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Intestinal microbiota and Anorexia Nervosa

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Abstract

Introduction: Eating disorders are severe psychiatric disorders. Anorexia nervosa (AN) has a mortality rate among the highest of any psychiatric illnesses. Anorexia nervosa is characterised by extreme weight loss and fear of gaining weight. Lifestyle and diet have a major influence on gut microbiota composition. Thus, studies of this subject may have potential in better understanding pathophysiology of AN.

The aim of the study: The purpose of this systemic review was to collect and analyse available data about correlations between anorexia nervosa and gut microbiota.

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed database was carried out using the following keywords: anorexia nervosa, gut microbiota, diet.

Description of the state of knowledge: Intestinal microbiota plays an important role in weight regulation. Alterations in bidirectional brain-gut microbiota interactions can be responsible for a number of diseases including irritable bowel syndrome or functional gastrointestinal disorders. Studies show differences of gut microbiota composition between AN patients and normal-weight control groups. Composition of intestinal microbiota changes during nutritional rehabilitation. However, the differences between AN and control groups are still present even after substantial weight gain. Moreover, some correlations according to BMI are observed. Also there might be a correlation between increased intestinal permeability and gastrointestinal complaints common in AN.

Summary: Studies showed alterations in intestinal microbiota composition in anorexia nervosa patients comparing to normal-weight individuals. However, more studies of this subject are needed. Knowing more correlations between gut microbiota, diet and weight may be helpful in understanding anorexia nervosa and improving its treatment.

Keywords: anorexia nervosa, gut microbiota, diet

Introduction

Anorexia nervosa (AN) is a mental illness with a mortality rate among the highest of any psychiatric illnesses [1]. Extreme weight loss or failure to gain expected weight is characteristic to AN patients as well as fear of weight gain [2]. Besides low body weight, there are other aspects of AN such as metabolic, immunological, biochemical and sensory abnormalities [3]. Other psychiatric and physiological disturbances are often present with anorexia nervosa. Those include anxiety, depression, and gastrointestinal (GI) distress [2]. Moreover, anorexia nervosa is associated with anxiety disorders, as a vulnerability factor, commonly premorbid to the onset of AN [4]. Diet influences gut microbiota, thus the intestinal microbiom seems to be an under-considered factor in anorexia nervosa pathophysiology and treatment [5]. Studies on animals showed that the gut microbiota is associated with traits present in AN such as dysregulated energy homeostasis and behavior [2].

Intestinal microbiota

The normal gut microbiota of humans consists of fungi, viruses, archaea and parasites but the main component is bacteria [6]. It is believed that there are up to 100 trillion of microbes in the human gastrointestinal tract, with the greatest density and diversity in the lower gastrointestinal tract, making about 2 kg of body weight [7]. Fetal intestine is thought to be sterile, although there are reports that colonization of the gut may also begin before delivery, through the placental barrier [8,9]. Colonization of gastrointestinal tract depends on the path of delivery. Vaginally born infants are initially colonized by maternal fecal and vaginal microbes, such as Bifidobacterium, Bacteroides, Prevotella, and Lactobacillus spp. Infants born by cesarean section are colonized by skin and hospital bacteria [10,11]. The collection of microorganisms are unique to each person and its composition depends on many factors, such as genetics, age, sex, health status, diet, geographical location and drug exposure [12,13]. The normal human's gut microbiota contains mainly Bacteroidetes, Firmicutes, Proteobacteria, Actinomyces, Fusobacterium,Verrucomicrobia. The main functions of gut microbiota are regulation of the mucosal immune system, gastrointestinal tract motility, epithelial barrier function, support for digestion and host metabolism, and prevention of colonization by pathogens [14].

Intestinal microbiota plays an important role in weight regulation. Study conducted by Ley et al. shows that differences in weight correlated with differential composition of gut microbiota. Intestinal microbiota in genetically obese mice showed 50% reduction of Bacteroidetes and increase of Firmicutes, compared with wild-type siblings. Both groups were fed fat-heavy diet [15]. Study on humans shows a similar phenomenon. Obese individuals have fewer Bacteroidetes and more Firmicutes than controls. However after one year with low calorie diet, level of Bacteroidetes can raise and Firmicutes can decrease[16]. One study shows that gut microbiota of obese mice is more effective at obtaining energy that in lean mice. It can be passed to another germ-free mice by microbial transplantation, causing increased adiposity [17].

Alterations in bidirectional brain-gut microbiota interactions can be responsible for a number of diseases, such as irritable bowel syndrome, functional gastrointestinal disorders, several brain disorders including autism spectrum disorders , Parkinson's disease, disorders of mood and affect, chronic pain and eating disorders [18,19].The microbiota-gut-brain axis, works by various pathways including the vagus nerve, the immune system, neuroendocrine pathways, and bacteria-derived metabolites [20]. There are two neuroanatomical pathways which gut can interact with the brain:

- Directly between autonomic nervous system and vagus nerve in spinal cord

- Between enteric nervous system in the gut and autonomic nervous system and vagus nerve in spinal cord

There are four-level of neural anatomic pathways for controlling gut functions. First level is enteric nervous system, second level is prevertebral ganglia, third is autonomic nervous system in spinal cord, brain stem nucleus tractussolitarius and dorsal motor nucleus of vagus nerve. The last level is created by the higher brain centers [21]. Direct communication between intestinal microbiota and the brain takes place mainly via the vagus nerve. Signal from vagus nerve can stimulate anti-inflammatory reaction in the gut [21,22].

