Gut microbiota and its implications for psychiatry: A review of 3 studies

Irene Pastis, MD, Sy Atezaz Saeed, MD, and Purushothaman Muthukanagaraj, MD

Sy Atezaz Saeed, MD
Department Editor

Increasing evidence links mental health outcomes to the gut microbiome

The "human microbiota" describes all microorganisms within the human body, including bacteria, viruses, and eukaryotes. The related term "microbiome" refers to the complete catalog of these microbes and their genes.[1] There is a growing awareness that the human microbiota plays an important role in maintaining mental health, and that a disruption in its composition can contribute to manifestations of psychiatric disorders. A growing body of evidence has also linked mental health outcomes to the gut microbiome, suggesting that the gut microbiota can modulate the gut-brain axis.[2]

Numerous neurotransmitters, including dopamine, serotonin, gamma-aminobutyric acid, and acetylcholine, are produced in the gastrointestinal (GI) tract, and our diet is vital in sustaining and replenishing them. At the same time, our brain regulates our GI tract by secretion of hormones such as oxytocin, leptin, ghrelin, neuropeptide Y, corticotrophin-releasing factor, and a plethora of others. Dysregulation of this microbiome can lead to both physical and mental illnesses. Symptoms of psychiatric disorders, such as depression, psychosis, anxiety, and autism, can be a consequence of this dysregulation.[2]

Our diet can also modify the gut microorganisms and therefore many of its metabolic pathways. More attention has been given to pre- and probiotics and their effects on DNA by epigenetic changes. One can quickly start to appreciate how this intricate crosstalk can lead to a variety of pathologic and psychiatric problems that have an adverse effect on autoimmune, inflammatory, metabolic, cognitive, and behavioral processes.[2,3]

Thus far, links have mostly been reported in animal models, and human studies are limited.[4] Researchers are just beginning to elucidate how the microbiota affect gut-brain signaling in humans. Such mechanisms may include alterations in microbial composition, immune activation, vagus nerve signaling, alterations in tryptophan metabolism, production of specific microbial neuroactive metabolites, and bacterial cell wall sugars.[5] The microbiota-gut-brain axis plays a part in regulating/programming the hypothalamic-pituitary-adrenal (HPA) axis throughout the life span.[3] The interactions between the gut microbiome, the immune system, and the CNS are regulated through pathways that involve endocrine functions (HPA axis), the immune system, and metabolic factors.[3,4] Recent research focusing on the gut microbiome has also given rise to international projects such as the Human Microbiome Project (Human Microbiome Project Consortium, 2012).[3]

Several studies have looked into psychiatry and inflammatory/immune

Dr. Pastis is Clinical Assistant Professor, Department of Psychiatry, East Carolina University Brody School of Medicine, Greenville, North Carolina. Dr. Saeed is Professor and Chair, Department of Psychiatry and Behavioral Medicine, East Carolina University Brody School of Medicine, Greenville, North Carolina. Dr. Muthukanagaraj is Assistant Professor, Department of Internal Medicine and Psychiatry, East Carolina University Brody School of Medicine, Greenville, North Carolina.

Disclosures
The authors report no financial relationships with any companies whose products are mentioned in this article, or with manufacturers of competing products.

pathways. Here we review 3 recent studies that have focused on the gut-brain axis (***Table***,[6-8] ***page 42***).

1. Rudzki L, Pawlak D, Pawlak K, et al. Immune suppression of IgG response against dairy proteins in major depression. BMC Psychiatry. 2017;17(1):268.

The aim of this study was to evaluate immunoglobulin G (IgG) response against 40 food products in patients with depression vs those in a control group, along with changes in inflammatory markers, psychological stress, and dietary variables.[6]

Study design

- N = 63, IgG levels against 44 food products, cortisol levels, tumor necrosis factor (TNF)-alpha, interleukin 6 (IL-6), and IL-1 beta levels were recorded. The psychological parameters of 34 participants with depression and 29 controls were compared using the Hamilton Depression Rating scale, (HAM-D-17), Perceived Stress scale, and Symptom Checklist scale. The study was conducted in Poland.

