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Multifaceted pathogenesis of liver steatosis in inflammatory bowel disease: a systematic review

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Abstract. – OBJECTIVE: Non-Alcoholic Fatty Liver Disease (NAFLD), as a hepatic manifestation of metabolic syndrome (MET)-related obesity, insulin resistance, dyslipidemia, and hypertension, is the main cause of chronic liver disease. Inflammatory Bowel Diseases (IBD), (Crohn's Disease (CD) and Ulcerative Colitis (UC)), are often associated with extraintestinal manifestations. Of these, NAFLD is one of the most frequently reported. To highlight the etiopathogenesis of NAFLD in IBD, we performed a systematic review emphasizing the relationship between NAFLD genetic alterations, metabolic syndrome, and drugs.

MATERIALS AND METHODS: According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) criteria, we performed a systematic literature search on PubMed, Google Scholar, and Web of Science for literature updated from 2010 to 1 March 2021. Inclusion criteria for studies were observational design and Randomized Controlled Trials (RCTs); written in English; primary research only; based on adult patients, and human research only.

RESULTS: We identified nine studies on the link between NAFLD and IBD. Among these, two described the genetic predisposition to NAFLD of patients with IBD. Four reported an association between MetS and NAFLD in IBD patients. Regarding medications, none of four studies included, detected a relationship between NAFLD onset and IBD treatment (corticosteroids, immunomodulators, methotrexate, or biologics). However, a retrospective study showed a protective effect of anti-TNF alpha therapies against altered liver enzymes.

CONCLUSIONS: In this interplay between genetic, metabolic, drug, and inflammatory factors, the underlying pathogenic mechanisms behind NAFLD in IBD are still far from clear. Further studies are needed to better clarify the role of individual components influencing the development of NAFLD in IBD.

Key Words:
Inflammatory bowel disease, Non-alcoholic fatty liver disease, Metabolic syndrome, Transient elastography, Controlled attenuation parameter, Liver stiffness, Anti-tumor necrosis factor alpha, Gut microbiota.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of conditions ranging from simple liver fat accumulation to inflammation, fibrosis, and, ultimately, cirrhosis and liver cancer[1]. The progression of NAFLD from simple steatosis to more severe conditions is strongly influenced by genetic heritability[2-4].

NAFLD is the hepatic manifestation of metabolic syndrome (MET)-related obesity, insulin resistance, dyslipidemia, and hypertension. Additionally, with a prevalence of 10 to 46%, NAFLD represents the main cause of chronic liver disease in Western countries[5-9]. Such variability in the prevalence of NALFD is due to the different clinical and instrumental methodologies used for its diagnosis[10,11].

Inflammatory Bowel Diseases (IBD) encompass Ulcerative Colitis (UC) and Crohn's Disease (CD) which are two chronic inflammatory disorders involving the gastrointestinal (GI) tract. These disorders are characterized by an unregulated and abnormal immune response induced by environmental stimuli in genetically predisposed subjects[12].

CD and UC are often associated with extraintestinal clinical manifestations involving joints, skin, eyes, liver, and biliary tract[13]. NAFLD represents one of the most frequently described IBD-related liver diseases. Indeed, the link between NAFLD and IBD has been suggested

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by epidemiological studies[14-16], with the rate of NAFLD ranging between 6.2 and 40% in patients with CD and UC. Using transient elastography, NAFLD prevalence is determined to be 71% in IBD patients. This broad variability is due to different diagnostic methodologies. Importantly, hospitalized patients affected by IBD, and chronic liver disease have a two-fold greater mortality risk than those affected by IBD only.

The pathogenesis of NAFLD in IBD involves intestinal disorders with specific risk factors such as chronic inflammation, pharmacological therapies, prolonged exposure to steroids, and intestinal dysbiosis[17]. Furthermore, currently observed changes in intestinal disease shape, better therapeutic options, and better nutritional conditions for patients may lead to a higher risk of developing NAFLD[18]. Additionally, NAFLD onset and progression is strongly influenced by genetic factors. However, the role of genetic factors in the etiology of NAFLD in patients with IBD has been poorly investigated so far.

