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Hypothesis: Mechanism of irritable bowel syndrome in inflammatory bowel disease

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ABSTRACT

Functional bowel symptoms can be occurred during remission from inflammatory bowel disease. In this case, a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet is effective for the amelioration or prevention of symptoms. However, the reason is not fully explained. This report proposes a hypothesis regarding the entire process in which inflammatory bowel disease with IBS-like symptoms (IBD-IBS) causes symptoms. A detailed process was assumed, starting from high pressure in the lumen and finally to abdominal symptoms. In this process, relationships were linked based on interactions such as ischemia, compliance, pain threshold, visceral hypersensitivity, mast cells, and permeability reported in IBD-IBS. In the process mapping, to understand the relationship between the amount of gas increased by FODMAP and ischemia, the hydrodynamic hypothesis and Ritchie's hypothesis were adapted. Ischemia in dilated intestines due to an increase in gas volume can induce excessive spasms via the mast cells and show the whole process of lowering the pain threshold. From the standpoint of the mechanism of IBD-IBS, the origin trigger may be FODMAP. Therefore, a low-FODMAP diet is recommended to relieve and prevent IBD-IBS symptoms.

Introduction

In 1983, Isgar et al. reported that 33% of patients in ulcerative colitis (UC) remission had irritable bowel syndrome (IBS)-like symptoms [1]. They speculated that these symptoms may be due to a reduction in the stimulation threshold for luminal distention due to previous inflammation [1]. Since 2002, inflammatory bowel disease (IBD) with IBS-like symptoms (IBD-IBS) has been attracted increasing attention [2–4]. In a systematic review and meta-analysis, Halpin and Ford reported that the prevalence IBD-IBS in all IBD patients is 39%, and odds ratio is 4.89 compared with controls; even in remission, the prevalence is 35% [5]. Since IBS is classified as a functional disease, IBD-IBS should not be recognized as a functional disease but as a symptom of organic disease. Even if it is endoscopically in remission, symptoms of residual low-grade inflammation may persist. Such conceptual denial complicates this problem. If the concept of minor organic diseases is correct, IBS with low-grade inflammation or minor histologic abnormalities might be regarded as a minor organic disease [6–8]. This conceptual problem has been investigated using fecal calprotectin as an indicator, but no consistent results have been obtained. To date, in research comparing IBD-IBS to IBD without IBS symptoms, only one study found higher fecal calprotectin than IBD without IBS symptoms [9], but 7 studies reported no significant differences between IBD-IBS and IBD without IBS symptoms. Interestingly, 31% showed normal fecal calprotectin levels in IBD-IBS [10–16]. In UC, it is reported that IBD-IBS is not a risk factor for UC relapse [17]. IBD-IBS symptoms should not be considered to be derived from inflammation. Mavroudis et al. reported that patients who developed IBS in remission did not have a high frequency of pre-symptomatic IBS compared to patients without IBS, and there was also no significant difference in the severity of UC; nevertheless, patients had more severe gastrointestinal symptoms with abdominal pain [18]. Studies have consistently reported that compared to patients without IBS-like symptoms, patients with IBD-IBS have higher rates of anxiety and depression and lower quality-of-life scores than active IBD patients [19–24]. These results suggest that physicians who treat IBD patients must understand IBD-IBS and administer appropriate therapies. However, especially regarding diet, there are concerns that clinicians do not properly guide IBD patients [25]. The IBD-IBS diet differs from active IBD (for example, enteral nutrition) and must conform to IBD-IBS. In AGA Clinical Practice in February 2019, Colombel et al. recommended restricting fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) in the management of IBD-IBS [26]. Indeed, a low-FODMAP diet is effective not only for IBS but also IBD-IBS [27–29], and a high-FODMAP diet aggravates these symptoms [30]. However, since the pathophysiological mechanism of IBD-IBS is unknown, the principle by which a low-FODMAP

