The interplay of gut microbiota and eating disorders: exploring potential links and treatment implications

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Abstract. Background: Eating Disorders (EDs), including Binge Eating Disorder (BED), Bulimia Nervosa (BN), Anorexia Nervosa (AN), Avoidant/Restrictive Food Intake Disorder (ARFID), and Other Specified Feeding or Eating Disorders (OSFED), manifest as complex psychiatric conditions. Recent evidence suggests a pivotal role of the gut microbiota in their pathophysiology. This review explores the intricate connections between gut microbiota and EDs, focusing on BED, BN, AN, ARFID, and OSFED. Examining distinct microbial profiles, antibiotic usage implications, and therapeutic interventions such as probiotics and fecal microbiota transplantation, it provides valuable insights into potential modifications of the gut microbiome for innovative ED management. Materials and Methods: The manuscript was drafted as per the SANRA guidelines. The included literature was reviewed by the authors as per the
analytical framework mentioned in detail. Objectives: The manuscript intends to explore
gut microbiota changes in Eating Disorders, identify biomarkers, evaluate interventions for
therapeutic insights, and enhance understanding for innovative management. Results: The
results revealed unique gut microbiota signatures in diverse Eating Disorders (BED, BN, AN,
ARFID, OSPED), showcasing altered levels of specific bacteria and concentrations of ClpB.
Elevated Anaerostipes, Bifidobacterium, and Roseburia, alongside reduced Akkermansia,
Desulfovibrio, and Intestinimonas, characterized BED. For BN, increased Bifidobacterium and
decreased Odoribacter were observed. AN exhibited elevated Methanobrevibacter smithii and
reduced anaerobes. ARFID displayed a distinctive microbiota profile. Therapeutic
interventions, such as probiotics and fecal microbiota transplantation, exhibited potential
in ameliorating symptoms across different Eating Disorders, suggesting novel avenues for
targeted interventions in ED management.

Keywords:
Eating Disorders
Human microbiome
Gut Health
Anorexia
Introduction

Eating Disorders (EDs) constitute a complex spectrum of psychiatric conditions, encompassing disorders such as Binge Eating Disorder (BED), Bulimia Nervosa (BN), Anorexia Nervosa (AN), Avoidant/Restrictive Food Intake Disorder (ARFID), and Other Specified Feeding or Eating Disorders (OSFED). Emerging evidence suggests a crucial role of the gut microbiota in the pathophysiology of these disorders, influencing both their development and progression. This narrative review explores the intricate connections between the gut microbiota and EDs, focusing on BED, BN, AN, ARFID, and OSFED, while also delving into potential modifications of the gut microbiome as therapeutic interventions (Himmerich et al., 2019, Carbone et al., 2020).

The gut microbiota is increasingly recognized as a potential contributor to the pathophysiology of BED. Distinct microbial profiles, characterized by elevated levels of Anaerostipes, Bifidobacterium, and Roseburia, and reduced levels of Akkermansia, Desulfovibrio, and Intestinimonas, have been identified in BED patients. Notably, antibiotic usage in BED patients suggests existing dysbiosis. Furthermore, the concentration of ClpB, a product of enterobacteria, is implicated in the production of autoantibodies against α-MSH, associated with specific psychological traits in BED. Probiotic interventions, particularly employing Lactobacillus and Bifidobacterium strains, show promise in attenuating binge eating symptoms.

BN is linked with sustained periods of food restriction, impacting the gut microbiota. Studies reveal alterations in relative abundances of specific bacterial strains in BN patients, including increased Bifidobacterium and decreased Odoribacter (Fetissov & Hökfelt, 2019). ClpB, produced by Escherichia coli, correlates with the severity of BN symptoms. Ghrelin, an appetite stimulant, may also play a role in BN. Probiotic and antibiotic interventions, along with fecal microbiota transplantation, emerge as potential therapeutic modalities for BN, Herman & Bajaka, 2021).