To highlight the etiopathogenesis of NAFLD in IBD, we performed this systematic review emphasizing the relationship between NAFLD and (1) genetic alterations, (2) Metabolic Syndrome, and (3) drugs.

Materials and Methods

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement (PRISMA) criteria[19], we performed a systematic literature search on PubMed, Google Scholar, and Web of Science for literature updated from 2010 to 1 March 2021. A combination of the following keywords has been used: "liver steatosis" OR "NAFLD" AND "Inflammatory bowel disease" OR "Crohn disease" OR "Ulcerative Colitis", as shown in **Supplementary File**. The inclusion criteria required that studies were: (1) quantitative observational studies and RCTs; (2) dated between 2010 and 2021; (3) written in English; (4) primary research only; (5) IBD patients, including UC and CD; (6) NAFLD patients; (7) adult population (aged ≥18 years); and (8) human research only. The study selection process comprised three steps. Step 1 consisted of the identification of the studies from a database search, as described above. Screening of the records was performed in step 2. Full-text papers were evaluated in step 3. The Critical Appraisal Skills Programme (CASP) tools (i.e., Cohort Checklist and Case-Control Checklist; 31.05.2013 version) were used to assess the quality of the included studies. Questions 1-6 relate to the internal validity of the studies, questions 7-8 relate to the validity of the results, and questions 9-11 relate to the external validity of the study. Disagreements were resolved by discussion, either between group partners or in consultation with the whole group.

Results

The flow diagram of the systematic research is shown in Figure 1. Of the 15 titles originally identified, two studies have been excluded because secondary (1 meta-analysis and 1 review), 4 because performed on animal models. Nine studies were included in our review. Data including the authors, title, country, year of publication, patients, aim, design, and results are summarized in Table I.

Quality Assessment

A quality assessment was conducted according to CASP-2013 for all the included studies, and the results are shown in **Supplementary Tables I, II**. All included studies – i.e., cross-sectional and cohort studies, and retrospective studies – were considered of good quality, based on them having an affirmative answer in at least 9 out of 13 and 8 out of 9 responses, respectively. No cohort and cross-sectional studies satisfied all 13 questions of the CASP appraisal tool. Of the eight cohort and cross-sectional studies, five scored 11 out of 13, one scored 10 out of 13, and one scored 9 out of 13. The only case–control study scored 8 out of 9, reporting good quality.

Genetics and NAFLD in IBD

The progression of NAFLD from simple steatosis towards more severe conditions has a strong genetic component[20]. Despite this, few studies investigated the role of genetic variants in the pathogenesis of NAFLD in IBD patients (Table I).

The most robustly associated and widely validated genetic determinants of NAFLD is the rs738409 variant on the patatin-like phospholipase domain-containing 3 (*PNPLA3)* gene[2]. The PNPLA3 protein is a highly expressed lipase in the human liver[21,22]. The target variant, encoding for an isoleucine to methionine substitution at position 148 (I148M), results in a loss of function of the protein activity[23]. In 2016, in patients with

