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The Study of Gut Microbiota Pattern in Anorexia Nervosa Patients

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Abstract

Introduction: Anorexia nervosa (AN) is a common eating disorder associated with weight, physiology and the gut microbiome. The main aim of this study was to gather taxonomical profile changes of intestinal bacteria in patients who suffer from AN and suggest possible treatment and prevention approaches for future studies.

Method: We had a review of the literature published between 2000 and 2021 in the databases of Web of Science, PubMed and the Scopus through the main keywords including eating disorders, anorexia nervosa, probiotic, microbiota, microbiome, gut pattern, and gut-brain axis.

Results: Based on reports, a reduction in gut bacteria richness such as enriched Coriobacteriaceae, which is implicated in lipid metabolism, Clostridium clusters, Roseburia, archaea, and Methanobrevibacter smithii in subjects were significantly higher compared to control groups.

Conclusion: This study provided evidences of intestinal dysbiosis in AN patients and sheds light on possible treatment and prevention approaches for AN patients such as nutritional interventions considering paraprobiotics, postbiotics, probiotics and prebiotics or dietary supplements as an important component for AN therapy.

Keywords: Anorexia nervosa; Eating disorders; Gut microbiome; Treatment

Abbreviations: AN: Anorexia Nervosa; BN: Bulimia Nervosa; GLP-1: Glucagon-like Peptide-1; SCFAs: Short Chain Fatty Acids; GABA: Gamma-Aminobutyric Acid; FMT: Fecal Microbiota Transplantation

Introduction

Human eating disorders such as anorexia nervosa (AN) is an increasing psychiatric disorder among citizens of modern societies [1,2] and is characterized by a series of psychological behaviors and clinical variables such as extreme dietary restriction resulting in a sustained low weight, imbalanced homeostasis energy, impaired brain and reduced gut function in patients [3].

Prevalence of eating disorders increased globally from 3.4% to 7.8% from 2000 to 2018 [4]. However eating disorders are traditionally considered to affect mainly women, men represent a growing proportion of subjects suffering from AN and bulimia nervosa (BN) [2,4]. Based on recent studies, around 1.5% of people suffer from AN in the world [5-7].

As far as the impact of eating disorders on health is concern, due to direct influence of an eating disorder, one person dies every hour [8], which AN is the deadliest mental illness caused by malnutrition among eating disorders with 56 times higher incidence of suicide attempts [9]. In addition, Mood disorders, such as major depression, anxiety disorders, obsessive-compulsive disorder, post-traumatic stress disorder, resulting in substance use disorder [10], beside electrolyte abnormalities, and organ damages including heart attacks, kidney failures, the gut problems, neurological disorders and reduction in total volume of brain are the most frequent health risks of such eating disorders [11,12]. The recent reports claim that abnormal composition of the intestinal microbiome may be a crucial factor supporting cachexia of AN patients [13,14]. We aim to gather the most recent surveys on the changes in the gut microbiome composition in AN patient and the role of the intestinal bacteria in the pathogenesis of AN. In addition, we tried to gather possible treatment and prevention approaches for AN patient. For this purpose, a review of the literature published between 2000 and 2021 in the databases of Web of Science, PubMed and the Scopus has been performed by importing keywords: eating disorders, anorexia

nervosa, probiotic, microbiota, microbiome, gut pattern, and gut-brain axis.

