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Current perspectives on irritable bowel syndrome: a narrative review

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Abstract

The pathophysiology of irritable bowel syndrome (IBS) has not yet been fully elucidated. We reviewed articles addressing IBS that have been published in the last 2 years and selected papers related to IBS pathophysiology and treatment. Studies of intestinal bacteria, low-grade mucosal inflammation, and increased mucosal permeability—factors involved in the pathophysiology of IBS—have been conducted. In addition, the involvement of intestinal bacteria in IBS pathology has been clarified; many studies of treatments related to intestinal bacteria have been reported. Moreover, several studies address the effect on IBS of antidepressants and psychotherapy through the brain–gut axis. The contents of these papers are described in this narrative review.

Keywords

Irritable bowel syndrome, pathophysiology, treatment, intestinal bacteria, mucosal inflammation, mucosal permeability, antidepressant, psychotherapy

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Introduction

The pathophysiology of irritable bowel syndrome (IBS) has not yet been fully elucidated. Many studies on the pathophysiology and treatment of IBS are ongoing and the publication of review articles is underway.[1] In recent years, intestinal bacteria, low-grade mucosal inflammation, and increased mucosal permeability have been confirmed to be involved in IBS pathophysiology and studies related to these factors have been actively conducted. Specifically, the involvement of intestinal bacteria in IBS pathology has been confirmed and many studies of treatments addressing intestinal bacteria have been reported. Moreover, several studies on the effects on IBS of antidepressants and psychotherapy via the

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brain–gut axis have been conducted. We created this narrative review to examine recent articles addressing this topic.

Methods

We used the search term "irritable bowel syndrome" to search articles in PubMed from July 2019 to September 2021. More than 2000 papers were extracted. Among the articles published during the search period, we selected 18 papers of interest related to the pathophysiology and treatment of IBS and explained the contents of these articles.[2–19]

Pathophysiology of IBS

Genetic factors are involved in the pathology of IBS.[20] A comprehensive analysis of colonic mucosal microRNAs was performed by Mahurkar-Joshi et al.[2] The authors performed reverse transcription polymerase chain reaction on biopsy specimens of the sigmoid colons of IBS patients and healthy participants to study genes that were differentially expressed between IBS patients and healthy controls. Results indicated that the expression levels of miR-219a-5p and miR-338-3p were reduced in IBS patients. Functionally, decreased expression of miR-219a-5p was associated with a decrease in trans-epithelial electrical resistance and an increase in the permeability of intestinal epithelial cells. Decreased expression of miR-338-3p was associated with changes in the expression of genes involved in the mitogen-activated protein kinase signaling pathway associated with visceral hypersensitivity. Further studies on qualitative and quantitative changes in gene expression in IBS patients are expected in the future.

Gut microbiota is involved in the pathology of IBS.[21,22] Some patients with infectious enteritis subsequently develop post-infectious IBS (PI-IBS).[23] Furthermore, some patients who suffer from *Campylobacter* enteritis are reported to develop PI-IBS.[24] Although some *Campylobacter jejuni* strains cause disease,[25,26] the genes and pathogenic characteristics that promote IBS development remain unclear. Using pangenome-wide association studies and phenotypic assays, Peters et al.[3] examined differences between *Campylobacter jejuni* strains isolated from patients who subsequently did or did not develop PI-IBS. The results showed that mutations in the stress response gene (*Cj0145_phoX*), adhesive protein gene (*Cj0628_CapA*), and core biosynthetic pathway gene (biotin: Cj0308_bioD; purine: *Cj0514_purQ*; isoprenoid: *Cj0894c_ispH*) were involved in the development of PI-IBS. The phenotypic assay further indicated that strains isolated from IBS-affected patients adhered to and invaded intestinal cells more powerfully and stimulated more interleukin(IL)-8 and tumor necrosis factor α (TNFα) secretion from intestinal cells than strains isolated from non-IBS-affected patients. In addition, Peters et al.[3] developed a risk score for developing PI-IBS using 22 genomic markers including four markers derived from the predicted heme oxidase gene linked to virulence.[27] The results of this study demonstrated that specific *Campylobacter* genotypes increased in vitro pathogenicity and the risk of developing PI-IBS.