Outcomes

- Patients who were depressed had lower IgG levels against dairy products compared to controls when there was high dairy consumption. However, there was no overall difference between patients and controls in mean IgG concentration against food products.
- Patients who were depressed had higher levels of cortisol. Levels of cortisol had a positive correlation with HAM-D-17 score. Patients with depression had lower levels of TNF-alpha.

Conclusion

- Patients with depression had lower levels of IgG against dairy protein. Patients with depression had high cortisol levels but decreased levels of TNF-alpha, which could explain an immune suppression of IgG in these patients. There were no differences in IL-6 or IL-1beta levels.

Hypercortisolemia is present in approximately 60% of patients with depression. Elevated cortisol levels have a negative effect on lymphocyte function. B-lymphocytes (CD 10+ and CD 19+) are sensitive to glucocorticoids. Studies in mice have demonstrated that elevated glucocorticoid levels are associated with a 50% decrease in serum B-lymphocytes, and this can be explained by downregulation of c-myc protein, which plays a role in cell proliferation and cell survival. Glucocorticoids also decrease levels of protein kinases that are vital for the cell cycle to continue, and they upregulate p27 and p21, which are cell cycle inhibitors. Therefore, if high cortisol suppresses B-lymphocyte production, this can explain how patients with depression have low IgG levels, since B-lymphocytes differentiate into plasma cells that will produce antibodies.[6]

Depression can trigger an inflammatory response by increasing levels of inflammatory cytokines, acute phase reactants, and oxidative molecules. The inflammatory response can lead to intestinal wall disruption, and therefore bacteria can migrate across the GI barrier, along with food antigens, which could then lead to food antigen hypersensitivity.[6]

The significance of diet

Many studies have looked into specific types of diets, such as the Mediterranean diet, the ketogenic diet, and the addition of supplements such as probiotics, omega-3 fatty acids, zinc, and multivitamins.[7] The Mediterranean diet is high in fiber, nuts, legumes, and fish.[7] The ketogenic diet includes a controlled amount of fat, but is low in protein and carbohydrates.[7] The main point is that a balanced diet can have a positive effect on mental health.[7] The Mediterranean diet has shown to decrease the incidence of cardiovascular disease and lower the risk of depression.[7] In animal studies, the ketogenic diet has improved anxiety, depression, and autism.[7] Diet clearly affects gut microbiota and, as a consequence, the body's level of inflammation.[7]

continued

Clinical Point

Patients who were depressed had lower IgG levels against dairy products compared to controls when there was high dairy consumption

Discuss this article at www.facebook.com/MDedgePsychiatry

Table

Gut microbiota and psychiatry: 3 studies

Study	Design	Outcome
Rudzki et al[6] (2017)	Serum IgG concentrations against 44 food products, plasma cortisol, TNF-alpha, IL-6, and IL-1beta concentrations and psychometric parameters were compared in 34 patients with depression and 29 healthy controls	Patients with depression had lower levels of IgG against dairy protein. Patients with depression had high cortisol levels but decreased levels of TNF-alpha, which could explain immune suppression of IgG. There were no differences in IL-6 or IL-1beta levels
Mörkl et al[7] (2018)	Narrative literature review	Authors concluded that utilization of nutritional advice, along with medication management, therapy, and physical activity, can provide a holistic approach to the biopsychosocial treatment of patients with psychiatric illness
Jiang et al[8] (2018)	Cross-sectional study of 40 patients with GAD in the active state and 36 healthy controls. Subgroup analysis of 12 patients who were treatment-naïve and 17 controls. Researchers also conducted a prospective study in a subgroup of 9 patients with GAD in both the active state and remissive state. Two stool samples were collected from each patient—one during the active state of GAD and one during the remissive state	Patients with GAD had less short chain fatty acid–producing bacteria compared with controls. Decreased formation of short chain fatty acids could lead to GI barrier disruption. *Fusobacterium* and *Ruminococcus* were increased in patients with GAD. *Fusobacterium* can cause disease and be invasive when it disseminates within the body. The inflammatory characteristics of *Fusobacterium* contribute to the immunologic activation in GAD. *Ruminococcus* breaks down mucin, which could then increase GI permeability by mucous degradation of the GI lumen

