is considered

to be the hepatic manifestation of MS, affecting 25-30 % of the general population, and the risk factors are nearly identical with MS(21).

A retrospective cohort study of IBD-NAFLD patients was conducted to monitor the severity of IBD, MS and NAFLD. A total of 84 IBD-NAFLD (24 UC, 60 CD) patients were involvedin this study and the prevalence of MS was 23% in IBD-NAFLD patients(22).This study revealed a higher prevalence of obesity, hypertension and diabetes or resistance to insulin in patients with MS ($p<0.001$). In addition to MS, the study found that IBD range, severity or medication may contribute to the severity of NAFLD. Remarkably, in this study IBD severity was not associated with NAFLD fibrosis. In their viewpoint, a greater number of IBD patients (77%) had NAFLD in absence of MS, obesity, diabetes, and/or insulin resistance. This proposes that metabolic risk factors were not the only reason for NAFLD and fibrosis development in IBD patients.

Intestinal inflammation and dysbiosis

The intestine is colonizedby a huge range of microorganisms, defined as the gut microbiota or microbiome. Changes of gut microbiota is called dysbiosis, are recognizedto lead to interruption of this homeostasis and, therefore, the development of pathology(23).IBD was associated with dysbiosis, although the relationship with the role of intestinal microbiota in IBD pathogenesis is persistent, but the exact role of dysbiosis is still less known(24).

In NAFLD dysbiosis can induce intestinal inflammation, damaging the gut barrier and as a result, microbial products provoke hepatic inflammation which participates in NAFLD and NASH development(25).

Supporting the previous findings, a study revealed presence of high amount of Escherichia in the NAFLD patients which is identified to enhance the gut permeability, and it is associated with inflammation(26).The study also found that in NAFLD patients the pathogenic streptococcus species (Streptococcus bovis and Streptococcus faecalis) related to IBD were also abundant. Asymmetrical arrange microvilli and widened tight junction were noticed under electron microscope. Since dysbiosis has been associated with both NAFLD and IBD, it can act as a pathogenic connection between them. Table 2 concludes the reported risk factors for NAFLD in patients with IBD.

Table2. Risk factors of NAFLD in IBD patients

Risk factors	OR	95%CI	*P*
age (7)	1.72	0.94–1.91	0.65
diabetes (7)	1.72	0.94–1.91	0.006
hypertension (7)	0.62	0.24–2.33	0.51
metabolic syndrome (7)	2.24	1.77–28.81	0.04
Morbidabdominal circumference(7)	1.68	1.15–14.52	0.007
small bowel surgery (11)	3.7	1.5, 9.3	0.005
hyperlipidemia(59)	2.8	0.82–7.2	0.7

IBD therapeutic agents

Glucocorticoids (GCs)

Glucocorticoids are effective inhibitors of T cell activation and cytokine secretion and are therefore an effective treatment for IBD(27).A study illustratedthat GCs can affect both liver and adipose tissues. In liver, GCs activate triglyceride synthesis and hepatic steatosis and in adipose tissue, it increases metabolism of non-esterified fatty acid and lipolysis which contribute in progress of NAFLD. In addition, GCs are also associated with peripheral resistance of insulin and worsening of hepatic injury(28).

However, it is believed long durations and high doses oftheir administration may cause macrovascularsteatosis and hepatomegaly(29).Bessissow, on the contrary, did not detect any link between NAFLD and corticosteroid utilization(30).GCs may increase the risk of developing hepatic steatosis and should be used cautiously in patients with earlier metabolic risk factors.

Methotrexate (MTX)

MTX is an analog of folic acid and aminopterin, which is the antagonist of folic acid(31).Liver hepatotoxicity due to MTX differs according to the therapeutic indication and appears less common in CD patients compared to other diseases. MTX-induced liver damage can range cumulatively from macrovascular steatosis to hepatic fibrosis and even cirrhosis(29).Newly, numerous studies focused on an exciting pathophysiological mechanism of liver damage. MTX can disturb the intestinal epithelial barrier leading to the leaky gut syndrome which is known to be related with the onset and progression of the fatty liver disease(32).

