Non-alcoholic fatty liver disease in irritable bowel syndrome: More than a coincidence?

Huw Purssell, Peter J Whorwell, Varinder S Athwal, Dipesh H Vasant

Abstract

Irritable bowel syndrome (IBS) and non-alcoholic fatty liver disease (NAFLD) are amongst the most common gastrointestinal and liver conditions encountered in primary and secondary care. Recently, there has been interest in the apparent coincidence of NAFLD in patients with IBS mainly driven by improved understanding of their shared risk factors and pathophysiology. In this paper we summarize the shared risk factors which include; overlapping nutritional and dietary factors as well as shared putative mechanisms of pathophysiology. These include changes in the gut microbiome, gut permeability, immunity, small bowel bacterial overgrowth and bile acid metabolism. This paper describes how these shared risk factors and etiological factors may have practical clinical implications for these highly prevalent conditions. It also highlights some of the limitations of current epidemiological data relating to estimates of the overlapping prevalence of the two conditions which have resulted in inconsistent results and, therefore, the need for further research. Early recognition and management of the overlap could potentially have impacts on treatment outcomes, compliance and morbidity of both conditions. Patients with known IBS who have abnormal liver function tests or significant risk factors for NAFLD should be investigated appropriately for this possibility. Similarly, IBS should be considered in patients with NAFLD...
INTRODUCTION

Irritable Bowel syndrome (IBS) is a disorder of gut-brain interaction (DGBI) resulting in recurrent abdominal pain associated with defecation and an altered bowel habit. Patients are considered to have IBS when they fulfill the Rome IV diagnostic criteria which include an altered bowel habit (constipation, diarrhea or a mix of both), associated with frequent abdominal pain and abdominal bloating or distension for at least 6 mo prior to diagnosis[1]. A recent systematic review and meta-analysis has shown a worldwide prevalence of IBS of 9.2% with significant regional variability[2]. In the United Kingdom, DGBIs such as IBS are very common, and account for around a third of gastroenterology outpatient referrals[3]. IBS can be debilitating often resulting in an increasing risk of anxiety or depression[4] with symptoms such as fecal incontinence that can be difficult to manage leading to poor quality of life and distress [5]. There is often significant clinician prejudice and frustration towards patients with IBS[6] resulting in unfair public perceptions and significant stigmatization[7].

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of more than 5% of fat in the liver in the absence of a secondary cause. It is one of the major causes of liver disease worldwide and its pathogenesis is linked to metabolic syndrome, obesity and Type 2 diabetes. The population based prevalence of NAFLD is between 25%-44% but rises to 70% in patients with Type 2 diabetes[8,9]. NAFLD is recognized as a heterogeneous condition with variable rates of progression. In certain patients isolated steatosis leads to steatohepatitis and fibrosis, progressing ultimately to cirrhosis, decompensated liver disease and sometimes hepatocellular carcinoma. Population based screening studies have shown a prevalence of advanced fibrosis in 8% of patients rising to 27% in those with risk factors[10,11]. Unfortunately, the majority of patients are only diagnosed with liver disease when they present with advanced disease and many are of working age. Consequently, liver disease is responsible for the loss of 38000 and 22000 working life years, in men and women, respectively. NAFLD has been increasing in incidence in the western world with a predictable concomitant increase in liver transplant in both the United States and Europe[12-14].

There is increasing recognition that both IBS and NAFLD share a number of overlapping risk and aetiological factors leading to growing interest in the possibility of an association between the two conditions. However, there is limited high quality data on the concomitance of IBS and NAFLD. As a result, IBS symptoms may not be routinely screened for in hepatology clinics and vice versa. Therefore, the aims of this article are
to summarize the current understanding of relevant overlapping patho-physiological and aetiological factors, and to highlight areas for future research and their clinical implications.

THE PREVALENCE OF CO-EXISTING IBS AND NAFLD

Table 1 summarizes the literature on the co-existing prevalence of IBS and NAFLD to date. Most studies have examined the incidence of NAFLD in previously diagnosed IBS. Unfortunately, a review of the literature of concomitant IBS and NAFLD revealed a very high variability in estimates of the prevalence from 12.9% to 74%, with significant differences in methodology in the diagnostic approaches for both conditions and the populations studied. Amongst the reasons for this heterogeneity and variability include the change in the Rome criteria for IBS from Rome III, to the current Rome IV iteration, which is known to be more restrictive. From a hepatology perspective, it is notable that all the studies to date have used raised liver transaminases, with a negative viral hepatitis screen, in the absence of excessive alcohol consumption, and abdominal ultrasound to diagnose NAFLD, which in the absence of objective liver fibrosis assessment could be considered sub-optimal.