Psychological stress and gut microbiota play important roles in the pathophysiology of IBS.[28,29] Mental stress may further affect not only intestinal bacteria but also intestinal mucosal permeability.[30] Given intestinal bacteria are involved in IBS pathophysiology, probiotic treatment may be effective in IBS. The mechanism by which probiotic treatment affects the psychological stress-induced change in intestinal mucosal permeability and activation of the immune system remains unclear. In an animal study, Wang et al.[4] examined how the

probiotic *Bifidobacterium bifidum* G9-1 (BBG9-1) affects macrophages and the colonic mucosal permeability in IBS model rats that were subjected to stress from maternal separation. The mucosal permeability of the colonic epithelium was significantly higher ($P < 0.05$), claudin-4 expression was significantly reduced ($P < 0.05$), the number of CD80-positive M1 macrophages in the colonic mucosa was significantly increased ($P < 0.01$), and the expression levels of IL-6 and interferon-gamma (IFN-γ) were significantly elevated ($P < 0.05$ and $P < 0.01$, respectively) in the maternal separated rats compared with control rats. Treatment with BBG9-1 significantly counteracted the increase in M1 macrophages and IL-6 and IFN-γ expression in the colonic mucosa of maternal separated rats. Treatment neutralized both the increase in mucosal permeability and the decline in claudin-4 expression in the colons of maternal separated rats. These results indicate that BBG9-1 acts protectively against increases in colonic mucosal permeability and M1 macrophages caused by psychological stress. Furthermore, IL-6 and IFN-γ significantly reduced the trans-epithelial electrical resistance of Caco2 cells in vitro, suggesting that *Bifidobacterium* strains may improve cytokine-stimulated epithelial cell barrier disruption.

The involvement of the gut virome in IBS pathophysiology has also been studied.[31] Following a metagenomic analysis of DNA and RNA viruses using stool samples from healthy individuals and IBS patients, Mihindukulasuriya et al. reported that the gut virome was stable over time but varied by IBS subtype.[5] The authors reported that the gut virome could be affected by diet and could affect host function through interactions with gut bacteria or changes in host gene expression.

Eosinophils are multi-functional granulocytes. Eosinophils in the intestinal mucosa contain substance P, vasoactive intestinal peptide, calcitonin gene-related peptide, and corticotropin-releasing hormone (CRH).[32,33] Also known as corticotropin-releasing factor, CRH plays an important role in the stress response[34] and is involved in IBS pathophysiology.[35] The brain–gut axis in IBS patients may have an exaggerated response to CRH.[35] The presence of CRH in intestinal mucosal eosinophils of IBS patients suggests that mucosal eosinophils play a role in IBS pathophysiology. Salvo-Romero et al.[6] reported that mucosal eosinophil degranulation was observed to a greater extent in diarrhea-predominant IBS (IBS-D) patients than in healthy controls, that IBS-D patients had an increased level of CRH in cytoplasmic granules compared with healthy controls, and that the amount of CRH in cytoplasmic granules correlated with the clinical severity of IBS, life stress, and a depressive score. Furthermore, the authors reported that substance P and carbachol enhanced the secretory activity of eosinophils and increased CRH synthesis and release from eosinophils. The results of this study demonstrated that eosinophils in the intestinal mucosa may affect the pathophysiology of IBS-D by synthesizing and releasing CRH. Recently, eosinophils in the colonic mucosa were reported to express the μ-opioid receptor, aβ-endorphin that binds to the μ-opioid receptor with high affinity, and cannabinoid receptor-2.[7] Eosinophils may be involved in the opioid and cannabinoid systems that regulate physiological functions such as intestinal perception and movement.

In addition to CRH, oxytocin is involved in IBS pathophysiology. Tsushima et al.[8] showed that oxytocin antagonists enhanced visceral hypersensitivity to colorectal distention stimuli in animal models and increased anxiety-like behavior. The authors explained that colorectal distention stimuli activate oxytocin neurons in the

paraventricular nucleus and the neurons containing CRH in the central nucleus of the amygdala, and that neuron activation was further enhanced by the administration of an oxytocin antagonist in addition to the strong colorectal distention stimuli. The authors further observed that neurons in the anterior cingulate cortex are activated by strong colorectal distention stimuli and that the activation is suppressed by the addition of a high-dose oxytocin antagonist. These results indicate that oxytocin suppresses CRH-containing amygdala neurons and promotes the anterior cingulate cortex. Further studies on brain activity and the roles of CRH, oxytocin, the anterior cingulate cortex, and the amygdala may lead to the development of methods for controlling visceral hypersensitivity.

