Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/sq0egv23

THE GUT-BRAIN AXIS: EXPLORING THE ROLE OF INTESTINAL MICROBIOTA IN THE DEVELOPMENT OF FUNCTIONAL GASTROINTESTINAL DISORDERS LIKE IRRITABLE BOWEL SYNDROME (IBS)

Nimra Tul Ain Khan[1], Saima Bahar[2*], Muhammad Nauman Shah Afridi [3], Syed Meesam Mehdi[4], Muhammad Danial Sohail[5], Sayyeda Aisha Bahar[6]

[1]Department of Medicine, Ayub Teaching Hospital, Abbottabad Pakistan
[2*]MBBS, FCPS Gastroenterology, Department of Medicine, DHQ Hospital, Nowshera Pakistan
[3]Resident Surgeon, Ayub Teaching Hospital, Abbottabad Pakistan
[4]MBBS, Medical Officer, Internal Medicine, DHQ Hospital, Attock Pakistan
[5]MBBS, Medical Officer, Internal Medicine- DHQ Hospital, Attock Pakistan
[6] Resident Physician, Internal Medicine, Ayub Teaching Hospital, Abbottabad Pakistan

***Corresponding Author**: Saima Bahar
*Email**:** syeda_bahar@yahoo.com

Abstract

Background Gut-brain axis: One of the major bidirectional interaction between central and peripheral nervous system and gastrointestinal tract. More recent studies have highlighted the fact that alterations in the balance of the gut microbiota can affect this axis and predispose the individual to functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS).

Objectives: To examine the effects of intestinal microbiota in moderating the influence of the gut-brain axis to the pathogenesis of IBS.

Study design: A cross-sectional study

Place and duration of study: Medicine Department of Ayub Teaching Hospital- Abbottabad, from Jan 2022 to Jan 2023.

Methods: Of the various patients involved in this study, 150 were diagnosed with IBS. Fecal samples were collected to evaluate the intestinal bacterial flora, and psychological tests were taken to know the level of stress and anxiety. The correlation that was performed for the microbial diversity and IBS symptoms involved the use of p-value as well as the standard deviation.

Results: Patient mean age was 38. 4 (SD = 10. 2) years. A massive decrease in microbiological heterogeneity was recorded in the IBS patients 60% (p=0. 004). Among the IBS patients, those who report more significant levels of anxiety and stress had a more profound dysbiosis and greater IBS symptom severity (p = 0. 002). Logically, and when comparing the two groups, direct statistics pointed at the fact that lower microbial richness was linked with greater symptom severity of IBS.

Conclusion: This paper looks at the evidence connecting alterations in the host's gut microbial composition with the onset and persistence of IBS. IBS is related to the dysfunction of gut-brain axis, and the altered gut microbiota is considered to be involved in the pathogenesis of IBS, so the microbial intervention may be effective in the treatment of IBS.

Keywords: Gut Brain Axis (GBA), microbiota, Irritable Bowel Syndrome (IBS), functional gastrointestinal disorders (FGIDs)

