Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 6 Issue 4 April 2023

Review Article

Study of Interrelationship Between Irritable Bowel Syndrome and Non-Alcoholic Fatty Liver Disease

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Received: March 13, 2023

Published: March 20, 2023

DOI: 10.31080/ASGIS.2023.06.0523

Abstract

A gastrointestinal disorder recognized by altered bowel routines in relation to cramping, bloating, abdominal pain, gas, chronic diarrhea, and constipation that affects the large intestine is diagnosed as Irritable Bowel Syndrome (IBS). On the other hand, the accumulation of fat and triglycerides in the liver leading to steatosis in patients who consume little or no alcohol relates to metabolic syndrome, obesity, diabetes, and insulin resistance recognized as Non-Alcoholic Fatty Liver Disease (NAFLD). Around 73 literature reviews were evaluated to examine the relationship between impaired intestinal motility and deposition of excess visceral adipose tissue in the organs affecting the metabolic mechanisms, IBS and NAFLD. This study is conducted to find the interrelationship between IBS and NAFLD through various predominant pathophysiological factors that are all interconnected which include Obesity, Gut Microbiota, Bile Acid Diarrhea, Small Intestinal Bacterial Overgrowth (SIBO), and Gut-Microbiome-Liver Axis. After studying various published literature, it was established that IBS and NAFLD are interlinked in nature and is associated with Gut microbiota, obesity, bile acid malabsorption and SIBO disrupting the gut-liver axis. IBS influences inflammation and immune activation through excess adiposity creating a disbalance in the composition of good microbes in the gut increasing intestinal permeability, hence, metabolites produced by microbes, such as lactate and ethanol, have the ability to directly trigger inflammatory cascades in the liver, creates an interlinked loop between IBS and NAFLD.

Keywords: IBS; BA-diarrhea; NAFLD; Gut Microbiota; Obesity; SIBO

Abbreviations

IBS: Irritable Bowel Syndrome; NAFLD: Non-Alcoholic Fatty Liver Disease; SIBO: Small Intestinal Bacterial Overgrowth; ROS: Reactive Oxygen Species; IHTG: Intrahepatic Triglycerides; TLRs: Toll-like Receptors; FXR: Farnesoid-X Receptor; FGF19: Fibroblast Growth Factor 19; BA: Bile Acid; SCFA: Short-Chain-Fatty Acids; TMAO: Trimethylamine N-oxide

Introduction

Two relatively common illnesses among the general population are irritable bowel syndrome (IBS) and non-alcoholic fatty liver disease (NAFLD). The large intestine is affected by the gastrointestinal illness known as irritable bowel syndrome, which is characterized by abnormal bowel habits in connection to cramping, bloating, abdominal pain or discomfort, gas, constipation, and diarrhea [1,2]. There have been theories regarding the pathogenesis of IBS, including visceral hypersensitivity, altered gastrointestinal motility, bacterial overgrowth, postinfectious

reactivity, brain-gut interactions, altered fecal micro-flora, intestine inflammation, carbohydrate malabsorption, and food sensitivity. Not all symptoms are thought to be gastrointestinal, such as fatigue or exhaustion, which are frequent occurrences. The disorder known as irritable bowel syndrome (IBS) is known to cause abdominal pain, discomfort, and gastrointestinal motor abnormalities that can result in diarrhea and constipation [3,4]. The consumption of specific meals, such as those that are fatty, carbonated, contain caffeine or produce gas, may start to be linked by patients to their difficulties. The consumption of specific dietary intake, such as those that are fatty, carbonated, contain caffeine or produce gas, may start to be linked by patients to their abdominal pain, bloating, or heightened gastric-colic reflex symptoms (urgent bowel movement after eating a meal) [3]. Whereas, with regard to metabolic syndrome, obesity, diabetes, and insulin resistance, NAFLD is the build-up of liver fat in individuals who consume little to no alcohol [5]. One of the main causes of liver disease and its pathophysiology is linked to metabolic syndrome, Type 2 diabetes, cardiovascular illnesses, and obesity [6]. NAFLD is thought to be associated with a variety of liver abnormalities, including fibrosis, macrovesicular steatosis, steatohepatitis and cirrhosis [7]. IBS and NAFLD are typically regarded as two distinct medical conditions. While IBS is a functional intestinal disease that is most similar to psychological conditions like depression and anxiety rather than liver ailments, NAFLD is associated with metabolic syndrome, obesity, diabetes, and insulin resistance. Surprisingly, there are considerable points of contact, including the dysfunction of the intestinal microbiota, the compromised intestinal barrier, intestinal dysmotility, and the dysfunction of the brain-gut axis, which are critical to their pathogenesis and are connected to immune activation and inflammation. The objectives of this present article was to summarize the current knowledge of pertinent overlapping pathophysiological and etiological factors between the intestine and the liver, to identify areas for further research, and also to discuss the clinical implications of this exquisitely first anatomical and then functional knowledge.