Treatment of IBS

Many studies report that IBS symptoms are related to diet. Dietary content that tends to cause IBS symptoms includes lipids, caffeine, and spices.[36] Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) are difficult to decompose, are absorbed in the small intestine, and are fermented and decomposed by bacteria in the colon. Although several studies report the usefulness of low FODMAP diets for IBS patients,[37,38] the usefulness of these diets is still debated. Wang et al.[9] conducted a meta-analysis to determine if a low FODMAP diet was useful for improving IBS symptoms. The authors selected 10 randomized controlled trials (511 participants) that compared a low FODMAP diet to control diets including high FODMAP, traditional IBS, and normal diets. When seven of these studies were combined, the low FODMAP diet was associated with better improvement of general IBS symptoms compared with the control diet ($n = 420$; relative risk = 1.54; 95% CI: 1.18–2.00; $I2 = 38\%$). The results further indicated that the low FODMAP diet had a considerable effect on stool shape and the frequency of stools per day and may be more effective in patients with diarrhea-predominant IBS. Study limitations cited included the small sample size of each study, the lack of assessment of the intervention effectiveness by IBS subgroup in several studies, and the lack of symptom evaluation using a unified evaluation scale. Therefore, this meta-analysis appears to provide moderate-quality evidence of the usefulness of a low FODMAP diet in improving IBS symptoms. Concurrently, Black et al.[10] conducted a network meta-analysis comparing low FODMAP diets with control diets including high FODMAP, traditional IBS, and regular diets. In a study of 13 randomized controlled trials (944 participants), a low FODMAP diet was ranked first in achieving overall IBS symptom improvement (relative risk = 0.67; 95% CI: 0.48–0.91, $P = 0.99$), and was shown to be more useful than any other diet. A meta-analysis by Hahn et al.[11] further demonstrated that a low FODMAP diet was useful in improving IBS symptoms, a finding supported by accumulating evidence.[39,40] However, the decreased function of the sucrase-isomaltase complex involved in sucrose and starch degradation is reportedly related to IBS pathophysiology. In IBS patients with a low-functioning sucrase-isomaltase complex, low FODMAP diets that do not limit sucrose intake are less effective than in IBS patients with normal function.[12] Randomized controlled trials on the effectiveness of low FODMAP diets have not been conducted in Japan. Further studies are needed to establish whether a low FODMAP diet can be considered a treatment for IBS.

Furthermore, in a study of dietary patterns, gut inflammatory markers, and the relationship between gut microbial composition and function, Bolte et al.[13] observed

that habitual dietary content affected the human gut ecosystem and the induction and suppression of inflammation; similar relationships were observed in IBS patients. The authors noted that dietary strategies targeting the gut flora may be useful in alleviating and preventing gut inflammation.

Several studies investigated the effectiveness of probiotics in IBS.[41–43] Wen et al.[14] conducted a meta-analysis of 17 randomized controlled trials (1469 participants) of adults with constipation-predominant IBS who were randomized to a probiotic or placebo group. After pooling the results of 11 studies, the authors observed that the probiotic group had a significantly higher weekly defecation frequency than the placebo group; probiotics increased stool frequency by 1.29 bowel movements/week (95% CI: 0.69–1.89 bowel movements/week; $P < 0.0001$). After pooling the results of 10 studies, the probiotic group reported having significantly softer stools than the placebo group ($P = 0.0001$). In addition, pooled results from three studies indicated that the probiotic group had significantly shorter intestinal transit times than the placebo group ($P = 0.004$). The authors concluded that studies with appropriately sized samples are needed to determine the optimal bacterial species and strain and the amount and duration of probiotic use. Thus, further research is required to support whether probiotics can be regarded as a treatment option for IBS.

