



Irritable Bowel Syndrome: A Review

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Abstract

The irritable bowel syndrome (IBS) is a disorder of bowel function (as opposed to being due to an anatomic abnormality). Patients who suffer from irritable bowel syndrome have changes in bowel habits such as constipation or diarrhea, and abdominal pain along with other symptoms including abdominal bloating, and rectal urgency with diarrhea. In addition, irritable bowel syndrome may be associated with a number of non-intestinal ("extra intestinal") symptoms, such as difficulty with sexual function (pain on intercourse or lack of libido), muscle aches and pains, fatigue, fibromyalgia syndrome, headaches, back pain, and sometimes urinary symptoms including urinary urgency, urinary hesitation or a feeling of spasm in the bladder. However, irritable bowel syndrome is not associated with serious medical consequences. People with irritable bowel syndrome tend to live long, and in some studies, somewhat longer than individuals who do not have irritable bowel syndrome. Irritable bowel syndrome is not associated with other serious GI diseases, such as inflammatory bowel disease (Crohn's disease or ulcerative colitis) or colon cancer. The presence of irritable bowel syndrome does not put extra stress on the other organs in the body such as the heart, liver or kidneys. Overall the prognosis for irritable bowel syndrome is excellent. Patients suffering from irritable bowel syndrome should not be worried about it leading to other serious diseases. The major problem with irritable bowel syndrome is not because it causes death or serious disease, but because it changes the quality of life for the patient. Here, the authors review the epidemiology and pathophysiology of irritable bowel syndrome, summarize diagnostic and treatment strategies. Evidence of biologic dysregulation has been reported in patients with IBS and efforts to understand the neurohormonal underpinnings of the disorder are ongoing, but the exact mechanisms leading to IBS symptoms are not completely understood. This article discusses recent developments in the field of IBS research and the updated diagnostic criteria. It summarizes the epidemiology, pathophysiology, and treatment of IBS.

Keywords: Irritable Bowel Syndrome; Crohn's Disease or Ulcerative Colitis; Urinary Urgency; Urinary Hesitation; Colon Cancer; Fibromyalgia Syndrome; Rectal Urgency

Abbreviations

IBS: Irritable Bowel Syndrome; IBS-D: Irritable Bowel Syndrome with Diarrhea; IBS-C: Irritable Bowel Syndrome with Constipation; IBS-M: Irritable Bowel Syndrome with Mixed Bowel; GI: Gastrointestinal Tract; F-GID: Functional Gastrointestinal Disorder; HAPC: High Amplitude Propagated Contractions; PI-IBS: Post Infectious Irritable Bowel Syndrome

Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by chronic or recurrent abdominal pain associated

with either relief or exacerbation by defecation, or a change in bowel habit [1]. Functional gastrointestinal disorders are defined as collection of functional symptoms that are not attributable to structural, mucosal or biochemical disease of gastrointestinal tract. Symptoms include indigestion, abdominal pain, bloating and distension. Irritable bowel syndrome (IBS) is one of the most commonly diagnosed functional bowel disorder, occurring most often in patients under age 50 [2]. In addition to its physiologic manifestations, IBS is recognized as having a psychological component. In 40% to 60% of cases, IBS is accompanied by such psychological disorders as depression or anxiety