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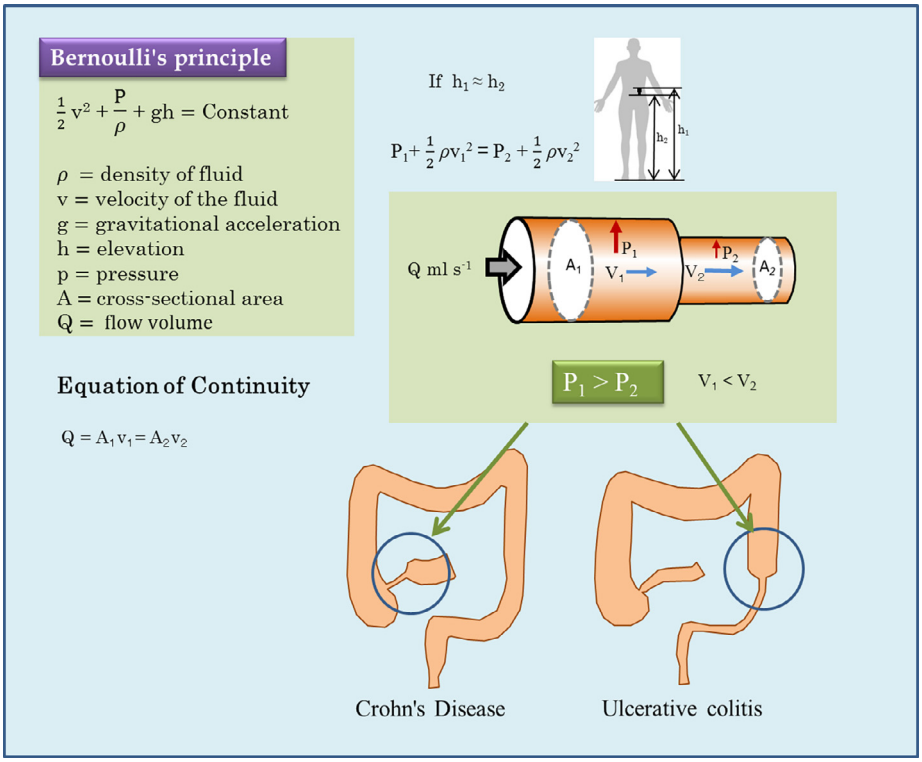

Fig. 1. Application of Bernoulli's principle to IBD. In Bernoulli's principle, the pressure increases in the wide lumen and the velocity increases in the narrow lumen. This law applies in the presence of stenosis and low compliance in the chronic phase of IBD.

diet is effective for IBD-IBS remains unclear. The follow suggestions may explain why a high-FODMAP aggravates abdominal symptoms in IBS: 1) increased intestinal fluid in the small intestine due to hyperosmotic contents, 2) excess gas is produced by fermentation in the large intestine, and 3) the intestinal mucosa might be injured by short-chain fatty acids (SCFA) [31]. However, in IBS, because a study by MRI did not show a correlation between intestinal lumen volume and symptoms, involvement of visceral hypersensitivity, not distention of the intestine due to gas, was noted as the cause of symptoms [32]. However, in that study, IBS was correlated with symptom peaks and colon gas peaks. Therefore, the relationship between increased gas and visceral hypersensitivity must be clarified. To address this issue, the present study applied flow dynamics to the intestinal lumen [33–40]. This report documents the mechanism by which IBD-IBS causes symptoms from a flow dynamic perspective.

Application of flow dynamics in IBD-IBS

Luminal flow of intestine and flow dynamics

When liquid is injected into the cecum, water rapidly advances into the narrow lumen and decelerates in the dilated lumen. This was observed in a prior cecostomy study [41], but the cause was long an enigma. The phenomenon was inconsistent with Bernoulli's principle. When applying fluid dynamics to the digestive tract, the motive force in the lumen is the inflow volume, not peristalsis. In a study by Ritchie investigating the relationship between ileal outflow and colonic propulsion using time lapse cinefluorography, an increase in ileal outflow in cases of diarrhea and malabsorption was associated with an increase in colonic propulsion [42]. However, in cases of constipation tendency, ileal outflow did not affect colonic propulsion. Furthermore, Ritchie suggested that the migration speed increases when the lumen narrows due to the increase in muscle tone. Consecutive peristalsis forms a narrow lumen, thus increasing velocity. This phenomenon seems as if the contents move by peristaltic movement. However, the phenomenon that the contrast agent rapidly flows to the proximal side in retrograde barium enema [43] and retrograde small intestine contrast [44,45] are evidence that the human intestinal tract cannot distinguish between the proximal and distal sides. Water moves faster in a tight, narrow lumen. The resulting change in continuous pressure might be observed as high-amplitude propagated contractions (HAPC) [34,40]. In a manometry study, HAPC increased in IBS patients without constipation [46], and HAPC decreased in slow transit constipation [47]. These phenomena can be rationally explained by flow dynamics. When the overall fluid propulsive force decreases, it remains in the intestinal tract without being excreted. An MRI study by Murray et al. found that free mobile water remained in the intestine even after overnight fasting, and confirmed that the pockets (fluid pool) increased by the oral ingestion of water [48]. This study may be indirect proof that fluid moves by the principles of fluid dynamics rather than by intestinal contraction. Because the flow between the stomach and the large intestine is interlocked by oral intake, the propulsive force in fluid dynamics is influenced by the liquid volume and gastric emptying ability [40]. As the proof, Lawal et al. reported that 70% of patients with accelerated gastric emptying had diarrhea [49]. Furthermore, a scintigraphy study by Read et al. observed that patients with IBS with predominant diarrhea (IBS-D) had a shorter small-bowel transit time and rapid colon filling, whereas constipated patients had a slower small-bowel transit time and delayed colon filling [50]. In flow dynamics, even if the flow to the cecum is the same, the colon transit time (CTT) changes depending on the form of the colon. In a theoretical calculation using a virtual model, CTT was prolonged in a megacolon model and shortened in a diarrhea-type IBS model compared to a normal colon model [34]. A high-FODMAP diet increases the amount of fluid in the small intestine, which increases the influx into the cecum. In the large intestine with continuous narrow lumens, diarrhea is caused by increased velocity. When gas increases due to fermentation in the lumen, the gas has less mobility due to its low density and further extends the lumen, causing constipation [34].

