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Newer Approaches for Managing Gut-Brain Disorders In Functional Gastrointestinal Diseased Patients.

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ABSTRACT

Functional gastrointestinal disorders (FGIDs) are characterized by the presence of chronic or recurrent symptoms that are felt to originate from the gastrointestinal (GI) tract, which cannot be attributed to an identifiable structural or biochemical cause. Food is associated with symptom onset or exacerbation in a significant proportion of FGID patients. Despite this, the role of food in the pathogenesis of the FGIDs has remained poorly understood. For this reason, dietary and life style modifications has largely played an adjunctive rather than a primary role in the management of FGID patients. In recent years, there has been a rapid expansion in our understanding of the role of food and life style changes in GI function and sensation and how these parameters relates to GI symptoms in FGID patients. Comprehensive reviews of the physiological changes are associated with nutrient intake, and the respective roles of carbohydrates, fiber, protein, and fats along with changes in lifestyle parameters. This concludes with a manuscript that provides detailed information on current treatment and proper management of Gut-Brain disorders in FGID patients by modifying the dietary and lifestyle changes.

Keywords: FGID, FD, IBS, GERD, GIT and CAM.

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INTRODUCTION

Functional gastrointestinal diseases (FGI) are common in the world and account for more than 40% of clinical visits to gastroenterology clinics. Common FGID include gastro oesophageal reflux disease (GERD), functional dysphasia (F Dyes), functional dyspepsia (FD), gastro paresis, irritable bowel syndrome (IBS), functional constipation, diarrheal, and faecal incontinence. While pathogeneses of FGID are not completely understood, major pathos physiological factors include impaired gastrointestinal motility, visceral hypersensitivity, and psychological issues as well as disruption of the gut flora and micro biota. [1]

Gastrointestinal dyes motility is most common in FGID. Functional Gaston intestinal disorder (FGIDs) are very Common and their global impact is often under estimated, [2, 3] due to their limited Associates mortality. [4] However, it is well documented that FGIDs have a negative impact on health-related quality of life (HRQOL) and have a burden of illness. FGID represent a common and important class of disorders with in gastroenterology. The large number of patients suffering from the FGIDs, as well as the high frequency of functional GI symptoms in general within the population, the health care burden produced by the use of medical services and medications for the above conditions, and its outcomes in terms of decreased quality of life (QOL) are reported. [2-5] FGIDs are a group of disorder characterized by repeated gastro intestinal distress for which no structural or biochemical cause can be predicted. FGIDs can affect any part of the gastro intestinal (GI) tract, including the esophagus, stomach and both intestines. The large number of patients of all age groups are suffering from the FGIDs, as well as the high frequency of functional GI symptoms within the population worldwide.

GUT-BRAIN AXIS

"Gut" include organs like mouth, esophagus, stomach, small intestine and colon. This helps in the transformation of food into the smaller nutrients for the body needs. If any body has a up set stomach, heart burn / gas problem or constipation the gut reactions get altered. The "gut reactions" may be disruptive, painful and embarrassing. Thus gut-brain axis is an important parameter in human health. The person experienced gut symptoms after perfectly healthy diet, the symptoms may be because of gut-brain axis issues. There are some defined and also some undefined relationship between digestive system with memory, depression, anxiety, cognitive function and other behavioral and mental issues. "The way to a man's heart is through his stomach" is the commonly used expression in everyday language suggesting a close association between psychological conditions and digestive functions. During the last few decades, psychological factors and particular stress, have been increasingly implicated in the etiological model of chronic, disruptive gastrointestinal (GI) conditions.

