



Associations between irritable bowel syndrome and non-alcoholic fatty liver disease: A systematic review

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS) is associated with obesity and metabolic syndrome. IBS and non-alcoholic fatty liver disease (NAFLD) are highly prevalent entities worldwide and may share similar mechanisms including gut dysbiosis, impaired intestinal mucosal barrier and immune system activation.

AIM

To systematically review their association according to the Preferred Reporting Items for Systemic Review and Meta-analyses guidelines.

METHODS

PubMed, EMBASE and Cochrane Database of Systematic Reviews were searched for relevant papers. Manual searches were also performed.

RESULTS

Six studies were included. Both IBS and NAFLD subjects had significantly more metabolic risk factors like hypertension, obesity, dyslipidaemia and diabetes. Our review showed that 23.2% to 29.4% of NAFLD patients had IBS. IBS was significantly higher in NAFLD patients compared with patients without NAFLD (23.2% vs 12.5%, $P < 0.01$). A higher proportion of IBS patients had NAFLD (65.8% to 74.0%). IBS patients were three times more likely to have NAFLD compared with non-IBS patients ($P < 0.001$). Two studies showed a significant correlation bet-

ween the severity of IBS and NAFLD. The proportion of NAFLD subjects with IBS increased with NAFLD severity.

CONCLUSION

Further prospective studies are warranted to evaluate the relationship and shared pathways between IBS and NAFLD, potentially leading to the development of future therapeutics.

Key Words: Irritable bowel syndrome; Functional gastrointestinal disorder; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Gut dysbiosis; Metabolic syndrome

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Core Tip: The relationship between irritable bowel syndrome (IBS) and non-alcoholic fatty liver disease (NAFLD) is increasingly recognised but their shared mechanisms remain poorly elucidated. We evaluate the association between IBS and NAFLD and discuss the risk factors and possible common mechanistic pathways including the brain-gut-liver axis, gut dysbiosis and translocation, altered hypothalamic-pituitary-adrenal axis and sleep quality.

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INTRODUCTION

The global surge in obesity has heralded the increasing prevalence of non-alcoholic fatty liver disease (NAFLD), which is the hepatic manifestation of the metabolic syndrome. NAFLD has emerged as the most common chronic liver disease and is increasingly recognised as a leading cause of morbidity and mortality[1]. It affects up to 25%-30% of the general population but is highly prevalent (up to 50%-90%) in patients with obesity and features of the metabolic syndrome[1,2]. Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction, characterised by chronic abdominal pain and altered bowel movements without an organic cause[3]. Given the degree of heterogeneity in criteria used for the diagnosis of IBS, the true global prevalence of IBS remains elusive but is estimated to affect 1 in 10 people globally[4,5]. IBS is a complex condition that is caused by a myriad of factors with interplay of genetics, epigenetics, immune activation, gut dysbiosis, abnormal gut-brain interactions, visceral hypersensitivity, altered gut motility, eating behaviours, psychological stressors, and environmental factors[6,7]. To date, studies have found an interesting relationship between obesity and IBS. As NAFLD is closely linked with obesity, insulin resistance and the metabolic risk factors, emerging evidence has shown a possible correlation between NAFLD and IBS due to purported shared underlying pathophysiological links[8].

IBS is significantly associated with a higher prevalence of the metabolic syndrome and a multitude of studies have determined a link and common pathogenic mechanisms between these two conditions. Obesity and metabolic syndrome are found more frequently in IBS patients compared with controls[9]. A cross-sectional study from Japan showed a positive association between IBS and increased prevalence of metabolic syndrome and triglyceride levels. The odds ratio (OR) (95%CI) in IBS subjects were 2.01 (1.13-3.55) and 1.50 (1.03-2.18) respectively as compared with non-IBS subjects[10]. There is a higher occurrence of pre-diabetes and higher low-density lipoprotein (LDL) levels in patients with IBS[11,12]. In a large population-based cohort study, increased bowel movement frequency was associated with elevated risks of cardiovascular disease, diabetes, heart failure and chronic kidney disease[13]. In IBS subjects, an elevated body mass index (BMI) is associated with significantly faster colonic and rectosigmoid transit and higher bowel frequency[14].

Obesity and the metabolic syndrome are linked with insulin resistance, oxidative stress, chronic low-grade inflammation, abnormal lipid metabolism and gut microbiota alterations, all of which play key roles in the pathogenesis of NAFLD and the more progressive non-alcoholic steatohepatitis (NASH)[15,16]. The gut-liver axis is implicated in the development of NAFLD and similar mechanisms have also been shown to be pivotal to the pathogenesis of IBS[17,18]. Several studies have highlighted the correlation between NAFLD and IBS. Lee *et al*[19] demonstrated an increased prevalence of elevated alanine aminotransferase and gamma-glutamyl transferase levels and metabolic syndrome in IBS patients[19].

In this systematic review, we aim to evaluate the association between IBS and NAFLD including the common mechanistic pathways and overlapping risk factors.

MATERIALS AND METHODS

Search strategy and screening

The Preferred Reporting Items for Systemic Review and Meta-analyses (PRISMA) guidelines were used for the purposes

of this systematic review. A two-step approach was adopted to identify studies: (1) A systematic search of electronic databases; and (2) A manual search of direct citations from potentially relevant papers and other peer-reviewed journals.

The following electronic libraries-PubMed, Embase and the Cochrane Database of Systemic Reviews were searched from inception to March 2023 to identify papers studying the associations between IBS and NAFLD. The uses of search strategies were described in [Table 1](#).

