Progress in Microbes and Molecular Biology

HH PUBLISHER

Review Article

Gut Microbiome in Obsessive Compulsive Disorder: Potential of Probiotics as an Adjuvant Therapy

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Article History

Received: 13 August 2022;

Received in Revised Form: 03 November 2022;

Accepted: 18 November 2022;

Available Online: 30 November 2022

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Abstract: The gut-brain axis concept has become an exciting area of research in psychiatry. Gastrointestinal inflammation and gut microbiome dysbiosis have been associated with mental health disorders. Obsessive-compulsive disorder (OCD) is a debilitating and complex mental illness that cannot be completely curable, stemming from many causes and risk factors. Generally, there is limited research on OCD and its association with the gut microbiome compared to other psychiatric conditions such as depression and anxiety. This review aims to provide insights into the association of gut microbiome and gastrointestinal inflammation with OCD. Besides, the role of probiotics as a potential therapy will be discussed in this review. The studies compiled in this review demonstrated variations in the gut microbial composition, often with lower microbial diversity in OCD patients compared to the controls. The gut microbiome is also involved in regulating the immune system. Alteration in certain groups of gut bacteria could give rise to inflammation and manifestations of gastrointestinal symptoms in OCD patients. As an approach to restoring the balance of the gut microbiome, probiotics serve as an effective solution. *In vivo* animal studies showed that probiotics can potentially improve OCD symptoms. Nevertheless, clinical trials are required to determine the efficacy of probiotics as an adjuvant therapy to alleviate OCD symptoms.

Keywords: OCD; mental health; obsession; compulsion; gut microbiota

1. Introduction

Obsessive-compulsive disorder (OCD) is a debilitating chronic neuropsychiatric disorder with a 2.3% lifetime prevalence and an average age of onset at 19.5 years old [1]. It is characterized by persistent intrusive thoughts (obsessions), often paired with repetitive behaviors (compulsions) that can alleviate anxiety [2, 3]. The etiology of OCD is still unclear. It may involve various factors such as genetic vulnerability, neurobiological dysfunction, and environmental influences. Recent research has also found that glutamate and inflammation could be involved in OCD [4]. The current OCD treatment options focus on serotonin imbalance and cognitive behavioral therapy [3]. However, up to 40% of patients do not respond to selective serotonin reuptake inhibitors (SSRIs). Those who respond tend to require higher dosages of SSRIs than those used in depression [4]. Hence, there is an increased risk of dose-dependent adverse effects such as gastrointestinal symptoms and sexual dysfunction. Meanwhile, only one-third of treatment-resistant OCD may respond to augmentation with antidopaminergic agents [4]. There is a need for research to understand the pathophysiological mechanisms of OCD further to discover new approaches for treatment-resistant OCD and augment existing therapies.

Recent advances in sequencing technologies have enabled research exploring the human microbiome. The gut microbiome may have a role in modulating inflammation and has been implicated in the pathogenesis of psychiatric conditions such as depression and anxiety [5]. Few studies have hypothesized that the gut-brain axis may be implicated in OCD because anxiety is a significant component of the disorder [6, 7]. Many OCD risk factors are known to disrupt the microbiome, such as stress and pregnancy [6, 8]. Animal studies have also shown anxiety and OCD-like behavior altered by microbial treatments such as probiotics and germ-free environments [9-11].

This review discusses the current literature on the association of gut microbiome and gut inflammation with OCD. Additionally, this review offers information on the roles of probiotics as a potential adjuvant therapy for OCD. Literature search was performed using keywords: “obsessive compulsive disorder”, “OCD”, “gastrointestinal microbiome”, “gut microbiome”, “inflammation”, and “probiotics” on three databases, including OVID Medline, ProQuest, and Scopus. There are limited studies available in this area of research; hence, studies of PANS (Paediatric Acute-Onset Neuropsychiatric Syndrome) and PANDAS (Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections) will not be excluded from this review. Considering the clinical overlap of PANS/PANDAS with OCD phenotypes, these findings may be useful for comparison and discussion [12]. Children with PANS are characterized by an acute onset of tics, OCD, or various other psychiatric disorders. Meanwhile, PANDAS is a subset of PANS associated with infection by *Group A Streptococci* [13]. Treatment for PANDAS includes antibiotics, immunomodulatory medications, SSRIs, and cognitive-behavioral therapy [13]. Thirteen English-language articles, including clinical trials and animal studies, were selected for qualitative analysis based on their relevance to this review.