Since the 2013 report of a randomized controlled trial investigating fecal microbiota transplantation (FMT) for the treatment of *Clostridium difficile* infection,[44] FMT treatment has been used to treat various diseases.[45–51] Reports of FMT treatment for IBS have increased in recent years and meta-analyses have been reported, but consensus has not yet been reached.[50,51] Studies of the effectiveness of multiple FMTs have since emerged.[54–56] In recent years, a double-blind, randomized controlled trial of donor and placebo stool (autologous stool) transplantation was conducted in IBS patients with abdominal distension as the main symptom.[15] At the 3-month post-transplantation assessment, IBS symptoms improved in 56% of patients who underwent donor fecal transplants while only 26% of patients who received placebo fecal transplants showed improvement ($P = 0.03$). Pre-transplanted fecal samples from treatment responders had greater bacterial flora diversity than samples from non-responders ($P = 0.04$), and the composition of fecal flora was significantly different between responders and non-responders ($P = 0.04$). At the evaluation 1 year post-transplantation, 21% of patients who received donor stool had no relapse of symptoms, while only 5% of patients who received placebo stool had no relapse. When a second course of FMT treatment was provided to symptomatic patients, 67% of the patients who responded to the initial course of treatment and 0% of non-responding patients showed symptomatic improvement. The results of this study suggest that FMT treatment is useful for some IBS patients and its effectiveness may be related to gut bacterial flora before FMT treatment. Moreover, findings indicate that the fecal flora characteristics before FMT treatment may be biomarkers for selecting responders to FMT treatment. Future studies can further identify the characteristics of patients who respond to FMT treatment.

Despite many reports on the use of tricyclic antidepressants and selective serotonin reuptake inhibitors for the treatment of IBS,[57]only a few studies report on the use of a serotonin-norepinephrine reuptake inhibitor (SNRI) and a noradrenergic and specific serotonergic antidepressant (NaSSA).[58,59] Sharbafchi et al.[16] conducted a double-blind randomized trial in which the SNRI venlafaxine or placebo was administered to 33 patients with

moderate-to-severe IBS. The authors reported that the venlafaxine group showed significant improvement in the severity of symptoms compared with the placebo group ($P < 0.001$). In Khalilian et al.'s[17] double-blind, randomized controlled trial, the NaSSA mirtazapine or placebo was administered to 67 patients with diarrhea-predominant IBS. The mirtazapine group showed significant improvement in symptom severity compared with the placebo group ($P = 0.002$). Appropriately sized future studies are required to verify the results of these studies.

Krouwel et al.[18] conducted a meta-analysis to elucidate the effects of hypnotherapy on IBS and predictors of its effects. By pooling data from seven reports, the authors observed that hypnotherapy reduced IBS symptoms (standardized mean difference 0.24, [−0.06, 0.54], $I2 = 66\%$). Subgroup analysis showed that higher volumes of intervention (i.e., total treatment time of 6 or more hours and eight or more sessions) provided significantly more symptom relief than lesser volumes ($P = 0.0001$). In addition, frequent treatment (e.g., more than once a week) and group treatment were shown to be potentially effective. The meta-analysis indicated that a high volume of intervention was one of the predictors of the therapeutic effect of hypnotherapy; however, the optimal number of sessions remained unclear. Therefore, Hasan et al.[19] randomly assigned six or 12 sessions of gut-focused hypnotherapy to 489 IBS patients, with 394 patients completing the assigned number of sessions. Results indicated that a course of six sessions of gut-focused hypnotherapy was not inferior to 12 sessions and that the course of six sessions had a lower percentage of dropouts. The unknown long-term effect of six sessions of hypnotherapy was cited as a limitation of the study. Further studies are required before hypnotherapy is established as a treatment for IBS.

Conclusion

This review presented topics related to IBS pathophysiology and treatment. Genetic factors, infectious enteritis, gut microbiota, stress, increased mucosal permeability, low-grade mucosal inflammation, and endocrine substances have been reported to contribute to IBS pathophysiology. While these factors are known to be involved in IBS pathology, further research is required to understand their role in disease pathophysiology. Furthermore, we reviewed studies of IBS treatments such as probiotics, FMTs, and low FODMAP diets that affect the gut microbiota. Previous studies have shown that treatments that affect gut microbiota are not equally effective in all IBS patients; future studies must identify the IBS characteristics these treatments are useful for. Finally, this review explains the findings of reports on the use of antidepressants and hypnotherapy in IBS. Although these approaches may be effective, further studies are required to establish psychotherapy as a recommended treatment for IBS.