Manual searches of direct citations from potentially relevant papers and other peer-reviewed journals were also performed to identify additional studies not included in the systemic search. No filters were used to refine search results. No linguistic or geographical restrictions were imposed.

The titles of all papers retrieved by the literature search were screened for relevance and any studies of obvious irrelevance were excluded. All full manuscripts of relevant papers were then retrieved and subsequently screened in its entirety. The entire screening process was done by two independent researchers to identify studies that met the study selection criteria. Consensus was reached regarding any discrepancies that arose without the need for a third independent reviewer.

Eligibility criteria

Studies that met the following inclusion criteria were included: (1) Observational studies that investigated the relevance between IBS and NAFLD that included cross-sectional, case-control or cohort studies; (2) Population studies that showed the relevance between IBS and NAFLD; and (3) Human studies. Due to predictions of limited number of studies regarding the topic of interest, a planned option of expansion of criteria was put in place to include studies published in the Chinese language, of which all of the authors are also proficient in.

Data extraction

The data extraction process was done independently as per the PRISMA checklist. Publication details were first extracted, which included: (1) Author's name; (2) Year and Country of study; and (3) Methodology (sample characteristics, study design, and modalities used to diagnose IBS and NAFLD). Further data extraction included any risk factors that predisposed patients to the incidence of IBS and NAFLD if present that included risk estimate, including OR with corresponding 95% CIs about the association between IBS and NAFLD.

Risk of bias assessment

All eligible studies were assessed for risk of bias using Cochrane Risk of Bias Assessment ([Figure 1](#)).

Search results

The search from PubMed, Embase and Cochrane identified 509 studies along with 2 studies *via* manual search. 441 studies were screened for after the removal of 70 duplicates. 428 studies were excluded and 13 studies were retrieved for and screened in full. Among these 13 studies, 7 studies were excluded for reasons that included (1) Review articles (2) No full papers available; and (3) Non-English or non-Chinese language ([Figure 2](#)). The final 6 studies were included in this systematic review ([Table 2](#)).

RESULTS

The studies that were included demonstrated associations between NAFLD and IBS. The criteria used to identify IBS patients included ROME III criteria (Ke *et al*[20], Hasanian *et al*[21], Zheng *et al*[22]) and ROME IV criteria (Franco *et al*[23]), whilst Wu *et al*[24] selected IBS patients according to international classification of diseases (ICD)-10 coding[20-24]. Singh *et al*[25], Hasanian *et al*[21], Ke *et al*[20], and Zheng *et al*[22] used ultrasonography for the diagnosis of NAFLD whereas the fatty liver index (FLI) was used by Wu *et al*[24] to assess for NAFLD[20-22,24,25]. Franco *et al*[23] recruited patients with NAFLD based on ICD-10 codes[23]. The mode of diagnosis of IBS was not stated by Singh *et al*[25].

All the included studies demonstrate overlap between IBS and NAFLD, either *via* a substantial proportion of sample population having both IBS and NAFLD, or *via* meta-analysis that showed increased risk of also having IBS or NAFLD should either condition be present. Two studies reported that patients with IBS had increased risk of metabolic syndrome, including higher BMI, dyslipidemia and diabetes mellitus[20,21]. One study demonstrated the same for the IBS and NAFLD overlap group compared to the group that had either IBS or NAFLD[22].

NAFLD in IBS patients

The 100 IBS patients were included in the study by Hasanian *et al*[21] according to the ROME III diagnostic criteria[21]. BMI and waist circumference were obtained. Laboratory investigations included fasting serum glucose levels, lipid profile, liver chemistry profile, international normalized ratio and a complete blood count. NAFLD was diagnosed in 74% of the study population using abdominal ultrasonography. Furthermore, it was noted that a higher prevalence of moderate/severe NAFLD were found among patients with moderate/severe IBS compared to mild IBS (22.4% *vs* 4.8%). This could signify a potential association between higher grades of NAFLD with more severe IBS. Multi-variate analysis affirmed the association of moderate/severe NAFLD with moderate/severe IBS which was independent of other risk factors of IBS (OR: 2.4, 95%CI: 1.3-62.7, $P = 0.026$). Metabolic syndrome was also found to be independently associated with moderate/severe IBS (OR: 3.1, 95%CI: 1.8-54.6, $P = 0.011$). The study observed that the most frequent metabolic parameter in IBS patients was high BMI (89%)[21].

Table 1 Search terms used

Database	
PubMed	(Irritable bowel syndrome[Mesh] OR "Irritable bowel syndrome"[tiab] OR "irritable colon*" [tiab] OR IBS[tiab]) AND (Fatty Liver[Mesh] OR fatty[tiab] AND (liver*[tiab] OR hepat*[tiab]) OR steatohepat*[tiab] OR NAFL*[tiab] OR NASH*[tiab]))
EMBASE	('irritable colon'/exp OR 'irritable bowel syndrome':ab,ti OR 'irritable colon':ab,ti OR 'IBS':ab,ti) AND ('Fatty Liver'/exp OR (fatty:ab,ti AND (liver*:ab,ti OR hepat*:ab,ti) OR steatohepat*:ab,ti OR NAFL*:ab,ti OR NASH*:ab,ti))
CENTRAL	#1 MeSH descriptor: [Irritable Bowel Syndrome] explode all trees #2 ('irritable bowel syndrome' OR 'irritable colon' OR 'IBS'):ti,ab,kw #3 MeSH descriptor: [Fatty Liver] explode all trees #4 fatty:ab,ti AND (liver*:ab,ti OR hepat*:ab,ti) OR steatohepat*:ab,ti OR NAFL*:ab,ti OR NASH*:ab,ti #5 (#1 or #2) and (#3 or #4)

CENTRAL: Cochrane Central Register of Controlled Trials.