Methodology

Present review consists of 72 references arranged as per the timeline of the gradual development of the understanding regarding the interlinked association between Irritable bowel syndrome (IBS) and Non-alcoholic fatty liver disease (NAFLD), therefore, we have studied literature papers ranging from 2001 to 2022. There is a considerable increment in the numbers of research papers established approaching the stated diseases as mentioned in the above table. Hence, our review paper has been designed to establish a plausible association between IBS and NAFLD on the basis of these literature research papers. Range of years, starting from (2001- 2005) had reviews originally on IBS as NAFLD as two distinct conditions as well as on the role of Farnesoid X receptor in bile acid homeostasis and relevance of it in human diseases. Between (2006-2010), the research focused on pathophysiological aspect of both the diseases and the interlinked connection of altered gut microbiota, inflammation, immunity, oxidative stress, effect of increased intestinal permeability and tight junctions' alteration in NAFLD binds with insulin resistance. Eventually, in the coming years between (2011-2015) the research studies elevated and focused the biochemical pathways of the diseases such as association of gastrointestinal microbiome and development of NAFLD with choline deficiency, Gut-liver axis, role of Farnesoid X receptor in hepatic triglycerides and glucose homeostasis and involvement of gut microbiota in the development of low- grade inflammation and Diabetes associated with obesity. Lastly, in the latest years ranging from (2016-2022), studies have shifted from addressing the diseases separately and finding a cycle between them such as how the long-term instability of the intestinal microbiome is associated with metabolic liver disease, low microbiota diversity, diabetes mellitus and impaired exocrine pancreatic function. In this review, our focus was to accumulate and study years of research and design a wholesome acknowledgement which provides a solution to the dilemma of understanding the association between IBS and NAFLD.

Association between irritable bowel syndrome (IBS) and non-alcoholic fatty liver disease (NAFLD)

Obesity: inflammation and immune activation

Obesity is a chronic state of excess adipose tissue accumulation in the body that further leads to dietary intake sensitivity towards glucose, fat and processed foods due to oxidative stress which can occur when there is an imbalance of free radicals and antioxidants in the body. Given that, adipocytes and preadipocytes have been identified as a source of proinflammatory cytokines, because these

Figure 1: Demonstrates the pathophysiological mechanisms connecting a bridge between the Irritable Bowel Syndrome (IBS) with Non-Alcoholic Fatty Liver Disease (NAFLD) such as obesity, gut microbiota, bile acid diarrhea, small intestinal bacterial overgrowth (SIBO) and Gut-Microbiome-Liver Axis [5-7].

Figure 2: Schematic presentation of obesity and its relationship with NAFLD [12-18].