However, anothermetanalysis study was performedwhichdidn't find any association between MTX and increase risk factor of NAFLD development. In this study dose, cumulative dose, or duration of treatment of MTX were not taken into consideration.That can be possibly the reason why this study was incapable to frame any link between MTX and development of NAFLD(33).MTX may associate with NAFLD it is stated that before starting therapy with MTX, NAFLD should be ruled out since it may worsen the condition(31).

Another cohort study was conducted where they found a tendency for MTX to be linked with NAFLD and advanced liver fibrosis(8).

Anti-TNFα

TNFα is a main pro-inflammatory cytokine exerting multiple effects on various cell types by triggering intracellular signaling.Inflammatory diseases such as IBD have been effectively treated with anti-TNFα agents(34).

Anti-TNFα was assumed to be able to protect against NASH as TNFα is involved in the development of hepatic inflammation and NASH development in pro-inflammatory pathways in NAFLD patients.Koca, S.S., et al presentedthat treatment with a single dose of anti-TNF-α antibody is effective on necrosis, inflammation and fibrosis in the experimental rat model of non-alcoholic steatohepatitis, intra-peritoneal infliximab (4 mg/kg) reduced the levels of AST, ALT and TGF-β(35). However, treatment with anti-TNFα have been connected with recurrence of hepatitis B virus (HBV) and it has been recommended that patients should be examined for HBV infection before anti-TNF therapy(36).

The likelihood of liver injury is associated with the use of TNF-α blockers in an autoimmune setting (especially in the presence of preexisting serological autoimmune signs such as anti nuclearantiobodies(ANA)). While the incidence of injury due to anti TNF-α therapy appears to be relatively low, hepatic damage is nevertheless significant(37). Anti TNF-α is not associated with NAFLD development is patients with IBD, which may be used in NAFLD treatment.

Azathioprine (AZA)and 6-mercaptopurine (6-MP)

AZA and 6-MPare purine nucleoside analogues (thiopurines) that have strong antiproliferative and immunosuppressive actions. These drugs are metabolized to 2 main metabolites, 6 thioguanine nucleotides (6-TGNs) and 6 methyl mercaptopurine (6-MMP) through a complex metabolic pathway. 15% –20% of patients produce 6-methylmercaptopurine (6MMP) hepatotoxic metabolite at the expense of 6-thioguanine therapeutic nucleotides (6TGN)(38,39). Soon after its introduction >100 cases of liver injury werereported.

AZA and 6-MP are connectedwith a range of drug-induced liver injuries (DILI) including asymptomatic liver enzyme elevations, hepatocellular necrosis, cholestasis and even mixed injuries. The mean prevalence of AZA and 6-MP-induced liver injury in patients with IBD was about 3%, and the mean annual drug-induced liver disorder rate was only 1.4%(40). Liver damage occurs frequently in patients taking AZA and 6-MP after 6 months of therapy. During follow-up, abnormal liver tests requiring the drug to be discontinued are rare (< 4 %) and can be resolved spontaneously(41).

A study demonstratedthat AZA/6-MP did not contribute to the progressof NAFLD(33).Utilizing Fibro scan in IBD patients (treated with thiopurines or methotrexate), it was implied that liver stiffness was not increased(42).

Parenteral nutrition (PN)

PN is composed of amino acids (AAs), dextrose, fat, vitamins, trace elements, electrolytes, and sterile water which is intravenously infused, circumventing the gastrointestinal (GI) system(43). Total parenteral nutrition(TPN) can be used as therapeutic agent or even as a lifesaver in IBD patients having nutritional problems(44).

Parenteral nutrition associated liver disease (PNALD) involves a range of hepatobiliary complications varying from liver steatosis to cirrhosis. It is estimated that PNALD occurs at up to 40% in adults and 50% in children on long-term PN(45).Steatosis is a relatively immediate complication of PN in adults, frequently discovered in patients after only 5 days of treatment and is a result of hepatocyte accumulation of fat globules without sign of inflammation, cholestasis or necrosis(46).Continuous PN can be a prompting factor in the buildup of fat in the liver for excess insulin levels(47).