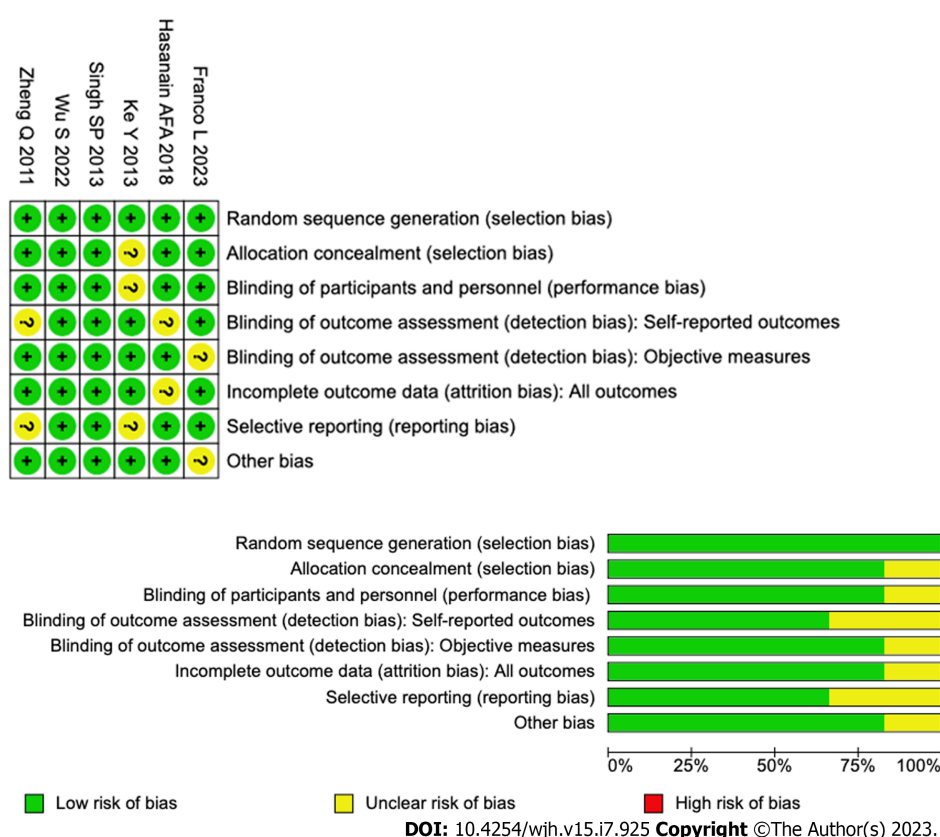


Figure 1 Cochrane risk of bias assessment.

IBS in NAFLD patients

Ke *et al* [20] aimed to detect the prevalence of IBS in NAFLD patients as well as normal patients. Patients who underwent health examination in Urumqi, China were randomised into 2 groups: NAFLD and normal controls. IBS was diagnosed using the ROME III criteria. NAFLD was diagnosed using ultrasound based on the 2006 Revised Diagnostic criteria by Fatty Liver and Alcoholic Liver Disease Group of Chinese Medical association Hepatology Branch. 65.8% of adults with IBS-like symptoms had NAFLD while the detection rate of IBS was higher in NAFLD patients compared to normal (23.2% *vs* 12.5%, $P < 0.01$), suggesting an association between NAFLD and IBS-like symptoms. NAFLD patients were subsequently subdivided based on severity into: (1) Mild: 212; (2) moderate: 188; and (3) severe: 48. The prevalence of IBS in NAFLD patients increased with the severity of NAFLD as noted by the IBS detection rate for the groups being 11.3%, 27.7% and 58.3% respectively. Further analysis showed that more IBS symptoms were experienced with increasing severity of NAFLD. Multivariate logistic regression analysis demonstrated that IBS-like symptoms were closely related to ethnicity (OR: 0.316, 95%CI: 0.134-0.745, $P = 0.008$), fatty liver (OR: 0.525; 95%CI: 0.278-0.991, $P = 0.047$), BMI (OR: 0.918; 95%CI: 0.844-1.000, $P = 0.049$) and triglyceride levels (OR: 0.855; 95%CI: 0.739-0.988; $P = 0.034$) [20].