[3] and patients with IBS have been found to have a greater frequency of somatic symptoms than patients who have GI symptoms in the absence of IBS [4]. Most studies suggest that irritable bowel syndrome is more common in women with almost twice as many women having the disorder compared to men. The reason why women are more commonly affected by irritable bowel syndrome is not completely understood. It does not seem to be merely due to hormonal differences between men and women. Rather it seems to be due to differences in how women and men process sensations from the intestines, both in the intestinal nervous system (“enteric nervous system”) as well as the brain and spinal cord (“central nervous system”). The frequency of IBS seems to be the same across racial, ethnic and national boundaries. Despite the fact that irritable bowel syndrome is so common, most people with IBS do not see a doctor for their symptoms. It is estimated that only 1 in 4 people with IBS see a doctor (and thus become a patient with IBS). Reasons why some people chose to see a doctor and others do not are not completely understood. Interestingly severity of gastrointestinal symptoms from IBS alone does not seem to be the major driving factor. Rather the impact of IBS on the patient’s ability to function on a day-to-day basis while having IBS symptoms, the stress from having IBS, and concerns about other diseases that they might have are some of the more frequent reasons patients see their doctor for IBS like symptoms. The exact cause of irritable bowel syndrome is not known. Abnormal motility in terms of the bowel moving too fast (which causes diarrhea) or too slow (which causes constipation) is certainly part of this syndrome. However, this represents only one part of a complicated disease. The symptoms of pain, incomplete emptying of the bowels, and bloating cannot be blamed only on abnormal GI motility. Over the last 20 years a number of very well done scientific studies have demonstrated that individuals with IBS tend to have higher levels of sensitivity in the intestines compared to individuals who do not have IBS. Certain chemicals present in the intestines, which send signals from nerve endings from the intestines to the brain, and also from the brain to the intestines. These chemicals are called “neuro transmitters” and work as messengers between nerve endings to carry signals in both directions between the brain and gut. This is very important because it has led to the development of new drugs. Some of these drugs are currently available. Others are being developed, as we better understand how these chemical ‘neurotransmitters’ work. One of the major neuro transmitters involved in sensation of pain in the gut as well as playing a key role in motility activity of the gut is serotonin. This chemical is also known by its chemical abbreviation 5-HT. However, serotonin is only one of a large number of neuro transmitters that are present in the gut. As we identify more and more of these substances and better understand their actions,

we may be able to further supplement the arsenal of medications that will influence these neuro transmitters and thus help relieve the symptoms of IBS. Clearly the future is quite bright both for better understanding this perplexing and disabling disorder as well as using this knowledge to make newer and better treatments for IBS [5]. Factors important to the development of IBS include alterations in the gut microbiome, intestinal permeability, gut immune function, motility, visceral sensation, brain-gut interactions, and psychosocial status. The diagnosis of IBS relies on symptom-based criteria, exclusion of concerning features (symptom onset after age 50 years, unexplained weight loss, family history of selected organic gastrointestinal diseases, evidence of gastrointestinal blood loss, and unexplained iron-deficiency anemia), and the performance of selected tests (complete blood cell count, C-reactive protein or fecal calprotectin, serologic testing for celiac disease, and age-appropriate colorectal cancer screening) to exclude organic diseases that can mimic IBS. Determining the predominant symptom (IBS with diarrhea, IBS with constipation, or mixed IBS) plays an important role in selection of diagnostic tests and treatments. Various dietary, lifestyle, medical, and behavioral interventions have proven effective in randomized clinical trials. The diagnosis of IBS relies on the identification of characteristic symptoms and the exclusion of other organic diseases. Management of patients with IBS is optimized by an individualized, holistic approach that embraces dietary, lifestyle, medical, and behavioral interventions [6]. In North America, the population prevalence of IBS is approximately 12%. IBS is most prevalent in South America (21.0%) and least prevalent in Southeast Asia (7.0%). In the United States, Canada, and Israel, IBS symptoms are 1.5 to 2 times more prevalent among women than men, whereas there appears to be greater parity in Asia. Women more commonly report abdominal pain and constipation, whereas men more commonly report diarrhea. It appears that IBS prevalence decreases with age. In the United States, patients are equally distributed among IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), and IBS with a mixed bowel pattern (IBS-M), whereas in Europe, IBS-C or IBS-M may be more prevalent [7].

