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Beyond the Digestive System: Understanding Gut-Brain-Microbiome Axis in Irritable Bowel Syndrome

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ABSTRACT

IBS affects a significant number of people worldwide, particularly those under the age of 50, with women being twice as likely to be affected than men. Although the underlying pathophysiology of IBS is not yet fully comprehended, current research indicates that it could be related to the Gut-Brain Axis (GBA). This communication is vital to the intricate balance of the gastrointestinal system. Through this axis intestinal motility, secretion, and sensation are harmoniously regulated, resulting in efficient digestion and optimal nutrient absorption. Disturbance in the Gut-Brain Axis is linked to a broad spectrum of psychiatric and gastrointestinal disorders, including IBS. Managing IBS effectively requires a multidisciplinary approach, including dietary modifications, stress management techniques, medications, and psychological therapies. Proper management of IBS can lead to a healthy and fulfilling life for individuals affected by the disorder. Further studies are required to clarify the causes and development of most effective treatments for IBS.

Keywords: Functional Disorders, Gut-Brain-Axis, Irritable Bowel Syndrome, Microbiota

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INTRODUCTION:

IBS is a common functional disorder that has a significant impact on individuals and society. It is a widespread and burdensome disorder that impacts both individuals and society at large. With a high personal and socio-economic impact, it emphasizes the need for effective management and treatment of this condition. It affects millions of people worldwide with global prevalence of 9.2%.[1] The condition is prevalent in individuals under the age of 50, with women being twice as likely to be affected than men.[2] It is challenging to treat due to the wide range of symptoms and underlying physiological factors.[3] Experts believe that genetics, environmental factors, psychological factors, and changes in the gut microbiome contribute to the development of IBS. Despite the vast majority of studies being conducted, the precise mechanism that results in the development of IBS remains unknown, with much still to be learned about the factors contributing to its development. However, recent studies have suggested that IBS may be a disease of the Gut-Brain Axis (GBA), which is the mutual communication between the brain and the gut.[4] The axis has a vital role in the normal functioning of the gastrointestinal tract. It is involved in regulating intestinal motility as factors which are responsible for intestinal secretion and sensations. Disruptions in the GBA have been linked to a wide range of gastrointestinal and psychiatric disorders, including IBS.[5] In IBS, the gut-brain axis is thought to be dysregulated, leading to alterations in motility, secretion, and sensation within the GI tract, as well as contributing to the development of psychological symptoms and comorbidities. The complex and chronic nature of the disorders has debilitating effect on the quality of life of an individual. It is associated with psychological comorbidities such as anxiety, depression, and migraines.[6] The enteric nervous system (ENS) is responsible for regulating GI functions. The ENS communicates with the CNS through the vagus nerve and spinal afferent pathways. In IBS, there is evidence of increased visceral hypersensitivity, which may result from alterations in the processing of sensory information at both the peripheral and central levels.[7] Various hormones, such as cortisol, serotonin, and ghrelin, act as messengers between the gut and the brain. In IBS, alterations in the levels of these hormones have been reported. Serotonin is involved in the regulation of GI motility, secretion, and sensation,

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and dysregulation of serotonin signaling has been implicated in the pathophysiology of IBS. The gut microbes play an essential role in maintaining immune homeostasis and have been shown to influence the gut-brain axis. In IBS, there is growing evidence to suggest that disruptions in the gut microbiota, or dysbiosis, may contribute to the development and persistence of symptoms. Furthermore, increased intestinal permeability, or "leaky gut," has been observed in some IBS patients, which can lead to the translocation of bacteria and their metabolites, ultimately activating the immune system and triggering an inflammatory response. Given the complex nature of the disorder, managing IBS effectively requires a multidisciplinary approach. Treatment options may include dietary modifications, stress management techniques, medications, and psychological therapies. With proper management, people with IBS can lead a healthy and fulfilling life.[8] This literature review aims to summarize the current understanding of IBS as a gut-brain-axis disease, and to identify potential implications for the diagnosis, treatment, and management of this complex disorder.

METHODOLOGY:

A comprehensive literature search was conducted using electronic databases such as Google Scholar, PubMed, Scopus, SpringerLink, ScienceDirect and MEDLINE, using the keywords: “irritable bowel syndrome’’, “gut-brain axis”, “functional disorders”, “pathophysiology”, “gut-microbiota”, “dysbiosis”, “psychological-disorders”. To find related articles, we Boolean operators were used to combine the terms. For the review, only English-language articles published between 2018-2023 were included, allowing for an up-to-date and thorough examination of the latest research findings in the field. Studies were selected based on specific inclusion and exclusion criteria. There was no restriction on age, color, gender, or location in the selection of articles. Observational, clinical trial, cross-sectional, systematic, and conventional reviews were all included. Publications that were not written in English or used animals as study subjects were not considered for this analysis. The data extracted from the selected studies were synthesized using a narrative synthesis approach and were reported according to the PRISMA guidelines.

