The Japanese Low FODMAP Diet Manual

Yoshiharu Uno and Mami Nakamura

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PREFACE

YOSHIHARU UNO

I have been working as a bowel disease specialist for 30 years; however, I was not interested in IBS at all until a few years ago because the cause of IBS was difficult to understand. I could only believe what I could actually see with my eyes. For that reason, I was devoted to research that used endoscopies. However, after researching endoscopic caecostomy in 2003, I became interested in constipation therapy. This was because, I noticed in an antegrade enema from a caecostomy that the transit time was in proportion to the width of the intestinal lumen. In addition, I noticed that the transit time was prolonged by colon gas.

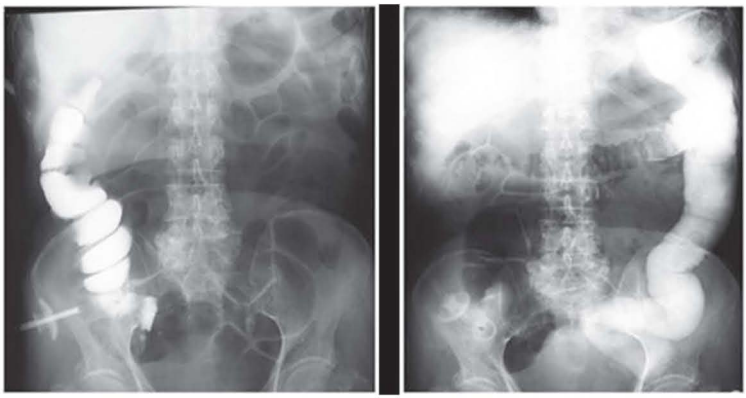


Figure 1. *ACE from caecostomy (left). Twenty minutes after ACE (right). The liquid contrast agent moved to the descending colon. However, the gas stayed in the transverse colon from caecum (Uno: 2003, 2004, 2006).*

After this, I treated many patients who were suffering from constipation. In addition, my sister, who had been taking laxatives for a long time, passed away due to colon cancer. Therefore, I read the past 100 years of research papers on constipation thoroughly. I found that there are many patients who are laxative dependent, and these patients have excessive dilation of the colon. Moreover, I found from abdominal X-rays that, in

addition to the quantity of stool, the quantity of gas was also significant in constipation. Therefore, I started to think that patients should reduce the total amount of both stool and gas. I told my patients to reduce their fiber intake, and to avoid wheat products, as these decrease gas production in the intestines. I also told them to avoid fermented foods, xylitol, or any gas producing foods.

In 2013, when I learned about FODMAPs, I realized the effect of dietary restriction of fermented foods. After 2013, I then became interested in low-FODMAP theory and made it my mission to spread this dietary method in Japan and the rest of the world. However, the more I read books or research papers, which were published in Australia and the West, I realized that not all the theories matched the Japanese diet or lifestyle. This made me think there was a necessity for a low-FODMAP diet modified for Japanese people. The most important problem was that low-FODMAP theory contradicts "the good bacteria theory", which is strongly believed in Japan. Therefore, I thought that for this new theory to be accepted in Japanese society, the establishment of a scientific theory that was logical and without contradiction was needed. Moreover, there were some other difficulties in spreading the word about a low-FODMAP diet as it could have a large impact on Japan's agriculture, the dairy industry, the restaurant industry, the instant food industry, and the confectionery industry. A vague, incomplete knowledge would not succeed in spreading the low-FODMAP diet in Japan. Therefore, I investigated the root cause of each FODMAP group, then learned all the details of how the research had been completed. However, when you walk into Japanese book stores, the shelves are full of health-related books that only advocate conventional dietary methods with new names, as though they were new inventions. Also, in Japan, fermented foods, which are high in FODMAPs, are very prevalent. Books advocating the health benefits of foods such as burdock, yoghurt, and garlic are widely sold in Japan. In 2015, I obtained the exclusive right to trademark low-FODMAP for education, speeches, publications, broadcasts, and merchandise. In this book, I have written my suggestions for a low-FODMAP diet for Japanese IBS patients. In addition, I will discuss the research that I have carried out on the subject matter.

Figure 2: *T-shirt from a Japanese low-FODMAP diet promotion group (JLFDPG)*

PURPOSE OF THE ENGLISH VERSION PUBLICATION

YOSHIHARU UNO

No one has doubt regarding the effectiveness of a low-F●DMAP diet. However, everyday meals are different, and dependent on the country's ethnic and religious differences. Many people around the world may think that Japanese only eat rice and fish. However, since the end of World War II, Japan has imported a large amount of flour, and bread and milk are also supplied for feeding hospital and school meals. Furthermore, it is currently believed that the high F●DMAP content of fermented food is healthy in Japan and, as a result, most F●DMAPs are included in Japanese foods. Even with such difficult circumstances, we are trying to help patients with IBS to follow a low-F●DMAP diet. To that end, we have provided a lot of information in this book, and we hope to share our knowledge about a low-F●DMAP diet around the world.

INTRODUCTION BY THE SECOND AUTHOR

MAMI NAKAMURA

I am a Japanese pharmacist living in Melbourne, Australia. I was diagnosed with IBS and was referred to a dietitian specializing in low-FODMAP diets. It took me a while to understand and accept a low-FODMAP as it was so different from what I knew. Since the day I met the dietitian, I have started reading lots of books related to IBS and low-FODMAP diet. However, luckily, I am in the leading low-FODMAP country and, through the program, I experienced the whole process and leaned how to manage IBS with a low-FODMAP diet.

Almost no information was available in Japanese but I managed to find Dr. Uno's colunm on the internet and I got to know him through his column. I was moved by his substantial contribution to Japanese IBS patients and, as we shared information about low-FODMAP diet in Japan and Australia, we decided to publish his book in English.

CHAPTER I

GENERAL DISCUSSION

1. Diseases related to FODMAP

1) What are FODMAPs?

F → fermentable
● → oligosaccharides
D → disaccharides
M → monosaccharides
P → polyols: these are sugar alcohols.

F●DMAPs are poorly absorbed from the small intestine because they are not easily, or even not at all, degraded in the small intestine. They are also highly osmotic, meaning that they attract water into the lumen of the ileum, and then they are fermented in the large intestine, contributing to the production of water and gas. High-F●DMAP foods lead to gut distention, resulting in abdominal pain, flatulence, abdominal bloating, diarrhea, and bowel movement disturbance. These are symptoms of irritable bowel syndrome (IBS).

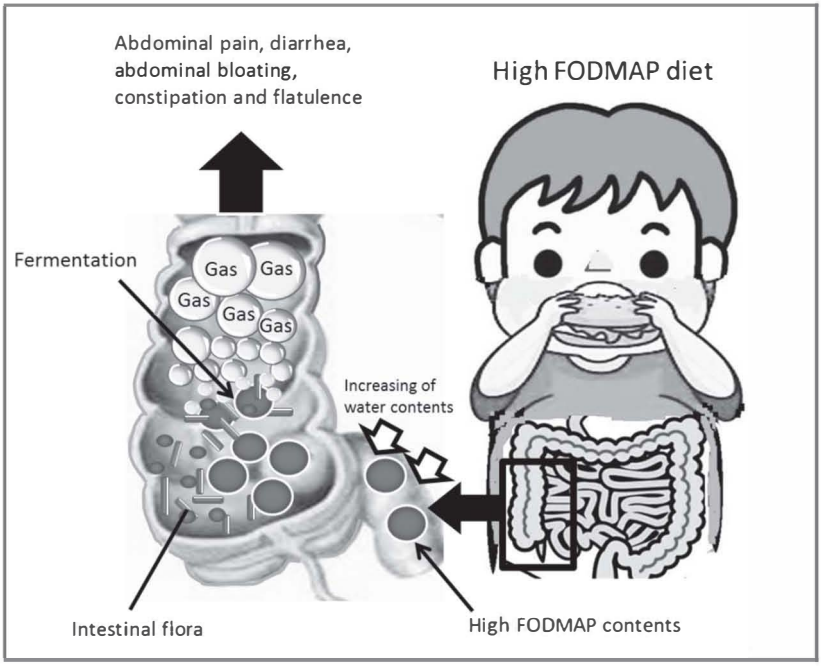


Figure 3: *High-FODMAPs increase the water in the lumen of the ileum, and are fermented in the large intestine. The production of gas by fermentation results in abdominal bloating, flatulence, stomach ache, diarrhea, and bowel movement disturbance.*

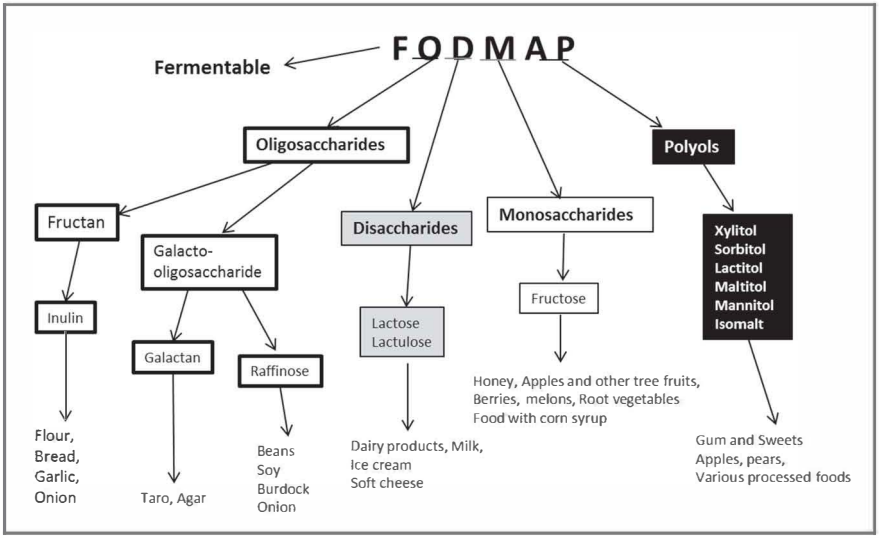


Figure 4: *High-FODMAPs chart*

High-FODMAP foods are also associated with many diseases other than IBS.

2) Criteria for diagnosing functional bowel disorder

The international diagnostic criteria for IBS were updated and revised: Rome III Criteria in 2006 and Rome IV for IBS diagnosis in 2016.

Criteria for IBS diagnosis in 2006 (Rome III)

Diagnostic criterion*

Recurrent abdominal pain or discomfort** at least 3 days/month in the last 3 months associated with two or more of the following:

(1) Improvement with defecation.

(2) Onset associated with a change in frequency of stool.

(3) Onset associated with a change in form (appearance) of stool.

* Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

** "Discomfort" means an uncomfortable sensation that is not described as pain.

IBS criteria of Rome IV in 2016

Diagnostic criterion*

Recurrent abdominal pain on average at least 1 day/week in the last 3 months associated with two or more of the following:

(1) Related to defecation

(2) Associated with a change in frequency of stool

(3) Associated with a change in form (consistency) of stool

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Diagnostic criteria for IBS subtypes

IBS with predominant constipation (IBS-C): > 1/4 (25%) of bowel movements with Bristol Stool types 1 or 2 and < 1/4 (25%) of bowel movements with Bristol stool types 6 or 7.

IBS with predominant diarrhea (IBS-D): > 1/4 (25%) of bowel movements with Bristol Stool types 6 or 7 and < 1/4 (25%) of bowel movements with Bristol Stool types 1 or 2.

IBS with mixed bowel habits (IBS-M): > 1/4 (25%) of bowel movements with Bristol stool types 1 or 2 and > 1/4 (25%) of bowel movements with Bristol Stool types 6 or 7.

IBS unclassified (IBS-U): Patients who meet diagnostic criteria for IBS but whose bowel habit cannot be accurately categorized into one of the three groups above should be categorized as having IBS-U.

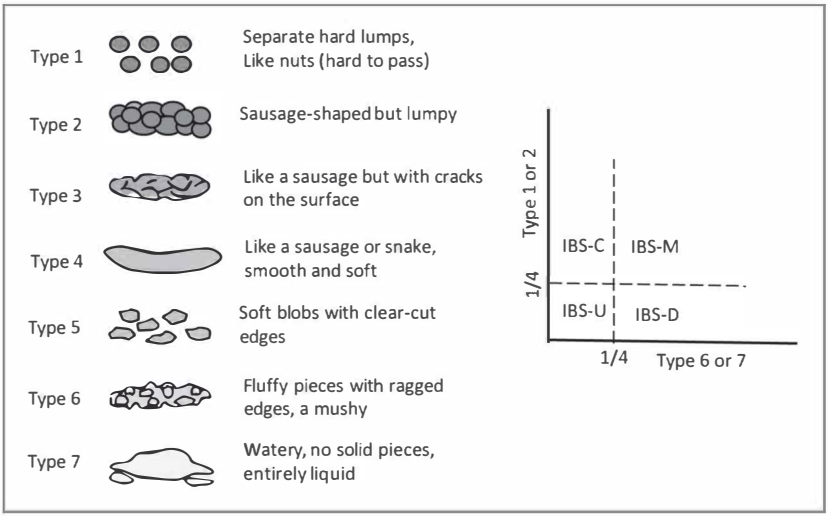


Figure 5: *Bristol Stool Scale (Drossman: 2016)*

Irritable Bowel Syndrome in Children (Rome IV)

Diagnostic criteria*

Must include 1 or more of the following:

(1) Abdominal pain at least 4 days per month associated with one or more of the following:

a. Related to defecation

b. A change in frequency of stool

c. A change in form (appearance) of stool

(2) In children with abdominal pain and constipation, the pain does not resolve with the resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS)

(3) After an appropriate evaluation, the symptoms cannot be fully explained by another medical condition

* Criteria fulfilled for at least 2 months prior to diagnosis

Functional Abdominal Bloating /Distension (Rome IV)

Diagnostic criteria*

Must include both of the following:

(1) Recurrent bloating and/or distension occurring on average at least 1 days/week; abdominal bloating and/or distension predominates over other symptoms**

(2) There are insufficient criteria for a diagnosis of irritable bowel syndrome, functional constipation, functional diarrhea, or postprandial distress syndrome

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

**Mild pain related to bloating may be present as well as minor bowl movement abnormalities

Functional Constipation (Rome IV)

Diagnostic criteria*

(1) Must contain 2 or more of the following:**

a. Straining during more than ¼ (25%) of defecations

b. Lumpy or hard stools (Bristol Stool Form Scale 1–2) more than 1/4 (25%) of defecations

c. Sensation of incomplete evacuation more than ¼ (25%) of defecations

d. Sensation of anorectal obstruction/blockage more than ¼ (25%) of defecations

e. Manual maneuvers to facilitate more than ¼ (25%) of defecations (e.g., digital evacuation, support of the pelvic floor)

f. Fewer than 3 defecations (spontaneous bowel movement) per week

(2) Loose stools are rarely present without the use of laxatives

(3) Insufficient criteria for irritable bowel syndrome

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

** For research studies, patients meeting criteria for opioid-induced constipation should not be given a diagnosis of FC because it is difficult to distinguish between opioid side effects and other causes of constipation However, clinicians recognize that these conditions may overlap.

Functional Constipation of Child (Rome IV)

Diagnostic criteria

Must include 1 month of at least 2 of the following in infants up to 4 years of age:

(1) 2 or fewer defecations per week

(2) History of excessive stool retention

(3) History of painful or hard bowel movements

(4) History of large diameter stools

(5) Presence of a large fecal mass in the rectum

In toilet trained children, the following additional criteria may be used:

(6) At least one episode/week of incontinence after the acquisition of toileting skills

(7) History of large diameter stools which may block the toilet

Functional Diarrhea (Rome IV)

Diagnostic criterion*

Loose or watery stools, without predominant abdominal pain or bothersome boating, occurring in more than 25% of stools**

* Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

**Patients meeting criteria for IBS-D should be excluded

Functional Diarrhea of Child (Rome IV)

Diagnostic criteria

Must include all of the following:

(1) Daily painless recurrent passage of four or more large, unformed stools

(2) Symptoms last more than 4 weeks

(3) Onset between 6 and 60 months of age

(4) No failure-to-thrive if calorie intake is adequate

Infant Colic (Rome IV)

Diagnostic criteria

For clinical purposes, must include all of the following:

(1) An infant who is less than 5 months of age when the symptoms start and stop

(2) Recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers

(3) No evidence of infant failure to thrive, fever, or illness

For clinical research, a diagnosis of infant colic must meet the preceding diagnostic criteria and also include both of the following:

(1) Caregiver reports infant has cried or fussed for 3 or more hours/day during 3 or more days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician

(2) Total 24-hour crying plus fussing in the selected group of infants is confirmed to be 3 hours or more when measured by at least one prospectively kept 24-hour behavior diary

Fecal Incontinence (Rome IV)

Diagnostic criterion*

Recurrent uncontrolled passage of fecal material in an individual with a developmental age of at least 4 years

*Criterion fulfilled for the last 3 months previously with 2–4 episodes of fecal incontinence over 4 weeks

2. Small intestinal bacterial overgrowth (SIBO) and IBS

The frequency of SIBO in patients with IBS is 4–78% (Ghoshal et al.: 2014). In addition to the IBS disease described in the Rome diagnostic criteria, small intestinal bacterial overgrowth (SIBO) is an important disease. Bacteria are normally present throughout the entire gastrointestinal tract, but relatively few bacteria live in the small bowel when compared with the large bowel. Less than 10,000 bacteria per milliliter of fluid live in the duodenum to the jejunum; however, when it comes to the distal ileum and colon, there are one billion and one trillion, respectively. There are also at least a quadrillion bacteria per kilogram of feces living throughout the gastrointestinal tract (Andoh. 2015).

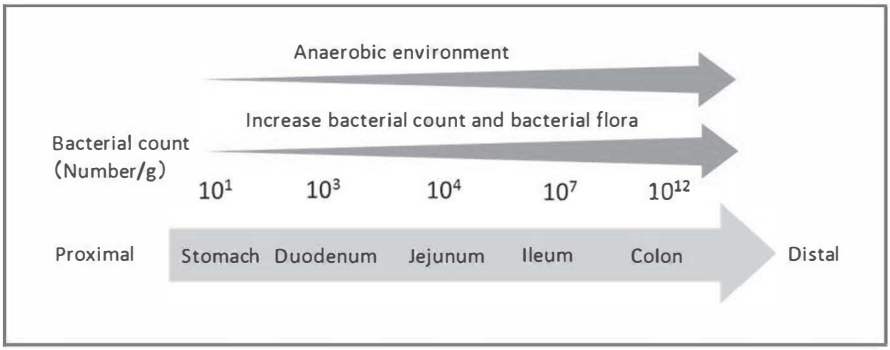


Figure 6: *Number of bacteria in the digestive tract (Andoh: 2015)*

The increased bacterial population due to SIBO causes excessive fermentation in the small intestine. Gas is produced by the fermentation of sugars, including glucose and sucrose, leading to the symptoms seen, such as gas production, bloating, pain, and diarrhea. In a study on patients with colectomy (Rao et al.: 2018), significant differences were found in the type of bacterial flora, with a predominance of aerobic bacterial organisms and fewer anaerobic organisms in post-colectomy SIBO patients when compared to controls. The duodenal cultures grew a variety of organisms primarily including *Streptococcus* species, *Escherichia coli*, *Klebsiella pneumoniae*, and *Lactobacilli.*

Diagnosis of SIBO

Historically, the diagnosis of SIBO was performed by the direct aspiration and culture of jejunal fluid, and was defined as an observation of 100,000 CFU/mL (colony forming unit per 1 milliliter of aspirated fluid from the jejunum). However, this cut off was not well-validated and has been a point of controversy. In a systematic review on the diagnosis of SIBO, it was observed that healthy controls have a bacterial concentration of $\leq 10^3$ CFU/mL, while concentrations of $\geq 10^5$ CFU/mL are mostly seen in patients with blind loop syndrome: such as patients with Billroth II procedure (Khoshini et al.: 2008). Currently, a bacterial concentration of > 1,000 CFU/mL is generally considered significant for diagnosis of SIBO (Erdogan et al.: 2015, Jacobs et al.: 2013, Pyleris et al.: 2012, Giamarellos-Bourboulis et al.: 2012).

However, because the aspiration-based method is an invasive test, indirect and non-invasive tests—LHBT (lactulose hydrogen breath test) and GHBT (glucose hydrogen breath test)—have been commonly used as alternatives (Ghoshal et al.: 2011, 2014). In SIBO, gas in the small intestine is increased by the fermentation of carbohydrates in the small intestine. Gas in the small intestine is carried to the blood circulation through capillaries and is excreted from the lungs. Therefore, the most common method for diagnosing SIBO has been to measure the hydrogen gas or methane gas exhaled after ingestion of 100g of glucose or 10g of lactulose.

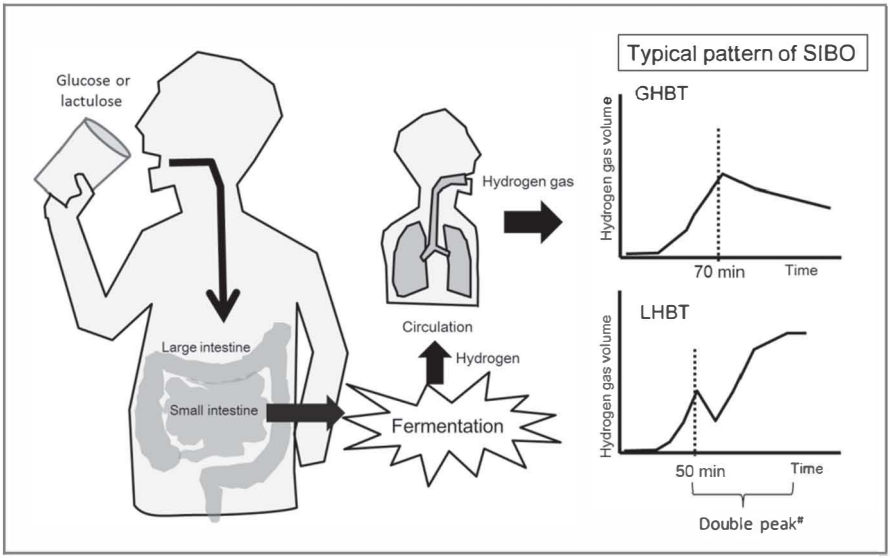


Figure 7: *GHBT and LHBT in SIBO*

#(Rezaie et al.: 2017)

SIBO breath test: patients drink a sugar solution of glucose or lactulose after a 1- or 2-day preparatory diet. The diet removes much of the food that would feed the bacteria, allowing for a clear reaction to the sugar drink. Breath testing measures the hydrogen gas produced by the bacteria in the small intestine that has diffused into the blood, then lungs, for expiration. Hydrogen is a gas produced by bacteria; therefore, the amount of hydrogen gas can be indirectly used to measure the number of bacteria present in the intestines. However, the credibility of this method has been doubted, since it shows a positive rate of between 4 and 78% (Ghoshal et al.: 2014), so it may not be accurate. In 2015, assessment of over 15,000 lactulose breath tests showed that median and mean gas production levels do not elicit a double peak (Chang et al.: 2015). The North American consensus meeting in 2015 (Rezaie et al.: 2017), suggested using a rise of $\geq$ 20 ppm from the baseline in hydrogen to diagnose SIBO. Additionally, this meeting suggested that, on the basis of current evidence, a double peak should not be used to diagnose SIBO and has no validity, and the test should be performed for at least 3 hours to ensure the presence of colonic

fermentation. Furthermore, these researchers suggested using a cut of ≥ 10ppm of methane positivity for a diagnosis of SIBO.

Usually, sucrose and glucose are absorbed in the small intestine and do not contribute to fermentation in the large intestine. In SIBO, however, these sugars can be fermented in the small intestine and, because of this, when the patient complains of wind-related abdominal symptoms after only the sucrose consumption it is highly likely to be due to SIBO. In a metagenomic analysis study in 2018 (Sundin et al.: 2018), researchers described that the glucose-based hydrogen and methane breath test was not sensitive to the overgrowth of jejunal bacteria. However, they also discussed that a positive breath test may indicate altered jejunal function and microbial dysbiosis. However, in a 2018 study using breath test and scintigraphy in combination, it was shown that the colon transit time increases when there is a high occurrence of methane gas in the small intestine (Suri et al.: 2018).

Abdominal imaging: In SIBO—whether methane or strictly hydrogen is produced—gas can have a significant effect on the patient's quality of life. For patients suspected of having SIBO, confirming the increase in small intestinal gas at the time of occurring symptoms will aid diagnostic determination. In order to determine the gas increase, it should be compared using abdominal imaging (CT, MRI, and X-ray) before and after the onset of symptoms. The easiest method would be to induce symptoms by ingestion of glucose and confirm the gas increase at that time (Uno Y: unpublished study).

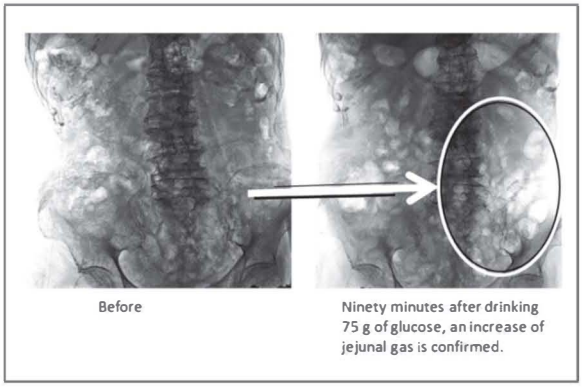


Figure 8: *Diagnosis of SIBO via an X-ray image (Personal data of Uno)*

Treatment of SIBO

In 2011, Pimentel et al. in the US indicated that SIBO is the main cause of IBS and advocated the eradication of gut bacteria using rifaximin (Pimentel et al.: 2011). As mentioned, the incidence of SIBO in IBS patients is under debate in terms of testing methods and facilities. However, as rifaximin suppresses bacterial growth: *E. coli* (85.4% inhibition rate), *Klebsiella* (43.6% inhibition rate), *Enterococcus* (100% inhibition rate), and *Staphilococcus aureus* (100% inhibition rate) efficiently, the effects could be promising. The problem in SIBO is usually sugars (carbohydrates), which are fermented by the bacteria in the small intestine before their absorption. If IBS symptoms are not relieved with low-FODMAP diet and if there is a chance that it could be SIBO, then the dietary restriction of all carbohydrates may be effective.

Drug-induced SIBO

Non-steroidal anti-inflammatory drugs (NSAIDs): In 2014, the Osaka Medical University in Japan reported that chronic non-steroidal anti-inflammatory drug users were susceptible to SIBO due to damage to the small intestinal mucosa (Muraki et al.: 2014).

Proton pump inhibitors (PPI): PPIs are used to treat gastric ulcers and the eradication of *Helicobacter pylori*. However, in 2010 it was reported that about 50% of patients treated with PPIs for a year develop SIBO and the incidence of SIBO is eight times higher than normal (Lombardo et al.; 2010). The diagnosis of SIBO in that study was done with a breath test. Also, a study into the diagnosis of SIBO via the culture of duodenal aspirate in 2013 also showed a similar increase in SIBO with PPI use (Jacobs et al.: 2013). In a 2018 meta-analysis study (Su et al.: 2018), a total of 19 articles met the eligibility criteria for the meta-analysis in 7055 subjects. The pooled odds ratio (OR) showed a statistically significant association between increased risk of SIBO and PPI use (OR 1.71). In a systematic review and meta-analysis of 50 studies in 2018 (Chen et al.: 2018), more than 1/3 of IBS patients tested positive for SIBO and the odds of SIBO in IBS were increased by nearly fivefold. The prevalence of SIBO varied according to the diagnostic modality performed. When the pH in the small intestine increases by one, then the bacteria in the small intestine is increased by 13.8%. Long-term use of PPIs causes an increase in the pH of the stomach, and the barrier function in the stomach decreases so that the number of bacteria in the small intestine increases. Omeprazole,

Lansoprazole, Pariet (rabeprazole), and Nexium (esomeprazole) are used clinically for the treatment of gastric ulcers, duodenal ulcers, reflux esophagitis (which increases after the eradication of *H. pylori*), and non-erosive gastro-esophageal reflux disease (GERD) in Japan. In particular, lansoprazole is commonly used in conjunction with aspirin or NSAIDs. H_2 blockers (famotidine) also increase the gastric pH. Unlike other countries, because Japanese people take PPIs frequently it is estimated that there are more potential SIBO patients in Japan. When PPIs were first used in Japan, the period of use was limited to 2 weeks. However, more recently there has been no limit on the length of administration period. PPIs are mainly formulated for chronic abdominal pain and continuous heartburn but, in practice, the symptoms (abdominal pain and heartburn) may be side effects from the administered drug.

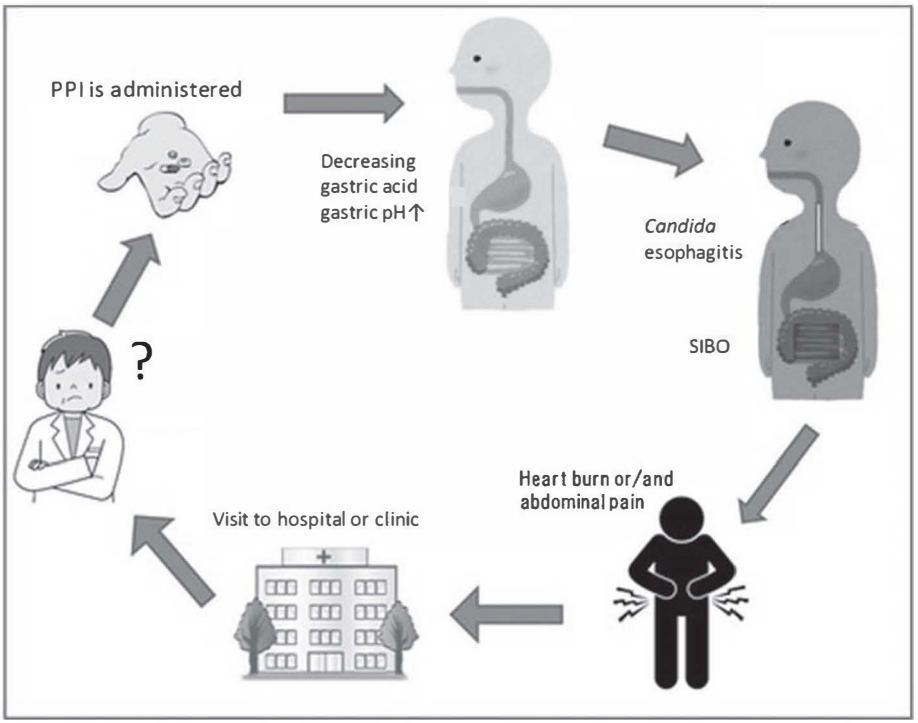


Figure 9: *The cycle between PPI and SIBO in Japan*

The problem with PPIs in Japan is that long-term administration is carried out easily by orthopedic surgeons and cardiologists who do not know the risk. In 2018, Italian researchers suggested that short-term PPIs could be considered effective and safe in adult patients with acid-related disorders but their long-term, and often inappropriate, use in patients carrying vulnerability to adverse events and/or high risk of drug-interactions should be avoided (Corsonello et al.: 2018).

3. Coeliac disease

IBS symptoms occur frequently (38%) in patients with coeliac disease (Sainsbury et al.: 2013). In addition to FODMAPs, gluten is also considered a trigger of IBS symptoms. Gluten-containing cereals, such as wheat, rye, and barley, have always been a main component of people's diet in Western countries. Gluten-related disorders (coeliac disease, wheat allergy, and non-coeliac gluten sensitivity) have emerged as an epidemiologically relevant phenomenon with an estimated global prevalence that comes close to 5% (Elli et al.). The diagnostic methods for coeliac disease, wheat allergy, and non-coeliac gluten sensitivity are different (Elli et al.: 2015).

Diagnostic tests for gluten related disorders (Ref. Elli et al.: 2015)

	Coeliac disease	Wheat allergy	Non-coeliac gluten sensitivity
Challenges	Gluten challenge is used in case of genetically predisposed patients following a gluten free diet	Challenges with the suspected allergens are still considered the gold standard although potentially dangerous for the patient	Double blind challenge with gluten could be considered the gold standard for diagnosis
Genetic	HLA typing is useful to exclude celiac disease	Not used	Not used
Historogy	Presence of duodenal atrophy is considered the gold standard in adulthood	Not strictly indicated	Not strictly indicated; a mild duodenal intraepithelial lymphocytosis is possible in up to 50% of suspected cases
Serology	Anti-transglutaminase antibodies	The research of IgE against the suspected allergens is sensitive	Anti gliadin IgG positive in 50% of cases
Skin tests	Not used	Skin reacti ons against allergens have a low sensitivity especially in case of wheat due to the absence of specific components in commercial reagents	Not used

Coeliac disease: The trigger for coeliac disease is a gluten which is contained in wheat, rye, barley, and oats. The ingestion of gluten in genetically predisposed individuals carrying HLA type II DQ2/DQ8 alleles can arouse a T cell mediated immune reaction for tissue transglutaminase (tTG); this is an enzyme of the extracellular matrix, leading to mucosal damage and, eventually, to intestinal villous atrophy (Elli et al.: 2015). Intestinal villous atrophy reduces the surface area of the bowel available for nutrient absorption. The clinical manifestations of coeliac disease are heterogeneous and range from the so-called "classical" syndrome with diarrhea, weight loss, and malnutrition, to selective malabsorption of micronutrients (iron, vitamin B12, and calcium). Non-classical features include irritable boweltype symptoms, hypertransaminasaemia, cerebellar ataxia, and peripheral neuropathy (Rubio-Tapia et al.: 2013). Coeliac is a life-long disease and potentially causes a growth deficit when it occurs in childhood (Isaac et al.: 2016). In adults, coeliac disease can also cause small intestinal adenocarcinoma, oesophageal cancer, melanoma, and non-Hodgkin's lymphoma (Green et al.: 2003). The diagnosis of coeliac disease is based on a combination of findings from a patient's clinical history, serologic testing, and gastroscopy by means of duodenal biopsies. Coeliac disease was genetically believed to be an illness peculiar to Caucasians. However, it has now been revealed that coeliac disease exists in other ethnicities. In 2006, the first epidemiological study of coeliac disease in Japan was carried out (Nakazawa et al.: 2006). They found that Japan has a 0.7% prevalence rate, with approximately 875,000 potential patients. Furthermore, it was reported that the prevalence of coeliac disease in Iran is 3%, as of 2017 (Mohammadibakhsh et al.: 2017); therefore, it is no longer considered to be a disease that is unique to Caucasians. In a 2010 report from Turkey (Korkut et al.: 2010), two people were diagnosed with coeliac disease as a result of scrutinising 100 people diagnosed with IBS using the Rome III diagnostic criteria. According to a meta-analysis by researchers in the UK in 2013 (Sainsbury et al.: 2013), encompassing data from 7 studies with 3383 participants, the pooled prevalence of IBS-type symptoms in all patients with coeliac disease was 38%. Furthermore, an Indian study of 2016 (Chowdhury et al.: 2016) found 10 (9%) out of 107 IBS patients who fulfilled the Rome III criteria tested positive for anti-tTG (IgA).

For diagnosis, a quantitative approach that can be defined as the "four out of five rule" was proposed (Catassi et al.: 2010):

1. Typical symptoms of coeliac disease

2. Positivity serum for coeliac disease IgA class autoantibodies at high titre

3. HLA-DQ2 and/or HLA-DQ8 genotypes

4. Coeliac enteropathy found on small bowel biopsy

5. Response to a gluten-free diet

Wheat allergy (WA): WA is defined as an adverse immunologic reaction to wheat proteins. Depending on the route of allergen exposure and the underlying immunologic mechanisms, WA is classified as a classic food allergy affecting the skin, gastrointestinal tract, or respiratory tract; wheat-dependent, exercise-induced anaphylaxis (WDEIA); occupational asthma (baker's asthma) and rhinitis; and contact urticaria. IgE antibodies play a central role in the pathogenesis of these diseases (Sapone et al.: 2012). Ingested wheat can cause IgE-mediated wheat allergies in both children and adults (Elli et al.: 2015). The majority of wheat-allergic children suffer severe atopic dermatitis. They may elicit typical IgE mediated reactions, including urticaria, angioedema, bronchial obstruction, nausea, and abdominal pain or, in severe cases, systemic anaphylaxis following wheat ingestion (Ramesh et al.: 2008). In adults, food allergy to ingested wheat is infrequent. In adults, food allergy gastrointestinal symptoms could be mild and difficult to recognize, the most common are diarrhea and bloating (Elli et al.). The diagnosis of WA is based on skin prick tests, in vitro specific immunoglobulin E assays, and functional assays. However, in some cases diagnosis is difficult, the challenge test is the definitive diagnostic method. In infants with challenge-proven wheat allergy, 20% showed elevated IgE concentrations to wheat, 23% had a positive skin prick test, and 86% had a positive patch test for wheat. The specificities of CAP RAST (the concentration of wheat - specific IgE antibodies), skin prick tests, and patch tests were 0.93, 1.00, and 0.35, respectively (Majama et al.: 1999).

Non-coeliac gluten sensitivity (NCGS): Recently it has also been called "non-coeliac wheat sensitivity". NCGS is the proposed definition for the condition in which gastrointestinal and extra-intestinal symptoms are triggered by gluten consumption, in the absence of coeliac-specific antibodies and villous atrophy as well as of any allergy related processes (Catassi et al.: 2013). People with NCGS experience symptoms similar to those of coeliac disease, which resolve when gluten is removed from the diet. However, they do not test positive for coeliac disease. Contrary to coeliac disease and wheat allergy, there are no clear serologic or histopathologic criteria for clinicians to confirm the diagnosis of NCGS. Some researchers have proposed that other components in wheat, in addition to gluten proteins, contribute to the activation of the innate immune response and elicit symptoms in patients with NCGS (Niland et al.: 2018). In a review study of 153 papers from 1966 to 2015, prevalence ranges of NCGS were between 0.55% and 6% of the general US population (Mansueto et al.: 2015). A 2013 US study found that 65% of American adults think gluten-free foods are healthier, and 27% choose gluten-free products to aid in weight loss (Jones et al.: 2017). A gluten-free diet does not contain any wheat, so it is also effective for wheat intolerance, wheat allergy, or fructan sensitivity (intolerance). Regarding the relationship between NCGS and nickel, in 2017 researchers in Italy demonstrated that contact dermatitis and nickel allergies were more frequently found in NCGS patients than in subjects with other gastrointestinal disorders (D'Alcamo et al.: 2017).

Recently in Japan, rice flour has been used as a wheat substitute for people with wheat allergy. However, because rice flour does not give fluffy textures, gluten is sometimes deliberately added to rice flour bread. Gluten is also used as a glue in buckwheat noodles, as it has viscosity (gliadin) and elasticity (glutenin).

4. Food allergies and intolerance

Adverse reactions to foods can be broadly divided in to those with an immune basis, such as food allergies and coeliac disease, or those without an immune basis, termed food intolerances (Turnbull et al.: 2015, Bartuzi et al.; 2017). FODMAPs cause symptoms in the absence of digestive enzymes and when they exceed the ability to be treated with enzymes. From that point of view, excess dietary fiber and resistant starches are

fermented in the large intestine, so they might be included in the concept of food intolerance.

Food allergies are classified as IgE-mediated, non-IgE-mediated, and mixed type. An IgE-mediated food allergy includes oral allergy syndrome (pollen food allergy) and food dependent exercise-induced anaphylaxis, and it affects both children and adults. Non-IgE-mediated allergies occur in newborn babies through infanthood only and have three types: food protein-induced enterocolitis syndrome, food protein-induced proctocolitis, and food protein-induced enteropathies. Conditions associated with a food allergy and involving both IgE-mediated and non-IgE-mediated mechanisms include cow's milk protein allergy, eosinophilic esophagitis, and eosinophilic gastroenteritis. Cow's milk protein allergy is very common in childhood; it is mediated through both IgE and non-IgE mechanisms, and it may be responsible for up to 40% of childhood gastro-esophageal reflux disease. This is due to milk protein-induced mast cell degranulation, which disturbs the stomach peristalsis and alters the lower esophageal sphincter tone, thereby leading to gastro-esophageal reflux (Turnbull et al.: 2015). Eosinophilic esophagitis is an increasingly recognized chronic inflammatory condition of the esophagus that affects both children and adults. Eosinophilic gastroenteritis includes eosinophilic gastritis, eosinophilic enteropathy, and eosinophilic colitis and can manifest at any age, with a male predominance. In the reports from Japan (Furuta et al.: 2013) and Germany (von Amim et al.: 2016), eosinophilic esophagitis and eosinophilic gastroenteritis are considered to be more common in people not infected with *Helicobacter pylori.* Therefore, it is expected that these allergic diseases will increase in Japan in the future (due to the eradication of *Helicobacter pylori*).

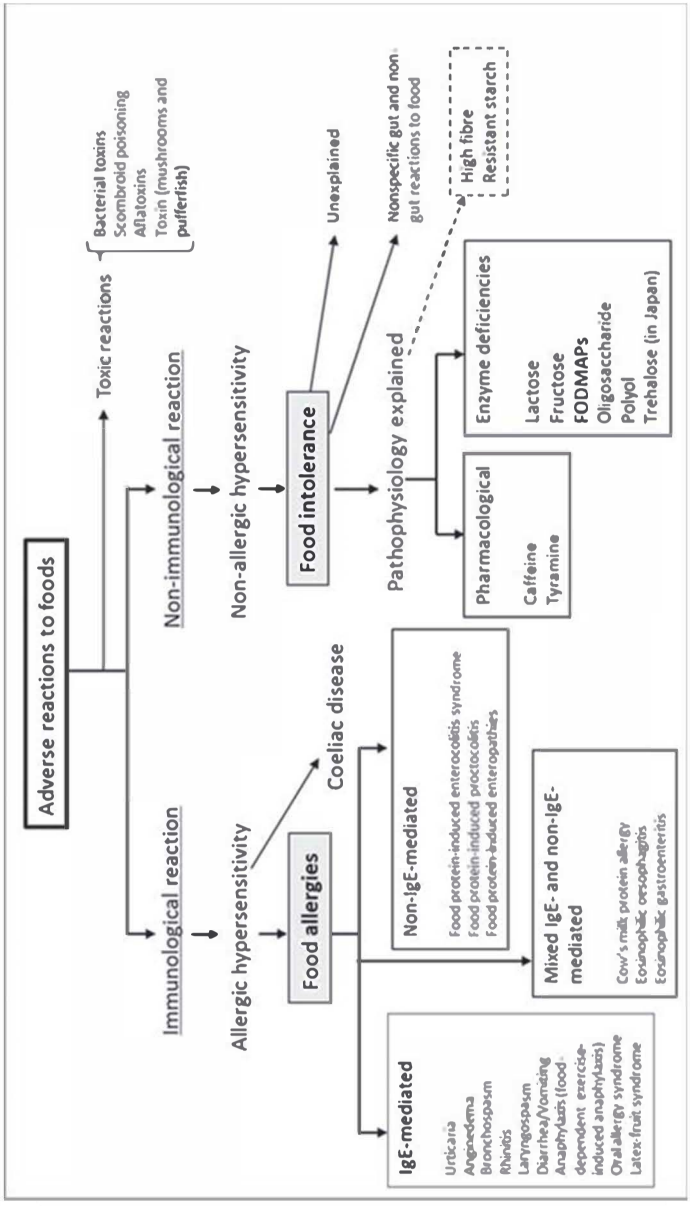


Figure 10: *Classification of adverse reactions to foods (Turnbull et al.: 2015, Bartuzi et al.: 2017)*

IgE-mediated food allergy

Food allergies are believed to develop in 2 to 4% of adults and 5 to 8% of young children, but a study in 2014 reported that a high incidence was recognized in individuals in their 20s and 30s, and approximately 15% of adults have been diagnosed with an initial food allergy (Kamdar et al.: 2015, Iweala et al.: 2018).

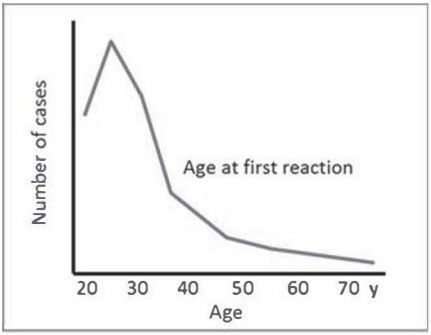


Figure 11: *Food allergy in adults (Savage et al.: 2007)*

IgE-mediated food allergy: Food and other proteins enter the body by ingestion, inhalation, or skin penetration. They are taken up by antigen presenting cells and presented to T cells. The resulting cytokine release determines whether there is a predominant TH_1 or TH_2 response. When food proteins inappropriately trigger a TH_2 predominant response the result is that IgE is produced by B cells, causing mast cells to sense allergens and release mediators such as histamine. Since histamine and so on causes the contraction of smooth muscle and capillary dilation, they lead to symptoms.

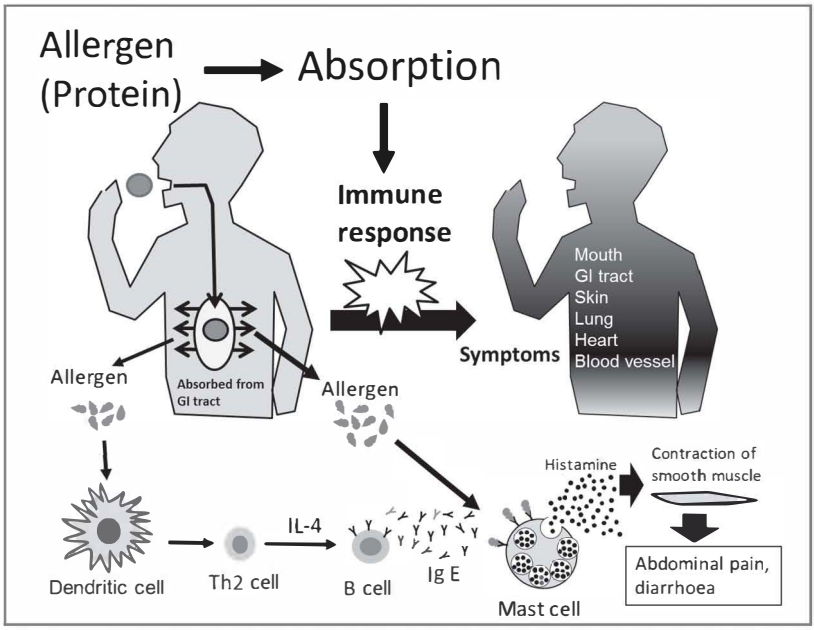


Figure 12: *The mechanism of an IgE-mediated food allergy*

The gastrointestinal symptoms caused by food allergies are similar to IBS, so it has been indicated that IBS patients may also suffer from a food allergy, and many research studies have been carried out on this area (Zar et al.: 2001, 2002, 2005, Stierstorfer et al.: 2013). IgE-mediated immediate phase reactions involve the release of inflammatory mediators (e.g. histamine) from previously sensitized mast cells (Zar et al.: 2005). Diagnosis methods of a food allergy include skin prick test, atopy patch test, and serum IgE level measurement, but sensitivity and specificity are not necessarily high. Therefore, depending on the likelihood of an allergy determined clinically based on the combination of history and the results of allergy tests, an oral food challenge may be indicated to confirm or exclude the diagnosis. An IgE response to dietary antigens may be localized to the bowel mucosa and may, therefore, not correlate with serum levels of the antibody. One study, carried out in Germany (Bischoff et al.: 1997), examined food antigen responses by injecting allergens into the submucosa by colonoscopy. They found increased numbers of mast

cells and eosinophils at the reaction site of the positive patients and 83% of the patients' symptoms disappeared after eliminating the positive-allergens from their diet. For those patients, the skin prick tests for common food antigens were negative and the level of serum IgE antibody was normal.

In 2013 in Japan, the government identified high-risk foods that could cause allergic reactions. According to a food labelling standards ordinance, it is mandatory to label the following 7 foods: prawn, crab, wheat, buckwheat noodles, eggs, milk, and peanuts. Also, it is recommended that the following 20 foods are labeled: abalone, squid, salmon roe, orange, cashew nuts, kiwi, beef, walnuts, sesame, salmon, mackerel, soy beans, chicken, banana, pork, matsutake mushrooms, peach, yam, apple, and gelatin. Food intolerance is also triggered through non-IgE-mediated hypersensitivity. It occurs due to consuming specific foods excessively or due to a reduction or absence of specific digestive enzymes, and is more frequent than IgE-mediated reactions.

In a report from Alaska, an allergy to cow's milk is the most common food allergy among infants and young children, as it affects approximately 2.5% of children during the first 2 years of life (Sicherer and Sampson: 2014). The incidence of this is gradual throughout childhood and adolescence with resolution occurring in 19, 42, 64, and 79% of children at ages 4, 8, 12, and 16 years, respectively (Skripak et al.: 2007). In general, the higher the cow's milk-specific IgE (sIgE), the less likely the child will become tolerant over time (Skripak et al.: 2007). Egg allergies also disappear with age (Savage et al.: 2007).

Rates of latex glove use and associated latex allergy remain high in some countries and in certain occupations, such as health-care workers, food handlers/restaurant workers, and housekeeping staff. Among patients with latex allergy, 30 to 50% show an associated hypersensitivity to some plant-derived foods, such as avocado, banana, kiwi, chestnut, peach, tomato, white potato, and bell pepper (Iweala et al.: 2018). Cutaneous exposure to hydrolyzed wheat protein in face soaps has been linked to wheat-dependent, exercise-induced anaphylaxis in Japanese women (Iweala et al.: 2018). Interestingly, food allergies are associated with morbidity of reflux esophagitis; furthermore, anti-ulcer treatment primes the development of IgE toward dietary compounds in long-term acid-suppressed patients (Untersmayr et al.: 2005). It is also known that reflux esophagitis and allergic diseases (asthma and atopy) have increased

due to the reduced prevalence of *H. pylori* infections in the stomach (Atherton and Blaser: 2009).

Food intolerance

In FODMAPs, lactose intolerance occurs because of reduced action by lactase. Fructan and sorbitol cause intolerance because of the absence of enzymes. Moreover, fructose causes intolerance when it exceeds the glucose amount. Food intolerances can also arise through direct effects that include gluten intolerance (NSGS), lectin intolerance, and alcohol intolerance. Intolerances to salicylic acid, amines, glutamate, food pigments, and antiseptic agents can also arise. These reactions tend to be milder than a food allergy and are dose dependent with dose allowances (threshold). Furthermore, interaction/synergic effects exist. The symptoms of food intolerance only occur in the gastrointestinal tract. As the antibodies are not formed in the blood, it is not easy to diagnose using a blood test. Therefore, it is usually diagnosed using a time consuming and inefficient method where each suspected trigger is eliminated from the diet and then, after any symptom relief is confirmed, the food is reintroduced to see if symptoms return, hence confirming the identity of the trigger food or food content. Therefore, a low-FODMAP diet has been designed for easier diagnosis. This basically involves eliminating all the substances that may potentially cause intolerance at once, then seeing if there is any symptomatic relief and identifying the problematic substance.

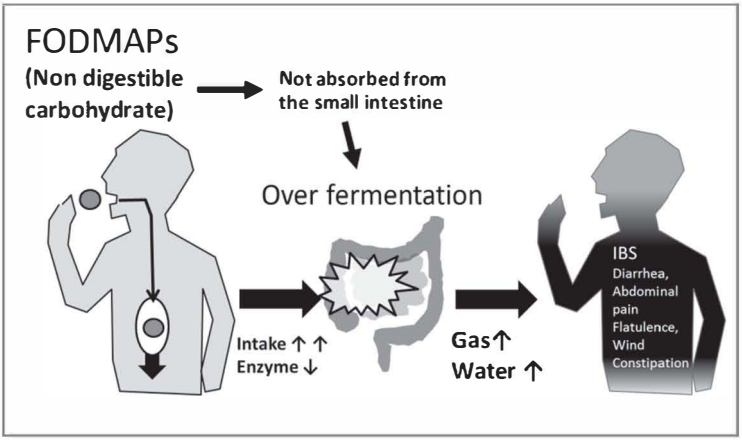


Figure 13: *Overview of food intolerance (FODMAPs)*

We take in food, digest, and absorb it to obtain the beneficial nutrients. However, currently, in order to reduce the prevalence of conditions such as diabetes and obesity, synthetic substitutes are often used in foods. Moreover, lots of food additives are added to improve the aesthetic appearance of the food or to increase the shelf-life of the food. These artificial additives can cause gastrointestinal functional disorders and many other problems. Enzymes that break down some of the additives do not exist naturally in the human body. Therefore, as they cannot be digested and absorbed, they interact with gut bacteria in the large bowel, leading to the massive production of gas and its related symptoms. Typical examples are hypoglycaemic agents used in the treatment of diabetes. Absorption of sugar from the small intestine is suppressed by hypoglycemic agents. Therefore, the spike formation of blood sugar levels does not occur. However, the unabsorbed sugar is transported to the large intestine and fermented.