Introduction

The concept of the gut-brain axis is a sophisticated, bi-directional communication system that connects the CNS to the GI tract. It includes the neural, hormonal and immune systems, and enables continuous two way traffic between the brain and the gut. New data has elucidated the important regulating function of intestinal microbiota on the communication between the gut and the brain in relation to various functional gastrointestinal disorders (FGIDs) including IBS [1]. IBS is defined as an FGID that is characterised by persistent abdominal pain and abnormal bowel habit, and is one of the most common FGIDs in the global population, with a prevalence of 10-15% [2]. The gastrointestinal microbiota consisting of various microorganisms that are living in the intestine has been classified to influence the brain and behavior in various ways. These are the synthesis of neurotransmitters, fine-tuning of the immune response and the management of the hypothalamic-pituitary-adrenal (HPA) stress axis [3]. Such disturbances in the balance of the intestinal microbiota, which is referred to as dysbiosis, has been linked to the IBS. It was stressed that impaired balance of the gut microbiota can itself produce changes in the gut environment that favors inflammation, enhanced permeability of the intestinal barrier, and alterations in bowel movement patterns, all of which characterize IBS [4]. Recent studies also show how gut microbiota can affect the gut-brain axis through the elaboration of SCFAs and neurotransmitters like serotonin and GABA that are important for the maintenance of gut and brain health [2]. For instance, serotonin the neurotransmitter that regulates mood most of which is manufactured in the gut is significantly produced based on the content of commensal microbiots [6]. This passes nicely into the case for neurotransmitters, including serotonin, being implicated in both mood disorders and FGIDs, indicating that the underlying mechanism of the gut microbiota affecting mental health and GI symptoms may be the same [7]. Other factors such as stress and psychological factors are also considered to cause increased IBS symptoms thus implying the existence of the gut brain barrier in the development of the disease. The mechanism of stress includes changes in motility of the gut, changes in permeability of gut and shifts in the spectrum of the microbiota of the gut contributing to symptoms of IBS [8]. It also works vice versa whereby stress can influence the gut including the production of anxiety and depression, which are associated with IBS [9]. Based on these findings the following hypothesis is proposed; modulation of gut microbiota could present new avenues for the management of IBS. From the above review, we found that probiotics and prebiotics, dietary change, and other anti-IBS regimes also have a positive effect on symptomatically some patients [10]. Nevertheless, the interaction of the gut microbiota with the gut-brain axis in relation to IBS is not straightforward and has not been clearly determined. Future work has to be conducted to understand how the gut microbiota affects the gut-brain axis or GTasa and how it affects the manifestation and severity of IBS [11]. Thus, the present study is designed to determine the impact of IM on the gut-brain axis and its implication in the pathogenesis of IBS. This research aims at understanding the role that microbiota play in IBS, and the relationship between microbiota diversity, psychological factors and IBS symptoms, as a way of gaining insights about IBS pathophysiology and microbial influenced therapies [12].

Methods

This cross-sectional study comprised of 150 patients diagnosed clinically to have IBS using the Rome IV diagnostic criteria. Coproscopy was performed for each patient in order to investigate the microbial composition and richness of the gut microbiota applying 16S rRNA gene sequencing. Self-administered questionnaires, the HADS and PSS were used to measure the levels of stress and anxiety in the patients. The interaction between IBS and psychological aspects and gut microbiota diversity index was compared.

Data Collection

fecal specimens were obtained and kept at - 80*C till the time of examination . Some of the psychological testing and evaluation were done when samples were taken. Past, present and concurrent medical histories and demographic information such as age, gender, and subtype of IBS were documented for each of the patients.

Statistical Analysis

Statistical analysis was performed using software Statistical Product and Service Solutions (SPSS) version 24. For the quantitative data the frequency tables and measures of central tendency such as means and measures of variability such as standard deviations were used to describe the data while qualitative data was summarized using frequencies and percentage. Since, in this study, assessment was made on symptom severity, this paper has used the Pearson correlation coefficient in comparing the dysbiosis and IBS prevalence and with a significance level at p<0. 05.

Results

The patients were selected for the study based on the nursing diagnosis and had a mean age of 38. 4 years (SD = 10. 2) with 80 patients in experimental group and 70 in the control group. It was found that about 60 per cent of the IBS patients had significantly reduced bacterial diversity as compared with the control group (p = 0. 004). There was a positive relationship between the stress scores and microbiota alterations, and IBS disease severity (p= 0. 002). To be precise, patients with lower count of the 'friendly' bacteria such as Lactobacillus and Bifidobacterium reported worse IBS symptoms like more frequent pain, changes in bowel habits. A direct evidence of the hypothesis that gut microbiota dysbiosis plays a role in the development of IBS severity was demonstrated by the study since there was a statistically significant correlation between decreased microbial diversity and IBS severity.