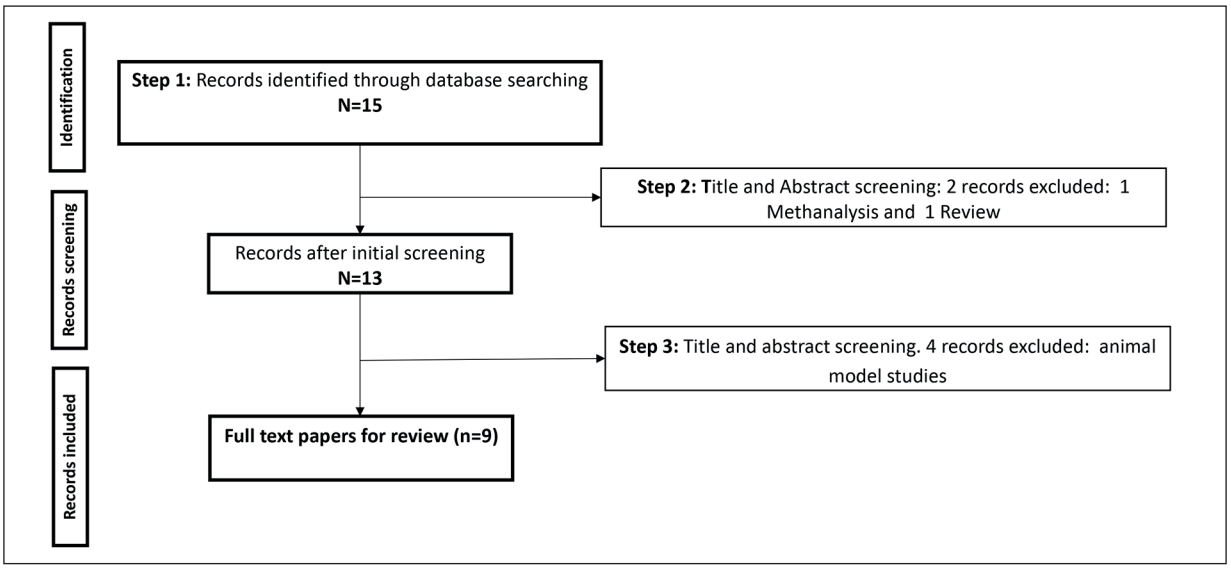

Figure 1. Study Flow Diagram.

IBD, this variant was found to be associated with a higher risk of hepatic steatosis, higher liver fat content measured as a controlled attenuation parameter, and increased circulating alanine transaminase. The conclusion of this study was that patients with IBD carrying the *PNPLA3* variant had a higher risk of liver disease progression[15].

In previous genome-wide association (GWA) studies, variants in two genes have been associated with increased susceptibility to CD: the autophagy-related 16-like 1 (*ATG16L1*), and the immunity-related GTPase M (*IRGM*) gene[23,24]. The latter gene has also been associated with increased accumulations of visceral adipose tissue (VAT) and hepatic fat content[25]. Additionally, in 2018, a cross-sectional study from Simon et al[26] assessed the relationship between *IRGM* gene variants, VAT, and the risk of NAFLD in patients with CD. In this study, hepatic fat was quantified by computed tomography (CT), and NAFLD severity was examined both *via* the FIB-4 index and ALT levels. They found that VAT volume was associated with an increased risk of NAFLD and with higher markers of NAFLD severity. This association was further enhanced by variants in the *IRGM* gene.

Metabolic Syndrome and NAFLD in IBD

Currently, data on the association between NAFLD and metabolic syndrome (MetS) in the IBD setting are discordant (Table I).

Some authors have highlighted a close relationship between MetS and NAFLD in IBD.

In a prospective study comparing a group of NAFLD patients with (n. 465) and without IBD (n. 189), the authors reported that in patients with IBD, NAFLD (measured by ultrasound evaluation) was independently associated with MetS, diabetes, fasting blood glucose, and abdominal circumference[16] (Table I).

Consistently, in 2017, a retrospective study of patients with IBD and NAFLD showed that the severity of NAFLD in both UC and CD patients was associated with the presence of MetS, but not with the severity of IBD. Specifically, both UC and CD patients with MetS had a higher NAFLD Fibrosis Score (NFS) than those without MetS[27] (Table I). The same results were obtained in an independent Italian study in 2020 in which the presence and severity of NAFLD were evaluated *via* both ultrasound and Transient Elastography (TE). In this study, the authors reported that NAFLD was associated both with MetS and obesity[28] (Table I).

Furthermore, in 2019, a study on 384 IBD patients reported older age, higher body mass index (BMI), and higher triglyceride levels as independent predictors of NAFLD. These parameters are specific and well-recognized MetS indicators[29].

Additionally, in a nested case-controlled study[30] conducted on 217 patients with IBD, NAFLD measured by US, CT, or MRI occurred in 8.2% of patients. These patients with NAFLD were older, had a later onset of disease and previous intestinal surgery compared to those with

Table I. Characteristic and results of included studies.