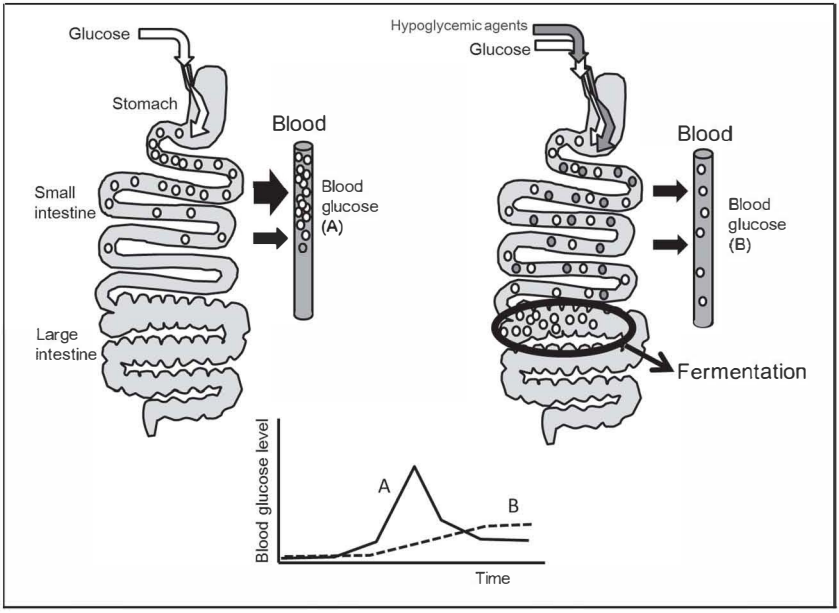


Figure 14: *Over-fermentation in colon by a hypoglycaemic agent*

5. Recognition of IBS and dietary transition in Japan after WWII

In Japan, a case with IBS symptoms was reported after the Second World War. In 1955, Matsunaga from Hirosaki University reported the first case with alternating diarrhea and constipation, which he named "alternating bowel movement disturbance" (Matsunaga: 1995). In 1956, Ikemi from Kyushu University wrote that bowel dysfunction should be called "irritable colon" in overseas patients and, moreover, patients should avoid the following foods: coffee, thick tea, alcohol, stimulating spices (garlic, spring onion, wasabi, etc.), cold foods, salted meat/fish, deep-fried foods (tempura), pork, bacon, onions, starch, beans, cabbage, corn, cucumber, and pumpkin. Milk, eggs, beer, chocolate, and some fruit are also listed as foods that patients can be sensitive to and should avoid (Ikemi et al.: 1956). In 1959, Ikemi and Inoue repeatedly reported that those foods were especially not suitable for patients with bowel dysfunction with diarrhea (Ikemi and Inoue: 1956). In 1959, Kono of the Japan National Center for Global Health and Medicine described that starch and legumes produce gases, and that the ingestion of large amounts of them causes abdominal distention and diarrhea (Kono: 1959). He explained the reason was because fructose and lactose are not digested but when they reach the large intestine, they cause abdominal symptoms due to their production of carbon dioxide and methane gases, as a result of fermentation. In 1961, Sannohe et al. of Keio University described dietary treatment methods for bowel dysfunction: "High-fiber foods like vegetables are not recommended for constipated patients. Food residues stimulate the intestine, and can increase spasms of the large intestine. Food residues induce excessive spasms by irritating the large intestine. Abstain from fruit and raw vegetables, except ripe banana, until diarrhea stops. Dairy milk as well as cold beverages needs to be avoided" (Sannohe et al.: 1961). In 1971, Kawakami stated that most Japanese people develop diarrhea after consuming 50g of lactose but that many people do not develop diarrhea or loose stools after consuming 180g of milk (about 6g of lactose) (Kawakami: 1971). In 1982, Watanabe argued that if the patient is sensitive to a particular food, it needs to be removed from the diet, and when flatus is problematic, legumes, cabbage, and other fermentable foods need to be restricted in quantity (Watanabe: 1982).

Later, over time, instant foods and sweets were also added to the list of foods that should be avoided. Dairy and wheat products had also gradually become recognized as trigger foods for IBS. However, after a while, it was believed that the main causes of IBS were stress and psychological problems. Meanwhile, the good/bad bacteria theory gained popularity as probiotics were touted. Due to the media promotions by lactic acid bacteria containing food manufacturers, the idea came to be considered common sense among Japanese citizens that prebiotic foods should be consumed every day in order to reduce bad bacteria. Therefore, patients with IBS were advised to have counselling, take antidepressants, and eat yoghurt to increase the beneficial bacteria in the gut. The Japanese guidelines in 2006 recommended that IBS patients should avoid spices and alcohol, and a high-fiber diet should be consumed (Kanazawa: 2006). The guidelines in 2009 stated that spicy foods and high-fat content foods should be avoided. The low-FODMAP die began to be introduced in Japan, via the Internet, from 2013. In 2014, the Japanese Society of Gastroenterology published onthe effectiveness of a low-FODMAP diet in an academic journal (Fukudo: 2014).

6. Modern history of IBS dietary treatments in the world (1980–present)

In the 1980s, dietary fiber was thought to prevent IBS symptoms. However, in 1985, Arffmann et al. reported that ingestion of wheat bran that was rich in fiber increased stool weight, but did not reduce the symptoms of IBS (Arffmann et al.). In 1989, food intolerance in IBS patients was confirmed, which suggested that the elimination of dietary triggers relieves symptoms (Nanda R et al.). In 1991, Friedman suggested that the reduced intake of large amounts of lactose-containing foods, sorbitol, and fructose may limit postprandial bloating. He also considered that flatus production can be lowered by reducing fermentable carbohydrates such as beans, cabbage, lentils, Brussel sprouts, and legumes (Friedman). In a survey of female university students in the US in 1996, slimming diets were associated with abdominal pain, bloating, diarrhea, and constipation (Krahn et al.). The prevalence of lactose malabsorption in the Caucasian population of northern Europe had been estimated to be low. However, in 1996 researchers from the Netherlands suggested that a substantial number of IBS patients could be treated with a lactose-restricted diet (Böhmer et al.). In 2001, researchers in Germany pointed out that coeliac disease

exists among IBS patients, and suggested that a gluten-free diet may work for some patients (Wahnschaffe et al.). In 2003, researchers from France described that patients with IBS with predominant diarrhea have to be carefully questioned about consumption of different kinds of food (e.g. coffee, alcohol, chewing gum, and soft drinks) (Dapoigny et al.). According to a study in London on constipation-predominant IBS in 2005, mean stool wet weight increased after 8 to 12 weeks of meals containing 10 to 20g/day of coarse wheat bran, but symptomatic benefits other than a placebo effect were not obtained (Rees et al.). In a study from the University of Colorado Denver on diarrhea-predominant IBS (IBS-D) in 2009, improvement of abdominal pain, stool habits, and quality of life was observed by 2 or more weeks on a very low-carbohydrate diet (VLCD: < 20g carbohydrate/day) (Austin et al.).

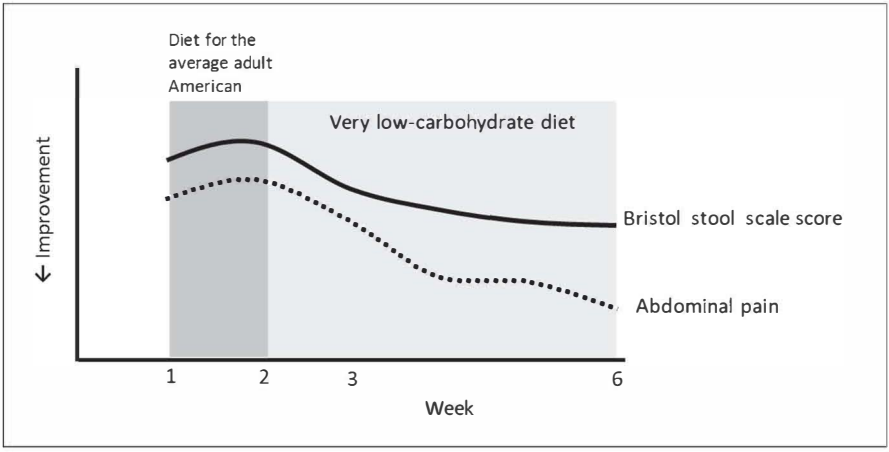


Figure 15: *Effects of VLCD in IBS-D (Austin et al.: 2009)*

According to a randomized, placebo-controlled trial in Denmark in 2011, 8 weeks of probiotic fermented milk intake did not show any significant effect in 50 people with IBS (Søndergaard et al.). In 2014, a systematic review and meta-analysis was undertaken by researchers in the UK, the US, and Canada to assess the effectiveness of prebiotics or synbiotics in managing IBS. This study identified 3,216 citations and 43 randomized, controlled trials were eligible for inclusion. They concluded that the validity of scientific evidence was uncertain, despite lots of literature

indicating effectiveness (Ford et al.). In the same year, researchers from the same group also reported the results of a systematic review and meta-analysis on the effect of fiber supplementation on irritable bowel syndrome. As a result, a benefit was only seen in RCTs from soluble fiber, but bran did not appear to be of benefit (Moayyedi et al.).

7. Low-FODMAP diet invention

Since the late 20th century, it has been believed that the cause of IBS is related to the diet. This idea was derived from the fact that hypersensitivity and intolerance to specific foods, such as wheat and milk, are associated with unexplained disease of the large intestine. However, before 1970 the only way to objectively assess food intolerance was component analysis of feces. In 1972, JH Bond Jr from Minnesota University (Bond et al.) reported that hydrogen was produced by fermentation up to 5 hours after ingesting 6.5-26g of lactulose, and the produced hydrogen penetrates into the blood and is excreted in the breath.

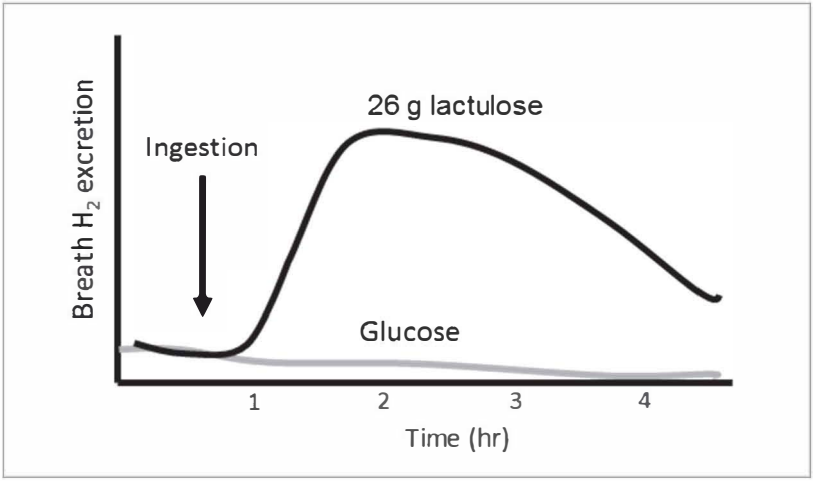


Figure 16: *Lactulose breath test (Bond et al.). Lactulose that is not absorbed at the small intestine is fermented in the large intestine and generates hydrogen gas. This hydrogen gas can be measured by expiration. However, glucose absorbed in the small intestine does not produce measurable hydrogen in exhalation.*

In normal subjects, fructose is absorbed in the small intestine. In contrast, in fructose intolerance hydrogen is overproduced by fermentation of fructose. In 1978, four patients were described with gastrointestinal symptoms after fruit ingestion in which symptoms could be reproduced with the ingestion of 100g of fructose (Andersson and Nygren). In research from 1983, it was demonstrated that fructose intolerance could be diagnosed by breath hydrogen volume after the ingestion of 50g fructose solution. Researchers suggested that the absorption of fructose may lead to gastrointestinal symptoms (Ravich et al.). In research from 1984, incomplete intestinal absorption of fructose was investigated in children by measuring breath hydrogen (Kneepkens et al.). After the ingestion of fructose (2g/kg body weight), breath hydrogen was increased in children with abdominal symptoms. Furthermore, sugar hindered the absorption of fructose, and the effect of glucose on fructose absorption was shown to be dependent on the amount of added glucose. In 1986, Rumessen and Gudmand-Høyer discovered that mixtures of the same dose of fructose and glucose could not alleviate symptoms of fructose intolerance (Rumessen and Gudmand-Høyer). According to a study in 1987, researchers investigated the relationship between symptoms and breath hydrogen volume during the ingestion of fructo-oligosaccharides (Stone-Dorshow et al.). Subjects had more severe flatulence and higher volumes of breath hydrogen while taking the oligosaccharide than the subjects taking sucrose.

In 1988, Rumessen and Gudmand-Høyer of Denmark reported the results of administering fructose, sorbitol, fructose-sorbitol mixtures, and sucrose in 25 patients with functional bowel disease. The occurrence of malabsorption was evaluated by means of hydrogen breath tests and the gastrointestinal symptoms, if any, were recorded. Based on a cut off level of 10ppm in the rise of H_2 concentration, malabsorption was apparent in 13 patients and in 7 of these patients the calculated absorption capacities were below 15g. The ingestion of fructose caused marked abdominal distress in patients with demonstrable malabsorption. The ingestion of sucrose in these patients gave less pronounced symptoms of abdominal distress. Malabsorption of a 5g dose of sorbitol could be detected in 8 of 13 patients. Mixtures of 25g of fructose and 5g of sorbitol caused significantly increased abdominal distress, and more than additive malabsorption was found in several cases. Namely, they found that pronounced gastrointestinal distress may be provoked by the malabsorption of small amounts of fructose, sorbitol, and fructose-sorbitol mixtures in patients with

functional bowel disease. They concluded that the findings may have a direct influence on the dietary guidance given to a majority group of patients with functional bowel disease and may make it possible to define separate entities in this disease complex.

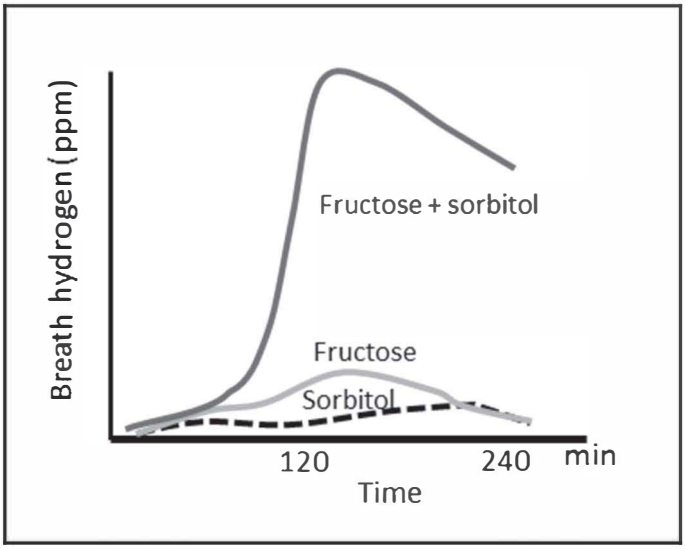


Figure 17: *Evidence that a mixture will be more adversely affected than the administration of unabsorbed carbohydrates alone (Rumessen et al.; 1988).*

In 1989, Frideman stated that avoiding lactose, sorbitol, and fructose alleviated motor dysfunction of the small intestine, and avoiding legumes, legumes plants, Brussel sprouts, apples, grapes, and raisins alleviated gas (Frideman). In 1990, in Japan, researchers from Yakult released their research data on 12 healthy men, revealing that bloating and flatus increased after consuming 5g of galacto-oligosaccharide daily, and abdominal pain developed after consuming 10g of galacto-oligosaccharide daily (Ito et al.).

A noteworthy article from Japan

In 1994, Professor Mikio Inoue of Fukuoka University in Japan wrote the following:

> Gas production in the large intestine: as a factor of gas evolution in the large intestine, fermentation by intestinal microbial flora of carbohydrates not absorbed at the small intestine is important. Hydrogen, carbon dioxide gas and methane gas are generated by fermentation. Such a mechanism can be useful for people with digestive absorption disorder, intake of milk (lactose) in lactase deficiency, various vegetable foods (in particular, indigestible oligosaccharides), and also caused by ingestion of lactulose. The occurrence of gas symptoms in IBS is not only an increase in intestinal gas, but also an obstacle to passage of gas in the intestines due to convulsion of the large intestine and an increase in susceptibility to dilation of the large intestine. An increase in internal pressure is also important, even normal amounts of gas as can cause symptoms in IBS. Treatment of gas symptoms should avoid fermentable foods such as beans. Also, lactose intolerant people should avoid milk.

Figure 18: *Mko Inoue (1924–2010)*

In 1995, Vernia et al. completed a study on the prevalence of lactose malabsorption (by means of a hydrogen breath test) and the clinical effects of a long-term lactose-free diet in 230 consecutive patients with a suggested diagnosis of irritable bowel syndrome but no organic disease of the gastrointestinal tract, and no history of milk intolerance. As a result, lactose malabsorption was diagnosed in 157 patients (68.2%). They concluded that a test for diagnosing lactose malabsorption should always be included in the diagnostic workup for IBS and a long-term lactose-free regimen recommended if the test is positive (Vernia et al.). In 1997, in a study of 64 healthy females it was reported that bloating and discomfort

developed significantly after consuming 14g of inulin daily for 4 weeks, and 12% experienced unbearable flatulence (Pedersen et al.). In 1998, King et al. measured breath hydrogen and methane excretion for 3 hours after 20g oral lactulose was ingested. As a result, colonic gas production, particularly of hydrogen, was greater in patients with IBS than in controls, and both symptoms and gas production were reduced by an exclusion diet. They concluded that fermentation could be an important factor in the pathogenesis of IBS (King et al.).

In 2000, Young in Australia reported that fiber rich foods increase IBS symptoms, as well as diverticular disease and inflammatory bowel disease, and poorly absorbable carbohydrates including lactose, fructose, and sorbitol also increase IBS (Young). In the same year, Goldstein et al. reported that the ingestion of solutions of 18g lactose, 25g fructose, or 5g fructose-sorbitol mixture increased gas production. They found that a marked improvement occurred in 56% of IBS and 60% of FC patients (patients did not fulfill IBS criteria and were defined as functional complaints) following restriction of these sugars, and the number of symptoms decreased significantly in both groups and correlated with the improvement index. They suggested that dietary restriction of the offending sugars should be implemented before drug therapy (Goldstein et al.). In the British Society of Gastroenterology guidelines for the management of IBS in 2000 (Jones et al.), it was stated that typical IBS symptoms, such as bloating, cramps, and diarrhea, occurred due to the ingestion of osmotically active and poorly absorbed fermentable carbohydrates.

In 2005, Spiller described potential future therapies and the effectiveness of excluding dairy and wheat products (Spiller). In 2005, Gibson and Shepherd at Monash University proposed the FODMAP hypothesis. They explained this theory in Crohn's disease (Gibson and Shepherd) as follows: the subsequent rapid fermentation of FODMAPs in the distal small and proximal large intestine induces conditions in the bowel that lead to increased intestinal permeability, which is a predisposing factor to the development of Crohn's disease. They presented evidence that supported this hypothesis, which included the increasing intake of FODMAPs in Western societies, the association of increased intake of sugars in the development of Crohn's disease, and the previously documented effects of the ingestion of excessive FODMAPs on the bowel. In 2006, Madsen et al. reported that a mixture of fructose and sorbitol

accelerated the transit time in the small intestine, resulting in diarrhea as well as increased gas production in the large intestine (Madsen et al.). In 2007, a group at Monash University reported the results of a pilot study on patients without a colon in which they found that the patients who tested positive on the lactulose hydrogen breath test might have carbohydrate malabsorption and a low-FODMAP diet could decrease the frequency of defecation (Croagh et al.). In a 2008 report from Monash University, the incidence of IBS symptoms was stated as being 14% in patients who drank glucose, but it was 70% for lactose intake, 77% for fructan intake, and 79% for a mixed intake of lactose and fructan (Shepherd et al.). All IBS symptoms were significantly greater in patients taking fructose, fructan, or a combination of the two foods, in comparison to those consuming glucose. Moreover, the aggravation of symptoms was dose-dependent and increased with multiple intakes.

A noteworthy article from the US

Should malabsorption syndromes, such as lactose intolerance, be excluded from IBS? In 2009 Rangnekar and Chey made the following comment:

> Recent studies suggesting that coeliac disease, microscopic colitis, and small intestinal bacterial overgrowth can masquerade as IBS should teach us that this condition likely represents a number of different diseases that happen to present with similar symptoms. As our understanding of the physiologic abnormalities that underlie the different disease subgroups that constitute IBS improves, so too will diagnostic testing strategies and, ultimately, our ability to choose the most appropriate therapy for an individual patient. However, until such a time, we are left with symptoms as the primary guide to the management of IBS patients. Older work tended to focus on lactose maldigestion in IBS patients. Whether or not lactose intolerance is more prevalent in IBS patients may not be the question of greatest clinical relevance. To clarify, the clinical consequences of lactose intolerance may be more profound in IBS patients than in healthy individuals. It seems reasonable to hypothesize that any circumstance that leads to a large load of unabsorbed, fermentable substrates in the colon could exacerbate IBS, a condition hallmarked by abnormalities in motility and visceral sensation. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols or FODMAPs are by definition highly fermentable and poorly absorbed foods. Restricting dietary FODMAP intake could benefit IBS patients through a number of mechanisms (Rangnekar and Chey).

In 2009, researchers from Monash University examined the effectiveness of a low-FODMAP diet on inflammatory bowel disease (Gearry et al.). Overall abdominal symptoms, abdominal pain, bloating, wind, and diarrhea improved in patients with Crohn's disease and ulcerative colitis, but constipation did not. Truly, does a high-FODMAP diet increase the moisture content in the small intestine? Also, can low-FODMAP diet reduce water content? To answer these problems, in 2010, researchers at Monash University investigated 10 volunteers with an enforced ileostomy, which had been created because of ulcerative colitis in 8 and Crohn's disease in 2 without a history of small bowel issues (Barrett et al.). In this study, the low-FODMAP diet contained 5.7g of total FODMAPs (excess fructose: 0g; lactose: 4.1g; sorbitol and mannitol: 0g; fructan: 1.3g; galactans: 0.3g) and the high-FODMAP diet contained 99.3g of total FODMAPS (excess fructose: 37.6g; lactose: 25.1g; sorbitol: 3.1g; mannitol: 0.1g; fructan: 26.9g; galactans: 0.8g). As a result, the volume of ileal effluent was significantly increased by the high-FODMAP diet and decreased by the low-FODMAP diet. Namely, they certified that FODMAPs increase the delivery of water and fermentable substrates to the proximal colon. In 2010, the same research group reported a relationship between FODMAPS and breath hydrogen volume (Ong et al.). 15 healthy subjects and 15 with IBS (Rome III criteria) were investigated in a single-blind, crossover intervention trial which involved consuming diets that were either low or high in FODMAPs for 2 days. Food and gastrointestinal symptom diaries were kept, and breath samples collected hourly for 14 hours on day 2 of each diet. As a result, higher levels of breath hydrogen were produced in IBS patients. Breath methane, which was produced by 10 subjects within each group, was reduced with the high-FODMAP intake in healthy subjects, but this was not different in patients with IBS. They concluded that dietary FODMAPs induce greater prolonged hydrogen production in the intestine in patients with IBS. This then influences the amount of methane produced, and induces the gastrointestinal and systemic symptoms experienced by patients with IBS.

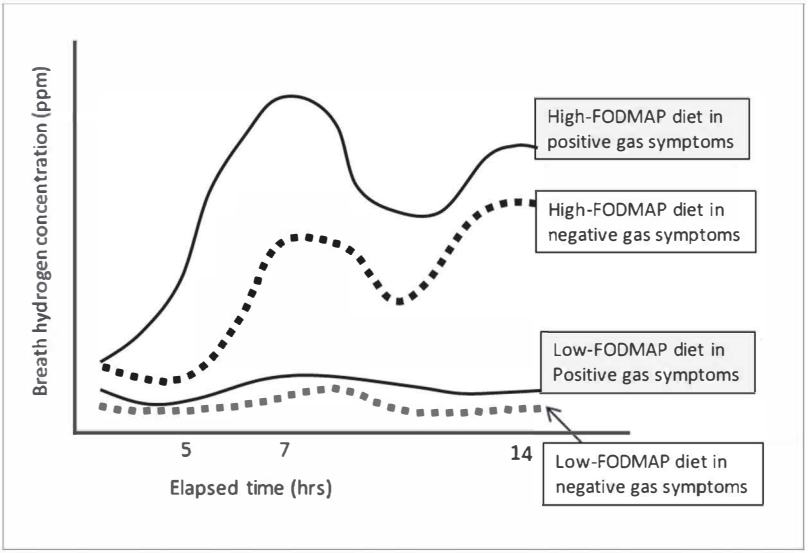


Figure 19: *Breath hydrogen increased with a high-FODMAP diet (total amount: 48.1g), but it did not increase with a low-FODMAP diet (total amount: 8.3g) (Ong et al.: 2010). This study seems to show positive results at first sight, but it also provided a new challenge. Namely, that volunteers were asymptomatic despite discharging a significant amount of exhaled hydrogen with high-FODMAP diet. This suggests the involvement of colon hypersensitivity and/or a discrepancy between breath hydrogen volume and colonic pressure.*

Also, in that year, under the hypothesis that diarrhea in enteral nutrition patients is due to high FODMAPs, researchers from Monash University (Halmos et al.) provided low-FODMAP and high-FODMAP diets to patients with ileostomy and the extracted intestinal fluid was compared. They found that a low-FODMAP diet reduced the amount of intestinal fluid by 20% compared with the high-FODMAP diet. Moreover, they suggested that the reason that 61% of patients under tube-feeding developed diarrhea was due to the high-FODMAP contents in the products (amount of FODMAPs in tube-feeding nutrient in Australia is 10.8-36.5g).

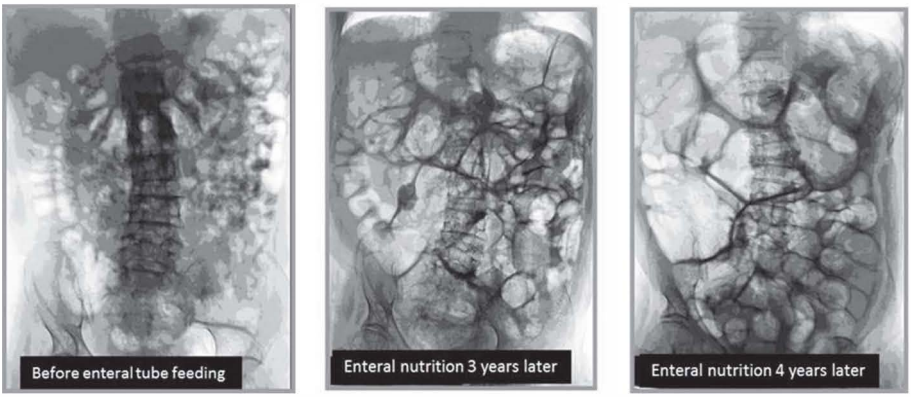


Figure 20: *Increase in gas through enteral tube feeding (Uno's personal data). This problem is even more serious in Japan. Enteral tube-feeding nutrients in Japan intentionally contains a large amount of FODMAPs. The longer the enteral nutrition is administered, the more likely that an increase in intestinal gas will be confirmed.*

In 2011, researchers at King's College London reported the results on a study into the effectiveness of low-FODMAP diet in patients with IBS (Staudacher et al.). The diet was compared with a standard diet based on the UK National Institute for Health and Clinical Excellence (NICE) guidelines. As a result, more patients in the low-FODMAP group were satisfied with their symptom response (76%) compared to the standard group (54%). Composite symptom score data showed better overall symptom response in the low-FODMAP group (86%) compared to the standard group (49%). In that year, there was a report from Korea about gas production in IBS (Youn et al.). A lactulose hydrogen breath test (LHBT) and abdominal X-ray were performed on 84 IBS patients, 24 functional bowel disorder patients, and 25 healthy people to measure the amount of gas produced. They found that LHBT shows a correlation between gas quantity and symptoms. In 2012, a review by Beth Israel Medical Center described the benefit of a low-FODMAP diet for IBS patients (Magge et al.). Additionally, they pointed out some problems: most foods do not list their FODMAP content, and the cutoff levels for FODMAPs content are not clearly defined. In same year, UK researchers found a reduction in concentration and proportion of luminal *Bifidobacterium* after 4 weeks of fermentable carbohydrate restriction

(Staudacher et al.). In 2013, researchers from Monash University examined an effective diet therapy for non-coeliac gluten sensitivity (NCGS) (Biesiekierski et al.). They performed a double-blind cross-over trial of 37 subjects with NCGS and IBS, but not coeliac disease. Subjects were randomly assigned to groups given a 2-week diet of reduced FODMAPs, and were then placed on high-gluten (16g of gluten/day), low-gluten (2g of gluten/day and 14g of whey protein/day), or control (16g of whey protein/day) diets for 1 week. As a result, in all subjects, gastrointestinal symptoms consistently and significantly improved with a reduced FODMAP intake. However, when gluten or whey protein was included in the diet, the symptoms of the subjects worsened significantly to the same extent. Gluten-specific effects were observed in only 8% of subjects. In that same year, a New Zealand group tested a low-FODMAP diet on 90 IBS patients and found 75.6% of patients had relief of symptoms (De Roest et al.). Also, in that year, the Rome foundation group certified the low-FODMAP diet as the most effective and safe treatment for IBS (Simrén et al.). They also expressed doubts about breath hydrogen tests in the diagnosis of SIBO.

2014

The countries publishing about the low-FODMAP diet were limited to Australia, the UK, and the US until 2012. However, New Zealand and Switzerland joined this list in 2013. Spain, India, the Netherlands, Germany, Denmark, Belgium, Singapore, Norway, and South Korea were then added in 2014. In 2014, the US reported that intestinal flora in humans can be changed within a few days when the diet is modified (David et al.).

Researchers at Monash University examined the difference in symptoms between a low-FODMAP diet and a typical Australian diet over 21 days in both patients with IBS and healthy individuals (Halmos et al.). They concluded that a low-FODMAPs diet effectively reduced functional gastrointestinal symptoms. They suggested that a low-FODMAP diet would be useful as a first-line therapy for IBS. What is noteworthy about this study is the amount of total FODMAPs. They specified that one meal should contain less than 0.5g of FODMAPs.

A study comparing a low-FODMAP diet and a probiotic capsule (lactic acid bacteria) took place in Denmark (Pedersen et al.). Two *Lactobacillus rhamnosus* capsules daily (containing 6 billion bacteria/capsule) were

given to 120 IBS patients. The authors concluded that both a low-FODMAP diet and probiotics were effective. Researchers from the University of Nottingham reported the correlation between the amount of gas in the large intestine and hydrogen in breath after consuming fructose and fructan (inulin) (Murray et al.). After consuming 40g of fructose, the gas in the large intestine increased along with the amount of exhaled hydrogen; however, gas in the large intestine continued to increase for up to 350 minutes, even after hydrogen and small bowel water content (SBWC) had decreased. The gases in both the large and small bowel increased up to 350 minutes after taking 40g of fructan (inulin).

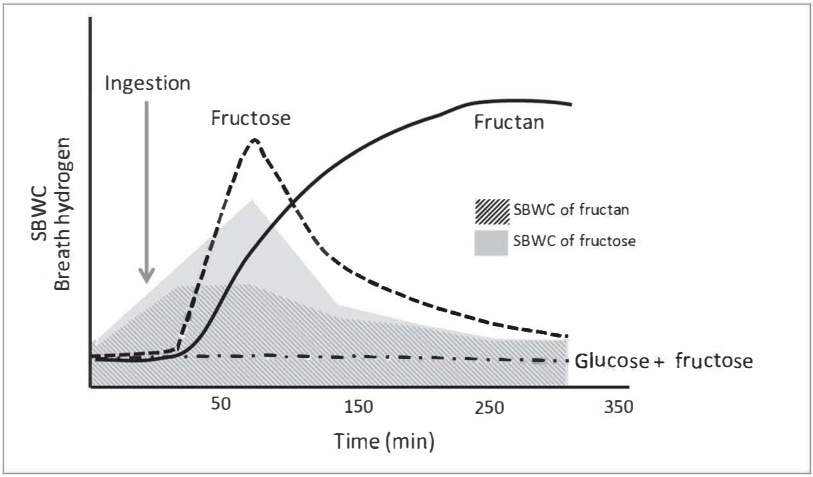


Figure 21: *Effects of fructan and fructose (Murray et al.). SBWC: small bowel water content. The results of this study showed the following:*

1) When fructose and glucose are ingested together, no gas is produced.

2) Fructose produces gas in a shorter time than fructan.

3) Fructan may create gas within 4 or 5 hours.

4) In fructan, the water content increase is lower than the increase in gas.

5) The effect of the increase of gas and water contents caused by fructose disappears within 3 hours.

Researchers from Norway estimated the water volume of the small intestine using (magnetic resonance imaging) MRI (Undseth et al.). Patients with IBS, according to the Rome III criteria, and healthy controls underwent a lactulose challenge test. Using MRI, they measured both SBWC and the distension (diameter) of the distal ileum and the colon in a fasting state and then 1 hour after the consumption of 10g of lactulose. As a result, SBWC increased more in the patient group compared to the control group. The postprandial diameter of the terminal ileum was larger in patients with IBS and the postprandial diameter of the ascending colon was smaller in patients with IBS-D. The symptoms were not correlated with a change in SBWC, nor with the diameters of the terminal ileum or the colon.

2015

In 2015, new reports from Italy, Mexico, Canada, and China were added. The results of measuring intestinal pH of IBS patients using SmartPill were published. As a result, it was discovered that IBS patients have significantly lower pH than the healthy controls. Their colonic pH levels correlated positively with colon transit time (CTT) and the severity of the IBS symptoms (Ringel-Kulka et al.).

The results of a systematic review and meta-analysis of a low-FODMAP diet by the University of Sydney were published in 2015 (Marsh et al.). Six RCTs and 16 non-randomized interventions were included in the analysis. There was a significant decrease in IBS symptom severity scoring (SSS) scores for those individuals on a low-FODMAP diet in both the RCTs and non-randomized interventions. In addition, there was a significant improvement in the IBS quality of life (QOL) score for the RCTs and for the non-randomized interventions. Further, following a low-FODMAP diet was found to significantly reduce symptom severity for abdominal pain, bloating, and overall symptoms in the RCTs. Similar findings were observed in the non-randomized interventions. The researchers supported the efficacy of a low-FODMAP diet for the treatment of functional gastrointestinal symptoms. Researchers in the US reported results showing a relationship between clinical response to a low-FODMAP diet and gut microbiome biomarkers in children (7–17 years) with Rome III-defined IBS. The low-FODMAP diet contained 0.15g/kg/day (maximum 9g/day) of FODMAPs (Chumpitazi et al.). The typical American childhood diet contains 0.7g/kg/day (maximum 50g/day) of FODMAPs.

Microbiome composition and metabolic capacity were investigated using DNA extraction, bacterial 16S rRNA gene amplification, and 454 sequencing of 16S rRNA gene libraries. As a result, they revealed that the bacterial flora involved in F●DMAP fermentation was affected by a low-F●DMAP diet in a short period of time.

Patients receiving enteral nutrition (EN) often have unexplained diarrhea and constipation. South Korean researchers focused on the EN ingredients and examined changes in defecation due to the amount of F●DMAPs (Yoon et al.). After the 14-day intervention period, diarrhea significantly improved in the low-F●DMAP group compared to the moderate- and high-F●DMAP groups. They concluded that a low-F●DMAP EN may improve diarrhea, leading to improved nutritional status and facilitating prompt recovery from illness. Researchers from Monash University reported the results of studies on the adverse effects of intestinal environment due to long-term continuation of a low-F●DMAP diet (Halmos et al.). In this study, a typical Australian diet (F●DMAPs: 23.7g/day) and a low-F●DMAP diet (F●DMAPs: 3.●5g/day) were compared. As a result, the low-F●DMAP diet was associated with higher fecal pH compared with the Australian diet. The low-F●DMAP diet reduced total bacterial abundance and the typical Australian diet increased the relative abundance for butyrate-producing Clostridium cluster XIVa and mucus-associated Akkermansia muciniphila, while reducing Ruminococcus torques.

●ne-to-one guidance with a nutritionist is the principle means of learning how to implement a low-F●DMAP diet, but collective guidance may be also effective with regard to proving a general introduction. London-based researchers reported that dietitian-led F●DMAP group education is clinically effective (Whigham et al.). In previous studies, IBS was believed to be attributed to stress. However, researchers in Belgium and UK stated that fermentable carbohydrates can have a detrimental effect on IBS and this has led to the introduction of the low-F●DMAP diet. They declared that the belief that "IBS is a largely psychological condition is no longer tenable" (Corsetti and Whorwell).

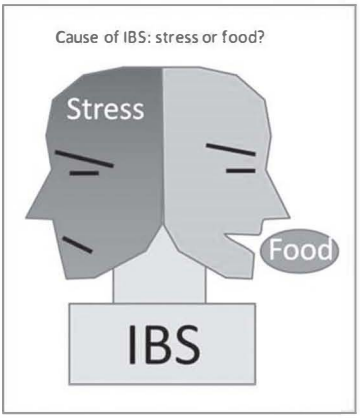


Figure 22

2016

In 2016, reports on low-FODMAP diets were published in Finland, Portugal, Hungary, Singapore, Japan (Uno Y), Netherlands, Austria, and Slovakia.

Researchers from King's College London pointed out the contradiction between the probiotic theory for IBS and the low-FODMAP diet theory (Staudacher et al.) because probiotic supplementation trials suggest intentional modulation of the gastrointestinal microbiota may be effective in treating IBS. In contrast, the low-FODMAP diet shows clinical efficacy but markedly reduces gastrointestinal microbiota. They suggested the possibility of combination treatment. Researchers from Monash University investigated the change in fecal microbiota after patients with Crohn's disease followed a low-FODMAP diet (Halmos et al.: 2015). After consuming a low-FODMAP diet (total FODMAPs: 3.05g), the patterns of change in the measured bacteria were almost identical to those observed in the IBS/healthy cohort who underwent the same intervention. Researchers from Denmark investigated patient-reported outcomes from and their adherence to a low-FODMAP diet among patients suffering from IBS and inflammatory bowel disease (IBD) (Maagaard et al.). 180 patients were included: 131 (73%) IBS and 49 (27%) IBD patients. The proportion of patients experiencing full efficacy tended to be greater in the IBD group than in the IBS group (42% vs 29%). The proportion of patients having

normal stools increased by 41% in the IBS group and 66% in the IBD group. One-third of patients adhered to the diet and high adherence was associated with longer duration of dietary course. Wheat, dairy products, and onions were the foods most often not reintroduced by patients.

Researchers in Finland noticed a relationship between IBS and rye bread (Laatikainen et al.). They then investigated symptomatic differences in IBS patients after ingestion of normal rye bread (fructans: 1.1g/100g, mannitol: 0.3g/100g) or low-FODMAP rye bread (fructans: 0.3g/100g, mannitol: 0.1g/100g). Symptoms were measured using IBS-SSS and visual analogue scale (VAS) assessments of individual symptoms. Colonic fermentation was measured using the breath hydrogen test and dietary intake by food diaries. Breath hydrogen values were significantly lower during the period of low-FODMAP bread consumption. Many signs of IBS—such as, flatulence, abdominal pain, cramps, and stomach rumbling––were milder on the low-FODMAP rye bread. They concluded that low-FODMAP rye bread helps IBS patients to control their symptoms and reduces gastrointestinal gas accumulation.

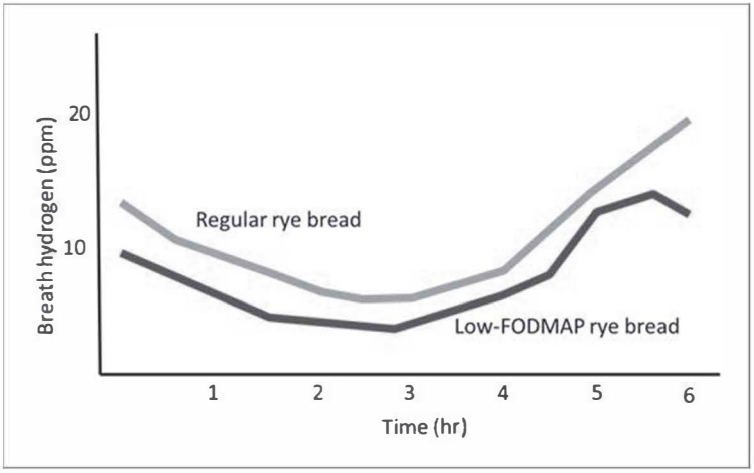


Figure 23: *Effect of low-FODMAP rye bread (Laatikainen et al.)*

Norwegian researchers measured the fecal short chain fatty acids of patients with IBS who consumed a low-FODMAP diet (Valeur et al.). As a result, dietary FODMAP restriction markedly modulated fecal fermentation

in patients with IBS. Saccharolytic fermentation decreased, while proteolytic fermentation increased and this was apparently independent of symptoms.

The Sport Performance Optimization Research Team from Australian and Canadian Sports Institutes investigated 910 athletes to assess behaviors towards self-selected food/ingredient avoidance to minimize gastrointestinal distress (Lis et al.). They found that 85% eliminated at least one FODMAPs food/category, with up to 82.6% reporting symptom improvement. In athletes lactose (86.5%) was most frequently eliminated, followed by galacto-oligosaccharides (23.9%), fructose (23.0%), fructans (6.2%), and polyols (5.4%); this indicated that high-FODMAP foods trigger gastrointestinal symptoms. They concluded that athletes avoid predominantly lactose and, to a lesser extent, other high-FODMAP foods to reduce gastrointestinal distress. A Hungarian researcher (Buzás) was concerned about the increase in fructose intolerance because the consumption of fructose had increased to 16.4kg/year with the increase in consumption of high fructose corn syrup in Hungary. Fructose intolerance increases intestinal motility and sensitivity, promotes biofilm formation, and contributes to the development of gastro-esophageal reflux. Long-term use of fructose fosters the development of dental caries and non-alcoholic steatohepatitis. Its role in carcinogenesis is presently being investigated. He described that the cornerstone of dietary management for fructose intolerance is the individual reduction of fructose intake and the FODMAP diet. In this year, there was also the first publication on a low-FODMAP diet in Japan (Uno and van Velkinburgh). It was theoretically concluded that a low-FODMAP diet would be effective in preventing colon diverticulitis. The results of a meta-analysis on a low-FODMAP diet was published by the University of Sydney (Marsh et al.). In this study, 6 RCTs and 16 non-randomized interventions were included in the analysis, and it was concluded that the meta-analysis supported the effectiveness of a low-FODMAP diet in the treatment of functional gastrointestinal symptoms.

In September 2016, an article on the effectiveness of a low-FODMAP diet was published in Singapore. In September 2016, Korean TV broadcast to the nation that people suffering with IBS should restrict their intake of FODMAPs. At the end of October 2016, a low-FODMAP diet for IBS was released by Reuter's communications.

2017

Not everyone will develop abdominal pain after consuming a high-F●DMAP diet. Is this just the difference in the amount of gas and water in the intestinal tract? ●r is it the influence of built-in hypersensitivity? In order to investigate this problem, researchers from the University of Nottingham performed a randomized trial with MRI analysis to investigate the correlations between symptoms and changes in small bowel and large bowel contents after oral challenge (Major et al.). As a result, symptoms peaked sooner after fructose than inulin. Fructose increased small-bowel water content in both patients and controls, whereas inulin increased colonic volume and gas in both. Fructose and inulin increased breath hydrogen levels; however, fructose produced a swifter increase than inulin. Controls had lower symptom scores during the period after consumption than patients with ■BS, despite similar M■RI parameters and breath hydrogen responses. Peak symptom intensity correlated with peak colonic gas in patients who reached the symptom threshold after inulin intake. Changes in MRI features and peak breath hydrogen levels were similar in patients who did and did not reach the symptom threshold. They concluded that colonic hypersensitivity to distension, rather than excessive gas production, produces carbohydrate-related symptoms in patients with ■BS.

Researchers in Canada compared the effects of low-F●DMAP and high-F●DMAP diets on symptoms, the metabolome, and the microbiome of patients with ■BS (McIntosh et al.). They performed a controlled, single blind study of patients with ■BS (Rome III criteria) randomized to a low-F●DMAP diet (n = 2●) or high-F●DMAP diet (n = 2●) for 3 weeks. Symptoms were assessed using ■BS-SSS. The metabolome was evaluated using the lactulose breath test (LBT) and metabolic profiling in urine using mass spectrometry. Stool microbiota composition was analyzed by 16S rRNA gene profiling. The results concerning the alleviation of symptoms and hydrogen breath test did not differ from previous reports. The metabolic profiling of urine showed groups of patients with ■BS differed significantly after the diet ($p < 0.01$), with three metabolites (histamine, p-hydroxybenzoic acid, and azelaic acid) primarily responsible for the differences between the two groups. Histamine, a measure of immune activation, was reduced eightfold in the low-F●DMAP group ($p < 0.05$). The low-F●DMAP diet increased Actinobacteria richness and diversity, and the high-F●DMAP diet decreased the relative abundance of

bacteria involved in gas consumption. Food intolerance/malabsorption is caused by food ingredients, such as carbohydrates (mainly lactose and fructose), proteins (gluten), and biogenic amines (histamine), which cause nonspecific gastrointestinal and extra-intestinal symptoms (Schnedl et al.). Furthemore, it has been pointed out that mast cells are involved in colon hypersensitivity in IBS. This study from Canada presents an important discovery, as it suggests the possibility that a low-FODMAP diet may suppress histamine secretion.

Consumption of a low-FODMAP diet can change intestinal flora. Does this lead to worse conditions in the intestine? Conversely, is high-FODMAP consumption better for the intestine? To investigate this problem, researchers from Norway examined the effects of a blinded low-FODMAP vs high-fructo-oligosaccharides (FOS) diet on symptoms, immune activation, gut microbiota composition, and short-chain fatty acids (SCFAs) (Hustoft et al.). Cytokines (interleukin (IL)-6, IL-8, and tumor necrosis factor alpha) were analyzed in blood samples to study immune activation. Serum levels of pro-inflammatory IL-6 and IL-8, as well as levels of fecal bacteria (Actinobacteria, Bifidobacterium, and Faecalibacterium prausnitzii), total SCFAs, and n-butyric acid, decreased significantly on the low-FODMAP diet in comparison to the baseline. Ten days of FOS supplementation increased the levels of these bacteria, whereas the levels of cytokines and SCFAs remained unchanged.

Researchers from Monash University reported that, a low-FODMAP diet could be used to improve symptoms in women who suffer from concurrent endometriosis and IBS (Moore et al.). Of the 160 women who met the Rome III criteria for IBS, 36% had concurrent endometriosis. The presence of dyspareunia, referred pain (due to endometriosis), bowel symptoms exacerbated by menstruation, and a family history of endometriosis were associated with concurrent endometriosis. 72% of these women reported a > 50% improvement in bowel symptoms after 4 weeks on a low-FODMAP diet.

Three reports were published in 2017 on the low-FODMAP diet and IBD. UK researchers reported that ulcerative colitis and Crohn's disease worsen with the consumption of 12g of fructan per day (Cox et al.). Researchers from Denmark reported that 6 weeks on a low-FODMAP diet (2g/day) reduced IBS-like symptoms and increased the quality of life in patients with IBD in remission (Pedersen et al.). Researchers in China reported the

results of a meta-analysis and systematic review on the effectiveness of a low-F●DMAP diet for IBD (ulcerative colitis, Crohn's disease) (Zhan et al.). The results of which were an improvement in incontinence and diarrhea, abdominal pain, fatigue, and nausea. They concluded that the present meta-analysis offers proof that a low-F●DMAP diet is beneficial at reducing gastrointestinal symptoms in patients with quiescent ■BD.

Fibromyalgia is a chronic, rheumatic disease characterized by widespread myofascial pain of unknown etiology, which has a major impact on quality of life. The available pharmacotherapy for fibromyalgia is only marginally effective. Researchers from Portugal suggested the possibility that a low-F●DMAP diet (total F●DMAPs: 2.5g/day) could be effective for fibromyalgia (Marum et al.).

Since a low-F●DMAP diet basically restricts the types of meal, there was concern about the deficiency of vitamins and so on over the long term. Researchers in Italy proved that vitamin D and folic acid deficiency do not occur when following a low-F●DMAP diet for 3 months (Vincenzi et al.).

A low-F●DMAP diet for ■BS has mainly been studied from youth to middle age. However, the effectiveness of a low-F●DMAP diet for ■BS in the elderly had not yet been investigated. Therefore, researchers from New Zealand investigated the relationship between gastrointestinal symptoms and F●DMAPs in aged care residents (Nanayakkara et al.). As a result, it was found that lactose from milk and milk-based desserts was the biggest F●DMAP contributor (16g/day) and a significant relationship was found between total F●DMAP intake and diarrhea.

2018

Non-coeliac gluten sensitivity is characterized by a symptom improvement after gluten withdrawal in the absence of coeliac disease. These people have symptom relief with a gluten-free diet but in most gluten-free diets (rice based) fructan is also restricted. Therefore, it was not known whether the effect of a gluten-free diet was due to gluten or fructan. Regarding this problem, researchers from Norway investigated a double-blind crossover challenge of 59 individuals on a self-imposed gluten-free diet (Skodje et al.). They found fructan induced symptoms. In other words, the effects of a gluten-free diet that does not contain wheat may actually be due to the fact that it is free of fructans.

Researchers in Germany reported the results of a systematic review and meta-analysis on the usefulness of low-FODMAP diet for IBS (Schumann et al.). In this study, nine RCTs with a total of 596 subjects were included. Three RCTs compared a low-FODMAP diet with a habitual diet, two RCTs provided all meals and compared low-FODMAP diet with a Western diet, one RCT each compared a low-FODMAP diet with a diet high in FODMAPs or a sham diet, and two RCTs compared their diets with other diet recommendations for IBS. Safety, quality of life, anxiety, depression, and the effect on gut microbiota were defined as secondary outcomes. As a result, the meta-analysis revealed significant group differences for the low-FODMAP diet compared with other diets with regard to gastrointestinal symptoms ($p = 0.0001$), abdominal pain ($p = 0.008$), and health-related quality of life ($p = 0.007$). Three studies reported a significant reduction in luminal bifidobacteria after the low-FODMAP diet. Adverse events were only assessed in three RCTs and no intervention-related adverse events were reported. They concluded that there was evidence of the short-term efficacy and safety of a low-FODMAP diet in patients with IBS.

Up until now, the amount of gas produced by fermentation of high-FODMAP foods has been evaluated based on the amount of hydrogen produced in the breath. Breath hydrogen concentration was considered an indirect expression of the amount of intestinal gas; thus, it has been considered to be an indicator of colon pressure as well. Finnish researchers investigated the degree of symptoms, the amount of exhaled hydrogen, and their relationship with colon pressure in patients with IBS (Pirkola et al.). The SmartPill was used to measure the internal pressure of the colon. SmartPill is an oral capsule that can measure temperature, pH, and pressure. Patients were investigated for 11 consecutive hours as they ate either low-FODMAP rye bread (FODMAPs: 1.2g/day) or regular rye bread (FODMAPs: 3.52g/day). In this study, intracolonic pressure correlated with IBS symptom severity, and hydrogen excretion did not correlate with intracolonic pressure. They suggested that any dietary or physio-anatomic factors that increase pressure in the gut might worsen symptoms in IBS. This study presented the important finding that breath hydrogen content does not reflect colonic pressure. Therefore, the following is suggested:

1) Even when the luminal gas volume is small, abdominal pain may be caused when high pressure is presented by the structure of the lumen.

2) Even if the luminal gas volume is large, abdominal pain may not occur if there is no tension on the luminal wall.

8. Pathogenesis of IBS and a high-FODMAP diet

IBS and a high-FODMAP diet

In this chapter, I (Uno) consider the cause of IBS and the involvement of high-FODMAPs.

I had the following doubts:

- Why does IBS have a constipation type and diarrhea type, and other alternatives?
- Why do IBS patients develop symptoms after a meal?
- Why does a high-FODMAP diet cause symptoms in IBS?
- Why are there people who do not have abdominal pain, even with a large amount of colonic gas?
- Why are there people with IBS who have abdominal pain without colonic gas?
- Why do IBS symptoms occur with long, intensive bouts of exercise?
- Why does colonic ischemia lead to IBS symptoms?
- Are there any concerns other than abdominal symptoms with a high-FODMAP diet?

If an expert on a low-FODMAP diet cannot answer these questions, then maybe a low-FODMAP diet may not much differ from the historical "detox diet". Therefore, the authors considered rational hypotheses.

The history of functional bowel disorders

The history of functional bowel disorders might have origins from the concept of "intestinal autointoxication" from ancient Egypt and ancient Greece. The concept of disease-causing toxins arising from the bowel was called "intestinal autointoxication" and, in 16th century BC, Egyptians practiced colon cleansing. At that time, physicians believed that feces was absorbed into the circulation and that it was responsible for producing

fever and pus (Muller-Lissner et al., Sullivan-Fowler). The Greeks also believed that residue from the incomplete digestion of food resulted in it ascending to the head and causing disease (Brown and Sonnenberg, Chen). Hippocrates viewed autointoxication as a major etiologic factor of disease. This idea was also adopted by Galen, who was from the Roman Empire (Ernst). The cure seemed all too obvious: to minimize the threat of autointoxication, the contact time of the toxic material in the intestines had to be shortened. For that purpose, laxatives and enemas were used. During the 19th century, the theory of autointoxication represented the ruling doctrine of medicine (Ernst). People from the Victorian era believed that the cause of disease was "ptomaine" made by the fermentation of rotten content, which lead to death when it entered the blood. Therefore, laxatives and rectal enema became popular in order to prevent constipation. By the late 19th century, markets were flooded with pills and tonics, as well as enema devices and practitioners of abdominal massage, which all aimed at ridding the colon of its contents and the patient of his or her money. Evacuation enemas were given for immediate results, and retention enemas offered the additional option of administering therapeutic agents. Anything from honey, wine, and beer to less benign substances, such as urine or tobacco, was used. Therapeutic claims became more daring as "colonic quackery" grew (Ernst). Furthermore, diet concepts related to vegetarianism and cereal products (cornflakes) became popular. Because Pythagoras of ancient Greece had denied meat (cause of rots) eclipses, vegetarianism was called “Pythagoranism” in the 19th century (Gratzer). When toxins invaded the body, it was called "toxaemia" according to autointoxication theory and the intestinal situation that produced the toxinosis was recognized to be “intestinal stasis”. Intestinal stasis referred to a situation in which the stool was stuffed in the intestines due to chronic constipation, but it was not defined by the amount and frequency of bowel movements. Rather, it was a term indicating a malfunction of the bowel situation (Morris et al.).