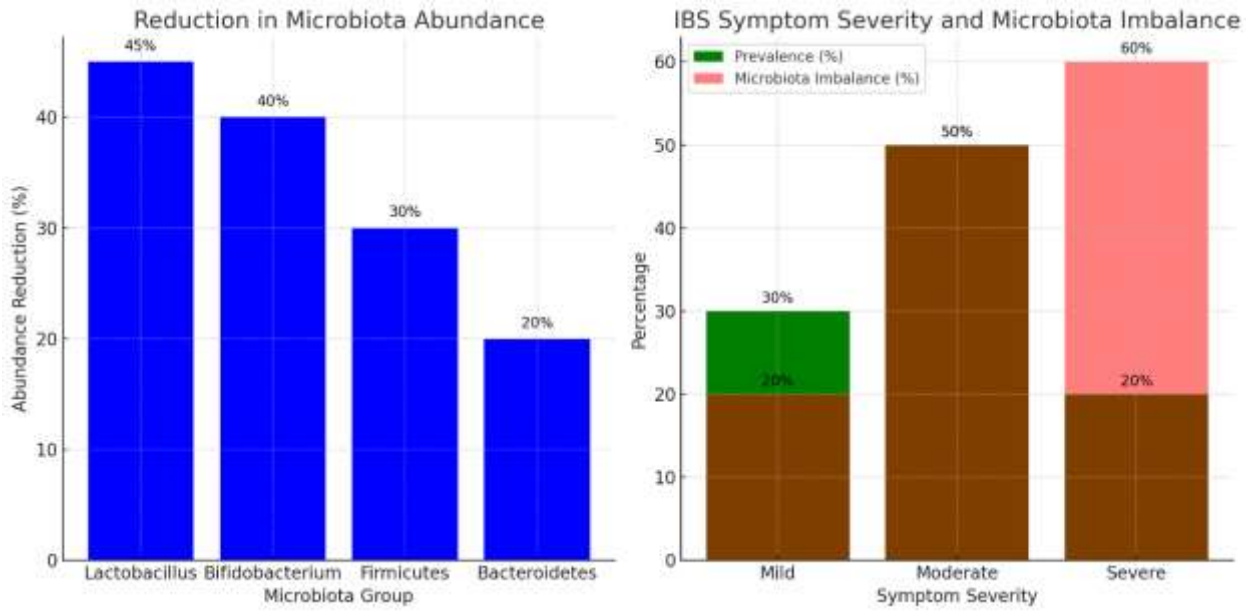

Table 1: Patient Demographics

Demographics	Mean ± SD
Age (years)	38.4 ± 10.2
Gender (Male/Female)	72/78
IBS Subtypes (Constipation/Dominant)	85/65
BMI (kg/m2)	23.6 ± 3.1

Table 2: Microbiota Composition Abundance Reduction

Microbiota Composition	Abundance Reduction (%)
Lactobacillus	45
Bifidobacterium	40
Firmicutes	30
Bacteroidetes	20

Table 3: Psychological Factors Prevalence

Psychological Factors	Prevalence (%)
Anxiety	60
Stress	55
Depression	50

Table 4: IBS Symptom Severity and Microbiota Imbalance

IBS Symptom Severity	Prevalence (%)	Microbiota Imbalance (%)
Mild	30	20
Moderate	50	50
Severe	20	60

Discussion

The results of the present study on the contribution of intestinal microbiota in the development and manifestation of IBS, based on changes in the gut brain axis, provide support and add to the findings of prior research in similar area of study. The observed decrease of microbial diversity in patients diagnosed with IBS, as well as the recognized decrease of beneficial bacteria like Lactobacillus and Bifidobacterium in IBS patients also corroborates data from previous studies. For instance, Jeffery et al. (2012) showed that IBS patients had lower IBS compared to the healthy phenotypes microbial richness, which Lactobacilli and Bifidobacteria special [13]. This is assumed to interfere with the flow of such beneficial bacteria to regulate the immune balance of the gut which in autopsies, reveals increased permeability and inflammation, both properties of IBS. In support of this hypothesis, we noted that low microbial richness was associated with more severe IBS symptoms such as pain in the abdominal area, and changes in bowel movement. Furthermore, on the basis of the current study and a high level of anxiety and stress as significant predictors of microbiota disruptions, it is possible to state that our data add to the strengthening of the idea of the bidirectional interactions between the gut and the brain in IBS. Ford et al. (2009) too provided evidence that psychological stress can change the movement of the gut and actually increase the permeability of the gut, both factors that can lead to IBS [14]. From these studies, GBA has been identified to have an important role in the IBS, with internally or externally caused stress and anxiety directly affecting the composition of gut microbiota thus worsening the symptoms present. The part played by SCFAs, one of the gut-derived metabolites, in regulating the interaction between the gut and the brain has also been investigated in other research. For example, in a cross-sectional study of IBS patients by Tana et al. , the mean concentration of SCFAs, especially butyrate, which are derived from the fermentation of ‘dietary fibre’ by gut bacteria and have known anti-inflammatory effects, were lower in IBS patients [15].