Pathophysiology of Irritable Bowel Syndrome

The underlying pathophysiology of IBS is complex and multifactorial. The precise mechanism that leads to the development of IBS is not yet fully understood.[9] The condition is likely to arise from a combination of genetic, environmental, and psychological factors. Additionally, there may be multiple subtypes of IBS, each with their own unique set of contributing factors.[10] Genetics is thought to be one of the contributing factors to the development of IBS. Research has shown that certain genetic variations may make individuals more susceptible to developing IBS.[11] Studies have identified several genes that may increase the risk of developing IBS. Genetic variations, such as those in the HLA-DQ and SCN5A genes, have been linked to an increased risk of IBS.[12] Genetic architecture of IBS appears to have commonalities with psychological disorder. Recent large-scale genome-wide association studies have discovered several risk loci that contain genes relevant to motor neuron function and nervous system activities.[13] Environmental factors, such as stress and gastrointestinal infections, may trigger the onset of IBS in those who are genetically predisposed to the condition.[14] Genetics may also play a role in determining the subtype of IBS that an individual develops, such as IBS with diarrhea or constipation. However, genetics alone is unlikely to be the sole cause of IBS, and it is likely that multiple factors contribute to the development of the condition.[15] Dysregulated gastrointestinal motility is thought to be one of the key factors contributing to the development of IBS, highlighting the intricate interplay between various physiological processes in the pathogenesis of this condition. Individuals with IBS may experience more frequent or forceful contractions of the muscles in the digestive tract, resulting in altered bowel movements and abdominal pain.[16] Studies have shown that individuals with a history of Psychiatric comorbidities, such as depression, anxiety, and other conditions may be at a higher risk of developing IBS.[17] Additionally, stress and other emotional factors may trigger or exacerbate IBS symptoms in some individuals.[18] Individuals with IBS may have altered intestinal permeability which allows toxins or bacteria to enter the bloodstream and cause inflammation and other symptoms.[19] SIBO and dysbiosis may contribute to the development of IBS.[20] Chronic infection, post-infectious autoimmunity, sensitivity to specific food items, alteration of gut flora, abnormal brain-gut interface, malabsorption of ingested food, food intolerance, increased reactivity after an infection, bile acid malabsorption, microcolitis, celiac disease, and inflammation of the intestinal mucosa are also potential factors that could contribute to the development of IBS.[9]

Gut Brain Microbiome Axis

The complex communication between gut microbiota and central nervous system through neuronal, endocrine, and immune signaling constitutes gut-brain-microbiome axis.[21] The first five years of an individual are vital for the development and establishment of gut microbiota, the immune system, and psychological changes. Alteration in gut microbiota can compromise the immune system. It plays a crucial role in the pathophysiology and symptomatology of the IBS. Alterations in gut microbiota, intestinal permeability, immune activation, and neurotransmitter production can significantly impact the gut-brain axis, thereby influencing the development and severity of IBS symptoms. Studies have demonstrated that individuals with IBS exhibit altered gut microbiota composition, which is associated with increased abdominal pain and altered bowel habits.[5] Certain factors like stress and gene activation in susceptible individuals will allow the nervous system to

alter the gut microbiome by modifying gut motility and enteric nervous system response. Studies have shown that the alteration of gut microbiota plays a crucial role in the development of IBS.[22]

Dysbiosis and Small Intestinal Bacterial Overgrowth (SIBO) have emerged as complex and multifaceted contributors to the pathogenesis of IBS, with potential links to a range of factors such as increased intestinal permeability, dysmotility, chronic inflammation, autoimmune disorders, and altered neuronal activity in the enteric and central nervous systems. Disruption of the gut flora is linked to certain neuropsychological symptoms. SIBO is highly prevalent in IBS. Diagnosis of SIBO is done through a small bowel aspirate culture or a positive hydrogen lactulose or glucose breath test. Constipation-predominant IBS has been associated to the organism found in a positive methane breath test.[23] Metabolites such as short-chain fatty acids (SCFAs) regulate the gut-brain-microbiome axis.[24] Inflammatory cytokine synthesis and T-cell and neutrophil migration are facilitated by SCFAs which leads to neuroinflammation. Butyrate is a gut microbiota derivative SCFAs responsible for nerve plasticity and memory. Enteroendocrine cells of the gut epithelium are stimulated by SCFAs, which then have impact on the ENS and vagal innervation.[25] The gut microbiota, a community of diverse microorganisms that resides in the gastrointestinal tract, is now recognized as a key player in the intricate interplay between the brain and the gut. When the gut microbiota is out of balance, it can interfere with the proper functioning of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), leading to a host of issues such as maladaptive coping, comorbid anxiety and depression, and changes in pain signaling by neurons. The growing body of evidence supporting the gut-brain-microbiome axis underscores the critical role of the gut microbiota in IBS pathogenesis.[26] Several bacteria have been identified as the culprits in studies linking increased cytokine production to the intestinal mucosa. IBS individuals who have elevated cytokine levels, especially IL6, have an increased risk of developing new-onset depression.[27] Patients with IBS exhibit a gut microbiota that differs from that of healthy individuals, with higher alpha diversity indices observed in IBS patients. Studies have found a positive association between dietary fiber intake and alpha diversity indices in individuals with IBS. This highlights the importance of a high-fiber diet in promoting a healthy gut microbiota and potentially alleviating symptoms of IBS.[28]