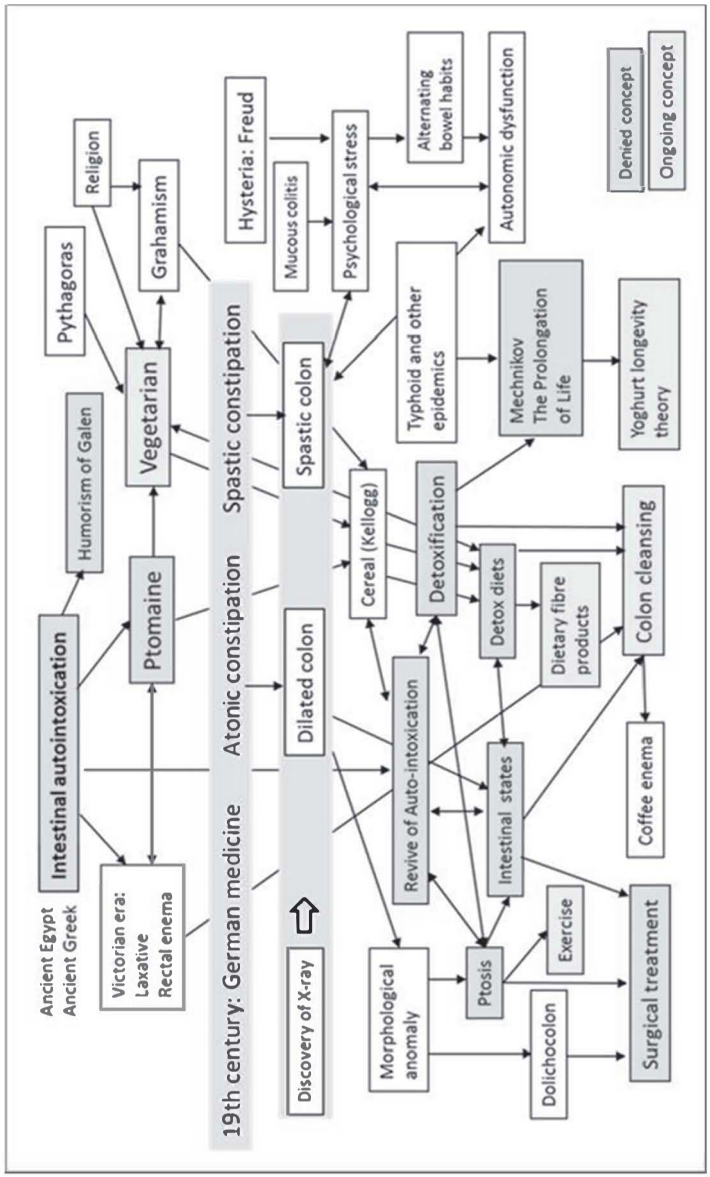


Figure 24: *History of functional bowel disorders*

Traditionally, chronic functional constipation had been classified into two types: atonic constipation or spastic constipation. This classification was used by German researchers (Strassburger, Fleiner et al.) before 1900, which was a time before X-ray was discovered. However, the use of X-rays to diagnose the large intestine revealed that many cases of constipation could not clearly classified into either of these two patterns. Britain's Lane named such constipation as "chronic intestinal stasis". In addition, he thought that chronic intestinal stasis was characterized by colonic ptosis and mobile dilated caecum (Lane).

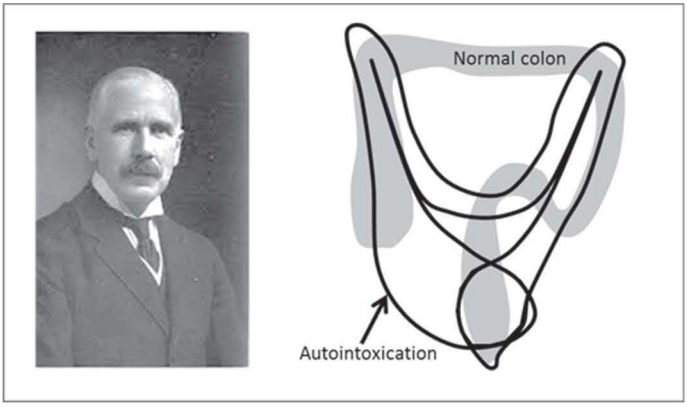


Figure 25: *William Arbuthnot Lane (left); form of colon with autointoxication in Lane's article (right) (Lane: 1908). The expansion of the ascending colon and caecum, as well as the ptosis of transverse colon is characteristic. Lane thought that development of rheumatoid arthritis, gout, gastric ulcer, and so on were due to toxins caused by stool stagnation. Therefore, he performed surgical treatment for large intestines suffering from this condition. Surgical treatment was not effective if the morphological abnormality was not the cause of autointoxication but the result of autointoxication. However, his unique theory of the relationship between colorectal dysfunction and morphological abnormality was a major historical achievement.*

Since enteroptosis mainly develops in women, the relationship with the female body type was studied in detail in the 1910s to 1920s. Martin et al. thought that the reason the stomach and intestines fell was due to a morphological abnormality in the abdominal cavity (Martin et al.). They

suggested that massage and exercise might be useful for the treatment of ptosis.

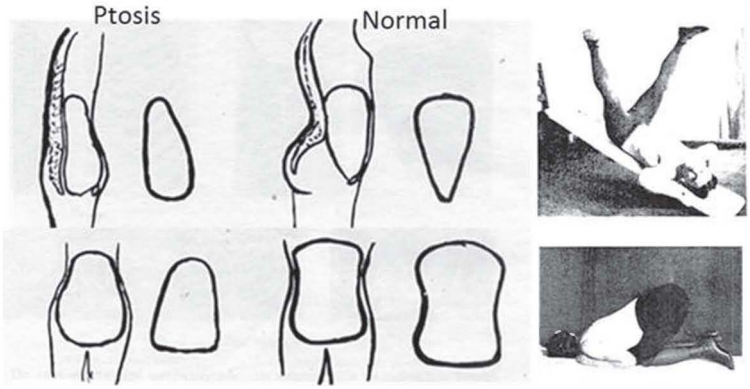


Figure 26: *Martin et al. described that the cause of ptosis was due to differences in the morphology of the abdominal cavity (left). The right image is the exercise they devised (Martin et al.).*

In this way, the theory of autointoxication prevailed not only in the medical world but also as a social phenomenon from the late 19th century to the early 20th century. However, with regard to intestinal autointoxication, the medical doctrine fell into disrepute in the 1920s as scientific advances failed to give support to these theories (Chen and Chen). Nevertheless, autointoxication was replaced by the word "detox", and colon cleaning became popular as a method of eliminating toxins. Meanwhile, specific foods were also believed to eliminate toxins. For example, Mechnikov thought that the ingestion of a large amount of Lactobacillus could eliminate the bacteria that produce toxins. This was the starting point of the current ideas about probiotics and prebiotics.

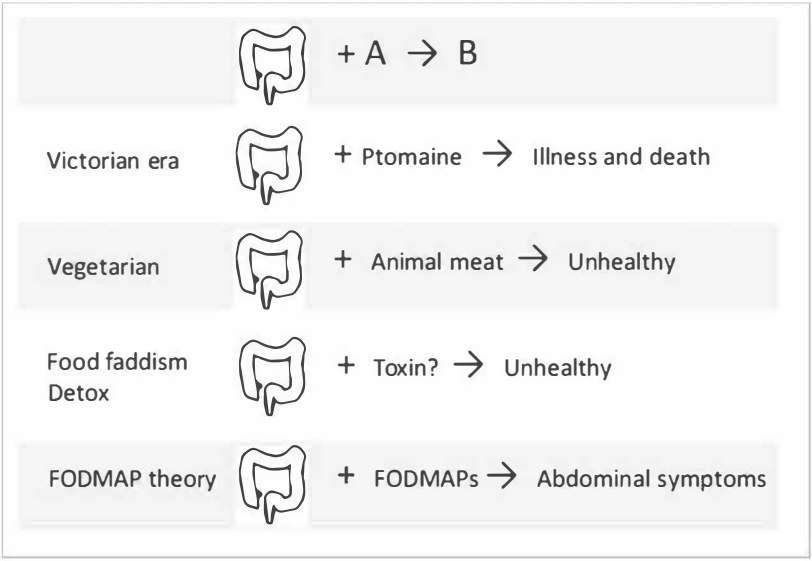


Figure 27: *Various theories. According to the theory so far, B was thought to be due to rotting of the meat. However, in FODMAPs, B is the fermentation of carbohydrates.*

Prebiotics and high-FODMAPs

In Japan, the "good bacterial theory" has been advocated for many years. For this reason, people who are conscious of health improvement or those who are interested in health actively consume yoghurt and fermented foods (rich in oligosaccharides) in order to grow *Bifidobacteria* in the intestine.

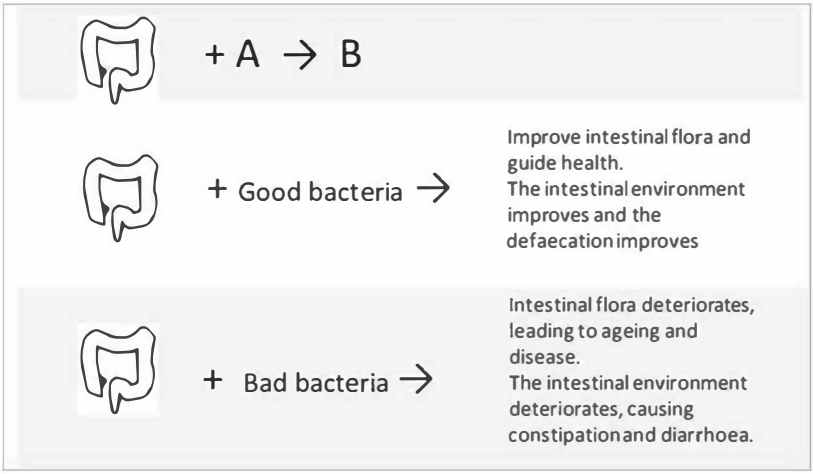


Figure 28: *The theory of "good bacteria and bad bacteria"*

In Japan, promotion of FOSHU (foods for specified health uses) was started in 1991. FOSHU means that the Japanese Ministry of Health, Labor, and Welfare have approved them as "healthy food" (Saito). These foods must contain ingredients that are effective for maintaining health. By 2011, 955 products had gained FOSHU approval.

Health claims	Functional ingredients (Examples)	FOSHU products	Share
Helps maintain good gastrointestinal condition	Oligosaccharides, Lactobacillus, Bifidobacterium, Dietary fibre	351	37%
Good for those who have high serum cholesterol / are concerned about serum triglycerides	Soy protein, Peptides, Dietary fibre, Plant sterol / Stanol (Esters), Diacylglycerol, MLCT	214	22%
Good for those who have high blood glucose levels	Dietary fiber, Albumin, Polyphenols, L-Arabinose	141	15%
Good for those who have high blood pressure	Peptides, Glucosides, Amino acids	120	13%
Helps maintain dental health	Xylitol, Polyols, Tea polyphenols, CPP-ACP	78	7%
Help improve absorption of calcium minerals Good for those who have bones health	CPP, CCM, Oligosaccharides, Heme iron, MBP, Vitamin k_2 Soy isoflavonoids	51	5%

In a low-FODMAP diet, the most important problem is that most prebiotics are high-FODMAPs. Their effective doses are consistent with a high-FODMAP diet. Therefore, Japanese FOSHU is also high-FODMAP.

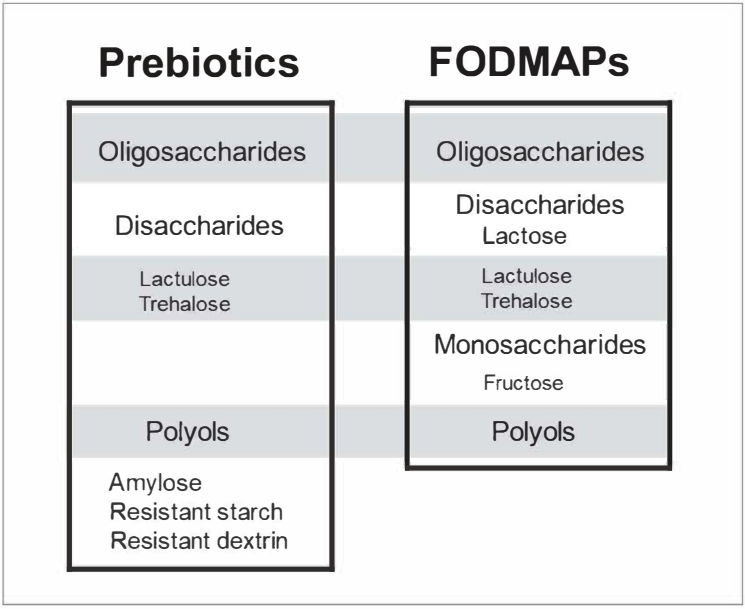


Figure 29: *Japanese probiotics and FODMAPs have almost the same components*

The actual effect was that they increased the frequency of defecation in healthy volunteers without abdominal symptoms. Therefore, IBS may cause symptoms even at doses below the lower limit of the effective dose. FOSHU's accreditation was approved for simple animal experiments and research on a small number of healthy subjects. In particular, oligosaccharides were approved with the ambiguous expression that they would "help maintain good gastrointestinal condition". However, in fact, people with chronic constipation were consuming them. And, due to the effects of a high-FODMAP diet, the amount of water contents in feces increased and some people also had a temporary increase in the number of feces produced. However, in many chronic constipation patients the symptoms were exacerbated by large amounts of gas created. Manufacturers of such fermentable foods advocate that the ingestion of

these fermented foods increases SCFAs, so that intestinal health becomes better, and constipation and diarrhea improve.

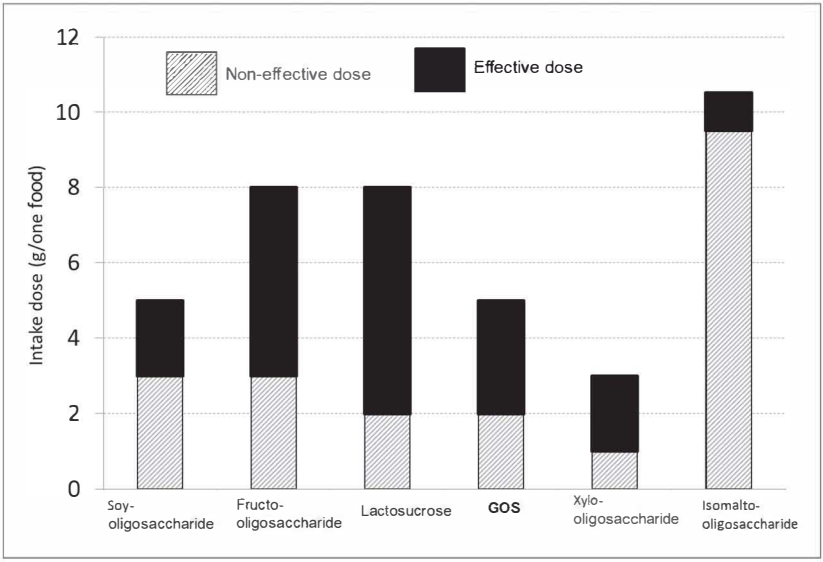


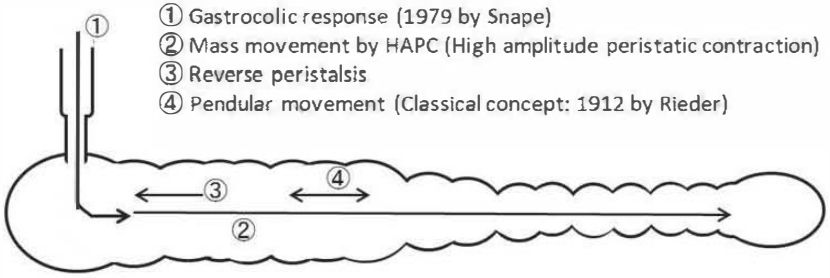
Figure 30: *Recommended doses for some FOSHU*

However, this concept was a hypothesis that had been guided by the fecal culture method, which could detect only limited bacteria and the measurement of SCFAs in feces. Recent metabolomics and metagenomic analyses research results could not demonstrate the usefulness of prebiotics (Verbeke et al.). It was revealed that SCFA increase was not related to health maintenance and, on the contrary, SCFAs in feces was increased in obese children (Payne). The majority of SCFAs (up to 95%) are rapidly absorbed by colonocytes, resulting in decreasing concentrations from the proximal to distal colon. Only a minor fraction of SCFAs (about 5%) are excreted in feces (Topping and Clifton). Namely, the number of SCFAs measured in feces cannot be said to be an accurate evaluation of the total amount of SCFAs. In the elderly the microbiota changes and it has higher levels of Bacteroidetes (Mariat et al.), which is likely to affect SCFA production. Nevertheless, it was reported that SCFAs in the elderly were not different from young people (Andrieux et al.) and it has also been said that elderly people have higher levels than young people (Gill et al.).

Furthermore, it was suggested that the uptake of SCFAs is induced by fiber feeding (pectin) and butyrate and, moreover, it is inhibited by bile acids (Verbeke et al.). Therefore, the "good bacteria theory" or prebiotics hypothesis must revalidate its theory. Surprisingly, in 2018, a study by researchers at the University of Toledo found that mice developed liver cancer when fed on diets fortified with refined soluble fibers, such as inulin (Singh, et al.)

Simplification of intestinal volume, velocity, and pressure

Conventional theory: The motion of the colon is affected by salt concentration and pH variation, as well as their stimulative factors associated with microbiota and cytokines/hormones, and their interaction with colonic epithelial and smooth muscle layers. The CTT is an important variable in constipation and diarrhea. High amplitude peristaltic contractions (HAPC) are believed to be an important factor that can change the CTT.



① Initial term was 'gastrocolic reflex'. Vagal reflex
② Giant migrating contractions (GMC: by Sarna). While most motor activity is segmental and non-propulsive, colonic HAPC can transfer colonic contents over long distances and often precede defecation.
IBS-D The frequency and amplitude of GMCs increase significantly in IBS-D patients.
The amplitude and frequency of GMCs decrease significantly in constipated patients.

Figure 31: *Classical theory of colon motility (Sarna)*

However, in the physiology of conventional colorectal movement, many factors are involved, but almost all act as the accelerator or brake. So, then what is the origin of the driving force? The only big movement is HAPC, and as a result the defecation process progresses. However, if it is the contractile force of the intestinal tract itself, is the muscular layer of the intestinal tract then too thin? There is no doubt that the force of the smooth

muscle of the large intestine may affect surface tension and convulsions. The contractile force of the smooth muscle in the colon does not move the contents, but contents may move due to some physical action. Even in that case, the intestinal tract contracts due to the surface tension. This phenomenon occurs almost at the same time, so it is as if the substance had migrated due to the muscle contraction of the intestinal tract. Also, other than the surface tension, smooth muscle has the ability to spasm. Spasms in the smooth muscle of the lumen wall act to reduce the diameter of the lumen and physically influence the velocity of the fluid and the pressure of the lumen. For example, in a convulsive lumen the internal diameter decreases and, therefore, the passage rate increases. This phenomenon may be misunderstood and incorrectly interpreted as the direct movement of the convulsions causing the contents to move faster.

Intraluminal movement by Bernoulli's principle

Starting in 2016, I (Uno Y) adapted the flow dynamics according to the Bernoulli principle to the basic movement of the colon (Uno: 2016, 2017, 2018).

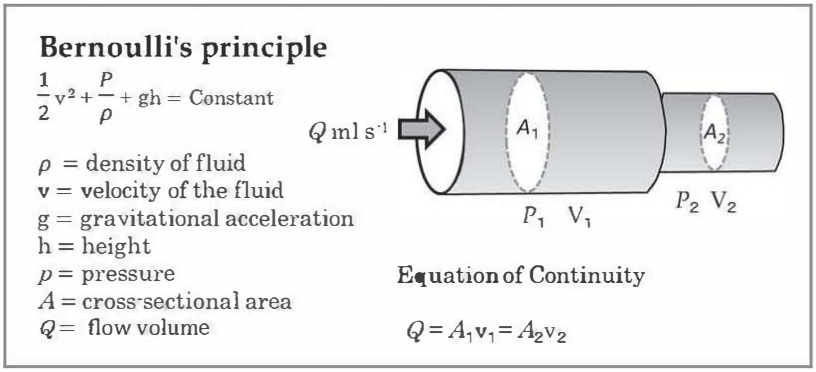


Figure 32: *Bernoulli's principle (Uno: 2016, 2017, 2018)*

It is possible that HAPC is not only a continuous conduction of smooth muscle contraction but that it is also a flow dynamic pressure transfer phenomenon. That is because pressure, velocity, gravity, inflow volume, and caliber changes in the continuous lumen are all variables of Bernoulli's principle, and equations of continuity.

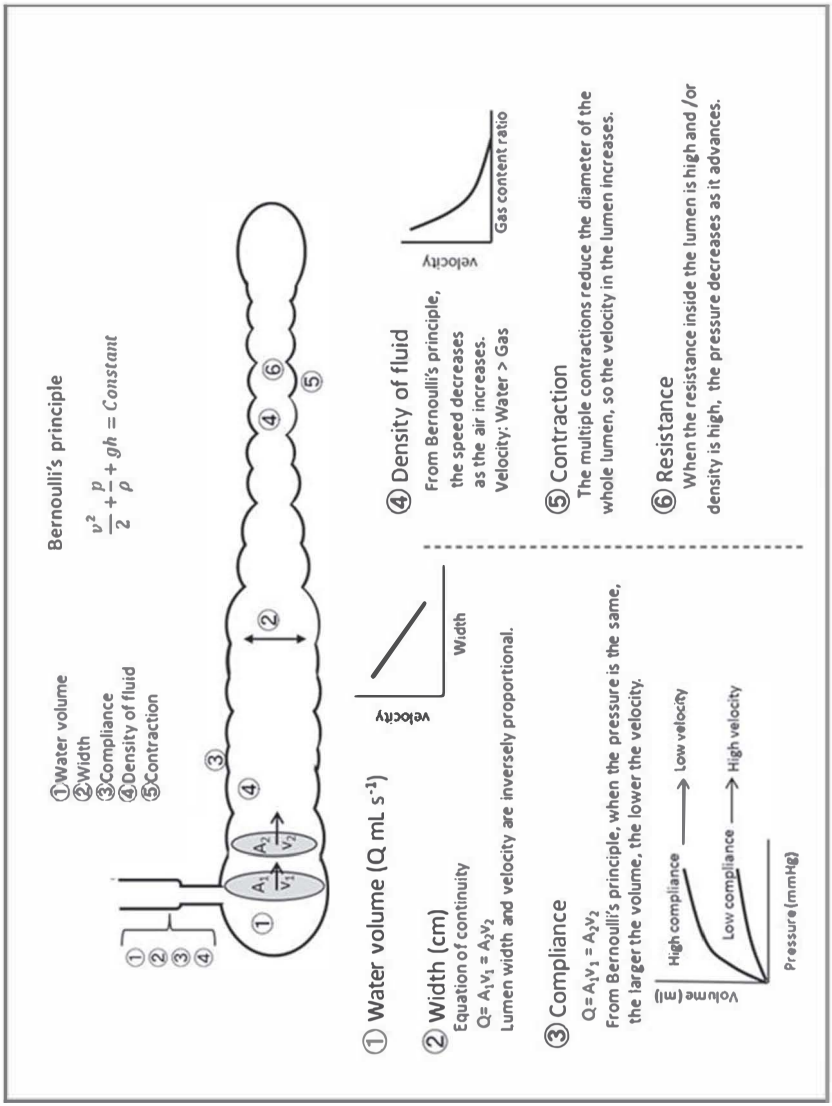


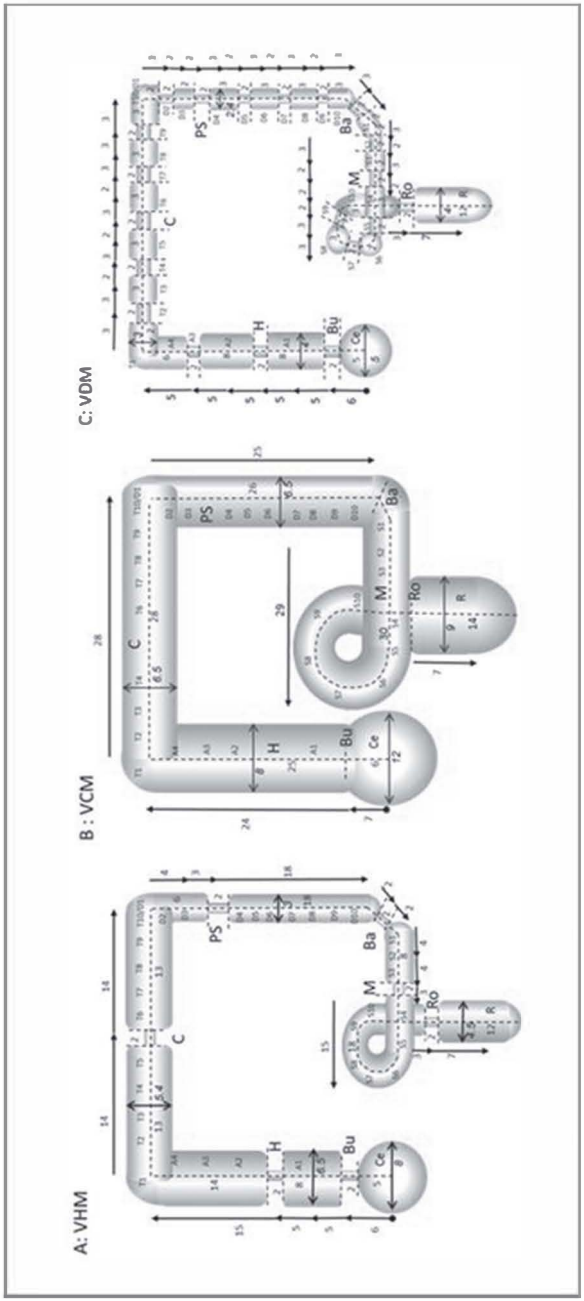
Figure 33: *Colonic physiology by flow dynamics (Uno's theory)*

Colonic transit time and pressure based on Bernoulli's principle: summary and extract of a discussion of Uno's research (Uno: 2018).

The empty colon has no motor activity (Costa et al.). Myogenic control is exerted by the oscillation of the smooth muscle membrane that occurs by stretching the smooth muscle (Sana). The degree of myogenic control can vary independently along the length and circumference of the gut wall (Sana). Contractions that strongly occlude the lumen and propagate are effective in producing rapid propulsion in the direction of propagation of the contraction (Sana). Such movements may occur in a narrow lumen with contraction. However, will it occur in a wide lumen, with a weak contractile force in the colon? Increasing the inflow volume of the colon can stretch the smooth muscle; however, the contraction force caused by the expansion is affected by the compliance of the colon wall. For example, in the megacolon, where the intestinal wall compliance is large, even the intestinal tract expands, meaning that effective pressure cannot be obtained and the volume, at the same pressure, is increased compared to healthy subjects (O'Dwyer et al.). However, even in patients with advanced colon failure (Hirschsprung's disease, Ogilvie's syndrome, chronic intestinal pseudo-obstruction, and megacolon) who do not respond to pharmacological stimulation, there is the fact that antegrade continence enema (ACE) from cecostomy provides adequate defecation (Rivera et al., Peeraully et al., Hanauer et al., Uno). This fact suggests that the flow volume to the caecum can affect CTT. Namely, when fluid flows into the caecum, colon motor activity may be influenced not only by the contraction force and compliance of smooth muscle, but also by fluid dynamics. In the closed colon of experimental animals, intraluminal pressure is increased by fluid infusion according to peristaltic contractions (Costa et al.). Pressure rise, due to this contraction, can be physically explained by Laplace's law. However, in living humans without ileus, another physical involvement within the colon must be considered because the colon is a long non-occluded space. Therefore, Bernoulli's principle rather than Laplace's law should be applied. For this reason, in the study under discussion, a virtual model of the large intestine was created and it was investigated whether or not Bernoulli's principle could be applied to constipation and diarrhea. Variations in the caliber of the human large intestinal tract cause changes in pressure and the velocity of its contents, depending on flow volume, gravity, and density, which are all variables of Bernoulli's principle. Therefore, it was hypothesized that constipation and diarrhea can occur due to changes in the CTT according to Bernoulli's

principle. In addition, it was hypothesized that HAPC, which are considered to be involved in defecation of healthy subjects, occur because of caecum pressure based on Bernoulli's principle. A virtual healthy model (VHM), a virtual constipation model (VCM), and a virtual diarrhea model (VDM) were created. For each model, the CTT was decided according to the length of each part and then the velocity due to the caecum inflow volume was calculated. In the VHM the pressure change was calculated, then its consistency with HAPC was verified.

Figure 34 (next page): *Setting of caliber and length. A: Setting of caliber and length of virtual healthy model. Narrow calibers were set due to the sphincters (Bu: Busi ring, H: Hirsch ring, C: Cannon ring, PS: Payr-Strauss ring, Ba: Balli ring, M: Moultier ring, Ro: Rossi ring). B: Setting of caliber and length of virtual constipation model (VCM). C: Setting of caliber and length of virtual diarrhea model (VDM). All lengths are given in cm. Italic type indicates the diameter. The number of arrow lines is the length of the calculation of velocity and pressure. The number of broken lines is the length of the calculation of CTT (Uno: 2018). The caliber of the normal model, constipation model, and diarrhea model were set according to analysis of measured values, and figures based on past literature (Lam, et al.:2016, 2017; Patriquin et al.; O'Dwyer et al.; Knudsen et al.; Matsuunaga).*



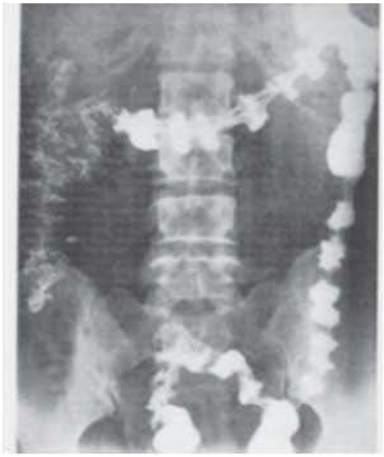


Figure 35: *The characteristic colon form of IBS-D by barium enema. This examination was performed without using antispasmodic agents (Matsunaga).*

The results showed that compared with VHM, the CTT was prolonged in the VCM and shortened in the VDM.

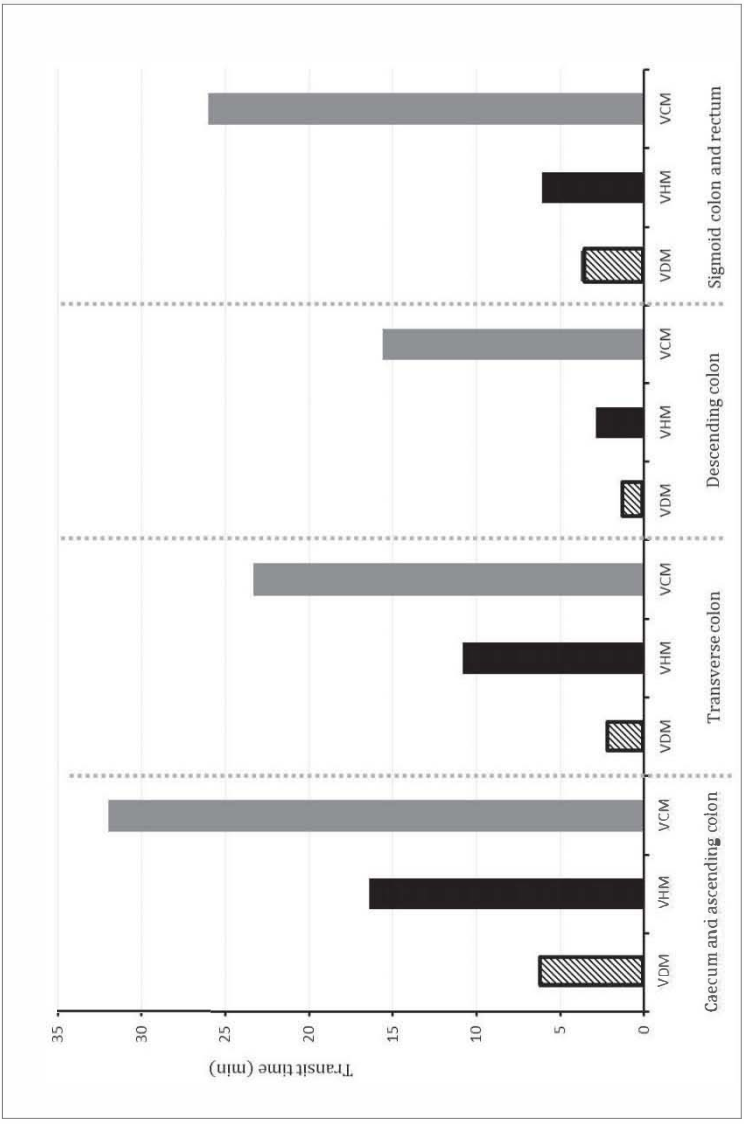


Figure 36: *Comparison of transit times in each model. Results with bolus flow volume (1 mL/s) (Uno: 2018)*

The calculated pressure of the VHM and the gradient of the interlocked graph were similar to that of HAPC.

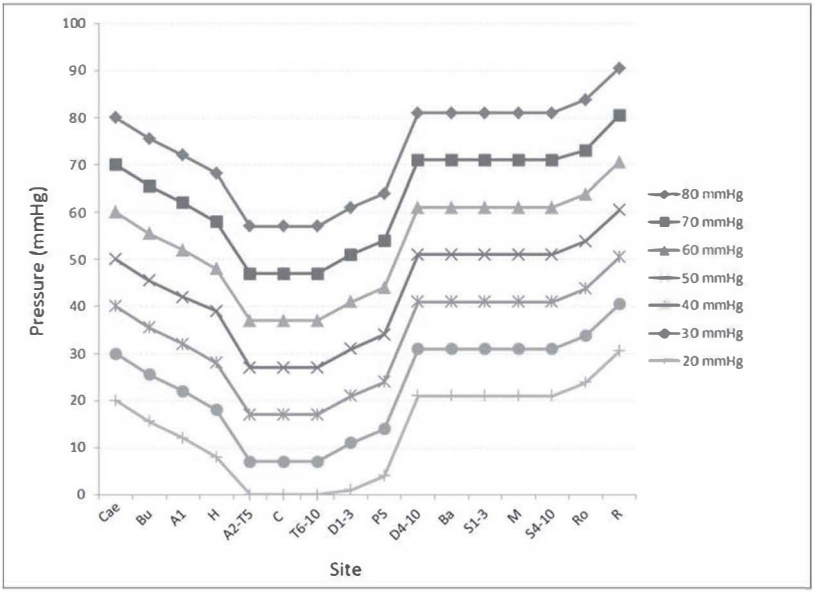


Figure 37: *The relationship between caecal pressure (20–80 mmHg) and pressure changes at each site (Uno: 2018).*

Colorectal movement is regulated by smooth muscle cells, interstitial cells of Cajal, Meissner's plexus, Auerbach's plexus, superior and inferior mesenteric nerve plexuses, and the parasympathetic nervous system (Furness et al., Sanders et al.). However, there are phenomena in colonic movement that cannot be explained by such nervous system control; for example giant migrating contractions and HAPC, where details regarding their transmission are still unknown (Cook et al., Bharucha et al.). Although it is known that the velocity of colonic contents decreases in the ascending colon and increases from the descending colon to the sigmoid colon, the physiological reasons for this have not been elucidated. Some studies of normal subjects, who were measured using a wireless capsule (SmartPill), showed that the pressure was 60–80mmHg in the caecum, which then decreased to 20–40mmHg in the central part of the large intestine, and then increased to 60–100mmHg at the proximity of the

rectum (Hasler et al., Saad et al., Tran et al., Sequeira et al.). Furthermore, this pressure fluctuation was very similar to the propagation data of high amplitude propagating sequences, which was measured by manometer in a healthy person. As shown by this research, such pressure fluctuations can be explained by positional energy due to the involvement of gravity.

In healthy humans, colonic motility exhibits multimodal rhythms over a period close to 24 hours, with peak activity occurring in the morning after waking and following meals. In addition, both propagating and non-propagating motor activity of the colon are suppressed at night (Rao et al., Bampton et al., Dinning et al., Roarty et al.). Within one to three minutes of the initial bites of a meal, segmental contractions begin in the proximal and distal colon (Szmulowicz et al.). Characteristic movement in the human colon was thought to be "reverse peristalsis" in the ascending colon, "pendular movements" in the transverse colon, and "mass peristalsis" in the descending colon (Netter et al.). Gastrocolic reflex (GCR) was described in 1979 as "gastrocolic response" by Snape et al. (Snape et al.). They explained that this response was an increase in distal colon motor activity related to food intake. In a whole colon manometric study in 1989, GCR was observed in both the proximal colon and distal colon, but the response of the descending colon to eating was the most intense (Moreno-Osset et al.). In addition, GCR in the proximal colon increased early on and was short-lived, but in the distal colon there was a more sustained increase (Bassotti et al.). GCR in the proximal colon is believed to be due to the stimulation of stomach dilatation, which occurs as a result of ingestion of food that has reached the medulla oblongata via the vagus nerve, and then gone from the spinal cord to the pelvic splanchnic nerve. However, this theory is doubted because GCR-like phenomenon can occur even in spinal cord injury patients (Suttor et al.). Furthermore, even with spinal cord injury, it is possible to immediately induce defecation by ACE (Hughes, Yang et al.). For example, in ACE by polyethylene glycol (PEG) from cecostomy, the mean toilet sitting time was 51.7 ± 3.5 minutes (range 10–180minutes), with a mean irrigation dose of 847 ± 55 mL (23 ± 0.7mL/kg) (Siddiqui et al.). For that reason, in order to examine the hypothesis of the pressure change in this study, the flow volume to the caecum was set at 1mL/s (60mL/min), an amount that is consistent with gravity-infused ACE.

Mass movement is synonymous with mass peristalsis, and the relationship with HAPC was found using a pressure measurement experiment (Cook et al.). The characteristics of HAPC are as follows (Bharucha): (1) occurs spontaneously, in response to pharmacological agents or colonic distention; (2) increases upon awakening; (3) much more common during the day; (4) increases after meals; (5) mainly originates in the proximal colon but most do not propagate beyond the mid-colon, and fewer than 5% reach the rectum; (6) can transfer colonic contents over long distances; (7) can be associated with internal anal sphincter relaxation; and (8) are reduced in slow transit constipation and increased in diarrhea predominant IBS, and may explain disturbances of colonic transit in these conditions. Namely, changes in the propagation pressures that were calculated by the inflow amount of the caecum in this study did not contradict the results of HAPC characteristics found in the previous report.

In research by Bouchoucha et al., the determination of segmental CTT divided the colon into three parts: the "right colon" (caecum, ascending colon, hepatic flexure, and right part of the transverse colon); the "left colon" (left part of the transverse colon, splenic flexure, and descending colon); and the "terminal intestine" (sigmoid and rectum) (Bouchoucha et al.). Schematically, this division corresponds to the embryologic origin of the colon and its neural, vascular, and lymphatic correspondents, and to the physiological functions of these segments. The "right colon" is of mid-gut embryological origin, and predominantly functions in the absorption of water, sodium, and chloride, as well as for microbiota metabolism. The major part of the "left colon" is of hind-gut embryological origin, and its main function is the transfer of feces; finally the "terminal intestine" plays a major role in defecation. Differences in the function of the left and right colon, as described above, may be due to the lower mobility of the right colon compared to the left colon. However, *in vitro* the electrophysiology and mechanical characteristics of smooth muscles in the human colon showed no obvious differences between the right and left colon (Choe et al.). For these reasons, the colon was regarded as a simple luminal organ, and the pure influence of colonic fluid dynamics was assessed. As a result of this study, the difference in movement and function between the right and left colon can be explained by a change in intestinal pressure and velocity, which is due to the influence of fluid dynamics.

Even if 1000–2000mL of water flows from the small intestine to the caecum in a healthy subject, it is absorbed in the large intestine and the fecal water content is reduced to 100–200mL (Debongnie and Phillips, 1976). Therefore, water is absorbed in each segment of the large intestine. If the inflow amount decreases, the CTT will be extended compared to the calculated result in this study. During saline lavage, fluid absorption of 2400–3200mL could be expected, while 4000mL of PEG would be expected to result in absorption of only 190–250mL over 3–4 hours of consumption (DiPalma et al.). In the case of peroral ingestion of PEG, the total gut transit time, including transition through the stomach and small intestine, is calculated to be about 4 hours by the ingestion of 0.2mL/s (720mL/hr). This is not inconsistent with real clinical evidence. In a study of colonoscopy preparation, subjects given 4000mL of PEG had a cleaning effect similar to subjects that were given 20mg of Bisacodyl, added to 2000mL of PEG (Sharma et al.). As Bisacodyl can induce HAPC (Hamid et al.), it provides evidence that increasing the non-absorbing liquid could have the same function as Bisacodyl. Interestingly, 2000mL of PEG plus Bisacodyl was not superior to 4000mL PEG for colonoscopy bowel cleansing in patients with chronic constipation (Parente et al.). This evidence suggests the usefulness of treatment by larger amounts of fluid in chronic constipation. Indeed, there are many studies that show the effectiveness of PEG in chronic constipation in children, adults, and the elderly (Treepongkaruna et al., Muenguez et al., Chassagne et al.).

In addition, not only the velocity of inflow but also the total volume, due to the inflow duration, influences the water absorption capacity in the large intestine. If the velocity increases in the same caliber—depending on the inflow volume into the large intestine—lubiprostone (Christie et al.), and linaclotide (Thomas and Allmon), which increase the amount of fluid in the gastrointestinal tract, can cause a decrease in the CTT. However, differences in luminal diameter may be influenced not only by flow dynamics, but also by absorbable colonic mucosa surface area. Namely, the effect of laxatives at increasing water content that can be reabsorbed may be limited in the case of chronic constipation with megacolon. Ischemic colitis has been reported as a side effect for both stimulant laxatives (Ajani et al.) and antidiarrhea drugs (Friedel, Gulstad and Thomsen), but the mechanism is unknown. This enigma can be explained by Bernoulli's principle because it causes ischemia of the intestinal tract when the difference between the lumen with a wide caliber and narrow bore is large (Uno). Namely, in a colon with a narrow colonic lumen,

partial rapid expansion with antidiarrhea drugs could cause partial high-pressure. Also, in the dilated colon, a partial strong contraction brought on by a laxative could cause high-pressure due to the partial expansion of its proximal lumen. In addition, when much fermentation occurs in the right colon, the gas build up from fermentation reduces the velocity of movement in the right colon. There is no positional energy in the gas so a large quantity of gas can accumulate in the transverse colon. Therefore, a large amount of gas is an important problem to be solved for constipation therapy.

Motility of the stomach and the colon

Under the hypothesis about the flow dynamics of the colon, if the flow volume to the caecum rapidly increases, diarrhea is likely to occur. Conversely, if the flow volume to the caecum is small, constipation occurs. Theoretically, when the transit time from ingestion at the mouth to the caecum is constant, inflow into the caecum will be affected by the amount of water taken orally. However, in an atonic stomach that has low surface tension, high pressure cannot be obtained even with a large ingestion volume. Gastroptosis is the abnormal downward displacement of the stomach and is associated with constipation (Christianakis et al.). However, when gastric surface tension is intact, gastric outflow is increased by contractions.

In Japan, a stomach X-ray with a barium meal is often performed for the screening of stomach cancer. In this examination, antispasmodic agents are normally not used. However, in a few people, within a few seconds after the barium meal enters the stomach, the barium flows into the small intestine before dilation of stomach without spasms. This will usually only occur in subjects with diarrhea. However, in subjects with constipation, despite sufficient stomach expansion, the barium remains stagnant in the stomach, and its flow into the small intestine is difficult. However, this might be contradicted by the gastrocolic reflex theory, which states that the proximal colon moves due to the expansion of the stomach.

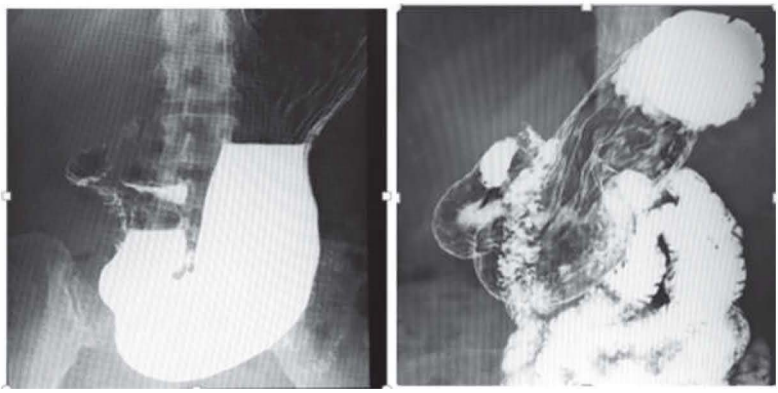


Figure 38: *Two motility differences in the stomach, visualized using barium meal/x-rays: constipation (left) and diarrhea (right) (Uno's personal data)*

Generally, gastric emptying of liquids is faster than solid meals. For this reason, in patients with functional diarrhea, semi-clotting of water (i.e., Jerry) may be effective.

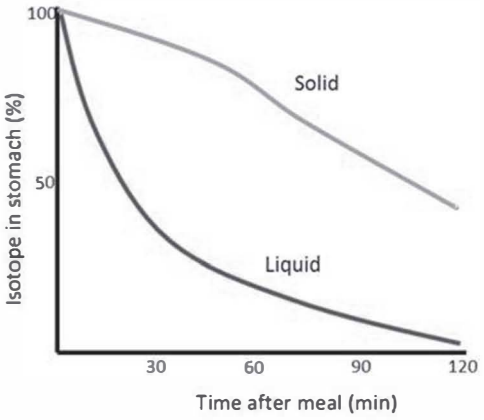


Figure 39: *Gastric emptying of a group of normal subjects using the dual isotope method (Minami and McCallum). Note the exponential nature of liquid emptying and the linear process of solid emptying.*

Traditionally, in Japan, it is believed that vitamin B1 deficiency will result in gastroptosis. The relationship between constipation and vitamin B1 has

not been studied in detail but, during interviews with constipation patients, it should be asked whether they have ingested vitamin B1 properly.

Professor Daisuke Sasaki

I (Uno) started performing research in the Department of Gastroenterology at Hirosaki University at a time when there were two research groups (the colorectal cancer research group and the IBS research group) in the gastrointestinal research group. The colorectal cancer research group was the first to insert a colonoscope up to the caecum in Japan on June 18, 1969. Due to this tradition, their colonoscopy technology was outstanding. The leader of the IBS research group was Dr. Daisuke Sasaki. He started research on measuring internal pressure but had the problem that it was not possible to place a pressure gauge in the right side of the colon. Therefore, he devised a method to simultaneously measure internal pressures of the ascending colon and sigmoid colon by applying colonoscopy technology. This method involved a colonoscope inserted into the caecum and then a guide wire was inserted from the colonoscope channel. After this, the endoscope was removed but the wire was left, and two pressure sensor catheters were placed using the Seldinger method. Unfortunately, his skills in colonoscopy were limited and therefore, in order to perform his method, the cooperation of an excellent endoscopist proved to be indispensable.

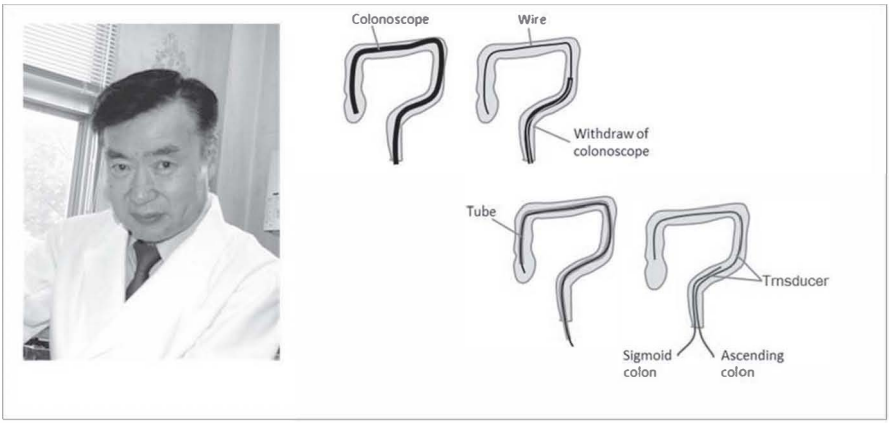


Figure 40: *Professor Daisuke Sasaki (left); colonoscopic method for measurement of colon motility (right)*

The article relating this method was published in English in 1986 (Sasaki et al.). However, the doctor who performed the colonoscopies was not named among the co-authors. Therefore, the relationship between the IBS group and colon cancer research group became increasingly strained. Ten years later, I belonged to the colorectal cancer research group and became the endoscopist who performed the colonoscopies, and I often inserted the colonoscope into the caecum for his study. And, while watching his experiment, I began to have doubts about his experiment. I inserted the colonoscope into the caecum without air and placed the guide wire. Even if a small amount of air remained, it was eliminated when inserting a tube. Then, a catheter for pressure measurement was inserted in the absence of air. In other words, the tip of the internal pressure measuring catheter was always in direct contact with the colonic mucosa. He said that "amplitude" measured in that state was "colonic pressure". However, I thought it was not the pressure inside the lumen but merely a tremor of the colon wall. He subsequently rose to the top position of the IBS division in Japan. In 2006, a very interesting passage appeared in his book.

> In IBS-C, sigmoid colon contracts strongly, which forms a so-called valve and stops the contents. There is no harmony between ascending colon and sigmoid colon. On the other hand, in IBS-D, fine spasm is seen throughout the colon, and the lumen is thin tubular. Luminal pressure of IBS-D is low.

He knew! He knew the zoologist's hypothesis that feces are transported directly by spasms cannot be adapted to human IBS. However, he did not know that flow dynamics could explain the phenomenon of the decrease in pressure and increase in the velocity as the lumen width narrows.

Morphology of the colon in IBS

In addition to IBS, functional bowel disorder can confirm the morphological abnormality of the colon as a result of some cause. These morphological features may be temporary or permanent in some cases. Long-term intestinal dilation will cause a decrease in surface tension and cause an atonic colon, in the same way that the skin sags after weight loss. In a permanent megacolon, abdominal pain, due to a large amount of gas, is rare.

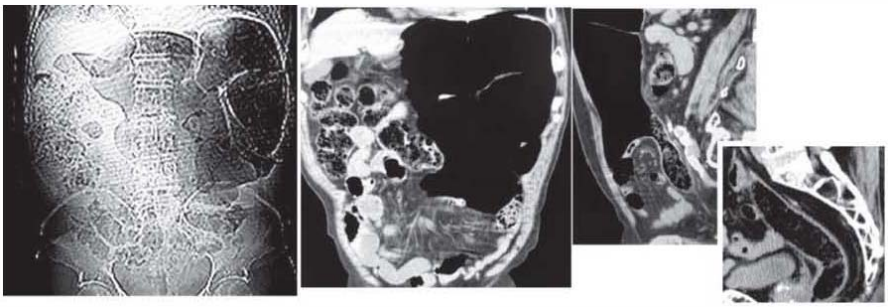


Figure 41: *Megacolon induced by long time use of oral hypoglycemic agents. No stenosis on the anal side of dilatation and no sigmoid volvulus. He had no abdominal pain, and had a small amount but defecation every day. This was followed up for 5 years, but he had no symptoms and his megacolon did not change (Uno's personal data).*

Supplementary explanation: megacolon

In a study from Canada in 1978 (Patriquin et al.), the diameter of megacolon measured by injecting a barium enema from a height of 1m was as follows: ascending colon: 6.8cm (control: 6.7cm); descending colon 4.7cm (control: 3.5cm); sigmoid colon: 4.1cm (control: 3.1cm); rectum: 6.7cm (control: 4.6cm). In a study of double-contrast barium enema films in 1985 (Preston et al.), the diameter of megacolon criteria was as follows (diameter): ascending colon: 8.2cm; transverse colon: 7.8cm; descending colon: 7.2cm; sigmoid colon: 10cm; rectum: 10cm. According to a study in 1991 (Stabile et al.), the megacolon was diagnosed as follows: a descending colon that is "usually" greater than 6cm and an ascending colon that is "usually" greater than 8cm.

In my (Uno) experience with 546 people with chronic constipation (including IBS-C), 70% were mixed type (right colon expanded and left colon constricted). However, the IBS diarrhea type is characteristic of a spastic type with strong contractions (Uno: 2011, 2012, 2013).

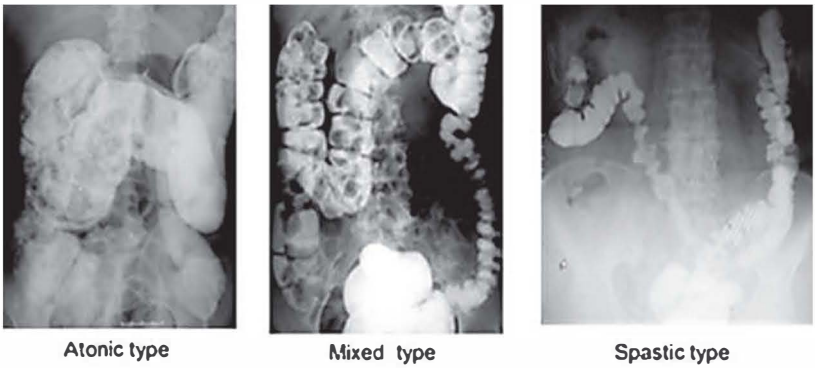


Figure 42: *Three types of colonic morphology in patients with bowel movement abnormalities (Uno: 2011, 2012, 2013)*

As mentioned earlier, morphological differences of the colon physically affect CTT. When the CTT is long it causes constipation, and a fast transit time results in diarrhea. Therefore, the reason why IBS is divided into diarrhea type and constipation type is basically because the patient's colon form is shifted to either side. In the case that it is not shifted to either side, then it is the intermediate type. When a lot of water contents exists in the colon, or when the secretion of bile acid is large, diarrhea results, and when gas is dominant it becomes constipation. In addition, symptoms change depending on degree of contraction and the contraction site. Basically, the colonic form is unsettled, so it is affected by diet, and so on.

Transient colonic morphological changes due to high-FODMAP diet

Traditionally, in animal models it was believed that intestinal motility (colonic spasm) was promoted by fermentation, an increase in SCFAs, and low pH of the intestine (Dass et al.). Namely, they considered intestinal cramping was caused by antegrade mobility. Additionally, this animal study was the first evidence of the effect of prebiotics. However, in 2014 Farmer and colleagues found that caecal pH was low and mobility (frequency of pressure amplitude) was decreased in IBS patients (Farmer et al.). In that study, the rectal motility was high in IBS and the overall transit time was short. They concluded that low pH is an indicator of decreased mobility.