FGID, in particular the irritable bowel syndrome (IBS), are the most common conditions resulting in patient visits to gastroenterologists. FGID patients exhibit a high prevalence of psychiatric comorbidity, psychosocial stress and maladaptive illness behavior. For these reasons, FGID have been associated with substantial socioeconomic and individual burden. The influence of acute stress on bowel functions including motility, GI secretion and visceral perception, well established in animals and humans. However, stress induced alterations of gastrointestinal functions have been suggested to be more pronounced in individuals with FGID. A variety of "stressors" such as early life stress, acute life-threatening or traumatic events, also chronic stress in the form of daily hassles and sustained psychosocial stress, have been associated with FGID. It has been postulated that in predisposed individuals, chronic stress modifies the responsiveness and the feedback mechanisms of regulatory psychophysiological systems. The long-term consequences of such alterations are a variety of somatic and psychological symptoms. Although previous findings provide evidence of stress-induced gut disturbances and psychosocial stress has been associated with the onset and maintenance of FGID, the physiological mechanisms linking stress and gut remain poorly understood. As one mediator of the brain-gut interaction, the hypothalamus-pituitary-adrenal (HPA) axis – a prominent biological stress system – has been proposed.

The vital players of gut-brain axis are the hypothalamus, frontal cortex, the insular cortex and the vagal motor nuclei. The brain basically communicates with the gut via neuronal projections and then hormones that are secreted through the hypothalamus. The frontal cortex primarily stimulates the vagal nuclei to initiate gut motility (also called as intestinal peristalsis), by which food contents move through the digestive tract, and do enzymes secretion. The sama to topic map present in the insular cortex, which basically

provide information regarding the location of gut. The vagal motor nuclei stimulate intestinal motility, further this modulate blood flow. These in turn activate the release of hydrochloric acid and other digestive enzymes. The enteric nervous system (ENS) has major role in the gut, the intestine's immune system, gut-Associates lymphoid tissue, and also the intestinal microglia.

Firstly, the intestinal motility and enzyme release performed by ENS and then the incoming input conveyed to the vagus nerve. Enterochromaffin cells (EC) in gut contain almost 80% of the total body's serotonin (5 HT) and this acts primarily to regulate peristalsis and motility. This is the pharmacological correlation of anxiety, depression and constipation often appear together. Remaining 20% of serotonin is produced in serotonergic neurons in the CNS which regulate appetite, mood, muscle contraction and sleep. So the cytokines, gut opiates, gut peptides like neurotensin and substance-P communicates gut with the brain.

FGIDs shows symptoms which are derived from different combinations of physiological activities: enhanced motor reactivity, increased visceral hypersensitivity, change in inflammatory function and mucosal immune (including changes in bacterial flora), and altered CNS-enteric nervous system (ENS) up or down regulation (influenced by sociological and psychosocial factors and exposures). FGIDs are not psychiatric abnormalities, though psychological difficulties and stress can worsen FGID symptoms. Inflammatory Bowel Syndrome (IBS) BS is the most common FGID, in which bowel consistency altered in combination with abdominal pain. IBS is a complex phenomenon, and results in various disorders like dysmotility, mucosal immune dysregulation, visceral hypersensitivity, alterations of bacterial flora and CNS-ENS dysregulation. [6]

The other general symptoms are ulcer-like symptoms, Dyspepsia with upper-GI pain, indigestion problem or milder discomfort with stomach fullness and in many times nausea immediately after eating. [7] The hypothalamic-pituitary-adrenal (HPA) axis serves as the primary endocrine stress system in humans and provides an important interface between the brain and the gut-immune system. Activators of the HPA axis including physical and psychological stress have been suggested to play a role in FD. A recent study involving IBS patients found over activation of the HPA axis with associated increases in pro inflammatory cytokines. [8] There is evolving evidence that cortocotropin releasing hormone (CRF) receptor antagonists may reduce stress-related alterations in upper gut function. [9]

There are three primary characteristics of FGIDs - brain-gut dysfunction, motility and sensation

- Brain-gut disorder relates to the altered communication between brain and GI tract. In FGIDs, the coordination between the gut and brain function may be impaired and this can lead to bowel difficulties, increased pain which can be worsened by stress.
- Motility (e.g., peristalsis) is the smooth muscle activity of the GI tract. In normal physiology motility is an sequencial muscular contractions from the start to the end of GI tract. In FGIDs, the peristalsis is abnormal - there may be muscular spasms which can cause pain. The muscular contractions can be very rapid (diarrhea) or very slow (constipation).
- The nerves of the GI tract cause sensation to stimuli (digesting a meal). In FGIDs, sometimes the nerves are so sensitive that normal contractions also can cause pain or discomfort.