Pathophysiology

Psychosocial factors: At the end of the 19th century Sir William Osler wrote that patients with ‘mucous colitis’ (what we would consider IBS now a days) have a normal colonic epithelium and that many of them are hysterical, hypochondriac, self-centered, neurasthenic, and suffered from colicky abdominal pains [8]. Indeed, compared with the general population, IBS patients have a higher prevalence of psychological comorbidity (e.g. affective disorders such as anxiety, hostility and phobia, history of emotional, physical, and sexual abuse) [9,10]. In addition, substantial evi-

dence supports a key role for stress in the pathophysiology of gut motor dysfunction and increased sensitivity in patients with IBS [11]. Nonetheless, it is obvious that psychological factors alone are insufficient to explain the complex, multifaceted manifestations of IBS. Certainly, not all subjects with disturbances of the psychological sphere develop IBS and the prevalence of anxiety, paranoid ideation, hostility, depression, and obsessive-compulsive disorders in patients in community samples is only slightly higher compared with those found in the general population without IBS [12]. In a recent study, a large group of community subjects was followed-up for 12 years in the attempt to detect the relative weight of psychological versus peripheral factors in the pathogenesis of Functional gastrointestinal disorder (FGID). As expected, the presence of psychological impairment at the beginning of the observational period represented a predictive factor for the development of IBS at the end of follow-up. However, FGID diagnosis at baseline was significantly associated with higher levels of subsequent anxiety and depression at follow-up [13]. Taken together, these data provide support to the notion that long-lasting gut dysfunction may well contribute to the stress, anxiety, and depression experienced by at least a subgroup of patients with IBS.

Intestinal Motility

In the past studies, IBS was termed as spastic colon and spastic colitis. IBS is characterised by changes in colonic motor function and mild mucosal irritation. Manometry studies showed altered patterns of colonic and small intestinal motor function, including a higher number of high amplitude contractions (HAPCs) [14] and enhanced responses to meal ingestion [15], cholecystokinin [16], or the stress hormone corticotrophin releasing factor [17,18]. Compared with healthy subjects, IBS-D patients show accelerated colonic transit [19]. Conversely, IBS-C patients showed fewer (HAPC), high amplitude propagated contractions, reduced motility, and delayed colonic transit. Although in the majority of studies the relationship between motility changes and symptoms was rather poor, one study showed that > 90% of HAPC were correlated with the occurrence of abdominal pain. More robust correlations have been described between bowel habit and transit time changes as detected with radiopaque markers or scintigraphy.

Visceral Hypersensitivity: Visceral Hypersensitivity is a common finding in functional gastrointestinal disorder, including non-cardiac chest pain, functional dyspepsia, and IBS [20]. Visceral hypersensitivity is considered a key element in the pathogenesis of pain perception in patients with IBS [21]. Hypersensitivity to balloon distension of the rectum was initially detected in 95% of IBS patients [22], but subsequently shown to be present only in about half of patients, particularly those with IBS-D [23]. The cor-

relation of visceral hypersensitivity with abdominal pain, quality-of-life, and psychological impairment have been reported to be poor. However, large sample studies showed that, compared with normosensitive IBS patients, those with rectal hypersensitivity had more pain, bloating, and diarrhea [24,25]. The pathophysiology of visceral hypersensitivity remains incompletely understood, but likely, involving both peripheral and central (i.e. central nervous system) mechanisms. Among peripheral factors, sensitisation of afferent nerve fibres by serotonin or immune activation has been the focus of recent studies. Brain imaging studies (e.g. functional magnetic resonance imaging, positron emission tomography) showed that, in response to experimental rectal distension, compared with healthy controls, IBS patients display enhanced activation of areas involved in pain processing (thalamus, insula, anterior cingulate cortex) [26]. Nonetheless, results of brain activation and reported pain to peripheral stimuli should be considered with caution as they are highly influenced by the patient's emotional status, including anxiety, anticipation of pain, and hypervigilance [27,28].