2. The Association of Gut Microbiome and OCD

The human gut microbiome consists of numerous bacteria species essential in metabolizing indigestible compounds, producing vitamins, developing gut-associated lymphoid tissue (GALT), and preventing pathogenic colonization [8, 14]. The gut microbiome profile is primarily stable in adults but can be affected by factors such as stress, infections, inflammation, diet, antibiotics, and probiotics [5]. Researchers discovered the importance of the gut microbiome in health and its implications for various diseases, such as cardiometabolic diseases, neuropsychological diseases, autoimmune diseases, cancers, and many more [15-20]. One of the most studied areas is the gut-brain axis (gut-microbiome-brain axis) [21]. The gut-brain axis describes the bidirectional relationship between the gut microbiome and the central nervous system. Stress and emotions can affect gut function, while the gut can modulate cognition and emotions [22].

Researchers have attempted to explore the connection between gut microbiome composition and the development of mental illnesses like OCD. Turna et al. [12] investigated the stool microbiome and inflammatory markers of OCD patients, and the confounding variables were taken into consideration, such as depression, antibiotics, probiotics, and SSRI intake. The 21 cases of OCD patients recruited in the study were not depressed and not on medications, matched to a control of the same age and sex. The OCD patients had lower species richness and evenness than the control group and a significantly lower relative abundance of 3 genera: *Oscillospira, Odoribacter,* and *Anaerostipes* [12]. *Odoribacter* is from the phylum *Bacteroidetes*, while *Oscillospira* and *Anaerostipes* are from the phylum *Firmicutes* and class *Clostridia* . These three genera of bacteria can produce butyrate, a short-chain fatty acid (SCFA) that provides energy and maintains the integrity of the gut epithelium, preventing "leaky gut" that would increase intestinal permeability to various compounds that can cause inflammation [23]. Therefore, the lower abundance of these bacteria could indirectly indicate the lower production of butyrate, which could confer health benefits to the host.

A study by Domènech et al. [24] also showed that OCD patients tended to lower α-diversity compared to the control group, which indicated lower species richness and evenness of the gut microbiome in OCD patients. The relative abundance of *Rikenellaceae*, especially the genus *Alistipes*, was increased in OCD patients. This family has a positive association with intestinal inflammation in mice [25]. Meanwhile, the relative abundance of the family *Prevotellaceae* was reduced compared to the control [24]. Several genera in this family, especially *Prevotella*, were reported to be reduced in children with other disorders, such as autism. *Prevotella* has been discovered to help prevent pathogen colonization as a commensal in the gut microbiome [26]. Compared to controls, OCD patients had a reduction in the abundance of 2 genera within the *Lachnospiraceae* family, which were *Agathobacter* and *Coprococcus* [24]. *Coprococcus* can be associated with DOPAC (a dopamine metabolite) synthesis, which may contribute to OCD via the dopaminergic pathway [24].

In addition, Domènech et al. [24] was the first study to investigate the oropharyngeal microbiome of OCD patients. The oropharyngeal samples also exhibited lower bacterial diversity than the stool samples. However, *Streptococcus* bacteria, a potential biomarker of OCD associated with PANDAS, was not detected as the top 15 most abundant species in both OCD and control samples. The ratio of *Fusobacteria* to *Actinobacteria* was significantly lower in the OCD group as compared to the control group due to OCD patients having an increase of species within the *Actinobacteria* and *Coriobacteria* classes (particularly the genera *Actinomyces* and *Atopobium*). In contrast, the control group had a higher percentage of *Fusobacteria* population than the OCD group. The study suggested that the *Fusobacteria* to *Actinobacteria* ratio was correlated with the presence of the *Coprococcus* genus, which may be implicated in the pathogenesis of OCD.

Furthermore, Nikolova et al. [27] recently conducted a meta-analysis based on the studies by Turna et al.[12] and Domènech et al.[24], and they found that OCD patients had 15 taxa of gut microbes that were significantly different in abundancies compared to controls. However, compared to other disorders like depression and anxiety, there were insufficient studies of OCD for more in-depth comparisons, such as analyzing the specific taxa involved and checking for overlap with other disorders.