The Gut Brain Axis: Definition, and Functions

The gastrointestinal tract colonized with the gut microbiome [15], referring to the bidirectional communication between the gut and the brain [16], which is crucial in mental health. Importance of gut microbiota have been illustrated on weight gain [17], digestive system, immune system, appetite hormones and autoantibody against them in have been reported in previous studies [18]. The gut-brain axis uses neural, immune, hormonal and microbial factors messages for the communication between the gut and the brain [2,17]. For instance, L cells, and endocrine cells, which release PYY, glucagon-like peptide-1 (GLP-1) and GLP-2, are stimulated by short chain fatty acids (SCFAs), which are generated by particular microbes [19,20]. SCFAs stimulate L cells via activating G protein coupled receptors such as Gpr41 [21]. One the other side, gut-derived hormones are undeniable links between the gut microbiome and physiological responses [22]. Furthermore, the taxonomic profile of the gut bacteria influences the profile of metabolites in the brain [15]. The gut microbiome is also able to generate neurotransmitters and neuromodulators such as 5-hydroxytryptamine, dopamine noradrenaline, acetylcholine, gamma-aminobutyric acid (GABA) [17]. Numerous intestinal microbes including *Lactobacillus*, *Bacteroides*, *Helicobacter pylori*, *Escherichia coli* and Candida species contain proteins that have amino acid sequences identical to these appetite-regulating peptides [23]. The circulating levels of autoantibodies against alpha-melanocyte-stimulating hormone, which are increased in AN, correlate with the psychobehavioural abnormalities of these eating disorders [24]. Figure 1 illustrates more details on the clinical agents and physiological changes involved in the communications between the gut microbiome and brain in AN patients.

