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Connection between gut microbiota and Anorexia Nervosa. Literature review

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ABSTRACT:

Introduction: Anorexia Nervosa (AN) stands as a severe mental disorder characterized by the highest mortality rate within the realm of psychiatric conditions. Its etiology encompasses genetic, neurobiological, environmental, and developmental factors. Recent investigations have shed light on the potential impact of the gut microbiota on the genesis and progression of AN.

Aim of the Study: The aim of this paper is to provide a comprehensive review of the existing findings on relationship between gut dysbiosis and AN. The intention is to present new perspectives that contribute to a more detailed understanding of the multifaceted nature of this serious disorder.

Description of the State of Knowledge: The gut microbiota takes a central role in modulating various physiological processes. Dysbiosis, which refers to an imbalance in gut microbiota composition, has recently drawn attention because of its association with several mental disorders. In the context of AN, studies have shown reduced microbial diversity and notable changes in specific bacterial populations. The influence of the gut microbiota on AN includes disturbances in the digestive system, changes in eating behaviours, and associations with related conditions such as anxiety and depression. Mechanisms such as the gut-brain axis, hormonal regulation and molecular mimicry contribute to these associations.

Conclusions: Recognition of the pivotal role played by the gut microbiota in AN opens up avenues for potential therapeutic interventions. Pro- and prebiotics, along with fecal transplantation, emerge as promising modalities in the treatment of AN. Ongoing research is essential to further elucidate this evolving field, ultimately facilitating the development of targeted interventions for individuals with AN.

KEY WORDS: Gut Microbiota; Dysbiosis; Anorexia Nervosa; Gut-Brain Axis

INTRODUCTION

Anorexia Nervosa (AN) is a relatively rare yet serious mental disorder, with a global prevalence ranging from 0,3% to 0,64% [1,2]. It predominantly affects women, with a frequency of 0.6%-4.3%, while only 0.2-0.3% of men worldwide experience it. The peak onset of AN occurs among adolescents aged 15 to 20 [2]. This condition is extremely perilous, having the highest mortality rate among all mental disorders, with a mortality risk over five times greater compared to the general population [3].

Anorexia nervosa manifests through diverse symptoms (both physical and psychological), creating a complex clinical picture. Individuals affected by this disorder experience disturbed body image and fears of gaining weight, leading to actions aimed at weight loss. These actions may involve excessive engagement in physical activity or purging [4]. It leads to the gradual depletion of the organism and triggers significant problems involving the hormonal system, digestive system, cardiovascular system, metabolism, and brain function, such as a reduction in brain volume [2,4].

So far, it has been established that the development of anorexia is influenced by genetic, neurobiological, environmental, and developmental factors [4]. However, it remains a significant medical challenge, difficult to treat due to its broad causes. Recent studies are focusing on the role of gut microbiome in mental disorders. It has been found that changes in the gut microbiome can be one of the factors affecting the development and course of anorexia nervosa [5].

This study aims to synthesise existing knowledge on the impact of the gut microbiota on the pathogenesis and course of anorexia nervosa. This will provide new insights, and a better understanding of this multifactorial disease, which may be crucial for developing more effective treatment strategies.

GUT MICROBIOME

The gut microbiota (GM) constitutes the largest micro-ecosystem in the human body, consisting of trillions of microorganisms [6,7]. Predominantly it is composed of bacteria, mainly from the Firmicutes, Bacteroides, Actinomycetes, and Proteus genera. The rest includes viruses, fungi, and archaea. These microorganisms interact with each other and play a crucial role in regulating various processes in the human body [7]. They are responsible for synthesizing vitamins from the B and K groups [8], strengthening the intestinal barrier, combating pathogens, and regulating the immune system. Additionally, they participate in the

fermentation process in which undigested food remains (dietary fibers and resistant starch) are transformed into substances that the intestines can absorb. During the fermentation process short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate, are produced. These SCFAs not only serve as an energy source for bacteria but also exhibit anti-inflammatory effects. They play a role in T-cell differentiation processes and, according to recent scientific research, may even impact the brain. This connection between short-chain fatty acids and brain function is a topic that is currently being explored in scientific studies [6,9,10].