PHYSIOLOGY OF FGID

Motility

Propulsion along the human digestive tract helps to mix the contents and present them to the absorptive surface area also support a temporary storage and dispose of residues. Local inflammatory, immune or degenerative, infilterative and factor scan directly influence the smooth muscle of the GIT or the ENS effector system. Visceral different fibers indirect can induce dysmotility via paravertebral angla and trigger autonomic changes inside brain stem, such as alteration in heart rate, alterations in colonic tone. Psychosocial factors can also initiate alterations in GI motility. Patient with any of the FGID symptoms have more stress induce GI motor response conditions than controls. [10]

Inflammation and post-infections IBS

Gastroduodenal inflammation has also been reported in functional dyspepsia (FD) paients who are devoid of ulcer. [11] A Meta-analysis has documented evidence for an inflammation in the plexus myentericus

in IBS patients [12] and increased cases of IBS after gastroenetritis.[13] Post infections IBS, diagnose by a little inflammation with increased number of T lymphocytes and mast cells, informed with a prevalence rate of 6-7% after an acute attack of bacterial gastroeneteritis. [14] Anxiety, depression, neurosis, female gender, a sevré episode, somatization are risk factors for initiation of post infections IBS. [15,16]

Bacterial flora:

Patients with *H. pylori* infection with non-ulcer dyspepsia, eradication of *H. pylori* may be a succesful therapy.[17] Though, followup studies after one year showed eradication of *H. pylori* actually produced no benefit when compared with placebo [18] or when compared to antacid therapy. [19] The fecal microbiota is also changed in IBS patients [20] and a connection between antibiotic therapy and IBS has been documented. [21] IBS patients may give positive response to the use of probiotic bacterial compositions [22, 23] and the eradication of GI bacterial growth. [24]

Treatment of FGIDs

The treatment schedule is individualized and include explanation, also required sometime alteration in diet, drug therapy aimed at predominant symptoms, psychotherapy and life style modification. [25] General dietary and life style alterations include regular sleep and exercise, smoking cessation, also avoiding restricted foods known to improve the function of the GIT. In FD, gastric acid inhibitors can produce some relief but for the patient with GERD, the studies some times include, the effinacy of the drug is difficult to assess. Maximum patients with FD are not infected with *H. pylori* but antibiotic therapy that eradicates *H. pylori* can offer a little relief. [26]

Life style And Dietary Modifications to Improve Gut-Brain Function of FGID Patients:

One of the best ways to improve mental health is through gut. Like the brain, the gut also has its own nervous system, informations from gut to the brain goes via the vagus nerve. Just as the brain impacts the gut-gut can also impact the normal functioning of the brain. A variety of different psychotherapeutic modalities have been used to treat FGID including insight-oriented psychotherapy, relaxation and stress management training, cognitive-based behavioural therapy, biofeedback and hypnotherapy. [27, 28] The best studied of these techniques is cognitive-behavioural therapy. This form of psychotherapy is designed to teach patients how to identify maladaptive behaviours and manage their responses to emotional and life stresses. In a cinical trial study 100 patients were randomised with FD to cognitive psychotherapy or no therapy and found that the psychotherapy patients experienced significant improvement in symptoms, such as bloating, epigastric pain and nausea. [29] In particular, with regard to treatments, the patients were asked whether during the last year (i) they had used conventional drugs such as anti-acids, proton pump inhibitors, H_2-antagonists, prokinetics, antispasmodics, analgaesics, antidiarrhoeals, stimulant or osmotic laxatives, antidepressants, or anti-anxiety agents; (ii) they had followed particular diets or had used dietary supplements, such as empirical exclusion diets, IgG/IgG_4-based exclusion diets, probiotics, prebiotics, or fibres; and/or (iii) they had used complementary and alternative medicine (CAM) such as herbal products, homeopathy, acupuncture, reflexology, hypnotherapy, relaxation techniques, and cognitive behavioural psychotherapy. Among non pharmlogical treatments (i.e. diet, dietary supplements, and CAM), those previously investigated for FGID were included. [30-49]