Table 2 Summary of study findings

Ref.	Location	Sample characteristics	Study design	IBS diagnosis	NAFLD diagnosis	IBS and NAFLD overlap	Associated risk factors
Ke <i>et al</i> [20], 2013	China	No. of patients: 945. NAFLD population: 470 (226 males, 222 females). Total without NAFLD: 475 (198 males, 234 females). Note: DM was in exclusion criteria	Cross-sectional study	ROME III	Ultrasound; Chinese Society of Hepatology, Chinese Medical Association diagnosis criteria for NAFLD	IBS incidence: 104 (23.2%) of NAFLD patients <i>vs</i> 54 (12.5%) of patients without NAFLD. NAFLD incidence in patients with IBS symptoms: 65.8% of patients with IBS-like symptoms had NAFLD. Higher detection rate of IBS-like symptoms with more severe NAFLD ($P < 0.05$). Mild NAFLD (Group A): 24 out of 212 (11.3%). Moderate NAFLD (Group B): 52 out of 188 (27.7%). Severe NAFLD (Group C): 28 out of 48 (58.3%)	Risk factors for IBS-like symptoms: BMI ($P = 0.049$). Triglycerides ($P = 0.034$). Fatty liver ($P = 0.047$). Ethnicity-Han, Uyghur ($P = 0.008$)
Hasanian <i>et al</i> [21], 2018	Egypt	100 consecutive patients diagnosed with IBS (49 males, 51 females): 45% IBS-C 23% IBS-D 32% IBS-M. Further divided into: Mild IBS ($n = 42$); Moderate IBS ($n = 43$); Severe IBS ($n = 15$)	Cross-sectional study	ROME III	Ultrasound	74% of IBS patients had NAFLD. Moderate/severe NAFLD significantly associated with moderate/severe IBS. 22.4% moderate/severe IBS patients (95%CI: 15.8%-31.5%) <i>vs</i> 4.8% mild IBS patients: (95%CI: 2.7%-7.9%) ($P = 0.001$)	Predictors of moderate/severe IBS: NAFLD ($P = 0.026$); Metabolic Syndrome ($P = 0.011$)
Zheng <i>et al</i> [22], 2011	China	No. of patients: 200 (89 males, 111 females) (1) Both NAFLD and IBS: 25; (2) Either NAFLD or IBS: 36; and (3) Neither IBS nor NAFLD: 139	Cross-sectional study	ROME III	Ultrasound; NAFLD diagnosis based on Chinese Society of Hepatology, Chinese Medical Association	25 subjects (12.5%) had both NAFLD and IBS	NAFLD and IBS overlap group compared to group without NAFLD and IBS Overlap had higher: BMI ($P = 0.045$); TG ($P = 0.035$); TC ($P = 0.038$); HDL-C ($P = 0.045$); LDL-C ($P = 0.031$); FBG ($P = 0.023$). NAFLD and IBS overlap group compared to the either NAFLD or IBS group had higher: Hypertension ($P = 0.041$); Obesity ($P = 0.034$); Dyslipidemia ($P = 0.020$); Diabetes ($P = 0.037$); Digestive system diseases ($P = 0.037$). GIT sensory threshold: NAFLD and IBS overlap group had lower threshold of the following compared to either NAFLD or IBS group: FSV ($P = 0.034$); DSV ($P = 0.032$); MTV ($P = 0.035$); PSV ($P = 0.027$)
Franco <i>et al</i> [23], 2022	United States	No. of patients: 130 patients with NAFLD (49 males, 81 females)	Cross-sectional study	ROME IV	ICD-10 Code	38 (29.2%) patients with NAFLD fulfilled Rome IV IBS criteria	Increased prevalence of depression (18.4% <i>vs</i> 5.4%, $P = 0.01$) and anxiety (31.6% <i>vs</i> 9.8%, $P = 0.002$) in NAFLD patients with IBS compared to those without IBS. Independent predictors of IBS in NAFLD: Female gender (OR: 5.69, $P = 0.001$); Depression (OR: 1.23, $P < 0.001$); BMI (OR: 0.90, $P = 0.02$)
Wu <i>et al</i> [24], 2022	United Kingdom	No. of patients: 396838 (189759 males, 207079 females). NAFLD population: 153203	Prospective cohort study; United Kingdom Biobank	ICD-10 Code	Fatty Liver Index	7129 cases of incident IBS in NAFLD patients (cumulative incidence rate of 1.49 (95%CI: 1.46-1.53) per 1000 person-years). NAFLD patients showed a 13% higher risk of developing IBS (HR = 1.13, 1.05-1.17). Increased risk of IBS in higher FLI quartile	Subgroup analysis showed increased IBS risk for: Age ($P < 0.003$); Gender (Female) ($P < 0.001$)

Singh <i>et al</i> [25], 2013	India	No. of patients: 632 patients with incidentally detected NAFLD (484 males, 148 females)	Retrospective analysis	Not documented	Ultrasound diagnosis and grading of liver steatosis by two radiologists in a blinded study	186 (29.4%) out of 632 NAFLD patients had IBS	-
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IBS: Irritable bowel syndrome; NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; FBG: Fasting blood glucose; FSV: First sensation volume; DSV: Defaecating sensation volume; MTV: Maximum tolerable volume; PSV: Painful sensation volume; ICD-10: International classification of diseases-10.