The autonomic nervous system mediates communication between the central nervous system (CNS) and viscera. It plays a role in modulation gut functions, such as motility, secretion of acid, bicarbonates and mucus, intestinal-fluid handling and mucosal immune response [23]. Disorders in the autonomic nervous system can have a large impact on the composition of the intestinal microbiota. It can have effect on the delivery of important nutrients to the enteric microbiota, pH and luminal environment. Impairment of bowel function such as slow intestinal transit is associated with bacterial overgrowth in the small intestine [24]. Also impact of autonomic nervous system on mucus secretion can have important effect on the size and quality of the intestinal mucus layer. It creates environment that is important for the biofilm. This mucus layer contains majority of intestinal bacteria [25]. The autonomic nervous system can also affect gut microbiota by modulation of the response of the gut immune cells or by changing the access of luminal bacteria to gut immunocytes. As a consequence, it may increase permeability of the intestinal epithelium, that allows bacterial antigens to penetrate the gut epithelium and triggers an immune response in the intestinal mucosa [23]. CNS has an important role of secretion molecules such as catecholamines, serotonin, dynorphin and cytokines by neurons, immune cells and enterochromaffin cells into the gut lumen. One study on rats shows serotonin secretion into stomach lumen after central injection of analog of thyrotropin-releasing hormone (it is mediator of the stress response to cold temperature) [23,26]. Tryptase and histamine secretion by mastocytes into jejunum was observed after exposure to cold pain [27]. Also gut microbiota can modulate intestinal motility. Some of bacteria increase motility of intestine, such as Bifidobacterium bifidum or Lactobacillus acidophilus and bacteria like Escherichia species decrease motility [28].

Gut microbiota can modulate brain development, function and behavior including immune, endocrine and neural pathways [29]. Intestinal bacteria produce large amount of molecules with neuroactive functions [30]. Those molecules are neurotransmitters such as gamma-aminobutyric acid, serotonin, catecholamines and acetylcholine. Study has reported

that Lactobacillus spp. and Bifidobacterium spp. produce gamma-aminobutyric acid, Escherichia spp., Bacillus spp. and Saccharomyces spp. produce noradrenalin, Candida spp., Streptococcus spp., Escherichia spp. and Enterococcus spp. produce serotonin, Bacillus spp. produce dopamine and Lactobacillus spp. produce acetylcholine [31,32]. Molecules produced by intestinal bacteria can affect epithelial cells that release molecules modulating nerve signaling in the intestinal nervous system and thus can control brain functions and behavior [29]. Precursor of serotonin and metabolites of kynurenine pathway is tryptophan. Around 5 % of systemic tryptophan is metabolized to serotonin and it depends on activity of two enzymes - indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase. When the activity of these enzymes increases, for example during inflammation, serotonin resources may be depleted and it can induce depressive mood. Studies on rats show that the oral ingestion of Bifidobacterium infantis led to increased level of tryptophan. This suggests that Bifidobacterium infantis may have potential antidepressant effects [33]. Microbial fermentation of dietary fiber in the colon is the short-chain fatty acid source such as butyrate, acetate and propionate. Short chain fatty acids (SCFA) are the primary end-products of fermentation of non-digestible carbohydrates that become available to the gut microbiota [34].In one study on rats, the administration of a high dose of propionate induce a neuroinflammatory response and behavioral alterations [35]. Literature reports that butyrate decreases depressive-like behavior [29]. Indeed short-chain fatty acid or their deficiency may affect the pathogenesis of a diverse range of diseases, from allergies and asthma to cancers, autoimmune diseases, metabolic diseases, and neurological diseases [36].However, it is not clear whether the short-chain faty acid produced in the colon can cross the blood-brain barrier [29].

Gut microbiota and Anorexia Nervosa

Gut microbiota is an important component of metabolic functions and is dependent on the diet and lifestyle [37]. The composition of gut microbiota may influence weight regulation and plays a role in gastrointestinal disorders, such as inflammatory bowel disease [38]. There are differences in composition of gut microbiota between obese and lean individuals [39]. Consuming carbohydrate- or fat-restricted low-calorie diets for 1 year or high-fat/low-fiber or low-fat/high-fiber diets for 10 days evoke statistically significant changes in the gut microbiota [40]. Although the relationship between eating disorders and the intestinal microbiota is still not fully discovered. The study at the University of North Carolina recruited 16 female participants age 15-64, who meet DSM-IV-TR criteria for AN and present at <75% of ideal body weight (IBW) and a healthy control group of 12 participants who were selected based on