A wide variety of treatments have been used to manage FD including dietary and lifestyle modifications, *H. pylori* eradication, antacids, mucosal protectants, antisecretory agents, prokinetics, antidepressants, behavioural therapies as well as CAM therapies. The fact that no single available therapy consistently provides relief to the majority of FD patients validates the heterogeneity of this disorder. Given this heterogeneity, it is difficult to generalize about the characteristics, which predict a greater or lesser response to therapy for this condition. The exercise and acupuncture are the two of the best ways to enhance blood flow to brain. Some research suggested that vinpocetine from periwinkle can enhance blood flow to brain. There are also certain botanicals and nutrients like ginko, fever few, cayenne which increases the blood supply to brain. Yoga and other stress reduction methods help to manage the stress level. A gut-healing chart might include the glycine rich bone broths, probiotics, jerusalem artichokes, prebiotic foods like sweet potatoes, can better manage the symptoms of FGID. [50, 51] Researchers have found that foods high in omega-3 fatty acids, like wild cold water fish (e.g., salmon, herring, sardines and mackerel), chicken fed on

flaxseed, seaweed, and walnuts, have been reported to reduce symptoms of schizophrenia, attention deficit hyperactivity disorder, depression and other mental disorders. Omega-3 fatty acids have crucial role on the production of neurotransmitters, including dopamine and serotonin. By supporting the synapses in the brain, omega-3 fatty acids also boost learning and memory. Though human brain is made up largely of fatty tissues and body cannot synthesize essential fatty acids, we have to rely on such omega-3s fatty acid rich diet to meet daily needs. Glucose provides the primary source of energy for the brain, which comes from carbohydrates.

Simple carbohydrates exacerbate low mood by creating spikes in blood sugar and have been shown to have effects on the brain. On the other hand complex carbohydrate releases glucose slowly, supply nutrition to the brain and body for long time. Natural sources of complex carbohydrates include whole-wheat products, barley, beans, soy, oats and wild rice. The amino acid tryptophan, a building block of protein also alters mood by producing the neurotransmitter serotonin. It is well proved that serotonin is associated with anxiety and depression. Lean protein sources; including eggs, beans, fish, turkey and chicken help keep serotonin levels maintained. Though complex carbohydrates are more important to facilitate the entry of tryptophan into the brain, reducing the symptoms of depression and anxiety and improving overall cognitive functioning.

Green leafy vegetables such as mustard greens, broccoli, spinach, turnip beets and lentils are high in folic acid. Deficiencies in folate as well as other vitamin B complex have been directly linked with higher rates of depression, anxiety, fatigue and insomnia. Broccoli contains selenium, a trace mineral that has an important role in maintaining immunity, reproduction and thyroid hormone metabolism. Some researchers found that low levels of selenium initiate depression, anxiety and fatigue. Other major sources of selenium include walnuts, brazil nuts, whole-grain products, onions, chicken, seafood. Fermented foods, such as yogurt with active cultures and certain pickled vegetables, contain probiotics (healthy bacteria) which have important role to reduce anxiety and stress disorders and also affect the neurotransmitter GABA. Eating too many processed foods may cause imbalance of the healthy and unhealthy bacteria in the gut.

Modern diet pattern has significantly changed from that of our ancestors. Busy lifestyles, food manufacturing and the affection and availability of processed foods are the reasons. Though most of us can make changes to overcome these influences like by increasing intake of fresh fruits and vegetables, avoiding processed foods. [52]

In a research study published in *Journal of Neurogastroenterology and Motility*, 2011 published that the probiotic, known as *Bifidobacterium longum* NCC3001 normalized the anxiety-like behavior in mice with infectious colitis. [53] Separate research also found the probiotic *Lactobacillus rhamnosus* had a significant effect on GABA (an inhibitory neurotransmitter) levels regulation in certain brain regions and lowered the stress-induced hormone corticoster one, which reduced depression and anxiety.