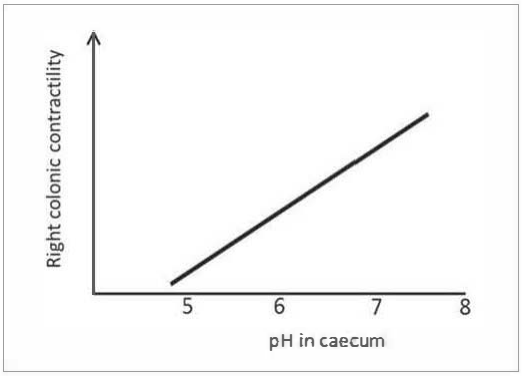


Figure 43: *Caecal pH and right colon contractility was positively correlated (Farmer et al.)*

Furthermore, they revealed the differential regional actions of the SCFAs, which means that there is an inhibition of motility in the right colon followed by a motility promoting effect in the more distal colon. Similarly, in a study using a wireless motility capsule in 2015, IBS patients demonstrated lower pH (total colonic pH, 6.8) throughout the colon compared to healthy controls (total colonic pH, 7.3). Certainly, fecal pH is a useful test that can strongly suggest the presence of carbohydrate malabsorption if the value is low. However, due to biliary acid diarrhea with alkali stools (McJunkin et al.) and the fact that the pH value of feces in subjects with magnesium hydroxide-induced diarrhea was > 7.0 (Eherer et al.), it is impossible to argue that motility of the intestines is influenced only by pH. A low pH suggests carbohydrates are more fermented in the caecum in IBS patients. Gas will be produced and the lumen will expand. It was reported that in IBS-D and IBS-M, there is impaired transit and tolerance of intestinal gas loads (Serra et al.). The reason can be explained by flow dynamics because the velocity of gas segments becomes very low due to the fact that gas density is very low.

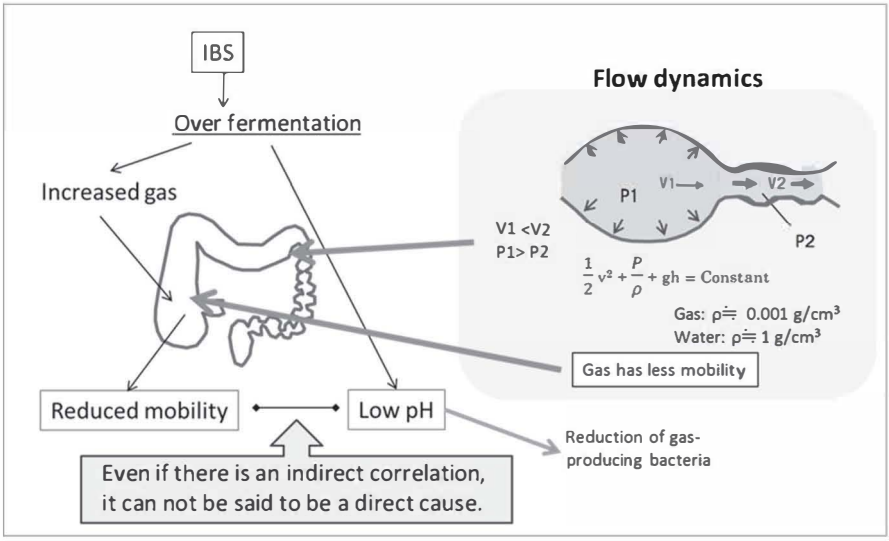


Figure 44: *Relationship between pH and gas in IBS*

Methane-producing bacteria, and many of the anaerobic hydrogen producing bacteria, produce methane and hydrogen gas and thrive at pH 6-7, at 36°C. In other words, the hypothesis is that continuing to consume large amounts of FODMAPs, which ferment in the large intestine, leads the intestinal flora to change so that it is better able to ferment. This means that a low-FODMAP diet, which inhibits fermentation in the large intestine, would inhibit the accumulation of gas and hinder the growth of bacterial species, which promote fermentation, in order to raise the intestinal pH. It is also known that the pH of the proximal colon is abnormally low, even in ulcerative colitis and Crohn's disease. This low pH might be related to high-FODMAPs.

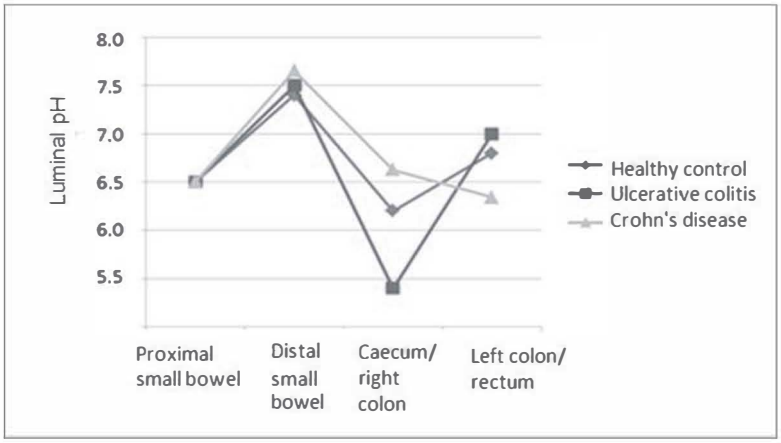


Figure 45: *Average luminal pH of healthy subjects and patients with ulcerative colitis (UC) or Crohn's disease (CD) (Nugent et al.: 2001). In the ulcerative colitis, the pH was lower in the caecum and proximal colon. In Crohn's disease, the pH was lowwe in the distal colon. From the above, it appears that IBD may be related to fermentation.*

9. Abdominal pain in IBS

Until the IBS patient is aware of abdominal pain, there are many factors that mediate (promote or suppress) transmission from the local factor to the brain. The author (Uno) has discussed luminal pressure, contraction, mast cells, and ischemia. First of all, it must be understood that an increase in colonic content (water and/or gas) does not necessarily correlate with abdominal symptoms. "Abdominal pain is due to response to gut distension, not gas volume". This fact was already related in 1975 (Lasser et al.). Important factors that cause abdominal pain in IBS are high luminal pressure and colonic pressure amplitude (Pirkola eta al). In a state where the surface tension is sufficiently maintained, rising pressure due to rapid increasing gas and/or water can cause abdominal pain. In 1980, researchers at St. Mark's Hospital endoscopically inflated a balloon in the large intestine of IBS patients with abdominal pain, thereby confirming the occurrence of spontaneous abdominal pain (Swarbrick et al.). However, an atonic colon (stretched out of shape) in the large intestine without

surface tension, high pressure cannot be obtained even with a large volume of gas.

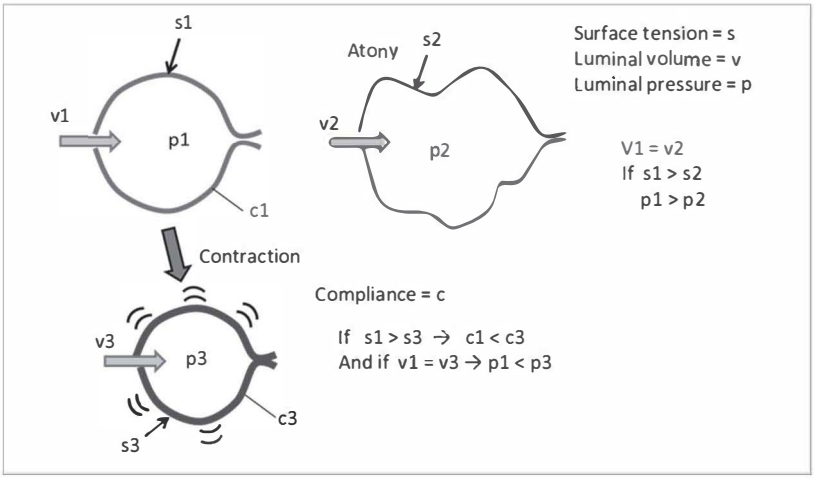


Figure 46: *Relationship between surface tension and luminal pressure*

However, luminal pressure is also increased by contractions in the intestinal tract within a tight and od space. In the IBS diarrhea type model, the inner diameter of the lumen is narrowed by shrinkage, so the transit time is shortened and, during that time, a lot of pressure amplitude spikes are present (non-enclosed space). In this case, abdominal pain is unlikely to occur because the accumulation of feces increases the volume more slowly than gas.

In 1991, Ritsema and Thijn discovered the strong sigmoid contractions in circular muscles using barium enema imaging, which are associated with IBS patients experiencing pain. They observed that the increased pressure is felt as pain (Ritsema and Thijn)). However, Trotman and Misiewicz found that pressure decreased during pain in IBS patients (Trotman and Misiewicz). Furthermore, colonoscopic research has shown that the pressure decreases with a luminal contraction (Sasaki et al.). If all of these are correct, then abdominal pain in IBS is guided by two different factors: high pressure in the lumen and excessive contraction (without high pressure). Therefore, I considered the mechanism of abdominal pain due to contraction. As a result, I found a possibility of abdominal pain due to transient ischemia caused by strong contractions.

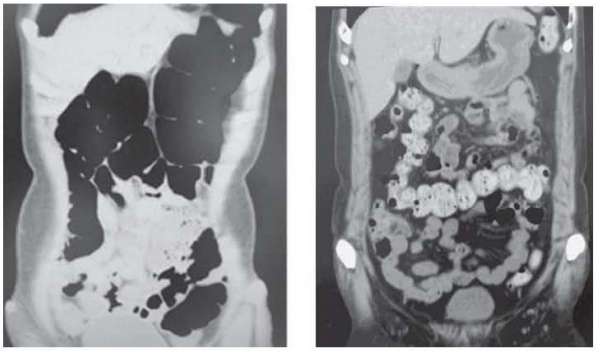


Figure 47: *Two cases of chronic constipation. These two cases did not have abdominal pain or abdominal distension. Left: A large amount of gas is shown. Right: lots of fecal matter is shown in the colon. (Uno's personal data)*

About ischemia due to colonic contraction: Uno Y

I investigated the possibility of ischemia caused by contraction of the colon. (The survey was not a limited literature search of articles posted on the Internet, but a steady task of going to the medical library every day and checking all the old medical books.) As a result, I discovered two important research papers. First, I discovered that the relationship between the muscular layer of the colon and blood vessels was reported in detail in 1925 (Lineback). The blood vessels suppling the colon pass along the longitudinal muscles through gaps in the circular muscle. These gaps allow passage not only of blood vessels but also nerves. And the circular muscle and the longitudinal muscle are not separated but connected. Another discovery was an article from 1927, which was a study on contractions in IBS (Kantor). Basically, the longitudinal muscle and the circular muscle shrink together, even if this is not excessive. If the intestinal tract of such a structure contracts then, theoretically, the gaps through which the blood vessels pass will be blocked. In other words, the human colon showed that contraction can reduce the blood supply from blood vessels.

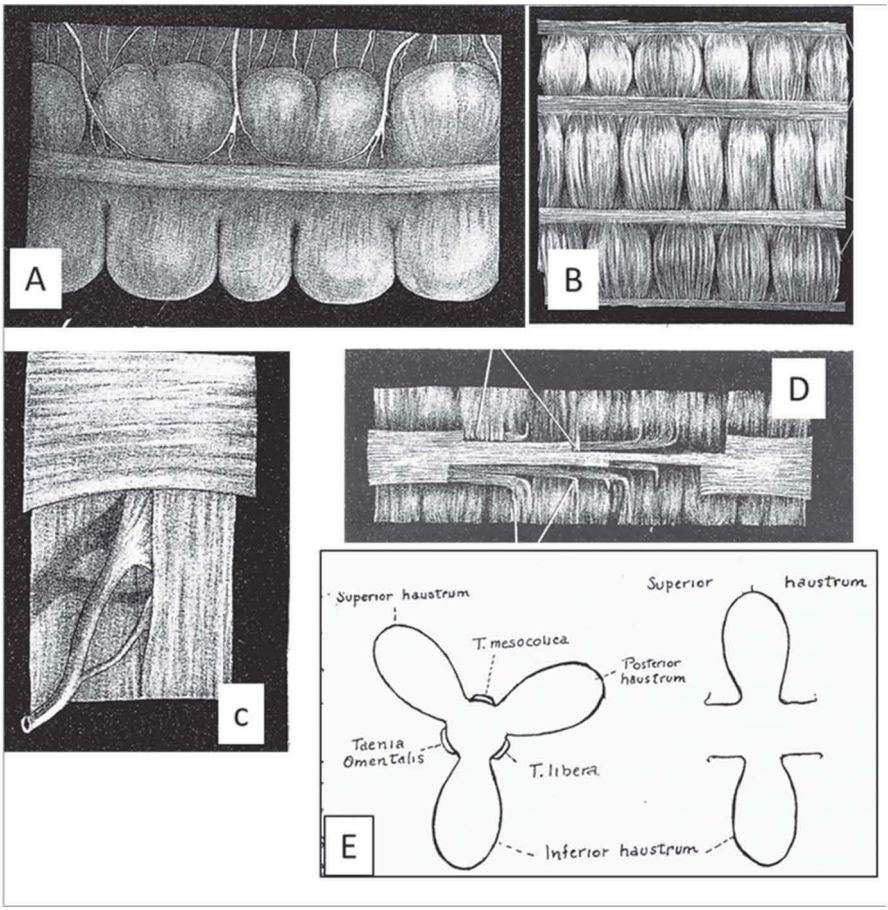


Figure 48: *Relationship between colonic muscularis, blood vessels, and colonic contraction. A: Relationship between colonic musculature and blood vessels. B: cleft of circular muscle. C: relationship between cleft and vessel nerve. D: relationship between circular muscle and longitudinal muscle. E: diagram of colonic contraction (A, B, C, and D: Lineback; E: Kantor).*

The human colon has many clefts in the circular muscle. The clefts are located along the outside of the longitudinal muscle. Blood vessels supplying blood to the mucosa pass through these clefts. Therefore, excessive smooth muscle contraction narrows the cleft, the blood vessel is tightened, and the blood flow decreases. Ischemia resulting from this

occurs along the longitudinal muscle, so in severe ischemic conditions three longitudinal ulcers can form at the position of the longitudinal muscle. The fact that longitudinal ulcers (ischemic colitis or ulcerative colitis) occur in the descending colon, the most contraction-prone place in the large intestine, and the fact that longitudinal ulcers do not occur in the rectum, which is without clefts, are the evidence for this theory. Also, ischemia of the intestinal tract may occur as the internal pressure of the intestine rises.

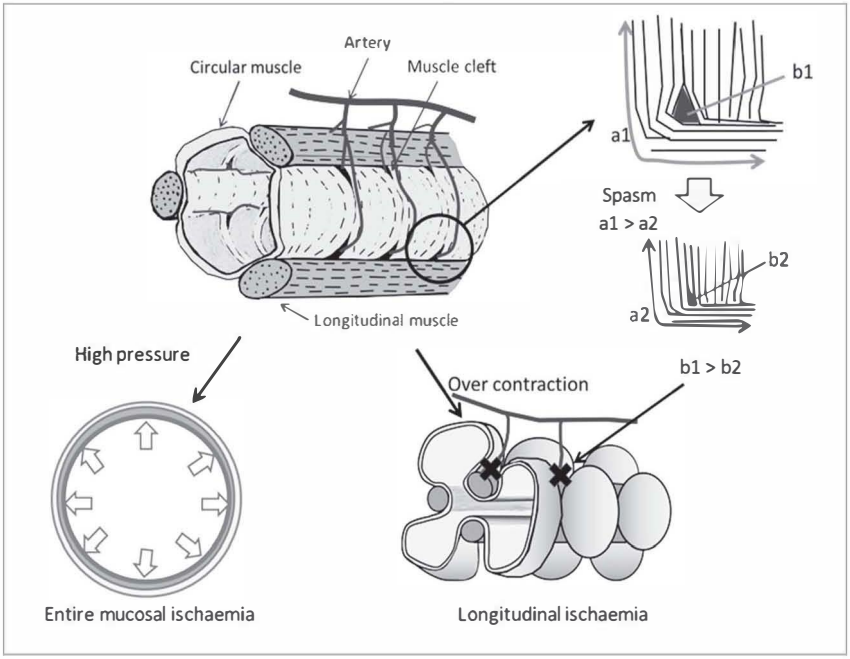


Figure 49: *Intestinal ischemia mechanism from an anatomical point of view. Ischemia due to high pressure is caused by both surface tension (contractile force) and intraluminal pressure. This form of ischemia mainly occurs in the right colon and the rectum. Ischemia due to over contraction is caused by contraction of the gaps through which blood vessels pass. Longitudinal and circular muscles form an "L" and are connected to each other (Lineback), and contraction occurs in both (Kantor). Therefore, the contraction of the muscles constricts the gap through which the blood vessel passes. This ischemia mainly occurs in the descending colon and sigmoid colon.*

Ischemia and abdominal pain

The relationship between ischemia and abdominal pain will be explained next. As previously mentioned, the increase in ischemia and mast cells is linked to the pathophysiology of IBS, and mediators released from mast cells may contribute to abdominal pain perception and colonic hypersensitivity in IBS. Research has confirmed that blood flow in the intestinal wall decreases when pressure in the large intestine increases. The blood flow of the intestinal mucosa decreases at a luminal pressure of 10mmHg. Moreover, when the internal pressure is maintained at 25mmHg for several hours, the intestinal wall undergoes ischaemic damage. At pressures of 60–70mmHg the blood flow rate decreases by 25% in 5–10 minutes and at pressures of 90–100mmHg blood flow drops to 50% in 5–10 minutes (Uno: 2017). Sympathetic stimulation, due to some kind of stress, causes colonic ischemia through decreased intestinal blood flow, and could be induced by colonic hypersensitivity. For example, protracted strenuous exercise (e.g. a triathlon), results in exercise-induced gastrointestinal syndrome due to reduced intestinal blood flow (Costa et al., Uno). Sleep apnea is related to acute and sustained activation of the sympathetic nervous system (Floras), and there is a positive association between sleep apnea and IBS (Ghiasi et al.). In contrast, activation of the parasympathetic nervous system causes intestinal vasodilation and increases colonic blood flow (Uno: 2018). Yoga has been confirmed to induce a preponderance of parasympathetic effects. Schumann et al. confirmed that symptom reducing effects can be achieved with yoga practice in IBS patients (Schumann et al.). These facts may be evidence that intestinal blood flow affects the cause of IBS. In IBS, 2 weeks on a low-FODMAP diet greatly reduces histamine, which is a mediator of mast cells in IBS patients (McIntosh et al.). This fact implies that the increase in mast cells in IBS is variable.

In the study of low-FODMAP diet for radiation-induced enteropathy (RE) by Larsen et al., they described the result that low-FODMAP diet relieves symptoms of RE, such as abdominal pain, bloating, diarrhea, and constipation (Larsen et al.). In 2011, Blirando et al. found mast cell hyperplasia in a model of radiation proctitis in mice and showed that mast cell-deficient mice were protected from both acute and late damage, which strongly supported a detrimental role for mast cells in radiation proctitis (Blirando et al.). In chronic radiation enteritis, microvascular damage is responsible for chronic radiation-induced fibrosis (Wang et al.).

Histopathologically, it was confirmed that abdominal pain in the chronic phase is affected by endarteritis due to ischemic changes in the intestine (Schofield et al.). Namely, there is objective evidence that abdominal pain in RE is related to intestinal ischemia. When IBS and RE are compared, RE is continuous and progressive ischemia; however, even if ischemia is involved in IBS it is transient and reversible. Nevertheless, when considering RE with IBS symptoms as an extreme model of the local cause of IBS, this research may have a significant influence on the elucidation of the cause of IBS (Uno: 2018). That is to say, it is necessary to consider the effect of persistent ischemia (and its reversible quality), such as ischemic enteritis, in the mechanism of abdominal pain related to IBS. The hypothesis must satisfy the condition that abdominal pain is induced after a meal and the pain disappears as the interior of the lumen becomes empty.

An increased serum lipopolysaccharide (LPS) concentration has been reported in patients with IBS-D compared to controls (Dlugosz et al., Ludidi et al.). Due to the fact that endotoxins—which are a component of the outer membrane of Gram-negative bacteria—stimulate various inflammatory mediators, it could be that the LPS from Gram-negative bacteria gain access to the gut lamina propria to induce local inflammation (Neuman et al.). Inflammation could lead to further elevation of blood endotoxin levels as a result of increased intestinal permeability due to mucosal damage (van Deventer et al.).

In 2018, Zhou hypothesized that FODMAPs cause endotoxemia and intestinal inflammation, which in tum modulates visceral nociception. To test this hypothesis, they conducted experiments in rats to determine if a diet with high levels of FODMAPs could cause dysbiosis and lead to the production of endotoxins, which cause gut inflammation and induce visceral hypersensitivity. In separate studies, they examined the effects of fecal supernatant obtained from rats fed a high-FODMAP meal (HFM) diet on visceral sensitivity in naive rats and the permeability of cultured human colonoids. In conclusion, they found that a HFM diet causes an increase in fecal LPS, which is most likely from gut dysbiosis. This induces mucosal inflammation, impairs permeability, and contributes to the development of visceral hypersensitivity. In contrast, a low-FODMAP meal (LFM) diet reduces fecal LPS by modulating gut microbial composition. This decreases mucosal inflammation, improves gut barrier function, and prevents stress-induced visceral hyperalgesia. Similar

observations were made in IBS-D patients who showed an elevated fecal LPS level that was normalized following 4 weeks of treatment with LFMs. Fecal supernatant from IBS-D patients receiving a LFM diet also failed to evoke visceral hypersensitivity in naive rats.

Previously, as a cause of IBS symptoms the author (Uno) has explained the relationship between intestinal pressure, flow volume, and intestinal contractions. Furthermore, Uno showed the relationship between hypersensitivity and mast cells, which covered the involvement of bile acid, food allergies, transient enteritis, and increased epithelial hyperpermeability. The unabsorbed abundant bile acid increases the fecal water content and, as a result, it increases the flow volume in the intestine and thus contributes to the increase in luminal pressure. Too much bile acid and high-FODMAPs both induce intestinal mucosa ischemia. As a result, mediators are released from mast cells and contraction of the colon progresses (Shea-Donohue). Transient inflammation and food allergies also induce the activation of mast cells, resulting in excessive contractions in the intestinal tract. This induces further ischemia of the intestinal tract in order to physically tighten the walled vessels surrounded by the smooth muscle. This leads to a sustained reduction in mucosal blood flow due to persistence of excessive contraction-induced mucosal damage, i.e. epithelial hyperpermeability, and affects the enteric nerve (e.g. via LPS). The permeability of LPS is increased under ischemic conditions and is predominantly enhanced by paracellular permeability and epithelial destruction (Drewe et al.). Solligård et al. performed a study in a pig in which the superior mesenteric artery was cross-clamped for 60 minutes followed by 4 hours of reperfusion. After that, the artery was cross-clamped again. However, it was confirmed that permeability was protected after reperfusion, and intestinal permeability did not increase upon repeated ischemia (Solligård et al.). In other words, it showed that an increased permeability due to a brief period intestinal ischemia is reversible.

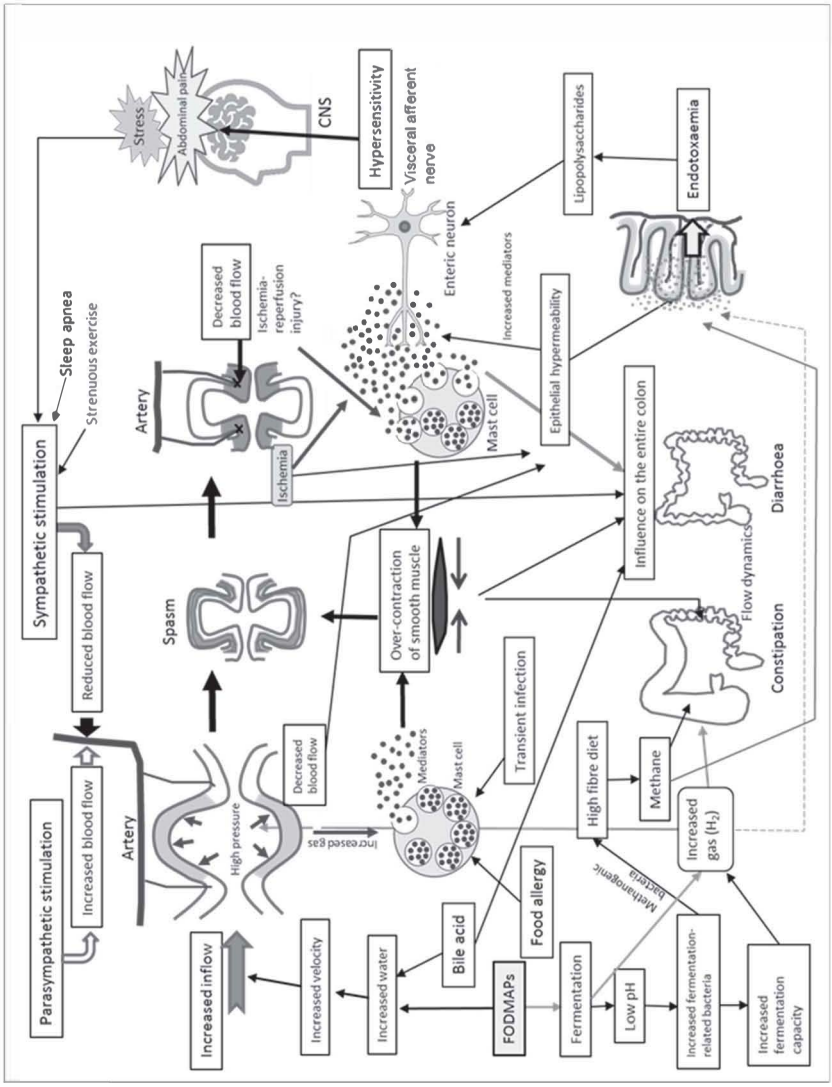


Figure 50: *Pathophysiology of IBS that emphasizes ischemia and mast cells (Uno's hypothesis)*

Theoretically, an ischemic response due to excessive contractions can easily occur in the descending colon and the sigmoid colon with the smallest lumen diameter. In that case, if the right colon is dilated with gas, then the reduction in velocity in the right colon will result in constipation with abdominal pain. However, when the sympathetic nerves are activated, the inner diameter of the entire large intestine narrows, and diarrhea with abdominal pain could occur. Winston et al. demonstrated that chronic stress-induced visceral hypersensitivity in rats is mediated by adrenergic-stimulated release of norepinephrine, resulting in increased expression of nerve growth factor, which in tum sensitizes the visceral afferent neurons (Winston et al.). The fact can be explained as the result of the sympathetic tension causing reduction of intestinal blood flow, thereby resulting in intestinal ischemia-induced hypercontraction and mast cell activity. High-fiber diets produce more methane gas in the large intestine than a low-fiber diet, suggesting that painful gut gas retention could be avoided by cutting back on high-fiber foods (RMIT University).

Risk of high-FODMAPs diet in IBS

In 2015, the results of a 10-year follow-up of 39,384 people (IBS: 9160, non-IBS: 30,244) investigating IBS in the incidence of colorectal neoplasm were published in Taiwan (Chang et al.). After allowing controls for age, gender, and a family history for colorectal cancer, subjects who had been diagnosed as having IBS exhibited a significantly elevated level: 21% with an adjusted hazard ratio—(HR)=1.21—of incident colorectal adenoma compared with those who had not been diagnosed with IBS. A similar finding was noted for invasive carcinoma.

So why does IBS increase the risk of colorectal cancer and colon adenoma? It may be due to repeated mast cell activation. Mast cells contribute to the development of neoplastic polyps. Gounaris et al. confirmed an increase in mast cells in stroma and submucosa of the polyps and tumors from 79 colon adenomas (including invasive cancer) (Gounaris et al.). The depletion of mast cells correlated with lowered levels of serum TNFα (tumor necrosis factor α), and the anti-TNFα treatment had a potent suppressive effect on polyp growth, expansion, and associated angiogenesis. This means that the suppression of mast cells can also suppress colon cancer.

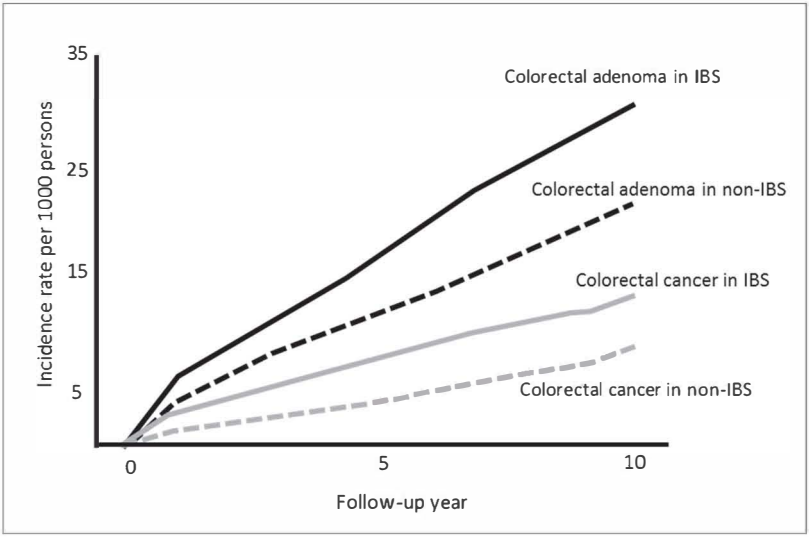


Figure 51: *Cumulative colorectal adenoma and cancer incidence rates by IBS status (Chang et al.)*

CHAPTER II

DETAILED EXPLANATION OF FODMAP COMPONENTS

1. Oligosaccharides

Oligosaccharides are carbohydrate polymers comprising 2 to 10 monosaccharides, or simple sugars with glycosidic bonds. They are called disaccharides, trisaccharides, or tetrasaccharides, depending on the number of monosaccharides and disaccharides (sucrose, maltose, and lactose), and they are also sometimes classified into oligosaccharide groups. However, an oligosaccharide usually indicates more than a trisaccharide. The oligosaccharides that should be avoided in the low-FODMAP diet are fructans, galacto-oligosaccharides (GOS), and fructo-oligosaccharides (FOS). Human beings lack the enzymes necessary to degrade oligosaccharides and so they are fermented by flora in the large intestine without being broken down in the small intestine. GOS includes galactan, raffinose, and stachyose. In 2017, researchers from Monash University defined a low-FODMAP food as containing less than 0.2g of oligosaccharides (per serving) (Varney et al.). The amount of GOS in 100g of food is 7.5g for artichokes, 3.8g for lentils, 1.2g for chickpeas, 0.3 to 0.6g for soy bean drinks, 0.2 to 0.6g for soy beans, and 0.1g for broccoli and beetroot. The following foods are high-FODMAPs: kidney beans, baked beans, black beans, cannellini beans, great northern beans, pinto beans, navy beans, lima beans, butter beans, red beans, soy beans, mung beans, fava beans, chickpeas, and lentils. Chickpeas are often used in Indian cuisine. They are also a popular high-protein resource among vegetarians. Other foods that contain GOS (in 100g) are yacón (8g), burdock root (2.3–3.6g), onion (2.8g), chicory (2.7g), "yama-gobo" (pokeweed, Phytolacca, 2.2g), edible dandelion (1.4g), rye (0.7g), the white part of a Japanese green onion (0.6g), soy bean flour (7g), "natto" fermented soy bean (2g), honey (1.5g), garlic (1g), soy milk (0.5g), and tofu (soft type, 0.42g).

According to the companies and people that promote the use of prebiotics, various theories have been presented about the induction of fecal softening due to oligosaccharides. For example, one surprising theory is that when GOS is fermented in the colon, the number of bacteria increases, thereby increasing volume and softening the feces. Therefore, this improves constipation (Sairanen et al.). In Japan, the hypothesis that "oligosaccharides increase bifidobacteria, thereby improving the intestinal environment and obtaining good defecation" is broadcast on TV commercials every day. This theory explains that oligosaccharides are not influenced by digestive fluids or enzymes and are, therefore, not absorbed in the small intestine. Subsequently, they reach the large intestine and increase the bifidobacteria numbers in the large intestine (Hernot et al.). While this is correct, for people with IBS, functional abdominal bloating, functional diarrhea, and functional constipation the large volumes of gas produced by fermentation and hyperosmolar substances that cannot be absorbed in the small intestine are significant problems.

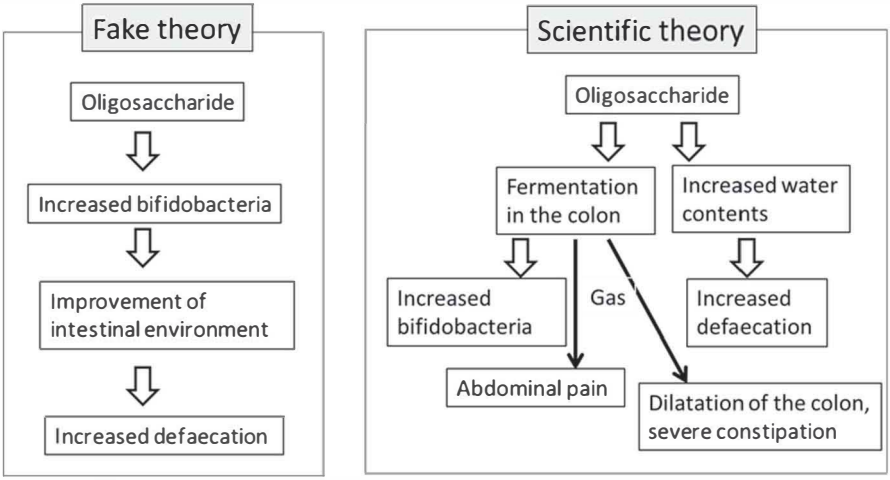


Figure 52: *Difference between fake theories and scientific theories*

Certainly, healthy people who consume GOS may have an increased stool frequency and may think that their intestinal environment has improved. However, there is a definite contradiction with the theory of "improving constipation symptoms by intestinal flora modification". GOS increases water contents prior to intestinal flora changes, and then an increase in

bifidobacteria occurs after fermentation (Hernot et al.). This means that symptoms arise due to an increase in water before a change in intestinal flora and so there is a time bias. Furthermore, an important problem is that the incidence of side effects is dose-dependent. A symptomatic response to FOS, which was used as a sweetener, was reported in 1987 (Stone-Dorshow et al.). The induction of gastrointestinal symptoms with GOS was discovered when GOS was evaluated as a prebiotic in 1990 (Ito et al.).

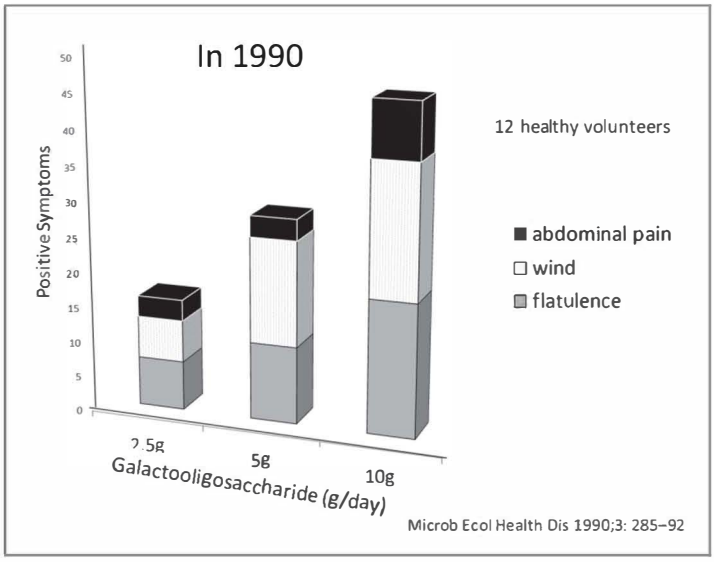


Figure 53: *The occurrence rate of side-effects occurrence from galactooligosaccharides in adults (Ito et al.)*

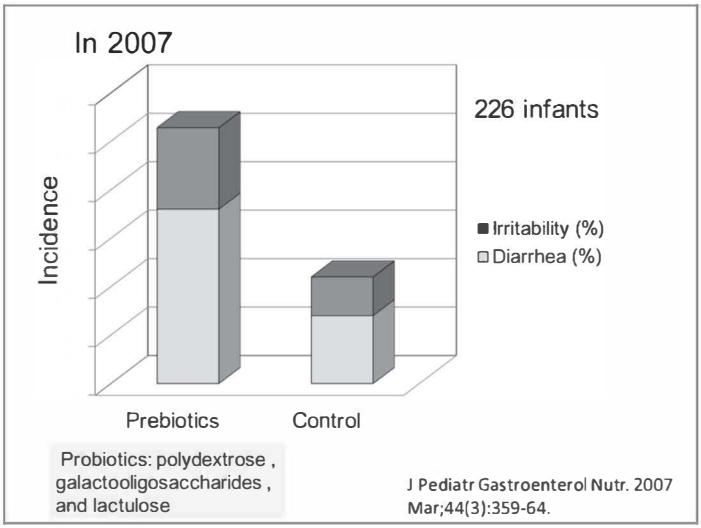


Figure 54: *The occurrence rate of side-effects from GOS in infants (Ziegler et al.).*

For example, in an article from Finland in 1998 (Teuri et al.), 12 healthy volunteers ingested yoghurt containing 15g of GOS. Fecal bifidobacteria did not increase in response to the volume of yoghurt, but the frequency of defecation did increase and, at the same time, abdominal bloating also increased. Thus, bowel habits cannot be controlled by the GOS-induced change of the intestinal flora, which can only be explained by increased water (before fermentation) and gas (immediate response of fermentation). In 2012 research from England (Staudacher et al.) revealed that 4 weeks of a low-FODMAP diet decreased the concentration and proportions of bifidobacteria in the intestine and abdominal conditions, including bowel habits, were improved. In other words, there is no evidence that abdominal symptoms improve with an increase in bifidobacteria.

The government of Japan recommends not only GOS and FOS, but also many of the artificial oligosaccharides as FOSHU (food for specified health use) that maintain human intestinal function. However, for low-FODMAP diets in IBS, these should be avoided due to their high-FODMAP content. In FOSHU research, the upper limit of intake was determined by the occurrence of side effects in healthy subjects, which means that symptoms will occur if the upper intake limit is exceeded even in healthy individuals. These are the recommended daily consumption

levels regarding standardized FOSHU: 2–6g soy oligosaccharide (containing more than 20% stachyose and raffinose); 3–8g FOS (containing 55–60% FOS, more than 95% powdered); 2–8g lacto-sucrose (55–60%); 2–8g GOS (20–55%); 1–3g xylo-oligosaccharide (more than 95% powdered, 70% in liquid); and 10g isomalto-oligosaccharides (more than 37%). In the low-FODMAP diet for IBS, these components need to be restricted to less than the stated amounts and could be replaced by an "effective dosage amount that produces symptoms" in IBS.

A research study of soy bean products in 1999 (Suarez et al.) compared regular soy bean products (3.33% stachyose, 0.51% raffinose, 3.84% total) and low oligosaccharide soy bean products (0.46% stachyose, 0.16% raffinose, 0.62% total). They found that breath hydrogen was significantly increased in the group consuming regular soy products.

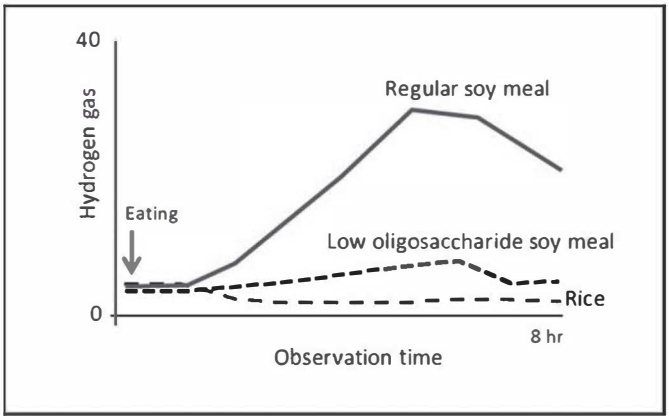


Figure 55: *High GOS foods generate hydrogen gas (Suarez et al.)*

The hydrogen content in the breath test may indirectly indicate the amount of gas produced in the intestine. The notable fact is that 4 hours after ingestion the gas increased rapidly. This fact is important to understand the direct relationship between symptoms and food. Moreover, more flatus was observed in the same group.

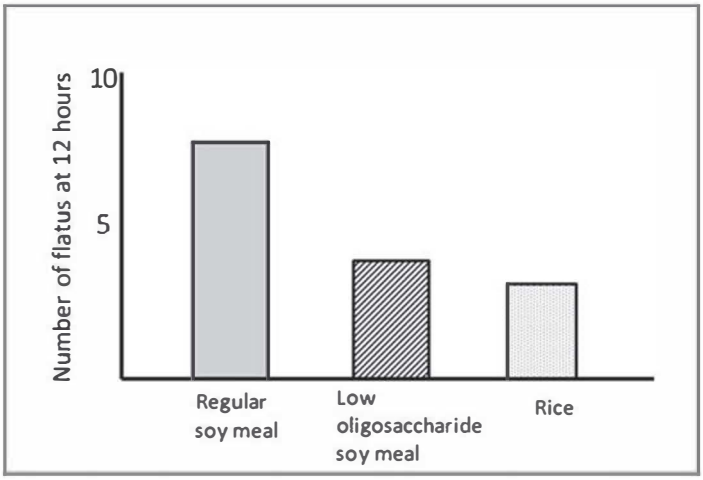


Figure 56: *Oligosaccharides increase flatus (Suarez et al.)*

In this study, the number of oligosaccharides contained in regular soy bean products and low oligosaccharide soy bean products were 3.072g and 0.497g, respectively. Due to the fact that even low oligosaccharide soy bean products produce significantly more breath hydrogen than rice, we believe that the number of oligosaccharides should be limited to less than 0.3g per day during the FODMAP restriction stage of the low-FODMAP diet in Japan.

In Japan, GOS is often added to milk for infants. However, in 2012 five cases of anaphylaxis caused by milk including GOS from Singapore were reported (Chiang et al.). Furthermore, in 2014, Swedish researchers (Meli et al.) reported that infantile colic might be increased by artificial milk containing oligosaccharides. In that study, higher rates of discontinuations were observed in the GOS groups (36.4%) compared with the control group (23.8%). The authors suggested this reason might be related to the higher incidence of colic and other gastrointestinal symptoms. Recently, in Japan, oligosaccharides have not only been mixed into artificial milk but also in enteral nutrients. Therefore, diarrhea and constipation are increasing in elderly people in nursing homes.

Raffinose: This is included in tofu. Japan has a variety of tofu products such as tofu fritter (*gan-modoki*), *Yose-tofu*, soy milk, soy pulp (*okara*), and silk *tofu* (*kinu-tofu*), all of which contain 1-2% raffinose. *Tofu* products that contain less than 1% raffinose are thick, deep-fried *tofu* (*astuage*), *momen-tofu*, fried *tofu*, frozen-dried *tofu* (*kohya tofu*), dried *tofu* powder (raffinose: 0.57g), and firm tofu. Soft cheese is a high-FODMAP food and hard cheese is low-FODMAP. As with cheese, soft *tofu* can be judged to be a high-FODMAP food.

Galactan: Galactan is a polysaccharide with many linked galactose molecules. Galactan is contained in the slimy part of *natto*, *okra*, Jew's mallow, basella rubra (Indian spinach), taro, yam, *nameko* mushrooms, *mozuku* seaweed, and *mekabu* (thick *wakame* leaves). Therefore, these foods need to be avoided during the high-FODMAP elimination period (phase 1). Galactan also might be contained in bread, *udon* noodles, pasta, confectioneries, biscuits, cookies, ice cream, jam, dairy milk, and cheese.

2. Wheat and fructan

Fructans are polymers of fructose molecules and they include inulin, levan, and graminan. However, in a low-FODMAP diet only the elimination of inulin is required. Therefore, the relevant fructan is inulin. Human beings do not have the enzymes to break down inulin. Therefore, inulin passes through the small intestine and is fermented in the large intestine, resulting in the production of SCFAs, carbon dioxide, and methane (Boets et al.). According to a 2015 research paper (Jung et al.), inulin increases intestinal flora including *Bacteroides*, *Lactobacillus*, bifidobacteria, *Clostridium*, and *E. coli.*, and inulin itself is fermented by *Lactobacillus* and bifidobacteria. The amount of fructan (inulin) in 100g of food with high-fructan content are as follows: Jerusalem artichokes, 16–20g; chicory root, 17.5g; asparagus, 1.4–4.1g; onion, 1.1–10g; leeks, 6.5g; wheat bran, 2.5g; wheat flour, 1–4g; and garlic, 12.5–17.4g.

The average consumption of fructan in the US between 1994–1996 was 3.91g/day (Shepherd & Gibson). However, wheat products—such as breakfast cereals, pasta, and bread—contribute to the increase in fructan consumption and, moreover, consumption continues to increase. In addition, whether or not fructan is affected by cooking remains unclear (Fedewa et al.). 24% of IBS patients are estimated to be sensitive to fructan (Fedewa and Rao).

●ut of all the F●DMAPs, fructan produces gas for the longest time (more than 5 hours) by fermentation (Murray et al.) and can clinically affect flatulence, abdominal distension, and abdominal pain due to this increase in gas. Theoretically, the amount of gas is larger than the amount of water, so it is highly likely to lead to ■BS-D. In 2●15, Monash University set the recommended daily number of oligosaccharides (including fructan) as up to 1.57g (●.47–2.66g during low-F●DMAP diet period) (Halmos et al.). Also, in a study comparing gluten and fructan, 2.1g/day of fructan affected patient symptoms (Skodje et al.).

According to the cut off values proposed by Monash University in 2●17 (Varney et al.), the highest amount of oligosaccharides (fructan plus G●S) allowed in one serving is as follows:

A = core grain products, legumes, nuts, and seeds < ●.3g.

B = vegetables, fruits, and all other < ●.2g.

Calculating this in a daily dose yields: (A + B) X 3 = 1.5g, so the daily cut off value for oligosaccharides is less than 1.5g.

If only fructan is ingested (all other foods are F●DMAP-free), then less than 1.5g/day can be consumed. However, considering that it has been less than 1●● years since Japanese people started eating wheat, then fructan consumption for the elimination phase of low-F●DMAP diet should be lowered to less than 1g/day in Japan. Japanese people most frequently consume fructan in bread, pasta, *udon*, *takoyaki*, sweets, Chinese noodles, *somen*, pizza, and other flours. And, as wheat flour is used in many processed foods in Japan, if patients do not strictly restrict consumption they will not benefit from a low-F●DMAP diet.

***Soba*:** Travelers coming to Japan from overseas may think that *soba* is a low-F●DMAP food, but that is a mistake. In Japan, "*soba*" does not mean pure *soba* only. Most "*soba*" in Japan contain wheat flour. Additionally, "*ramen*", "Chinese noodles", and "*yakisoba*" are high-F●DMAP foods.

Figure 57: *Yakisoba is wheat flour noodles fried in oil*

Figure 58: *Ramen is made from wheat flour noodles soaked in soup*

Figure 59: *Nihon-soba (Japanese soba/Japanese noodles)*

Japanese *soba* contains many types of flour. Noodles that are 100% buckwheat with no wheat flour are called "*jyuuwari-soba*" and noodles containing 70% buckwheat are called "*nanawari-soba*". 50% buckwheat noodles "*gowari-sob*a" are used in many Japanese buckwheat restaurants. Pure *soba* is not white but gray. White *soba* is likely to contain a lot of wheat flour. Okinawa *soba* is almost 100% wheat flour noodles.

In Japan, wheat imports have increased significantly. Following World War II, large amounts of wheat were imported from America as "American powder" (*meriken-ko*) to prevent starvation. Subsequently, wheat has had a significant impact on the current Japanese diet.

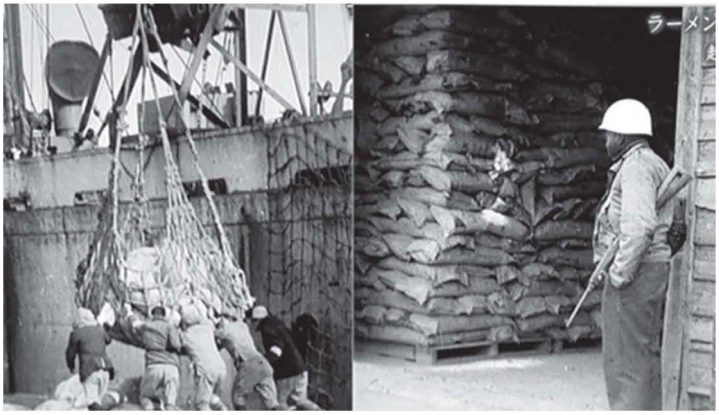


Figure 60: *Meriken-ko was imported from the US to Japan (NHK: Ramen and Japanese, 5th September, 2018 television broadcast).*

Recent reports suggest that for breakfast only 32–43% of Japanese people eat rice and 35–56% of them eat bread (Mainichi Broadcasting on 13/Oct/2015). Ramen and udon noodles contain 100g of wheat per serving. Thus, the Japanese people can easily exceed the tolerated amount.

Figure 61: *The amount of wheat imported into Japan has increased year after year.*

Japanese people are consuming about 100g per day, which is equivalent to 1–4g of fructan.

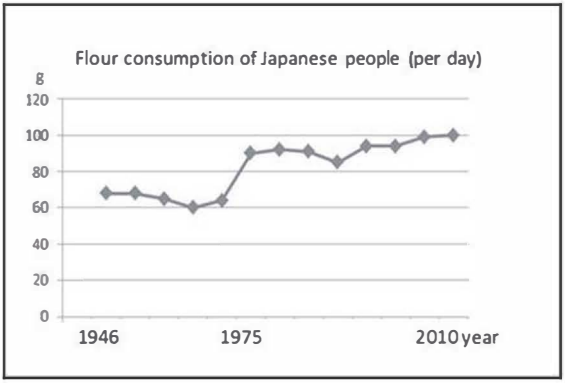


Figure 62: *The daily consumption of wheat by the Japanese (Data from Japan Health, Labor and Welfare National Health and Nutrition Survey Report)*

In a low-FODMAP diet, rice flour, spelt wheat, and white sorghum are used as substitutes for wheat. Although whole meal flour is high-FODMAP, 100% spelt flour only contains 0.2g of fructan and 25% flour contains 0.14g fructan/100g. This means that 500g of spelt flour can be used when 1g of fructan is the daily tolerated amount. However, the number of total oligosaccharides, including raffinose and maltose, contained in spelt flour is 0.3g for milled flour and 0.45g for wholegrain. Therefore, it is recommended that more than 200g of spelt bread should be avoided during the elimination period and it could also be used as a test in the challenge period.

Figure 63: *Tandoor bread that is eaten in Central Asia can also be made with spelt wheat http://fanblogs.jp/nene2016/archive/143/0*

3. Disaccharides (lactose, lactulose, and trehalose)

Disaccharides (also called double sugars) are composed of two molecules of simple sugars (monosaccharides) linked together. Disaccharides include lactose, lactulose, and trehalose and are non-absorbable from the small intestine when in its double sugar form.

Lactulose: Lactulose is a synthetic disaccharide of galactose and fructose, which was invented in the 1930s. It is produced by heating cow's milk. There is 3.5mg/L and 744mg/L in pasteurized milk and sterilized milk, respectively. Lactulose is known to cause diarrhea and is used to treat hyperammonemia caused by cirrhosis of the liver. Although there are some skeptical opinions, lactulose produces lactic acid and acetic acid in the large intestine by fermentation, and those acids decrease the pH of the intestine and, therefore, prevents the growth of ammonia-producing *Bacteroides* and *E. coli* (Vince et al.). In 1988 an interesting case was reported concerning lactulose side effects (Wright). An elderly patient with constipation developed megacolon syndrome (12cm width) due to the large amount of gas produced from excess fermentation after taking lactulose in lavage fluid.

Lactose: Lactose is a disaccharide sugar composed of galactose and glucose, and it is an essential calorie source for all mammals, except sea lions. Lactose is not able to be absorbed from the small intestine due to its disaccharide form, but this changes after it is broken down to glucose and galactose by lactase. Lactase becomes active on the mucosal surface of a fetus' intestines after 8 weeks of pregnancy. Mucosal activity increases until the 34th week of pregnancy and peaks at birth (Deng et al.). Human milk contains about 7% lactose (Silanikove et al.). Lactase is also present in breast milk; however, congenital lactase deficiency is a life-threatening condition. Lactose, which passes through the gastrointestinal tract without being absorbed by the small intestine, is carried to the large intestine and is fermented by lactobacilli or bifidobacteria, which is orally ingested from the mother (e.g. vaginally). Due to intestinal peristaltic hyper-reactivity caused by this fermentation, the baby's defecation frequency is two to five times per day. However, the increase in gas from fermentation can cause infantile colic.

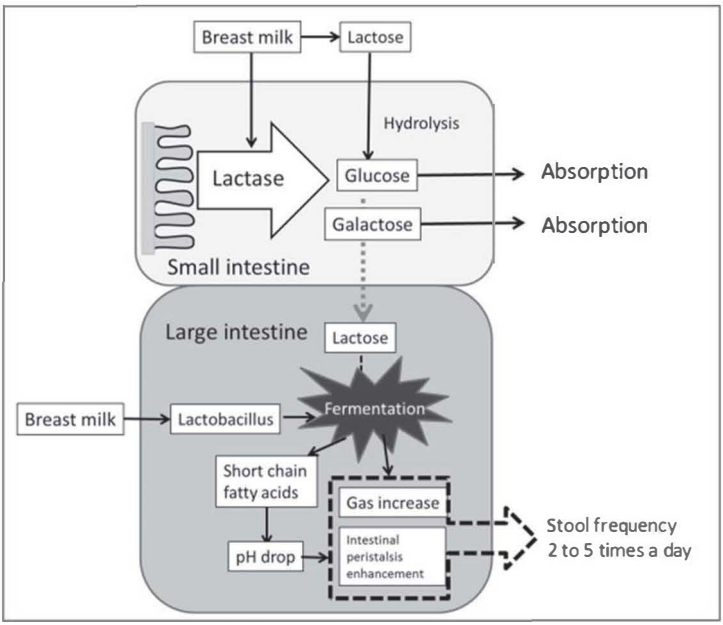


Figure 64: *The metabolism of lactose and function during infancy*

Usually, the activity of lactase decreases several months after birth when breast milk becomes non-essential for the infant. The decrease in the synthesis of lactase after lactation ceases occurs in about 2/3 of the population in the world and its activity decreases by 5–10% before the age of 5. Unlike Japanese people, lactase activity continues in adults among the descendants of ethnic groups with a digestive capacity for milk and other dairy products. This can often be seen in Northern Europe: in 90% of Scandinavians and Dutch, and 50% of Spaniards, Italians, and Arabian nomads, whereas 1% of the Chinese population and 5–20% of people from West African agricultural regions retain this ability (Swallow). Most human populations before the Neolithic Revolution were lactose intolerant (Malmström et al.). It is thought that this persistence of lactose activity among ethnic groups depends on whether or not farming of cows occurred in the past 10,000 years. This gene is inherited due to Mendelian characteristics.