Author contributions

MH designed the work and drafted the manuscript. MH and AN reviewed and approved the final version of the manuscript.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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References

1. Bonetto S, Fagoonee S, Battaglia E, et al. Recent advances in the treatment of irritable bowel syndrome. *Pol Arch Intern Med* 2021; 131: 709–715.
2. Mahurkar-Joshi S, Rankin CR, Videlock EJ, et al. The Colonic Mucosal MicroRNAs, MicroRNA-219a-5p, and MicroRNA-338-3p Are Downregulated in Irritable Bowel Syndrome and Are Associated With Barrier Function and MAPK Signaling. *Gastroenterology* 2021; 160: 2409–2422.e19.
3. Peters S, Pascoe B, Wu Z, et al. Campylobacter jejuni genotypes are associated with post-infection irritable bowel syndrome in humans. *Commun Biol* 2021; 4: 1015.
4. Wang X, Fukui H, Ran Y, et al. Probiotic Bifidobacterium bifidum G9-1 Has a Preventive Effect on the Acceleration of Colonic Permeability and M1 Macrophage Population in Maternally Separated Rats. *Biomedicines* 2021; 9: 641.
5. Mihindukulasuriya KA, Mars RAT, Johnson AJ, et al. Multi-Omics Analyses Show Disease, Diet, and Transcriptome Interactions With the Virome. *Gastroenterology* 2021; 161: 1194–1207.e8.
6. Salvo-Romero E, Martínez C, Lobo B, et al. Overexpression of corticotropin-releasing factor in intestinal mucosal eosinophils is associated with clinical severity in Diarrhea-Predominant Irritable Bowel Syndrome. *Sci Rep* 2020; 10: 20706.
7. Dothel G, Chang L, Shih W, et al. μ-opioid receptor, *β*-endorphin, and cannabinoid receptor-2 are increased in the colonic mucosa of irritable bowel syndrome patients. *Neurogastroenterol Motil* 2019; 31: e13688.
8. Tsushima H, Zhang Y, Muratsubaki T, et al. Oxytocin antagonist induced visceral pain and corticotropin-releasing hormone neuronal activation in the central nucleus of the amygdala during colorectal distention in mice. *Neurosci Res* 2021; 168: 41–53.
9. Wang J, Yang P, Zhang L, et al. A Low-FODMAP Diet Improves the Global Symptoms and Bowel Habits of Adult IBS Patients: A Systematic Review and Meta-Analysis. *Front Nutr* 2021; 8: 683191.
10. Black CJ, Staudacher HM and Ford AC. Efficacy of a low FODMAP diet in irritable bowel syndrome: systematic review and network meta-analysis. *Gut* 2021; 71: 1117–1126.
11. Hahn J, Choi J and Chang MJ. Effect of Low FODMAPs Diet on Irritable Bowel Syndromes: A Systematic Review and Meta-Analysis of Clinical Trials. *Nutrients* 2021; 13: 2460.
12. Zheng T, Eswaran S, Photenhauer AL, et al. Reduced efficacy of low FODMAPs diet in patients with IBS-D carrying sucrase-isomaltase (SI) hypomorphic variants. *Gut* 2020; 69: 397–398.
13. Bolte LA, Vich Vila A, Imhann F, et al. Long-term dietary patterns are associated with pro-inflammatory and anti-inflammatory features of the gut microbiome. *Gut* 2021; 70: 1287–1298.
14. Wen Y, Li J, Long Q, et al. The efficacy and safety of probiotics for patients with constipation-predominant irritable bowel syndrome: A systematic review and meta-analysis based on seventeen randomized controlled trials. *Int J Surg* 2020; 79: 111–119.
15. Holvoet T, Joossens M, Vázquez-Castellanos JF, et al. Fecal Microbiota Transplantation Reduces Symptoms in Some Patients With Irritable Bowel Syndrome With Predominant Abdominal Bloating: Short- and Long-term Results From a Placebo-Controlled Randomized Trial. *Gastroenterology* 2021; 160: 145–157.e8.
16. Sharbafchi MR, Afshar H, Adhamian P, et al. Effects of venlafaxine on gastrointestinal symptoms, depression, anxiety, stress, and quality of life in patients with the moderate-to-severe irritable bowel syndrome. *J Res Med Sci* 2020; 25: 115.
17. Khalilian A, Ahmadimoghaddam D, Saki S, et al. A randomized, double-blind, placebo-controlled study to assess efficacy of mirtazapine for the treatment of diarrhea predominant irritable bowel syndrome. *Biopsychosoc Med* 2021; 15: 3.
18. Krouwel M, Farley A, Greenfield S, et al. Systematic review, meta-analysis with