Meanwhile, Quagliariello et al. [28] investigated the gut microbiome of 30 patients with PANS/PANDAS. They discovered an increase in anti-streptolysin O titer (ASOT) correlated with increased levels of *Odoribacter* and reduced levels of *Dehalobacterium*, *Corynebacterium*, *Gemella*, and *Lactobacillus*. The younger age group of children at 4-8 years old had an increased abundance of *Bacteroidetes*, especially *Bacteroides*, *Odoribacter*, and *Oscillospira*, and a reduction in *Firmicutes* . In general, the gut microbiota of the younger PAN patients lacked several pathways involved in modulating inflammation and neurological function. In the older group of PAN children above 9 years of age, there was a greater abundance of *Peptostreptococcaceae* and *Erysipelotrichaceae* with reduced *Rikenellaceae* and *Barnesiellacea* [28]. Besides, it is important to note that the different findings in the two age groups might also be due to the gut microbiome changes throughout different stages of life [13].

Animal studies have also provided evidence of the changes in the gut microbiome of mice or rats with OCD behaviors. For instance, Jung et al. [29] conducted an experiment by inducing compulsive checking and locomotor sensitization (OCD-like behaviors) in 15 rats by injecting the dopamine agonist quinpirole. The rats injected with quinpirole were found to have changes in several bacterial communities compared to the control group of 16 rats injected with saline. After statistical analysis of fecal samples, 25 gut bacteria clusters were found to be likely altered due to long-term injection of quinpirole. There were 22 clusters from the *Firmicutes* phylum, with the highest prevalence in the *Lachnospiraceae* family, followed by the *Ruminococcaceae* family. This increase in *Ruminococcaceae* is consistent with another study that investigated the gut microbiome of rats injected with an indirect dopamine agonist [30]. The remaining 3 clusters consisted of *Deferribacteres*, *Proteobacteria*, and *Tenericute*s phyla [29].

Nevertheless, Jung et al. [29] could not confirm the relationship between changes in the gut microbiome and the onset of obsessive-compulsive behaviors. The changes in the gut microbiome could be due to chronic drug injections or other confounding factors like stress. Rather than directly stimulating behavioral change via the gut-brain axis, Jung et al. proposed that behavior change only reflects the supportive role of the gut microbiome. This alternative infrastructure support model suggested that gut bacteria adapt to different circumstances to fulfill their roles in processing nutrition and immune regulation [29]. With this model, a change in the gut microbiome reflects the presence of adapting to support different physiological demands. The *Firmicutes* phylum consists of Gram-positive bacteria that produce butyrate, a short-chain fatty acid (SCFA), as their primary end-product that can be used for energy, fatty acid oxidation, and lipolysis [31]. In this study, the changes in these microbes reflected a shift towards free fatty acids (FFA) utilization, which may be an adaptation of the gut bacteria to support energy use requirements because FFA is a denser energy source. The obsessive-compulsive behaviors induced by quinpirole, such as enhanced locomotor sensitization, and actions of compulsive checking, can increase the energy requirements of the rats [29, 31].

Another study by Scheepers et al. [32] examined deer mice with large nest building (LNB) behavior, which is considered a compulsive-like behavior in mice. The gut microbiome of 11 deer mice expressing LNB was compared to 11 normal nest-building (NNB) deer mice. The study found that both groups have significantly different overall gut microbiome compositions. In NNB deer mice, there was an increased prevalence of *Prevotella* and *Anaeroplasma* compared to LNB mice. *Prevotella* and *Anaeroplasma* have anti-inflammatory properties that may be protective against developing NNB behavior [32]. Meanwhile, LNB mice have an increased prevalence of *Desulfovermiculus, Aestuariispira, Peptococcus*, and *Holdemanella* compared to NNB mice. *Desulfovermiculus* and *Peptococcus* are hydrogen sulfide-releasing bacteria linked to inflammation and injury to the gut mucosa, suggesting that OCD-like behavior development could be driven through the gut-brain axis [32].