Intestinal Gas: Bloating is extremely common in patients with FGID and occurs in up to 96% of patients with IBS. Most patients consider this symptom extremely distressing and about two-thirds of them consider it the worst of their symptoms [29,30]. Bloating is more frequent in patients with IBS-C (75%), than in those with IBS-D (41%), and in IBS-C bloating correlated with abdominal distension [31, 32]. There is no evidence that bloating is caused by an increased amount of gas in the intestine [33]. On the other hand Serra, *et al.* [34] showed that 18 out of 20 IBS patients, compared with only 4 of 20 healthy subjects, developed gas retention, gastrointestinal symptoms or abdominal distension (> 3 mm girth increment) after an infusion of a gas mixture in the jejunum. These data suggest that impaired handling rather than increased gas plays a role in the development of bloating in patients with IBS.

Luminal factors and Microbiota: Food ingestion often aggravates symptoms in patients with IBS. Attention has been recently directed on fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), which are poorly absorbed in the small intestine and reach the colon where they are fermented by bacteria with consequent production of gas and stimulation of colonic motor activity. Diets containing low-FODMAPs have been shown to be beneficial in IBS, although the exact role of these diets in IBS and their applicability in everyday practice remains unclear [35]. Non-coeliac gluten sensitivity is another area of great interest as it is potentially involved in symptom development in a subgroup of IBS patients [36]. A randomised, controlled trial of a gluten-containing diet versus a gluten-free diet in IBS-D, showed that those

receiving gluten had increased frequency of bowel movements, intestinal permeability, and peripheral blood immune responses [37]. The introduction of molecular techniques to detect gut microbial communities has renewed interest in intestinal microbiology. The role of microbiota in FGID including IBS has been the subject of an exhaustive recent review [38]. A recent study indicates that although the majority of patients with IBS do not have significant changes in faecal microbiota compared with healthy controls, two clusters of patients showed abnormal Firmicutes: Bacteroidetes-related taxa ratios. Interestingly, these patients showed changes in bowel physiology including altered bowel transit times while those with normal microbiota had more psychological impairment (i.e. anxiety and depression) [39]. Altered microbiota can contribute to abnormal bowel physiology and pain perception through the release of numerous metabolites, including the production of short chain fatty acids as a result of fermentation of polysaccharides unabsorbed in the small intestine. Interestingly, IBS patients had increased faecal levels of acetic and propionic acids which correlated with the severity of abdominal pain and bloating [40]. Other effects of abnormal microbiota on bowel physiology could be related to the activation of the innate immune system as shown by increased mucosal expression of toll-like receptor-4 and 536 and the luminal release of mucosal beta-defensin-2.37 Bile acid malabsorption has been identified in a subgroup of IBS-D patients. Excessive colonic bile acids stimulate secretion and colonic motility and stimulate pain pathways, hence contributing to diarrhoea and abdominal pain. According to a recent study, about 25% of patients with IBS-D had increased levels of intracolonic bile acids as the result of bile acid malabsorption or excessive bile acids biosynthesis in the liver [41,42]. Among the potential mechanisms involved in this effect, of mention are the mutation of bile acids transporter in ileum [43] and the decreased expression fibroblast growth factor 19 (FGF19), which is produced by ileal enterocytes and regulates bile acids synthesis in the hepatocyte through a negative feedback [44].

Mucosal Permeability: Several structures contribute to the intestinal mucosal barrier, hence regulating intestinal permeability. These include the mucus layer, the enterocytes, and intercellular tight junctions (TJs) positioned between epithelial cells. Disruption of the mucosal barrier leads to mucosal immune activation and stimulation of sensory pain pathways, leading to visceral hypersensitivity and pain perception. Increased mucosal permeability has been first shown in patients with post-infectious IBS (PI-IBS) by means of the lactulose/mannitol method [45] and