Shin et al. found that the prevalence of presumed NAFLD was 12.9% in patients with diarrhoea predominant IBS (IBS-D) compared to 9.0% in patients with constipation predominant IBS (IBS-C), although the reasons for this apparent difference are unclear and merit further investigation. In an interesting study by Lee et al.[19], rather than evaluating patients with a formal diagnosis of NAFLD, the authors assessed the incidence of elevated liver transaminases and the metabolic syndrome in patients with IBS, compared to an age and sex matched control group. Those with IBS were found to have a significantly higher alanine aminotransferase (ALT) (16.9% vs 7.7%; P = 0.015) and Gamma-glutamyl transferase (GGT) (24.1% vs 11.5%; P = 0.037) compared to the control group, and there was a significantly higher prevalence of metabolic syndrome in the IBS group (32.5% vs 12.7%; P < 0.001).

To our knowledge, there have only been three previous reports on the incidence of functional bowel symptoms in patients with NAFLD. Appleby et al.[20] found that in 127 patients with NAFLD, 25% had chronic diarrhea, and 12% had features of bile acid diarrhoea with both being associated with a raised NAFLD fibrosis score. Furthermore, Singh et al.[21] studied 632 patients in India diagnosed with fatty liver disease and found that 29.4% had co-existing clinical features of IBS. Similar findings were reported by Jones-Pauley et al.[22] in a cross sectional study looking at IBS diagnosed by Rome IV criteria in 130 NAFLD patients and as many as 38 (29.2%) patients had IBS based on Rome IV criteria. Interestingly, depression and anxiety were found to be more prevalent in the IBS cohort, compared to the non-IBS cohort, indicating the detrimental effect of co-existing bowel symptoms may have on quality of life, and the resulting need for a multi-systems approach in NAFLD patients with IBS symptoms.

In summary, regardless of the iteration of the Rome IBS diagnostic criteria used and the highlighted limitations of the previous studies, the data summarized in Table 1 on the co-existing prevalence of IBS in patients with NAFLD consistently report a much higher prevalence of IBS than that reported in global prevalence studies using either Rome III or Rome IV diagnostic criteria.[2]

OVERLAPPING ETIOLOGICAL FACTORS IBS AND NAFLD

Multiple etiological factors overlap between IBS and NAFLD leading to interest in possible associations including obesity, gut microbiome, dietary factors and immune mediated causes as illustrated in Figure 1.

OBESITY

NAFLD is intrinsically linked with obesity, diabetes and the metabolic syndrome. In obese populations, NAFLD has a prevalence of up to 95%.[23] Excess adipose tissue exhausting peripheral storage capacity resulting in deposition in the liver and increased insulin resistance is thought to be the main culprit for NAFLD pathogenesis.[24] Weight loss through diet and exercise reduces hepatic steatosis and fibrosis, and in 109 obese patients[25], Lassailly et al.[26] showed that bariatric surgery resolved non-
alcoholic steatohepatitis (NASH) within a year.

The association between IBS and obesity is more unclear[27]. Aro et al[28] found a significant association between the obesity and IBS symptoms such as abdominal pain and diarrhoea using the Abdominal Symptom Questionnaire as well as a positive association between obesity and a formal diagnosis of IBS. However, these have not been confirmed in several other studies[29-31]. Interestingly, Lee et al[30] found visceral abdominal adiposity was associated with increased risk of IBS-D. There is evidence that IBS is more prevalent in patients who are obese[32]. Schneck et al[33]...
described a cohort of patients with obesity undergoing bariatric surgery of which 30% fulfilled Rome III criteria for IBS. Further evidence for role of obesity in IBS is supported by the observation that increased visceral adiposity enhances perception of luminal stimuli, dysmotility and abdominal pain\cite{34}. Higher body mass indexes have been associated with accelerated colonic and rectosigmoid transit and increased stool frequency\cite{35}. Furthermore, weight loss through diet or bariatric surgery has been shown to improve symptoms\cite{32,36}. Aasbrenn et al\cite{37} prospectively analyzed the effect of a weight loss program on bowel symptoms using the IBS severity scoring system (IBS-SSS) and Gastrointestinal Symptom Rating Scale and found that there were significant improvements in the IBS-SSS in patients with IBS compared to those without.