Publication (year)	Country	Study sample	Study design	NAFLD assessment	Results
Sartini et al (2018)[31]	Italy	223 NAFLD	Retrospective pts: 78 IBD+; 145 IBD-	Liver US	MetS: IBD+ *vs.* IBD- (56.6 *vs.* 23.1%, $p < 0.001$). Associations with NAFLD: ≥ 1 IBD relapse/year (OR 17.3, 95% CI 3.6–84, $p < 0.001$), IBD surgery (OR 15.1, 95% CI 3.1-73.7, $p = 0.001$) more extensive intestinal involvement (OR 19.4, 95% CI 3.4-110.9 $p = 0.001$). anti-TNFα independent factor protecting towards altered liver enzymes (OR 0.15, 95% CI 0-0.8, $p = 0.02$)
Principi et al (2018)[16]	Italy	465 IBD+ pts; 189 IBD-pts	Prospective	Liver US	NAFLD in IBD: MetS (OR = 2.24, 95% CI 1.77-28.81, $p = 0.04$), diabetes (OR = 1.71, 95% CI 1.43-12.25 $p = 0.006$), GGT levels (OR = 2.77, 95% CI 1.82-8.64, $p = 0.007$), FBG (OR = 1.36, 95% CI 1.13-1.68, $p = 0.03$), abdominal circumference (OR = 1.68, 95% CI 1.15-14.52, $p = 0.007$). No association between IBD treatment and NAFLD. ($p > 0.05$)
Carr et al (2017)[27]	USA	84 IBD + NAFLD + Pts.	Retrospective	NFS	NFS scores MetS+ *vs.* NFS scores MetS- (UC -0.4 *vs.* -2.5, $p = 0.02$; CD -0.8 *vs.* 2.3, $p = 0.03$). No association between IBD treatment and severity of NAFLD. ($p > 0.05$)
Glassner et al (2017)[32]	USA	168 Pts: 56 IBD + NAFLD +; 56 IBD +; 56 NAFLD +	Retrospective	Liver US, CT, MRI	IBD+ NAFLD+ *vs.* IBD+ NAFLD-: longer disease duration (20 ± 12.2 *vs.* 10 ± 7.7 $p = 0.004$); diabetes (16% *vs.* 2%, OR = 10.2, 95% CI 1.2-47.2, $p = 0.01$), obesity (40% *vs.* 20%, OR 2.2, 95% CI 1.4-6.2, $p = 0.02$). NAFLD+ IBD- *vs.* NAFLD+ IBD+: obesity (59% *vs.* 40%, OR 2.2, 95% CI 1.0-4.5, $p = 0.03$), hypertension (55% *vs.* 33%, OR 2.5, 95% CI 1.1–5.4, $p = 0.02$), hyperlipidemia (53% *vs.* 17.5%, OR 6.7, 95% CI 2.8-16.2, $p = 0.0001$), diabetes (40%/16%, OR 3.5, 95% CI 1.3-9.1, $p = 0.0001$). No association between IBD treatment and NAFLD
Magrì et al (2019)[28]	Italy	178 IBD Pts: 72 NAFLD+; 106 NAFLD-	Prospective	Liver US	NAFLD associated with MetS (OR: 4.13, 95% CI 1.85-9.24, $p = 0.001$), obesity (OR 9.21, 95% CI 3.06-27.70). LF associated with MetS (OR: 3.40, 95% CI 1.26-9.20 $p = 0.01$).
Sourian Arayanane et al (2013)[30]	USA	217 IBD+ pts: 76 NAFLD+; 141 NAFLD-	Retrospective	Liver US, CT, MRI	NAFLD associated with hypertension (OR = 3.5, 95% CI 1.5-8.1), obesity (OR = 2.1, 95% CI 1.05-4.0), small bowel surgery (OR = 3.7, 95% CI 1.5-9.3).
Saroli Palumbo et al (2019)[29]	Canada	384 IBD Pts: 126 NAFLD+, 258 NAFLD-	Prospective	LE, CAP	Predictors of NAFLD: older age (aOR 1.45, 95% CI 1.15-1.82); higher BMI (aOR = 1.31, 95% CI 1.20-1.42); higher triglycerides (aOR = 1.45, 95% CI 1.01-2.09). No association between IBD treatment and NAFLD.
Mancina et al (2016)[15]	Italy	158 IBD Pts.	Prospective;	Liver US; CAP	IBD with PNPLA3 148M allele: hepatic steatosis (OR 2.9, 95% CI 1.1-7-8), higher CAP values ($p = 0.029$), increased ALT ($p = 0.035$)
Simon et al (2018)[26]	USA	462 CD Pts.	Cross-sectional	CT	Relationship between VAT and NAFLD was modified by IRGM variants rs4958847 (GA or AA) (aOR: 1.44, 95% CI 0.87-2.36, $p = 0.005$) and rs13361189 (TC or CC) (aOR: 1.57, 95% CI 1.11-2-23, $p < 0.001$)