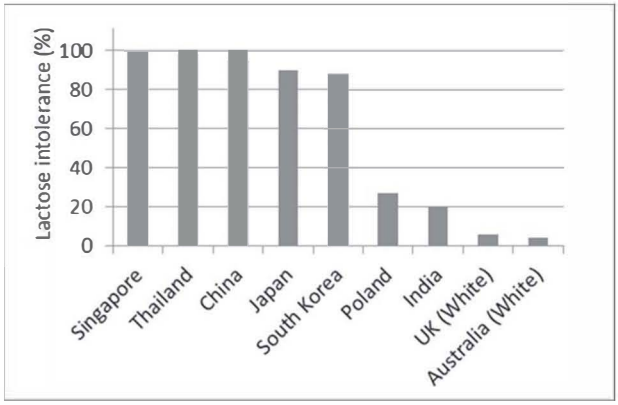


Figure 65: *The proportion of lactose intolerance (Uno and van Velkinburgh)*

Differences in lactase activity between ethnic groups are explained by genetic analysis: mainly due to the difference between Finnish-type genes and Chinese-type genes. This reason may be due to a mutation based on the long-term relationship with dairy cows. In contrast, lactose intolerance is observed in 1% of the Dutch population, 4% of Caucasians in Australia, 5–15% in England, 19% in Italy, 20% in India, 85% in Aborigines in Australia, 90% in Bantu in Africa, 95% in Chinese, 98% in South East Asia, 98% in Thailand, and 100% in American Indians. In the Japanese, lactose malabsorption increases after two years of age, reaching 86% in primary school age children and 90% in adults (Uno and van Velkinburgh, Nose et al.).

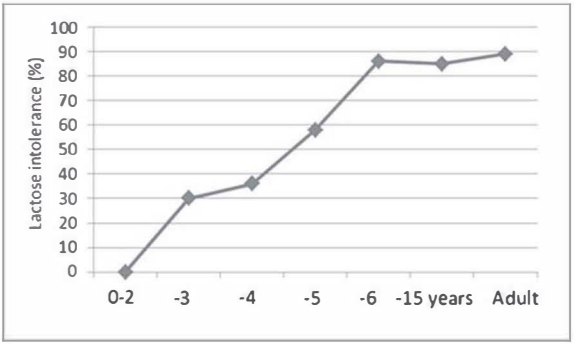


Figure 66: *Morbidity rate and its connection to lactose intolerance in Japanese (Nose et al.).*

Therefore, many Japanese people cannot break down lactose and lactose passes to the large intestine. In high concentrations, lactose is hyperosmotic and pulls water in the intestinal tract into the stool, which causes diarrhea. Moreover, excess fermentation of lactose produces gases (hydrogen and carbon dioxide) triggers pain, abdominal bloating, and lactose intolerance. On a Japanese TV show, there is an agronomist who says, "Let's actively drink milk to overcome lactose intolerance". Certainly, if Japanese people continue to drink milk, lactose intolerance may decrease after 10000 years, but it is not applicable to living people. Even though it is overly fermented, an abnormally decreased intestinal pH continues when drinking milk. Therefore, even bacterial species that ferment lactose may be reduced. In that case, symptoms caused by milk may be alleviated. However, this does not mean that lactose intolerance has improved.

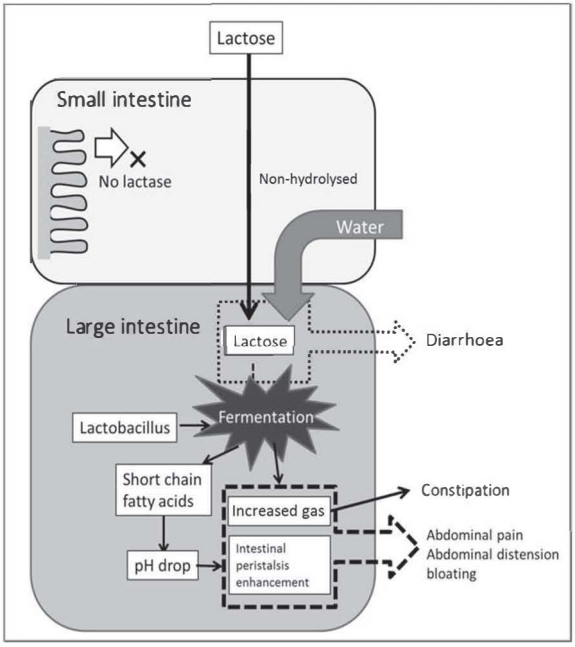


Figure 67: *The mechanism of lactose intolerance*

Lactose intolerance and IBS

Hippocrates first described lactose intolerance in around 400 years BC (Lomer et al.). Symptoms of lactose intolerance generally do not occur until there is less than 50% of lactase activity (Deng et al.). Its main symptoms are bloating, flatulence, abdominal pain, and diarrhea. These symptoms overlap with IBS. Initially, the most accurate method available for the diagnosis of lactose maldigestion was direct biochemical assay of lactase activity from a jejunal sample. However, this test has problems due to the inhomogeneous expression of lactase and the invasiveness of the test (Deng et al., Mattar et al.). Of all the indirect lactose tolerance tests, breath hydrogen after the ingestion of 50g of lactose was considered the most suitable test to screen for lactase deficiency. However, this has been criticized, because it is equivalent to 1L of milk, which an amount that is far more than an individual usually ingests at one time. Therefore, an oral load of 25g (i.e. the mean quantity contained in 500ml of milk) may be

considered a more appropriate amount, with regard to high sensitivity and specificity (Mattar et al.). An abnormally high measurement in the lactose hydrogen breath test (peak hydrogen breath excretion of 20ppm above the baseline level within 3 hours of lactose ingestion) can identify the patient as lactose intolerant (Gasbarrini et al.).

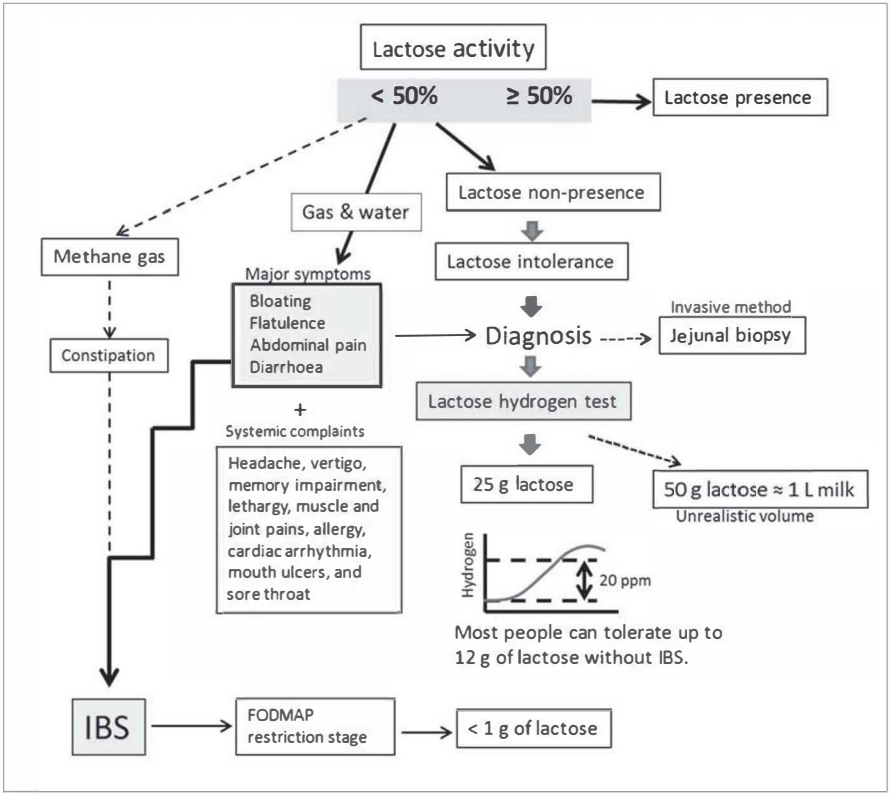


Figure 68: *Diagnosis of lactose intolerance and its relationship with IBS*

The lactose breath test is based on the fermentation of undigested lactose by intestinal flora that produces hydrogen, carbon dioxide, and methane which are absorbed and eliminated via the lungs; however, these gases also cause bloating, flatulence, abdominal pain, and diarrhea. Despite being widely used, the reliability of this test depends on the activity of bacterial flora. A false-negative result can occur if antibiotics have been

taken within 1 month of being tested, if colonic pH is acidic enough to inhibit bacterial activity, or if there has been adaptation in the bacterial flora as a result of continuous lactose exposure (Mattar et al.). In patients with lactose intolerance, systemic complaints, such as headache, vertigo, memory impairment, lethargy, muscle and joint pains, allergy, cardiac arrhythmia, mouth ulcers, sore throat, and gastro-esophageal reflux disease, have been reported (Matthews et al., Harrington et al., Minenna et al.). Putative toxic metabolites, such as acetaldehyde, acetoin, ethanol, peptide, and protein toxins (which are generated by lactose fermentation created by colonic bacteria), can alter cell signaling mechanisms and are possibly responsible for these systemic symptoms (Mattar et al.). Commonly, it is believed that most individuals with lactose malabsorption can tolerate up to 12g of lactose without significant symptoms. However, in theory, continuous lactose intake among people with lactose non-presence may also cause continual exposure to such toxins. With doses larger than 18g, intolerance becomes progressively more frequent, and quantities over 50g elicit symptoms in most individuals (Shaukat et al.). It has been shown that patients with irritable bowel syndrome are at particular risk of both self-reporting dairy intolerance (Zheng et al., Bohn et al.) and experiencing symptoms after lactose and FODMAP ingestion (Yang et al., Halmos et al.). The accumulation of chronic methane gas may cause constipation because animal models have shown a marked reduction in the major migratory complexes of the gut when infused with methane, which slows gut transit (Pimentel et al.). Some patients experience abdominal pain with 12g of lactose, and the cut off value (daily dose) of lactose tested in the low-FODMAP diet study was about 0.04–1.5g. For these reasons, in 2016 we (JLFDPG) recommended that individuals should limit the lactose amount at the FODMAP restriction stage of the low-FODMAP diet to 1.25–1.5g or less. In 2017, researchers from Monash University defined more than 1g of lactose (per serving) as high-FODMAP (Varney et al.).

The lactose amount in 100ml/100g of milk is 4.5–7 g, 3.5–6 g in yoghurt, 6g in ice cream, 3.2g in cream cheese, 0.3g in cottage cheese, 0.06–0.23g in cheddar cheese, and 1–3.2g in onions. While there are fewer people with lactose intolerance in Australia, Europe, and North America than in Japan, lactose-free products are produced and sold for lactose intolerant individuals. Lactose-free milk is sold in Korea. In Korea, it has been reported that lactose-free milk causes less gas production than lactose-containing milk and dramatically improves symptoms (Park et al.).

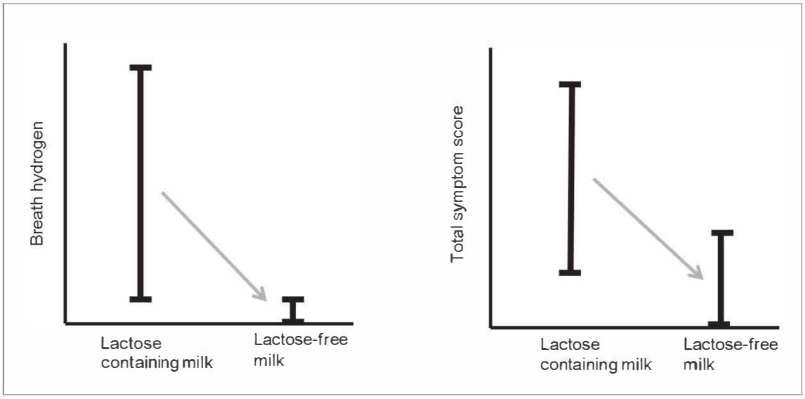


Figure 69: *The effect of lactose-free milk on lactose intolerance (Park et al.)*

However, such products are rarely seen in Japan and lactose-free milk powder, which is imported, is only for pets. This is a fact that should be considered when traveling to Japan. Almond milk is a prominent milk substitute; however, Japanese almond milk may have high-FODMAP contents (fructose, honey, etc.) added. In addition, soy milk and rice milk are high in oligosaccharides and coconut milk is high in sorbitol and should be avoided for people with abdominal symptoms. Therefore, in a low-FODMAP diet pure almond milk is recommended as a substitute for milk. In addition, if symptoms develop in response to very small amounts of milk that contains less than lg of lactose then the cause could be an allergy triggered by the other components of milk such as casein. In this case, patients should avoid it altogether.

Trehalose: Trehalose is a disaccharide in which two glucose molecules are bonded. It is present in mushroom, sunflower seeds, and marine algae. *Shiitake*, *matsutake*, *maitake*, *shimeji*, *nameko*, *eringi*, and *enokidake* are popular mushrooms due to their high-fiber and low calorie content. Trehalose is contained in 1–17% of dried mushrooms and it is also called mushroom sugar. In 2016, a Japan low-FODMAP diet promotion group recognized trehalose as high FODMAP and recommended limiting trehalose-containing food during the exclusion stage.

Figure 70: *Mushrooms sold at the grocery store in Japan.*

Trehalose is also present in microorganisms, including baker's yeast, and honey. Human beings cannot produce trehalose; however, trehalose is hydrolyzed to two molecules of glucose by the specific enzyme trehalase, which is localized in the brush border membrane of the small intestine, allowing it to be absorbed into our body (Oku & Nakamura). A potential association between low trehalase activity and abdominal symptoms has been reported, and malabsorption of trehalose could trigger similar symptoms to lactose intolerance (Arola et al.). A 2009 research study (Petermann et al.) confirmed that some Crohn's disease patients suffered from mushroom intolerance. In mushroom-intolerant patients, trehalase activity was significantly lower. When subjects ingested 25g of trehalose, their volume of gas increased significantly. Trehalase insufficiency is observed in 3% of the Finnish population and 10–15% of Eskimos; it is also potentially higher in non-white races. In a research paper from Tokyo University in 2000, it was reported that 28% of healthy Japanese women (from 18 tested) developed diarrhea in response to 40g of trehalose (Oku & Nakamura). It has unique properties: stability when faced with heat and acid, excellent recourse from freezing and drying, and it prolongs the shelf life of food products containing starch. In 1994, a new method which

derives trehalose from starch at a low cost was developed in Japan, and this broadened its application to food products (Oku & Nakamura). Japan became the largest consumer globally. It is used to prevent dryness in foods and variety in not just restaurant food but also in many processed foods including Japanese-style confections (red bean paste, *mochi*, and *dango*), western-style confectionary (cream, custard cream, and pudding), bread, beer, side dishes, processed marine products, processed meat products, pre-packed food, frozen food, and soft drinks. The amount of trehalose contained in each food is not shown on the labels and trehalose is one of the high-FODMAP foods used, particularly in Japan.

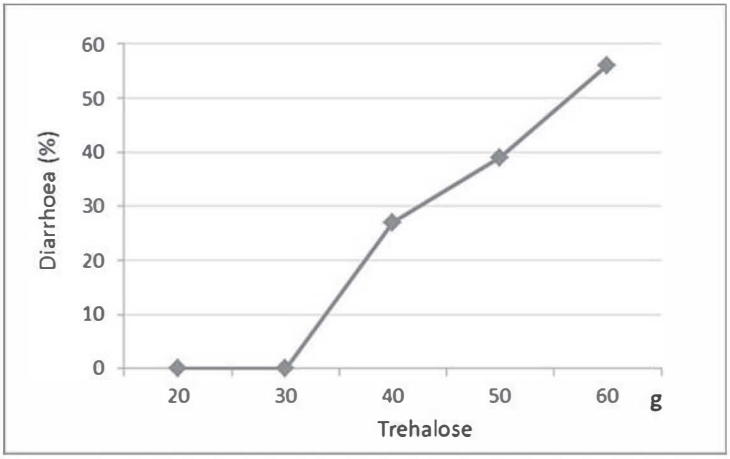


Figure 71: *Relationship between trehalose intake and incidence of diarrhea (Oku & Nakamura)*

Since the amount of trehalose is not indicated in Japanese foods (e.g. cakes, pastry, and candy), "confectionery that can be stored at room temperature for a long time" must be avoided.

4. Fructose

Fructose is a natural hexose (hexose is a sugar molecule containing six carbon atoms). Fructose is contained in specific fruits, vegetables, honey, and artificial isomerized sugars such as high-fructose corn syrup. In 1959, genetic fructose intolerance was reported in Germany (Wolf et al.).

Subsequently, it has been researched in Germany and France. Genetic fructose intolerance occurs due to a lack of aldolase B, which is the enzyme that breaks down fructose. In normal subjects, fructose is absorbed in the small intestine. In contrast, in fructose intolerance hydrogen is overproduced due to the fermentation of fructose. In 1978, Andersson and Nygren described four patients with gastrointestinal symptoms after fruit ingestion in whom symptoms could be reproduced with the consumption of 100g of fructose (Andersson and Nygren). Research in 1983 (Ravich et al.) showed that fructose intolerance could be diagnosed by breath hydrogen volume after the ingestion of 50g of fructose solution. Researchers suggest that the malabsorption of fructose may lead to gastrointestinal symptoms. In research from 1984 (Kneepkens et al.), incomplete intestinal absorption of fructose in children was investigated using measurements of breath hydrogen. After the ingestion of fructose (2g/kg bodyweight) breath hydrogen was increased in children with abdominal symptoms, and fructose was the only sugar incompletely absorbed. Furthermore, the effect of glucose on fructose absorption was shown to be dependent on the amount of added glucose.

Up to 1/3 of IBS patients are estimated to potentially have fructose malabsorption and intolerance (Choi et al.). To be precise, 36–75% develop symptoms to 25g of fructose and 80% to more than 50g. When the ratios of fructose and glucose are equal (a minimum of 1:1 is the optimal ratio of glucose to fructose), fructose is absorbed together with glucose from the small intestine (Ravich et al., Murray et al.). This was discovered in 1986 in Denmark (Rumessen & Gudmand-Høyer) and subsequently verified. When the fructose amount outweighs glucose, absorption occurs slowly and the unabsorbed fructose will enter the large intestine. Unabsorbed fructose in the colon ferments and produces carbon dioxide and hydrogen, which trigger abdominal bloating, flatulence, and soft stools (Latulippe et al.).

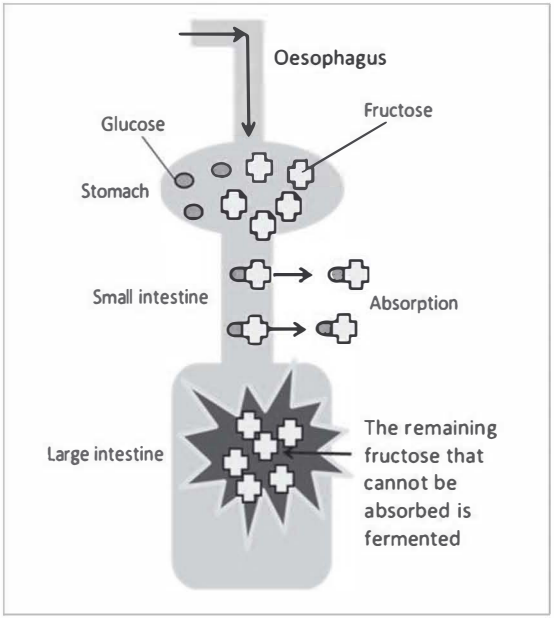


Figure 72: *The mechanism of fructose fermentation*

Breath testing after ingestion of fructose has been widely adopted as a standard method of identifying fructose malabsorption and intolerance. A dose of 25g of fructose dissolved in a 10% solution is generally accepted as the appropriate amount of fructose for clinical hydrogen and methane breath testing. A study (Rao et al.) that compared three doses of fructose (15, 25, and 50g) found that 100% of healthy volunteers could absorb 15g of fructose, 90% could absorb 25g of fructose, but only 20–30% could absorb 50g. In padiatrics the appropriate dosage still requires standardization, but a dose of 0.5–1g/kg with a maximum dose of 10–15g has been suggested (Jones et al.).

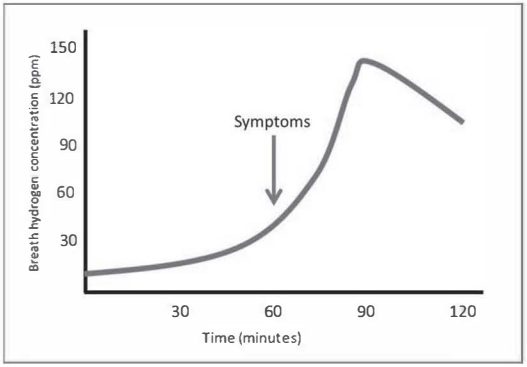


Figure 73: *A significant rise in hydrogen after an oral dose of 25g of fructose in a patient with fructose malabsorption or intolerance. There was a reproduction of symptoms that correlated with the significant rise in hydrogen (Fedewa et al.).*

In the world's most popular "Low-FODMAP diet textbook", by Shepherd and Gibson, it is stated that excess fructose becomes a problem in IBS from 0.2g (Shepherd & Gibson). However, in 2017, the same group at Monash University changed the definition of high-FODMAP fructose content to 0.4g and over (Varney et al.). For example, the fructose content per 100g of lime is 0.7g; however, the amount of glucose is also 0.7g and so lime does not induce symptoms. Honey contains 40g of fructose and 33g of glucose and, therefore, induces symptoms. Mango contains 3.1g of fructose and 0.7g of glucose and also induces symptoms. Apples are high-FODMAP as they contain 6g of fructose, 1.4g of glucose, and 0.7g of sorbitol. The highest fructose-containing food is agave syrup, which contains 55.6 g of fructose and 12.43 g of glucose.

In a Monash University study from 2017, it was reported that the addition of glucose to whole foods containing fructose–in patients with functional bowel disorders and healthy controls had no significant effect on breath hydrogen production or symptom response (Tuck et al.).

The tolerance range of excess fructose in the low-FODMAP diet varies depending on the researcher: 2014, 1.24g/day (Halmos et al.); 2015, 0.9g/day (Böhn et al.); and in 2017, 1.9g/day (Staudacher et al.). As excess fructose is more than 0.2g/day, this criteria may be inconsistent with the concept of the low-FODMAP diet. In 2016, we (JLFDPG) decided that at

the F●DMAP restriction stage of the low-F●DMAP diet excess fructose should be less than ●g/day.

Peaches, apples, pears, cherries, and strawberries are rose-family fruits. Sorbitol is produced in their leaves by photosynthesis. Sorbitol moves to the fruit and is converted into fructose and glucose. In Japan, varieties were made to increase fructose and make these fruits sweeter (Watanabe et al.). With regard to fruit, the low-F●DMAP standards of other countries may not be applicable to Japan. In Japan, fruit with high fructose and sorbitol content is considered delicious. However, the combination of fructose and sorbitol is known to accelerate small bowel transit (Madsen et al.).

High-fructose corn syrup (HFCS): HFCS is an artificial sweetener made from a mixture of sugar and glucose derived from starch. The raw starch material used in Japan was previously from potatoes and sweet potatoes i, but is currently cornstarch produced from imported com. Since 1980, when the Coca-Cola Company in America began using HFCS as a replacement for sugar, the market has expanded globally. According to Japanese Agricultural Standards (JAS), sugar syrups are classified into four varieties. If the fructose content percentage is less than 50, it is called glucose-fructose syrup; if the percentage is more than 50 and less than 90, it is called fructose-glucose syrup; and if the percentage is more than 90, it is called high-fructose syrup. When more than 10% sugar is added to one of the above, it is called sugar-mixed isomerized syrup. Therefore, the syrups that potentially trigger symptoms when they ferment are high-fructose syrup and fructose-glucose syrup. In the US, HFCS-55 (fructose content 55%; glucose 45%) is often used in soft drinks and it needs to be avoided on a ow-F●DMAP diet. In the EU, syrup containing more than 50% fructose is called fructose-glucose syrup and when it is less than 50%, it is called glucose-fructose syrup (iso-glucose).

Comparison of HFCS and sucrose

	Fructose (%)	FODMAP
Glucose-fructose syrup (Japan)	< 50	Low
Fructose-glucose syrup (Japan)	50-90	High
High fructose syrup (Japan)	90 <	High
HFCS-55 (US)	55	High
HFCS-42 (US)	42	Low
Fluctose-glucose syrup (EU)	50 <	High
Glucose-fructose syrup (EU)	< 50	Low
Sucrose	50	Low

DiNicolantonio and Lucan stated that 10% of healthy individuals and 47% of patients with IBS have one or more symptoms upon the consumption of HFCS-55 that provides 40g of fructose, and 20% of healthy individuals and 30% of IBS patients have fructose malabsorption (DiNicolantonio and Lucan).

5. Polyols

Sorbitol, xylitol, mannitol, maltitol, isomalt, lactitol, and erythrol are sugar alcohols that are fermented by intestinal bacteria without being absorbed in the small intestine. Artificial polyol is used as a low-calorie sweetener and Japanese nutritionists recommend it for diabetes and obesity patients. In addition, even in non-obese women polyol is widely used for the purpose of maintaining a slim body shape. In my (Uno) outpatient experience, almost all chronically constipated women use such supplements. Many use laxatives on a daily basis to improve the gas symptoms that are a side effect of supplements. As a result, they get laxative poisoning.

Unfortunately, using the hydrogen breath test for sorbitol is impossible for IBS because it failed to obtain a clear cut off value (Yao et al.). Therefore, polyols induce gastrointestinal symptoms in patients with IBS independent of their absorptive patterns, suggesting that dietary restriction of polyols may be efficacious. In 2016, the JLFDPG stipulated the polyol volume in the exclusion stage in Japan to 0.1–0.2g/day. According to the cut off values proposed by Monash University in 2017 (Varney et al.), the cut off value of polyol (sorbitol or mannitol) should be less than 0.2g in one serving. In any case, in the FODMAP restriction stage of a low-FODMAP diet, obviously food containing polyol must be eliminated.

Sorbitol: Most sorbitol is made from corn syrup and added to a variety of foods, but it is also found in nature: for example in apples, pears, peaches, and prunes. This substance was first discovered in 1868 and described by French chemist Jean-Baptiste Boussingault in 1872 in the course of studying rowanberry enzymes, which he described in detail and named sorbitol (French, lesorb; Latin, *Sorbus aucuparia L.*). In 1966, a case of a child with repetitive diarrhea was reported in the NEJM (Gryboski). The child had developed abdominal bloating and pain 2 hours after consuming a packet of sugarless mint candy and produced more than tenfold the normal amounts of yellowish, watery stools 4 hours later. The symptoms were relieved the following morning. However, the child had the same symptoms repeatedly after a dentist gave them sugarless candies. The same hospital reported similar cases with 10 children from 20 to 36 months old over a 15-month period. The amounts of sorbitol in the stools were 1mg/g for children without symptoms and 5–20mg/g for those with diarrhea. They also reported that children should avoid sorbitol, as the side effects are dependent on bodyweight. Moreover, in 1978 (Goldberg and Ditchek) a case was reported involving a 66-year-old that had developed chronic diarrhea after the use of sugarless gum on a daily basis. This was caused by 85–170g of sorbitol and it was called chewing gum diarrhea. In JAMA a case of diarrhea caused by weight control products was reported in 1980. A 29-year-old man had developed abdominal bloating, pain, and diarrhea 5–6 times a day a few days after taking weight loss products. He consumed two packets of the sugarless gum (1.2g of sorbitol/stick, five sticks per packet), two rolls of sugarless mints (1.4g of sorbitol/tablet, one tablet per roll), and weight loss wafers, which contained xylitol and sorbitol. The total amount of sugar alcohol he consumed from food was still within the daily range of 50.9–55.1g/day (Ravry). In 1983, it was reported that 5g of sorbitol increased hydrogen in the breath, 10g caused

gas and abdominal bloating, and 20g caused intestinal spasms or diarrhea (Hyams). In 1985, after Caucasians and non-Caucasians took 10 g of sorbitol, 43% of Caucasians and 55% of non-Caucasians were symptomatic. However, severe sorbitol intolerance was significantly higher in non-Caucasians (32%) than in Caucasians (4%). There was an association between the severity of the symptoms and the hydrogen content in the breath (Jain et al.).

Sorbitol is used in Japan as a carbohydrate laxative, and the effective amount is 6.5g. Currently, sorbitol is added to a variety of foods in Japan. It is used to enhance the color of food and as a sweetener in weight loss products. In Japan, however, the sugar alcohol content does not have to be clearly shown on the packaging. In 2015, the Tokyo Metropolitan Food Safety Commission published the following, with regard to the allowable amount of sugar alcohol.

Maximum no-action amount: Reference value

Amount per unit weight that does not cause laxative action when ingested at one time:

Erythritol: man 0.66g/kg body weight, female 0.8g/kg body weight

Maltitol: man 0.3g/kg body weight, female 0.3g/kg body weight

Lactitol: man 0.075g/kg body weight, female 0.15g/kg body weight

Xylitol: man 0.3g/kg body weight, female 0.3g/kg body weight

Sorbitol: man 0.15g/kg body weight, female 0.3g/kg body weight

For example, for a child weighing 25 kg, more than 7.5g xylitol exceeds the limit. For a woman weighing 50kg the limit is 15g. However, we need to be careful, as even one packet of chewing gum with a label that proclaims "good oral health" contains 64.3g of xylitol and 50g of maltitol. The amount of sorbitol contained in 100g of food in Japan are as follows: 1.9–2g in baked confectionaries; 2.4g (and 39g of erythritol) in weight loss candies; 1.3g in sausages; 8.2g (also 66g of erythritol and 60g of maltitol) in gummy candies; 65g (plus 120g of xylitol and 14g of maltitol) in soft candies; and 12g (plus 12g of maltitol) in mirin. With regard to other sugar alcohols, chewing gum contains 12g of xylitol; low calorie sweeteners contain 38g of erythritol and 58g of maltitol; and low-calorie

marmalades contain 0.g of sorbitol, 10 g of erythritol, and 22g of maltitol. 20g of cherries contain 4.6g of sorbitol and 100g of strawberries contain 0.36g of xylitol.

According to legal regulations in Japan, if the amount of sorbitol is 20g or more it is necessary to apply for classification as a medicine (laxative). Therefore, foods containing a higher content of this product are regulated.

Xylitol: Xylitol is a sugar alcohol sweetener that is often used in Japanese foods. In Japan, it is used for preventing caries and treating diabetes. The Japanese dental association society recommends gum containing maltitol (6.6g per 14 tablets) in addition to xylitol (7g). Xylitol is naturally found in low concentrations in the fibers of many fruits and vegetables; can be extracted from various berries, oats, and mushrooms; and can be produced by the action of yeast on the xylose contained in fibrous materials, such as comhusks. Diarrhea (Mäkinen and Scheinin, Mäkinen, Oku et al.) and/or abdominal distension (Gong et al.) caused by xylitol alone has been reported.

Reduced-sugar syrup: Many artificial sweeteners, which are not indicated in raw materials and ingredients, are used in Japan. Reduced-sugar syrup is one such ingredient. Reduced-sugar syrup is a sugar alcohol, which normally contains less than 75% maltitol, less than 50% sorbitol, and other sugar alcohols such as tri- or tetrasaccharides. As sugar alcohol contained in the reduced-sugar syrup is rarely able to be absorbed in the small intestine, the calorie count is lower than normal sugar (about 2/3 at 230–340 kcal/100g). Additionally, blood sugar and insulin elevation are slower, which is why it is sometimes used as a sugar substitute for diabetic patients. Reduced-sugar syrup is acid-stable, heat-stable, and non-tinting, and so it is often used in cooking or processing. Currently, it is one of the most common sweeteners used in low calorie sugars or weight loss products. "Marvie" and "Sugar Cut S" are common Japanese sweeteners that mainly contain reduced-sugar syrup.

Mannitol: Mannitol is 2 kcal/g (half that of sugar) and the sweetness is 60% of sugar. Mannitol is a sugar alcohol widely present in nature. The white membrane on the surface of dried seaweed and persimmon is crystalline mannitol.

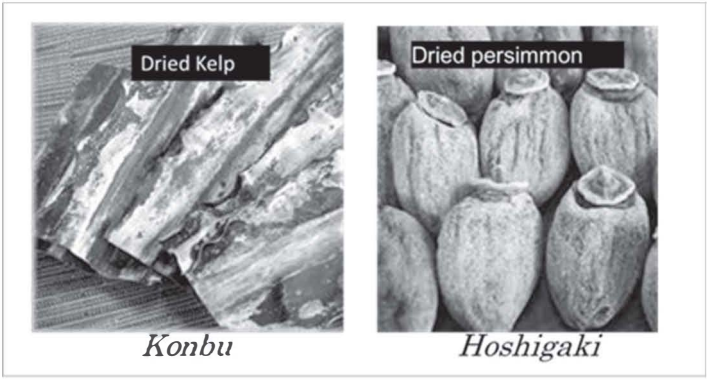


Figure 74: *Mannitol of dried kelp and dried persimmon.*

Mushrooms also contain mannitol and *shiitake* mushrooms contains more mannitol than *enoki* mushrooms. However, mushrooms also contain trehalose, which triggers indigestion. There are other foods that have a high content of mannitol: cauliflower: 2.6g; mushrooms, 2.6g; and peaches, 0.5g (all in 100g). Artificial mannitol is made from sucrose. Mannitol causes diarrhea and mannitol solution (5% mannitol in 350ml of water with an osmolality of 300mOsmol) has been used as an experimental diarrhea model (Placidi et al.). Studies that use a series of MRIs have confirmed that the amount of water in the small intestine significantly increases 40 minutes after the consumption of mannitol (Marciani et al.).

CHAPTER III

PRACTICING A LOW-FODMAP DIET

1. Who should follow a low-FODMAP diet?

Changes in the Japanese diet

In Australia, the average FODMAP content in food is 23.7g (16.9–30.6g). For this reason, Professor Gibson in Australia suggested the correlation between the increase in high-FODMAP food and IBS and IBD. In doing so, he invented the low-FODMAP diet theory. However, the concept of FODMAPs need to be understood more clearly in Japan. This is because sudden changes in dietary habits in Japan are considered rare in human history. Needless to say, the staple food in Japan for 2000 years was rice.

Figure 75: *Japanese meal in 1150: rice, soup, and a few side dishes (Ehara and Higashiyotsuyagagi)*

Figure 76: *Typical pre-war Japanese food: rice, miso soup, fish, and a small amount of vegetables.*

The staple Japanese did not change until WWII. For example, the total FODMAP content in hospital meals before WWII was about 7g per day, which was comprised of 30g of miso (6g of oligosaccharides), 70g of tofu (less than 0.3g of oligosaccharides), and 2 teaspoons (1g) of soy sauce, if needed. Prior to WWII, most Japanese did not consume flour-containing bread and cows' milk. However, due to the lack of food after the war, skim milk powder and wheat flour were imported from the US. School meals provided after the war were hot dog buns and skim milk. After that, the idea that milk is beneficial for health became established in Japan. In addition, the amount of food products made from wheat flour increased. As a result, the modern Japanese population no longer eat as much rice and, therefore, flour consumption has surpassed rice consumption. In other words, Japan's dietary history, which was stable for 2000 years, underwent a sudden change in just a few years and this has continued for 70 years.

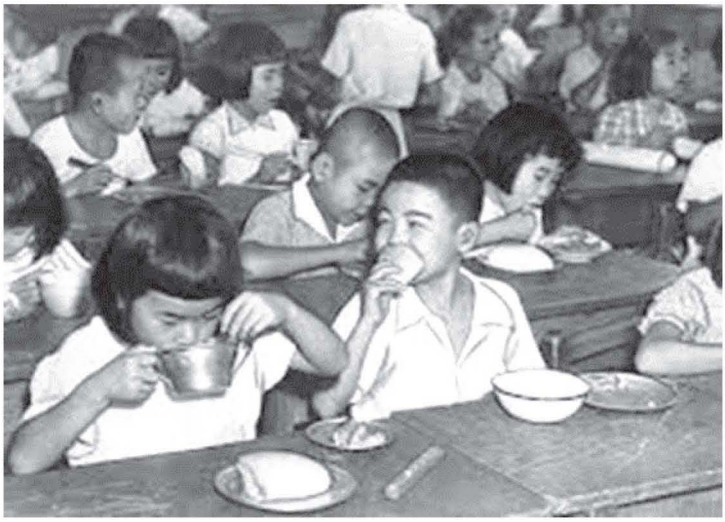


Figure 77: *School lunch in Japanese primary school in 1951*
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Figure 78: *School lunch in Japanese primary school in 1968*
http://mamechishiki.aquaorbis.net/mamechishiki/0918-skimmed-milk/

Figure 79: *School lunch in 2018. Distribution of rice instead of bread has increased, but milk is always distributed.*
http://shikige-jh.ed.jp/wordpress/2018/02/%E5%B9%B3%E6%88%90%EF%BC%93%EF%BC%90%E5%B9%B4%EF%BC%91%E6%9C%88%EF%BC%92%EF%BC%92%E6%97%A5%EF%BC%88%E6%9C%88%EF%BC%89/

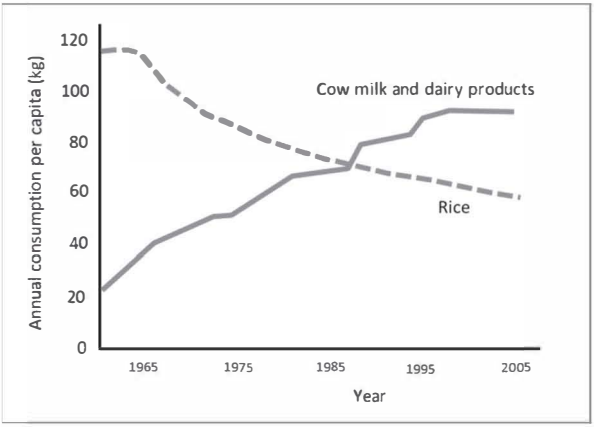


Figure 80: *Trends in the consumption of rice and dairy products in Japan. (Data Source: Japan Agriculture, Forestry and Fisheries)*

Milk consumption has decreased in the US, but is increasing in Japan. In Japan, the total consumption of milk and dairy products is 258g/day (94kg/year). Although more than 80% of Japanese are lactose intolerant, lactose-free milk is not sold in Japan. Most chewing gum sold in Japan contains xylitol and dentists recommend it for the prevention of tooth decay. Also, sugar-free diets have become popular in Japan; sugar in many sweets has been replaced by sorbitol. The number of Japanese patients with IBS has increased steadily and, according to the Rome III criteria, the prevalence of IBS among the Japanese population is 13.6%. In 1958, instant noodles, which are made with wheat flour, were developed in Japan and the Japanese eat an average of 45 cups per person of instant noodles annually. For example, an average Japanese meal consists of two servings of bread (150g; fructan 3g) and 200g (lactose 14g) milk for breakfast, lunch consists of ramen (fructan 4g), and dinner is likely to contain 200g of silk tofu (1g oligosaccharides) and 100g (6g) of cream (in ice cream); therefore, the average amount of FODMAPs per day is 28g.

In Japan, IBS and IBD started to be reported after the war, and since then the number of IBS and IBD reports have increased, leading to a high prevalence rate. In other words, FODMAP foods increased in association with the change of diet in Japan after WWII and it is possible that IBS and IBD have also increased.

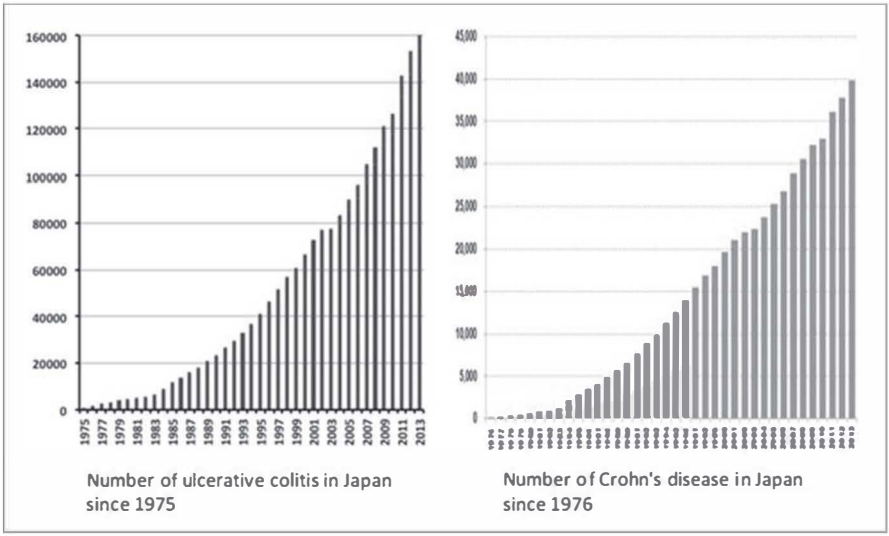


Figure 81: *Number of cases of ulcerative colitis and Crohn's disease in Japan (Data: Japan Intractable Diseases Information Center)*

Figure 81 shows that the total FODMAP amount contained in the Japanese diet has clearly increased post-war. In particular, since Japanese have a higher prevalence of lactose intolerance than Caucasians, and wheat flour began to be consumed more than half a century ago, low-FODMAP meals are expected to be more effective for the Japanese than Westerners. So, who should follow the low-FODMAP diet? The answer is "almost all Japanese people".

Japanese and farts (passage of wind)

The older Japanese generations did not feel shame in expelling intestinal gas. In fact, the 12th century Japanese drawing pictured below depicts a figure fighting using his bodily functions.

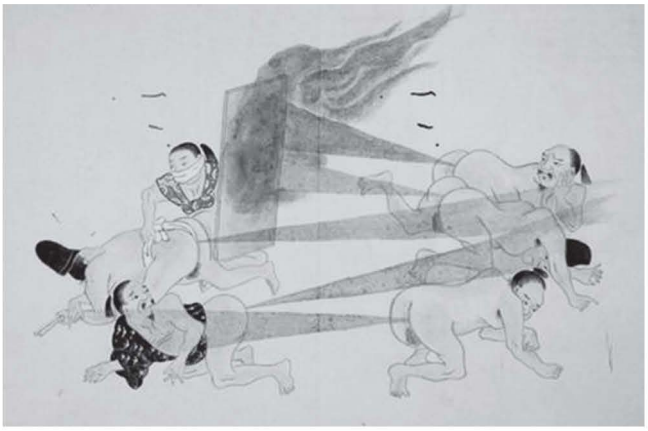


Figure 82: *Battle of farts: replica image from the 17th century (the original picture was drawn in the 12th century).*

Figure 83: *Before the fight, it is drawn that people eat a large amount of Taro.*

These figures suggest that previous generations of Japanese had no intestinal dysfunction and that gas was sufficiently excreted immediately after production.

Note: Relationship between the smell of farts and breath

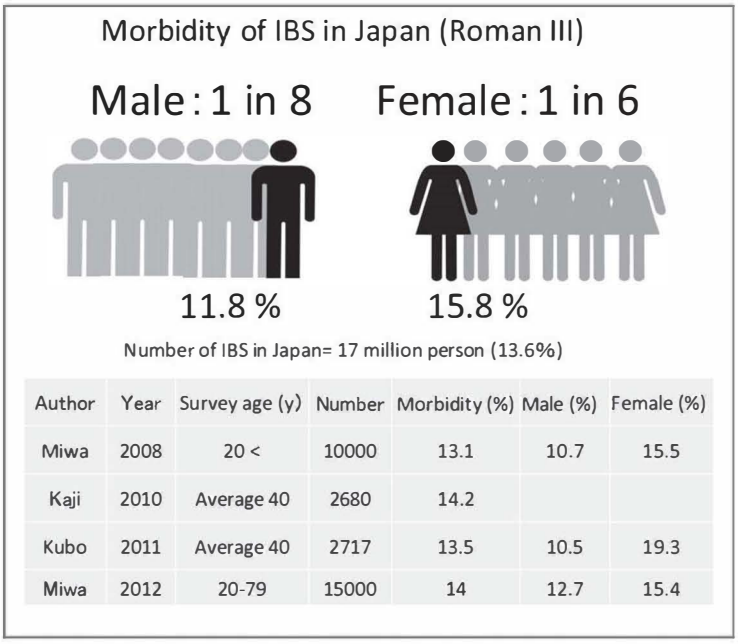
If someone suffers from farts, does their breath also smell? Everyone may care about this. However, it seems that there is no connection. The records of the Rome consensus meeting in 2009 state the following (Gasbarrini et al.): More than 99% of intestinal gas is composed of five non-odorous gases (nitrogen, oxygen, carbon dioxide, hydrogen, and methane) and, in particular, nitrogen ranges from 11% to 92%; oxygen from 0% to 11%; carbon dioxide from 3% to 54%; hydrogen from 0 to > 86%; and methane from 0% to 56%. Various other odoriferous gases, such as ammonia, hydrogen sulphide, indole, skatole, volatile amines, and SCFA, are present in trace quantities and account for less than 1% of flatus. For many years, the aromatic breakdown products of amino acids such as indole and skatole were believed to be the primary malodorous compounds in flatus. On the contrary, more recent studies have shown that sulphur-containing compounds, like hydrogen sulphide, dimethyl sulphide, and methanethiol, are mainly responsible for the unpleasant smell of human feces. In particular, hydrogen sulphide was the predominant sulphur gas in 78% of samples and the concentration of this gas has the strongest correlation with odor. Sulphur-containing compounds were not detected in breath samples.

IBS in Japan

IBS affects 4–30% of the population worldwide; the prevalence rate in Japan is estimated to be 13.6%.

In addition, the prevalence of IBS has increased remarkably in Japan. According to the various revised definitions of IBS made by the Rome diagnostic criteria, the incidence has increased by the following percentages: 3.6% in 1996 (Rome I) (Itasaka and Takahashi); 10.7% in 2006 (Rome II) (Shiotani et al.); 14.0% in 2010 (Rome III) (Miwa). In the literature to date, it is proven that a low-FODMAP diet improves symptoms in 50–75% of IBS patients. Specifically, a low-FODMAP diet is effective for IBS-D. It is also effective for IBS-M. For IBS-C, a low-FODMAP diet is not as effective as it is with IBS-D; however, it is worth trying a low-FODMAP diet to determine if it actually improves symptoms. High-FODMAP food produces highly osmotic diarrhea and fermentable gas. A low-FODMAP diet prevents hyperosmolar diarrhea in IBS-D. In IBS-C, it shortens the CTT by preventing gas generation. The reason why a low-FODMAP diet only has a limited effect with IBS-C may be due to the fact that it does not restrict other gas-producing foods.–For

example, gas evolution also occurs in the fermentation of cellulose and hemicellulose of dietary fiber. In Japan, where dietary fiber myths are pervasive, this is a serious problem because people with constipation are taking too many dietary fibers in order to try to resolve their constipation. Therefore, in IBS-C, it is necessary to eliminate not only FODMAPs but other gas-producing foods, such as dietary fiber.



Author	Year	Survey age (y)	Number	Morbidity (%)	Male (%)	Female (%)
Miwa	2008	20 <	10000	13.1	10.7	15.5
Kaji	2010	Average 40	2680	14.2		
Kubo	2011	Average 40	2717	13.5	10.5	19.3
Miwa	2012	20-79	15000	14	12.7	15.4

Figure 84: *Morbidity of IBS in Japan (Miwa)*

Functional diarrhea or functional constipation

In 2016, Rome IV revised the diagnostic criteria of IBS so that abdominal discomfort without abdominal pain was eliminated. Therefore, patients with only abdominal discomfort who were previously diagnosed with IBS using the diagnostic criteria of Rome III are now classified as having functional diarrhea and functional constipation in Rome IV. Therefore, a low-FODMAP diet is effective for functional diarrhea and functional constipation. In addition, when the intestinal tract is dilated by chronic constipation, the intestinal tract is easily dilated by gas. The influence of

the accumulated gas further prolongs the transit time of the large intestine and exacerbates constipation. This phenomenon can be explained by the fluid density (ρ).

Bernoulli's principle

$$\frac{1}{2}v^2 + \frac{P}{\rho} + gh = \text{Constant}$$

P: pressure, v: velocity of the fluid, g: gravity acceleration, h: height

When the water density is 1g/cm^3, the density of the gas is about 0.001g/cm^3. Since the p / ρ of the gas is 1000 times that of the liquid, the velocity markedly decreases and so the velocity varies depending on the ratio of gas in the volume. From the point of view of fluid dynamics, it is clear that gas causes constipation (Uno: 2017). Therefore, suppressing gas production through a low-FODMAP diet might also suppress the deterioration of chronic constipation and IBS-C. Even if patients do not have diarrhea or constipation, when experiencing extreme flatus and abdominal bloating there is a high possibility that the symptoms would be alleviated by limiting their intake of FODMAPs.

IBD (Ulcerative colitis and Crohn's disease)

Functional-like gastrointestinal symptoms are common in IBD and are reported in 57% of patients with Crohn's disease (CD) and 33% of patients with ulcerative colitis (UC) despite no evidence of active inflammation (Simrén et al.). In 1977, Mishkin et al. reported an increased prevalence of lactose malabsorption in CD patients with small bowel involvement (Mishkin et al.). In 2009, Gibson suggested that a low-FODMAP diet could lighten IBD, and same year his research group reported the results of a pilot study showing the effective reduction of abdominal symptoms of IBD by following low-FODMAP diet (Gearry et al.). In 2017, the effects of a low-FODMAP diet for IBD was reported by a randomized, double-blind, placebo-controlled, cross-over, and re-challenge trial (Cox et al.) and a meta-analysis study (Zhan et al.). Symptoms of relief included an improvement in overall abdominal symptoms, such as reduction in abdominal pain, bloating, nausea, wind, and diarrhea. Specifically, the improvement of abdominal pain was significantly higher and this also improved the patient QOL. Until now, there has been no report that a low-FODMAP diet improves IBD inflammation and causes remission. My (Uno) younger brother suffered

ulcerative colitis with chronic rectal bleeding for more than 10 years, during which time he never achieved remission. He was prescribed mesalazine and steroids, but he was suffering from abdominal bloating as well as rectal bleeding. Therefore, a low-FODMAP diet was introduced. After following a low-FODMAP diet for 6 months, the rectal bleeding disappeared and drugs were no longer necessary. After that, following a low-FODMAP diet for 6 more months cleared all mucosal inflammation and he was diagnosed as being in remission.

Infant colic and functional gastrointestinal disorders in children

A maternal low-FODMAP diet may be associated with a reduction in infant colic symptoms (Iacovou et al.: 2018). Chronic diarrhea and functional abdominal pain in childhood relates to adult IBS. In a proportion of adults with IBS, the natural history of their symptoms might begin during their childhood (Iacovou: 2017, Marugán-Miguelsanz). It has been suggested that IBS affects up to 20% of school-aged children in the US (Chumpitazi et al.). The evidence supporting dietary therapies in children with IBS suggests that the reduction of a single or a few dietary sugars such as, lactose, sorbitol, or fructose, can be effective (Däbritz et al.). In 2015, a randomized, controlled trial investigating the use of the low-FODMAP diet proved its efficacy in children aged 7–17 years old (Chumpitazi et al.).

Anal incontinence caused by spina bifida

Due to the fact that many cases of anal incontinence are aggravated by flatus or diarrhea, a low-FODMAP diet might alleviate anal incontinence caused by spina bifida or anorectal dysfunction. Actually, I (Uno) have experienced a few cases where patients have improved their symptoms by following a low-FODMAP diet.

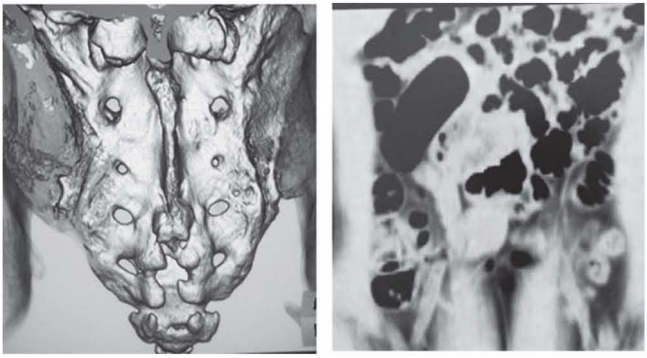


Figure 85: *CT image of spina bifida (left) with a large amount of intestinal gas (right). In this case, fecal incontinence was improved with a low-FODMAP diet. His fecal incontinence had been misdiagnosed and was attributed to mental retardation as his school teachers believed that he was was doing this on purpose. A large amount of gas was found in his abdomen. His incontinence occurred mainly with the excretion of gas. Therefore, a low-FODMAP diet was expected to be effective.* When he followed a *low-FODMAP diet, his fecal incontinence disappeared, he graduated from high school, and he is now going to university.*

In 2017, French researchers reported glucose breath test for patients with flatus incontinence and 44% were diagnosed as having SIBO (Melchior et al.). The symptoms of these patients was relieved with metronidazole. In other words, flatus incontinence was related to the excessive fermentation of carbohydrates in the intestinal tract. This evidence suggests that a low-FODMAP diet may be effective in fecal incontinence from all causes.

SIBO

For patients who have chronic constipation, intestinal bacteria in the large intestine flows to the small intestine due to ileocecal valve dysfunction. This can develop into SIBO simultaneously, leading to an increase in gas in the small intestines and causing abdominal bloating.

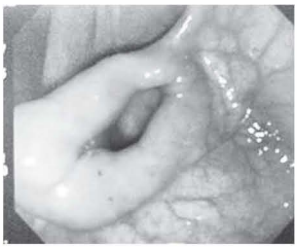


Figure 86: *Ileocecal valve dysfunction: the ileocecal valve is always open, allowing bacterial backflow from the colon to the small intestine.*

Depending on whether the patient is taking a PPI (Su et al.) and/or NSAID (Murak et al.), SIBO may occur. Also, if bile flows back into the stomach chronically, the pH of the stomach will rise and cause SIBO. In this case, most of the gas is generated in the jejunum.