subsequently confirmed in patients who developed IBS after a waterborne outbreak of gastroenteritis in Walkerton, Ontario [46]. Increased intestinal permeability has been documented also in patients with non-specific IBS [47]. Electron microscopy studies showed enlarged paracellular spaces and cytoskeleton condensation suggestive of TJ dysfunction in the jejunum of IBS-D patients [48]. Piche., *et al.* [49], demonstrated that colonic biopsies had significantly higher permeability compared with controls. Increased permeability was associated with significantly lower expression of tissue zonula occludens mRNA (one of the main TJ components) compared to asymptomatic controls. In addition, mucosal supernatants of patients with IBS, but not from healthy controls, markedly increased permeability of epithelial cell monolayers. Although the origin of these mediators remains unknown, proteases, which are produced in excess by intestinal mast cells or by luminal bacteria, are likely participant in increased mucosal permeability. The trigger factors involved in the increased intestinal permeability of IBS remain elusive. Recent studies suggest the participation of stress [50], food allergy [51] or gluten.

Gastrointestinal Infections: Up to now, acute infectious gastroenteritis is the strongest known risk factor for the development of IBS, with a relative risk around 12 [52]. PI-IBS may develop after bacterial infection (e.g. Shigella, Salmonella, and Campylobacter) or viral gastroenteritis [53]. Risk factors for PI-IBS comprise the virulence of the pathogen, younger age, female sex, the long duration of the initial gastroenteritis, the use of antibiotics, and psychological factors. Genetic factors, including polymorphisms for genes involved in the control of pro-inflammatory cytokine production (IL-6), host-bacteria interactions and epithelial paracellular permeability, have been demonstrated in patients with PI-IBS [54]. More than half of these patients also have a mild immune activation including higher numbers of mast cells, intraepithelial lymphocytes, lamina propria T cells, calprotectin-positive macrophages, and enteroendocrine cells likely contributing to pain and abdominal pain perception.

Neuro-Immune Interactions: The development of IBS after infectious gastroenteritis and the higher prevalence of IBS-like symptoms in patients with inflammatory bowel diseases in remission, microscopic colitis or coeliac disease on a gluten free diet, support the potential involvement of immune activation in the pathogenesis of IBS [55]. While there is no evidence of elements typical of acute inflammation or mucosal architecture distortion, a high proportion of these patients has higher mucosal counts of mast

cells, T cells and B cells along with increased release of immune mediators (e.g. cytokines, prostanoids, histamine, and proteases). In our laboratory we have introduced the use of mucosal biopsy supernatants in the assessment of the impact of the mucosal milieu on bowel physiology. This is obtained by applying colonic supernatants obtained from IBS patients or controls to intestinal tissues of laboratory animals or human colon specimens obtained from the disease-free margins of surgical resections for colon carcinoma. Our studies showed that IBS supernatants, infused through a mesenteric artery of the isolated intestinal rat loop, elicited higher sensory fibre activation compared to control supernatants [56]. These effects were significantly inhibited by antagonists of the histamine receptor type-1, proteases inhibitors and serotonin type-3 receptor antagonists, suggesting the participation of mast cells and enterochromaffin cells releasing serotonin in the sensory activation in IBS. Cenac, et al. showed that intracolonic injection of IBS supernatants in mice evoked visceral hypersensitivity [57]. This effect was blunted in proteinase activated-2 receptor knock-out mice implying the participation of proteases acting on PAR-2 receptors on sensory nerves. Using sophisticated computerized optical techniques, Buhner, *et al.* showed a rapid histamine, serotonin, and protease-dependent hyper-activation of human enteric nerves in response to IBS supernatants [58]. Although most of these effects could be reduced by inhibitors/antagonists of immune mediators or serotonin, a potential implication of factors derived from luminal bacteria has also been proposed [59]. In addition, the severity and frequency of perceived abdominal painful sensations in IBS patients were directly correlated with the number of activated mast cells in proximity of nerve endings [60]. Thus, taken together, these studies provide not only evidence of infiltration of immune cells in subgroups of patients with IBS, but also implications of immune activation for disturbed intestinal function.