Abbreviations: aHR, Adjusted Hazard-Ratio; aOR, Adjusted Odds-Ratio; BMI, Body-Mass Index; CAP, Controlled Attenuation Parameter; CD, Crohn's Disease; CT, Computed Tomography; HSI, Hepatic Steatosis Index; FBG, Fasting Blood Glucose; FIB-4, Fibrosis-4; IBD, Inflammatory Bowel Disease; LE, Liver Elastography; MetS, Metabolic Syndrome; MRI, Magnetic Resonance Imaging; NAFLD, Non-Alcoholic Fatty Liver Disease; NFS, NAFLD Fibrosis Score; TNF-α, Tumor Necrosis Factor-α; UC, Ulcerative Colitis; US, Ultrasonography.

IBD alone. In this study, the use of steroids was associated with NAFLD development, while anti-TNF drugs showed a protective effect.

Interestingly, patients with IBD developed NAFLD with lower metabolic factors than those without IBD.

On the contrary, a more recent study performed on NAFLD patients with and without IBD showed that those with IBD were less likely to have impaired transaminases, a smaller waist circumference, and a lower BMI. In this study, MetS had a higher prevalence in NAFLD patients without IBD[31](Table I).

A retrospective study performed in 2017 examined a total of 168 individuals divided into 3 groups (56 individuals *per* group): 1) IBD + NAFLD, 2) IBD only, 3) NAFLD only[32].

Patients from the "NAFLD only" group had an increased prevalence of obesity, hypertension, hyperlipidemia, and diabetes compared to the "NAFLD+IBD" group. Additionally, patients from the "NAFLD+IBD" group showed an onset of NAFLD with less metabolic parameters than patients with NAFLD only, highlighting the possible involvement of other factors in the pathogenesis of NAFLD in the IBD population.

IBD Drugs and NAFLD

The role of medical treatments including glucocorticoids, immunomodulators, and tumor necrosis factor-α inhibitors in the pathogenesis of NAFLD in IBD remains unclear (Table I). Glucocorticoids and immunomodulators may increase the risk of NAFLD progression because of their effect on metabolic parameters and inherent hepatotoxicity. Conversely, further data suggest a potential role of biological treatments used in maintenance and remission therapies[33], such as TNF-α inhibitors, as protective factors against NAFLD in IBD patients.

So far, no association between the use of IBD medications and the prevalence of NAFLD has been highlighted. A recent meta-analysis performed on 1610 IBD patients from seven observational studies (five cross-sectional[32,34-37], one case-control[30] and one retrospective[38]) failed to show an association between the use of IBD medications and NAFLD. In this study, NAFLD pooled ratios in patients using biological agents, immunomodulators, methotrexate, and steroids were 0.85 (95% CI: 0.49-1.46, p=0.55), 1.19 (95% CI: 0.70-2.01, p=0.52), 3.62 (95% CI: 0.48-27.39, p=0.21), and 1.24 (95% CI: 0.85-1.82, p=0.27), suggesting a complex and multifactorial relationship between IBD and the development of NAFLD that is probably not associated with treatments.

After 2018, other studies, already mentioned in the previous section, were performed in this context with similar results. More specifically, Magri' et al[28], using ultrasound to define NAFLD, reported no associations between NAFLD and the use of steroids (Table I). Similar results were obtained by Saroli Palumbo et al[29] using TE to define NAFLD. A single retrospective study showed that anti-TNFα would have a protective role in the progression of NAFLD in IBD patients, suggesting that this treatment is an independent protective factor against the presence of altered liver enzymes[31].