subgroup analysis of hypnotherapy for irritable bowel syndrome, effect of intervention characteristics. *Complement Ther Med* 2021; 57: 102672.
19. Hasan SS, Whorwell PJ, Miller V, et al. Six vs 12 Sessions of Gut-focused Hypnotherapy for Irritable Bowel Syndrome: A Randomized Trial. *Gastroenterology* 2021; 160: 2605–2607.e3.
20. Levy RL, Jones KR, Whitehead WE, et al. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. *Gastroenterology* 2001; 121: 799–804.
21. Halvorson HA, Schlett CD and Riddle MS. Postinfectious irritable bowel syndrome–a meta-analysis. *Am J Gastroenterol* 2006; 101: 1894–1899; quiz 942.
22. Sabo CM and Dumitrascu DL. Microbiota and the irritable bowel syndrome. *Minerva Gastroenterol (Torino)* 2021; 67: 377–384.
23. Thabane M, Kottachchi DT and Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther* 2007; 26: 535–544.
24. Thornley JP, Jenkins D, Neal K, et al. Relationship of Campylobacter toxigenicity in vitro to the development of postinfectious irritable bowel syndrome. *J Infect Dis* 2001; 184: 606–609.
25. Pascoe B, Schiaffino F, Murray S, et al. Genomic epidemiology of Campylobacter jejuni associated with asymptomatic pediatric infection in the Peruvian Amazon. *PLoS Negl Trop Dis* 2020; 14: e0008533.
26. Nielsen LN, Sheppard SK, McCarthy ND, et al. MLST clustering of Campylobacter jejuni isolates from patients with gastroenteritis, reactive arthritis and Guillain-Barré syndrome. *J Appl Microbiol* 2010; 108: 591–599.
27. Ridley KA, Rock JD, Li Y, et al. Heme utilization in Campylobacter jejuni. *J Bacteriol* 2006; 188: 7862–7875.
28. Whitehead WE, Crowell MD, Robinson JC, et al. Effects of stressful life events on bowel symptoms: subjects with irritable bowel syndrome compared with subjects without bowel dysfunction. *Gut* 1992; 33: 825–830.
29. Simrén M, Barbara G, Flint HJ, et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut* 2013; 62: 159–176.
30. Fukui H, Oshima T, Tanaka Y, et al. Effect of probiotic Bifidobacterium bifidum G9-1 on the relationship between gut microbiota profile and stress sensitivity in maternally separated rats. *Sci Rep* 2018; 8: 12384.
31. Coughlan S, Das A, O'Herlihy E, et al. The gut virome in Irritable Bowel Syndrome differs from that of controls. *Gut Microbes* 2021; 13: 1–15.
32. Aliakbari J, Sreedharan SP, Turck CW, et al. Selective localization of vasoactive intestinal peptide and substance P in human eosinophils. *Biochem Biophys Res Commun* 1987; 148: 1440–1445.
33. Zheng PY, Feng BS, Oluwole C, et al. Psychological stress induces eosinophils to produce corticotrophin releasing hormone in the intestine. *Gut* 2009; 58: 1473–1479.
34. Axelrod J and Reisine TD. Stress hormones: their interaction and regulation. *Science* 1984; 224: 452–459.
35. Fukudo S, Nomura T and Hongo M. Impact of corticotropin-releasing hormone on gastrointestinal motility and adrenocorticotropic hormone in normal controls and patients with irritable bowel syndrome. *Gut* 1998; 42: 845–849.
36. Böhn L, Störsrud S, Törnblom H, et al. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. *Am J Gastroenterol* 2013; 108: 634–641.
37. Goyal O, Batta S, Nohria S, et al. Low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol diet in patients with diarrhea-predominant irritable bowel syndrome: A prospective, randomized trial. *J Gastroenterol Hepatol* 2021; 36: 2107–2115.
38. Zhang Y, Feng L, Wang X, et al. Low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet compared with traditional dietary advice for diarrhea-predominant irritable bowel