**MICROBIOME**

The gut microbiota plays a vital role in the intestinal barrier function, metabolism of nutrients and development of immune tolerance and response. Dysregulation of the microbiome has been shown to be a component for the development of both NAFLD and IBS\cite{38}.

Long-term perturbation of the gut microbiota has been shown to contribute to metabolic syndrome and fatty liver disease\cite{39}. Several mechanisms have been proposed on how the gut microbiota results in NAFLD development. This includes increased intestinal permeability leading greater lipopolysaccharide exposure to the host. This, in turn, results in toll like receptor (predominantly TLR4) activation of the innate immune system, causing liver inflammation as they are transported from the gut to the liver. Additionally, microbially produced metabolites, such as lactate and ethanol, can directly activate inflammatory cascades within the liver. Enterohepatic bile acid homeostasis is important for multiple processes, including fat absorption,
inflammation, immunity and microbial diversity. Significant differences have been noted in bile acid composition in metabolic diseases associating with progression of NAFLD[38,40].

Patients with hepatic steatosis and NASH have been shown to have increased Proteobacteria, Enterobacteriaceae, Escherichia and Citrobacter with reductions in abundance of Rikenellaceae, Ruminococcaceae, Anaeropirorobacter and Coprococcus.[39,40] Reductions in Bifidobacteria have also been observed and Bifidobacteria possibly reduce gut wall permeability to lipopolysaccharides, suggesting a relationship with the development of disease[39]. Interestingly, Frost et al[39] followed up patients who had incidental findings of fatty liver or diabetes and found changes in Clostridium XIVa as a result of dysbiosis with a strong association for increasing fatty acid biosynthesis. Type 2 diabetes is also noted to result in increased gut permeability. Aron-Wisnewsky et al [40] found significant overlap in microbial signatures between patients with NAFLD and NASH with obesity and diabetes, finding changes in abundance of Oscillospira and Bacteroides. Further evidence on the importance of the gut microbiome in metabolic syndrome, is shown by fecal microbiota transplant being associated with a temporary improvement in peripheral insulin resistance[41].

Changes in intestinal microbial diversity is also thought to contribute to the development of IBS as the microbiota impacts on intestinal motility and sensitivity. Some patients with IBS have been shown to have changes in the Firmicutes-to-Bacteroides ratio, reduced lactobacilli and bifidobacterial as well as reduced microbial diversity[38,42].

The gut-brain-microbiome axis is known to have an important role in glucose regulation. Gut microbiota modulation produces changes in the immune, neurotransmitter and monoaminergic activity of this axis. Serotonin secretion affects motility, pain perception but also plays a role in mood control[43]. NAFLD and the gut-brain axis may also be inter-related. There is evidence that depression is associated with NAFLD. However, disentangling the multiple contributors to depression in multi-factorial disease states (as often seen in patients with metabolic syndrome) can be exceptionally difficult[44,45].

Dysregulation of the microbiome itself can lead to poor glycaemic control, acting through nitric oxide formation which affects the neuronal response to gut hormone Glucagon-like peptide-1 (GLP-1)[46]. The GLP-1 receptor antagonist, Semaglutide, has been shown to reduce liver fat and NASH resolution in patients with NAFLD[47]. It has also been used to treat weight loss and type-2 diabetes mellitus[48]. Given the known functions of GLP-1 on the gut microbiota, the effect seen in these studies may well be related to beneficial alterations in microbiome composition[49].

**DIETARY FACTORS**

Dietary factors have been shown to be integral to the man-agement of both IBS and NAFLD. Weight loss through diet and exercise is the mainstay of NAFLD management. Adherence to a Mediterranean diet reduces hepatic steatosis and achieves a greater weight loss in patients with NAFLD[50]. By contrast, patients with IBS have been shown to have a poorer adherence to a Mediterranean diet than healthy controls[50], a dietary factor which may therefore be relevant in the development of NAFLD in those with IBS. There is also some evidence that conservative weight loss can help IBS symptoms. Aasbrenn et al[37] found that a weight loss program resulted in a significant improvement in IBS symptoms as assessed by IBS-SSS questionnaires and Gastrointestinal Symptom Rating Scale[37].