Just as neurons present in brain, also present in gut and release neurotransmitters like serotonin, which plays an important role in management of FGID. Serotonergic agents which may offer benefit to FD include the 5-HT_4 antagonists and 5-HT_7 agonists showed. [54]

CONCLUSION

Functional gastrointestinal diseases (FGID) are common in the world and account for more than 40% of clinical visits to gastroenterology clinics. However, treatment options for FGID have been limited. Only a few medications have been developed for the treatment of FGID and few or none are available in the market currently depending on where one lives. CAM and dietary modifications are more likely used as an adjunct to rather than instead of conventional drugs. CAM has received more and more attention among the patients with FGID and gastroenterologists. So from this review we include that CAM therapy, changes in life style and dietary modifications are the preferred treatment for patients with FGIDs.

REFERENCES

[1] Palma GD, Collins SM, Bercik P. Gut Microbes 2014;5(3):419–429.
[2] Hungin APS, Whorwell PJ, Tack J, Mearin F. Alimentary Pharmacol Therap 2003;17(5):643–650.
[3] Halder SLS, Locke GR, Schleck CD, Zinsmeister AR, Melton LJ, Talley NJ. Gastroenterol 2007;133(3):799–807.

[4] Woods MD, Critchley S. Family Practice 2000;17(2):108–113.
[5] Agarwal N, Spiegel BMR. Gastroenterol Clin North America 2011;40(1):11–19.
[6] Drossman DA, Thompson WG, Talley NJ, Jensen FP, Janssens J, Whitehead WE. Gastroenterol Int 1990; 3:159-172.
[7] Koloski NA, Talley NJ, Boyce PM. Am J Gastroenterol 2001;96:1340-49.
[8] Saito YA, Schoenfeld P, Locke GRI. Am J Gastroenterol 2002;97:1910-15.
[9] Longstreth GF, Wilson A, Knight K. Am J Gastroenterol 2003;98:600-7.
[10] Drossman DA. Gastroenterol 2006;130(5):1377-90.
[11] Toukan AU, Kamal MF, Amr SS, Arnaout MA, Abu-Romiyiyeh AS, Dig Dis Sci 1985;30(4):313-20.
[12] Tornblom H, Lindberg G, Nyberg B, Veress B. Gastroenetrol 2002;123(6):1972-9.
[13] Halvorson HA, Schlett CD, Riddle MS. Am J Gastroenterol 2006;101(8):1894-9.
[14] Spiller RC. Gastroenterol 2007;10(4):312-21.
[15] Neal KR, Hebden J, Spiller R. BMJ 1997;314(7083):150-3.
[16] Gwee KA, Graham JC, McKendrick MW, Collins SM, Marshall JS, Walters SJ, Read NW. Lancet 1996; 347(8995):150-3.
[17] Moayyedi P, Soo S, Deeks J, Delaney B, Harris A, Innes M, Oakes R, Wilson S, Roalfe A, Bennett C, Forman D. Cochrane Database Syst Rev 2000;2:CD002096.
[18] Talley NJ, Vakil N, Ballard ED, Fennerty MB. N Engl J Med 1999;341 (15):1106-11.
[19] Delaney BC, Qume M, Moayyedi P, Logan RF, Ford AC, Elliott C, MeNulty C, Wilson S, Hobbs FD. BMJ 2008;336(7645):651-4.
[20] Kassinen A, Krogius-Kurikka L, Makivuokko H, Rinttila T, Paulin L, Corander J, Malinen E, Apajalahti J, Palva A. Gastroenterol 2007;133(1):24-33.