syndrome: a parallel-group, randomized controlled trial with analysis of clinical and microbiological factors associated with patient outcomes. *Am J Clin Nutr* 2021; 113: 1531–1545.
39. Goyal O, Batta S, Nohria S, et al Low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol diet in patients with diarrhea-predominant irritable bowel syndrome: A prospective, randomized trial. *J Gastroenterol Hepatol*. 2021; 36: 2107–2115.
40. Zahedi MJ, Behrouz V, Azimi M. Low fermentable oligo-di-mono-saccharides and polyols diet versus general dietary advice in patients with diarrhea-predominant irritable bowel syndrome: A randomized controlled trial. *J Gastroenterol Hepatol*. 2018; 33: 1192–1199.
41. Xu H, Ma C, Zhao F, et al. Adjunctive treatment with probiotics partially alleviates symptoms and reduces inflammation in patients with irritable bowel syndrome. *Eur J Nutr* 2021; 60: 2553–2565.
42. Skrzydło-Radomańska B, Prozorow-Król B, Cichoż-Lach H, et al. The Effectiveness and Safety of Multi-Strain Probiotic Preparation in Patients with Diarrhea-Predominant Irritable Bowel Syndrome: A Randomized Controlled Study. *Nutrients* 2021; 13: 756.
43. Oh JH, Jang YS, Kang D, et al. Efficacy and Safety of New Lactobacilli Probiotics for Unconstipated Irritable Bowel Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients* 2019; 11: 2887.
44. Van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med* 2013; 368: 407–415.
45. Tian H, Ge X, Nie Y, et al. Fecal microbiota transplantation in patients with slow-transit constipation: A randomized, clinical trial. *PLoS One* 2017; 12: e0171308.
46. Bajaj JS, Kassam Z, Fagan A, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. *Hepatology* 2017; 66: 1727–1738.
47. Allegretti JR, Kassam Z, Mullish BH, et al. Effects of Fecal Microbiota Transplantation With Oral Capsules in Obese Patients. *Clin Gastroenterol Hepatol* 2020; 18: 855–863.e2.
48. Sokol H, Landman C, Seksik P, et al. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. *Microbiome* 2020; 8: 12.
49. Fretheim H, Chung BK, Didriksen H, et al. Fecal microbiota transplantation in systemic sclerosis: A double-blind, placebo-controlled randomized pilot trial. *PLoS One* 2020; 15: e0232739.
50. Rossen NG, Fuentes S, Van der Spek MJ, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. *Gastroenterology* 2015; 149: 110–118.e4.
51. Moayyedi P, Surette MG, Kim PT, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology* 2015; 149: 102–109.e6.
52. Xu D, Chen VL, Steiner CA, et al. Efficacy of Fecal Microbiota Transplantation in Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2019; 114: 1043–1050.
53. Ianiro G, Eusebi LH, Black CJ, et al. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2019; 50: 240–248.
54. El-Salhy M, Hatlebakk JG, Gilja OH, et al. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. *Gut* 2020; 69: 859–867.
55. Lahtinen P, Jalanka J, Hartikainen A, et al. Randomised clinical trial: faecal microbiota transplantation versus autologous placebo administered via colonoscopy in irritable bowel syndrome. *Aliment Pharmacol Ther* 2020; 51: 1321–1331.
56. Madsen AMA, Halkjær SI, Christensen AH, et al. The effect of faecal microbiota transplantation on abdominal pain, stool frequency, and stool form in patients

with moderate-to-severe irritable bowel syndrome: results from a randomised, double-blind, placebo-controlled study. *Scand J Gastroenterol* 2021; 56: 761–769.
57. Xie C, Tang Y, Wang Y, et al. Efficacy and Safety of Antidepressants for the Treatment of Irritable Bowel Syndrome: A Meta-Analysis. *PLoS One* 2015; 10: e0127815.
58. Brennan BP, Fogarty KV, Roberts JL, et al. Duloxetine in the treatment of irritable bowel syndrome: an open-label pilot study. *Hum Psychopharmacol* 2009; 24: 423–428.
59. Thomas SG. Irritable bowel syndrome and mirtazapine. *Am J Psychiatry* 2000; 157: 1341–1342.