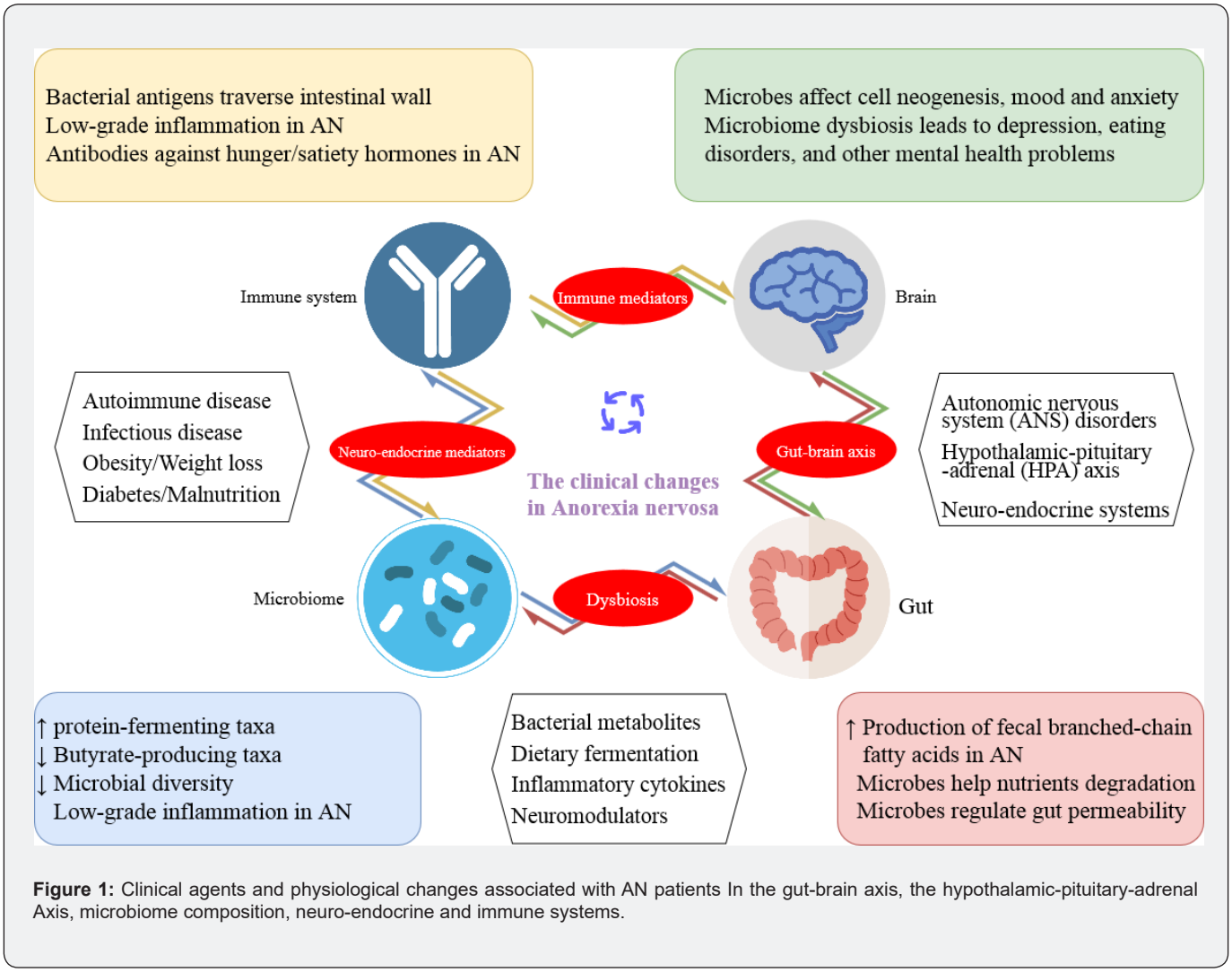

Figure 1: Clinical agents and physiological changes associated with AN patients In the gut-brain axis, the hypothalamic-pituitary-adrenal Axis, microbiome composition, neuro-endocrine and immune systems.

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The Role of the Gut Microbiota in AN

The intestinal microbiota control the formation of IgG and IgA autoantibodies against neuropeptides involved in appetite control including lpha-melanocyte-stimulating hormone, NPY, PYY, agouti-related protein, ghrelin, leptin and some other neuropeptides/peptides [23,25,26]. Researchers reported a reduction in gut bacteria richness in AN subjects, in which the enriched *Coriobacteriaceae* was significantly dominant [27]. *Coriobacteriaceae* colonize the human gastrointestinal tract and are implicated in lipid metabolism [28]. Moreover, the taxa corresponding to various Clostridium clusters, *Roseburia*, *archaea*, and *Methanobrevibacter smithii* in an subjects were significantly higher compared to control groups [29,30]. *Methanobrevibacter smithii* is most abundant bacteria in the intestines of people with malnutrition, which enables them to effectively metabolize nutrients to calories [30]. In addition, Bacteroides and Firmicutes bacteria and those archaea species enhance the fermentation yield of indigestible fiber contents to SCFAs [31], which play a critical role in neuro-immunoendocrine regulation [32]. Table 1 presents studies related to the taxonomical profile changes in AN patient. There are conceivable reasons for a synergistic effect of the gut microbiota in AN patient. In addition, several antidepressants may have antimicrobial effects [40], which could indeed be responsible for the paradoxical results that studies have found in AN patient. More studies are required to find out in more detail the influence of intestinal bacteria on prescription of antidepressant medications in AN patient.

Table 1: Reported potential differences in microbiome composition in AN patients.