GAD: generalized anxiety disorder; GI: gastrointestinal; IgG: immunoglobulin G; IL: interleukin; TNF: tumor necrosis factor

Clinical Point

Adding nutritional advice to standard therapies can provide a holistic approach to psychiatric treatment

The following review highlighted the significance of diet on gut microbiome and mental health.[7]

2. Mörkl S, Wagner-Skacel J, Lahousen T, et al. The role of nutrition and the gut-brain axis in psychiatry: a review of the literature. Neuropsychobiology. 2018; 17:1-9.

Study design

- These researchers provided a narrative review of the significance of a healthy diet and nutritional supplements on the gut microbiome and the treatment of patients with psychiatric illness.

Outcomes

- This review suggested dietary coaching as a nonpharmacologic treatment for patients with psychiatric illness.

Conclusion

- The utilization of nutritional advice, along with medication management, therapy, and physical activity, can provide a holistic approach to the biopsychosocial treatment of patients with psychiatric illness.

This review also emphasized the poor dietary trends of Westernized countries, which include calorie-dense, genetically altered, processed meals. As Mörkl et al[7] noted, we are overfed but undernourished. Mörkl et al[7] reviewed studies that involve dietary coaching as part of the treatment plan of patients with mental illness. In one of these studies, patients who received nutritional advice and coaching over 6 weeks had a 40% to 50% decrease in depressive symptoms. These effects persisted for 2 more years. Mörkl et al[7] also reviewed an Italian study that found that providing

nutritional advice in patients with affective disorders and psychosis helped improve symptom severity and sleep.[7]

Mörkl et al[7] also reviewed dietary supplements. Some studies have linked use of omega-3 fatty acids with improvement in affective disorders, Alzheimer's disease, and posttraumatic stress disorder, as well as cardiovascular conditions. Omega-3 fatty acids may exert beneficial effects by enhancing brain-derived neurotrophic factor and neurogenesis as well as by decreasing inflammation.[7]

Zinc supplementation can also improve depression, as it has been linked to cytokine variation and hippocampal neuronal growth. Vitamin B_9 deficiency and vitamin D deficiency also have been associated with depression. Mörkl et al[7] emphasized that a balanced diet that incorporates a variety of nutrients is more beneficial than supplementation of any individual vitamin alone.

Researchers have long emphasized the importance of a healthy balanced diet when treating patients with medical conditions such as cardiovascular or cerebrovascular diseases. Based on the studies Mörkl et al[7] reviewed, the same emphasis should be communicated to our patients who suffer from psychiatric conditions.

The gut and anxiety

The gut microbiome has also been an area of research when studying generalized anxiety disorder (GAD).[8]

3. Jiang HY, Zhang X, Yu ZH, et al. Altered gut microbiota profile in patients with generalized anxiety disorder. J Psychiatr Res. 2018;104:130-136.

The aim of the study was to determine if there were changes in the composition of the gut microbiome in patients with GAD compared with healthy controls.[8]

Study design

- A cross-sectional study of 76 patients in Zhejiang, China. Forty patients with GAD in the active state and 36 healthy controls were compared in terms of composition of GI microbacterial flora.
- Researchers also examined a subgroup of 12 patients who were treatment-naïve and 17 controls. Stool samples were collected from the 12 patients who were treatment-naïve before initiating medication.
- Researchers also conducted a prospective study in a subgroup of 9 patients with GAD in both the active state and remissive state. Two stool samples were collected from each patient—one during the active state of GAD and one during the remissive state—for a total of 18 samples. Stool samples analyzed with the use of polymerase chain reaction and microbial analysis.
- Patients completed the Hamilton Anxiety Rating (HAM-A) scale and were classified into groups. Those with HAM-A scores >14 were classified as being in the active state of GAD, and those with scores <7 were classified as being in the remissive state.