Giving discontinuous parenteral nutrition while letting few hours for a metabolic rest (cyclic parenteral nutrition as cPN) improves liver dysfunctions associated with PN. This is achieved via restoring abnormal AST, GGT to normal levels and dropping ALT to almost normal levels. The results show that in reversing PNALD, cPN administration is effective(48). PN-induced fatty liver disease can be prevented and even reversed by administering primary omega-3-fatty acid with PN rather than by administering standard intravenous lipid emulsions containing primarily omega-6 fatty acid from plants(49).

Clinical Implications

Screening

To date, routine NAFLD screening in high-risk groups appearing at primary care is not recommended due to restrictions on diagnostic testing and treatment options, with a lack of long-term benefit related

knowledge and screening cost-effectiveness. It is important to exclude competing etiologies for steatosis and common chronic liver disease when assessing a patient with suspected NAFLD(50).

Ultrasound is aprecise, consistent imaging technique for spotting fatty liver compared to histology with a combined sensitivity of 84.8 % and specificity of 93.6% for detecting steatosis between 20% and 30%, and a summary area of 0.93% under the receiver operating characteristics (ROC) curve(51).

Liver enzymes, indirect markers of liver injury, have lower sensitivity (0.30-0.63) and specificity (0.38-0.63) than ultrasound(52). Liver biopsy is still the most accurate test to assess the nature and severity of liver disease. However, the cost and potential complications are its disadvantages.

In qualifying steatosis and liver fat plotting, magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) have the maximum accuracy (sensitivity and specificity). They may soon become the gold standard, but because of their cost and availability they are limited.

For now, studies of abdominal imaging are unable to diagnose NASH accurately. As far as considering non-invasive diagnostic methods in hepatic stiffness evaluation, Magnetic Resonance Elastography (MRE) is superior to MRI in NAFLD patients(53).

For the diagnosis of advanced fibrosis, numerous non-invasive serum biomarker scores are used with relatively high sensitivity and specificity, such as NAFLD fibrosis score (NFS), fibrosis-4 (FIB-4) index, based on routine clinical parameters and inexpensive biochemical measurements(54).A cross-sectional study shown thatliver stiffness measurement (LSM) by Fibroscan and FibroMeter^{V2G}has the most accuracyamong the non-invasive diagnostic proceduresin liver fibrosis in NAFLD(55).

IBD patients with higher risks of NAFLD or those with imaging features of hepatic steatosis, assessment of NAFLD may be helpful in them.

Treatment

Lifestyle improvements are currently the first line of treatment in NAFLD and NASH, including dietary habit and physical activity. Weight loss of approximately 10% almost resolved non-alcoholic steatohepatitis and improved fibrosis by at least one stage. However, weight loss (> 5%), can also bring significant benefits to the NAFLD activity score (NAS) components.

Following a Mediterranean diet (defined by lower carbohydrate intake, particularly sugars and refined carbohydrates, and increased consumption of monounsaturated and omega-3 fatty acids), liver fat can be reduced even without weight loss and is NAFLD most suggested dietary pattern(56).There is no pharmacologic drug which is currently approved for NASH therapy. However, there are studies which indicated useof vitamin E and pioglitazone arebeneficialin treating NASH. Astonishingly,coffee consumption with or without caffeine may have a beneficial effect on NAFLD disease(57).

As described above in the pathogenesis of NAFLD, gut dysbiosis was a risk factor that may affect and promote the pathogenesis of NAFLD. Current studies revealed that probiotics can reverse intestinal dysbiosis and be used as an alternative therapeutic optionfor patients with NAFLD and/or NASH(58).In obese patients, bariatric surgery may also result in an improved NASH status.

II. Conclusions

According to the current studies, the prevalence of NAFLD was greater in IBD related to non-IBD patients. This is apparently linked to an increase in MS, dysbiosis, chronic inflammation, small bowel surgery and therefore, it is possible that some medications (GCs, MTX) may contribute in risk factors for NAFLD advancement in IBD patients. Studies regarding dose and duration of IBD medications related with NAFLD, screening of IBD patients for NAFLD, prolong outcomes of IBD-NAFLD patients and treatment methodologies of NAFLD in IBD patients may further need to be investigated.

Conflict of interest

The authors have declared that no competing interests exist.

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