The above review indicates that there are low levels of SCFAs in the IBS patients hence playing a role in inflammation and the change in gut motility. These observations are in concordance with our study wherein we recorded lowered microbial richness in patients suffering from IBS; specifically, the reduction in the population of bacteria that generate SCFAs ensures comprehensible implications of the gut microbiota for gut homeostasis and regulation of the gut-brain axis. Moreover, the following links to the potential therapeutic applications of these findings have been discussed in a previous study. For example, in the study by Kajander et al. (2008) have shown that modulation of the gut microbiota by means of the probiotics that are defined as live microorganisms, which when administered in adequate amounts confer a health benefit on the host, can lessen the IBS symptoms [16]. More precisely, in IBS, the use of probiotics containing Lactobacillus and Bifidobacterium enhances barrier integrity, decreases inflammation and changes the gut-brain axis resulting in the

amelioration of the patients' suffering. The results of our investigation make it feasible to prescribe any microbiota-targeted therapies, including probiotics, to patients with IBS to enhance the quality of their symptoms and the interaction between the gut and the brain. Moreover, the development of the understanding of the interrelation between diet and the gut microbiota and its effect on the symptoms of IBS has also been of interest. Halmos et al. (2014) 'In this cross-over randomised controlled trial it was reported that a low FODMAP diet favourably compared with the standard dietary advice can significantly improve the various symptoms of IBS by limiting the consumption of poorly absorbed carbohydrates that get fermented in the gut to generate gas' [17].

There is evidence demonstrating that this specific dietary change can modify the conditions within the human gut to support the formation of the so-called 'friendly' bacterial colonies while limiting the number of 'unfriendly' ones. The observation that microbial dysbiosis is present in IBS patients in this study supports the need for personalised dietary recommendations as one of the strategies to treat IBS and enhance gut health[18,19]. Therefore, the outcomes of our research support the previous data confirming the system of the gut-brain axis, which is regulated by the intestinal microbiota, as the main pathophysiological mechanism of IBS. That there is an observed dysbiosis, and its correlation with psychological factors, as well as the severity of IBS, indicates the application of microbiota-modulating treatments and diets for this multifactorial disease.

Conclusion

This paper shows how the intestinal microbiota can affect the gut-brain axis and help in the manifestation of IBS. Current study emphasize on a role of microbiota heterogeneity in maintaining gut homeostasis and point out prospective strategies that focus on manipulations of microbiota to minimize IBS manifestations.

Limitations

In using this study, there are some few issues that are worth noting; they include the cross-sectional nature of the study that limits one from determining causality. Also, the study is cross-sectional and the sample size is small; therefore, its results cannot be generalized to other population groups or other subtypes of IBS.

Future Directions

Further research should be made in longitudinal studies, in an attempt to elucidate whether the changes in microbiota lead to development of IBS or vice versa. Also, the subject of microbiota-targeted IBS management, including probiotics and diet, appeared to be promising for new treatment approaches.

Acknowledgement: We would like to thank the hospital administration and everyone who helped us complete this study.