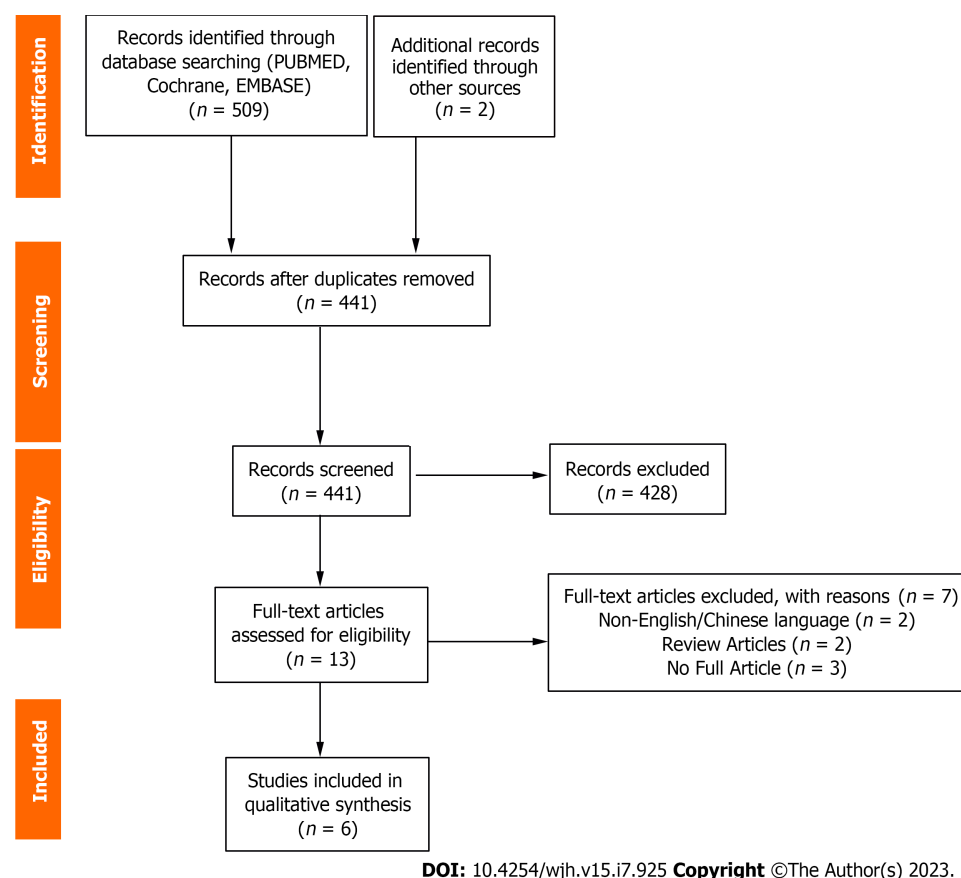


Figure 2 Preferred Reporting Items for Systemic Review and Meta-analyses flowchart.

A cross-sectional study by Franco *et al*[23] included 130 NAFLD patients of which up to 29.2% of patients had co-existing IBS according to ROME IV criteria[23]. A higher prevalence of depression (18.4%) and anxiety (31.6%) was detected using the Hospital Anxiety Depression Scale in NAFLD patients with IBS compared to those without IBS (5.4% and 9.8%) respectively. Female gender (OR: 5.69, 95%CI: 2.01-16.12, $P = 0.001$) and depression (OR: 1.23, 95%CI: 1.10-1.38, $P < 0.001$) were independent risk factors for IBS[23].

A recent prospective cohort study followed 153203 patients diagnosed with NAFLD using FLI over 12.4 years[24]. IBS patients were determined *via* ICD-10 codes and diagnosis was based on self-report, primary care and hospital admission data. 7129 cases of incident IBS were detected with a cumulative incidence rate of 1.49 (95%CI: 1.46-1.53) per 1000 person-years. NAFLD patients showed a 13% higher risk of developing IBS (HR = 1.13, 1.05-1.17) compared with non-NAFLD patients. The highest FLI quartile was associated with a significant increase in risk of IBS compared to the lowest FLI quartile (HR q4 *vs* q1 = 1.21, 1.13-1.30, $P < 0.001$). This positive association between NAFLD and IBS was also observed by per SD change of FLI (adjusted HR = 1.08, 1.05-1.10) and predominantly in females[24].

Singh *et al*[25] showed that a proportion of NAFLD patients initially presented with IBS, though this was not elaborated upon. Out of 16225 patients with various gastrointestinal complaints, 632 patients with NAFLD were included. These patients attended the clinic not because of NAFLD but rather for a variety of gastrointestinal symptoms and the initial reason for evaluation for 29.4% (186) of these individuals with NAFLD was IBS[25].

Patients with both IBS and NAFLD

Zheng *et al*[22] grouped patients into those with IBS and NAFLD overlap and those without[22]. 200 subjects were recruited and split into 3 groups: (1) Both IBS and NAFLD; (2) either IBS or NAFLD; and (3) neither NAFLD nor IBS. IBS was diagnosed according to the ROME III criteria while NAFLD was diagnosed based on the Chinese Society of Liver Diseases on NAFLD. Out of 200 subjects, 25 (12.5%) had both IBS and NAFLD while 36 (18%) had either NAFLD or IBS. The rest of the 139 (69.5%) subjects had neither IBS nor NAFLD. Results suggested that the combined effect of IBS and NAFLD can implicate the metabolic parameters of patients. The IBS and NAFLD overlap group had a significant higher incidence of hypertension (8% *vs* 5.56%, $P = 0.041$), obesity (12% *vs* 5.56%, $P = 0.034$), dyslipidemia (12% *vs* 2.78%, $P = 0.020$), diabetes (4.0% *vs* 2.78%, $P = 0.037$) and digestive illnesses (24.0% *vs* 11.11%, $P = 0.037$) compared to the group with either IBS or NAFLD. The extent of dyslipidemia was greater in the IBS and NAFLD overlap group compared to the group with either IBS or NAFLD as higher triglycerides (2.34 ± 1.22 *vs* 1.71 ± 0.98 , $P = 0.035$), total cholesterol (5.78 ± 1.57 *vs* 4.99 ± 1.06 , $P = 0.038$), LDL cholesterol (LDL-C) (3.34 ± 1.12 *vs* 2.90 ± 0.99 , $P = 0.023$) were noted. The IBS and NAFLD overlap group had a higher BMI (26.30 ± 3.03 *vs* 25.12 ± 2.59 , $P = 0.045$) and higher fasting blood glucose levels (6.02 ± 1.01 *vs* 5.11 ± 0.97 , $P = 0.023$)[22].

Anorectal manometry assessment was also performed which suggested that when both IBS and NAFLD were present the multiple risk factors from both conditions had a synergistic effect in irritation of the gastrointestinal tract. There was decreased gastrointestinal volume sensory threshold for patients in the IBS and NAFLD overlap group in comparison with the group that had either IBS or NAFLD as indicated by the decreased first sensation volume (22.56 ± 6.04 *vs* 30.27 ± 5.38 , $P = 0.034$), defaecating sensation volume (63.22 ± 5.29 *vs* 78.34 ± 6.41 , $P = 0.032$), maximum tolerable volume (82.39 ± 7.45 *vs* 131.78 ± 23.22 , $P = 0.035$) and painful sensation volume (132.56 ± 19.29 *vs* 228.32 ± 17.36 , $P = 0.027$) in the IBS and NAFLD overlap group[22].