cytokines are strong inducers of reactive oxygen and nitrogen synthesis by macrophages and monocytes, a spike in cytokine concentration may be the cause of the increased oxidative stress. Because of the pressure created by the fat cells, excessive fat build-up might lead to non-alcoholic steatohepatitis. In turn, cellular injury triggers a high production of cytokines like TNFα, which produce reactive oxygen species (ROS) in the tissues and accelerate lipid peroxidation [8] leading to a state of chronic inflammation. Therefore, obesity induced chronic inflammation increases adiposity and activates inflammatory responses in fat and liver. Additionally, increased chemokine production draws pro-inflammatory macrophages into the adipose tissue, where they form crown-like structures around massive dead or dying adipocytes. Following the release of cytokines by these tissue macrophages, the inflammatory response in nearby adipocytes is further triggered, aggravating inflammation and insulin resistance by suppressing and impairing insulin signaling pathways, making the body less responsive to insulin and increasing blood glucose levels in the blood stream leading to hyperinsulinemia [9]. Now, this hyperinsulinemia manifests bacteria in the small intestine where the majority of food digestion and absorption takes place [10]. By the time food reaches the large intestine, considerable amount of water and minerals have been absorbed, but the remaining fiber and starch sustain the bacteria in this tract, causing fermentation and the production of protective short chain fatty acids that serve as energy for the intestinal cells affecting the intestinal mucosal lining responsible for forming a barrier between the intestinal epithelium and the luminal content to protect the intestine from pathogenic invasion leading to neuroinflammation [11], an inflammatory response in the brain or spinal cord. The synthesis of cytokines, chemokines, reactive oxygen species (ROS), and secondary messengers mediates this inflammation through gut-brain axis leading to Irritable Bowel Syndrome (IBS) [12-18]. The findings that increased visceral adiposity improves sensory perception of luminal stimuli, dysmotility, and stomach pain [19] provides more support for the hypothesis that obesity plays a role in IBS. Higher body mass indexes have been linked to rapid colonic and recto sigmoid transit durations as well as more frequent stools [20]. Increased insulin resistance is regarded to be the primary factor in the pathophysiology of Non-alcoholic fatty liver disease (NAFLD), and excess adipose tissue is also likely to contribute to liver deposition by exhausting peripheral storage capacity [21].

NAFLD is related with an increased risk of obesity. When the rate of hepatic fatty acid intake from plasma and fatty acid synthesis is higher than the rate of fatty acid oxidation and export, steatosis, the defining feature of NAFLD occurs. Therefore, an excess of intrahepatic triglycerides (IHTG) indicates a mismatch between intricate interactions of metabolic processes. A number of harmful changes in the metabolism of glucose, fatty acids, and lipoproteins are linked to the occurrence of steatosis. The development of insulin resistance and other cardiovascular risk factors linked to NAFLD are most likely influenced by anomalies in fatty acid metabolism, along with adipose tissue, hepatic, and systemic inflammation. Non-alcoholic fatty liver disease (NAFLD), or steatosis, is a range of liver disorders linked to obesity that may or may not include inflammation and fibrosis (also called steatohepatitis). Due to its high incidence, risk of developing severe liver disease, and correlation with serious cardio metabolic abnormalities such type 2 diabetes mellitus (T2DM), metabolic syndrome, and coronary heart disease, NAFLD has emerged as a significant public health concern [22].

Gut microbiota and its importance

The viability of the gut microbiota is essential for maintaining the stability of the mucosal barrier function, nutritional absorption, the growth of immunological tolerance and response, and the preservation of energy balance [23,24]. Both NAFLD and IBS have been demonstrated to be influenced by dysregulation of the microbiome [25]. The development of the metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) has been linked to long-term disruption of the gut microbiota [26]. One example of this is enhanced intestinal permeability, which raises lipopolysaccharide exposure because the portal vein is the intestine's primary venous outflow, the liver is constantly exposed to stimuli of intestinal origins, such as bacteria and bacterial components. Due to its biggest population of tissue macrophages, the liver is a crucial location for the phagocytosis and clearance of microorganisms. As a result, the resident macrophages of the liver are the nitrogenous species that cause liver damage in the presence of proinflammatory cytokines and are a significant source of inflammatory mediators such as reactive oxygen species (ROS) [27]. Through pattern-recognition receptors, such as toll-like receptors (TLRs), which are the main microbe sensors, the innate immune system can identify conserved pathogen associated molecular patterns [28]. This promotes leakage of the intestinal cells, which are connected by tight junctions and are essential for maintaining the integrity of the intestinal barrier [29]. This causes leaky gut, which then causes liver inflammation as the microbes are transported from the gut to the liver. Due to an increased abundance of ethanol-producing bacteria that alters endogenous alcohol concentrations, the leaky gut, which is defined by decreased intestinal barrier function, is a well-documented feature of dysbiosis in patients with NAFLD [30,31]. Metabolites produced by microbes, such as lactate and ethanol, have the ability to directly trigger inflammatory cascades in the liver. It has been demonstrated that patients with hepatic steatosis have decreased levels of bifidobacteria, which may have decreased gut wall permeability to lipopolysaccharides and suggested a link between the two disorders [26]. A fecal microbiota transplant transitory in mice has shown improvement in peripheral insulin resistance and provides additional proof of the gut microbiome's significance in metabolic syndrome [32]. As the microbiota affects intestinal motility and sensitivity, changes in intestinal microbial diversity may possibly play a role in the onset of IBS. Reduced bifidobacterium, as well as reduced microbial diversity, have both been found in some IBS patients [33]. Dysbiosis of the gut microbiome and ensuing reduced gut permeability cause a rise in the amount of gut-derived toxins in the bloodstream that make up metabolic endotoxemia, which in turn encourages to cause the chronic low-grade inflammatory state associated with obesity and NAFLD [34].