Discussion

The prevalence of NAFLD in the Western population is increasing. Given the shared characteristics between NAFLD and IBD, such as chronic relapsing inflammation and immune activation, hepatotoxic drugs, surgery, and parenteral nutrition, patients with IBD are potentially more susceptible to NAFLD[28]. In this systematic review, we sought to clarify the main pathogenic hypotheses for NAFLD in IBD patients.

Genetic studies suggest a close and articulated correlation between metabolic factors, IBD, and NAFLD, with reciprocal interplay. Notably, there are evidence suggesting that *IRGM* gene which mediates autophagy is involved in the pathogenetic mechanisms of both Crohn's disease and NAFLD.

An appealing pathogenic hypothesis is related to the very complex relationship between MetS and NAFLD in IBD. Some of the studies examined in the present review, identified the same metabolic risk factors in IBD patients as in the general population using different methodologies. Improvements in treatment for IBD have led to a change in this scenario. Indeed, weight loss and malnutrition are characteristics of IBD patients during flare-up periods. Instead, a normal or even higher BMI is currently related to a stable course of disease with longer remission periods[39]. We are, therefore, witnessing the potential negative effects of weight gain or obesity on the long-term general health of IBD patients[18].

On the other hand, other authors suggest a more prominent role of factors related to inflam-

matory bowel disease, such as a longer duration of disease, later onset, previous bowel surgery, and steroid use as pathogenic hypotheses for NALFD in IBD patients.

So far, no treatment used in IBD has been associated with higher rates of NAFLD. However, there are some methodological limits in the metanalysis examined, such as the lack of consideration for dosage, duration, and cumulative exposure to medication.

To the best of our knowledge, in preclinical mouse models[40-42] and only in the clinical study from Sartini et al[31], there is evidence of a protective role of anti-TNF alpha inhibitors (infliximab and adalimumab). However, to date, there are no well-conducted prospective studies on this topic.

In this interplay between genetic, metabolic, inflammatory, and drug factors, the existing relationship and the underlying pathogenic mechanisms that could recognize the gut microbiota as a key link remain unclear. Indeed, the role of intestinal dysbiosis in IBD pathogenesis is well recognized[43]. In addition, many studies have focused on changes in the gut microbiota in obesity, NAFLD, and MetS patients, also determining the presence of specific phyla in the composition of the microbiota of such patients[44-46]. No studies investigated the role of microbiota in IBD patients with NAFLD so far. Therefore, it can be speculated, as in our previous study[47], that the increased fat and liver inflammation in IBD patients is the result of exposure to numerous inflammatory cytokines, bacterial products, and hepatotoxic catabolites coming through the portal system from the compromised intestinal mucosal integrity and permeability, and the altered gut microbiota composition. This is in line with the concept of the gut–liver axis, in which the gut microbiota plays a strong mediating role. To our current knowledge, a disrupted gut mucosal barrier may allow gut-derived microbial factors and metabolites to reach the liver and induce pathological modifications, including inflammation and fibrosis and stimulating the pathological processes of chronic liver diseases. However, this may not be the sole culprit. Animal model studies suggest that a functional barrier is present in the liver itself, made by liver sinusoidal endothelial cells (LSECs)[48]. In animal models, intact and well-functioning LSECs contribute to the elimination of Gram-negative lipopolysaccharide (LPS) from the bloodstream, acting as scavengers to avoid or reduce sepsis-related inflammation[49]. In contrast, in other mouse models of liver diseases, LSEC disruption promotes the activation of Kupffer cells and Hepatic Stellate Cells (HSCs), leading to liver injury[50]. Further molecular and prospective clinical studies are needed to confirm these hypotheses.

Conclusions

The data available so far still show poor and controversial results regarding the pathogenesis of NAFLD in patients with IBD. Clarification of the coexistence of these two disorders and their pathogenic interconnection should be pursued in order to better define potential therapeutic options in a tailored way. Further studies are needed to better clarify the role of individual components influencing the development of NAFLD in IBD.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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