The gut microbiome in AN is characterized by changes in bacterial abundances, with elevated Methanobrevibacter smithii and reduced anaerobes such as Clostridia and Bacteroides. Short-chain fatty acids (SCFAs), crucial in
weight gain, are diminished in AN patients. Fecal microbiota transplantation shows promise in improving microbiota species richness and SCFA levels, correlating with increased body weight (Million et al., 2013, Papadimitriou et al., 2016). The bidirectional link between the brain and the gut, influenced by inflammatory metabolites, hormones, and microbial composition, underscores the significance of the gut microbiota in AN pathophysiology.

ARFID, characterized by sensory sensitivity and food avoidance, presents a unique challenge in understanding its pathophysiology. Recent studies suggest a distinctive gut microbiota signature in ARFID patients, emphasizing the potential role of the microbiome in its development. Exposure-based Cognitive Behavioral Therapy and Family Therapy are proposed interventions, considering the intricate relationship between gastrointestinal conditions, eating behavior challenges, and gut-brain interactions.

OSFED, encompassing diverse disorders, demonstrates associations between gut dysbiosis and psychopathology. Gut dysbiosis, leading to dysregulation of the hypothalamic-pituitary-adrenal axis, is implicated in OSFED development (Riesco et al., 2018). Treatment approaches, including Enhanced Cognitive Behavioral Therapy (CBT-E) and nutritional therapy, vary based on specific OSFED subtypes, with fecal microbiota transplantation emerging as an experimental but promising avenue for future research (Terry et al., 2022b).

This review aims to provide insights into the intricate interplay between the gut microbiota and various EDs, highlighting potential avenues for therapeutic interventions by modifying the gut microbiome. Understanding these connections can pave the way for innovative approaches in the management of EDs, offering hope for improved outcomes and enhanced well-being for affected individuals.

**Methodology**

Relevant literature across Google Scholar and PubMed was gathered, analyzed, and studied to gather factoids and support the research. Reputed sources and relevant time stamps were included in the manuscript.

The following inclusions and exclusion criteria were employed.
Inclusion Criteria:
1. Relevance to Gut Microbiota and Eating Disorders: Studies directly investigating the relationship between gut microbiota and different types of eating disorders (AN, BN, BED, ARFID).
2. Published Research: Peer-reviewed articles, reviews, meta-analyses, and observational studies exploring the interaction between gut microbiota and eating disorders.
3. Clinical Relevance: Studies focusing on the impact of gut microbiota alterations on the etiology, symptomatology, treatment outcomes, or potential therapeutic interventions for eating disorders.
4. Recent Studies: Preferably studies published within the last decade (or as per the current relevance of available literature) to ensure inclusion of the most recent research findings.

Exclusion Criteria:
1. Irrelevant Studies: Articles unrelated to the interplay between gut microbiota and eating disorders or lacking relevance to the review's scope.
2. Animal Studies Only: Exclusion of studies conducted solely on animal models without direct applicability to human eating disorders.
4. Duplicate or Redundant Studies: Exclusion of duplicate publications or studies presenting redundant information already covered by included articles.
5. Case Reports or Single-Case Studies: Exclusion of individual case reports or case studies lacking broader implications or generalizability to the topic.

The Manuscript was drafted using the SANRA guidelines (Baethge et al., 2019).

BINGE EATING DISORDER
The role of Microbiota in the pathophysiology of Binge Eating Disorder (BED)
Among the various factors implicated in the pathophysiology of Binge Eating Disorder (BED), intestinal dysbiosis is hypothesized to play a crucial role (Herman & Bajaka, 2021). According to several studies, BED patients
exhibit increased levels of Anaerostipes, Bifidobacterium, and Roseburia, along with decreased levels of Akkermansia, Desulfovibrio, and Intestinimonas in their gut microbiota (Leyrolle et al., 2021, Navarro-Tapia et al., 2021). Intestinimonas is known to maintain gut function by metabolizing toxic products from processed foods and Akkermansia is known to impact food intake behavior via modulation of gut peptides. Bifidobacterium and Roseburia are associated with cardiometabolic benefits, and Anaerostipes regulate human behavior (Navarro-Tapia et al., 2021). The heightened usage of antibiotics in BED patients before the onset of Eating Disorders (ED) also suggests existing dysbiosis in these individuals (Navarro-Tapia et al., 2021, Himmerich et al., 2019). Despite limited data on BED, available evidence suggests a trend toward low alpha diversity and increased Firmicutes and Enterobacteriaceae (Carbone et al., 2020).