Overall, α-diversity in the gut microbiome was lower in OCD [24, 28] and PANS/PANDAS patients [12], as compared to controls, indicating the presence of fewer bacterial species with a more unbalanced distribution. *Firmicutes* was one of the phyla being affected in the gut microbiome of the OCD population. A younger group of PANS/PANDAS showed increased *Oscillospira* [28]. Besides, *Ruminococcaceae* and *Lachnospiraceae* also increased in OCD-like rats, which were attributed to increased metabolic demands [29]. However, these were inconsistent with the findings in other clinical trials showing a reduction within the families *Lachnospiraceae* [24], *Oscillospira* [12], and *Anaerostipes* [12]. The *Odoribacter* family was found to be reduced in OCD patients [12], but increased in younger PANS/PANDAS patients [28]. These organisms could produce butyrate to prevent intestinal permeability and inflammation. The discrepancy in the findings of gut microbiome composition levels in PANS/PANDAS as compared to adult OCD patients may reflect changes in the microbiome throughout the lifetime or as a compensatory response to an abnormal childhood level of the microbe.

The *Rikenellaceae* family, especially the *Alistipes* genus, was increased in OCD patients, and these bacteria were associated with gut inflammation [24]. Meanwhile, the family *Prevotellaceae* was reduced in OCD patients [24]. These findings were consistent with the animal study, in which higher levels of *Prevotella* and *Anaeroplasma* in normal rats than in OCD-like rats, with these bacteria having anti-inflammatory properties [32]. Other organisms shown to be altered in the OCD population include *Desulfovermiculus, Aestuariispira, Peptococcus,* and *Holdemanella,* which are increased in mice with OCD-like behaviors [32]. A raised anti-streptolysin O titer indicating streptococcal infection was correlated with reduced levels of *Dehalobacterium, Corynebacterium, Gemella, and Lactobacillus* in PANS/PANDAS patients. Thus, streptococcal infection could alter the gut microbiome composition by favoring certain gut bacteria that promote a pro-inflammatory state [28].

3. Relationship between Gastrointestinal Diseases and OCD

Obsessive-compulsive, anxiety and depression symptoms can arise due to a need to control unpredictable gastrointestinal symptoms that affect the quality of life [33]. Young adults with chronic gastrointestinal diseases such as Coeliac disease, inflammatory bowel disease (IBD), and irritable bowel syndrome (IBS) were significantly more likely to have obsessive-compulsive, depression, and anxiety symptoms with more mentally unhealthy days than their healthy controls [34-36]. Another study on adult IBD patients found that those with active disease have more obsessive-compulsive, depression, anxiety, and psychosis symptoms than those in remission [33]. Stress and psychiatric disorders can alter the gut microbiome. A dysfunctional gut microbiome can lead to inflammation and manifestations of gastrointestinal symptoms.

A cross-sectional study on men in the Korean army found that obsessive-compulsive and somatization behaviors are independent predictive factors for functional gastrointestinal disorders (FGIDs) [37]. In this study, men with FGID were also found to have more psychopathological symptoms than controls, assessed by a modified Symptom Checklist-90-R (SCL-90-R) [37]. Serving in the army is a stressful environment that may precipitate psychiatric symptoms and alter the gut microbiome. FGID includes conditions such as irritable bowel syndrome (IBS), functional heartburn, or functional diarrhea, of which IBS is the most common FGID. IBS is hypothesized to involve the gut-brain axis, with IBS patients having higher rates of anxiety and depression [36]. OCD patients are also found to have a higher prevalence of IBS, with 47.6% meeting the Rome III criteria for IBS, compared to 4.5% of controls [36]. The outcome is consistent with an earlier study that showed 35.1% of OCD patients meeting the Rome I criteria for IBS compared to that 2.5% of controls [38]. Compared to controls, OCD patients were also found to have more severe gastrointestinal symptoms such as reflux, indigestion, bowel dysfunction, and abdominal symptoms [36].

4. Potential Therapeutic Roles of Probiotics in OCD

Given that a dysfunctional gut microbiome could serve as a contributing factor to psychiatric disorders, probiotics may be an alternative remedy to alleviate these conditions. Probiotics have been shown to reduce depression-like symptoms, improve gut function and regulate corticosteroid release in animal studies [11, 39]. Currently, the use of probiotics as a therapeutic regime for OCD remains unclear. Evidence on the effect of probiotics on OCD patients is limited. A secondary analysis performed on a study regarding the impact of the probiotic *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 (PF) revealed obsessive-compulsive scores in 25 healthy subjects improved after 30 days of PF intake [40]. A case report on a 16-year-old boy with autism spectrum disease, OCD, and self-injurious behavior (SIB) showed a significant reduction of OCD symptoms (as rated by his parents) and a decrease in SIB episodes [41]. He was given *Saccharomyces boulardii* at 6 capsules daily for 3 months, then began to wean the dose by 4 capsules per week [41].