According to Bernoulli's principle, intraluminal pressure changes in

the lumen where there is a difference in its inner diameter (Fig. 1) [33–40]. This law also applies to the local and transient flow of the intestinal tract. Assuming the ileocecal valve and anal canal are narrow lumens, the proximal side (the terminal ileum and rectum) is easily influenced by high pressure. Intraluminal velocity increases where the inner diameter of the intestine is narrow due to spasm and fibrosis of the intestine Therefore, if the narrow lumen continues from the rectum, it causes frequent incontinence and urgent defecation. That is, poor compliance across the colon causes diarrhea. Therefore, this theorem can be applied to the lumen of IBD with low compliance and/or stenosis due to inflammatory fibrosis. In principle, due to uneven lumen configuration, the proximal intestine dilates and pressure increases. Intestinal stricture in Crohn's disease (CD) was present at diagnosis in 27.1% of cases over 10 years [51]. Many studies have reported pre-stenotic dilatation in CD [52–55]. This justifies the application of Bernoulli's principle to the intestinal tract. Intestinal stricture in UC is present in 6.3% to 11% of cases [56,57]. Currently, pre-stenotic dilatation in the toxic megacolon of UC has not been considered, but toxic megacolon by sigmoid stenosis was reported [58]. Megacolon due to overfermentation of lactose may be evidence that gas increase by FODMAP causes intestinal dilation [59].

To explain the symptoms caused by a high-FODMAP diet with flow dynamics, increasing the gas and/or water in the proximal lumen of the high compliance site is required. In CD, lactose and fructose may be more related in FODMAP because they increase the gas and water content 1–2 h after ingestion, much faster than fructan [60–62]. In fact, lactose and fructose continue to be suggested as a cause of CD [63–65]. Small intestinal bacterial overgrowth (SIBO) is a condition that causes more fermentation in the small intestine, in particular the fermentation of lactose and fructose increases [66]. CD and SIBO are closely related, and the presence of fibrostenosis rather than inflammation increases the incidence of SIBO [67]. In inactive CD with luminal constriction, when the gas increase is caused by fermentation in the pre-constrictor lumen, on the flow dynamics, it will result in an increase in internal pressure and a decrease in velocity. This phenomenon may be observed as a strong transient wave in manometry study. In fact, in the manometry test of inactive CD, single propagated contractions and propagated clustered contractions are frequently observed [68]. Interestingly, frequent clustered contractions have also been observed in the small intestine of SIBO without CD [69]. Therefore, it can be hypothesized that inactive CD results in SIBO due to stenosis and causes abdominal symptoms due to overfermentation. However, since the fermentation of fructan peaks at 4–5 h after ingestion [60], it is more likely to affect UC than CD. In a study of IBD with functional abdominal symptoms, Cox et al. found that the continuous administration of fructan worsened the symptoms (abdominal pain, bloating, and flatulence) and suggested that fructan had a cumulative effect [30]. This means that even if short-term high-FODMAP administration is insufficient for fermentation, daily intake of a high-FODMAP diet generates enough gas to cause symptoms.

Intestinal blood flow and flow dynamics

It has been reported that intestinal ischemia is caused by an increase in intraluminal pressure. Clinical cases and experimental studies have demonstrated that the blood flow in the intestinal wall decreases when the luminal pressure in the large intestine increases [70–72]. Boley et al. observed that when intraluminal pressure in the intestinal tract exceeds 30 mmHg, intestinal ischemia occurs, and when it exceeds 60 to 70 mmHg, the blood flow velocity decreases by 25%, and when it reaches 90 to 100 mmHg, the blood flow falls to 50% [72]. Boley et al. also suggested that peristalsis of the pre-stenotic lumen caused stronger transient ischemia. If the muscularis propria artery is transiently and repeatedly tightened by strong contractions, the serosal side artery may be dilated. A study by Lunderquist et al. using angiography and blood flow found dilation of the arteries without peripheral taper in CD [73]. This may be the result of repeated strong transient contractions in CD.

Induction of functional gastrointestinal symptoms in IBD-IBS by FODMAP

In 2005, Gibson and Shepherd reported the FODMAP hypothesis in CD [31]. They posited that carbohydrates that are slowly absorbed or difficult to digest in the small intestine increased water in the small intestine in a highly osmotic nature, SCFA and gas increased due to fermentation, SCFA impaired the intestinal barrier, and intestinal permeability increased. In the report of Ong et al. healthy subjects did not have symptoms even with the amount of gas that causes symptoms in IBS, but those with IBS tended to have a shorter time to peak gas volume than healthy people [74]. This means that the rate of gas increase affects IBS symptoms. If IBD-IBS is related to a rapid increase in gas, it is necessary to consider the process from gas increase to visceral hypersensitivity. To that end, it is necessary to present a complete picture of visceral hypersensitivity, starting with the intake of a high-FODMAP diet. The key is some shared mechanisms for the development of IBS-type symptoms both in patients with IBS and those with IBD [75,76]. For this reason, in the process, the involvement of elements of IBD-IBS such as fermentation, intestinal pressure, ischemia, mast cells, histamine, mucosal barrier, and lipopolysaccharides must be included (Fig. 2).