Author(s), Year, References	Study Groups			Taxonomic Profile in AN Patients	Notes
	Number of Patients	Mean BMI (kg/m^2)	Mean Age		
Mörkl et al. [33]	AN patients=18	15.3±1.3	22.4	↑ *Coriobacteriaceae* ↓ Alpha-diversity ↓ Microbial richness	
	Athletes=20	22.1±1.8			
Kleiman et al. [34,35]	AN patients=3	15.6, 17.6, and 13.7	25, 29, 16 years old		Changes in composition the phylum (n = 4), class (n = 8), order (n = 14), family (n = 28), and genus (n = 68) levels.
	AN patients = 16 Controls= 12	16.2±1.5 17.4±0.9	28.0±11.7	↓ Microbial alpha-diversity ↑ Bacilli ↑ *Coriobacteriales*↓ Phylogenetic richness ↓ *Clostridia* ↓ Faecalibacterium ↓ *Anaerostipes*	After treatment: Alpha-diversity and microbial richness increased. Changes at the phylum and genus levels were demonstrated, for example: ↑ *Ruminococcus* spp. Alpha-diversity remained low
Borgo et al. [36]	AN patients=18	13.9±2.1	Not reported	↑ Gram-negative bacteria ↑ *Proteobacteria* ↑ *Enterobacteriaceae* ↑ *Methanobrevibacter smithii* ↓ *Firmicutes* ↓ Ruminobacteria ↓ Roseburia ↓ Ruminococcus ↓ *Clostridium* ↓ SCFAs, propionate, butyrate	No differences: Phylogenetic diversity, phylogenetic richness, beta-diversity, faecal acetate, isovalerate and isobutyrate
	Athletes=20	22.1±2.6			
Mack et al. [29]	AN patients = 55	15.3±1.4		↓ Number of OTUs and the Chao1 index in AN patients who used laxatives ↑Mucin-degrading bacteria (including *Verrucomicrobia, Bifidobacteria*) ↑ Branched-chain fatty acids and valerate ↓Butyrate-producers (e.g., Roseburia)	No differences in SCFAs
	Controls= 55	21.6±2.0	23.8±6.8		
Morita et al. [37]	AN patients = 25	12.8±1.3	30.0±10.2	↓ *Clostridium coccoides* group, *Clostridium leptum* subgroup, *Bacteroides fragilis, Streptococcus* ↓ Abundance of *Lactobacillus plantarum* ↓ SCFAs	Clostridium difficile was only detected in the AN group
	Controls= 21	20.5±2.1			

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Million et al. [38]	AN patient = 15	13.5	27.3±10.8	↓ *Lactobacillus reuteri* ↑ *Escherichia coli* ↑ Archeon *Methanobrevibacter smithii*	Faecal levels of Lactobacillus reuteri positively correlated and E. coli negatively correlated with BMI in all study groups
	Obese controls= 134	40			
Armougom et al. [39]	AN patients = 9	12.7±1.6	27.3±10.8	↑ *Archeon Methanobrevibacter smithii* No differences: *Firmicutes, Bacteroidetes* and *Lactobacillus*	
	Controls= 20	20.7±2.0			

Possible Therapeutic Approaches for AN Patients

Unfortunately, the above-mentioned abnormalities do not translate as yet for effective methods of treatment for AN patient. However, the knowledge about the gut-brain interaction in AN patients is constantly growing and the results are very promising so far, the findings are not precise in some sections and many questions remain unanswered that must be clarified before any recommendations for AN treatment and prevention. On the other hand, dietary behavior is an important factor affecting the gut microbiome composition, the clinical impacts of diet, which are typically made quickly in patients with AN, should be examined in more detail. The nutritional interventions considering paraprobiotics, postbiotics, probiotics and prebiotics or dietary supplements could become an important additional component of multimodal AN therapy in the future. As far as fecal microbiota transplantation (FMT) as a treatment approach for AN is concern, a patient who had been suffering for 2years was able to gain weight of 6.3kg and led to the improvement of gut barrier function after FMT from a healthy control subject of normal weight [41]. Furthermore, in another patient, decreased the fungal alpha diversity, bacterial species richness and enhanced gut microbiome evenness in the patient were observed [42]. Overall, the relatively young research field of gut-brain interaction in the context of AN appears extremely promising. It might help to also consider AN and its underlying mechanisms from a nutritional and microbiome-gut-brain-axis perspective in the existing biopsychosocial model. Appropriately specifically developed individual nutritional therapeutic interventions could complement the previous multimodal therapy.

Conclusion

In this review article, we gathered the most recent published surveys on the changes of taxonomic profile of microbiome composition in AN patient and the possible approaches for treatment and prevention of heating disorders considering diet supplements, probiotics, probiotics, postbiotics, and paraprobiotics as well as the outcomes on FMT in AN patients.

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