Researchers discovered significantly elevated concentrations of ClpB (caseinolytic protease B) produced by enterobacteria in patients with ED, including those with BED, compared to healthy participants (Himmerich et al., 2019, Carbone et al., 2020). In BED, the concentration of ClpB stimulates the production of autoantibodies against α-MSH. The distinct binding of ClpB is proposed to be associated with specific psychological traits in BED (Carbone et al., 2020).

**Treatment for BED by employing a modification in the Gut Microbiome**

Despite the existence of studies on probiotic supplementation in Anorexia Nervosa (AN), clinical trials in BED are lacking. Given the potential influence of the microbiota on appetite regulation and symptom reduction in BED, it is recommended to conduct clinical trials with probiotics as a potential treatment option for BED (Herman & Bajaka, 2021). In a randomized controlled trial (RCT) conducted on patients one year after undergoing Roux-en-y gastric bypass, specific strains of bacteria, namely Lactobacillus and Bifidobacterium, were used as probiotic supplements in one group of post-op patients. The results were then compared to a placebo group, revealing a significant
positive effect of probiotic treatment in attenuation of the binge eating score and FA symptoms 1 year after bariatric surgery, compared to the placebo (De Oliveira Carlos et al., 2022).

**BULIMIA NERVOSA**

*The Role of Microbiota in the Pathophysiology of Bulimia Nervosa*

An increasing number of studies confirm a relationship between the composition of intestinal microbiota and the regulation of appetite, mood, and body mass. Severe sustained periods of food restriction (Terry et al., 2022, Herman & Bajaka, 2021) such as those seen in Bulimia Nervosa (BN), are strongly linked with intestinal microbial dysbiosis. A study conducted by Monteleone et al. showed BN patients had a significant increase in relative abundances of *Bifidobacterium*, *Bifidobacteriaceae*, *Bifidobacteriales*, and *Eubacteria Cape* and a significant decrease in relative abundances of *Odoribacter*, *Haemophilus*, *Pasteurellaceae*, and *Pasteurellaceae* (Herman & Bajaka, 2021).

Evidence indicates that the gut microbiota and its metabolites are closely linked to the host’s central nervous system through bidirectional communication. For instance, lipopolysaccharides (LPS) produced by intestinal bacteria increase the permeability of the blood-brain barrier making cytokines have a larger impact on appetite regulation (Herman & Bajaka, 2021). Researchers have recently discovered, caseinolytic protease B (ClpB), a production of *Escherichia coli* (Fetissov & Hökfelt, 2019). The MC (melanocortin) system, operated by α-MSH signaling, is a pathway regulating appetite (Fetissov & Hökfelt, 2019). ClpB stimulates the production of autoantibodies against α-MSH, causing pharmacological blocking leading to pronounced hyperphagia (Navarro-Tapia et al., 2021). Breton et al. found that ClpB was present in the serum of healthy people. In contrast, in ED patients its level was elevated, and ClpB concentration correlated with the severity of ED symptoms (Bretón et al., 2016, Santonicola et al., 2019).

**Treatment for Bulimia Nervosa by employing a modification in the Gut Microbiome**

Ghrelin, an appetite stimulant such as may also play a
role in BN (De Oliveira Carlos et al., 2022). These peptides are synthesized in the digestive tract and affect the “centers” in the hypothalamus responsible for maintaining the body’s energy homeostasis (Herman & Bajaka, 2021). Santonicola et al. stated that higher ghrelin levels in ED could be an effort to compensate for the state of malnutrition of these patients (Navarro-Tapia et al., 2021) but can vary with the purging habits often displayed by patients suffering from BN.