Serotonin: Serotonin, or 5-hydroxytryptamine (5-HT), is released by enterochromaffin cells in response to mechanical and chemical stimuli (food, short chain fatty acids produced by intestinal microbiota). 5-HT regulates and generally stimulates secretory, motor, and sensory functions of the gastrointestinal tract acting on receptors spread all over the gut. 5-HT biological activity is terminated by the serotonin reuptake transporter (SERT) located on enterocytes [61]. The potential role of 5-HT in IBS is supported by the therapeutic efficacy of 5-HT 3 receptor antagonists and 5-HT 4 receptor agonists on IBS symptoms [62]. Decreased postprandial 5-HT platelet-depleted plasma levels have been detected in patients with IBS-C, suggesting a problem with 5-HT release to physiological stimuli [63]. Increased plasma levels of 5-HT have been shown under fasting and fed conditions in patients with

IBS-D or PI-IBS, suggesting a reduced 5-HT reuptake and/or metabolism [64]. Although several studies demonstrated a reduced SERT expression in the colon of patients with IBS [65], conflicting data have been reported. We showed that the spontaneous release of 5-HT was significantly increased in patients with IBS irrespective of bowel habit and correlated with the severity of abdominal pain [66].

Genetic Factors: Overall, IBS exhibits typical features of a complex disorder with interactions between environmental and genetic factors. Epidemiological studies of familial aggregation and twins suggest a role of genetic predisposition in the incidence of IBS, although social learning is probably at least as important [67]. Several studies assessed the risk effects of single nucleotide polymorphisms (SNPs) in IBS candidate genes. However, at present, our knowledge on genetic predisposition to IBS remains limited. Previous small studies identified polymorphisms in serotonergic [68] and inflammatory genes as susceptibility SNPs for IBS [69]. As previously mentioned in this review, SNPs in genes involved in immune activation, epithelial barrier and host-microbiota interaction (TLR9, IL-6, and CDH1) were associated with PI-IBS. Another study correlated colonic transit and pain sensation with polymorphisms in the neuropeptide S receptor gene (NPSR1), a gene involved in inflammation, anxiety and nociception [70]. A functional Klotho β gene variant regulating hepatic bile acid synthesis was associated with colonic transit in IBS-D [71]. In the largest genetic study of IBS, Zucchelli, et al. demonstrated in two independent cohorts from Sweden and USA a strong association between rs4263839 in TNFSF15 and IBS, particularly IBS-C [72]. The association between this gene which is involved in Th17 immune response and IBS (although in this case with a different subtype, i.e. IBS-D) was recently replicated in UK individuals. In this study, polymorphisms in TNF were also associated with PI-IBS [73].

Diagnosis [74]

Initial assessment

Healthcare professionals should consider assessment for IBS if the person reports having had any of the following symptoms for at least 6 months:

1. Abdominal pain or discomfort
2. Bloating
3. Change in bowel habit

All people presenting with possible IBS symptoms should be asked if they have any of the following 'red flag' indicators and should be referred to secondary care for further investigation if any are present:

1. Unintentional and unexplained weight loss
2. Rectal bleeding
3. A family history of bowel or ovarian cancer
4. A change in bowel habit to looser and/or more frequent stools persisting for more than 6 weeks in a person aged over 60 years.

All people presenting with possible IBS symptoms should be assessed and clinically examined for the following 'red flag' indicators and should be referred to secondary care for further investigation if any are present:

1. Anaemia
2. Abdominal masses
3. Rectal masses
4. Inflammatory markers for inflammatory bowel disease

A diagnosis of IBS should be considered only if the person has abdominal pain or discomfort that is either relieved by defaecation or associated with altered bowel frequency or stool form. This should be accompanied by at least two of the following four symptoms:

1. Altered stool passage (straining, urgency, incomplete evacuation).
2. Abdominal bloating (more common in women than men), distension, tension or hardness.
3. Symptoms made worse by eating.
4. Passage of mucus.