GUT-BRAIN AXIS

The bidirectional communication between the microbiome and the Central Nervous System (CNS) is called the “gut-brain axis”. CNS can affect the microbiota directly via the expression of the virulence genes in response to stress mediators or through the Autonomic Nervous System (ANS) that controls gut function and motility [11]. While the brain's control over gut physiology is very well-studied, the gut's communication with the brain has been explored quite recently [10]. It is known that signals from the GI tract go to the CNS through neuronal, endocrine, and immune pathways [11]. These signaling channels consist of the hypothalamic-pituitary-adrenal axis (HPA axis), the vagal nerve, immune mediators, hormones (cortisol, ghrelin, leptin, and glucagon-like peptide), bacterial metabolites, neurotransmitters and their precursors (serotonin, tryptophan, gamma-aminobutyric acid, dopamine, l-dopa, and noradrenaline) [12,13].

DYSBIOSIS – definition and consequences

The composition of the gastrointestinal microbiota is formed around the age of three and remains relatively constant until senior age [14]. However, there can be many factors that disrupt the gut microbiome balance, which may contribute to the development of various psychiatric and neurological disorders, such as mood and anxiety disorders, autism spectrum disorder, schizophrenia, Alzheimer's, and Parkinson's diseases [15]. This disturbance is called "dysbiosis" [16]. Dysbiosis is a phenomenon in which an imbalanced gut microbiota impacts negatively on human health [17]. The imbalance is characterised by a reduction in commensals, an increase in pathobionts, or a combination of both [18]. The composition of the microbiota and its metabolites can be modified by many factors, such as a short and long-term change in diet, excessive use of antibiotics, and physical and mental stress [14].

DYSBIOSIS IN ANOREXIA NERVOSA

Three aspects of biodiversity are also applicable to describing the composition of the gut microbiota. Alpha-diversity is the observed richness (number of taxa) or evenness (the relative abundances of those taxa) of an average sample within a habitat type. Beta-diversity is the variability in community composition (the identity of taxa observed) among samples within a habitat. Finally gamma-diversity is the total observed richness of all samples within a habitat [19]. Many studies conducted in the last years showed that alpha-diversity in patients with anorexia nervosa was lower compared to the healthy control groups [20–22]. Undeniably, diet is one of the factors which can impact the composition of intestinal microbiota [23]. A diet low in nutrients can decrease the level of intestinal biodiversity, resulting in a weakness of the immune system and a reduced ability to obtain energy from food, thereby sustaining malnutrition in people with AN [24,25]. Some studies in people with AN have found a reduced amount of SCFA-producing bacteria, which are essential for, among other things, the proper functioning of the immune system or maintaining the tightness of the intestinal barrier. Dysbiosis was associated with enhanced gastrointestinal symptoms, whereas increasing body weight helped to alleviate these symptoms [26,27]. The study by Borgo et al. showed an increased abundance of Proteobacteria, Enterobacteriaceae (including *E.coli*), and Actinobacteria (especially *Bifidobacterium*) in people with AN. In contrast, *Roseburia*, a bacteria responsible for the production of butyric acid in carbohydrate fermentation, was found in reduced amounts. A decreased population of this bacteria, resulting in low butyric acid concentrations, is associated with increased anxiety symptoms in anorexia patients [28]. Gouba et al.'s study is noteworthy as they analysed the eukaryotic composition of the gut microbiota in a woman with Anorexia Nervosa (AN) and noted a decrease in fungal diversity. Interestingly, they also detected four new microeukaryotes – *Tetratrichomonas* sp., *Aspergillus ruber*, *Penicillium solitum*, and *Cladosporium brunei* – which had never been described before in the human gut [29].

THE IMPACT OF GUT MICROBIOTA ON ANOREXIA NERVOSA PATHOPHYSIOLOGY

GASTROINTESTINAL DISTURBANCES

Patients suffering from anorexia nervosa frequently have some functional gastrointestinal disorders such as epigastric pain, bloating, feeling of fullness after meals, constipation,

regurgitation, and nausea [30]. Some of the symptoms described above are also observed in Irritable Bowel Syndrome (IBS) patients. Studies on the composition of the intestinal microbiota in patients with AN and IBS show similarities that may underlie the occurrence of constipation as one of the symptoms in both syndromes. *Methanobrevibacter smithii* is responsible for extracting methane from hydrogen and carbon dioxide, which could potentially account for the occurrence of constipation. The presence of this microorganism has been demonstrated in the microbiota of both IBS-C and AN patients [31,32].