Intraluminal pressure

The first problem is whether gas pressure will cause direct pain. When FODMAP is fermented by intestinal bacteria, a large amount of gas is produced. Because gas has much lower density than water, the intraluminal mobility becomes low, according to Bernoulli's principle. Inside the lumen, the gas expands the higher compliant site in the intestinal tract, creating a lumen with a difference in diameter. A difference in intestinal lumen diameter causes an increase in intestinal pressure at the dilation site. IBS with visceral hypersensitivity may have the potential to induce abdominal pain.

The concept of visceral hypersensitivity in IBS was first introduced by Ritchie. He showed that latex balloon inflation in the sigmoid colon of patients with IBS evoked increased pain perception compared with healthy controls [77]. This observation has been subsequently confirmed in several studies [78,79]. In many previous barostat test studies, pain threshold in IBS was lower than normal and was approximately 30 mmHg [80–82]. However, the perception threshold by the barostat test in IBD is affected due to the compliance of the intestinal wall. In UC, the compliance of quiescent colitis is between active colitis and normal [83]. In a study of remission UC, when wall compliance was comparable to normal subjects, the perceptual threshold was 32–40 mmHg. However, even at a pressure of 32 mmHg, the 100-mm visual analog scale in UC remission was less than 50 mm [84]. This suggests that pressure over 30 mmHg may induce abdominal pain in the low compliance lumen, but pressure over 30 mmHg may not always induce pain in high compliance lumens. In a study of UC with mild chronic proctitis without IBS symptom by Chang et al., the mean discomfort threshold was 39.6 mmHg, This was a higher pressure than in normal subjects (32.5 mmHg) and IBS patients (27.8 mmHg) [85]. However, even if pain does not occur directly, sustained high pressure of 30 mmHg or more may lead to intestinal ischemia [72]. Ritchie noted that inflation of a balloon in the colon may induce a contraction that migrates down the colon, suggesting that the pain reported by patients with IBS may be caused by contractions at a site distal to the site of balloon distention. This is Ritchie's hypothesis in IBS [78]. In the barostat test, the balloon is dilated at the rectum or sigmoid colon, but the gas by FODMAP increases throughout. In the dilation test with the balloon attached to the colonoscope, the dilatation of the sigmoid colon mainly caused pain in the lower left abdomen, but the dilatation of the right colon tended to cause pain in the areas other than the dilation part