Certain food groups appear to worsen IBS symptoms and contribute to NAFLD development. High fructose corn syrup (HFCS) is a disaccharide which is frequently used in artificial sweeteners, processed, canned and baked goods worldwide. HFCS has been shown to induce IBS symptoms through increased osmotic pressure and bacterial fermentation resulting in gas production, abdominal bloating and pain[51]. HFCS has also been shown to downregulate the insulin signaling pathway which would contribute to the pathogenesis of NAFLD[52]. Fructose consumption has also been shown to increase intestinal permeability potentially leading to the development of both NAFLD and IBS through the processes already outlined[53].

Certainly more research into the dietary implications on NAFLD and IBS is needed. Many patients with IBS notice that ‘healthy’ foods such as fruit and vegetables can make their symptoms worse and this results in some of them adopting a more ‘unhealthy’ diet which may lead to weight gain. There is evidence that a low FODMAP diet with excludes some fruits and vegetables improves IBS symptoms.
however to the authors’ knowledge, there is a paucity of data on the effects of a low FODMAP diet on the progression of NAFLD.

IMMUNE MEDIATED FACTORS

Chronic inflammation is a critical driver of progressive disease in NAFLD and significant advances have been made to understand the role of inflammation\([54,55]\). The role of toll-like receptors (TLRs) and macrophage activation has already been discussed. Additionally, Natural killer cells and natural killer T cells contribute to inflammation by releasing cytokines and reactive oxygen species\([56]\). Tumor necrosis factor (TNF-)\(\alpha\), alongside other cytokines and growth factors, have also been shown to possible have a role in the development of NAFLD and NASH, in both animals and humans\([38]\). TNF-\(\alpha\) in combination with interleukin (IL)-6 stimulates the production of leptin activating neutrophils and the innate immune system\([38]\). In addition, adaptive immune responses drive NASH as hepatic infiltration of B cells and CD4 and CD8 T cells exacerbate parenchymal injury and inflammation\([56]\). B cells play a profibrogenic role involving the stimulation of hepatic stellate cells and liver macrophages\([57]\). CD4+ T cells differentiate to type-17 T helper cells, producing IL-17 which has been implicated in the progression of NAFLD\([38]\). The balance of the adaptive immune cellular compartment within the liver can transition from a pro-resolution composition to pro-inflammatory subset, driving disease and fibrosis.

In IBS, a similar chronic low-grade inflammatory picture has also been described. The innate immune system is implicated with an increased number of mast cells throughout the intestines in some patients\([59]\). The adaptive immune response is also important with CD3+, CD4+ and CD8+ T cells increased in intestines and blood of patients with IBS\([38]\). Interestingly, an increase in IL-6 and IL-8 with reduced anti-inflammatory cytokines has been seen in serum of IBS patients\([59]\). The role of TLRs is also felt to be important with IL-6 and other cytokines acting through this mechanism \([38]\). TNF-\(\alpha\) can act on the nervous system to cause hypersensitivity, gastric hypomotility and nausea\([59]\).

SMALL INTESTINAL BACTERIAL OVERGROWTH

Small intestinal bacterial overgrowth (SIBO) can cause abdominal pain, bloating and chronic diarrhea. Although an area of controversy due to conflicting evidence, a number of previous studies have suggested that some patients with IBS have a relatively high prevalence of SIBO\([60,61]\). A recent metanalysis has shown that patients with IBS were more likely to test positive for SIBO than healthy controls\([61]\). Further circumstantial evidence for the gut-brain-microbiome-liver axis can be drawn from the effects of the non-absorbable antibiotic Rifaximin in both IBS and in liver disease. Whilst the mechanism is unclear, improvement in IBS symptoms have been demonstrated in patients in randomized controlled trials of Rifaximin\([62,63]\). Rifaximin is also often used to treat SIBO\([64]\), a condition which has been shown to affect cognitive function in a subset of patients who present with brain fog\([65]\). Interestingly, treatment with Rifaximin has recently been shown in brain imaging studies to alter neuronal connectivity and increase cognitive flexibility through its effect on the gut microbiome particularly in beta and theta frequencies with a particular focus on the insular cortex, a region known to be affected in patients with IBS\([66]\). Furthermore, Rifaximin has an immunomodulatory action counteracting the pro-inflammatory response seen in gut microbiota dysbiosis\([67]\). In liver disease, Rifaximin is an established treatment for hepatic encephalopathy, with its effects attributed to alterations in the gut microbiome and resultant positive effects on cognitive function. Specifically in patients with biopsy proven NASH, Rifaximin has also been shown to reduce insulin resistance, inflammation and NAFLD fat scores\([68]\). Therefore, the effects of Rifaximin are multifactorial including reduced endotoxia, modulation of inflammatory cytokines, and intestinal permeability as well as changing functional brain connectivity\([62,66]\).