[21] Maxwell PR, Rink E, Kumar D, Mendall MA. Am J Gastroenterol 2002;97 (1):104-8.
[22] Nobaek S, Johansson ML, Molin G, Ahrne S, Jeppsson B. Am J Gastroenterol 2009;95 (5):1231-8.
[23] Saggioro A. J Clin Gastroenterol 2004;38 (6 Supply):S104-6.
[24] Pimentel M, Chow EJ, Lin HC. Am J Gastrolenterol 2003;98 (2):412-9.
[25] Longstreth GF, Thompson WG, Chey WD, Haughton LA, Mearin F. Gastroenterol 2006;130(5):1480-91.
[26] Swedish Council on Technology Assessment in Health Care.
[27] Talley NJ, Owen BK, Boyce P, Paterson K. Am J Gastroenterol 1996;91:277–83.
[28] Calvert EL, Houghton LA, Cooper P, Morris J, Whorwell PJ. Gastroenterol 2002;123:1778–85.
[29] Haug TT, Wilhelmsen I, Svebak S, Berstad A, Ursin H. J Psychosom Res 1994;38:735–44.
[30] Brun R, Kuo B. Therap Adv Gastroenterol 2010;3:145–64.
[31] Lacy BE, Talley NJ, Locke GR. Aliment Pharmacol Ther 2012;36:3–15.
[32] Whitehead WE, Levy RL, Von Korff M. Aliment Pharmacol Ther 2004;20:1305–15.
[33] Nahin RL, Pontzer CH, Chesney MA. Health Aff 2005;24:991–93.
[34] Spanier JA, Howden CW, Jones MP. Arch Intern Med 2003;163:265–74.
[35] Langmead L, Rampton DS. Aliment Pharmacol Ther 2001;15:1239–52.
[36] Hussain Z, Quigley EMM. Aliment Pharmacol Ther 2006;23:465–71.
[37] Kong SC, Hurlstone DP, Pocock CY. J Clin Gastroenterol 2005;39:138–141.
[38] Lim B, Manheimer E, Lao I. Cochrane Database Syst Rev 2006;5:CD005111.
[39] Webb AN, Kukuruzovic R, Catto-Smith AG., Cochrane Database Syst Rev 2007;4:CD005110.
[40] Hussain Z, Quigley EMM. Aliment Pharmacol Ther 2006;23:465–71.
[41] Spanier JA, Howden CW, Jones MP. Arch Intern Med 2003;163:265–74.
[42] Langmead L, Rampton DS. Aliment Pharmacol Ther 2001;15:1239–52.
[43] Hoveyda N, Heneghan C, Mahtani KR. BMC Gastroenterol 2009, 9, 15.
[44] Liu J, Yang M, Liu Y. Cochrane Database Syst Rev 2006 1:CD004116.
[45] Madisch A, Holtmann G, Plein K. Aliment Pharmacol Ther 2004;19:271–79.
[46] So S, Moayyedi P, Deeks JJ. Cochrane Database Syst Rev 2005;2:CD002301.
[47] Atkinson W, Sheldon TA, Shath N. Gut 2004;53:1459–64.
[48] Dross man DA, Talley NJ, Whitehead WE, The Rome II Modular Questionnaire: investigator and respondent forms. In: Dross man DA, Corazziari E, Talley NJ, Thompson WG and Whitehead WE (eds) Rome II. The functional gastrointestinal disorders. 2006, vol. 2, McLean, VA, USA: Degnon Associates, 669–78.
[49] Paterson WG, Thompson WG, Vanner SJ. CMAJ 1999, 161, 154–160.
[50] http://chriskresser.com/the-healthy-skeptic-podcast-episode-9
[51] http://chriskresser.com/heal-your-gut-heal-your-brain/
[52] www.psychologytoday.com

[53] Bercik P, Park AJ, Sinclair D, Khoshdel A, Lu J, Huang X, Deng, Blennerhassett PA, Fahnestock M, Moine D, Berger B, Huizinga JD, Kunze W, Mclean PG, Bergonzelli GE, Collins SM, Verdu EF. Neurogastroenterol Motil 2011;23(12):1132–39.
[54] Ponti DF. J Gut 2004;53:1520–35.