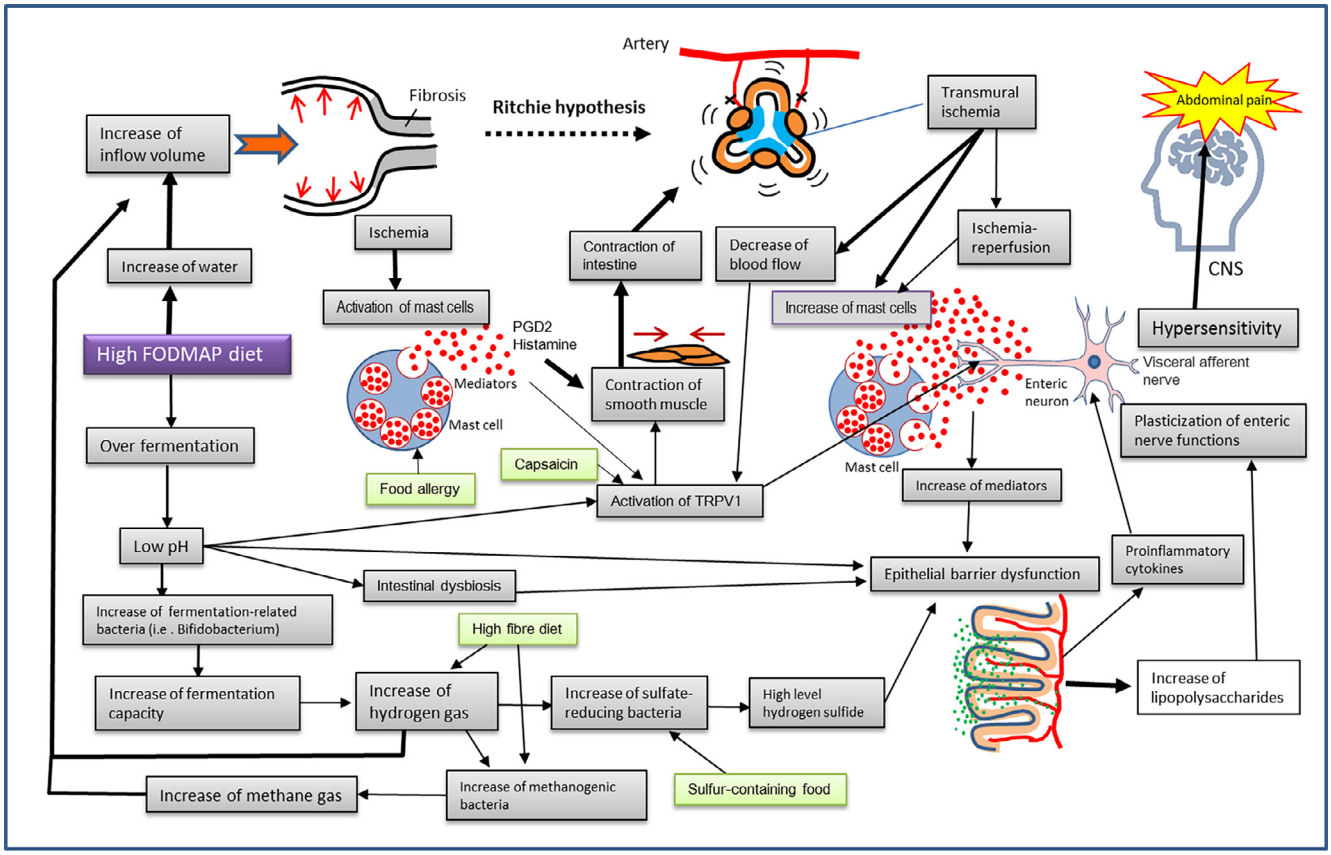

Fig. 2. Hypothesis of the mechanism by which IBD-IBS causes abdominal pain. Ingestion of a high-FODMAP diet increases water and gas. Fermentation produces SCFA and lowers the pH. Low pH not only directly damages the mucosal barrier but also causes bacterial dysbiosis and activates TRV1. Low pH also increases fermentable bacteria and increases hydrogen production. Increased hydrogen induces the production of H_2S. H_2S damages mucosal barriers. With increased gas in the lumen, luminal pressure induces ischemia of the intestinal wall with poor blood flow. Ischemia activates the mast cells. Mediators released from the mast cells cause smooth muscle contractions at distant sites, resulting in strong spasms. As a result, the mast cells are activated and large amounts of mediators are released, damaging the mucosal barrier. Thus, a lower visceral hypersensitivity threshold is induced.

[86]. Bassotti et al. expanded the balloon sequentially in the transverse colon, descending colon, sigmoid colon, and rectum of 15 healthy subjects. At the same time, contraction waves were measured via manometry. As a result, high contraction waves (> 50 mmHg) with pain were measured at locations other than the balloon dilation [87]. These facts may be evidence to support Ritchie's hypothesis.

Ischemia

Ritchie's hypothesis in IBS

In 1927, Kantor observed by barium enema that the shape of the large intestine changed over time, and found the large intestine demonstrated an abnormally strong contraction in IBS [88]. In 1933, Kuruse noted that abdominal pain was caused mainly due to a dilated cecum and spastic sigmoid colon in IBS [89]. He found that abdominal pain was accompanied by gurgling and bumbling, the sigmoid colon became ropy or cordlike, and the cecum was shaped like a bag containing gas and water. He also described roentgen findings in which strong convulsions continued throughout the large intestine, even when the contents of the intestine had nearly emptied. Interestingly, he also mentioned intestinal fermentation as a cause of IBS. These statements imply that the abdominal pain of IBS is caused by a fermented diet and a dilated cecum and cramped sigmoid colon. Subsequent studies have suggested that there is a close relationship between intestinal spasm and abdominal pain [90–92], and research is being conducted to reduce abdominal pain in IBS with muscle relaxants [93].

Ischemia in IBD

Concerning ischemia in CD, Wakefield reported that granulomatous vasculitis produces microvascular injury [94,95]. In 1997, Anthony et al. suggested that ischemia may be affected by low blood flow [96]. Longitudinal UC ulcers often occur along the taenia coli (three lines), and longitudinal CD ulcers occur along the mesentery (one line). Regarding the reason for the occurrence of longitudinal ulcers of the small intestine in CD at the site where the artery is supplied from the mesentery, Anthony et al. suggested that the peripheral artery supplied to the intestines might be involved in ischemia caused by muscularis propria spasms. They explained that these sites did not have direct communication with the potential compensatory collateral circulation that supplies the rest of the bowel wall [96,97]. This leads to the possibility that when severe spasms occur due to Ritchie's hypothesis, the muscularis propria can squeeze the peripheral arteries and cause ischemia. In addition, a pathological study of obliterative muscularization of the submucosa in CD reported the involvement of ischemia due to excessive intestinal spasms [98]. From the cecum to sigmoid colon, because the blood vessels enter the submucosa from the gap between the longitudinal muscle and the circular muscle [99], ischemia due to strong contractions might be occurred along the colon cord.

