Effect of diet and individual dietary guidance on gastrointestinal endocrine cells in patients with irritable bowel syndrome (Review)

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Abstract. Irritable bowel syndrome (IBS) is a common chronic gastrointestinal (GI) disorder that is characterized by a combination of abdominal pain or discomfort, bloating and alterations in bowel movements. This review presents recent developments concerning the roles of diet and GI endocrine cells in the pathophysiology of IBS and of individual dietary guidance in the management of IBS. Patients with IBS typically report that food aggravates their IBS symptoms. The interactions between specific types of foodstuffs rich in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) and GI endocrine cells induce changes in cell densities. Providing individual dietary guidance about a low FODMAP intake, high soluble-fiber intake, and changing the proportions of protein, fat and carbohydrates helps to reduce the symptoms experienced by patients with IBS and to improve their quality of life. These improvements are due to restoring the densities of the GI endocrine cells back to normal. The reported observations emphasize the role of GI endocrine cells in the pathophysiology of IBS and support the provision of dietary guidance as a first-line treatment for managing IBS.

Contents

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1. Introduction

Irritable bowel syndrome (IBS). IBS is a common chronic disorder of the gastrointestinal (GI) tract (1-4) that seems to have multifactorial causes (2). It is more common in women than in men, and occurs more often under the age of 50 years (5-11). IBS is reportedly the most commonly diagnosed disorder of the GI in general practice (12), being an even more common reason for seeking medical care than diabetes, hypertension or asthma (13-15). Typically, 12-14% of visits to general practitioners and 25-28% of referrals to gastroenterologist involve patients with IBS (4,13,15,16).

The estimated prevalence of IBS ranges between 5 and 20% of the population worldwide (1,2,4,6,8-10,17-22), with marked geographical variations (9). Using Rome II criteria, the prevalence is 11.5% in Europe (9), 12.1% in Canada (23), 4.7% in the USA (24), 6.9% in Australia (25), 34% in Egypt (26), 4% in India (27,28) and 4.6-5.6% in China (29). The prevalence of IBS in Scandinavian countries is as follows: 10.5% in Denmark (30), 14.5% in Sweden (31), 8% in the south of Norway (32) and 25% in the north of Norway (33).

IBS is mainly diagnosed clinically based on the presenting symptoms due to the lack of biochemical, histopathological or radiological diagnostic tests (3,4,34,35). The symptoms of IBS comprise abdominal pain or discomfort, abdominal bloating or distension and alterations in the stool (1,4,34,36). Based on the predominant bowel movements, patients with IBS are classified into diarrhea-predominant (IBS-D), constipation-predominant (IBS-C) and mixed diarrhea and constipation (37,38). Rome IV criteria are the currently used symptom-based diagnostic criteria (39).

It is known that IBS neither increases mortality (40) nor develops into serious diseases, such as cancer or inflammatory bowel disease (41,42). However, the morbidity associated with IBS can be as serious as that for major chronic diseases, such as congestive heart failure (43), hepatic cirrhosis (44), renal insufficiency and diabetes (11), with considerable costs to society (17,45-48). Patients with IBS tend to be less productive at work or school due to frequent absences (6,13,36,49,50), changing or losing jobs and turning down promotions more

frequently (13,36). These patients have to pay high healthcare costs due to the need to undergo numerous diagnostic tests, frequent visits to the doctor, recurrent hospital admissions and the consumption of more medications than patients without IBS (36). IBS is therefore considered an economic burden for both the patients themselves and society as a whole (2,17,43,45,51-53). The quality of life is lower for patients with IBS than for healthy subjects (4,6,9,19-22,52) due to IBS negatively affecting several aspects of the life of patients, such as sleep, diet, work, leisure, travel, sexual activity and mood (depression or anxiety) (36).

Pathogenesis. Several factors seem to be involved in the pathogenesis of IBS, including hereditariness, diet, mucosal low-grade inflammation, GI microbiota and abnormal endocrine cells in the GI tract (Fig. 1) (4,35,54-78). This review discusses the effects of applying individual dietary guidance on symptoms, quality of life and GI endocrine cells in patients with IBS.