Further overlapping evidence for SIBO in this context comes from the obesity literature. There is evidence that obesity reduces gut motility, which may predispose to SIBO due to stasis, and plausibly this is thought to damage barrier function, which can result in bacterial translocation and altered gut-liver axis\([33]\). Furthermore, changes in the gut-liver axis may well a result of increased intestinal permeability. A high prevalence of SIBO has been observed in obese subjects however the association
between NAFLD and SIBO is less clear\[53\]. Studies have found the prevalence of SIBO in NAFLD to range from 39%-60% albeit in small numbers of patients. However, more recently, some research found 8% of NAFLD patients in their cohort had SIBO and there was no evidence that SIBO was associated with a higher risk of fibrosis\[69-71\].

**BILE ACID DIARRHOEA**

Bile acid malabsorption is a cause of chronic diarrhea and has been shown to be associated with an increased NAFLD fibrosis score. Hepatic bile acid production is regulated by Fibroblast growth factor 19 (FGF19) and Farnesoid-X-receptor (FXR) and obeticholic acid (a FXR agonist) has shown therapeutic potential in both bile acid related diarrhea and NAFLD\[20\]. Appleby *et al*[20] found that increased hepatic bile acid production and diarrhea were associated with an increased NAFLD score. Of further relevance to the link with NAFLD, bile acid diarrhea has also been shown to be associated with raised body mass index\[72\]. This is therefore an important point to be considered in clinical practice when evaluating patients with suspected overlapping IBS and NAFLD, as up to a third of patients meeting the criteria for IBS-D have been shown to have bile salt malabsorption when investigated\[72\], and this condition should therefore be excluded in the context of watery diarrhea.

**APPLICABILITY TO CLINICAL PRACTICE**

Pulling this together, there is consistent evidence to show that IBS and NAFLD have a similar pathogenesis and therefore applying this to clinical practice, physicians should be aware that NAFLD may co-exist silently in patients with IBS and vice versa. Patients with IBS and incidental findings of elevated liver enzymes or with risk factors for NAFLD should be considered for non-invasive liver screening through ultrasound and appropriately available non-invasive fibrosis assessment using FIB-4 scoring, enhanced liver fibrosis testing or mechanical liver stiffness measurement.

Conversely, patients with NAFLD may not admit to the debilitating symptoms of IBS due to stigma or feeling that their symptoms are not relevant to their liver consultation. Screening for positive clinical features of IBS and targeted treatment for both conditions in unison may aid compliance with treatment, improve quality of life and ultimately improve morbidity.

However, as highlighted in this review, there is a lack of large, high quality cross-sectional data on the incidence of IBS in NAFLD patients and vice versa. To date, studies have been limited to the use of ultrasound and blood tests to diagnose NAFLD, however there is a lack of data that quantifies a fibrosis score which may be useful to correlate with IBS severity. From the currently available data (summarized in Table 1), whilst there is a suggestion that the IBS-D sub-type may be more common than IBS-C in patients with NAFLD, whether this is a genuine finding merits further evaluation in studies which have excluded bile salt malabsorption with appropriate investigations given its apparent independent association with NAFLD.

**CONCLUSION**

IBS and NAFLD are common conditions that can have significant effects on both physical and mental health\[73\], as well as significant healthcare and socioeconomic implications. There is some evidence that patients with IBS are more likely to develop NAFLD, and there are multiple different pathophysiological mechanisms that could contribute to both conditions, however more data is needed. Until such data clarifies this picture, the possibility of these conditions existing concomitantly should be considered proactively and investigated appropriately.

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