DISCUSSION

The results overall support the possible association between IBS and NAFLD. NAFLD was more prevalent in patients with IBS compared to those without IBS. Individuals with both IBS and NAFLD overlap had more metabolic risk factors including high BMI, hypertension, dyslipidemia, and diabetes. The proportion of NAFLD patients with IBS increased along with the severity. IBS patients were three times more likely to have NAFLD compared with non-IBS patients ($P < 0.001$) with a significant correlation between the severity of IBS and NAFLD.

IBS and NAFLD have been postulated to share similar characteristics which are further discussed (Figure 3).

The brain-gut-liver axis and microbiome

The bidirectional relationship between the gut and the liver is well-established. The gut-liver axis involving gut dysbiosis, intestinal barrier dysfunction, intestinal dysmotility plays a vital role in the pathogenesis of NAFLD[18,26]. Changes in the intestinal microbiota is associated with severity of hepatic fat deposition through several mechanisms: Increasing low-grade mucosal inflammation, immune system activation, altering intestinal permeability, bile acid metabolism, dietary choline metabolism, and generating endogenous ethanol[27,28]. The brain-gut axis likewise shares a bidirectional relationship and similar changes in the brain-gut axis are implicated in the pathogenesis of IBS. The hypothalamic-pituitary-adrenal (HPA) axis and serotonin (5-HT) signalling are some of the pathways affected by dysregulation in the brain-gut axis[28,29]. These alterations lead to abnormal gut motility and visceral hypersensitivity[30]. Emerging evidence suggests a link between NAFLD and IBS symptoms such as diarrhoea. Population-based data from the National Health and Nutrition Examination Surveys revealed that NAFLD and diabetes were independently associated with diarrhoea as opposed to constipation or normal bowel patterns even after adjusting for BMI[31]. This is consistent with our results showing a correlation between IBS and NAFLD with the common mechanism of gut dysbiosis.

The gut microbiota has a significant role in the regulation of the various mechanisms and dysregulation of the gut microbiome contributes to the development of both NAFLD and IBS[26,32]. NAFLD patients have been shown to have increased *Firmicutes*, *Proteobacteria*, *Actinobacteria*, *Escherichia*, *Clostridium*, and *Bacteroides*, and decreased *Bifidobacterium*, *Prevotella* and *Faecalibacterium*[27,33-35]. Somewhat similarly, IBS patients have shown increased abundance of *Ruminococcus*, *Streptococci*, *Firmicutes*, and decreased *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus*[18,36-38]. However, no specific microbial signature exists for IBS and NAFLD patients to distinguish them from healthy controls, in part due to the variability of sequencing techniques and population groups, as well as various confounding factors such as dietary habits[35,39].

Chronic inflammation and immune system activation

Activation of the innate and adaptive immune pathways has been implicated in the pathogenesis of IBS, both in the intestinal mucosa and neuroinflammation *via* the brain-gut axis. This involves an overall state of inflammatory overdrive, a dysregulated HPA axis and serotonergic signaling[40]. IBS patients display persistent signs of low-grade mucosal inflammation with increased counts of CD3⁺, CD4⁺ and CD8⁺ T-lymphocytes, mast cells[41]. Enhanced expression of pro-inflammatory cytokines including interleukin (IL)-1 β , tumour necrosis factor (TNF)- α , IL-6, IL-8 are observed in IBS patients[18,41,42]. Higher baseline TNF- α , lipopolysaccharide-induced TNF- α , IL-6 and IL-8 levels were significantly correlated with increased bowel frequency and severity of IBS symptoms[42,43].

NAFLD shares similar points of contact with IBS with a low-grade chronic inflammation as a main driver of disease progression in NAFLD[18,44]. Obesity triggers activation of innate and adaptive immune pathways and adipose tissue inflammation exacerbates NASH[18]. Liver metabolism is affected directly *via* circulating free fatty acids (FFA) from food,