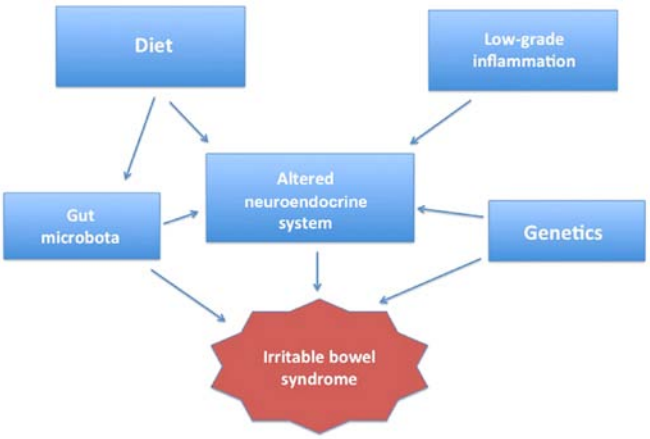

Figure 1. Factors considered to be involved in the pathogenesis of irritable bowel syndrome (IBS).

2. Diet

More than two-thirds of patients with IBS associate the development of their symptoms with the consumption of certain foodstuffs (71-73), such as milk and other dairy products, wheat products, caffeine, certain meats, cabbage, onion, peas, beans, tomatoes, hot spices and fried foods (13,52,71,79), as well as raw vegetables, raw broccoli, paprika, leeks, garlic and mushrooms (52). These foodstuffs are rich in the poorly absorbed rapidly fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) (13,52,80-82). The time delay between the consumption of food until the appearance of IBS symptoms varies, with 28% of patients experiencing symptoms within 15 min of eating, and 93% reporting that the symptoms become more severe between 15 min and 3 h (71).

FODMAPs. Carbohydrates constitute the largest source of energy for humans, ranging from 40 to 80% of the total energy requirements (81). There are two types of dietary carbohydrates, namely long-chain carbohydrates (starch, resistant starch and non-starch polysaccharides) and short-chain (sugars, polyols and oligosaccharides) (80). Long-chain carbohydrates provide benefits of fecal bulking, accelerating colonic transit and causing slight acidification of the luminal milieu (80). On the other hand, short-chain carbohydrates, also referred to as prebiotics, stimulate the growth of beneficial bacteria in the colon (*Bifidobacteria* and *Lactobacillus*) and include fructans (fructo-oligosaccharides and inulin) and galacto-oligosaccharides (80,83). Prebiotics help to reduce the risk of GI infections (84), improve laxation (85) and calcium absorption (86), preserve the GI mucosal barrier (87) and stimulate the immune system of the GI tract that may reduce the risk of colon cancer (demonstrated in animals) (88).

The microbiota in the colon ferments undigested long-chain carbohydrates and produces gases (carbon dioxide, hydrogen and/or methane) and short-chain fatty acids (butyrate, which is an important source of energy for colonocytes and the colonic microbiota) (80,89-91). The poorly absorbed short-chain carbohydrates increase the volume of fluid in the bowel through osmosis (80,91,92), which results in a natural laxative effect in healthy individuals and diarrhea in patients with IBS (80). The gut microbiota in patients with IBS comprises fewer *Lactobacillus* and *Bifidobacterium* spp. and more *Clostridium* spp. that ferment FODMAPs and fiber and produce gas, leading to luminal distension with symptoms of abdominal pain and bloating (93-95).

The importance of both the presence of specific types of FODMAPs and the total content of FODMAPs in the diet should be noted (75,80,81). Some foods contain several types of FODMAPs; for example, white onion contains excess fructose, raffinose, nystose and kestose, which are particularly problematic for patients with IBS (81). The main clinical problems associated with the total content of a major FODMAP are likely to be due to fructans in vegetables and, to a lesser extent, to free fructose and sorbitol in fruits (81).

Dietary fiber. Dietary fiber is defined as the sum of indigestible polysaccharides and lignin (96). The various types of fiber are categorized based on their holding capacity of water into water-soluble and water-insoluble. Water-soluble fiber (with a high water-holding capacity) such as pectin, gums and psyllium accounts for 4 to 21% of the dietary fiber in cereal bran and 19-59% of that in legumes, vegetables and fruits. Oat is the grain that is richest in water-soluble fiber. Water-insoluble fiber (with a low water-holding capacity) is found in wheat, rye, rice and most other grains. Legumes and beans contain both water-soluble and water-insoluble fiber (96).

It has been reported that foods containing a higher proportion of dietary fiber, particularly water-soluble fiber, can help to prevent diseases, such as coronary heart disease, diabetes, irritable bowel disease and colon cancer and obesity (96, and refs therein).