Outcomes

- Among the samples collected, 8 bacterial taxa were found in different amounts in patients with GAD and healthy controls. *Bacteroidetes*, *Ruminococcus gnavus*, and *Fusobacterium* were increased in patients with GAD compared with controls, while *Faecalibacterium*, *Eubacterium rectale*, *Sutterella*, *Lachnospira*, and *Butyricicoccus* were increased in healthy controls.
- Bacterial variety was notably lower in the 12 patients who were treatment-naïve compared with the control group.
- There was no notable difference in microbial composition between patients in the active vs remissive state.

Conclusion

- Patients with GAD had less short chain fatty acid–producing bacteria (*Faecalibacterium*, *Eubacterium rectale*, *Sutterella*, *Lachnospira*, and *Butyricicoccus*) compared with controls. Decreased formation of short chain fatty acids could lead to GI barrier disruption. *Fusobacterium* and *Ruminococcus* were increased in patients

Clinical Point

Compared with controls, patients with GAD had less short chain fatty–acid producing bacteria

with GAD. *Fusobacterium* can cause disease and be invasive when it disseminates within the body. The inflammatory characteristics of *Fusobacterium* contribute to the immunologic activation in GAD. *Ruminococcus* breaks down mucin, which could then increase GI permeability by mucous degradation of the GI lumen.

Changes in food processing and manufacturing have led to changes in our diets. Changes in our normal GI microbacterial flora could lead to increased gut permeability, bacterial dissemination, and subsequent systemic inflammation. Research has shown that the composition of the microbiota changes across the life span.[9] A balanced intake of nutrients is important for both our physical and mental health and safeguards the basis of gut microbiome regulation. A well-regulated gut microbiome ensures low levels of inflammation in the brain and body. Lifestyle modifications and dietary coaching could be practical interventions for patients with psychiatric conditions.[5]

Clinical Point

A well-regulated gut microbiome ensures low levels of inflammation in the brain and body

Current advances in technology now offer precise analyses of thousands of metabolites, enabling metabolomics to offer the promise of discovering new drug targets and biomarkers that may help pave a way to precision medicine.

References

1. Dave M, Higgins PD, Middha S, et al. The human gut microbiome: current knowledge, challenges, and future directions. Transl Res. 2012;160:246-257.
2. Nasrallah HA. It takes guts to be mentally ill: microbiota and psychopathology. Current Psychiatry. 2018;17(9):4-6.
3. Malan-Muller S, Valles-Colomer M, Raes J, et al. The gut microbiome and mental health: implications for anxiety-and trauma-related disorders. OMICS. 2018;22(2):90-107.
4. Du Toit A. The gut microbiome and mental health. Nat Rev Microbiol. 2019;17(4):196.
5. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13(10):701-712.
6. Rudzki L, Pawlak D, Pawlak K, et al. Immune suppression of IgG response against dairy proteins in major depression. BMC Psychiatry. 2017;17(1):268.
7. Mörkl S, Wagner-Skacel J, Lahousen T, et al. The role of nutrition and the gut-brain axis in psychiatry: a review of the literature. Neuropsychobiology. 2018;17:1-9.
8. Jiang HY, Zhang X, Yu ZH, et al. Altered gut microbiota profile in patients with generalized anxiety disorder. J Psychiatr Res. 2018;104:130-136.
9. Douglas-Escobar M, Elliott E, Neu J. Effect of intestinal microbial ecology on the developing brain. JAMA Pediatr. 2013;167(4):374-379.