Other features such as lethargy, nausea, backache and bladder symptoms are common in people with IBS, and may be used to support the diagnosis.

Diagnostic tests

In people who meet the IBS diagnostic criteria, the following tests should be undertaken to exclude other diagnoses:

1. Full blood count (FBC)
2. Erythrocyte sedimentation rate (ESR) or plasma viscosity
3. C-reactive protein (CRP)
4. Antibody testing for coeliac disease (endomysial antibodies [EMA] or tissue transglutaminase [TTG]).

The following tests are not necessary to confirm diagnosis in people who meet the IBS diagnostic criteria:

1. Ultrasound
2. Rigid/flexible sigmoidoscopy
3. Colonoscopy; barium enema
4. Thyroid function test
5. Faecal ova and parasite test
6. Faecal occult blood
7. Hydrogen breath test (for lactose intolerance and bacterial overgrowth).

General Management [75]

Lifestyle changes

The following lifestyle changes may help to prevent or ease your IBS symptoms:

1. Exercise regularly to promote movement of the colon and reduce stress. Exercise can take many forms, but 20 to 30 minutes of activity at least three times per week can be helpful.
2. Get enough rest. A lack of sleep and fatigue can worsen the symptoms of IBS.
3. Minimize stress and tension. The brain and colon are linked through many complex pathways and emotional stress can disrupt intestinal function and cause pain. Yoga, meditation, and slow, relaxed breathing techniques can help people with IBS manage stress.
4. Limit intake of caffeine, alcohol, carbonated drinks and fatty foods.
5. Follow through on an urge to have a bowel movement, if at all possible.

Dietary changes

Food intolerances have been linked to IBS symptoms for many years, however conflicting information often creates confusion and frustration as to what foods IBS patients should include, or avoid, in their diet. Recent research has identified six key strategies for the successful dietary management of IBS.

1. **Rule out lactose intolerance:** The symptoms of lactose intolerance (an inability to digest the sugar in milk) and the symptoms of IBS often overlap.
2. **Limit insoluble fibre:** The type of fibre in the diet is important for people with IBS. Insoluble fibre (cannot dissolve in water) which is found primarily in wheat bran, brown rice, seeds, nuts, dried fruit and whole grain breads, adds bulk to the stool and can aggravate IBS symptoms in some people. Peeling fruits and vegetables to remove the high insoluble fibre skin or peel can be beneficial.

3. **Supplement with linseeds for constipation:** Linseeds (also known as flaxseed) may help to relieve constipation, abdominal discomfort and bloating. For IBS patients with constipation, adding ground linseeds to the diet for a 3-month trial may help bowel function.
 4. **Reduce fermentable carbohydrates (FODMAPs):** Fermentable carbohydrates (also known as FODMAPs), are small carbohydrate (sugar) molecules found in everyday foods that may be poorly absorbed in the small intestine of some people. FODMAPs are fermented (digested) by intestinal bacteria, which can lead to symptoms of abdominal pain, excess gas, constipation and/or diarrhea. Following a low-FODMAP diet may help to reduce gastrointestinal symptoms in 75% of IBS patients.
 5. **Try a probiotic:** Probiotics are live microorganisms that, when taken in adequate amounts over sufficient time, may provide a health benefit. They are natural, 'healthy' bacteria that may help with digestion and offer protection from harmful bacteria in the intestines. Studies have found that, in some cases, probiotics may help to improve symptoms of IBS. If other dietary strategies have not been successful, a 4-week trial of a probiotic (in the dose recommended by the manufacturer) may be helpful. Probiotics are not medicine. They are available to purchase as capsules, tablets or powders, and can also be found in some fortified yogurts and fermented milk products. However, not all probiotics are the same. It is important to choose a product that is reliable, proven to be safe and offers benefits for the specific symptoms you want to relieve. Speak to your doctor or pharmacist about which probiotic may be right for you. It is important to take the probiotic in the dose and duration recommended by the manufacturer to achieve the best results.
 6. **Eliminate a suspected trigger food for 2 - 4 weeks:** If a particular food seems to trigger IBS symptoms, eliminate the food from your diet for a period of 2 to 4 weeks. If symptoms do not improve during that time, the food is unlikely to cause IBS symptoms.
- a. Optimal or maximum tolerated doses of previous laxatives from different classes have not helped
 - b. They have had constipation for at least 12 months.
 - c. Follow up people taking linaclotide after 3 months [76].
4. Loperamide should be the first choice of antimotility agent for diarrhoea in people with IBS.
 5. People with IBS should be advised how to adjust their doses of laxative or antimotility agent according to the clinical response. The dose should be titrated according to stool consistency, with the aim of achieving a soft, well-formed stool.
 6. Consider tricyclic antidepressants (TCAs) as second-line treatment for people with IBS if laxatives, loperamide or antispasmodics have not helped. Start treatment at a low dose (5-10 mg equivalent of amitriptyline), taken once at night, and review regularly. Increase the dose if needed, but not usually beyond 30 mg.
 7. Consider selective serotonin reuptake inhibitors (SSRIs) for people with IBS only if TCAs are ineffective.
 8. Take into account the possible side effects when offering TCAs or SSRIs to people with IBS. Follow up people taking either of these drugs for the first time at low doses for the treatment of pain or discomfort in IBS after 4 weeks and then every 6 -12 months.