Fiber has been used as a bulking agent in the treatment of IBS (74,96). Consuming water-soluble fiber tends to improve the symptoms of IBS compared to consuming water-insoluble fiber (74,97-99). Indeed, consuming water-insoluble fiber may actually worsen the symptoms of IBS (74,97) by causing increased bloating and abdominal discomfort (100). For example, it is recommended for patients with IBS to consume psyllium (mostly water-soluble fiber) rather than bran (water-insoluble fiber) in order to alleviate their symptoms (100).

Fat. The lipolysis of triglycerides comprising >12 carbon atoms is initiated in the stomach with the formation of emulsions of finely dispersed lipids that bind to gastric lipase. This process of fat digestion is completed in the duodenum by pancreatic lipase and releases fatty acids and monoglycerides. The lipid components (fatty acids and monoglycerides) then form water-soluble micelles with conjugated bile acids and are absorbed across the enterocyte membrane. The triglycerides are then reassembled and incorporated into chylomicrons and transported via the lymphatic system. On the other hand, medium-chain triglycerides (comprising 8-12 carbon atoms) are absorbed directly into the bloodstream without the need for luminal lipolysis and micelle formation. Under physiological conditions, no dietary fat enters the colon since fat is digested and completely absorbed in the small bowel.

Fat modulates the functions of the GI tract in healthy individuals (89). Different meals with different caloric contents activate several braking mechanisms in the GI tract at different rates (101-103). In healthy individuals, fat in the stomach slows gastric emptying, while in the duodenum it stimulates pyloric pressure (89,102) and increases biliopancreatic secretion (104), thus activating the gastroduodenal brake (89,105,106). When fat reaches the proximal small intestine, it promotes a jejunal brake to decrease biliopancreatic secretions (103,104) and slow the intestinal transit (107). Finally, an ileal brake is activated upon the arrival of fat at the ileum (108), which allows more time for fat digestion and absorption and thereby prevents it being lost into the colon (107). The jejunal and ileal brakes are mediated by different GI hormones (107,108).

Patients with IBS have abnormal lipid-dependent motor dysfunction that affects the small intestine, but not the colon (109). These patients also exhibit increased small intestine sensitivity to lipid exposure, which induces symptoms of bloating (89,109), fullness and nausea at lower nutrient loads, and enhances GI sensitivity to mechanical distension (89). In addition, intraluminal fat in the small intestine of patients with IBS impairs gas transit and results in the development of gas retention (bloating) and abdominal distension, particularly in the jejunum (109). Lipids also exacerbate rectal hypersensitivity (89,110) and increase the perception of rectal distension in patients with IBS (89,111), causing pain in patients with IBS-C patients, but urgency in patients with IBS-D (89).

Some patients with IBS reportedly relate the development of their symptoms to the consumption of fat-rich meals. However, no consistent differences in dietary fat consumption have been observed between patients with IBS and healthy controls (52,89).

Protein. Almost 20% of the dietary protein enters the distal colon and undergoes putrefaction by colonic bacteria to produce ammonia, amines, phenols and sulfides (112,113). Ammonia is essential for bacterial metabolism and protein synthesis. Branched-chain fatty acids (isovalerate and isobutyrate) (113,114) and short-chain fatty acids (butyrate) (113,115) are produced in the distal part of the colon in the absence of carbohydrate fermentation (which occurs at the proximal colon) (113). Another product of protein putrefaction is sulfur-containing gas (hydrogen sulfide), which has a foul odor (112). The products of protein putrefaction are potentially harmful, phenols are carcinogenic in other systems and hydrogen sulfide is toxic to the epithelium. However, only the malodorous flatus is of concern to patients with IBS, and no definitive effects of malabsorbed protein on intestine motility or visceral hypersensitivity have been identified (112).

Gluten is a mixture of two proteins (gliadin and glutenin) that is found in wheat, barley and rye (112). Consuming gluten activates the immune system so as to change the function of the mucosal barrier that increases intestinal permeability, a condition known as celiac disease that presents with symptoms mimicking IBS. A gluten-free diet usually reduces bowel frequency in patients with IBS-D who are positive for human leukocyte antigen (HLA)-DQ2/8 due to the reduction in intestinal permeability (116). In addition, a gluten-free diet improves the symptoms of IBS due to the associated reduced intake of FODMAPs in wheat rather than of gluten in foods with gluten as a common component (117).

Food chemicals. Natural chemicals, such as amines, glutamates and salicylates occur in foods. Salicylates are found in plants whereas amines and glutamates are products of protein breakdown in animal meat (118). Food additives, such as glutamates are used as flavor enhancers and benzoates, sulfites, and nitrates are used as preservatives (118). These bioactive chemicals interact with the GI luminal chemoreceptors and influence the function of the enteric nervous system of the GI tract (112). A diet that is low in these chemicals may be beneficial to patients with IBS, whereas there is no evidence of the benefits of reducing caffeine or ethanol consumption (112).