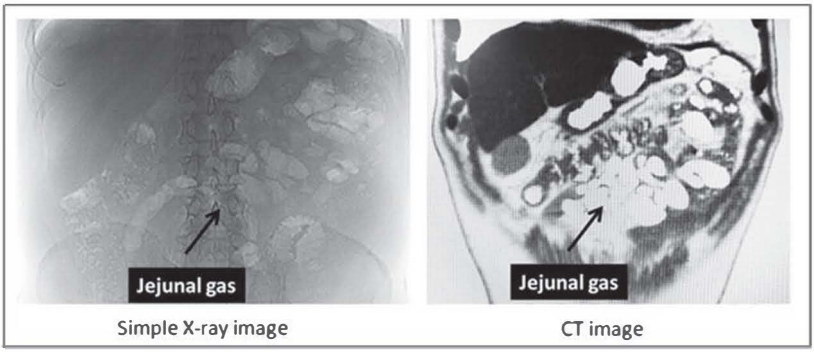


Figure 87: *A CT is the most effective method to confirm the small intestine SIBO gas of SIBO.*

A cholecystectomy might also increase the incidence of gastritis, alkaline gastroduodenal reflux, and gastro-esophageal reflux. In 2015, Korean researchers reported that post-cholecystectomy patients had SIBO more often (Sung et al.).

When SIBO coexists with IBS, the symptoms are worse as the fermentation occurs in the small intestine as well as the large intestine. The prevalence of SIBO in systemic sclerosis has been reported to be 30–62% (Braun-Moscovici et al.). Systemic sclerosis increases the death rate by

comorbidity with SIBO as it triggers malabsorption (Jaovisidha et al.). Moreover, SIBO is related to chronic pancreatitis (Kumar et al.), Parkinson's disease (Houben et al.), hypothyroidism (Patil et al.), myotonic dystrophy (Tarnopolsky et al.), type 1 diabetes (Ojetti et al.), cystic fibrosis (Lisowska et al.), chronic renal failure (Strid et al.), and chronic rheumatoid arthritis (Henriksson et al.). Interestingly, it was reported in Italy that after metronidazole was administered to patients with type 1 diabetes with SIBO in order to eradicate the intestinal bacteria HbA1c levels reduced from 8.25% to 7.63% and methane gas production also decreased (Cesario et al.). Treating SIBO could have promising secondary effects on this associated disease.

Exercise-induced gastrointestinal syndrome

If a person with gastrointestinal symptoms partakes in intense exercise on a daily basis, they may need to consider the possibility of exercise-induced gastrointestinal syndrome (EIGS). EIGS is a disease that induces gastrointestinal symptoms with intense long-term exercise. Symptoms include nausea, vomiting, belching, bloating, abdominal pain, constipation, and diarrhea. This is due to ischemia of the intestinal wall due to a decrease in blood flow to the intestinal tract, which causes a malfunction in the epithelial tight junctions of the small intestine mucosa. A low-FODMAP diet has been reported to alleviate EIGS symptoms (Costa et al.).

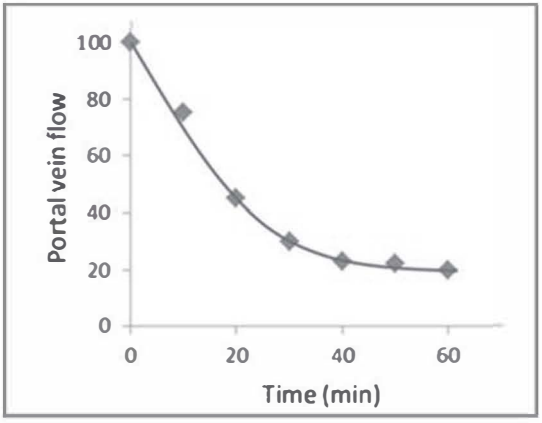


Figure 88: *Continuous exercise for more than 30 minutes significantly reduces intestinal blood flow (Rehrer et al.).*

However, in addition to this, intestinal pressure rises due to gas from intestinal fermentation. As the intestinal blood pressure increases, the intestinal blood flow decreases, so it is recommended that athletes follow a low-FODMAP diet.

Diverticulosis and diverticulitis of the colon

This was proposed by Uno for the first time in the world (Uno and van Velkinburgh), and so I (Uno) will explain it in detail below.

The theory of colon diverticulitis and diet association was expanded upon by Painter (Painter: 1969). First in 1969, when he reported that diverticular disease (DD) occurred in people who ate a low residue diet with refined flour and sugar, and then again in 1970 when he stated there was no DD in Africa (Painter: 1970). Painter went on to reveal that Denis Parsons Burkitt, the famed UK surgeon and dietary fiber proponent, provided a personal communication of his observation of short oral-anal transit time in Africans. This information helped to inspire Painter to theorize that a low residue intake, related to what he described as the "civilized diet", would lead to a viscous stool that passes through the colon more slowly, and that this difference in fecal consistency would explain the incidence of DD in civilized nations. In 1971, Painter and Burkitt (Painter: 1971) jointly published their "fiber hypothesis" for DD, suggesting that a diet based on unrefined, natural foods with adequate fiber may prevent DD. However, findings from several recent studies have cast doubt on the validity of the high-fiber hypothesis (Tan et al., Ünlü et al., Peery et al., Tursi et al., Elisei et al.). A subsequent study by Peery et al. found no association between a low-fiber diet and DD (Peery et al.: 2012). More concerning, however, were their results from a cross-sectional study of 2104 participants between the ages of 30 and 80 years old that included 878 cases of DD and 1226 controls without DD, which indicated that a high fiber intake was associated with an increased prevalence of multiple diverticula. The particular fiber subtypes that showed a significant association with the occurrence of multiple diverticula were grains, insoluble fiber, and soluble fiber. Another study by the same group a year later found no increased risk of diverticulosis in the descending or sigmoid colon associated with either less frequent bowel movements or symptoms of constipation, and no association between dietary fiber intake and diverticulosis (Peery et al.: 2013). A subsequent study by Braunschmid et al. found that colonic diverticular disease did not correlate with constipation

symptoms (Braunschmid et al.).

Japan has a high incidence of DD in the proximal colon. Moreover, a study of Japanese cases of DD, that specifically focused on the right side, showed a high intraluminal pressure (>20mmHg) and abnormal motility in the ascending colon (Sugihara et al.). Dietary fiber increases gas within the colon (Marthinsen et al.). The primary dietary fiber contained in vegetables and fruits is inulin, and its intake leads to flatulence (Muir et al.). The 2015 American Gastroenterological Association (AGA) guidelines cited at the beginning of this article recommend that dietary fiber be obtained through an intake of legumes (such as lentils), yoghurt, and fresh fruit (ASA). However, yoghurt and beans contain oligosaccharides, which are known to generate gas in the gut by fermentation (Suarez et al., Cummings et al.). In individuals with fructose intolerance, eating fresh fruit can result in abdominal pain, belching, bloating, an uncomfortable feeling of fullness, indigestion, and diarrhea (Choi et al.). Therefore, the diet components recommended by the AGA are expected to produce a substantial amount of gas in the intestines.

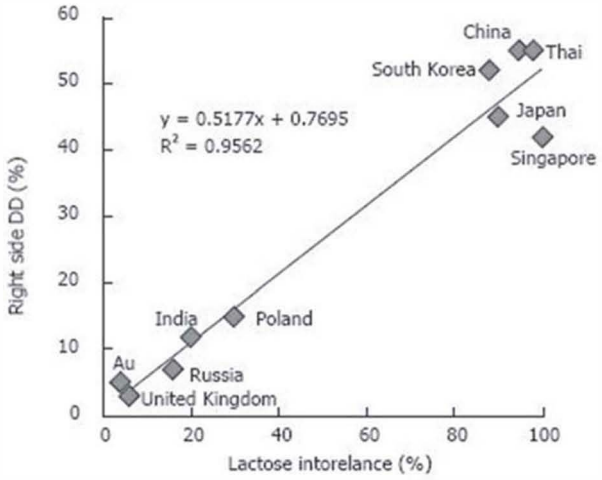


Figure 89: *Relationship between lactose intolerance and the right-side diverticular disease. Au: Australia; DD: diverticular disease. (Uno and van Velkinburgh)*

The prevalence of lactose intolerance is high in Asia and Africa, and lower in Caucasian populations. Among the nine countries with reports of right diverticular disease (RDD) and lactose intolerance in the publicly available literature (Uno and van Velkinburgh), all show a strong correlation ($R2 = 0.9562$). The occurrence of RDD is lowest in European countries, while the occurrence of lactose intolerance is lowest in the US; however, Asian countries show the highest occurrence of both RDD and lactose intolerance.

In Japan, DD in young individuals almost exclusively involves the right side of the colon (Kubo et al.). Left diverticular disease (LDD) risk was found to increase with age, which is likely due to the increased vulnerability of the muscle layer over a person's lifespan. In adults under 29 years of age, 100% of the DD cases involved the right side. In Japan, pediatric DD between the ages of 7–15 is not rare and these cases occur in the caecum and ascending colon (Watanuki et al.). This finding cannot be explained merely by the age-related vulnerability of the muscle layer and may indicate factors related to childhood. It has been reported that up to 86% of Japanese children develop lactose intolerance by the age of 6 (30% at 3 years, 36% at 4 years, and 58% at 5 years) (Nose et al.). The time that it takes for gas to increase in the intestines after lactose intake is 1–2 hours (Mummah et al., Yang et al., Schommer et al.), which is shorter than the times required for any of the other constituents of a high-FODMAP diet. Therefore, lactose intake may induce a large amount of gas and liquid in the right colon of Japanese children, especially those with lactose intolerance. The physical pressure brought on by the increased gas and fluid will affect the mucous membrane, presumably pushing it outward into the physiological cleft that exists from birth. This may explain why diverticulum in young Japanese tends to be generated only on the right side.

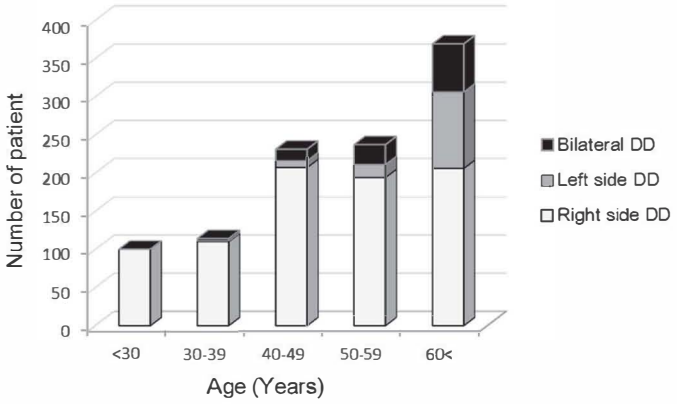


Figure 90: *The relationship between the site and age at onset for diverticular disease in Japan. DD: diverticular disease. (Uno and van Velkinburgh)*

However, many Europeans and Americans experience DD of the left colon (LDD). This phenomenon may be related to the higher ingestion of wheat (De Giorgio et al.) compared to Asian societies. The fructan component of wheat is considered to be a high-FODMAP. The time required for fermentation of fructan in the gut is relatively long, between 2 and 6 hours (Murray et al., Fedewa et al.), which means that there is a high pressure in the left colon. In Japan, however, the consumption of wheat has increased since World War II, and this change in dietary pattern towards one that more closely resembles the European and American diets has been accompanied by an increase in colonic DD. For example, DD was reportedly 2% in the 1960s (Inoue et al.) but increased to 20% by the 1980s (Miura et al.). Additionally, cases of LDD have increased in Japan as well (Takano et al., Yamada et al., Tarao et al.). This trend is similar to that reported in South Koreans (Oh et al.). Several reports have addressed the potential correlation between IBS and DD (Annibale et al., Sirinthornpunya et al., Jung et al.). Symptoms consistent with IBS are common among patients with DD, and this symptomology has been reported as significantly higher in DD patients when compared to non-DD controls (Jung et al., Longstreth et al., Cuomo et al.). Therefore, the increase in colonic pressure is related to the development and progression of the colon diverticulum and so it is inferred that a low-FODMAP diet, which suppresses an increase in colonic pressure, may be effective for the

prevention of diverticulitis. In contrast, fiber-rich foods also increase methane gas and potentially worsens diverticulosis in the colon.

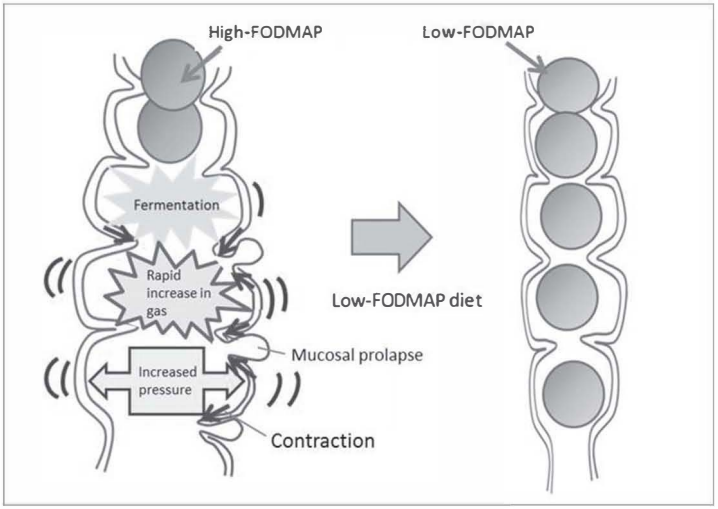


Figure 91: *The process of diverticulosis in the colon due to high-FODMAPs and its prevention through a low-FODMAP diet (hypothesis).*

In 2018, the increase of mast cells in the rectosigmoid and descending colon of IBS patients (IBS-C and IBS-D) was observed (Bashashati et al.). Patients with diverticular disease displayed an increase of mast cells in the large bowel (Bassotti et al.). As we will discuss later, mast cells are associated with ischemia of the colon, and a low-FODMAP diet could reduce histamines. This fact is evidence for the effectiveness of a low-FODMAP diet in diverticular diseases.

Radiation enteritis (RE)

A study on low-FODMAP diet for RE by Larsen et al. revealed that a low-FODMAP diet relieves the symptoms of radiation enteritis (RE), such as abdominal pain, bloating, diarrhea, and constipation (Larsen et al.).

Non-coeliac gluten sensitivity

For non-coeliac gluten sensitivity (NCGS), a gluten-free diet is effective. However, a low-FODMAP diet is clearly effective for NCGS with

intolerances other than wheat (van Gils et al., Biesiekierski JR et al.). Some people who have gluten sensitivity and believe that IBS symptoms improved with gluten free diet might benefit from reducing FODMAP consumption rather than excluding gluten.

Fibromyalgia

70% of patients with fibromyalgia overlap with IBS symptoms. A low-FODMAP diet has been reported to reduce the severity of fibromyalgia symptoms as well as reduce weight gain in fibromyalgia patients (Marum et al.: 2015, 2017).

Objective method to determine the necessary adaptations to a low-FODMAP diet

The breath test has been useful for the diagnosis of food intolerance (Rana et al.). In fact, the breath hydrogen test has been used as a method to indirectly evaluate symptoms due to a high-FODMAP diet (de Roest et al.). It is no exaggeration to say that research on carbohydrate intolerance has developed through the use of the hydrogen breath test. However, as its use has expanded, differences in results and interpretations have appeared. The breath test is not perfect with regard to determining the benefits of an adaptation to a low-FODMAP diet. This is because there is the possibility that other sugar(s) can be the trigger factor and the hydrogen amount in the breath may not be relevant to the symptoms, which may give a false-positive/negative. In a study in 2017, the fructose breath test was able to predict symptomatic the relief of a low-FODMAP diet, but the lactose breath test was not effective (Wilder-Smith et al.). Furthermore, research from Monash University in 2017 (Yao et al.) investigated the reproduction of lactulose and fructose breath hydrogen testing and assessed the symptoms response to fructose testing. They observed the poor results of lactulose and fructose breath testing, as well as the poor correlation of these test outcomes with symptoms induced from these sugars. Basically, the concept of a low-FODMAP diet is not only to alleviate the symptoms of intolerance to individual carbohydrates, but also to eliminate the interaction and synergism of each carbohydrate. Therefore, it is theoretically contradictory to determine the effectiveness of low-FODMAP meal by individual carbohydrate breath test results. So, in order to solve those problems, more highly accurate tests are expected to be developed in the near future. Although the amount of gas excreted in the breath test correlates with the actual gas volume in the large intestine,

it is not known whether the increase in colon gas is slower than the increase in expiratory gas (Murray et al.).

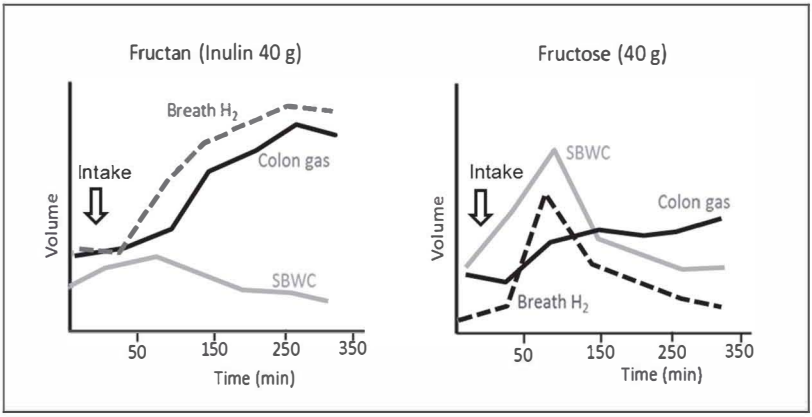


Figure 92: *Relationship between small bowel water content (SBWC), colonic gas, and breath hydrogen (H_2) (Murray et al.).*

Also, the emergence of IBS symptoms may be related to a rapid increase in abdominal gas and a gradual increase in gas may be associated with symptoms of bloating without abdominal pain. Furthermore, since the breath test indirectly estimates the increase of gas in the whole intestinal tract, it cannot accurately judge where the gas actually increases. There is also no evidence that the amount of gas excreted in the breath test correlates with the actual amount of gas in the large intestine.

I (Uno) performed abdominal X-rays 4–5 hours after administering 13g of lactulose (a high-FODMAP) and observed the increase in gas in IBS patients. (Uno: 2015).

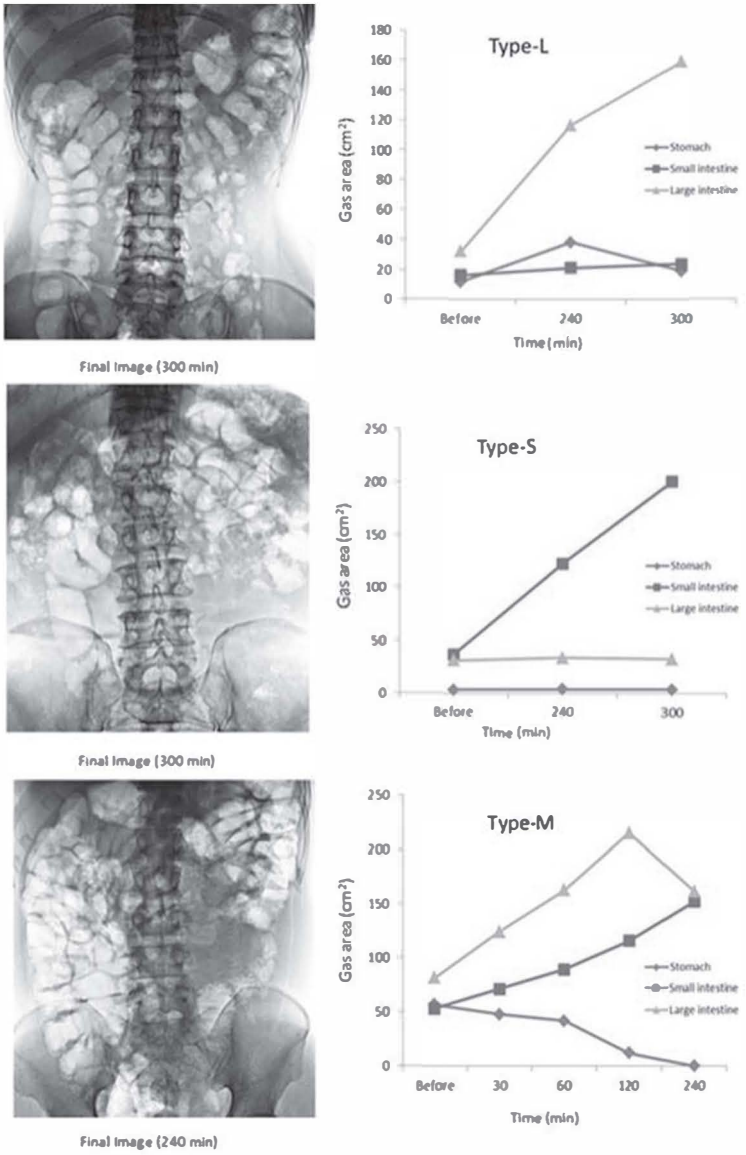


Figure 93: *It is possible to distinguish SIBO, IBS, or both by the gas production in the intestine 4–5hours after 13g of lactulose is administered (Uno: 2015).*

With this method, we are able to see the clearer association between symptoms and the increase in gas, as well asto distinguish IBS, SIBO, or both. This study shows that, when given excessive FODMAPs, it might be possible to determine the adaptation of low-FODMAP diet by the presence of symptoms, without confirming the hydrogen during respiration.

Examination before the diagnosis of IBS

Before a patient with abdominal symptoms is diagnosed with IBS, it needs to be confirmed they have no intestinal diseases (organic disease), such as colorectal cancer, ulcerative colitis, Crohn's disease, infectious enterocolitis, colon diverticulitis, and coeliac disease. Radiation enteritis and previous food allergies must also be excluded. Furthermore, it is necessary to check for the presence or absence of hyperthyroidism and hypothyroidism. Therefore, the necessary tests are colonoscopy (or barium enema), occult blood test, serum chemistry, complete blood count, and measurement of thyroid hormone. In the US, for an exclusion diagnosis of IBS, a serology test for coeliac sprue is used (Spiegel et al.). However, because Japanese gastroenterologists recognize that there is no coeliac disease in Japanese adults, the exam is not usually used. Instead, in Japan gastro-jejunoscopy is often performed for patients with abdominal symptoms. In this examination, observation of the papilla of Vater is routine in Japan, so advanced coeliac disease might be diagnosed through this process. In any case, it is certain that the possibility of coeliac disease in Japanese IBS patients cannot be denied. In Japan, SIBO and NCGS are not excluded, so they are highly likely to be diagnosed as IBS. Small intestine endoscopy (balloon assisted enteroscopy) and capsule endoscopy have the problem that the diagnosis of small bowel disease is not accurate because the facilities that can perform these endoscopies are limited in Japan. However, since abdominal CT is frequently performed, small intestinal diseases that can be diagnosed by CT are often excluded.

Subjective method of determining adaptation

Clinically, even if the intestinal gas and water contents increase due to high FODMAPs, those who do not have abdominal symptoms do not need to adopt a low-FODMAP diet. Briefly, when symptoms are caused by high-FODMAP, the cure is adaptation to low-FODMAP diet. It is possible to self-diagnose whether or not the low-FODMAP is effective by checking if symptoms occur within 5 hours after eating an exclusively high-FODMAP

meal. Specifically, adaptation of the low-FODMAP diet can be judged as shown in the following figure.

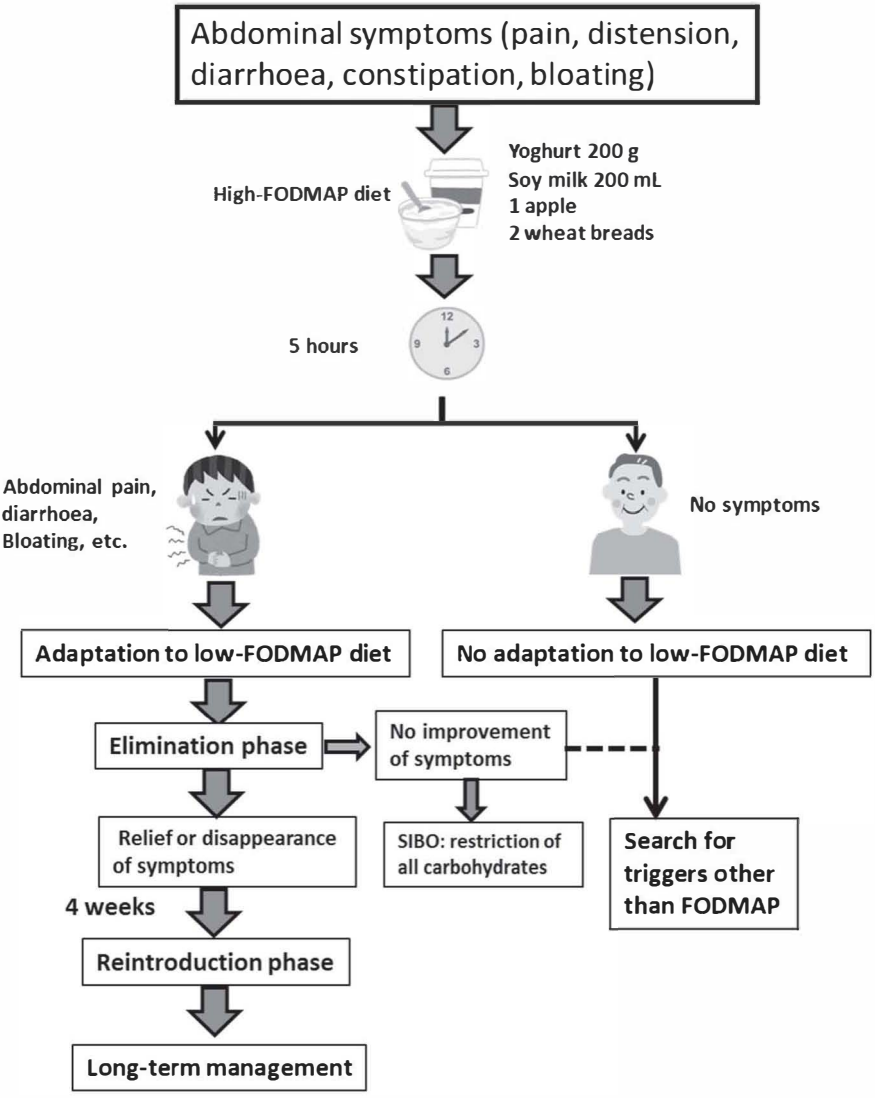


Figure 94: *Indication for a low-FODMAP diet and dietary methods*

When no obvious symptoms occur, the patients are highly likely to not be intolerant of FODMAPs and symptomatic relief cannot be obtained by the low-FODMAP diet. If people with a mild constipation tendency without intestinal dilation intentionally eat high-FODMAP and high fiber food, then a low-FODMAP diet may not be applied.

2. FODMAP restriction stage

Preparation before the start

Basically, avoid foods that generate a negative impact on IBS (caffeine, alcohol, food coloring, preservatives, and oily food), binge-eating, and skipping meals. If symptomatic relief still cannot be achieved, then a low-FODMAP diet should be introduced. Diet recording helps to compare the symptomatic changes before and after the low-FODMAP diet is introduced. Therefore, it is recommended that the patient keeps dietary records at least 1 week before starting the low-FODMAP diet. The meal time, what was eaten, beverages (including alcohol), pain (time, duration, and extent), stools (diarrhea, constipation, number of defecations), sense of satiety, headache, back pain, insonmia, depression, and so on should all be noted.

Shepherd recommends continuing the elimination phase for 6 weeks (Shepherd). In 2016, the JLFDPG set the period of exclusion phase in Japan at 4 to 6 weeks (Uno). 4 weeks was the most common length of time in the FODMAP restriction stage given by the 15 studies selected in a 2017 review of the low-FODMAP diet, although some were as long as 9 weeks or more (Pourmand et al.). Therefore, it seems that there is no problem with the FODMAP restriction stage being 4–6 weeks in Japan.

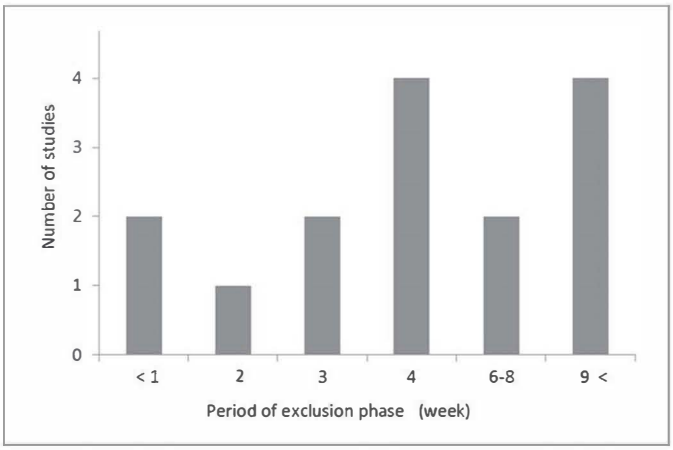


Figure 95: *Period of the FODMAP restriction stage of 15 studies selected in the review of low-FODMAP diets (Pourmand et al.).*

Total FODMAP amount during the FODMAP restriction stage

Every food in each high FODMAP category can cause intolerance. It is known that symptoms get worse by the synergetic effects when multiple high-FODMAPs are ingested together (Shepherd et al.). In Japanese processed foods, there are a lot of hidden high-FODMAPs. Therefore, it is recommended that high-FODMAPs are completely limited for a period of time to bring the body back to normal. In the FODMAP restriction stage, the most appropriate total volume of FODMAPs must be decided in conjunction with the volume of the components of the low-FODMAP diet.

It is not easy to quantify the FODMAPs in daily life; however, it is possible to estimate an accurate dose in research involving patients receiving complete enteral nutrition. Experiments with nutrition based on exact FODMAP calculations have shown that participants given low-FODMAP nutrition (low-FODMAP: 2.03g in 1267.2kcal/day; moderate-FODMAP: 4.9g in 1302.6kcal/day; high-FODMAP: 7.76g in 1270.5kcal/day) had significantly improved diarrhea and nutritional status (Yoon et al.). A double-blind, controlled trial involving enteral nutrition in a patient incapable of eating by themselves may be the best way to exclude a placebo or nocebo effect. For example, the volume of low-FODMAP diet used by Staudacher et al. (9.9g/day in 1861kcal) is

consistent with the high-FODMAP in the enteral nutrition study (Staudacher et al.). Even if the body weight is corrected, this corresponds to a medium- to high-FODMAP diet in the enteral nutrition study. Namely, the effectiveness of this diet might be the result of a placebo effect. The total volume of FODMAPs in the low-FODMAP diet was relatively high in the preliminary Monash University study, but in the recent study it fell to 3–4g.

The total FODMAPs in low-FODMAP diets vary depending on the facility or country, and even vary within the same laboratory facility, depending on the year.

FODMAPs (g)	Ong et al. (2010)	Barett et al. (2010)	Staudacher et al. (2012)	Halmos et al. (2014)	Böhn et al. (2015)	Staudacher et al. (2017)
Oligosaccharides	3.9	1.6	2.7	1.57	1.2	3.3
Lactose	4.4	4.1	5	0.05	1.5	4.3
Excess fructose	0	0	n/a	1.24	0.9	1.9
Polyols	0	0	0.1	0.2	0.1	0.4
Total FODMAPs	8.3	5.7	7.8 <	3.05	3.8	9.9

Monash University

King's College London

Figure 96: *Various definitions of "low" in the study of low-FODMAP diets (Ong et al., Staudacher et al.: 2012, 2017, Barrett et al., Halmos et al., Böhn et al.).*

Frequencies of food intolerance vary depending on ethnic differences and food is different depending on the country. The number of Japanese patients with IBS has increased steadily and, according to the Rome III criteria, the prevalence of Japanese IBS is 13.6%. In 2016, the JLFDPG decided that the total daily FODMAPs volume during the elimination phase should be less than 3g/day in Japan (Uno). Deregulation may be effective for the spread of a low-FODMAP diet. However, poor trial results may reduce patient confidence.

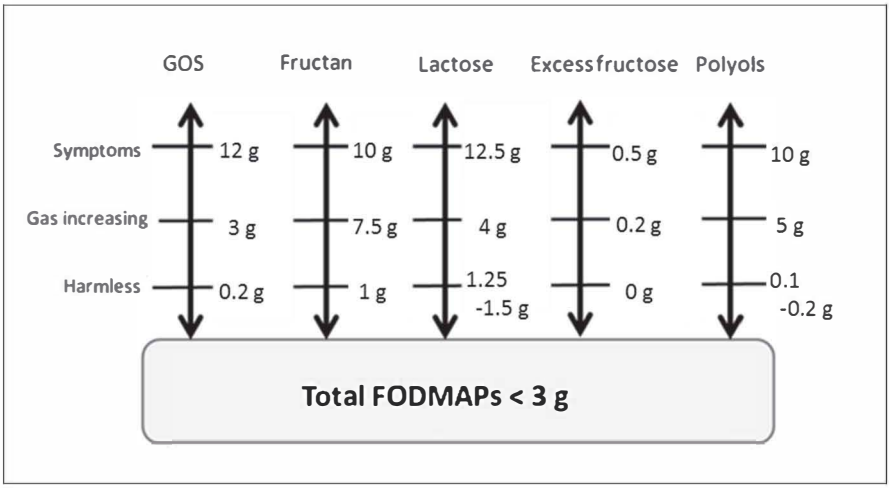


Figure 97: *Recommended total FODMAP amount during the elimination phase in Japan (in 2016) (Uno).*

Then, in 2017, Monash University set a new cut-off value for FODMAPs (Varney et al.). They recommended less than 0.3g of cereal and bean oligosaccharides, less than 0.2g of vegetable and fruit oligosaccharides, less than 0.2g of sorbitol and mannitol, less than 0.4g of total polyols, less than 0.4g of excess fructose, and less than 1g of lactose per serving. Therefore, they were almost the same as those set by JLFDPG.

The important task in the FODMAP restriction stage

The most important task in the elimination phase is to record all the food and drinks consumed and the symptoms that arise during this period. Apart from abdominal pain, bloating, defecation, fecal property, pain during defecation, and a sense of incomplete evacuation, feelings and sleep also need to be recorded. This record will help the patients realize the symptomatic relief even when symptoms are not improved as it helps to determine their cause. Even without soy beans and milk, protein intake can be substituted with meat, fish, and eggs. As for sweeteners, sucrose, superfine sugar, and maple syrup can be used. Legumes are a high-FODMAP food that is commonly eaten in India and Mexico as a staple food. However, a low-FODMAP diet is also effective in those countries. Fortunately, Japanese people eat rice. It is critical that Japanese persons with IBS eat rice instead of bread. However, almost all rice balls

or rice on the shelves of convenience stores in Japan contain trehalose in order to prevent food from drying out and decomposing. Unfortunately, trehalose is hard to digest; therefore, the best alternative is to cook rice and make rice balls at home. However, when the boiled rice is cooled, the resistant starch, which is an indigestible starch, is increased. Resistant starch goes through the small intestine without being absorbed and gets fermented in the large intestine, as do FODMAPs (Grabitske et al.). Therefore, at the FODMAP restriction stage of the low-FODMAP diet, you must eat hot rice. When the rice is cool, it is necessary to warm it in a microwave oven. If it cannot be warmed, increasing the number of chews decreases indigestible starch, so it is necessary to chew sufficiently (Muir et al.). This applies to all resistant starches, including potatoes, bananas, and corn (Muir et al.). When you really want to eat bread, it is best to choose one that is made of rice flour (choose gluten free), spelt flour (adaptation at reintroduction stage, but a small amount can be used), or white sorghum. In Japan, some rice flour bread contains gluten, so it is best to confirm with the bakery before purchasing. "*Joshin-ko*" is made from rice and "*shiratama-ko*" is made from glutinous rice, so it is low-FODMAP.

Figure 98: *Rice flours in Japan. These are the raw materials for rice cake and Japanese sweets. In Japan, you can make low-FODMAP sweets at home.*

Buckwheat flour noodles (*soba*: 100% buckwheat noodles) and rice cake (*mochi*) are also low-FODMAP foods. In Japan, during the elimination phase, dairy products need to be avoided completely. Western and Japanese confectioneries (with no ingredient label) are to be avoided as

well. For soy bean products, *momen-tofu* or bean curds with no additives, such as oligosaccharides, are recommended instead of soy milk and *kinu-tofu* (soft tofu). The number of oligosaccharides varies depending on the production method of the tofu. *Tofu* that is acceptable for low-FODMAP diet is limited to *momen-tofu* and *shima-tofu*.

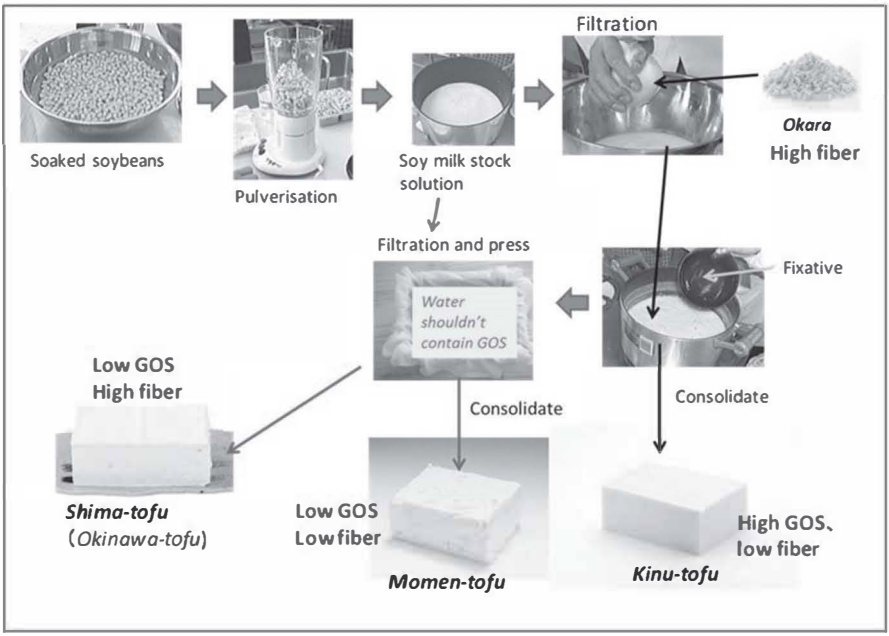


Figure 99: *The relationship between tofu and GOS.*

To strictly comply with the total FODMAP amount (3g/day) and less than the safety levels of each ingredient amount, it is necessary to avoid foods that are high in each FODMAP ingredient. In addition to rice, pick cereal foods made from rice flour such as rice cake, rice vermicelli, pho (Vietnamese noodle), and rice flour pasta. The most popular rice in Japan is medium grain rice (Japonica rice) and this contains low amylopectin that easily leads to blood sugar and insulin spikes. Japonica rice is not recommended for those who are diabetic, as it contains low levels of amylopectin. In the FODMAP restriction stage, you do not need to limit meat, fish, or eggs. But the important thing is to not use any high-FODMAP seasoning. Almond milk is a good alternative to regular milk or yoghurt.

For vegetables, please choose lettuce, cucumbers, carrots, and radishes. Use spelt flour or rice flour to make batter. Small amounts of soy sauce can be used as the amount of soy bean is almost negligible. If possible, choose soy sauce without wheat as an ingredient.

Exclusion foods in the FODMAP restriction stage

The foods that need to be avoided during the elimination period are as follows:

Wheat products: bread flour, all-purpose flour, pastry flour, bread crumbs, egg noodles, *udon* noodles, *somen* noodles (thin wheat noodles), *gyoza* (dumplings), *ramen*, pasta, pizza, naan, curry, cake (except 100% rice flour), wheat bread, pastries, instant noodles, *soba* (except *jyuwari-soba*), and bean products such as tofu, fermented soy beans (*natto*), and any products with soy milk.

Dairy products: milk, yoghurt, custard pudding, Japanese/Western confectioneries, chocolate (containing lactose), ice cream, soft serve, custard, and condensed milk.

Sugar alcohol products: products that contain xylitol or sorbitol (sorbit) such as xylitol gum, reducing sugar, high-fructose corn syrup, trehalose, mannitol, rum, beer, black tea, oolong tea, honey, and jam.

Fruits: mangos, mango juice, fruit juice, dried fruit, pears, nashi pears, plums, apples, apple juice, nectarines, grapes, mandarin oranges, oranges, orange juice, apricots, vegetable juice, cherries, black cherries, guava, dates, and canned fruits. See list of food.

Vegetables: asparagus, onions, leeks, cauliflower, garlic, green peas, and fruit tomatoes. See list of food.

Legumes: all kinds of legumes such as kidney beans, peas, etc.

Mushrooms: all kinds of mushrooms.

The main purpose of a low-F●DMAP diet is to not ingest foods that are not absorbed in the small intestine and which ferment in the intestine. Therefore, low calorie foods and F●SHU (food for specified health use), which "maintain the gut function" and "lower the blood sugar level", are non-absorbable in the small intestine and go through the fermentation process and, therefore, must be avoided.

If you are taking alpha-glucosidase inhibitor for diabetes, you may need to consult with your doctor to discontinue it. If IBS symptoms are relieved just by stopping the alpha-glucosidase inhibitor, this is sufficient evidence that the IBS symptoms are a result of side effects from the medication.

Strawberries, tomatoes, cabbage, celery, and potatoes are considered to be low-F●DMAP foods around the world. However, in Japan they must be tried in the reintroduction stage because their sweetness has increased due to breed improvement. Tomatoes do not increase glucose during maturation but increase fructose and sweeter tomatoes are made by genetic manipulation, which increases the fructose content. Also, not only are cabbage varieties sold in Japan not listed, but different varieties are sold in each region.

During this period, people must check the food labels every time to determine if the food contains high-F●DMAPs or not. This should be made into a habit for all. It helps to plan ahead when dealing with menus. Before starting the elimination phase, people should plan a few meals ahead that use low-F●DMAP foods. These menus can be repeated in the following weeks or changed to make new combinations that put a twist on the recipes used.

Sample meals for the FODMAP restriction stage

Example 1: *Soba (jyuwari)*, deep fried shrimps (Figure 100), lettuce (*salada-na*), ripe banana, and lemonade (use table sugar).

Figure 100: *Deep fried shrimps*

Example 2: rice, deep-fried chicken (spelt flour), lemon, and lettuce (*salada-na*)

Example 3: egg sandwich (Figure 101) with rice flour bread, sautéed spinach, and almond milk.

Figure 101

Example 4: *Soba* (*jyuwari*) in soup topped with an egg (*tsukimi-soba*).

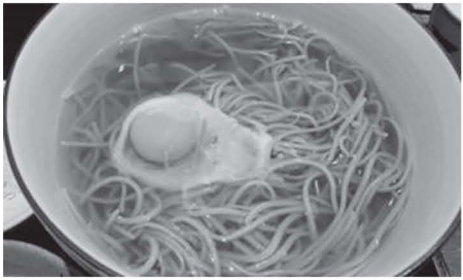


Figure 102: *Tsukimi-soba*

Example 5: rice, fish (*sashimi* or grilled), sautéed *daikon* radish, green tea.

Example 6: rice, beef steak, stir-fried carrots, red capsicum.

Example 7: boiled rice topped or mixed with raw egg, commonly with soy sauce poured on it and often served with grilled pork.

Example 8: Almond milk soup (chicken breast meat, carrot, almond milk, and parsley) (Figure 103).

Figure 103

Example 9: Pancake (rice flour), boiled daikon, and pork (Figure 104).

Figure 104

Example 10: Steamed bread (rice flour), steamed eggplant, and tuna (canned tuna) (Figure 105).

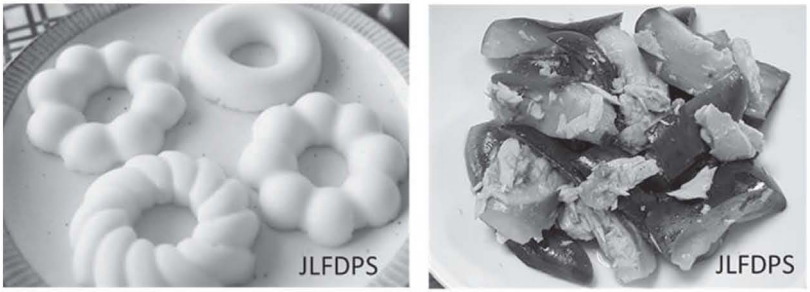


Figure 105

Example 11: Rice flour biscuits and maple syrup (Figure 106).

Figure 106

Example 12: Vongole (rice pasta) (Figure 107).

Figure 107

3. When the symptoms do not improve

If symptomatic relief cannot be seen after the 6th week of the elimination phase, it is advised to revise the food logs. The reasons could be either there is no relationship between the symptoms and the food, or a high-FODMAP food was inadvertently consumed. If the person looks back on the record and strictly adheres to a low-FODMAP diet, there is a need to think about the influence of meals other than FODMAPs. For example, salicylate (Raithel et al.) and amine (Niec et al.), etc. can influence symptoms, so the individual should consider whether these are causing the effect.

Food allergy: In Japanese people, care should be taken with allergy-inducing foods common among the Japanese. Allergy-inducing foods include the following: shrimp, crab, buckwheat, eggs, abalone, kiwi fruit, beef, walnuts, sesame, salmon, mackerel, soybean, chicken, bananas, pork, yams, and gelatin. For example, in a banana allergy, skin redness, convulsion, diarrhea, nausea, runny nose, teary eyes, and sneezing occur within several minutes after eating bananas. People who keep logs can better verify if they have experienced these symptoms by referring to their records.

Sodium glutamate and amine: Sodium glutamate and amine are potential causes of IBS, so they also need to be avoided. In 2012, researchers from the US reported that in patients with fibromyalgia, monosodium glutamate was proved to induce IBS symptoms (Holton et al). For example, kelp contains a lot of sodium glutamate. In Japan, the most common intake source might be the "seasoning (amino acids, etc.)" contained in many foods as a flavor ingredient. Such seasonings are also often used in Chinese cuisine. Moreover, as amines are a cause of IBS, they need to be avoided. Histamine is the most problematic amine substance in foods. It is included in fish, processed goods, and cheese. In cheese, it is often included in cheddar, camembert, gouda, and blue cheese. It is also included in wine and soy sauce.

Fish: In a low-FODMAP diet, fish and meat are not restricted; however, it has been reported in the US that IBS can be triggered by shellfish or fish. The influence of histamine is suspected to be the cause. Histamine food poisoning is an allergy-like food poisoning that develops by eating foods with histamine accumulated at high concentrations, especially fish and

processed foods. Histamine is produced by histamine-producing bacteria (e.g. *Morganella morganii*) by enzymes acting on histidine (one of 20 kinds of amino acids constituting proteins) contained in food and converted into histamine. Therefore, improper management, such as leaving food containing a lot of histidine at an ambient temperature, increases histamine-producing bacteria in food and histamine production. Since histamine is stable to heat and cannot be removed during the cooking process, cooking cannot prevent food poisoning once it has been produced. Lean fish such as tuna rich in histidine, marlin, bonito, mackerel, sardine, saury, brush, horse mackerel, and processed fish are reported as the main food responsible for this (Japan Health, Labor, and Welfare).

Salicylic acid: Salicylic acid is also a trigger of IBS and it is contained in curry powder, cumin, dill powder, apricots, oranges, pineapples, raspberries, strawberries, dried grapes, tea, Worcestershire sauce, and rosemary.

Resistant starch and fiber: The substrates that are fermented in the large intestine of Japanese people are resistant starches (8–40g), non-starch fiber (8–18g), oligosaccharides and sugar alcohols (4–14g), and resistant proteins (4–10g). Fermentation of resistant starch or fiber might be more concerning than that in high-FODMAP food. Immediately after boiling, the resistant starches, beans, cereals, and tubers (potatoes, etc.) are 4.18%, 1.86%, and 1.51%, respectively, but after cooling the resistant starch increases to 8.16%, 3.25%, and 2.51%, respectively (Yadav et al.). Cellulose and hemicellulose in dietary fiber turn into pyruvic acid and ferments in the large intestine (Hara).

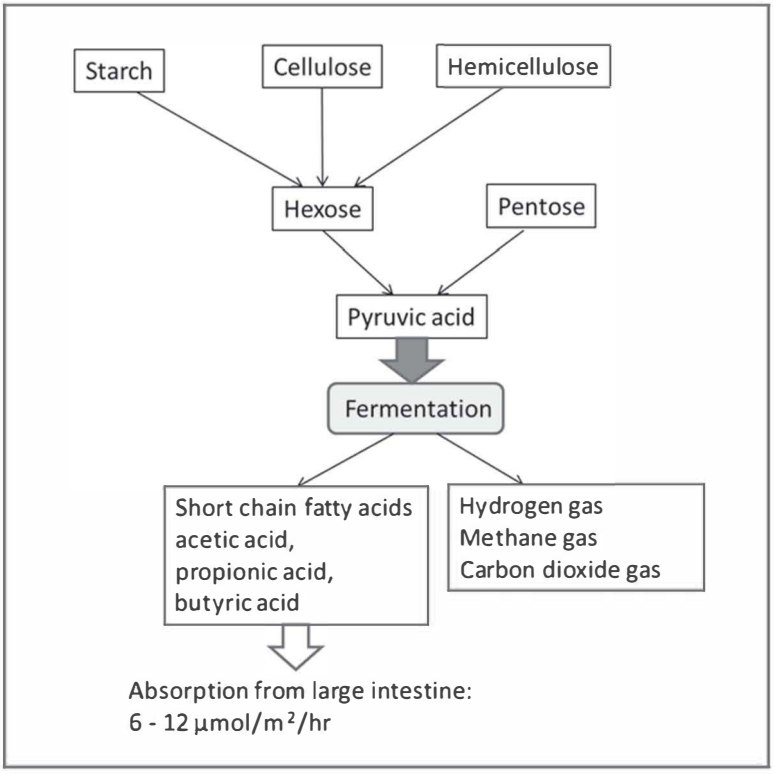


Figure 108: *The fermentation process of cellulose and hemicellulose (Hara).*

In addition to resistant starches, guar gum and pectin also produce acetic acid, propionic acid, and butyric acid by fermentation (Hara).

Pectin and guar gum: Since there is no enzyme that degrades pectin in the human intestinal tract, if it is added to the diet, the absorption of blood glucose is suppressed. Due to this action, there is a risk of fermentation in the large intestine without it being absorbed by the small intestine, even in foods that are not high-FODMAP. Partially hydrolyzed guar gum is a product that is purified by the enzymatic degradation of guar gum. Like a high-FODMAP, it is not broken down in the small intestine and is fermented in the large intestine to produce SCFAs (Hara).

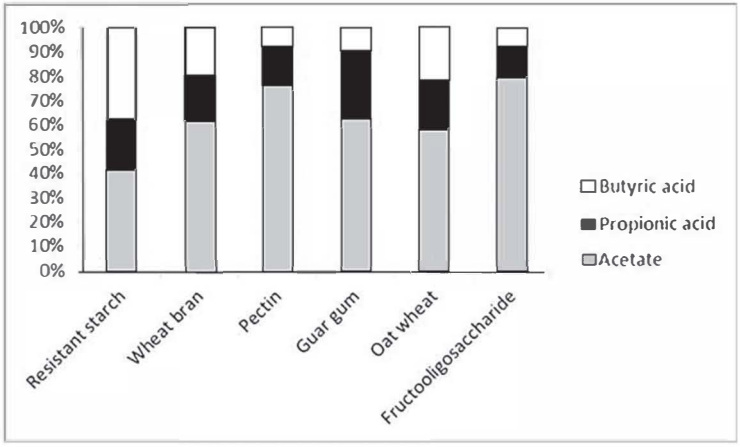


Figure 109: *Ratio of butyric acid, propionic acid, and acetate (Hara).*

In 2010, researchers from Tohoku University in Japan (Tana et al.) suggested that high levels of acetic and propionic acids may be associated with abdominal symptoms, impaired QOL, and negative emotions in IBS. In addition, a report from Norway in 2016 found that among SCFAs, propionic acid adversely affects IBS and the greater the difference between propionic acid and butyric acid, the more it affects IBS (Farup et al.). Therefore, guar gum and pectin may induce symptoms more than high-FODMAPs. In Japan, pectin and guar gum are used a lot in prepared food. Guar gum is used often in ice cream, fish paste products, dressing, dipping sauce, soup and sauce as a thickener, stabilizer, and gelling agent. Pectin is used in jam, jelly, and yoghurt as a polysaccharide thickener. If there is not much improvement with a low-FODMAP diet, reducing or eliminating these food additives should be considered.

Alpha-glucosidase inhibitor: Fabry disease is characterized by a deficiency or decrease in α-galactosidase. The prevalence of gastrointestinal symptoms in Fabry disease is 52%, as many people experience abdominal pain and diarrhea (Hoffmann et al.). The gastrointestinal symptomatology of Fabry disease is very similar to diarrhea-predominant IBS. In 2017, a group from Monash University reported that IBS symptoms are relieved when galacto-oligosaccharide foods are ingested with α-galactosidase (Tuck et al.). Alpha-glucosidase inhibitors (αGI) are a remedy for diabetes. Ingesting αGI before meals suppresses the rise in blood glucose by

decreasing the glucose absorption from the small intestine. The unabsorbed carbohydrates ferment in the large intestine. This mechanism is the same as the high-FODMAP theory. The side effects of αGI include pneumatosis cystoids intestinalis, bowel obstruction symptoms, diarrhea, increased flatus, abdominal distension, and pneumatosis cystoids intestinalis. Therefore, αGI may cause functional bowel disorder (FBD), including IBS. IBS induced by FODMAPs is a side effect of FODMAPs. According to that theory, the side effects of αGI are not just side effects and αGI is a trigger for IBS. Therefore, when diabetic patients take αGI and symptoms of IBS do not improve due to a low-FODMAP diet, they should consult their doctor.

For defecation difficulty due to a low-FODMAP diet

The reason that a low-FODMAP diet reduces the volume and pressure inside the large intestine is because it decreases moisture and gas. In such cases, it is important to know that defecation was triggered by the excess gas and osmotic diarrhea. Then, ask yourself whether the prior condition was better or not. If you think that abdominal pain and bloating have decreased but you are still having defecation problems, then using an over the counter laxative is recommended. For example, use magnesium oxide (1–2g/day) or castor oil (15–30mL/day) to promote defecation at first, then gradually reduce the amount taken.