Ischemia in IBD-IBS

In IBD-IBS, due to fibrosis, low compliance and reduced blood flow must be considered. Decreased blood flow has been confirmed in both inactive UC and inactive CD [100,101]. In a study of laser Doppler flowmetry in CD, the blood flow in the lesion area of longitudinal ulcers and stenosis were 50% and 20%, respectively, relative to the normal

area [102]. This suggests that in the case of remission UC with stenosis and low compliance, even a slight increase in pressure within the lumen may result in severe hypoxia in the tissue.

Low pH and SCFA

In carbohydrate malabsorption syndrome, high luminal concentrations of short-chain fatty acids (SCFA) can reversibly impair barrier function due to low pH [103]. Since IBS and IBD are linked to carbohydrate malabsorption [64,104], FODMAP may directly induce mucosal damage. In a study using a wireless motility capsule, the colonic pH levels were significantly lower in the IBS group (all IBS subtypes) compared to healthy controls, and colonic pH levels correlated positively with the (CTT) and IBS symptom severity [105]. Although no consensus has been reached for IBD and intraluminal pH, it may indicate a normal or high pH [106], but it is not uncommon for IBD patients to have significantly lower intraluminal pH [107]. A high-FODMAP diet can exacerbate functional gastrointestinal symptoms in patients with quiescent IBD [30]. In addition, a low-FODMAP diet has improved the symptoms of IBD-IBS [27–29]. Many reports have promoted prebiotics to increase SCFA. Inulin, fructo-oligosaccharides, and galacto-oligosaccharides are representative prebiotics that can increase SCFA in the intestinal tract, and health promotion effects in healthy people have been proposed [108]. However, in IBS and IBD, FODMAP causes various problems. FODMAP can lead to a low pH in the colon, potentially compromising the efficacy of IBD medications [109]. Because pH-dependent delayed-release formulations of 5-ASA release the active moiety when their Eudragit coating dissolves as the luminal pH rises above a critical value (for Asacol, Eudragit S dissolves when pH $>$ 7.0), low pH by high FODMAP in the colonic lumen may reduce the effect of 5-ASA [106]. Furthermore, low luminal pH may increase the fermentable bacteria and increase the ability of fermentation in the intestine [110]. Increasing the number of lactobacilli and bifidobacteria in the gut by stimulating intestinal carbohydrate fermentation and enhancing the production of SCFA is often assumed to be beneficial for intestinal health and resistance to infections. However, this may cause a reduction in immunity against infectious enteritis. For example, fructo-oligosaccharides and lactulose impair the resistance of rats to intestinal salmonella infection [111]. An IBS mouse model dosed with fructo-oligosaccharide for 14 days enhanced visceral hypersensitivity and intestinal inflammation [112]. In 1996, Wasan and Goodlad described the carcinogenicity of fermentable dietary fiber [113]. In 2018, the development of hepatocellular carcinoma (HCC) due to long-term administration of inulin was confirmed in animal experiments by Singh et al. [114]. They hypothesized that HCC was due to intestinal dysbiosis. They proved that pharmacologic inhibition of fermentation or depletion of fermenting bacteria markedly reduced intestinal SCFA and prevented HCC.

Hydrogen sulfide (H_2S)

H_2S has no direct cause-and-effect relationship with FODMAP, but may be affected by the excess of hydrogen produced by FODMAP and the acidic intestinal lumen. The influence of H_2S in IBD is mainly discussed as the pathogenesis of UC [115]. Hydrogenotrophic microbes fall into three functional groups: sulfate-reducing bacteria (SRB), methanogenic archaea, and acetogenic bacteria, which can convert hydrogen into H_2S, methane, and acetate, respectively [116]. Sulfide is released into the acidic luminal environment and at low pH, HS- is hydrolyzed to biologically active free H_2S [117]. Lower levels of H_2S exert multiple physiological, cytoprotective, antioxidant, and anti-inflammatory functions. Although the major reported effect of H_2S in the context of smooth muscle is relaxation [118], excess hydrogen gas increases the amount of bacteria that generate methane and H_2S, and a diet rich in sulfur produces high levels of H_2S. High levels of H_2S weaken the epithelial barrier function and cause endotoxemia [119]. Baskar et al. showed that H_2S causes DNA damage, cell cycle arrest at G1, and induces p53 to cause apoptosis [120]. At higher concentrations, it inhibits butyrate oxidation, which is the principal energy source for colonocytes [121]. H_2S reduces disulfide bonds present in the mucus network, thereby breaking the mucus barrier. Pitcher et al. reported that the total viable counts of sulphate reducing bacteria in feces were significantly related to the clinical severity grade in UC patients [122].

Mast cell

Many studies have reported the relationship between mast cells and IBS. Studies of IBS and mast cells in humans indicated not only an increase in mast cell numbers but also the activation rate of mast cells and the mediator mucosal content released [123]. A study using mucosal biopsy tissue from proximal descending colon by Barbara et al. confirmed a significant increase in histamine and tryptase with the number of mast cells in IBS compared to controls [124]. Furthermore, nerve fiber and mast cell proximity and the number of degranulated mast cells and abdominal pain/discomfort severity were associated. Barbara et al. suggested the involvement of latent food allergy in the cause of mast cell activation. Mekkel et al. reported that the presence of increased IgE type immune response against any food allergens was 34.5% (comparison with control group: $p = 0.01$) in a group of IBS, in patients with CD or UC the immune response against food allergens was also more frequent than in a control group [125]. Therefore, even in IBD-IBS, involvement of food allergy may be one of the amplification factors of symptoms.