Psychological interventions

Referral for psychological interventions (cognitive behavioural therapy [CBT], hypnotherapy and/or psychological therapy) should be considered for people with IBS who do not respond to pharmacological treatments after 12 months and who develop a continuing symptom profile (described as refractory IBS).

Complementary and alternative medicine (CAM)

1. The use of acupuncture should not be encouraged for the treatment of IBS.
2. The use of reflexology should not be encouraged for the treatment of IBS.

Instruction of irritable bowel syndrome [77]

Foods to avoid

1. Raw fruits should not eat during irritable bowel syndrome.
2. Raw vegetables (Ex: broccoli cabbage, cauliflower, onions) should not be eaten with IBS.
3. Fried foods are also restricted with IBS.

Pharmacological therapy

1. Healthcare professionals should consider prescribing antispasmodic agents for people with IBS. These should be taken as required, alongside dietary and lifestyle advice.
2. Laxatives should be considered for the treatment of constipation in people with IBS, but people should be discouraged from taking lactulose.
3. Consider linaclotide for people with IBS only if:

4. Rich foods (e.g. chocolate cake, cookies) should not eat during IBS.
5. Salad (or any foods that contain lettuce, cucumbers, etc.) is restricted with IBS.
6. Sugarless products (candy gum) should not eat with IBS.
7. Beans (pinto beans red beans chili, burritos) should not eat during IBS.

Drinks to avoid

1. Soda, Milk, Ice Cream Alcohol should not drink during IBS.
2. Caffeinated beverages should not drink during IBS.

Medicine to avoid

1. Non-steroidal medication should not be administered with IBS.

What to eat with IBS

Foods

1. Cooked canned vegetables (except cabbage) can eat with IBS.
2. Meat, poultry and fish (not deep fried) can institute in diet chart during IBS.
3. Dairy Cheese, Yogurt (limited amounts) can eat with IBS.
4. Most sandwiches (turkey, ham, chicken, bread) can be eaten during IBS.

Drinks

1. Juice without pulp, and water.
2. Iced tea

Medicine

- Acetaminophen as needed

Conclusion

IBS is a disease suffered by both the brain and the gut. Stress itself is not necessary to make the diagnosis but it is related to disease onset, severity, or course of the disease. One good way to cope with stress is cognitive behavior therapy. Even if the patients succeed in reducing their stress, some of their symptoms may last for a long time. The therapeutic goal is not a symptom free state but self-control of symptoms.

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