sex, age and BMI. Stool samples were collected from AN group at inpatient admission (T1) and discharge (T2). They were used to isolate genomic DNA and characterise the composition and diversity of microbiota in AN and compared from both points to healthy control group. The results showed changes in the composition of the intestinal microbiota in AN group during hospital-based weight restoration, in particular in the family Ruminococcaceae. Within-sample diversity of microbiota of participants before and after renourishment were significantly lower comparing to healthy control group. However, in comparison to T2 samples, composition of intestinal microbiota of T1 samples was far more different from control group. Moreover, the study showed associations between psychopathology at T1 and composition and diversity of microbiota [41]. The study at Kyushu University Hospital investigated the differences between fecal microbiota of female AN patients and healthy female control group. In this study there were a group of 25 AN participants including 14 restrictive (ANR) and 11 binge-eating (ANBP) subtypes and the control gropu of 21 age-matched healthy female. Comparing to control group, AN group had significantly lower amounts of total bacteria, Clostridium coccoides group, Clostridium leptum subgroup, Bacteroides fragilis group, and Streptococcu. The detection rate of the Lactobacillus plantarum was also lower in AN compared to control group. Another result was that the AN group had lower fecal concentrations of acetic acid and propionic acid compared to control group [42]. Another study by Mack I. et al. compared the intestinal microbiota and short-chain fatty acids (SCFA) of patients with AN before and after weight gain with normal weight control group along with dietary intake and gastrointestinal complaints. The study showed that the composition of microbiota in AN changes due to weight gain. Both AN group and control group had the same dominant phyla of Bacteroidetes, Firmicutes, and, to a lesser extent, Actinobacteria, Proteobacteria and Verrucomicrobia. However, the relative abundance of these bacterial phyla differed between those groups. AN group had significantly lower relative abundance of Bacteroidetes, which decreased even more after weight gain. Nevertheless, the relative abundance of Firmicutes increased after weight gain. The results showed that gut microbiota of AN still differs from normal weight control group even after substantial weight gain. Moreover, the level of SCFA in stool samples is similar to control group, but levels of branched chain fatty acids (BCFA) is increased both before and after weight gain compared to control group [38]. Another study by Armougom et al. was based on the feces of 20 obese subjects, 9 patients with anorexia nervosa, and 20 normal-weight healthy controls. In AN group there was much higher concentration of Methanobrevibacter smithii than in control group. In this study it is suggested that the development of Methanobrevibacter in AN may be an attempt to increase the transformation of nutrients into calories or that it is linked to

constipation [43]. The study by Borgo et al. concerning intestinal microbiota and anorexia nervosa showed significant dysbiosis in AN patients, which may be related to AN pathophysiology. There was unbalanced Gram positive/Gram negative relative abundance in AN. Intestinal microbiota had increased level of Bacteroidetes and decreased level of Firmicutes compared with control group. Furthermore, AN microbiota was enriched in Methanobrevibacter smithii. Also some correlations according to BMI were observed. Bacteroides uniformis was negatively correlated with BMI. Moreover, BMI was inversely correlated with all psychological tests [37]. Increased intestinal permeability is called "leaky gut" and it can occur due to abnormalities among mucins, antimicrobial molecules, immunoglobulins, and cytokines [34]. Because of a leaky gut, exterior antigens from the gut lumen may enter into the host [34]. That can contribute to a chronic low-grade inflammation presumed to be present in AN [35]. Interestingly, this increased permeability may be linked to gastrointestinal complaints which are common in AN [45]. Anorexia nervosa often co-exist with anxiety and depression [46]. Abnormal microbiota and dysfunction on axis microbiota–gut–brain may cause mental disorders [47]. Considering this role of gut microbiota may be helpful in defining more precisely the pathophysiology of anorexia nervosa. Microbiota can be manipulated by either the administration of pro/prebiotics or by direct transfer of gut microbiota from another organism [48]. Nutritional rehabilitation is part of AN treatment. Moreover, it is very important that the patients consume large variety of foods. That applies also to food considered 'unhealthy' from gut microbiome's perspective, but 'healthy' from psychological perspective like saturated fats or sugar to solve the problem of the fear of eating [46]. Interestingly, gut microbiome seems to quickly react to short-term macronutrient changes [45]. The diet of AN patients changes rapidly after hospitalization and this may influence their gut microbiota including the possible growth of inflammation-inducing bacteria. Some studies suggest the effectiveness of prebiotics in depression and anxiety treatment [45]. However, a 'healthy' microbiome should be defined on both population and individual level before introducing bacteria-based therapy [49].

Summary

The composition of gut microbiota differs between AN patients and normal-weight individuals. Nutritional rehabilitation also causes changes in intestinal microbiota. There is a great need for more researches of this subject. It is still not know whether those alterations of gut compositions are primary or secondary to the illness. Moreover, the consequences of changing diet as part of

AN treatment are also unknown. However, better knowledge of gut microbiota may be helpful in understanding anorexia nervosa and improving its treatment.

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