There is a dramatic lack of data that is evident for clinical management for BN. So far, probiotic use has been the most extensively studied. Enterococcus-based and Lactobacillus-based probiotics can be useful for the modulation of α-MSH autoAbs due to their Clp proteins sequence homology with α-MSH. Some antibiotics, such as Cephalosporins, are efficient against Enterobacteriaceae. Bacteriophages targeting specific Enterobacteriaceae species also exist and have been used for decades in a few countries, such as Russia, against dysbiosis (Fetissov & Hökfelt, 2019). Fecal microbiota transplantation emerges as a promising therapy (Herman & Bajaka, 2021).

ANOREXIA NERVOSA

The Role of Microbiota in the Pathophysiology of Anorexia Nervosa

Disordered eating habits in patients of AN may influence changes in the gut microbiome and inflammatory metabolites produced by these new strains may perpetuate neuropsychological changes, thus suggesting a bidirectional link between the brain and the gut (Achamrah et al., 2019, Frostad 2022). Of particular importance is the activation of the hypothalamic-pituitary-adrenal (HPA) axis and corticotropin-releasing hormone (CRH) secretion, which along with leptin, ghrelin, serotonin, glucagon-like peptide-1, and cholecystokinin target brain centers leading to decreased appetite, food consumption, and gastric emptying. It is hypothesized that gut microbiota affect the levels of these hormones and thus contribute to the pathophysiology of AN (Frostad 2022, Garcia-Gil et al., 2022).

Armougum et al. and Million et al. both found increased amounts of Methanobrevibacter smithii in the anorexic
patients compared to normal-weight and obese controls and found a positive correlation between Lactobacillus and body mass index. The relative abundance of *M. smithii* has been postulated to be involved in efficient absorption in a hypocaloric diet while low Lactobacilli levels are a likely consequence of a calorie-poor diet (Armougom et al., 2009, Million et al., 2013, Papadimitriou et al., 2016).

**Treatment of Anorexia Nervosa by employing a modification in the Gut Microbiome**

Borgo et al. and Morita et al. both found reduced levels of anaerobes such as Clostridia and Bacteroides in the fecal microbiota samples of anorexic patients when compared to controls. Short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which are produced by gut anaerobes, were consequently found to be reduced in fecal samples of anorexic patients in both studies (Borgo et al., 2017, Morita et al., 2015, Nogal et al., 2021).

SCFA levels have been found to correlate with weight gain in recovering patients of anorexia. Mack et al. (Xu et al., 2022), on the other hand, found increased levels of Clostridia but decreased levels of another SCFA-producing species, Roseburia. Decreased levels of Roseburia were corroborated by (Borgo et al., 2017) and (Hanachi et al., 2019). Gouba et al. report a unique case in which four fungal species were isolated from the gut of an anorexic woman namely, Tetratrichomonas, Aspergillus ruber, Penicillium solitum, and Cladosporium bruhnei. Procházková et al. and de Clercq et al. observed improvement in gut microbiome species richness and SCFA levels following fecal microbiota transplant (FMT) in patients of anorexia nervosa, with an increase in body weight and body fat percentage. This suggests both the role of gut microbiota in anorexia pathogenesis and the potential use of FMT as a therapeutic modality (Gouba et al., 2014, Procházková et al., 2019).

**AVOIDANT OR RESTRICTIVE FOOD INTAKE DISORDER (ARFID)**

**The Role of Microbiota in the Pathophysiology of ARFID**

It is a complex condition spanning childhood to adulthood, characterized by sensory sensitivity, low appetite, or post-traumatic food avoidance. A key diagnostic criterion is the manifestation of significant medical or psychosocial issues

Given the poorly delineated diagnostic boundaries and large heterogeneity in patient symptoms, the pathophysiology of ARFID remains elusive. The genetic basis of ARFID is particularly understudied, distinguishing it from other Eating Disorders (ED).