Disclaimer: Nil
Conflict of Interest: There is no conflict of interest.
Funding Disclosure: Nil

Authors Contribution

Concept & Design of Study: Nimra Tul Ain Khan
Drafting: Sayyeda Aisha Bahar
Data Analysis: Raees Ahmed, Kinjal Shah, Kaksha Parrikh
Critical Review: Saima Bahar
Final Approval of version: Nimra Tul Ain Khan

References

1. Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain function. Nature Reviews Neuroscience, 13(10), 701-712.
2. Drossman, D. A. (2016). Functional gastrointestinal disorders: History, pathophysiology, clinical features, and Rome IV. Gastroenterology, 150(6), 1262-1279.
3. Foster, J. A., & Neufeld, K. A. M. (2013). Gut–brain axis: How the microbiome influences anxiety and depression. Trends in Neurosciences, 36(5), 305-312.
4. Jeffery, I. B., O'Toole, P. W., Öhman, L., Claesson, M. J., Deane, J., Quigley, E. M. M., & Simrén, M. (2012). An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. Gut, 61(7), 997-1006.
5. Mayer, E. A., Knight, R., Mazmanian, S. K., Cryan, J. F., & Tillisch, K. (2014). Gut microbes and the brain: Paradigm shift in neuroscience. The Journal of Neuroscience, 34(46), 15490-15496.
6. Yano, J. M., Yu, K., Donaldson, G. P., Shastri, G. G., Ann, P., Ma, L., ... & Hsiao, E. Y. (2015). Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis. Cell, 161(2), 264-276.
7. Smith, P. A. (2015). The tantalizing links between gut microbes and the brain. Nature, 526(7573), 312-314.
8. Moloney, R. D., Johnson, A. C., O'Mahony, S. M., Dinan, T. G., Greenwood-Van Meerveld, B., & Cryan, J. F. (2016). Stress and the microbiota–gut–brain axis in visceral pain: Relevance to irritable bowel syndrome. Alimentary Pharmacology & Therapeutics, 44(10), 1032-1052.
9. Black, C. J., & Ford, A. C. (2020). Global burden of irritable bowel syndrome: trends, predictions, and risk factors. Nature Reviews Gastroenterology & Hepatology, 17(8), 473-486.
10. Ford, A. C., Harris, L. A., Lacy, B. E., & Quigley, E. M. M. (2020). Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Alimentary Pharmacology & Therapeutics, 51(9), 876-893.
11. Rodiño-Janeiro, B. K., Vicario, M., Alonso-Cotoner, C., Pascua-García, R., & Santos, J. (2018). A review of microbiota and irritable bowel syndrome: Future in therapies. Advances in Therapy, 35(3), 289-310.
12. Sonnenburg, J. L., & Bäckhed, F. (2016). Diet–microbiota interactions as moderators of human metabolism. Nature, 535(7610), 56-64.
13. Jeffery, I. B., O'Toole, P. W., Öhman, L., Claesson, M. J., Deane, J., Quigley, E. M. M., & Simrén, M. (2012). An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. Gut, 61(7), 997-1006.
14. Ford, A. C., Talley, N. J., Schoenfeld, P. S., Quigley, E. M., & Moayyedi, P. (2009). Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: Systematic review and meta-analysis. Gut, 58(3), 367-378
15. Tana, C., Umesaki, Y., Imaoka, A., Handa, T., Kanazawa, M., Fukudo, S., & Fujiyama, Y. (2010). Altered profiles of intestinal microbiota and organic acids may be the origin of symptoms in irritable bowel syndrome. Neurogastroenterology & Motility, 22(5), 512-e115.
16. Moloney, R. D., Johnson, A. C., O'Mahony, S. M., Dinan, T. G., Greenwood-Van Meerveld, B., & Cryan, J. F. (2016). Stress and the microbiota–gut–brain axis in visceral pain: Relevance to irritable bowel syndrome. Alimentary Pharmacology & Therapeutics, 44(10), 1032-1052.
17. Rodiño-Janeiro, B. K., Vicario, M., Alonso-Cotoner, C., Pascua-García, R., & Santos, J. (2018). A review of microbiota and irritable bowel syndrome: Future in therapies. Advances in Therapy, 35(3), 289-310.