4. FODMAP reintroduction stage

If the person is symptom-free after the FODMAP restriction stage, the next phase would be the reintroduction stage. This stage is the period to investigate and know what food is causing the problem. In principal, each FODMAP is tested for a week. The first thing to test could be anything the patient wants to have the most or polyols, as recommended by the researchers at Monash University (Shepherd & Gibson). For instance, incorporating a 1/2 cup of mushrooms, which contain mannitol, into low-FODMAP meals and determining if symptoms persist within a few days. If symptoms do not occur, it means that the person can tolerate that much mannitol. Next, lactose can be tested. A 1/2 cup or 170g of yoghurt are usually reintroduced; however, it is better for Japanese people to drink Acadi (low lactose milk in Japan), as most Japanese people are lactose intolerant and tend to have a lower threshold for lactose than Caucasians. Most of the yoghurt that is sold in Japan contains oligosaccharides, so they

are not suitable during the F●DMAP restriction stage. After that, fructose should be tested. A slice of mango is recommended to test tolerance. The next test will be fructans, and this will involve consuming two slices of white bread. The last group is oligosaccharides, which are tested with a 1/2 cup of legumes. If a lot of high-F●DMAPs are suddenly eaten during this phase, one would not be able to determine the maximum acceptable amount. For this reason, testing should be performed using a small amount to find out one's sensitive food.

The methods of the reintroduction stage vary; one of the methods that is used in England is to test with 4●g of mushrooms on day 1, then increase to 8●g on day 2, and then 12●g on day3. Even if the food causes symptoms, try again with half the amount. When the symptoms are triggered by a small amount of food, then try another food in the same F●DMAP category. If symptoms still occur, it is best to avoid it in the long term as it means that the enzyme that breaks down the particular F●DMAP category is lacking or hypersensitive.

〈Plan 1〉 Test lactose. Start with a cup of Acadi (low lactose milk) and continue for the next 3 days if symptoms are not triggered. When there are no symptoms for a week, move onto Plan 2. If any problem occur that indicate the person is lactose intolerant, avoid lactose in the future.

〈Plan 2〉 Test fructans with half of a slice of white bread followed by the same procedure as in Plan 1.

〈Plan 3〉 Test fructose with one green banana (not ripened).

〈Plan 4〉 Test polyols with 15● g of sweet potatoes.

5. Long-term management of a low-FODMAP diet

Broadly speaking, a low-FODMAP diet consists of three stages: FODMAP restriction, FODMAP reintroduction, and FODMAP personalization (Whelan et al.). Ideally, personalization is the continuation of the diet that excludes only the ingredients that caused IBS symptoms. However, even after understanding that one component of FODMAP did in fact cause symptoms, many people repeat the challenge of this component with different foods. There are also people who give up restricted foods and return to high-FODMAP meals.

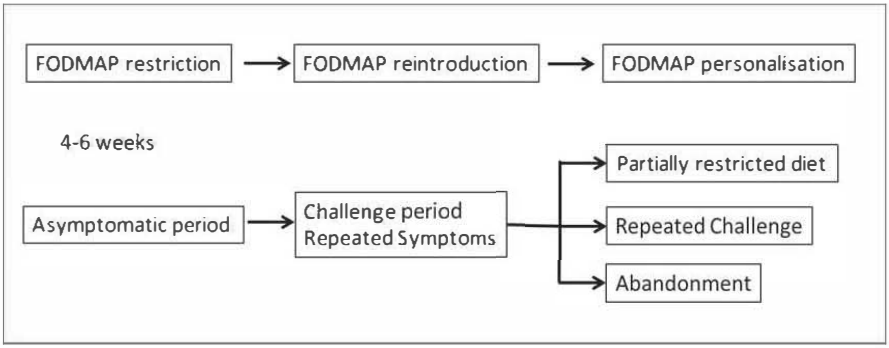


Figure 110: *Long-term course of a low-FODMAP diet*

When continuing a diet in which specific foods are eliminated, the concerns are as follows:

- Is it biased nutritionally?
- Is there malnutrition in the intestinal flora?
- Can the relief of symptoms continue?

These will vary depending on the type and amount of the exclusion component. But, is there the essential food needed to live? Water, minerals, vitamins, proteins, carbohydrates, and lipids can be adequately supplied with a low-FODMAP diet.

In a report from England in 2018 (O'Keeffe M et al.), it was confirmed that if the exclusion of trigger food(s) is continued for a long period of time, the remission of symptoms will also continue. In this study, even if certain foods were excluded in the long term, there were no nutritional problems. However, symptoms were affected by having to follow a high-FODMAP diet due to social causes. Moreover, in a long-term observation study published in 2017 in New Zealand (Harvie et al.), the most frequently excluded FODMAP component was lactose. There was no significant differences in energy, protein, fat, carbohydrate, fiber, or calcium intake, even over the long term. In addition, there was no significant change in intestinal flora. Namely, it has been confirmed that a low-FODMAP diet decreases bacteria with greater saccharolytic capacity (such as genera *Sporobacter* and *Subdoligranulum* and *Bacteroides*, *Ruminococcaceae*, and *Faecalibacterium prausnitzii*) (Chumpitazi et al.: 2014, 2015), but this is a short-term temporary change of the FODMAP restriction stage and, in the subsequent reintroduction stage, intestinal microbial flora could return with this diet (without symptoms returning).

Low-FODMAP food rich in vitamins

It has also been hypothesized that patients who follow a low-FODMAP diet may be at risk of a reduced intake of fiber and some micronutrients, such as calcium, iron, zinc, folate, vitamins B and D, and natural antioxidants (Catassi et al., Staudacher et al., Bellini et al.). However, a study in Italy showed that this diet does not seem to cause vitamin D and folic acid deficiencies, even in the restriction phase (Altobelli et al., Vincenzi et al.). However, a low-FODMAP diet over a long period of time has concerns about the reduction of vitamins. Therefore, we introduce low-FODMAP foods containing many vitamins.

Vitamin B1 (thiamin): The daily requirement is 1.1mg/day for adult males and 0.8mg/day for adult females. Chronic fatigue syndrome in ulcerative colitis and Crohn's disease involves thiamine deficiency, and there are reports that symptoms have been improved by administration of large quantities of thiamine (Costantini et al.). Also, with constipation caused by SIBO, symptoms may be improved with the administration of thiamine (Shah et al.).

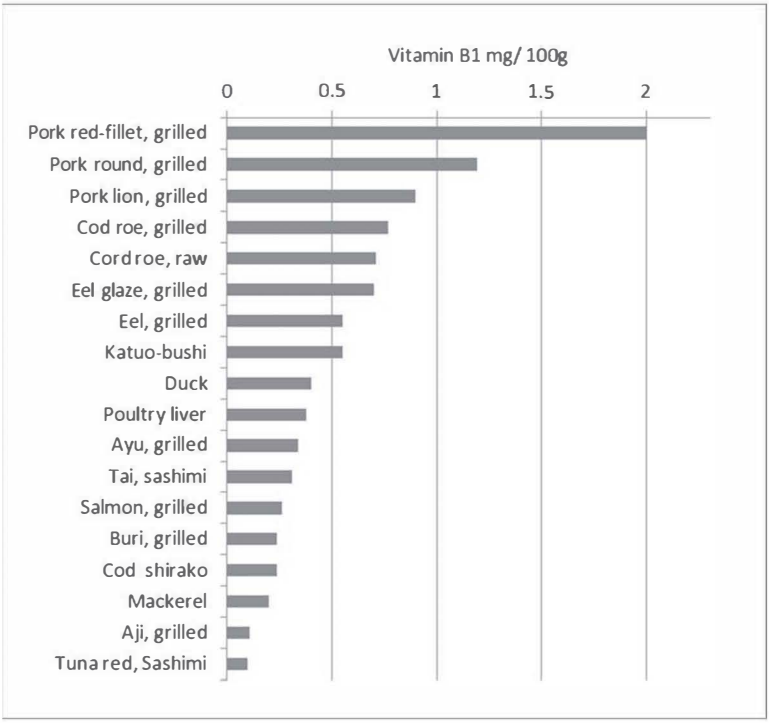


Figure 111: *Low-FODMAP food with a high content of vitamin B1*

In a low-FODMAP diet, the ingestion of fish and pork is important to prevent vitamin B1 deficiency.

Vitamin B2 (riboflavin): For adults, the required amount is 1.2mg/day for males and 1.0mg/day for females. In a prospective trial that involved 24 patients with Crohn's disease compared to healthy controls, the serum levels of several vitamins (including vitamins A, E, B1, B2, B6, and B9) were found to be significantly more depleted in the affected individuals. However, only vitamin B2 and nicotinic acid deficiencies were shown to have a negative correlation with the Crohn's disease activity index (Kuroki et al., Masri et al.).

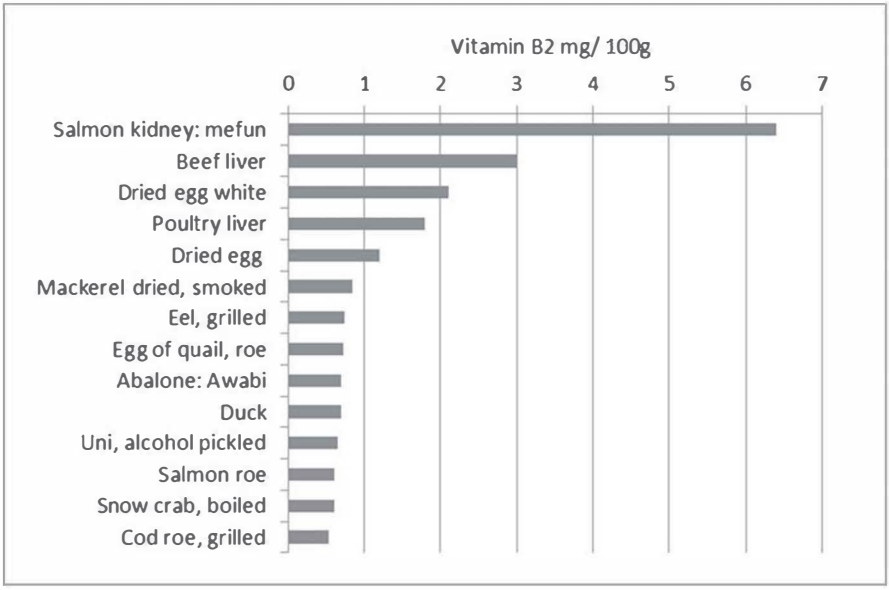


Figure 112: *Low-FODMAP food with high content of vitamin B2*

Vitamin B_3 (niacin): For adults the required daily amount is 13 to 15mg/day for men and 10 to 13mg/day for females. It is also produced in the body from tryptophan, which is one of the amino acids. The graph below shows the amount of pure niacin in various foods.

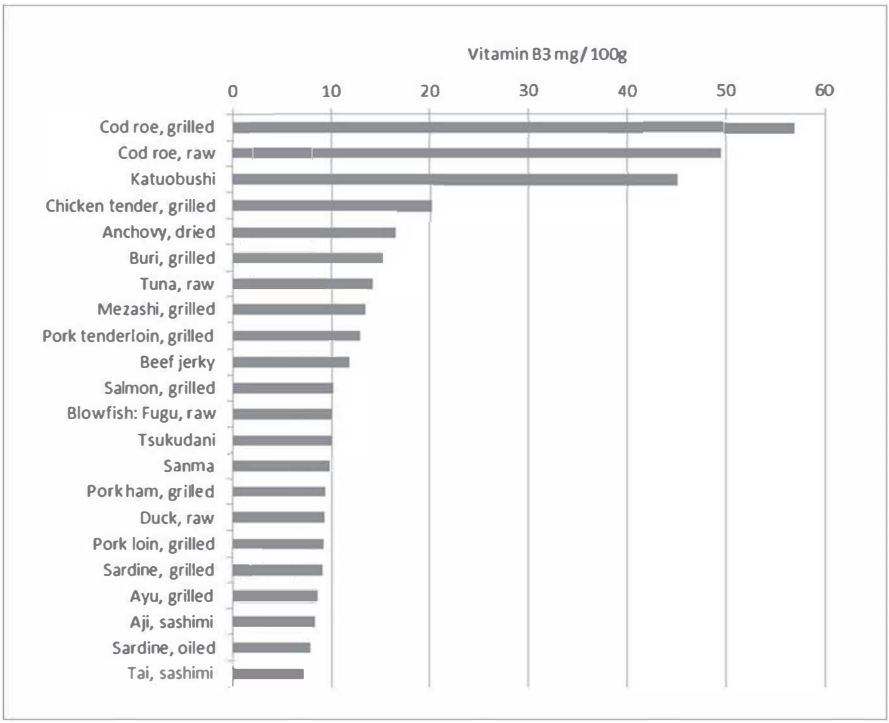


Figure 113: *Low-FODMAP food with a high content of vitamin B3*

Vitamin B5 (pantothenic acid): The daily requirement for adults is 5mg/day.

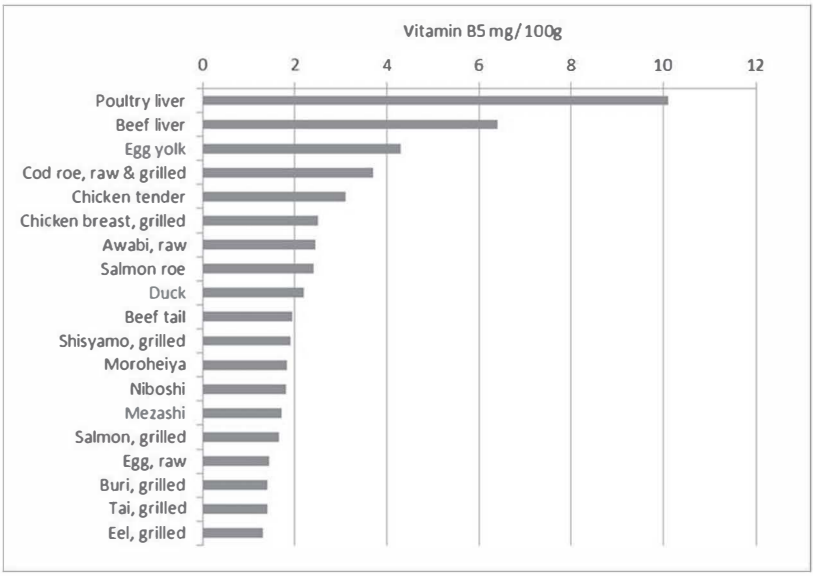


Figure 114: *Low-FODMAP food with a high vitamin B5 content*

Vitamin B6 (pyridoxine): For adults the required daily amount is 1.6mg/day for men and 1.2mg/day for women. Pyridoxine deficiency is relatively common in IBD affecting 10–15% of patients in general and up to 25% of patients with active disease (Saibeni et al.).

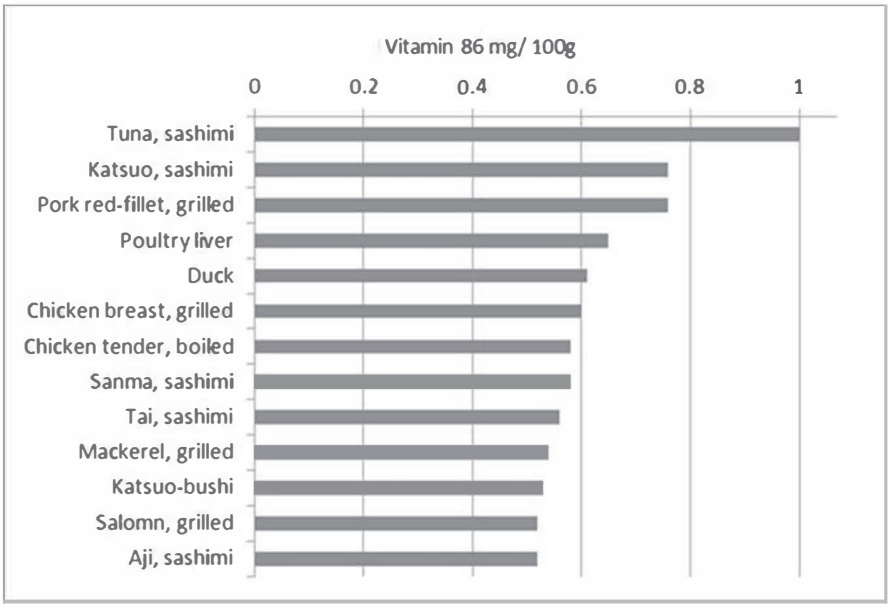


Figure 115: *Low-FODMAP food with a high content of vitamin B6*

Vitamin B12 (cyanocobalamin): A daily intake of 2.4µg/day is recommended.

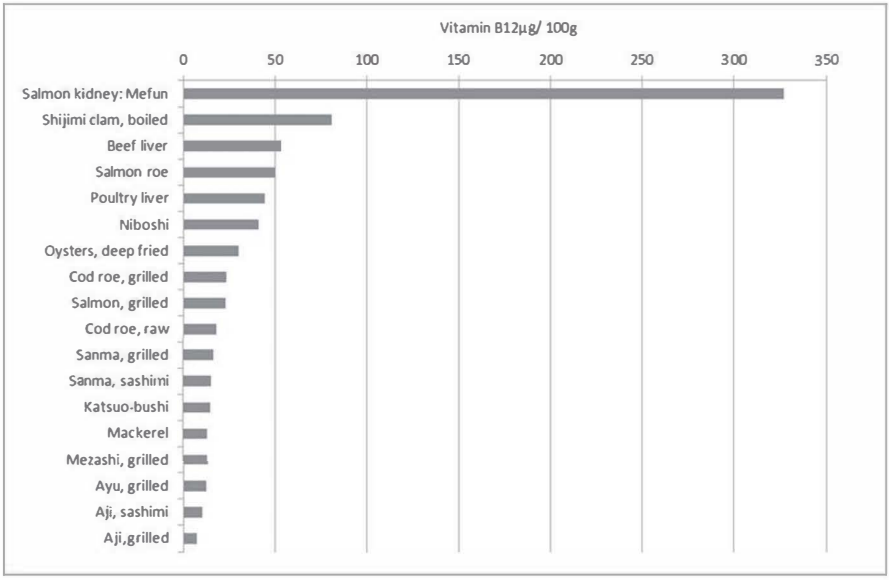


Figure 116: *Low-FODMAP foods with a high content of vitamin B12*

Folic acid: The required amount of folic acid is 200μg/day, and the intake necessary for pregnant women is 400μg/day. The upper limit of the daily intake for adults is 1000μg.

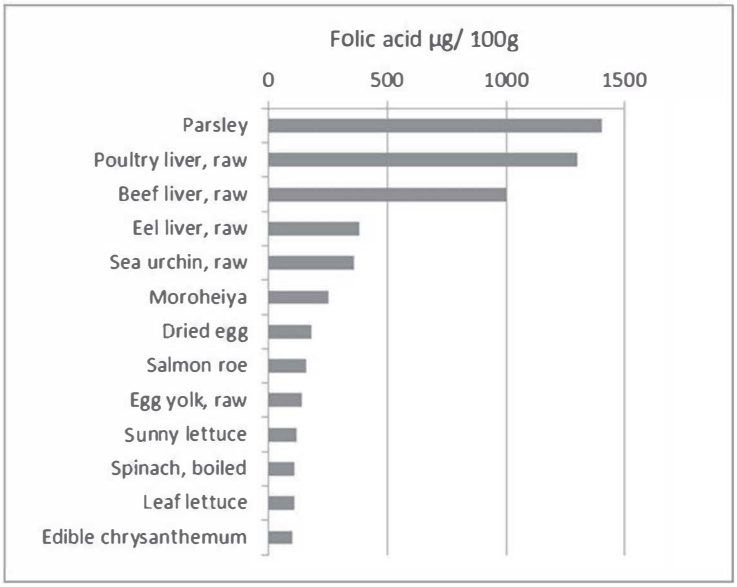


Figure 117: *Low-FODMAP food with a high content of folic acid*

Vitamin C: A daily intake of 100mg/day is recommended.

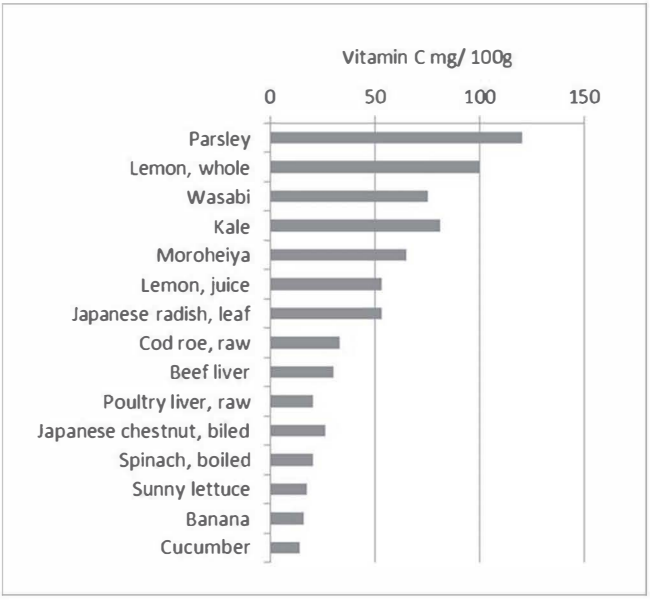


Figure 118: *Low-FODMAP foods with a high content of vitamin C*

Vitamin D: A daily intake of 2.5μg/day is recommended. The upper limit of the allowable amount is 50μg/day. Fish, such as salmon, are loaded with vitamin D so it is adequately acquired from the low-FODMAP diet.

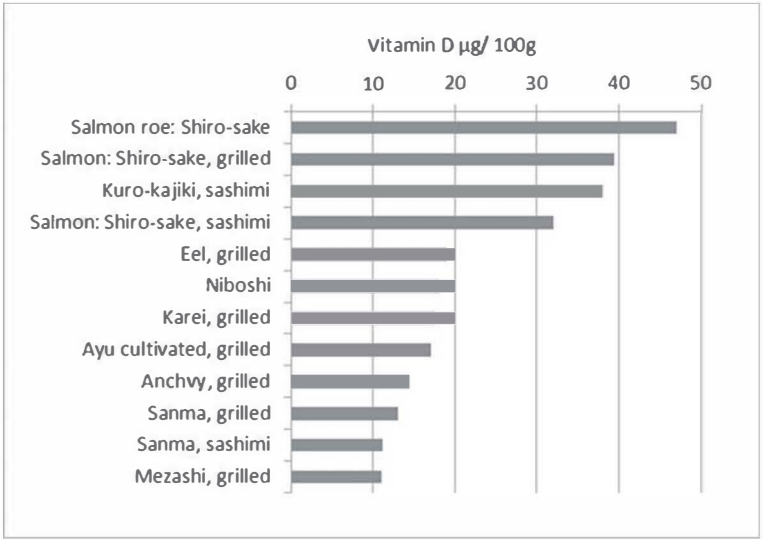


Figure 119: *Low-FODMAP foods with a high content of vitamin D*

Calcium: A daily intake of 700–900mg/day is recommended. The upper limit of the allowable amount is 2500mg/day.

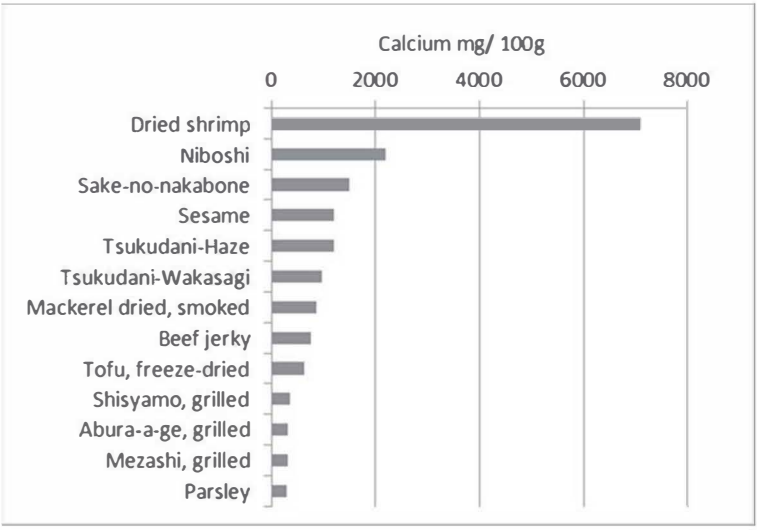


Figure 120: *Low-FODMAP food with a high calcium content*

The effect of a low-FODMAP diet on the megacolon

The author (Uno) confirms that inhibiting gas or liquid in the intestine over a long period of time can shrink the excessively stretched large intestine. In other words, to get a better outcome for chronic constipation related to the megacolon, a low-FODMAP diet should be continued for approximately 2 years.

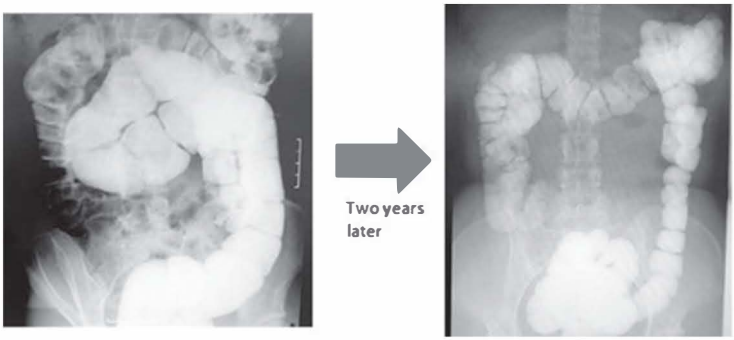


Figure 121: *A case of chronic constipation related to the megacolon. Before treatment, the colon stretched out and did not reach the caecum when 2L of contrast medium was injected. Many gases were found in the ascending colon and caecum as well as in the small intestine. As a result of continuing treatment for 2 years, the width of the colon normalized (Personal data of Uno)*

How to reset symptoms

The inevitable problem with a long-term low-FODMAP diet is that the symptoms may worsen after a while. The reason may be that even if there does not appear to be a problem in the challenge test, the influence will accumulate. Furthermore, even if there is no problem individually, symptoms will appear when the total amount exceeds the threshold value.

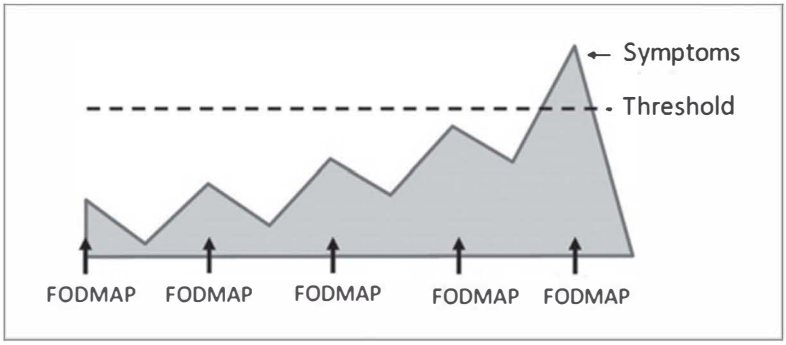


Figure 122: *The deterioration of symptoms due to the intermittent intake of a low volume of high-FODMAP (Figure of Barrett et al.).*

In this case, re-trying the elimination phase is theoretically correct; however, one must consider how to reset the intestinal environment. Research from University of Helsinki, University of Nottingham, and Wageningen University shows that the total microbial load was decreased by 31-fold after receiving 2L of intestinal lavage liquid (Jalanka et al.); however, the number returned to the same value as before the lavage after 14 days and 28 days.

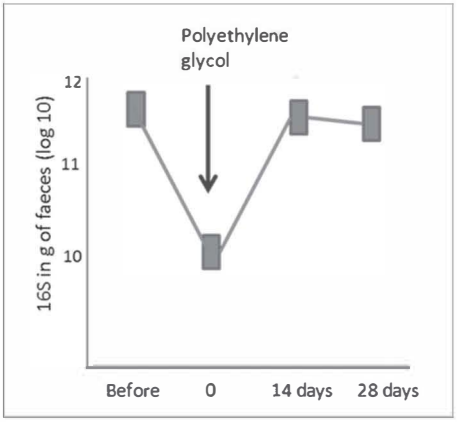


Figure 123: *The transient decrease of intestinal bacteria due to intestinal lavage (Jalanka et al.)*

This indicates that intestinal lavage potentially temporarily reduces the number of intestinal bacteria. It is thought that this application of resetting to reduce the total intestinal bacteria would be effective in a low-FODMAP diet since, in some patients, their IBS symptoms are relieved a few days after colonoscopy (in our experience). However, in Japan, the use of intestinal lavage fluid is confined to colonoscopy or intestinal surgery and is not practical to use on a daily basis. As an alternative method, a retrograde enema from the anus may be considered. In this method, lavage with warm tap water can be used. An intestinal lavage kit can even be purchased on the internet and the only other component needed is warm tap water. The pH of tap water is 8.5 and it, therefore, raises the pH in the intestines and inhibits the growth of gas-forming bacteria. The pH of the intestine in IBS patients is low, indicating that it is acidic and, therefore, in this environment gas-forming bacteria can easily grow. Two to three liters of warm water can be used for

chronic constipation and for IBS-D (diarrhea type) and, to be frank, even less than 2L will work. This method potentially resets the intestinal environment by alkalizing it.

Combined use with eradication therapy

In 2005, it was reported in England that metronidazole inhibits the gas produced by bacterial fermentation in the intestines. Metronidazole is prescribed for infectious enteritis, but it can be expected to reduce the intestinal bacteria in the intestinal tract (Dear et al.). As described in the chapter on SIBO, neomycin is used to treat SIBO in the US; however, it is not approved in Japan. Although, kanamycin, which also decreases the intestinal bacterial flora, has the same action as neomycin; this medicine is used to treat infectious enterocolitis and is often given before colon surgery. In the US, rifaximin is used for IBS patients with SIBO or as eradication treatment for IBS-D (FDA approved three times daily for 2 weeks as a treatment for IBS-D in May 2015); however, rifaximin (Pimentel et al.: 2011, 2014, 2016, Meyrat et al.) is only approved for use in hepatic encephalopathy in Japan, so private import is the only way to obtain it in Japan.

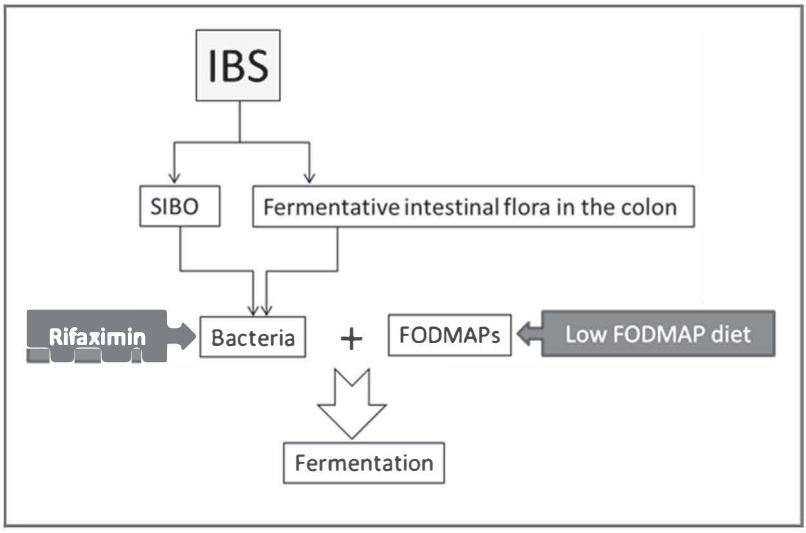


Figure 124: *Theory of eradication therapy.*

Low-FODMAP diet and nutrition

Although most of the time nutrients are absorbed in the small intestine in human beings, high-FODMAP ingredients are poorly absorbed. This means that a high-FODMAP diet will not lead to a rapid increase in blood glucose and insulin. Therefore, in a sense, high-FODMAP ingredients may be effective at blood glucose control. However, in overweight and obese individuals, SCFA may promote obesity by increased colonic energy availability (Rahat-Rozenbloom et al.: 2014). Furthermore, the rapid increase in SCFAs by inulin has been found to increase ghrelin: an appetite enhancing hormone (Rahat-Rozenbloom et al.: 2018). Namely, the hypothesis that "suppressing SCFA production by low-FODMAP diet is not good for the human body" might be too simple an idea. For that reason, further research is needed on this problem.

LIST OF FOOD AND INGREDIENTS

●: Adapted to the F●DMAP restriction stage

△: Pay attention to quantity

▲: Warning

◆: Prohibition during the F●DMAP restriction stage

※: Unknown

☆: Recommended

Italic type: Japanese

Bold: Data from 2018 "Standard tables of food composition in Japan" (STFCJ)

JLFDPG: Japan low-F●DMAP diet promotion group

A

☆●*Abalone, Awabi*: Shellfish found in coastal waters. It is expensive as it cannot be harvested in large quantities. It can be eaten raw *(sashimi)* or grilled. Vitamin B_5 content is 1.9g per 100g (Figure 125).

☆●*Aburaage, Aburage*: Deep-fried thin-cut *Momen-tofu. Inari-sushi* is a traditional food stuffed with seasoned rice into a bag-shaped *Abura-a-ge* (Figure 126).

●*Aji*: Horse mackerel. It used in *sushi* and *sashimi*; it can also be deep fried or grilled with salt. If rice flour or potato flour is used when frying, it is a low-F●DMAP food (Figure 127).

◆*Ajinori*: Processed and seasoned seaweed. Attention should be paid to whether additives are present.

▲*Atsuage, Agedashi-doufu*: Deep fried *tofu*. ●riginally *atsuage* was fried ***monen-tofu*** (low-F●DMAP), but recently *kinu-tofu* (high-F●DMAP) is used instead (Figure 128).

※Acerola

※◆ *Kanten*, agar: Extracted and dried mucus from seaweed. Contains a significant amount of galectins. It is used to make sweets and jelly (Figure 129).

◆Agave syrup: Sweetener. A large proportion of this product is fructose.

△Almond: Up to 8g may be consumed. ●ver 24g may cause symptoms.

●Almond milk: Pure almond milk is limited to imported products, or can be made at home. Japanese products include honey.

◆*American-dog*, com dog: In Japan, after World War II, wheat flour was imported in large quantities from the U.S., and the flour was called *Meriken-ko*. Therefore, com dogs using wheat flour are called *American-dog* in Japan. In Japan, low-F●DMAP American-dogs can now be made at home by rice flour or spelt wheat (Figure 130).

△▲*Anko*: Smooth red-bean jam. It is made from *azuki* beans. Sugar is added and it is used as a sweet jam for rice cakes and sweets. *Azuki* beans contain 3.1g of oligosaccharides per 100g. *Anko* diluted with hot water, mixed with ***mochi*** is called *oshiruko* (Figure 131).

☆●*Ayu*: A representative river fish in Japan. Grilling with salt is recommended (Figure 132).

◆*An-man*: A Japanese cake cooked by steam heating. *Anko* is covered by wheat bread. It is often sold at convenience stores in Japan (Figure 133).

◆ *Ringo*, apple: High-F●DMAP fruit. It contains **1.4g of glucose, 6g of fructose and 0.7g of sorbitol** per 100g (STFCJ).

◆Apple juice: It contains **2.8g of glucose, 6.4g of fructose and 0.4g of sorbitol** per 100g (STFCJ).

●Arugula: The STFCJ indicated fructose present in trace amounts.

◆Asparagus (raw): Contains **0.8g of glucose and 1.1g of fructose** per 100g (STFCJ). Also, it contains 2.5g of inulin in 100g.

○Avocado: Contains **0.4g of glucose and 0.1g of fructose** per 100g (STFCJ).

◆*Azuki:* Smooth red-bean. See *Anko.*

B

○△Banana: Contains **2.6g of glucose and 2.4g of fructose** per 100g (STFCJ). There is a possibility that the amount of fructose exceeds the amount of glucose in a blue banana (Figure 134). However, in ripe or cooked bananas, the amount of glucose exceeds the amount of fructose. Also, it contains 0.3g of oligosaccharides per 100g (STFCJ).

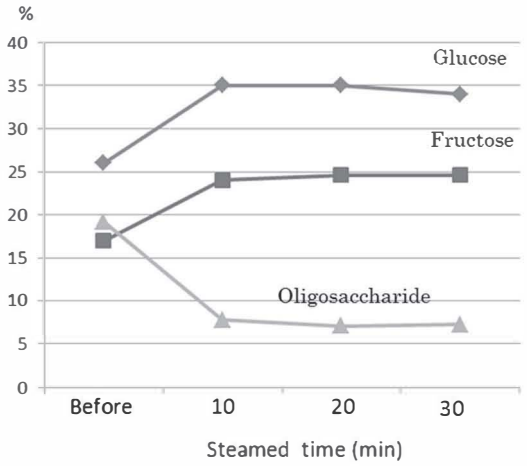


Figure 135: *Time to steam banana and change in carbohydrate (Ito et al.).*

In 1971, Painter and Burkitt considered that diverticulitis would not develop due to high-fiber diets in Africa. This was based on Burkitt's experiences in Uganda. Uganda's staple food at that time was "Maotoke" (a kind of banana), which was steamed before eating (Figure 136). In short, it was a complete low-FODMAP food.

◆Barley: Contains 0.8g of inulin per 100g.

◆ *Mugi-cha,* barley tea: The Japanese have a habit of drinking it in the summer.

◆ *Kuro-satoh,* Barbados sugar: Mostly sucrose, but also contains oligosaccharides (raffinose). Also contains **0.6g of glucose and 0.9g of fructose** per 100g (STFCJ).

◆ *Moyashi,* beansprouts: There are many kinds. In Japan, mainly soybeans, green mung beans, and black mung beans are eaten. There are differences in the amount of oligosaccharides present depending on species and degree of germination (Figure 137).

Soy beans, *moyashi,* (raw) contain **0.1g of glucose and 0.3g of fructose** per 100g. Black mung beans contain **0.5g of glucose and 0.7g of fructose** per 100g (STFCJ).

●Beef: In Japan, *Wagyu* beef is recognized as a "high-class" meat (i.e. expensive). However, *Wagyu* has rich lipids, high calories, low protein, and low vitamins. Most others are imported beef. F●DMAP may be contained in the sauce used in the Japanese steak shop. Therefore, please select salt and pepper during the F●DMAP restriction stage. Meanwhile, in ●kinawa, red beef streaked with less fat (mainly imported from the U.S.) is most prized (Figure 138).

●Beef jerky

◆Beet sugar: Contains many oligosaccharides.

◆Blueberries: Contains **4.2g of glucose and 4.3g of fructose** per 100g. (STFCJ).

△●*Bīfun*, rice vermicelli*:* Rice flour noodles are called *bifun* in Japan. In ●saka and Kobe, there is a restaurant where rice vermicelli can be eaten. However, because it includes onion and garlic, you must ask for them to be excluded. Avoid mixing with high-F●DMAP products at the cooking stage (Figure 139).

◆Biscuits: Spelt-flour biscuits are recommended (Figure 140).

●Bok Choy, *Chingensai*: Used for salads and simmered dishes. It contains (raw) **0.3g of glucose and 0.1g of fructose** per 100g (STFCJ).

◆ *Pan*, bread: In Japan, all breads containing flour are high FODMAP. Rice flour bread may contain wheat. It contains **1.1g of glucose and 1.4g of fructose** per 100g (STFCJ). Rice flour bread sold in Japan is not low-FODMAP. You must make 100% rice flour bread at home. 100% rice flour bread can be eaten in the FODMAP restriction stage. Please eat spelt wheat with low fructans in the challenge phase.

◆Broccoli: Contains (raw) **0.3g of glucose and 0.9g of fructose** per 100g (STFCJ). However, the amount of raffinose is unknown.

◆ *Gobou-cha*, burdock and burdock tea: Contains (raw and boiled) **0.1g of glucose and 0.3g of fructose** per 100g (STFCJ). These teas have recently become popular in Japan. However, they contain 2.3–3.6g of oligosaccharides per 10g. Advertisements state that it improves constipation and rejuvenates with its detoxifying effect.

△Butter: Contains (raw) **0.5–0.6g of lactose** per 100g (STFCJ).

●*Buri*: Amberjack. Aquaculture began in 1960 and now farmed *Buri* is eaten regularly. It is mainly eaten with *sashimi*, or grilled, or boiled with soy sauce (Figure 141).

C

△◆Cabbage: Many varieties are grown all over the world, and also in Japan. The kind used varies according to season and region. Contains (raw) **1.8g of glucose and 1.4g of fructose** per 100g (STFCJ). However, the amount of raffinose in Japanese cabbage is unknown. There are various FODMAP amounts depending on variety, and there is no evidence that all Japanese cabbage is low-FODMAP. It should be avoided during the FODMAP restriction stage in Japan's low-FODMAP diet.

●◆Cake: Needless to say, ordinary commercial cake is a high-FODMAP food. However, recently in Japan, homemade recipes for low-FODMAP cakes have been introduced by a member of JLFDPG. They are made using rice flour, spelt wheat, sugar, and bananas. Recipes for non-wheat flour cake without butter, milk, and eggs have also been introduced (Figure 142).

●▲Camembert cheese

●Carrot, *Ninjin*: This is an important vegetable for a low-FODMAP diet. Contains (raw) **1.6g of glucose and 1.5g of fructose** per 100g (STFCJ).

◆Cashew nuts (Cashews): Oligosaccharides are abundant in this product.

※◆Cauliflower: Contains (raw) **1.3g of glucose and 1.1g of fructose** per 100g (STFCJ). However, the volume of polyol is unknown.

△▲◆Celery: Contains (raw) **0.6g of glucose, 0.6g of fructose, and 1g of mannitol** per 100 g (STFCJ). However, the total volume of polyol is unknown.

△▲◆*Chahan, Yakimeshi*: Fried rice. This is one of the most popular Chinese dishes in Japan. To create it, mix rice, eggs, pork, and onions and then heat with oil. Garlic is sometimes used. Variations, such as *ebi-Cha-han,* adding shrimp; *kani-Cha-han,* crabs, etc., are available (Figure 143).

△▲◆Cheese: It depends on the amount of lactose. Avoid lactose-rich cottage and cream cheese and in the challenge period start with cheddar, ricotta, mozzarella, gouda, or Swiss cheese. When unclear about the dose of lactose, the daily intake of total sugars should be 1.25g or less. Lactose may be added to Japanese cheese, so be sure to check sugar content. In Japan, the volume of lactose per 100g is **2.4g in cream cheese and 3.5g in mascarpone** (STFCJ).

◆Cherries: The amount of fructose in Japanese cherries is lower than the amount of glucose, but they contain 2.3g sorbitol per 100g. Many Japanese people experience diarrhea due to overeating cherries.

●Chestnut (Japanese), *Kuri*: The sweetness comes from maltose. Lactic acid bacteria produces fructose and glucose from maltose. It is necessary to check whether gas symptoms will occur after ingestion.

▲◆Chewing gum: Because of polyol content, it is prohibited in the FODMAP restriction stage.

●Chicken

◆Chicory root: Contains (raw) 17.5g of inulin per 100g.

●Chinese cabbage, *Hakusai*: Primarily used for stew or soup. Contains (raw) **1.1g of glucose and 0.8g of fructose** per 100g (STFCJ).

◆Chinese yam: *Nagaimo*: This contains sticky galactans. Contains (raw) **0.4g of glucose and 0.5g of fructose** per 100g (STFCJ). In Japan, it is eaten with rice.

▲*Chikuwa*: A bamboo-shaped fish cake. It was baked of fish meat wrapped around a bar such as bamboo. This taste resembles that of *kamaboko* (fish cake). It contains sorbitol as a preservative (Figure 144).

●Chili oil, *Ra-yu*: In Japan, this is mixed with soy sauce, mainly when eating *gyoza*.

△▲*Chinsuko*: ●kinawa biscuit (similar to shortbread, but made with lard); ●kinawa biscuits are made with wheat flour (Figure 145).

▲ ◆Chocolate: Most Japanese chocolate contains lactose and soybean-derived ingredients. In addition, it may contain polyols (isomalt, lactitol, and maltitol). The amount of lactose contained per 100g is **7.5g in almond chocolate, 10.2g in white chocolate, and 11.7g in milk chocolate** (STFCJ).

●▲Cocoa: Japanese cocoa beverages may contain lactose or soy-bean ingredients.

▲◆Coconut Milk: Contains (water), **0.4g of glucose and 0.5g of fructose** per 100g (STFCJ). In Japan, because many of thse products contain a large amount of sorbitol, avoid it during the restriction stage.

▲Cod roe, *Tarakoi*: In Japan, most processed foods contain sorbitol.

●▲Coffee: Coffee itself may be a laxative.

◆Condensed milk: Contains 9.1–10.8g lactose per 100g.

▲△Com (maize): Although this has less fructose than glucose, the problem is that it also contains xylo-oligosaccharides.

◆Com syrup, *Iseikatou*: Contains (water), **28.3g of glucose and 39.4g of fructose** per 100g (STFCJ) of fructose-glucose syrup. High-fructose syrup contains **0.9g of glucose and 69.5g of fructose** per 100g (STFCJ).

▲Cornflakes: In Japan, oligosaccharides are mixed in many products.

●Cotton candy, *Wata-ame*: Made from sugar and sold at festivals in Japan.

●▲Crab, *Kani*: Beware of allergies. Almost all processed crab contains sorbitol.

△ Cranberry (dry)

◆Cream cheese: Softer cheeses are more popular in Japan than hard cheeses. See cheese.

◆Croissant: A popular bread in Japan.

◆Cucumbers, *Kyuri*: Contains (raw) **0.9g of glucose and 1g of fructose** per 100g (STFCJ).

◆Cup noodles: see instant noodle.

△◆*Curry rice*: Curry and rice was born in the U.K.; it is based on Indian cuisine, and was transmitted to Japan as a Western cuisine. This meal was based on the curry powder used in the UK, but the taste of Japanese curry was adjusted by adding soy sauce, dried bonito, and so on. It has been sold in Japan since 1905, but its adoption was limited. It became more popular in Japan after WWII. High-F●DMAP ingredients such as onions, flour, and apples may be present. Gluten-free curries are now available.

◆Custard cream: This is used for cream puffs (choux pastry) and pastries in Japan. Contains **2.9g of lactose** per 100g (STFCJ).

D

☆●*Daikon*, Chinese (white) radish: Contains (raw) **1.5g of glucose and 1.1g of fructose** per 100g (STFCJ). When chopped thin and fried with oil, it is closer to an onion in texture. It is an important low-F●DMAP vegetable in Japan. Boiled radish is used for *●den*. A radish cut like a noodle is called *tsuma* and is an accompaniment for *sashimi*. Grated-radish is called *daikon-oroshi* and this is mixed with soy sauce and used for *sashimi*, etc. (Figure 146).

●△◆*Don*: *Donburi*. Various dishes are put on top of a bowl of rice. Depending on the dish, the F●DMAP amount varies (Figure 147).

◆Dried fruits: Contain many polyols (mannitol) and fructose.

◆Dried potato, *Hoshi-imo*: Many dried potatoes are made from sweet potato (*sastuma-imo*). However, there is a possibility that Yacon potato is used. Yacon potato contains 8g of oligosaccharides per 100g. The white powder on the surface is maltose (Figure 148).

●Dried shrimp: *Hoshi-ebi*. Contains a large amount of calcium. This is used for all kinds of dishes such as soup and pasta.

E

●Edible chrysanthemum

●Eel: See *Unagi*

●Eggplant, *Nasu*: Japanese eggplant is acceptable under FODMAP. Contains (raw) **1.2g of glucose and 1.1g of fructose** per 100g (STFCJ).

☆●Egg

●Egg (quail): Often used for *chuka-don*. Also eaten fried.

◆*Enoki* mushroom: Because there is a high amount of trehalose and mannitol, it is prohibited in the FODMAP restriction stage.

◆*Eringi*, King trumpet mushroom: Contains (grilled) **3.8g of trehalose** per 100g (STFCJ).

F

●Fig, *Ichijiku*: Contains (raw) **5.6g of glucose and 5.2g of fructose** are per 100g (STFCJ).

●Fish: Can be consumed in all FODMAP stages. The Japanese eat many fish such as salmon, *sake*; tuna, *maguro*, *buri*; squid, *Ika*; pacific saury, *sanma*; horse mackerel, *aji*; righteye flounder, *karei*; octopus, *tako*; bonito, *kastuo*; red snapper, *tai*; mackerel, *saba*.

●Foie gras

▲French fries: No problems with FODMAP, but gas is generated in proportion to intake amount.

<Fruit>

Below are the fruits with fructose contents higher than the amount of glucose (per 100g; STFCJ). Regardless of the amount of other FODMAPs, it is judged to be a high-FODMAP food.

	Gulucos: G (g)	Fructose: F (g)	F-G (g)	Sorbitol
Apple	1.4	6	4.6	0.7
Annona cherimola	6.3	6.7	0.4	
Blueberry	4.2	4.3	0.1	
Gooseberry	5.1	5.2	0.1	
Grape	8.1	8.7	0.6	
Grapefruit	2	2.2	0.2	
Guava	1.5	1.7	0.2	
Japanese pear	1.4	3.8	2.4	1.5
Kiwifruit: green	3.7	4	0.3	
Kiwifruit: yellow	5.2	5.7	0.5	
Mango	0.7	3.1	2.4	
Melon	1.2	1.3	0.1	
Mikan	1.7	1.9	0.2	
Navel ●range	1.9	2.1	0.2	
Peache	0.6	0.7	0.1	0.3
Pineapple	1.6	1.9	0.3	
●uince	3.5	5.5	2	
Raisin	36.4	38	1.6	
Strawberry	1.6	1.8	0.2	
Valencia ●range	1.7	1.9	0.2	
Watermelon	1.9	4.1	2.2	

Below are the fruits whose glucose content is higher than their fructose content (per 100g; STFCJ). If the amount of other FODMAPs is low, then it is a low-FODMAP food.

	Gulucos: G (g)	Fructose: F (g)	F-G (g)	Sorbitol
Apricot	1	0.3	-0.7	0.3
Avocado	0.4	0.1	-0.3	
Banana	2.6	2.4	-0.2	
Coconut (water)	3.2	2.9	-0.3	
Figs	5.6	5.2	-0.4	
Lime	0.7	0.7	0	
Litchi	7.3	7	-0.3	
Lemon	1.5	0.7	-0.8	
Papaya	3.7	3.4	-0.3	
Persimmon	4.8	4.5	-0.3	0.7
Prune	5.5	3.3	-2.2	

G

▲*Gan-modoki*: Deep-fried *tofu* mixed with thinly sliced vegetables. This is often used for *Oden*.

◆Garlic, *Nin-niku*: In Japan, garlic is often baked. A typical dish containing garlic is *Gyoza*. Contains 12.5g of inulin per 100g.

◆Garlic chives, *Nira*: Often eaten in Japan, *Nira* is used for scrambled eggs.

Often, it is used for topping *ramen* or *gyoza* (Figure 149).

◆Grape, *Budou*: Generally, fructose exceeds glucose. Contains (raw) **8.4g of glucose and 8.7g of fructose** per 100g (STFCJ).

◆Grapefruit (yellow): Contains **2g of glucose and 2.2g of fructose** per 100g (STFCJ).

◆Green Beans: Japanese Green beans contain 3.7g of oligosaccharides per 100g.

△▲Green onions: See "White part of green onion" (Figure 150).

△ Green peas

○Green pepper: Contains (raw) **1.2g of glucose and 1g of fructose** per 100g (STFCJ).

●Green tea

◆*Gyoza*: Crescent-shaped pan-fried dumplings stuffed with minced pork and vegetables; they include garlic and wheat. It is a popular food in Japan. As well as typical *gyoza* sheets (wheat flour), sheets made of rice flour are also on sale in Japan (Figure 151).

◆*Gyū-don*, beef bowl: Bowls of rice topped with cooked beef and onions, which are popular in Japan. There are many specialty restaurants that serve these. Please try eating it without onions in the challenge phase (Figure 152).

H

△▲Hand-rolled *sushi*, *temaki-zushi*: By choosing the ingredients to be wrapped, it can be a low-F●DMAP food (Figure 153).

▲Ham: Most Japanese ham contains sorbitol as a preservative.

▲◆Hamburger: At Japanese hamburger shops, burgers with buns using rice instead of wheat flour are sometimes sold. In Japan, recipes of fish- and rice-only burgers have also been released (Figure 154).

▲◆*Hampen*: A cake made by heating a liquid-state fish powder and yams. Although the amount of fructan is unknown, the possibility of it being a high F●DMAP is high, due to the fructans in the yams.

◆*Harumaki*: Pork, mushrooms, etc. wrapped with a flour sheet and fried with oil. It is one of the most popular Chinese dishes in Japan. It can also be made with rice flour.

△▲ Herbal tea: Up to 2●●ml is low-F●DMAP.

●Herring roe, *kazunoko*: The Japanese eat it over the New Year. Sorbitol is often added to processed products.

●*Hie*: barnyard millet, Japanese (barnyard) millet, barnyard grass. A low-F●DMAP food. ●ne of the traditional cereals in Japan. Until 1●● years ago, Japanese farmers would eat it instead of rice.

◆*Hijiki:* Black seaweed. Contains (dry) **3.1g of mannitol** per 1●●g (STFCJ). It is mixed with carrots, etc. and eaten like a salad (Figure 155).

◆*Hiyamugi:* Wheat noodles chilled with ice. The Japanese eat them in the summer (Figure 156).

◆Honey: The amount of fructose exceeds the amount of glucose. It also contains 1.5g of oligosaccharides per 100g. It contains **33.2g of glucose and 39.7g of fructose** per 100g. (STFCJ).

◆Horseradish: Used instead of the root of Japanese *Wasabi*, especially in *sushi* and *sashimi*.

I

▲Ice bars: Avoid bars containing lactose, sorbitol, or corn syrup. Unfortunately, in Japan it will not be possible to find an ice bar that only contains sucrose.

◆Ice cream: Because it contains 6 g/100g of lactose, it is prohibited during the FODMAP restriction stage. In the challenge period, begin with 50g. Avoid products containing sorbitol or corn syrup. Unfortunately, there is no low-FODMAP ice cream in Japan.

△●*Inari-zushi, inari-sushi, oinari-san*: *Inari-sushi* is a traditional food stuffed with flavored rice in *abura-a-ge*. Eastern Japanese (Kanto) and West Japanese (Kansai) versions are different in shape (Figure 157).

●▲Instant coffee: See coffee

◆Instant noodle: Almost all instant noodles are made from flour.

●*Ito-kon-nyaku*: Noodles made from *kon-nyaku*. They are 4–8 mm thick and are used for *oden* (Figure 158).