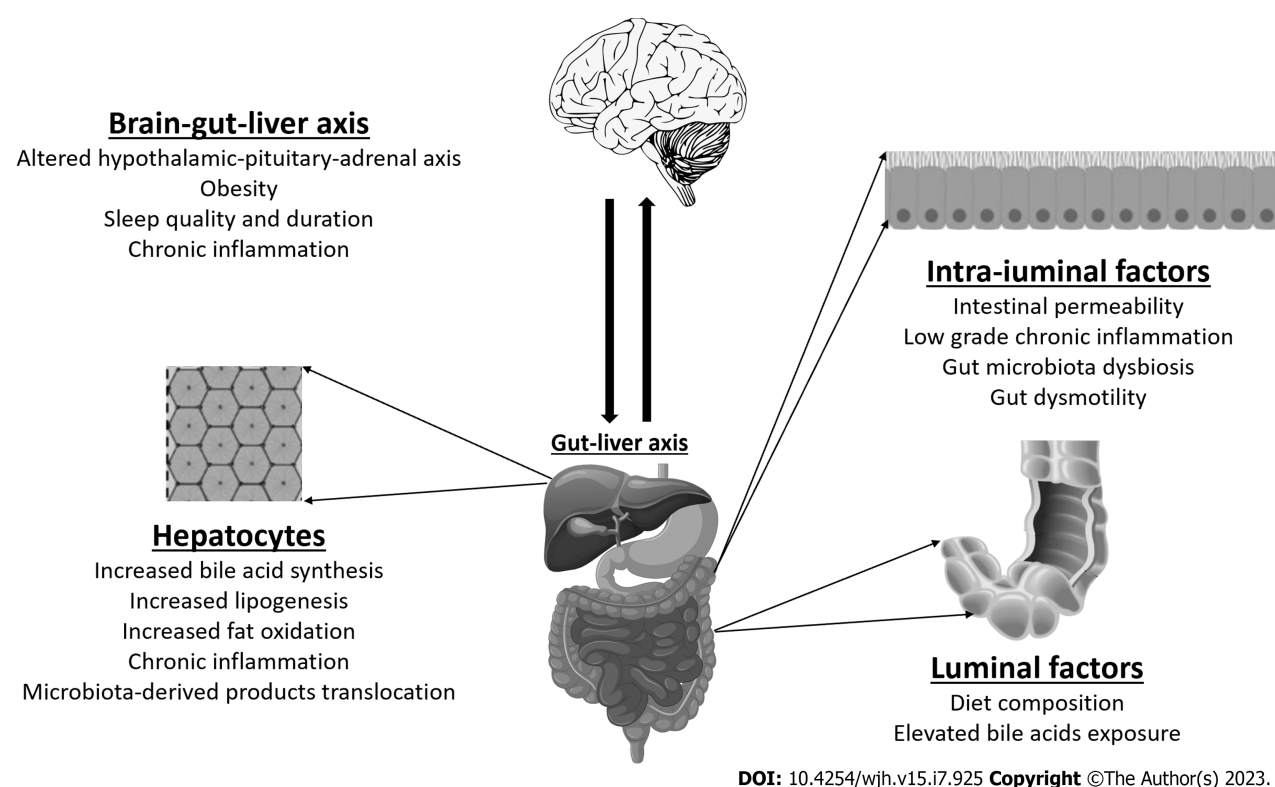


Figure 3 Postulated pathophysiology.

adipose tissue, intestinal bacteria, and indirectly *via* pro-inflammatory cytokines[18,45]. Higher levels of IL-6, C-reactive protein, TNF- α are detected in NAFLD subjects[18,46]. FFA binds toll-like receptors (TLR) on immune cells and in the liver, contributing to activity of the immune system. FFA are also involved in production of reactive oxygen species, mitochondrial dysfunction and endoplasmic reticulum stress in the liver[18,46]. Increased natural killer (NK) cell and NKT cell activity is linked with hepatic expression of inflammatory cytokines and activation of Kupffer cells[47]. All these mediators drive the inflammatory cascade and consequent fibrogenesis in NAFLD.

Bile acids

Bile acid-mediated mechanisms are involved in the pathophysiology of both NAFLD and IBS. There is bile acid signaling dysregulation resulting in increased bile acid production and bile acid malabsorption[48]. Altered bile acid metabolism with defective farnesoid X receptor (FXR) and fibroblast growth factor 19 (FGF19) contributes to abnormal hepatic lipid metabolism in NAFLD[48,49]. Patients with IBS have higher colonic bile acid exposure compared with healthy controls which affects bowel habits in IBS patients, predominantly in the IBS-D subgroup[50,51]. This stimulates colonic motility with acceleration of colonic transit, activation of visceral fluid sensation and fluid secretion[52].

In NAFLD, patients were found to have higher total faecal bile acid levels, increased rates of bile acid synthesis in the liver and a predominance of primary bile acids in the stool[53]. Primary unconjugated faecal bile acids correlated with the degree of hepatic steatosis, the presence of ballooning and severity of fibrosis in NASH subjects[53]. A retrospective study described an increased prevalence of NAFLD in individuals with bile acid diarrhoea[54]. These findings were further confirmed in a prospective study of 127 NAFLD patients that showed a correlation between increased hepatic bile acid production and diarrhoea with increased NAFLD fibrosis scores[49].

Small intestinal bacterial overgrowth

A higher prevalence of small intestinal bacterial overgrowth (SIBO) has been reported in patients with IBS[55]. Studies have demonstrated that IBS patients were more likely to develop SIBO compared with healthy controls, predominantly of the diarrhoea subtype[56,57]. SIBO is also found to be more prevalent in NAFLD patients attributed to proposed mechanisms including endotoxaemia and induction of TLR and pro-inflammatory cytokines[58,59]. A study by Sabaté *et al*[60] showed an association between SIBO and severity of hepatic steatosis in obese individuals[60].

Intestinal permeability

Impaired intestinal permeability is a key factor in the development of IBS[61]. Alterations in gut barrier function were observed in IBS patients which correlated with severity of symptoms[62,63]. A subgroup of IBS-D patients with increased intestinal permeability experienced more severe IBS symptoms and visceral hypersensitivity[62]. This is in part due to bacterial translocation and inflammatory agents through disruption of the epithelial tight junctions[7,18].

NAFLD is similarly associated with increased gut permeability which has an important role in the pathogenesis of NASH[64]. Several studies have described increased intestinal permeability in correlation with the degree of hepatic steatosis[65,66]. Impaired intestinal permeability allows for translocation of bacterial-derived products into the portal circulation and increasing hepatic exposure to harmful substances resulting in inflammation and fibrosis[66]. Conversely, a study by Luther *et al*[67] suggests that initial hepatic injury may contribute to impaired intestinal permeability although the mechanism is undetermined[67].