3. Gastrointestinal endocrine cells

General. The GI endocrine cells are scattered among the epithelial cells lining the GI lumen (61,119-121). They comprise almost 1% of all epithelial cells in the GI tract and are considered to be the largest endocrine organ in the body (121-123). All epithelial cell types in the GI tract (including GI endocrine cells) originate from pluripotent stem cells with an endodermal origin (124-133). Gastrointestinal stem cells differentiate into endocrine cells over a period of 2-6 days (134,135). The GI endocrine cells project specialized microvilli into the GI lumen to sense the luminal contents (mainly nutrients) and release specific hormones into the lamina propria (61,119,120,136-145).

There are at least 15 different types of GI endocrine cells in the GI tract releasing different types of hormones (2,127). The types of released hormones depend on the types of sensed nutrients: protein and fat trigger the release of serotonin; somatostatin, ghrelin, polypeptide YY (PYY) and carbohydrates suppress ghrelin release; and carbohydrates and fat trigger the release of oxyntomodulin (enteroglucagon) (2,93,146). Particular GI endocrine cells are located either in specific parts of the GI tract or throughout the GI tract (93,127,146,147). Cells producing gastrin and ghrelin are found in the stomach, those producing secretin, cholecystokinin and gastric inhibitory peptide are found in the duodenum, those producing oxyntomodulin (enteroglucagon) and PYY are located in the lower small and large intestines, and those producing serotonin and somatostatin are found throughout the GI tract (93,127,146,147). The functions of the different hormones are summarized in Table I (2).

Table I. Functions of the hormones of the gastrointestinal endocrine cells.

Hormones	Function
Gastrin	Stimulates gastric acid secretion and histamine release; trophic action on gastric mucosa and stimulates contraction of lower esophageal sphincter and antrum
Ghrelin	Increases appetite and feeding; stimulates gastric and intestinal motility
Secretin	Stimulates pancreatic bicarbonate and fluid secretion; inhibits gastric emptying; and inhibits contractile activity of small and large intestine
CKK	Inhibits gastric emptying; stimulates gall bladder contraction, intestinal motility and pancreatic exocrine secretion; stimulates growth; and regulates food intake
GIP	Belongs to incretins. Inhibits gastric acid secretion
Oxyntomodulin (enteroglucagon)	Inhibits gastric and pancreatic secretions
PYY	Major 'ileal brake' mediator. Delays gastric emptying; inhibits gastric and pancreatic secretion. Anti-diarrheal effect by stimulating the absorption of water and electrolytes
Serotonin	Stimulates gastric antrum, small intestinal and colonic motility
Somatostatin	Inhibits intestinal contraction, gut exocrine and neuroendocrine secretions

CKK, cholecystokinin; GIP, gastric inhibitory peptide; PYY, peptide YY.

Several functions of the GI tract, such as motility, secretion, absorption, microcirculation, local immune defense, cell proliferation and food intake, are regulated by the interactions of GI endocrine cells with themselves and with the enteric nervous system, independent of the central nervous system but also communicating and integrated with it (2,119,146,148-151). The GI endocrine cells release their hormones that exert their effects via endocrine signaling (through the bloodstream to distant targets), paracrine or autocrine signaling (locally), synaptic signaling or neuroendocrinally (being released from synapses into the bloodstream) (2,93,146,148).

GI endocrine cells in IBS. There is increasing evidence of an altered neuroendocrine system, namely the GI endocrine cells, being a cause of IBS, since the densities of different types of GI endocrine cells in the different parts of the GI tract are abnormal in patients with IBS (4,35,61-70). Such alterations are responsible for abnormal functions of the GI tract, such as visceral hypersensitivity, dysmotility and abnormal secretion, all of which are characteristics of IBS (35).