Ravnefjord et al. reported that mast cells are increased by acute ischemia due to increased intestinal pressure [126]. Interestingly, mast cells increased not the mucosa and submucosa but on the serosa, predominantly located around the blood vessels. From the aforementioned studies, the following hypothesis holds: FODMAP increases gas, increases lumen pressure, causes intestinal dilatation, and further causes transient acute ischemia, and increased mast cells release mediators in the adjacent intestine through blood flow and/or the abdominal cavity. As a result, mediators are released to the smooth muscle of the intestine other than the dilation site. De Schepper et al. reported that “alterations in gut motility and sensitivity frequently occur at a level remote from the actual site of inflammation” [127]. The enigma of this phenomenon may be elucidated by this hypothesis.

Concerning IBD, in 1980, a study confirmed that mucosal histamine release was significantly increased in UC, whether the patients were in remission or relapse [128]. In 1987, a report demonstrated significantly higher histamine of the mucosa in UC and CD compared with non-IBD [129]. The relationship between IBD and mast cells has been well documented, and in active IBD, there is a consensus that inflammation increases mast cells [127]. Regarding IBD-IBS, as with the IBS tract, a higher percentage of mucosal mast cells in close proximity to nerve endings was confirmed [84].

The large amount of mediator released from the increased mast cells reduces the function of the epithelial barrier and facilitates the entry of bacteria into the intestinal mucosa. This produces endotoxemia and increases lipopolysaccharides, inducing the plasticization of the peripheral nerves. In addition, proinflammatory cytokinase also acts on the peripheral nerves to promote hypersensitivity [130]. These are considered to have the effect of lowering the visceral hypersensitivity threshold. When supernatants of mucosal biopsies from patients with IBS were injected into the mesenteric vessels of rats, intestinal sensory neurons were activated [131]. This may mean that visceral hypersensitivity is triggered by local reactions such as mast cell activation and mediator release.

Transient receptor potential vanilloid type 1 (TRPV1)

TRPV1 may be involved in pain and hyperalgesia throughout the alimentary canal from the mouth to the anus [132], and affects the