J

△ Japanese Pumpkin, *Kabocha*: Contains (boiled) **1.7g of glucose and 1.7g of fructose** per 100g (STFCJ). It is a low-FODMAP food, up to 60g (Figure 159).

◆Jerusalem artichoke, *Kikuimo*: Chicory root. It contains (raw) 18g of inulin per 100g.

K

△◆*Kakino-ta-ne:* Spicy rice crackers that look like persimmon seeds (Figure 160). ●ligosaccharides and/or sorbitol and wheat flour are often included. It is popular with the Japanese, who eat them as appetizers with beer.

●Kale: Contains (raw) **0.5g of glucose and 0.5g of fructose** per 100g (STFCJ).

▲*Kamaboko:* A fish-paste loaf. It is an indispensable food for *osechi*, which has been a New Year's meal since ancient times. Recently, almost all *kamaboko* contains sorbitol (Figure 161).

●*Karei*: Righteye flounder. It is used in *sushi* and *sashimi*, and it can also be deep-fried, boiled with soy sauce, or grilled with salt (Figure 162).

◆*Katsu*Meat (beef, pork, chicken) or oysters deep fried with oil after being coated with bread crumbs. It was first served in Japan in the 1930s. There are many specialty *Katsu* restaurants in Japan (Figure 163)

◆*Katsu-kare*: Curry and rice with a pork cutlet. This is a curry dish that is unique to Japan (Figure 164). Japanese curry contains plenty of apple and honey.

◆*Kara-age*: Japanese fried chicken. This is a popular food for all ages in Japan. Wheat flour is used. *Kara-age* breaded with rice flour is not sold, but original recipes by individuals in Japan are available to the public on the internet. Also, if you use potato starch instead of wheat flour, it becomes low-F●DMAP (Figure 165). See *Katakuri-ko*.

●*Katsuo*, bonito flakes: This is not suitable for heated cooking because of its low fat content. For that reason, moisture is removed by smoking it to make a hard-preserved food called *Katsuo-bushi* (Figure 166). It is sliced thinly and used for soup seasoning or to top food.

●*Katsuo-no-tataki*: Cut *Katsuo* on the long axis, bake the surface, then chill it, cut it, and eat it with sauce (Figure 167). It is a specialty dish from the Kochi prefecture, but it is also sold at grocery stores in other places.

☆●*Katakuri-ko*, potato flour: This is an important powder as a substitute for wheat flour. It can be used for deep frying instead of wheat flour. In

addition, it is used for soups that need stickiness. It is not an exaggeration to say that using this powder successfully is the key to making a low-FODMAP diet fun and successful. The Japanese call deep frying with *Katakuri-ko, Tatsuta-age* (Figure 168).

△◆*Ken-chin-jiru*: Historically, this was a meal eaten Buddhist temple monks. It is a chowder of vegetable and tofu (Figure 169). If the burdock and mushrooms are removed, it becomes a low-FODMAP food.

◆Kidney beans, *Ingen-mame*: Avoid eating during the introduction period, since 0.2–0.6g galacto-oligosaccharides are contained per 100g. In the challenge period, start with 50g.

◆*Kinako*: Roasted soy-bean flour. In Japan, it is often used for rice cakes and Japanese confectionery (Figure 170). It contains 7g of oligosaccharides per 100g. It is a high-FODMAP powder that you must pay attention to in Japan.

◆*Kinpira Gobo*: Chopped burdock root (and sometimes carrot) cooked in sugar and soy sauce (Figure 171). See Burdock.

▲*Kintsuba*: A confection of sweetened beans wrapped in wheat-flour dough (Figure 172). A small amount of beans are acceptable but be careful with sorbitol.

◆*Kinu-tofu* (soft *tofu*): Soft *tofu*, which is like a pudding, and the oligosaccharides have not been removed during the manufacturing process.

◆*Kimuchi* (Korean pickles): They are a high FODMAP food, containing garlic.

◆Kiwifruit: Contains (green) **3.7g of glucose and 4g of fructose** per 100g (STFCJ). Yellow kiwifruit contains **5.2g of glucose and 5.7g of fructose** per 100g (STFCJ).

▲*Konbu*, kelp: Attention should be paid to the ingredients in processed goods. Since the white powder frequently covering the kelp is mannitol, it is necessary to wash it. It contains (dried Kelp) 19.7g of mannitol per 100g.

●*Kon-nyaku:* Used for *●den.* It can be grilled like a steak, and also eaten raw like *sashimi* (Figure 173).

☆●*Kohri-tofu, Kohya-tofu, Shimi-tofu*: Freeze-dried tofu. Preserved tofu was developed over 3●● years ago. Frozen *tofu* ice (oligosaccharide mixed ice) is removed and dried. Most of the oligosaccharides are removed by classical production methods. It is a sponge-like tofu, which is mainly used for stewed dishes (Figure 174). It contains 5●.5g protein, 63●mg calcium per 1●●g.

●*Kurokajik*: Indo-Pacific blue marlin. It is eaten in ●kinawa. It contains high amounts of vitamin D.

▲*Kusa mochi*: A rice flour dumpling mixed with mugwort (*yomogi*). It is a high F●DMAP food because there is *Anko* inside.

L

◆Lactic acid bacteria (lactic acid bacteria beverage): Maltose is converted to fructose and glucose by lactic acid bacteria.

◆*La France* pear: In Japan, it is popular as a fruit that does not raise blood sugar. It is a pear which is said to have been transmitted from France to Japan. However, it is a Japanese fruit that is not produced in France (Figure 175). It contains 1.17g of glucose, 2.1g of sucrose, and 6.45g of fructose per 1●●g.

◆Leaf lettuce: Contains **0.4g of glucose and 0.5g of fructose** per 1●●g (STFCJ). Red leaf lettuce is called "sunny lettuce" in Japan. Red leaf lettuce contains **0.3g of glucose and 0.4g of fructose** per 1●●g (STFCJ).

◆Leeks: The white part is judged to be high-F●DMAP. Contains 6.5g of inulin per 1●●g.

☆●Lemon: Contains **1.5g of glucose and 0.7g of fructose** per 1●●g (STFCJ).

◆Lentil (Lens culinaris)

◆Lettuce (Iceberg lettuce): Lettuce includes lectins, which might be a cause of diarrhea (Wilkinson-Smith et al.). Contains (under soil

cultivation) **0.7g of glucose and 0.8g of fructose** per 100g (STFCJ). Under hydroponic (water) cultivation contains **0.8g of glucose and 1g of fructose** per 100g (STFCJ). See *Salada-na.*

●Lime: Contains **0.7g of glucose and 0.7g of fructose** per 100g (STFCJ).

●Lobster: Pay attention to ingredients of sauces and additives.

●Lotus Root, *Ren-kon*: Under water cultivation (raw, boiled), contains **0.1g of glucose and 0.1g of fructose** per 100g (STFCJ).

●Lychees: Contains **7.3g of glucose and 7g of fructose** per 100g (STFCJ). As Shrivastava et al. (2017) reported the low blood sugar effect of lychees in India. Therefore, a small intake is desirable.

M

●◆Mackerel, *Saba*: It is a popular fish that is eaten all over the world (Figure 176). In Japan, *Saba* and *Buri* bones that are more than 3000 years old have been found at archaeological sites. Japanese eat *Saba* with *sushi, Sime-saba*, salt-grilled etc. Histamine is easily increased in this fist by histamine-producing bacteria; therefore, urticaria and histamine food poisoning may occur. This means that it might exacerbate IBS symptoms. See *Shime-saba.*

◆*Maitake* mushrooms: Sold all year in Japan. Served tempura style and covered with flour is popular way of eating them (Figure 177).

◆Maltose (malt, maltose): Produced from fructose by lactic acid bacteria.

◆Mango: Contains (raw Mango) **0.7g of glucose and 3.1g of fructose** per 100g (STFCJ). However, dried Mango contains **4.8g of glucose and 20.4g of fructose** per 100g (STFCJ). The difference between fructose and glucose is 2g/ 100g when fresh. However, when left for 14 days at room temperature, it can be 3g/100g or more.

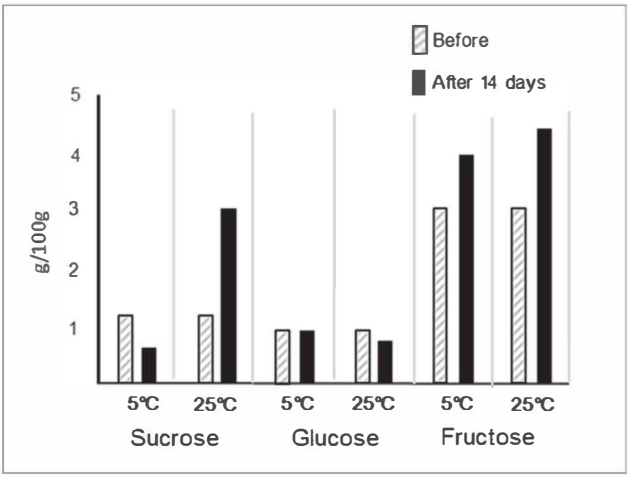


Figure 178: *Changes in carbohydrates in preserved mango*
https://www.jstage.jst.go.jp/article/sasj1971/27/2/27_2_65/_pdf/-char/ja

◆*Manjyu:* A Japanese cake wrapped in bean curd with flour (Figure 179). Sometimes it is heated with steam (such as in *An-man*). There are unique *Manjyu* in each region of Japan. Many hot springs have hot spring *Manjyu*.

○Maple syrup: Contains **0.6g of glucose and 0.3g of fructose** per 100g (STFCJ).

△ Margarine: Contains **0.67g of lactose** per 100g (STFCJ).

○▲Marshmallow: Basically, it is made with egg white and sugar and is low FOMAP food, but recently, in Japan, oligosaccharides have been added.

○▲Mayonnaise: *KEWPIE* mayonnaise has been manufactured since 1925 and is the most popular mayonnaise in Japan. The original product is low-FODMAP food. In Japan, persons who top all foods, such as bread and rice, with mayonnaise are called *Mayo-la* (Figure 180). However, other mayonnaises may have high FODMAP ingredients mixed in.

◆*Mekabu*: Seaweed (*wakame*) leaves near the stalk (Figure 181). They contain large amounts of galactans. It is a popular food in Japan, thought

to helpt to strengthen immunity, aid slimming, prevent constipation, and so on. However, in cases of chronic constipation, it may cause intestinal obstruction.

◆Melon: Contains **1.2g of glucose and 1.3g of fructose** per 100g (STFCJ). However, the amount of fructose differs depending on type and place of cultivation.

▲*Men-ma:* Bamboo shoots that have been boiled, dried, or preserved in salt, soaked in hot water, and then seasoned for use in Chinese food (Figure 182). Pay attention to additives.

◆*Mentaiko:* Pay attention to sorbitol. *Tarako* and *mentaiko* are both cod roe products. Sorbitol is added to enhance color enhancement, as well as to retain sweetness and moisture (Figure 183).

●*Mezashi:* After salting small fish such as sardines, they are bundled together through several bamboo skewers and dried. They are eaten grilled or deep fried (Figure 184).

◆*Mikan (Satsuma* mandarin orange, *unshu mikan):* ●range in Japan (Figure 185). Contains **1.7g of glucose and 1.9g of fructose** per 100g (STFCJ).

◆Milk: Acceptable if it is lactose-free. However, non-lactose milk is not sold in Japan. However, lactose-free milk for infants is on sale.

◆*Mirin,* sweet sake: It is a seasoning often used in Japan, which contains maltitol and oligosaccharides.

▲◆*Miso:* Since the amount of oligosaccharides varies depending on the raw material, please start during the challenge period.

●▲*Mitarashi-dango*: This is a type of rice cake (*mochi*) that is eaten with sugar and soy sauce (Figure 186). It is a commercially available *mochi* that is recommended as low-FODMAP food.

●◆*Mochi*: Rice cake. Different kinds of rice cakes are on sale in Japan. Rice cakes eaten with sugar and soy sauce are a perfect low-FODMAP food. See *Noshimochi.*

Noshimochi (left) and Noshimochi with sugar and soy sauce (right) (Figure 187)

See Mitarashi-dango

However, green rice cakes are high-FODMAP food.

Relationship between soybean and anko in rice cakes (Figure 188)

▲△ *Momen-tofu*: This is the low-FODMAP version of *tofu*, but only start eating it during the challenge period.

◆*Monjayaki*: Savory pancake (wheat flour) with various fillings (Figure 189). Thinner and soft than *Okonomiyaki.*

◆*Monaka*: Bean-jam*(Anko)*–filled wafers (Figure 190).

◆*Motsunabe*: Hot pot stew made with offal, garlic, vegetables, and (often) miso.

●*Moroheiya,* Corchorus olitorius: It is an Egyptian-origin summer vegetable. It is boiled like spinach (Figure 191).

◆*Mozuku:* A seaweed from the Spermatochnaceae family. It is considered a delicacy when seasoned with vinegar (Figure 192). There is galactan in the slime.

▲Mozzarella cheese: Note any additives.

◆Mushrooms, *Kinoko:* Avoid during the FODMAP restriction stage, as they contain mannitol and trehalose.

▲Mustard: note any additives.

N

※*Namako,* Sea cucumber: Contains 0.5g carbohydrate per 100g. It is recorded that these There grotesque sea creatures have been eaten in Japan since the 8th century (Figure 193). In 1866, when Sir Harry Smith Parkes, the British minister in Japan, came to Kagoshima, he ate grilled *Namako.* It is regarded as a healthy food from ancient times, but there is no scientific basis behind this.

◆*Nameko* mushroom: Contains galactan slime. Contains (grilled) **1.9g of trehalose** per 100g (STFCJ).

▲Namuru: Namuru is one of the home dishes on the Korean Peninsula, in which vegetables, such as bean sprouts, and salt-spilled edible wild plants, such as *Warabi*, are mixed with seasonings and sesame oil. It is similar to Japanese *Goma-ae*.

◆Naan: It is made with wheat flour. Recipes made with rice flour are available to the public in Japan.

◆*Nanbu-Senbei*: Historically made with buckwheat (*soba*) flour. Although it is a type of *senbei* but, unlike hard rice crackers (rice flour), it is made with wheat flour (Figure 194).

◆*Neri Wasabi*, Wasabi paste: This might contain mixed products of sorbitol and oligosaccharides.

◆*Natto*: A Japanese fermented food, soybean fermented by *Bacillus Natto*. It is eaten with rice (Figure 195). However, it contains 2g of oligosaccharides per 100g. In addition, the stickiness of *Natto* is due to its fructan content. Start with a small amount during the challenge period.

◆Nectarines: There are variations in the amount of fructose and glucose. It is possible that nectarines can contain 1.8g of sorbitol per 100g.

●*Niboshi*: Dried Anchovy. *Niboshi* is dried after boiling the small fish, and it is mainly used for soup (Figure 196). It can also be eaten as is, or as a powder. Anchovies are the most commonly used. It is also used to make *tsukudani*.

▲*Niku-dan-go*, Meat balls: A small hamburger steak in Japan (Figure 197). Pay attention to the possible presence of wheat flour and onion.

◆*Niku-man (Chu-ka-man)*: A Japanese cake cooked by steaming (Figure 198). The spicy meat is wrapped in bread made from flour. It is often sold at the convenience stores and Chinatowns in Japan. It is limited to the challenge phase due to the wheat flour and onion content.

※△*Nigauri (Goya)*, Bitter gourd: In Okinawa, the famous *Goya Chample* uses this (Figure 199). It contains **0.2g of glucose and 0.1g of fructose** per 100g (STFCJ). However, *Nigauri* also contains oligosaccharides.

●*Noshimochi* (plate *mochi*): *Kiri-mochi* (cut mochi) is a piece of *mochi* that has been cut out from plate *mocha* (Figure 200)

▲*Nori*, Seaweed (laver): Avoid seasoned seaweed or Korean seaweed during the FODMAP restriction stage (Figure 201).It is important to note that most Japanese people have decomposing enzymes for laver, but their influence on the intestines is still unknown.

◆*Nukazuke*: Pickles made in brine and fermented rice bran (Figure 202). These include oligosaccharides.

O

◆Oats: Raw materials for granola. Although it is in the rice family, oligosaccharides are mixed in at the processing stage. Avoid during the introduction phase. In the challenge period start with 50g.

●Octopus, *Tako*: It is used in *sushi*, *sashimi* and *takoyaki* in Japan. It is also used deep-fried and simmered (Figure 203). Some areas sell dried octopus.

▲*Oden*: In Japan, it is a popular dish in winter (Figure 204). Eggs, *konnyaku*, and radish are good, but be careful of the soup.

●Oil sardines

▲*Okaki* (*kaki-mochi)*: Japanese traditional snack (Figure 205). It is made from a small rice cake, which is baked or fried with oil. Originally it was low-FODMAP, but now the oligosaccharide, sorbitol, has been included.

◆*Okonomiyaki*: A type of *teppanyaki* that uses flour and cabbage, meat, shrimp, squid, and the like (Figure 206). Eaten with seasonings such as sauce, mayonnaise, and blue paste, etc. There are regional differences between foods added. It is popular with overseas travelers who visit Japan, but unfortunately it is a high-FODMAP food.

△◆※*Okura*: Contains **0.6g of glucose and 0.6g of fructose** per 100g (STFCJ). However, it contains many galactans.

▲◆*Ohagi*: *Mochi* rice ball coated with *Anko* (Figure 207).

△ Olive oil: Ingestion of large amounts causes IBS symptoms.

●▲*Onigiri* (rice ball): This is good to make yourself, because trehalose and sorbitol are mixed into the rice balls when it is sold at convenience stores (Figure 208).

◆Onions, *Tamanegi*: The amounts of fructose and glucose are almost equal, but it contains 4.3g of inulin per 100g.

▲Omelette rice, *Omu-rice*: An original Japanese cuisine devised in 1900. Rice flavored with tomato ketchup is wrapped in eggs like an omelet (Figure 209). Variations: *Omu-cha-han*, which wraps *yakimeshi* in eggs, and *Omu-soba*, which wraps *yaki-soba* in eggs. It might include onions.

△◆Oolong tea: Oolong tea in Japan may contain oligosaccharides.

◆Orange: Valencia and Navel Oranges are sold in Japan. Valencia Oranges contain **1.7g of glucose and 1.9g of fructose** per 100g (STFCJ), and Navel Oranges, **1.9g of glucose and 2.1g of fructose** per 100g (STFCJ).

●△◆*Osechi-ryori*: New Year dishes in Japan. Many foods have been salted that can be stored for several days (Figure 210). However, recently, sorbitol has been used in many foods to further extend the shelf life.

●Oyster, *Kaki*: In Japan, it is eaten raw but sometimes it causes norovirus gastroenteritis (Figure 211).

◆Oyster, fried: A popular food sold at a Japanese food store, which is breaded in flour.

P

◆Pancake: Lactose is mixed in pancakes sold in Japan. If it is 100% rice without contamination by wheat flour, it might be started during the FODMAP restriction stage. See Cake.

●Papaya: Contains **3.7g of glucose and 3.4g of fructose** per 100g (STFCJ).

●◆Pasta: Needless to say, wheat flour pasta is a high-FODMAP food. If it is 100% rice without contamination by wheat flour, it may be trialed in the FODMAP restriction stage (Figure 212).

☆●Parsley: Contains 850μg of vitamin K, 220μg of folic acid and 120mg of vitamin C in 100g, so it is recommended for all stages of low-FODMAP diets (Figure 213).

▲Pea: Contains 3.1g of oligosaccharides per 100g.

△◆Peanuts: Small amounts are considered low-FODMAP, but the Japanese often have peanut allergies. Namely, peanuts may worsen IBS symptoms.

△◆Peanut butter: When made in the USA, they tend to only contain peanuts, sugar, and food oil. There is a high possibility that oligosaccharides are added to Japanese peanut butter.

◆Peach, *Momo*: Japanese regular peaches contain 0.7g of fructose, 0.6g of glucose, and 0.4g of sorbitol per 100g. White peaches contain **2.7g of glucose, 3.1g of fructose, and 0.4g of sorbitol** per 100g (STFCJ) (Figure 214).

◆Pear (Japanese pear), *Nashi*: A typical Japanese pear is *nijuu-seiki* or *hoh-sui* varieties. *Nijuu-seiki* contains 4.9g of fructose, 1.8g of glucose and over 0.8g of sorbitol per 100g. In *hoh-sui*, the sugar content varies depending on the harvest time, containing 1–6g of fructose, 0.5–2.5g of glucose and 3–5g of sorbitol per 100g (Figure 215).

◆Persimmon, *Kaki*: Traditionally, the fructose content of Japanese persimmon is lower than the glucose level (Figure 216). However, recently there is a possibility that fructose is increasing due to varietal improvement. There is also a danger of exacerbating constipation due to tannins. Please start with a small amount in the challenge phase.

◆Pineapple: Contains **1.6g of glucose and 1.9g of fructose** per 100g (STFCJ).

◆Pistachios: Contains a large number of oligosaccharides.

●△Phở: A type of rice noodle originating from Vietnam and recommended on a low-FODMAP diet (Figure 217). However, Japanese leek and/or onions may be added to the soup.

△Popcorn: Please pay attention to high fiber content.

●Pork feet: In Japanese it is called *Ton-soku*; in Okinawan it is called *tebichi* (Figure 218). Basically, it is a low-FODMAP food.

●△Potato: In principle this is not a high FODMAP food, but gas increases dependent on the quantity consumed. In other words, too much potato may reduce the effects of a low-FODMAP diet.

☆●Poultry liver: Includes high amounts of vitamin B_6 and B_{12}, folic acid, and pantothenic acid.

◆Prebiotic food: Basically, prebiotic foods (fermentation in the intestine) are high-FODMAP.

Q

●Quinoa: A substitute for wheat. Unfortunately, in Japan it is not very popular.

R

◆Raisins: A high fructose food. Contains (raw) **36.4g of glucose and 38g of fructose** per 100g (STFCJ).

◆*Ramen:* From around 1910, the Japanese began to eat *ramen*; in the 1930s wheat flour became difficult to obtain, so consumption decreased. After WWII, a large amount of wheat from the US was imported and *ramen* became a very popular Japanese food. The flavors and style of noodles depend on the area (Figure 219). It is a popular dish among travelers coming to Japan from abroad, but since noodles are made from wheat flour, it is a high FODMAP food.

△ Rapeseed oil

◆Raspberry: Contains (raw) **2.4g of glucose and 2.9g of fructose** per 100g (STFCJ).

◆Red kidney beans

△Red peppers: There is a danger of irritating the anus.

◆*Rei-men*: Korean style cold noodles (Figure 220). Noodles are made of buckwheat flour and wheat flour.

☆●Rice, rice flour: Warmed rice dishes are better. Resistant starch can be increased in cooked rice by cooling. Also, because resistant starch suppresses absorption in the small intestine, unabsorbed carbohydrates may ferment.

◆Rice milk: May contain oligosaccharides in Japan.

☆●Rice noodles

☆●Rice pasta: See pasta

△ Ricotta cheese

◆Roll cabbage: Be careful with onions.

◆Rye: Contains a great deal of fructan. Low-F●DMAP rye bread cannot be obtained in Japan.

S

●*Saba*: See mackerel.

●*Saba-bushi*: Mackerel dried and smoked

▲Sauce: In Japan, several sauces contain com syrup.

●*Sawara*: Japanese Spanish mackerel (Figure 221).

●*Sake* (fish): Salmon

●*Sake* (alcohol): Japanese traditional alcoholic drink. It is made of rice.

☆●*Sake-no-nakabone*: Middle bones of salmon boiled in water (Figure 222). It contains 20 times the calcium of milk.

☆●*Salada-na*: A type of lettuce sold in Japan (Figure 223). It is the only low-F●DMAP lettuce. It ontains (under soil cultivation) **0.3g of glucose and 0.3g of fructose** per 100g (STFCJ).

☆●Salmon, *Sake* (*Shake*): The Japanese eat it as *sushi* and *sashimi*. It is also baked, steamed, fried, and made intosoup dishes (Figure 224). It contains vitamin B1, B2, B5, B12, and D.

☆●*Ikura*, salmon roe: Sorbitol might be added in processed products (Figure 225). It contains a large number of vitamins B1, B2, B5, B12, and D.

●*Sanma*, Pacific saury: It is mainly eaten broiled with salt (Figure 226).

●*Sansho*: Japanese pepper used in *Unagi* dishes.

●Sardine, *Iwashi*.

◆*Sasa-kamaboko*: This is a specialty food in Miyagi Prefecture (Figure 227). It is made from fish that have been shredded and shaped into a small cake. Seasonings (amino acids etc.), sorbitol, and xylose are included.

△●*Sashimi*, sliced raw fish: The meaning of *sashimi* indicates raw cut food (fish, meat, and *Konnyaku*, etc.) cut thinly (Figure 228). But, in general it is a fish. Remove artificial horseradish before eating.

▲*Sausage*: Pay attention to additives.

△●*Uni*, sea urchin: Fresh *Uni* are low-FODMAP. This is used for a *sushi* bowl (*don*) (Figure 229). However, in processed foods, sorbitol is added.

▲※Seaweed: Although it is recognized as a low-FODMAP in the West, it contains trehalose, which is excluded in the FODMAP restriction stage in Japan.

△●▲*Seiro-mushi*: Cooked by heating with steam. The most famous dish is Yanagawa (Fukuoka) eel basket (Figure 230).

△▲*Sekihan*: Rice boiled with red beans (Figure 231). It is mainly a salty dish, but in some regions (Aomori and Hokkaido) it is sweet.

●▲◆*Senbei*: Japanese rice crackers. Originally it was a hard cracker made from rice flour, but soft crackers made from wheat flour are sold these days.

Traditional senbei and senbei stores (Figure 232)

●*Goma*, sesame: This has been recognized as a health food in Japan and has been eaten for a long time but, recently, opportunities to eat have decreased. It contains calcium, and vitamins B1 and B2.

▲*Shabu-shabu*: Thin beef, *tofu*, vegetables, and *udon* boiled with hot water or soy milk (Figure 233). The centre of the pan rises and a hole is opened. It is derived from the equipment used in China (In the past, the container was heated by putting a charcoal fire in the hole in the center).

●*Hotate*, scallops: A popular shellfish used for *sashimi* and *sushi* (Figure 234).

◆Shallot (Échalote): Contain 2.8g oligosaccharides per 100g.

●*Fukahire*, shark's fin: "High-class" dishes that can be eaten at Chinese restaurants (Figure 235). Shark's fin is low-FODMAP, but please check whether the soup contains high FODMAP ingredients.

◆*Shimeji* mushrooms: Contains (boiled) **1.3g of trehalose** per 100g (STFCJ) (Figure 236).

●*Shishamo*, capelin: *Shishamo* from Hokkaido is popular (Figure 237).

◆*Shiitake* mushrooms: Used for soup. Contains (dried) **10.9g of trehalose** per 100g (STFCJ) (Figure 238).

◆*Shimarakkyou*: Okinawan shallots. They contain lots of fructans (Figure 239).

▲◆*Shime-saba*: Mackerel processed with vinegar and salt. When *sushi* using thi, it is known as *Saba-sushi* (*Saba-sushi)* (Figure 240). In this type of *sushi*, sorbitol is used as a preservative.

●*Shirasu*: baby sardines (Figure 241).

●*Shirako*: Fish testicles (such as salmon or cod). It can be grilled or boiled (Figure 242).

●*Shirataki*: Noodles made from *konnyaku*. Their diameter is 2–3mm (Figure 243).

●*Shochu*: A traditional Japanese distilled spirit.

● Shrimp: No problem in any phase, regardless of the type of shrimp.

◆*Ebi-ten-don*, shrimp tempura bowl: A rice bowl with *shrimp tempura*. There is also fried shrimp or *Ebi-furai* (Figure 244). They are all covered with wheat flour, so please only try it in the challenge phase.

▲*Soba* (Japanese buckwheat): Except for 100% *soba*, wheat is usually an ingredient and, therefore, is avoided in the FODMAP restriction stage. The challenge period starts with 100g of 80% buckwheat *soba*. Until the 1800s, *soba* was on the low-FODMAP diet because they used to be made with 100% *soba* flour. However, because it is technically simple to make noodles, wheat flour was mixed in. There is also a traditional *soba* restaurant offering 100% *soba* noodles.

◆*Sohki-soba*: These are generally referred to as Okinawa-style noodles (Figure 245). The raw material is wheat flour.

◆*Somen*, flour noodles: The Japanese eat these in the summer.

◆Soybeans

◆Soy-milk: Contains 0.5g oligosaccharides per 100g.

△ *Shouyu*, soy sauce: Limited use is advised in any phase.

△◆Spelt wheat: JLFDPG is studying the bread manufacture of spelt wheat (Figure 246). During the challenge phase, up to 200g of bread can be consumed.

☆●*Hourensou*, spinach: Contains (raw, boiled) **0.2g of glucose and 0.1g of fructose** per 100g (STFCJ).

●*Ika*, squid: Eaten in *sushi* and *sashimi*; it can also be deep fried, grilled, or boiled with soy sauce (Figure 247).

△▲*Ichigo*, strawberry: This contains fructose and xylitol (0.4g per 100g). Choose non-sweet and small berries. Japanese strawberries possibly contain high levels of fructose due to breed improvement. For example, per 100g, *AMAOU* (product name) contains 2g of fructose and 1.9g of glucose, *TOYONAKA* (product name) contains 2.2g of fructose and 1.9g of glucose (Figure 248).

◆*Subuta*: Sweet and sour pork dish that included onion and flour (Figure 249).

●Sucrose

●▲Sugar (white): This is basically sucrose (fructose + glucose) but, depending on the region, sometimes sugar beets (containing oligosaccharides) are used.

◆Sugar beet: This contains high amounts of oligosaccharides (raffinose).

△◆*Sukiyaki*: Thinly sliced beef, with vegetables such as onion and kelp, *Tofu*, *Shirataki*, and mushrooms are common (Figure 250). People in the eastern part of Japan cook soup using soy sauce, *Sake*, *Miso*, and sugar.

◆*Sumomo*, Japanese plum (Figure 251): Contains 1.54g of fructose, 1g of sorbitol, and 1.59g of glucose per 100g. Try during the challenge phase.

●△▲*Sushi*: Remove artificial horseradish.

Menu showing "conveyor belt sushi" (Figure 252)

●△▲*Surume*, dried shredded squid: Sorbitol is used in products with seasonings (Figure 253).

△◆ *Satsuma-imo*, sweet potato: Because there are many polyols, the amount allowed is only up to 70g.

T

●*Tai*, Red snapper: Japanese have been eating *Tai* since about 3000 years ago. In Japanese, a congratulation is called an ●*mede-Tai*. In this regard, it is an essential dish for celebrations (New Year parties, wedding ceremonies, etc.). It is mainly eaten with salt grill, *sushi*, and *sashimi*; sometimes, it is also used for soup (Figure 254).

◆*Taiyaki*: Fish-shaped pancake filled with bean jam (Figure 255). Everything sold in Japan is made from flour. However, it can also be made with spelt wheat flour at home.

●*Takenoko*, bamboo shoots (Figure 256). Contains (boiled) 0.5g of glucose and 0.5g of fructose per 100g (STFCJ). Note that it contains large amounts of fiber.

▲△*Takenoko* rice: Rice mixed with bamboo sprouts (Figure 257). Pay attention to additives (oligosaccharides etc.) in prepared foods.

◆*Takoyaki*: Wheat balls containing one piece of octopus (Figure 258). This is a popular food in Osaka. *Takoyaki* also spread to other parts of Japan after WWII alongside other wheat-based foods.

▲*Takuan:* Pickled *Daikon* (radish) (Figure 259). It may contain Oligosaccharides, sorbitol and xylitol.

◆*Tan-men*: Chinese noodles (wheat flour) in lightly seasoned soup with vegetables and meat (Figure 260).

●▲*Tansan-senbei* (rice powder): The t*ansan-senbei* of Arima Hot Spring in Hyogo Prefecture is made with rice flour and sugar (Figure 261).

◆*Tantanmen*: Szechuan dish of noodles (wheat flour) covered with a sauce of sesame paste and chili oil (Figure 262).

●Tapioca powder: Use instead of wheat flour.

●*Tamago-kake-gohan*: Fresh eggs seasoned with soy sauce cooked in rice Figure 263). This is recommended for the FODMAP restriction stage. Recently, it has been quite popular in Japan because salmonella bacteria have been completely removed from Japanese eggs, there is no problem of food poisoning even if you eat them raw.

◆Taro: Contains galactan (a slimy polysaccharide).

●*Tatsuta-age:* See *Katakuri-ko*.

▲Tartar sauce: Often onions are used in the production process.

△ Tea: Pay attention to the products that are added to the tea.

●▲*Tekka-don*, Tuna Don: Tuna bowl. Vinegared rice covered with sliced raw tuna (Figure 264).

◆*Ten-don*; *Tempura* bowl: Rice covered with *Tempura* (Figure 265).

△*Ten-don (Tempura* using spelt wheat).

Mixed Tempura using spelt wheat by JLFDPG (Figure 266)

◆*Tempura*: Seafood (i.e. shrimp and fish) or vegetables (i.e. potato, lotus root, and squash) covered with flour and fried in oil (Figure 267).

Although this is a traditional Japanese food, it was originally covered with rice flour, not wheat flour.

△▲Tempe: Made from soybeans.

●◆*Teppanyaki*: A style of Japanese cuisine that uses an iron griddle to cook food. The word *Teppanyaki* is derived from *teppan*, which means iron plate, and *yaki*, which means grilled, broiled, or pan-fried. In Japan, *Teppanyaki* refers to dishes cooked using an iron griddle, including steak, shrimp, *okonomiyaki*, *yakisoba*, and *Monjayaki* (Figure 268, 269).

◆*Ton-katsu*: Pork cutlet. It is coated with egg, then bread crumbs, and fried it in oil (Figure 270). See *Katsu*.

◆Tomato: Contains (boiled) **1.4g of glucose and 1.6g of fructose** per 100g (STFCJ). Furthermore, dried tomato contains **10.8g of glucose and 18.3g of fructose** per 100g (STFCJ). Fructose in tomato is slightly higher than glucose and the amount of fructose increases with maturity.

▲*Tsukudani*: This is preserved food and contains ingredients such as fish, shellfish, and seaweed (Figure 271). They are cooked in sweetened soy sauce. Pay attention to additives. The calcium content increases in fish *Tsukudani*.

▲*Tsukune*: Chicken or fish meat balls mixed with egg (Figure 272). Frequently, flour and garlic are mixed in as well. It is also a kind of *yakitori*.

●Tuna; *Maguro*: This is widely used in *sashimi*, *sushi*, grilled fish, steak, canned products and so on. It is believed that Japanese people ate tuna as early as 3000 years ago. Recently, it has been of concern that tuna may be contaminated with organic mercury and radioactive substances. A grilled head of tuna is called *Kabuto-yaki* (Figure 273).

▲*Tuna-can,* canned tuna: Be careful with additives such as sorbitol.

●Turnip, *Kabu:* Contains (boiled) **1.7g of glucose and 1.4g of fructose** per 100g (STFCJ).

U

◆*Udon* (original): Wheat flour noodles. *Kishimen* is similar to *Udon* but it is harder and wider (Figure 274). They are high in FODMAPs; the same as flour-containing bread. *Kishimen* is mainly eaten in Nagoya.

△*Udon* (spelt wheat) (Figure 275)

◆*Uguisu-mochi*: *Mochi* filled with *Anko* and topped with green soy flour.

△▲◆*Uiro, Uirou*: Traditional Japanese confectionery in Nagoya, Kyoto, and Kobe. Originally, it was only made from rice flour and sugar. However, recently, it is highly possible that sorbitol and wheat flour are added ingredients (Figure 276).

●▲◆*Unagi*, eel; *Una-jyu* (*Unagi* and rice) (Figure 277): Eel is a low-FODMAP. Commonly, *Unagi* is eaten with it after being glaze-grilled. Sometimes, the glaze sauce contains oligosaccharides.

◆Unagi-pai: Eel pie. This is a Shizuoka sweet (Figure 278). It is a cracker of wheat containing fructo-oligosaccharides. There is no eel included in it.

▲*Umeboshi*: Salted plum (Figure 279). Sometimes honey is included.

●*Uri*: Japanese melon. The ones that are not sweet are acceptable (Figure 280). If the amount of fructose is unknown, taste it during the challenge period.

V

Vegetables

Below are the vegetables with fructose contents higher than the amount of glucose (per 100g; STFCJ). Regardless of the amount of other FODMAPs, they are judged as high-FODMAP foods.

		Gulucos:G (g)	Fructose: F (g)	F-G (g)
Asparagus	Raw	0.8	1.1	0.3
	Boiled, oilfried	0.8	1.2	0.4
Bean sprout	Boiled	0.1	0.3	0.2
Black matpe sprouts	Boiled	0.4	0.6	0.2
Broccoli	Raw	0.3	0.9	0.6
	Oilfried	0.2	0.7	0.5
Brussels sprouts	Raw	1.2	1.4	0.2
Burdock	Raw, Boiled	0.1	0.4	0.3
Cucumber	Raw	0.9	1	0.1
Chicory	Raw	0.3	0.4	0.1
Leaf lettuce	Raw	0.4	0.5	0.1
Leek	Raw	0.8	0.9	0.1
	Boiled	0.8	0.9	0.1
Lettus: soil cultivation	Raw	0.7	0.8	0.1
Lettue: water cultivation	Raw	0.8	1	0.2
Mini-tomato	Raw	2.1	2.4	0.3
Red bell pepper	Raw	2.5	2.8	0.3
Red pepper	Raw	3.5	4.2	0.7
Red-tip leaf lettuce	Raw	0.3	0.4	0.1
String beans	Raw	0.5	0.9	0.4
	Boiled	0.5	1	0.5
Tomato	Raw	1.4	1.6	0.2
	Dried	10.8	18.3	7.5
	Juice	1.3	1.5	0.2
Yellow bell pepper	Raw	2	2.9	0.9
	Oilfried	2.1	3	0.9

Below are the vegetables that have more glucose than fructose (per 100g; STFCJ). If the amount of other FODMAPs is low, then it is a low-FODMAP food.

		Gulucos:G (g)	Fructose: F (g)	F-G (g)
Bambooshoot	Raw	0.4	0.4	0
	Boiled	0.5	0.5	0
Bitter gourd	Raw, Oilfried	0.2	0.1	-0.1
Bok Choy	Raw	0.3	0.1	-0.2
	Boiled, Oilfried	0.3	0.2	-0.1
Cabbage	Raw	1.8	1.4	-0.4
	Boiled	1.1	0.8	-0.3
	Oilfried	1.5	1.1	-0.4
Carrot	Raw	1.6	1.5	-0.1
	Boiled	1.4	1.3	-0.1
	Oilfried	2.1	1.9	-0.2
	Juice	1.4	0.9	-0.5
Cauliflower	Raw	1.3	1.1	-0.2
	Boiled	1.2	1	-0.1
Celery	Raw	0.6	0.6	0
Chinese cabbage	Raw	1.1	0.8	-0.3
	Boiled	1	0.8	-0.2
Edible chrysanthemu	Raw, Bolied	0.2	0.2	0
Eggplant	Raw	1.2	1.1	-0.1
	Boiled	1	1	0
	Oilfried	1.4	1.4	0
Ginger	Raw	0.6	0.5	-0.1
Green pepper	Raw	1.2	1	-0.2
	Oilfried	1.3	1	-0.3
Japanese mustard spinach	Raw, Boiled	0.2	0.1	-0.1
Japanese white radish	Raw	1.4	1.1	-0.3
	Boiled	1.5	1.1	-0.4
Kale	Raw	0.5	0.5	0
Kan-pyoh	Boiled	1.7	1.7	0
	boiled in sugar	1.3	0.8	-0.5
Lettus (Slada-Na)	Raw	0.3	0.3	0
Lotus Root	Boiled	0.1	0.1	0
Mini-carrot	Raw	1.4	1.2	-0.2
Okura	Raw	0.6	0.6	0
	Boiled	0.7	0.7	0
Parsley	Raw	0.3	0.2	-0.1
Pumpkin (Japanese)	Raw	1.4	1.4	0
	Boiled	1.7	1.7	0
Red cabbage	Raw	1.5	1.4	-0.1
Rhubarb	Raw	1	0.8	-0.2
	Boiled	0.7	0.6	-0.1
Shishi-to pepper	Raw	0.6	0.5	-0.1
	Oilfried	0.7	0.5	-0.2
Spinach	Raw, boiled	0.2	0.1	-0.1
	Oilfried	0.2	0.2	0
Turnip	Raw	1.6	1.4	-0.2
	Boiled	1.7	1.4	-0.3
Watercress	Raw	0.3	0.1	-0.2
Zucchini	Raw	0.6	0.6	0

◆Vienna sausage: Pay attention to sausages containing starch syrups and reduced malt sugar.

W

◆Wafers: There is no prohibited ingredient other than wheat flour.

●Walnut, *Kurumi*: Up to 30g may be eaten as a low-FODMAP food.

▲*Wanko-soba*: A specialty dish of Iwate (Morioka) (Figure 281). See *Soba*.

▲*Warabi-mochi*: Contains *Kinako* (soybean flour). See *Kinako*.

●*Wasabi*: Japanese horseradish

◆Watermelon, *Suika*: Contains **1.9g of glucose and 4.1g of fructose** per 100g (STFCJ).

◆Wheat flour: Contains **2.4g of inulin** per 100g. Bread and noodles often do not clear, even in the challenge period. A small amount of wheat flour may be mixed in processed Japanese foods in some cases.

◆Wheat bran: high in dietary fiber and inulin. May worsen chronic constipation symptoms. Contains **2.5g of inulin** per 100g.

▲Whipping cream: Contains **2.1–2.3g of lactose** per 100g (STFCJ).

◆White chocolate: Contains **10.2g of lactose** per 100g (STFCJ).

◆White part of green onion (Japanese leek, *Negi*): It contains a great deal of inulin (Figure 282).

Y

▲*Yakiniku*: Japanese dish of grilled meat similar to that found on a Korean barbecue (Figure 283). Note the ingredients of sauces served with the meat, which often contain wheat, soybeans, and apple.

◆*Yaki-meshi*: See *Cha-han*.

◆*Yaki-soba*: Noodles made with flour. Onion is mixed with the noodles in many dishes. The thin red vegetable often seen in *yaki-soba* dishes is ginger. It contains sodium glutamate and sodium sorbate.

●*Yakitori*: Grilled meat on a stick, which is often roast chicken (Figure 284). Salt is desirable and onion is sometimes placed on the stick between the pieces of meat.

◆*Yatsuhashi*: Traditional confectionery made with *Anko* (local delicacy in Kyoto). This is a cinnamon-seasoned cracknel (Figure 285). Trehalose and sorbitol are often included.

◆Yeast: This is related to mannitol.

◆*Yuba*: Delicacy made from the skin of gently boiled soybean milk (Figure 286).

▲ *Yubeshi*: Traditional Japanese confectionery. This is a sweet *Yuzu*-flavored steamed *mocha* (Figure 287). If it is made with glutinous rice flour and sugar, it is a low FODMAP food.

◆Yoghurt: Contains **2.6–3.5g of lactose** per 100g (STFCJ). Lactose-free yoghurt is not sold in Japan.

▲*Yōkan*: Sweet bean jelly. *Azuki* bean is in the ingredients. This is a traditional Japanese sweet, but recently sorbitol has been included (Figure 288).

Z

●*Zenmai*: *Osmunda japonica*. Spring wild plants (Figure 289). Contains a great deal of insoluble dietary fiber but because it can only be eaten in small amounts, it is a low-FODMAP food.

●Zucchini

Figure 125

Figure 126

Figure 127

Figure 128

Agar

Kanten jelly

Figure 129


American dog made from wheat flour


American dog made from spelt flour

Figure 130

Figure 131

Grilled

Figure 132

Figure 133

Figure 134 *Sugar Spot is a sign of a low-FODMAP.*

Figure 136
The matooke (left), the Ugandan who boils the matooke (middle), and the boiled matooke (right).

Figure 137

Wagyu Okinawa steak

Figure 138

Grilled noodles *Soup with noodles*

Figure 139

Figure 140 *Spelt-flour biscuits*

Figure 141

Figure 142 *Various homemade cakes made by JLFDPG*

Original *Chahan* *Ebi-Chahan* *Kani-Chahan*

Figure 143

Figure 144

Chinsuko made from wheat flour

Chinsuko made from rice flour

Homemade *Chinsuko* made from rice flour

Figure 145

Figure 146

Figure 147

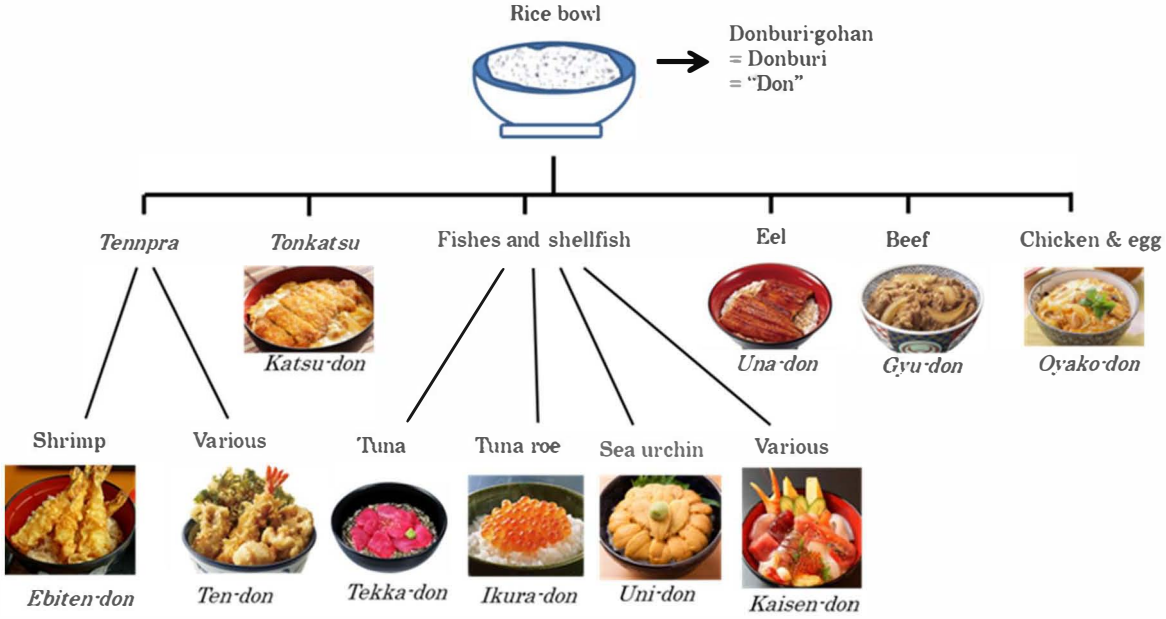


Figure 148

Scrambled eggs

Figure 149

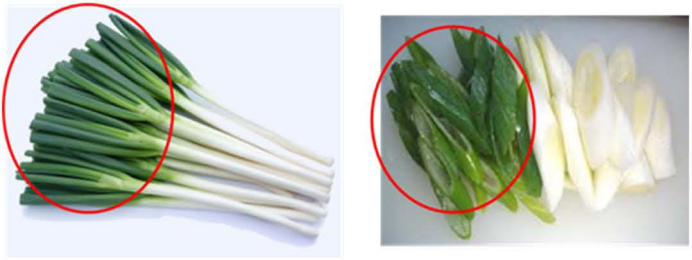


Figure 150

Figure 151

Regular: High-FODMAP food (YOSHINOYA)

Without onion: Low-FODMAP food (YOSHINOYA)

Figure 152

Figure 153

Rice burger with grilled meat

Rice burger with fish

Figure 154

Figure 155

Figure 156

Figure 157

Figure 158

Figure 159

Figure 160

Figure 161

Figure 162

Figure 163
A Katsu restaurant display window

Figure 164

Kara-age with wheat flour

Kara-age with *Katakuri-ka*

Figure 165

Kastuobushi

Topping of *Tofu*

Topping of *Okonomiyaki*

Figure 166

Figure 167

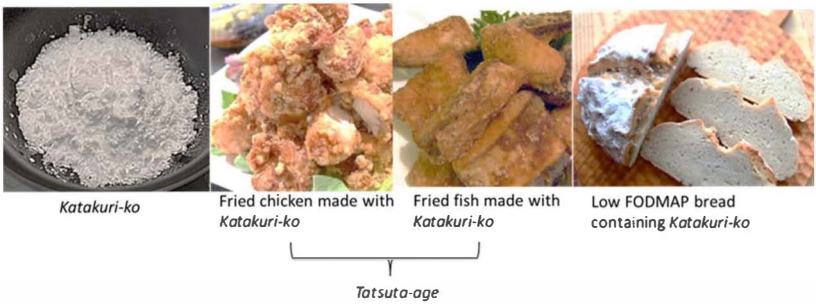


Figure 168

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Figure 176

Figure 177

Figure 179

KEWPIE Mayonnaise *Mayo-la*

Figure 180

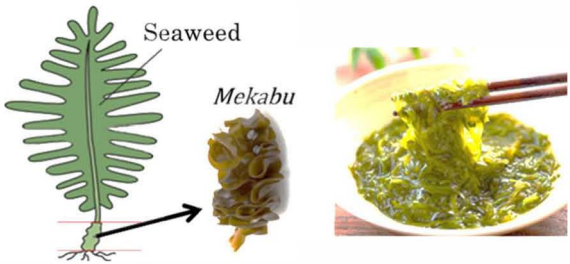

Figure 181

Figure 182

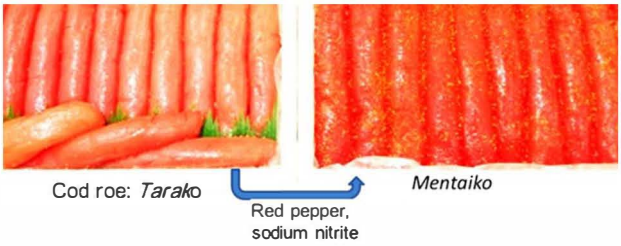

Figure 183

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Figure 194

Figure 195

Nibosh

Tsukudani

Figure 196

Figure 197

Figure 198

Figure 199

Figure 200

Figure 201 Figure 202

Figure 203

Figure 204

Figure 205

Figure 206

Figure 207

Figure 208. *Rice ball*

Figure 209

Figure 210

Figure 211

Commercially available rice pasta

Carbonara by rice pasta

Spelt flour Genovese without garlic

Spelt flour shrimp pasta

Figure 212
Commercially available rice flour pasta (upper left). With string hoppers (upper right) you can make pasta from various flours.
Various homemade pasta by JLFDPG (bottom)

Figure 213

Regular peach

White peach

Figure 214

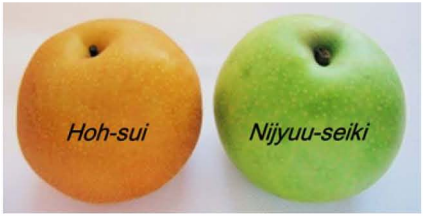

Figure 215

Figure 216

Figure 217

Figure 218

Classic soy sauce *ramen*

Tonkostu-ramen: Many in Fukuoka

Miso-ramen: Many in Sapporo

Figure 219

Figure 220

Figure 221

Figure 222

Figure 223

Figure 224

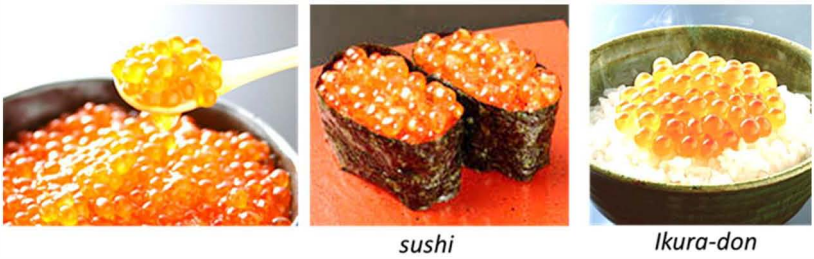

Figure 225

Figure 226

Figure 227

Figure 228

sushi

Uni-don

Figure 229

Figure 230

Figure 231

Figure 232

Figure 233

Figure 234

Figure 235

Figure 236

Figure 237

Figure 238

Figure 239

Saba-sushi

Figure 240

Figure 241

Figure 242

Figure 243

Figure 244

Figure 245

Figure 246
JLFDPG offers a variety of spelt wheat bread recipes.

Figure 247

Figure 248

Figure 249

Figure 250

Figure 251

Figure 252

Figure 253

Figure 254

Homemade baking machine

Figure 255

Figure 256

Figure 257

Figure 258

Figure 259

Figure 260

Figure 261

Figure 262

Figure 263

Figure 264

Figure 265

Figure 266

Figure 267

Steak

Okonomiyaki

Yakisoba

Figure 268
In *Okonomiyaki*, self-service restaurants are popular.

Figure 269
In *Okonomiyaki*, self-service restaurants are popular.

Figure 270

Figure 271

Figure 272

Figure 273

Figure 274

Figure 275
Homemade *Udon* by JLFDPD

Figure 276

Figure 277

Figure 278

Figure 279

Figure 280

Figure 281

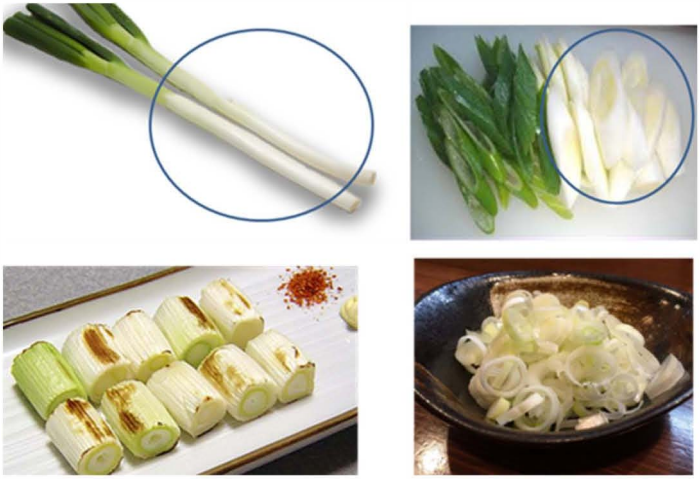

Figure 282

Figure 283

Figure 284

Figure 285

Figure 286.

Figure 287

Figure 288
The most famous yokan. Sorbitol is not included.

Figure 289

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Chapter III: Practicing a low FODMAP diet

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