4. Individual dietary guidance

Several studies have shown that a low-FODMAP diet can improve the symptoms experienced by patients with IBS (78,90,91,152-157) and that these patients tend to comply with consuming such a diet; one study found that >75% of patients were compliant (75). However, consuming such a diet over a long period of time is associated with several complications, such as a lack of nutrients (52), and changes in the fecal microbiota (158,159). Many patients with IBS make a conscious choice to avoid certain foodstuffs, some of which belong to the FODMAPs group. However, they also tend to 'unknowingly' consume other foodstuffs that are rich in FODMAPs and avoid food sources that are important to their health (52). A Norwegian study on food intolerance and IBS found that 62% of the included subjects limited or excluded some foodstuffs from their daily meals, while 12% made drastic changes in their diet that could result in nutritional deficiencies in the long term (72). Patients with IBS tend to have low intakes of calcium, potassium, magnesium, vitamin A, vitamin B_{12} and vitamin B_2 (52,160-162). Avoiding such adverse effects of the long-term consumption of a low-FODMAP diet therefore requires the administration of dietary guidance (75).

Administering individual dietary guidance. Educating patients can facilitate changes in their behavior for the purpose of disease management and prevention (163). Patients with IBS are particularly interested in learning about dietary modifications, coping strategies and the causes of the disease (163). Dietary guidance can be administered individually, whereby patients are provided with information via one-to-one consultations; this approach is useful due to the tolerance to different FODMAPs, varying widely between individual patients (164). When being provided with individual dietary guidance, patients are scheduled to attend several relatively short sessions, administered by a physician, nurse or nutritionist, to receive information concerning IBS and the appropriate foodstuffs they should consume to reduce their symptoms. The main emphasis should be on consuming foodstuffs that are low in FODMAPs and water-insoluble fiber, and changing the proportions of protein (increase), fat (decrease) and carbohydrates (decrease). Providing several sessions of consultation gives the patients reassurance and confidence while they are receiving dietary guidance. Using a daily diary to register the daily consumption of food and fluids and the accompanying IBS symptoms (if any) helps in identifying which foodstuffs worsen the symptoms experienced by the patients (52,165,166).

Effect of individual dietary guidance on symptoms and quality of life of patients with IBS. Individual dietary guidance helps patients with IBS to choose dietary items that are low in

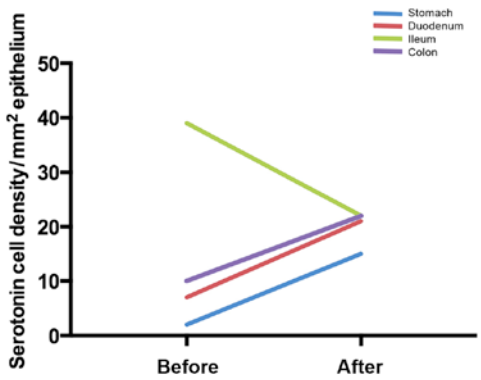

Figure 2. Mean serotonin cell densities in different parts of the gastrointestinal (GI) tract in patients with irritable bowel syndrome (IBS) before and after receiving dietary guidance.

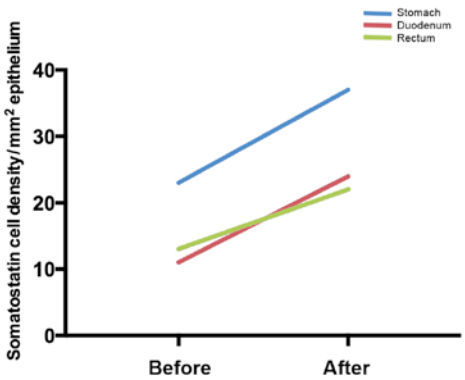

Figure 4. Mean somatostatin cell densities in different parts of the gastrointestinal (GI) tract in patients with irritable bowel syndrome (IBS) before and after receiving dietary guidance.

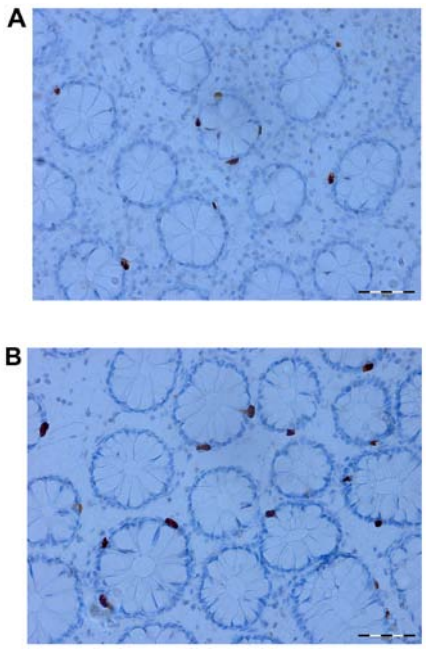

Figure 3. Serotonin cells in the colon of an irritable bowel syndrome (IBS) patient before (A) and after (B) receiving dietary guidance.