Figure 3: Role of GUT microbiome in the development of IBS/ NAFLD [23-34].

Bile acid diarrhea

Figure 4: Bile acid malabsorption and development of NAFLD/IBS [35-47].

A higher Non-alcoholic fatty liver disease (NAFLD) fibrosis score has been linked to bile acid malabsorption, which is a factor responsible for persistent diarrhea. The precursor 7-hydroxy-4-cholesten-3-one (C4), a metabolic intermediary, whose serum levels are determined by hepatic bile acid synthesis, is controlled by the farnesoid-X receptor (FXR)-dependent ileal hormone fibroblast growth factor 19 (FGF19). The symptoms of chronic BA diarrhea include low FGF19 and high C4. An FXR agonist called obeticholic acid increases FGF19 and has demonstrated therapeutic potential in both bile acid diarrhea and NAFLD [35]. Both NAFLD and irritable bowel syndrome with diarrhea (IBS-D) are prevalent diseases that may be impacted by similar mechanisms including altered bile acid (BA) signaling and homeostatic control. Changes in ileal enterokinase and fibroblast growth factor 19 (FGF19) signaling as well as elevated levels of 7-hydroxy-4-cholesten-3-one, which indicates increased hepatic bile acid production from cholesterol, the primary source of bile acids in the liver, are some of the pathophysiological connections between IBS-D and altered bile acid metabolism [36-38]. Deoxycholic and lithocholic acids are secondary bile acids, while chenodeoxycholic and cholic acids are primary bile acids [39]. Primary bile acids are retained in the gallbladder following a meal, where they further undergo glycine conjugation before being released into the gut. The main function of bile acids and their salts is to enhance lipid and fat-soluble vitamin digestion and absorption because they are amphipathic molecules with emulsifying activity by nature [40]. Through deconjugation and dehydroxylation, the gut microbiota [41,42] transforms main bile acids into more hydrophobic secondary bile acids, which are then reabsorbed in the distal ileum and transmitted back to the liver through the portal vein [42]. Dysregulation of lipid and glucose metabolism results from an imbalance between secondary and primary bile acids [43] and a decrease in signaling via the bile acid receptor FXR [44]. Reduced FXR activation also inhibits CYP7A1, a vital enzyme that catalysis the first step in the breakdown of cholesterol and the creation of bile acids [45], enhancing lipogenesis and the production of free fatty acids [46] in the liver leading to bile acid diarrhea due to poor absorption of bile acids in the ileum, demonstrating disruption in the enterohepatic bile acid homeostasis important for multiple processes, including fat absorption, inflammation, immunity and microbial diversity in patients with NAFLD [25,47].

Small intestinal bacteria overgrowth (SIBO)

Figure 5: Small intestinal bacterial overgrowth (SIBO) and NAFLD/IBS Development [48-58].

Small intestinal bacterial overgrowth (SIBO) occurs when stagnant food in the small intestine becomes an ideal environment for microbes to multiply as a result of decreased intestinal motility, allowing food to ferment and the lesser presence of bile. This condition causes symptoms that are similar to those of irritable bowel syndrome (IBS), such as abdominal pain, bloating, and chronic diarrhea, tends to suggest that some IBS patients may have a relatively high predominance of SIBO [48,49]. The production of ethanol by bacteria as a metabolic byproduct, which causes triglyceride accumulation and oxidative stress in the liver, as well as abnormalities in the mucosa that make it easier for toxins to enter the body, are some potential mechanisms for the development of NAFLD in SIBO [50,51]. Additionally, the intestinal bacteria create short-chain fatty acids (SCFAs), which contribute to dysregulated glucose metabolism [53-55] decreased intestinal motility, and increased bacterial product absorption [52]. Likewise, bacterial overgrowth in the small intestine will cause the bacteria there to catabolize choline, inhibiting absorption. Very low density lipoprotein (VLDL) particles are secreted by the liver, and choline is necessary for this process [56,57]. Evidence suggests that obesity decreases gut motility, which may increase the risk of SIBO due to stasis. It is conceivable that this damages barrier function, which may lead to bacterial translocation and a disrupted gut-liver axis [58].