One of the causes of functional gastrointestinal disorders is dysfunction of the intestinal barrier, which is expressed through the disruption of the epithelial barrier or increased gut permeability [33]. Intestinal permeability is defined as the ability of components of the intestinal lumen to penetrate through its mucosa. The tightness of the intestinal barrier depends on the function of tight junction proteins such as occludins and claudins [34]. The microorganisms inhabiting the intestine affect the expression of genes encoding tight junction proteins [33]. Jesus et al. have investigated intestinal barrier permeability in experimental anorexia by using the activity-based anorexia (ABA) model in rodents. They determined that rodents with anorexia display increased colonic permeability with altered tight junction protein expression and localization [35]. Another factor that plays an important role in maintaining the intestinal barrier is the mucus layer covering the inside of the intestines [33]. A study conducted by Mack et al. revealed that patients with anorexia have an increased amount of mucin-degrading bacteria. Compared to normal-weight patients, the stools of anorexia patients were found to contain higher amounts of *Verrucomicrobia*, and *Anaerotruncus* bacteria [27]. These bacteria contribute to the degradation of mucin leading to an impaired tightness of the intestinal barrier and an increased risk of inflammations and infections caused by opportunistic pathogens [33].

EATING BEHAVIOURS

Intestinal dysbiosis may disrupt appetite regulation mechanisms. There are several theoretical explanations for this relationship. Ongoing studies are investigating these issues and need further exploration to confirm potential interrelations.

Hormones such as leptin, ghrelin, peptide YY (PYY), and neuropeptide Y (NPY) play a role in eating behaviours and may be influenced by gut microbiota. Leptin and PYY are hormones that inhibit hunger, while ghrelin and NPY have the opposite effect [36]. Queipo-Ortuño MI et al. conducted a study on rodents with dietary restrictions and found that leptin levels were positively correlated with the quantities of *Bifidobacterium* spp. and *Lactobacillus*

spp., and negatively correlated with the quantities of *Clostridium* spp., *Bacteroides* spp., and *Prevotella* spp. In contrast, ghrelin levels were negatively correlated with the abundance of *Lactobacillus* spp. and positively correlated with the abundance of *Bacteroides* spp. [37]. Due to prolonged malnourishment, individuals with AN exhibit decreased levels of leptin and increased levels of ghrelin [38]. The aforementioned observations suggest that the gut microbiome may be involved in the endocrine disorders that occur in anorexia.

Another example of the gut microbiota's influence on appetite regulation is the action of SCFAs, which are produced by gut bacteria during polysaccharide fermentation. SCFAs stimulate enteroendocrine intestinal epithelial cells to produce peptide YY (PYY) and glucagon-like peptide 1 (GLP-1), both of which are satiety hormones [39]. PYY demonstrates its anorexigenic effects by inhibiting intestinal motility and reducing ghrelin levels. In comparison, GLP-1 suppresses appetite by delaying gastric motility and by acting on the brain, thanks to its ability to cross the blood-brain barrier [40].