In 2014, researchers in the United States produced OCD-like behaviors in house mice with RU 24969, a serotonin receptor agonist [10]. Pretreatment with 2-weeks and 4-weeks of *Lactobacillus rhamnosus GG* resulted in mice with lesser OCD-like behavior than controls. Pretreatment with 2-weeks of the probiotic was found to be comparable to 4-weeks fluoxetine pretreatment in preventing the induction of OCD behaviors. In 2020, researchers in Iran induced OCD-like behaviors in 4 groups of 6 rats with a chronic injection of quinpirole (a dopamine agonist) to compare with 1 group of rats injected with normal saline [11]. For 4 weeks, the first group of rats was given the probiotic *Lactobacillus casei Shirota* (*L. casei)* as an intervention, the second group was given fluoxetine, the third group was given fluoxetine, and the probiotic, while the fourth group was given no treatment as the control group [11]. *L. casei* has been reported to improve autism spectrum disorder symptoms and improve mood by having an anti-inflammatory effect [11, 42]. Rats treated with *L. casei*, fluoxetine, or both showed improvement in OCD symptoms in terms of their exploratory behavior. The expression of 3 genes involved in the serotonergic pathway of OCD pathogenesis (brain-derived neurotrophic factor [*Bdnf*], 5-hydroxytryptamine receptor type-2A [*Htr2a*], and solute carrier family-6-member-4 [*Slc6a4*]) were measured using PCR analysis. Quinpirole led to decreased expression of *Bdnf*, increased *Htr2a*, and no difference in *Slc6a4* compared to controls. In contrast, the treatment with fluoxetine or probiotics resulted in the upregulation of Bdnf and downregulation of Htr2a [11]. *L. casei* Shirota appeared to modulate these gene expressions and alleviate OCD symptoms.

4. Conclusion

Adult OCD patients, children with PANS/PANDAS, and mice/rats with OCD-like behaviors demonstrated changes in the gut microbiome composition. The gut bacteria that have been identified to be altered prominently include the *Firmicutes* phylum (*Ruminococcaceae, Lachnospiraceae*, Oscillospira, *Anaerostipes*), genus *Odoribacter, Rikenellaceae* family, and *Prevotellaceae* family. Other organisms shown to be altered in OCD include *Desulfovermiculus, Aestuariispira, Peptococcus, Holdemanella,*

Dehalobacterium, *Corynebacterium*, *Gemella*, and *Lactobacillus.* The supplementation of probiotics to modify the gut microbiome composition and reduce OCD symptoms are successful in two animal studies involving probiotics *Lactobacillus rhamnosus GG* and *Lactobacillus casei Shirota* (*L. casei).*

There is a need to raise awareness of OCD and encourage research in this area. It is crucial to study and discover the specific gut microbes that might trigger the development of OCD or as a biomarker of the disease to select the appropriate probiotic as adjuvant therapy. To date, the studies investigating the gut microbiome composition of the OCD population are still limited, and their relationship remains inconclusive as the gut microbiota changes can be either part of the aetiology of OCD or a consequence of the condition. There is room for improvement in future studies pertaining to the gut microbiome and OCD. For instance, a germ-free mouse model experiment can be explored to determine if changes in the gut microbiome could lead to the development of OCD. Meanwhile, future studies should consider confounders that can affect the microbiome, such as medication usage, comorbidities like depression or anxiety, stress, or diet. It may also prove useful to analyze the severity of OCD symptoms with regards to the microbiome profile or if there are any differences in treatment-responsive compared to treatment-resistant patients.

Author Contributions: The literature searches, data collection, and manuscript writing were performed by GY-EK. The manuscript was critically reviewed, proofread, and edited by LT-HL, and VL. The project was conceptualized and supervised by JW-FL.

Funding: No external funding was provided for this research.

Acknowledgments: This work was inspired by the Jeffrey Cheah School of Medicine and Health Sciences "MED5101 Scholarly Intensive Placement (SIP)", Monash University Malaysia.

Conflicts of Interest: The authors declare no conflict of interest.

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