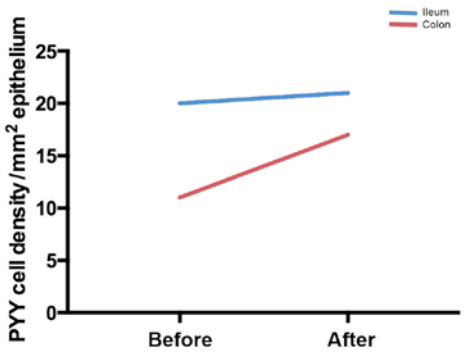

Figure 5. Mean peptide YY (PYY) cell densities in the ileum and colon of patients with irritable bowel syndrome (IBS) before and after receiving dietary guidance.

FODMAPs and water-insoluble fiber (166). The effects of this approach on symptoms and the quality of life of patients with IBS have been assessed using several questionnaires, such as the Birmingham IBS Symptom Questionnaire, the Irritable Bowel Syndrome - Quality of Life (IBS-QOL) questionnaire, and the Short-Form Nepean and Dyspepsia Index (SF-NDI) quality-of-life questionnaire (52,166). The Birmingham IBS symptom questionnaire is disease-specific and measures the symptoms experienced by IBS patients, namely pain, diarrhea and constipation (167). IBS symptoms, as assessed by the Birmingham IBS symptom questionnaire, improve significantly after receiving dietary guidance, particularly the symptoms of pain (52,166) and diarrhea (166), but not constipation (52,166).

The IBS-QOL questionnaire is IBS-specific and assesses physical and psychosocial functioning as a result of IBS (168,169). The SF-NDI questionnaire is a disease-specific questionnaire that assesses the health-related quality of life and was constructed and validated primarily in patients with dyspepsia (170). However, a validated version of the questionnaire translated into Norwegian was demonstrated to perform well in patients with IBS (171). The total scores, as assessed by the IBS-QOL and SF-NDI questionnaires, showed significant improvements in the quality of life of patients with IBS after they received dietary guidance (52,166).

Individual dietary guidance helps to reduce IBS symptoms, improving the quality of life of patients with IBS (52,165,166), and ensures that they have an adequate intake of necessary vitamins and minerals, thus avoiding multiple nutrition deficiencies (52,166).

Effects of individual dietary guidance on GI endocrine cells. At the cellular level, changing the diet through individual dietary guidance changes the densities of different GI endocrine cells in different parts of the GI tract (172-175), as shown in Figs. 2-5. Chromogranin A (CgA) is considered to be a general marker of endocrine cells (176-178). As previously demonstrated, the densities of CgA-immunoreactive cells are abnormal in the stomach, duodenum, ileum and colon of patients with IBS, and dietary guidance tends to change these densities toward the values measured in healthy control subjects (173,179,180). These changes are considered to be brought about by changes in different endocrine cells in the respective parts of the GI tract after providing dietary guidance. For example, in the stomach, the densities of several endocrine cells (gastrin,

ghrelin, serotonin and somatostatin) changed toward the values measured in healthy control subjects after providing dietary guidance, but only somatostatin cell density showed a significant change in the gastric corpus (181). The densities of serotonin cells in the duodenum and ileum changed significantly (172,175), and the density of somatostatin cells in the duodenum changed significantly after providing dietary guidance toward that measured in healthy control subjects (175). After providing dietary guidance, the densities of serotonin and PYY cells tend to normalize in different segments of the colon, with the density of somatostatin cells increasing in the rectum (174).

The observation that dietary guidance can alter the densities of several GI endocrine cells in patients with IBS, particularly serotonin, PYY and somatostatin cells, to approach those in healthy control subjects suggests that these changes underlie the reduction in pain and the improvement in diarrhea as quantified using the Birmingham IBS symptom questionnaire, and consequently the improvement in the quality of life of these patients.

5. Conclusion

Patients with IBS typically report that food aggravates their IBS symptoms. The interactions between specific types of foodstuffs and GI endocrine cells result in changes in these cell densities. Providing individual dietary guidance about a low FODMAP intake, high soluble-fiber intake, and changing the proportions of protein, fat and carbohydrates helps to reduce the symptoms experienced by IBS patients and to improve their quality of life. This improvement is accompanied by changes in the densities of the GI endocrine cells where some densities are restored back to the normal values. These observations emphasize on the role of GI endocrine cells in the pathophysiology of IBS, and support the provision of dietary guidance as a first-line treatment for managing IBS (76).

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