Recently, the role of the gut microbiota has been increasingly implicated in EDs. Ye Q et al. found distinct gut microbiota differences in 135 children, including 102 with ARFID. The ARFID group exhibited a unique microbial signature, notably higher Bacteroides abundance, and alterations in functional genes, emphasizing the potential role of the gut microbiome in ARFID pathogenesis. Antibiotic resistance gene analysis further revealed a unique profile in ARFID, underscoring the relevance of gut microbiota (Ye et al., 2023).

ARFID is recognized as a disorder of gut-brain interaction, sharing similarities with gut microbiota-eating disorder correlations seen in anorexia nervosa. Moreover, ARFID symptoms often coexist with Disorders of Gut-Brain Interaction (DGBIs), emphasizing the intricate relationship between gastrointestinal conditions and eating behavior challenges. Notably, exclusion diets may put some patients at risk for developing ARFID and continued food avoidance may perpetuate preexisting ARFID symptoms (Murray et al., 2020, Weeks et al., 2023)

**Treatment of ARFID by employing a modification in the Gut Microbiome**

Current treatments for ARFID and anorexia nervosa are limited, necessitating innovative approaches. Exposure-based Cognitive Behavioral Therapy (CBT), integrating inhibitory learning principles, emerges as a promising intervention. This therapy aims to challenge distorted cognitions about food intake, reduce food neophobia, and alleviate associated symptoms, reflecting a nuanced understanding of ARFID’s psychological underpinnings (Dumont et al., 2019).

Family Based Therapy (FBT) is additionally a comparable and effective area in the ARFID context, showing potential in a range of studies. There are, however, no established...
guidelines from a psychopharmacological perspective for ARFID. Medication may be considered to target specific symptoms such as decreased appetite or severe situational anxiety about eating, but curative treatment in the near future is unlikely, considering the pathophysiology and diagnostic classification of ARFID remains poorly elucidated (Di Cara et al., 2023).

Other Specified Feeding or Eating Disorders (OSFED)
The Role of Microbiota in the Pathophysiology of OSFED

The Other Specified Feeding or Eating Disorders (OSFED) is a category of eating disorders that includes people with eating disorders by whom the complete criteria for any of the three main eating disorders including anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED) are not satisfied. The category ‘Eating Disorder Not Otherwise Specified (EDNOS) from the Diagnostic and Statistical Manual of Mental Disorders-4 (DSM-4) was reclassified as OSFED in the update of the DSM-5. OSFED encompasses diversified disorders such as atypical anorexia nervosa (atypical AN), purging disorder (PD), night eating syndrome (NES), bulimia nervosa of limited duration, and binge eating disorder of limited duration (Riesco et al., 2018).

The gut microbiota has been found to be associated with the psychopathology of eating disorders including OSFED. Gut dysbiosis is defined as a disturbance within the gut microbiome that results in a decrease in beneficial bacteria and an increase in potentially harmful organisms in the gut. The gut dysbiosis eventually leads to dysregulation of the hypothalamic pituitary adrenal axis (HPA) parallels the development of eating disorders like OSFED (Terry et al., 2022b).

Treatment of OSFED by employing a modification in the Gut Microbiome

Since the disorders grouped under OSFED are diversified, it constitutes a challenge to figure out treatment options (Jenkins et al., 2021). However, enhanced cognitive behavior therapy (CBT-E) along with carefully monitored nutritional therapy is effective as first-line treatment in all ED patients (Balasundaram, 2023).

The studies regarding the treatment of atypical AN suggest
consistent weight gain through nutritional rehabilitation ensuring proper electrolyte monitoring. This approach should be individualized.

The treatment of the purging disorder is similar to bulimia nervosa involving CBT and FDA-approved pharmacotherapy like fluoxetine, a selective serotonin reuptake inhibitor (SSRI) (Balasundaram, 2023, Vo & Golden, 2022). Fecal microbiota transplantation is an experimental treatment that has been shown to improve the gut microbiota but requires future research (Terry et al., 2022c).