Obesity and metabolic syndrome

A multitude of studies denotes the association between IBS and obesity including the metabolic syndrome. Talley *et al*[68] demonstrated that older age, less early satiety, increased stool frequency and heartburn were all independently associated with increasing BMI[68]. Visceral abdominal obesity is correlated with an increased risk of developing IBS, primarily diarrhoea-predominant IBS. This is attributed to alteration in visceral fat metabolism which triggers production of adipokines and immunologic factors[69]. IBS patients have an augmented visceral perception of luminal stimuli, dysmotility and abdominal pain related to increased visceral adiposity[70]. Conversely, recent studies have shown that IBS subjects with morbid obesity achieved significant improvement in bowel symptoms after undergoing weight loss intervention[71].

The interplay between NAFLD, obesity and the metabolic syndrome with insulin resistance as a key pathogenic driver has been well-established. A meta-analysis by Li *et al*[72] showed that obese individuals had a 3.5-fold increased risk of developing NAFLD which has a dose-dependent relationship with BMI[72]. A high pooled prevalence of NAFLD was found in type 2 diabetes patients, with 60% of diabetes patients being diagnosed with NAFLD[73].

Sleep

Poor sleep quality and circadian misalignment have been implicated in the pathogenesis of IBS[74]. Exacerbation of symptoms have been observed after a night of poor sleep in IBS patients[74]. Likewise, impaired sleep quality, short sleep duration and daytime sleepiness are associated with NAFLD risk with correlation with insulin resistance[75,76]. The hypothalamus-pituitary-adrenal axis can also be affected with impaired cortisol metabolism leading to hepatic steatosis [75]. In addition, obstructive sleep apnoea could have deleterious effects on liver metabolism in the disease progression of NAFLD[76].

Clinical impact

In view of the postulated shared mechanisms underlying IBS and NAFLD, therapeutic strategies for IBS may also be beneficial for patients with NAFLD and vice versa. Lifestyle modification with diet and exercise leading to weight loss remains the cornerstone of NAFLD management[77]. Weight loss in IBS subjects showed marked improvement in bowel symptoms along with subjective well-being[71].

Rifaximin has been established as an effective drug in improving global IBS symptoms and bloating[78]. The administration of Rifaximin in NAFLD demonstrated effects including the reduction of serum endotoxin, pro-inflammatory cytokines, NAFLD-liver fat score and improvement in insulin resistance[79,80]. The postulated mechanism could be due to Rifaximin's effect on gram-negative bacteria leading to the inhibition of endotoxin proinflammatory cytokine production in NAFLD patients[79]. Several studies have shown that probiotics can lead to decrease in serum cytokine levels, oxidative stress markers, liver fat and biochemistry in NAFLD[81-83]. Similarly, studies have identified that probiotics can aid in alleviating IBS symptoms[84,85].

Obeticholic acid (OCA), a semi-synthetic FXR agonist, has been shown to stimulate FGF19 and decrease bile acid synthesis, improve stool form and diarrhoea in patients with IBS-D symptoms[86]. The promising impact of OCA on NASH and its associated metabolic features has been described with significant improvement in fibrosis and NASH histology[87]. Lubiprostone has been demonstrated to be effective in treating global IBS-C symptoms[88]. It has also been shown to decrease hepatic enzyme levels in NAFLD patients with constipation. Greater reduction in hepatic steatosis levels and levels of endotoxin were seen in those with improved intestinal permeability[89]. This may provide a basis for the role of Lubiprostone in a subset of NAFLD patients.

There are several limitations. The number of studies included was small given the lack of data on this topic to date. Different ultrasonographic diagnostic criteria was used for NAFLD. One study used codes from the International Disease Classification of diseases for identification of IBS while the other did not disclose how IBS patients were diagnosed, resulting in heterogeneity among the studies. Statistical analysis was unable to be carried out as not all studies assessed OR and 95%CI.

CONCLUSION

In conclusion, the evidence supports the association between IBS and NAFLD. IBS and NAFLD may co-exist and patients with IBS should be assessed for NAFLD and vice versa. Given the common postulated pathophysiology of both conditions, this may form the basis for further studies to assess suitability and benefits of utilising known therapeutics for IBS to treat NAFLD. This may guide future therapeutic strategies, especially in patients who suffer from both conditions. However, further prospective studies are required to confirm this association.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease with the rise of obesity and metabolic syndrome. Functional gastrointestinal disorders like irritable bowel syndrome (IBS) are increasing in prevalence.

Research motivation

At present, there is limited understanding regarding the links between the two conditions despite there being suggestions of possible overlap between IBS and NAFLD. We hope to explore literature to assess this overlap and also possible common pathophysiological links.

Research objectives

To review the current literature regarding the overlap of NAFLD and IBS and potentially identify common pathophysiological links which may show potential for utilizing common therapeutics to treat both conditions.

Research methods

A systematic search was done to assess current literature showing overlap between NAFLD and IBS in human subjects from PubMed, EMBASE and Cochrane.

Research results

We identified studies showing overlap between NAFLD and IBS. Both IBS and NAFLD patients demonstrated more metabolic risk factors like obesity, hypertension, dyslipidaemia and diabetes. IBS was seen to be more common in NAFLD patients and vice versa. Common pathophysiological links included the brain-gut-liver axis, intestinal permeability, gut microbiota dysbiosis, bile acid signalling dysregulation, obesity and metabolic syndrome.

Research conclusions

Our systematic review summarizes the current literature regarding IBS and NAFLD and demonstrates overlap between the two conditions. Common pathophysiological links were identified between both conditions.

Research perspectives

The evidence supports the association between IBS and NAFLD. With common postulated pathophysiology of both conditions discussed, further studies would be useful to further strengthen the association between both conditions and also look into possible common therapeutics.

FOOTNOTES

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