A further plausible mechanism for the influence of the gut microbiota on the function of the hunger and satiety centres in the brain is based on the phenomenon of antigenic mimicry between the bacteria *Lactobacillus* spp., *Bacteroides* spp., *Helicobacter pylori*, *E. coli*, fungi *Candida* spp. and the appetite-regulating peptides leptin, ghrelin, PYY, and NPY. Autoantibodies of IgG and IgA against these peptides can cross the blood-brain barrier and influence the hunger and satiety centres. Antibodies directed against the bacteria may have a similar effect due to the similarity of the antigenic sequence of the peptides and the bacteria [41]. Another example of molecular mimicry is bacterial protein caseinolytic protease B (ClpB), which shares homology with the anorexigenic/anxiogenic peptide α -melanocyte-stimulating hormone (α -MSH). ClpB produced by *Escherichia coli* induces α -MSH cross-reactive autoantibodies, which form immune complexes (IC) with α -MSH (α -MSH/Ig IC). These complexes activate MC type 4 receptors (MC4R) in the brain, signalling satiety [42,43]. Interestingly, stimulation of MC4R also triggers anxiety [42]. Breton et al. conducted a study to measure ClpB levels in the plasma of patients with ED and normal-weighted people. The results revealed that bacterial protein was present in both groups, but its concentration was increased in people with ED, which may correlate with the psychopathological features of these syndromes. These results support the presumption of a link between the bacterial ClpB protein and ED pathophysiology [44]. Another study conducted by Tennoune et. al showed a link between changes in the microbiota and the occurrence of eating disorders. By introducing *E. coli* bacteria into the stomachs of mice, a significant reduction in food intake was observed and, at the same time, an increase in ClpB- and α -MSH-reactive antibodies was recorded. In

the control group, no significant changes in food intake or antibody levels were observed. Furthermore, in a human study, elevated plasma levels of anti-ClpB IgG antibodies crossreactive with α -MSH were found in patients with AN, bulimia, and BED compared to the general population. The above data indicate a potential role for the ClpB protein produced by gut bacteria in the pathogenesis of eating disorders [45].

ANXIETY AND DEPRESSION

Anorexia nervosa commonly occurs alongside other psychiatric disorders, such as depression, anxiety, obsessive-compulsive disorders, substance abuse, and personality disorders [46]. Approximately 80% of individuals with AN are predicted to experience major depression at some point in their lives, and around 75% are likely to suffer from anxiety disorders [47,48].

The role of the gut microbiome in the pathogenesis of depression and anxiety disorders is a hot topic and many papers have been published on it in recent years. The mechanism of this relationship is based on dysbiosis-dependent dysfunction of the gut-brain axis [49]. In 2015, Kleiman et al. conducted a microbiological study on the faeces of sixteen anorexia patients before and after treatment resulting in weight gain. The study revealed that the severity of mood and anxiety disorders was correlated with lower diversity of gut microbiota species. Successful treatment was associated with an increase in the diversity of gut microbiota species, which in turn was correlated with mood improvement and reduced anxiety. The researchers used the Beck Depression Inventory to assess symptom severity. Additional research on a larger study group is necessary to confirm the aforementioned relationship (20).

A noteworthy issue is the effect of the gut microbiota on regulating the production of neurotransmitters such as serotonin, dopamine, and norepinephrine [50]. Serotonin (5-hydroxytryptamine [5-HT]) is widely recognized for its role in regulating mood, but it also affects various physiological functions in the peripheral tissues. This neurotransmitter is produced in the gut by intestinal enterochromaffin cells and in the central nervous system (CNS) in the raphe nucleus from the essential amino acid tryptophan [51]. The gut microbiome is involved in the regulation of serotonin synthesis primarily through the regulation of tryptophan metabolism [52]. Bifidobacterium spp. influence the maintenance of homeostasis between the different pathways of metabolism of this amino acid [53]. Research has shown that patients with AN have elevated levels of Bifidobacterium spp. in their gut microbiome. However, further research is needed to fully understand these correlations [54].

CONCLUSIONS

The influence of the microbiota on the development and course of anorexia nervosa is a relatively new area of research and requires further investigation. Nevertheless, understanding the important role of the gut microbiota in maintaining the homeostasis of the organism is becoming increasingly important. The results obtained so far show that imbalances in the composition of the gut microbiota can influence different symptoms of AN through a variety of mechanisms. This opens up new potential therapeutic perspectives for individuals with AN, such as the use of pro- and prebiotics and faecal transplantation.

Author's contribution

Conceptualization, PP, and KS; methodology, DB, MK; software, PP, ML; check, IM, DB, and ML; formal analysis, BW, MK, IM; investigation, PP, BW, DB; resources, KS, IM; data curation, ML, BW; writing - rough preparation, PP; writing - review and editing, KS, IM, MK; visualization, BW, MK; supervision, PP, ML, DB; project administration, PP. All authors have read and agreed with the published version of the manuscript.

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Conflicts of Interest

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