DISCUSSION

The presented narrative review synthesizes current evidence on the interplay between gut microbiota and Eating Disorders (EDs), shedding light on potential therapeutic interventions. The discussions encompass Binge Eating Disorder (BED), Bulimia Nervosa (BN), Anorexia Nervosa (AN), Avoidant/Restrictive Food Intake Disorder (ARFID), and Other Specified Feeding or Eating Disorders (OSFED).

Microbiota Alterations in Eating Disorders

The observed dysbiosis in BED, characterized by imbalances in specific bacterial strains, underscores the need for a comprehensive exploration of microbial communities. The association between enterobacterial ClpB and psychological traits in BED raises intriguing questions about the bidirectional communication between gut microbes and the central nervous system. The identification of potential probiotic candidates, such as Lactobacillus and Bifidobacterium, offers a promising avenue for therapeutic interventions in BED.

Similarly, the dysregulated gut microbiota in BN, marked by changes in Bifidobacterium and Odoribacter, aligns with the intricate connections between microbiota and appetite regulation. The role of ghrelin, an appetite stimulant, emphasizes the complexity of hormonal influences in BN. Probiotics, antibiotics, and fecal microbiota transplantation emerge as potential interventions, highlighting the multifaceted nature of microbiota-based therapies. AN exhibits distinct alterations in microbial composition, with implications for the bidirectional communication between the gut and the brain. Changes in Methanobrevibacter smithii,
Clostridia, and Bacteroides emphasize the role of gut microbiota in hormone regulation and appetite control. Fecal microbiota transplantation shows promise in addressing microbiota imbalances and promoting weight gain, providing a novel perspective on AN management.

In ARFID, the unique microbial signature identified in children with ARFID highlights the disorder's complexity. The connections between gut-brain interactions and gastrointestinal conditions in ARFID emphasize the necessity for nuanced therapeutic approaches. Exposure-based Cognitive Behavioral Therapy and Family Therapy emerge as potential interventions, recognizing the intricate relationship between psychological factors and gut microbiota in ARFID.

**Challenges and Opportunities in Therapeutic Interventions**

Despite promising findings, challenges persist in translating microbiota-based therapies into effective clinical interventions. Variability in ED subtypes and individual responses to treatment necessitate tailored approaches. The lack of established guidelines for psychopharmacological interventions in ARFID exemplifies the need for further research.

The potential of fecal microbiota transplantation as a therapeutic modality across EDs warrants careful consideration. While it shows promise in promoting microbiota diversity and addressing dysbiosis, the long-term effects and safety profiles require extensive investigation. Additionally, ethical considerations and patient preferences must be integrated into the discussion surrounding fecal microbiota transplantation.

In OSFED, the diversity of disorders within this category poses a challenge for uniform treatment strategies. Enhanced Cognitive Behavioral Therapy and nutritional therapy, while effective, may need adaptation based on specific OSFED subtypes. The experimental nature of fecal microbiota transplantation in OSFED highlights the ongoing need for research to establish its efficacy and safety.

**Future Directions and Implications**

The reviewed literature underscores the dynamic nature of the gut microbiota in influencing EDs. Future research should focus on unraveling the mechanisms underlying microbiota-gut-
brain interactions and their role in ED pathophysiology. Longitudinal studies exploring the trajectory of microbiota alterations throughout EDs can provide valuable insights into causality and potential early intervention strategies.

Therapeutically, the exploration of targeted probiotics, prebiotics, and precision medicine approaches tailored to individual microbiota profiles holds promise. Collaborative efforts between clinicians, researchers, and microbiome experts are essential to translate research findings into evidence-based interventions. Moreover, ethical considerations, patient autonomy, and the integration of microbiota-based therapies into comprehensive treatment plans should be central in future discussions and developments.

CONCLUSION

The integration of gut microbiota research into the understanding and management of EDs represents a paradigm shift in the field. While challenges exist, the potential for microbiota-based therapies offers hope for more effective and personalized approaches to ED treatment, ultimately improving the well-being of individuals affected by these complex disorders.

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