Patients with IBS have a low density of enteroendocrine cells in their intestines. These cells play a significant role in regulating gastrointestinal motility, secretion, absorption, and visceral sensitivity. The low density of these cells in patients with IBS is believed to contribute to gastrointestinal dysmotility, abnormal absorption/secretion, and visceral hypersensitivity, which are common symptoms of IBS. Understanding the role of enteroendocrine cells in IBS may help in developing new treatment approaches for this condition.[29]

Association of Psychological Disorders with IBS

Gaining valuable insights into IBS may involve analyzing patients based on factors other than stool form and frequency. Studies have found that subgroups with high psychological comorbidity had a greater percentage of participants with severe IBS symptoms, perceived stress, and gastrointestinal symptom-specific anxiety.[30] Studies have reported that around one third of IBS patients exhibit psycho-social comorbidities, with approximately 30% to 50% experiencing anxiety and feelings of hopelessness, thirty percent presenting with mood disorders, and rest experiencing suicidal ideation.[31] Dysregulation of the brain-gut axis is mediated by various neurotransmitters which are responsible for pathophysiology of IBS. These chemical messengers facilitate communication between the CNS and the ENS to modulate gastrointestinal motility, secretion, and sensation, which are all implicated in IBS. Norepinephrine, Dopamine, GABA and Glutamate are involved in the regulation of GI motility, blood flow as well as in visceral pain. Alteration in neurotransmitters signaling have been implicated in the development of symptoms of IBS. Studies have found that there is a strong link between gastrointestinal symptom-specific anxiety, somatization, and symptom severity in patients with irritable bowel syndrome (IBS). It is crucial to assess both gastrointestinal and extra-intestinal symptoms to better understand the severity of symptoms in IBS patients.[32] Patients with IBS commonly exhibit psychological changes. The severity of GI symptoms is significantly linked to multiple factors, including physical exhaustion, anxiety related to gastrointestinal problems, perceived stress, pain catastrophizing, and trait anxiety. The greater the number of psychological alterations experienced by an IBS patient, the more intense their GI symptoms are expected to be.[33] The number of psychological comorbidities has a strong correlation with the severity of IBS symptoms at baseline. People with more psychological comorbidities tend to consult gastroenterologists more frequently, try more treatments, and experience more severe IBS symptoms, including persistent abdominal pain and interference with daily activities. With each incremental increase in psychological comorbidity, individuals diagnosed with IBS based on Rome IV criteria are more likely to experience a worsening prognosis.[34]

IBS patients are more susceptible to psychological co-morbidities than the general population. Patients with two or three psychological co-morbidities are at a significantly higher risk of experiencing negative outcomes, such as flare-ups, hospitalization, or surgery. The cumulative impact of psychological factors on IBS can worsen disease progression, regardless of the patient's biochemical state. Therefore, addressing both physiological and psychological aspects of

the disease is crucial for managing and improving patient outcomes.[35]

The relationship between stress and IBS flares is complex and multifactorial. One proposed mechanism is that stress can activate the HPA axis, leading to the release of stress hormones such as cortisol, which can affect gut motility, secretion, and sensitivity. Additionally, stress can lead to changes in the gut microbiota composition and function, which in turn can influence the gut-brain axis and contribute to IBS symptoms. Interestingly, recent research has suggested that the gut microbiota may play a role in modulating the stress response, highlighting the intricate interplay between stress, the gut microbiota, and IBS.[36]

There is a correlation between psychological stress, depression, and dysbiosis, which can lead to the development of IBS.[37] Research studies have reported reduction of certain microbes in individuals experiencing chronic psychological stress. Similarly, patients with depression have been found to exhibit an overproduction of specific microbes. Moreover, individuals with major depressive disorder have been shown to have an elevated presence of specific species of gram-negative microbes as well as an altered ratio of Bacteroidetes.[38]