Gut-microbime-liver axis

Figure 6: Inflammation and its relationship with Dysbiosis [59-70].

In addition to changes in bile acid profiles and metabolite levels, such as an increase in endogenous ethanol, a decrease in choline levels, and dysregulation of short-chain fatty acids (SCFA) metabolism caused by the gut microbiome, the altered gut-liver axis is characterized by a number of pathological mechanisms. These mechanisms include the impairment of the gut barrier and subsequent increase in intestinal permeability, which cause endotoxemia and inflammation. The disturbance of the gut-liver axis is mostly attributed to gut microbiome dysbiosis. These byproducts may come from the bacteria themselves, from the microbial digestion of food sources, or from the modification of molecules like bile acids. Establishing the involvement of gut microbiome-derived metabolites in NAFLD pathogenesis, the dysbiotic gut microbiome generates microbial chemicals that may adversely affect immune response and homeostasis, energy metabolism, and preservation of mucosal integrity. Some microbes in the gut microbiome have the ability to produce ethanol from dietary carbohydrates [59,60]. The production of fatty acids and liver oxidative stress, two key factors in the emergence of NAFLD, are brought on by the breakdown of ethanol into acetate and acetaldehyde [61]. In addition to being directly harmful to the liver, it has been demonstrated that ethanol produced by the digestive system also increases intestinal permeability and endotoxemia, both of which can aggravate liver damage [62]. The metabolism of fat in the liver depends on choline, a phospholipid found in cell membranes [63]. It aids in the transfer of lipids from the liver and the production of very low-density lipoproteins (VLDL) [64-66]. Choline-deficient patients of hepatic steatosis have shown that choline shortage can consequently lead to fat deposition in the liver [67]. Choline is known to be converted to trimethylamine by gut microorganisms (TMA). Hepatic monooxygenases in the liver can oxidize TMA to produce trimethylamine N-oxide (TMAO), which is subsequently released into the bloodstream [68]. Increased liver TMAO levels are linked to metabolic diseases such obesity and NAFLD [69,70] and have negative effects on glucose homeostasis, insulin resistance, and glucose tolerance. Therefore, the idea that intestinal microbes are implicated in NAFLD is supported by the responses of the gut bacteria to dietary choline deficit and the generation of bacterial biomarkers of fatty liver [67,71,72].Overall the prevalence of constipation, NAFLD & IBS is increasing day by day [1-7,73]. Which is alarming and Further research needs to be conducted with a larger number of subjects to understand more specific mechanisms of these complications.

Conclusion

Obesity, gut microbiota, SIBO, bile acid malabsorption, the gut-microbiome-liver axis, IBS, and their interconnected loop of relationship with NAFLD are all discussed in the aforementioned review. Randomized controlled trials on a sizable sample of IBS patients are required to evaluate the effectiveness of manipulating the gut microbiota and demonstrate a potential link between IBS and NAFLD. Increased intestinal permeability and both quantitative and qualitative abnormalities of intestinal bacteria are linked to the aetiology and progression of gut abnormality and liver disease. The gut-liver axis is thought to function properly when gut bacteria are in balance. There is growing evidence that indicates that the gut-liver axis dysfunction that underlies NAFLD. Due to dysregulation of the gut-liver axis, gut microbiome dysbiosis causes increased intestinal permeability and uncontrolled transport of microbial metabolites into the liver, both of which contribute to the onset of NAFLD. IBS and NAFLD are serious disorders that can have a substantial impact on socioeconomic factors, significant healthcare, and both physical and emotional health.

Acknowledgement

The authors acknowledge Amity University Kolkata for the facilities provided.

Conflict of Interest

The authors declare no conflict of interest.

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