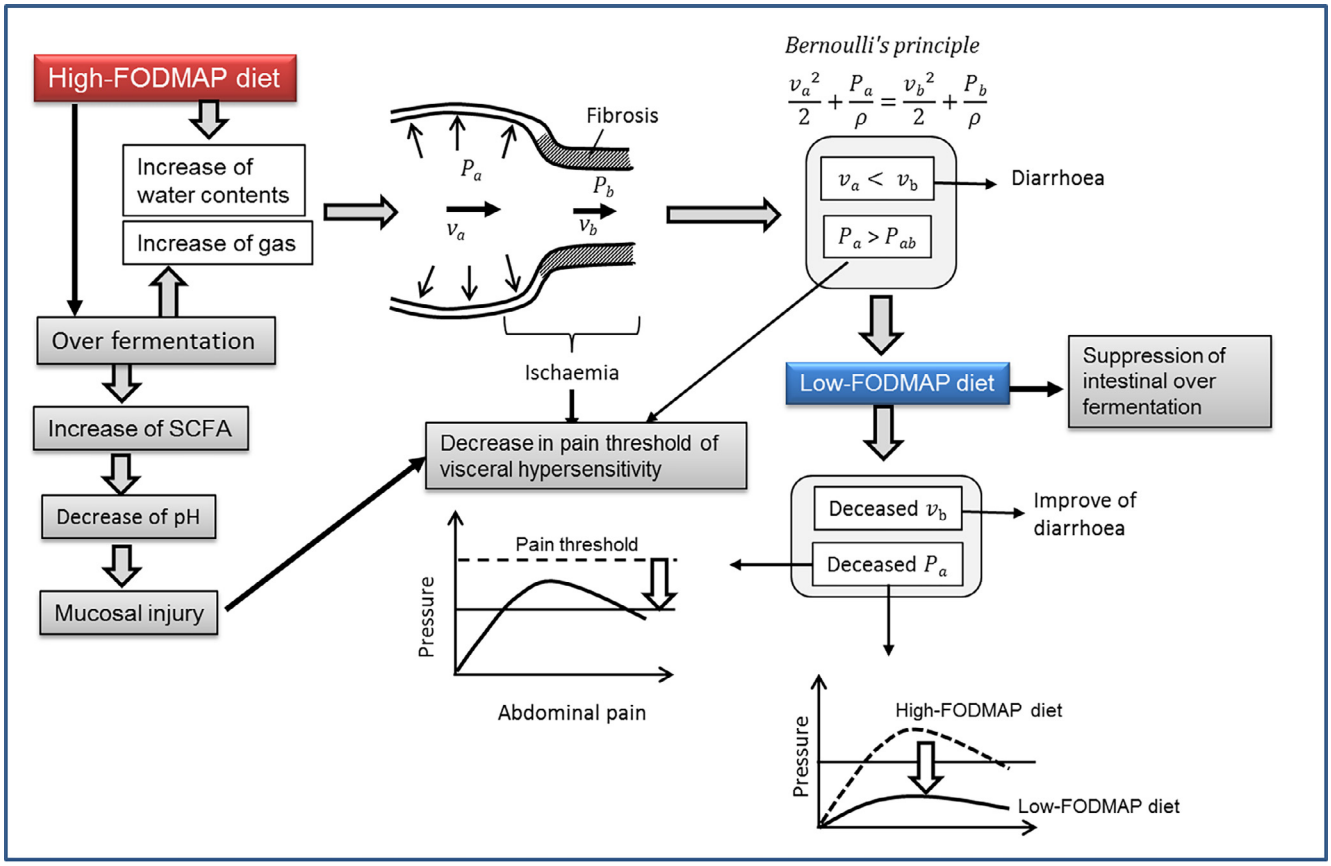

Fig. 3. Relationship between FODMAP and pain threshold applying Bernoulli's principle. A low-FODMAP diet reduces gas and water. As a result, it improves diarrhea and constipation. In addition, lumen pressure reduction can achieve a condition that does not exceed the pain threshold.

abdominal pain of IBS and IBD [133]. It is observed that abdominal pain in IBS is associated with increased TRPV1 nerve fibers and mast cells [134]. In an investigation of TRPV1-immunoreactive fibers, a significant 3.9-fold increase in the median number of TRPV1-immunoreactive fibers was found in biopsies from patients with IBD-IBS compared with the controls ($p < 0.0001$) and a 5-fold increase compared with the asymptomatic quiescent IBD group ($p = 0.0003$) [135]. TRPV1 is activated by ischemia and acidosis ($pH \leqq 5.9$) in tissues [136,137]. In a study of intestinal contraction by capsaicin, strong contractions were observed in the proximal colon and rectum, which have a high density of TRPV1-immunoreactive axons [138]. TRPV1 is also upregulated by mediators released from the mast cells [139]. A low-FODMAP diet does not consider capsaicin exclusion, but with a high-FODMAP diet, capsaicin may cause or worsen abdominal pain.

Intestinal permeability

Increased intestinal permeability (IP) is a feature of IBS-D and has been linked to symptom generation [140]. In IBD-D patients, increased IP may lead to more severe IBS symptoms and visceral hypersensitivity [141]. In IBD, endotoxemia has been reported to occur 48% in CD and 28% in UC [142]. Increased IP also occurs in inactive IBD [143,144]. In the quiescent IBD, Vivinus-Nébot and others reported that there is an increase in IP in IBD-IBS than in IBD without IBS symptoms [145]. Elevated serum concentrations of endotoxin and lipopolysaccharide-binding protein were even detected in patients with inactive CD [142]. FODMAP may have an impact on IP. Zhou et al. presented a hypothesis that causes intestinal barrier dysfunction and visceral hypersensitivity, as a high-FODMAP diet results in intestinal dysbiosis and elevates lipopolysaccharides (LPS) [146]. They also observed that a low-FODMAP diet reduces LPS in feces. Under ischemic conditions, the intestinal permeability of the enteral absorption of LPS is increased mainly by an enhanced paracellular permeability and epithelial destruction [147]. Intestinal ischemia due to luminal pressure and the excessive contraction of the intestine may enhance intestinal permeability.

Effect of low FODMAP diet in IBD-IBS

If the first IBD-IBS trigger is an increase in gas and water due to a high-FODMAP diet, a low-FODMAP diet can prevent the symptoms. A low-FODMAP diet can avoid the process of the activation of mast cells and intestinal contractions by preventing an increase in intraluminal pressure. As a result, it prevents abdominal pain, discomfort, and distension (Fig. 3). Diarrhea and constipation are determined by the balance of water and gas of different specific gravities. As the lumen diameter increases, the colon transit time is extended. An increase in gas remaining without being excreted increases the diameter of the lumen, further prolonging the transit time. Excessive conduction throughout the intestine results in faster passage and diarrhea due to the narrowing of the lumen throughout the intestine. A low-FODMAP diet prevents constipation and diarrhea by preventing abnormal dilation and contraction of the intestine.

Conclusion

A number of hypotheses were introduced to map the mechanism of IBD-IBS. These processes are consistent and have no contradictions. IBD-IBS may be regarded as sequelae of blood flow reduction, and a low-FODMAP diet is theoretically recommended for the prevention and alleviation of its symptoms.

Specific author contributions

Uno Y contributed to the writing of the manuscript, creation of theory, reference collection, and creation of the figure.

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None.

Declaration of Competing Interest

Uno Y is granted a trademark of low FODMAP diet from the Japan Patent Office, and has published a book on the low FODMAP diet from Japan and UK.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109324.

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