The neurotransmitter serotonin has an important role in a wide variety of physiological activities, including gastrointestinal secretion and peristalsis, vasoconstriction, behavior, and brain processes. It is a vital neurotransmitter in the regulation of GI motility, secretion, and sensation. A major percentage of the body's serotonin is found in the GI tract. In IBS, there is altered serotonin signaling, leading to changes in gut motility and sensation. As compared to healthy persons, those who suffer from irritable bowel syndrome have been reported to have lower mucosal levels of 5-HT (5-hydroxytryptamine) and greater systemic levels of kynurenic acid (KYNA). It's thought that the high prevalence of mental health issues in IBS patients is connected to the high diversity of gut flora.[39] Large amount of pyruvate produced by certain gut microbes has toxic effects on gut epithelium.[25]

Treatment Modalities of IBS

To manage IBS, a combination of lifestyle changes, psychological counseling, and medication adherence is necessary. Effective strategies include modifying dietary habits, avoiding trigger foods, and using stress management techniques like cognitive-behavioral therapy, hypnotherapy, and relaxation methods. Various therapeutic approaches, including probiotics, prebiotics, antibiotics, and fecal microbiota transplantation (FMT) for the treatment of IBS.[5]

Medications like antibiotics, antispasmodics, laxatives, and antidepressants can also be helpful. The neurotransmitters like noradrenaline, serotonin, and dopamine can play a role in pain relief mechanisms and psychopharmacology. Both primary and secondary neuromodulator treatment options are available for managing abdominal pain associated with IBS.[17] Additionally, complementary, and alternative medicine treatments like herbal remedies, and acupuncture may be beneficial, but it's crucial to keep in mind that their effectiveness varies depending on the individual and cannot be generalized.[40] The management of IBS has made progress in recent times with the emergence of new medications such as serotonin synthesis inhibitors LX-1031, ramosetron, spherical carbon adsorbent, benzodiazepine receptor modulators, and peripheral k-agonists. These advances have the capability to alleviate symptoms and enhance the well-being of individuals who suffer from IBS.[41]

CONCLUSION:

The majority of individuals suffering from IBS complain of chronic and debilitating gastrointestinal symptoms. Although it is not a fatal disorder, it has a negative impact on the quality of life of the patients suffering from it. The chronic nature of the disorder creates a great economic burden on the health system. Multiple hereditary and environmental factors have been identified which contribute to the development of this complex disorder. In terms of its precise pathophysiology, IBS is still not very well understood; however, recent studies show that it may be a dysregulation of the Gut-Brain-Microbiome Axis. In patient with IBS, the communication between gut microbe and central nervous system is disrupted by either a genetic triggering mechanism or through an environmental factor leading to development of gastrointestinal symptoms by affecting the motility, secretion, and sensation of GI tract. In addition, mental comorbidities such as depression and anxiety, as well as emotional factors, may either be the cause of IBS in the first place or may exacerbate symptoms in susceptible individuals. Management of IBS with conventional therapies is either not effective or has very low effect in improving the symptoms. There is a need for development of innovative therapeutic techniques which may entail targeting the gut microbiome. Better understanding of the gut-brain axis and its mechanisms will help in developing targeted therapeutic interventions that address the root causes of IBS. Manipulating gut microbiota through the use of prebiotics, probiotics, and dietary modifications has shown promising results in alleviating IBS symptoms. Additionally, treatments targeting the central nervous system have been found to improve the psychological well-being and overall quality of life in individuals with IBS. The use of antidepressants is a potential treatment option which makes use of knowledge of gut-brain-microbiome axis. Considering multifaceted nature of IBS, further studies are required to get a better knowledge of pathophysiology as well as to develop treatment option for disorder so that people who suffer IBS have a better chance of leading a life that is both healthy and satisfying. A better understanding of the gut-brain axis is crucial for the improved management of IBS disease. Furthermore, elucidating the role of the gut-brain axis in IBS may pave the way for the discovery of novel biomarkers

that can aid in the diagnosis and monitoring of the disease. This would enable clinicians to provide more personalized and effective treatment plans for patients suffering from IBS. By unravelling the intricate communication between the GI tract and the CNS, we can develop targeted therapeutic interventions, identify novel biomarkers, and ultimately enhance the quality of life for individuals living with IBS.

Authors Contribution:
Rashid Ali Khosa: Topic Selection, Introduction, Literature Review, Conclusion
Syed Ijaz Hussain Zaidi: Abstract Writing, Methodology
Muhammad Sajid Abbas Jaffri: Pathophysiology, Clinical Diagnosis
Shahid Mehmood: Treatment Modalities
Allah Bakhsh: Gut-Brain-Microbiome Axis

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