Review

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# Role of Intestinal Microbiota in Patients with Anorexia Nervosa

## *Anoreksiya Nervosalı Hastalarda İntestinal Mikrobiyotanın Rolü*

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**ABSTRACT**

Anorexia nervosa is a psychiatric disorder characterized by severe low body weight, impaired self-body image, and intense fear of gaining weight, however its etiopathogenesis is not fully known. Some studies show that nutritional rehabilitation and corresponding weight restoration are not effective enough in the management of intestinal dysbiosis in patients with anorexia nervosa, but results are inconclusive. This work aims to review the existing studies to provide information about the possible role of intestinal microbiota in the pathophysiology of anorexia nervosa, characteristics of intestinal dysbiosis in patients with anorexia nervosa, and possible treatment approaches in the management of intestinal microbiota.

**Keywords:** Anorexia nervosa, microbiota, dysbiosis

**ÖZ**

Düşük vücut ağırlığı, bozulmuş beden algısı ve kilo alma korkusu ile karakterize psikiyatrik bir bozukluk olan anoreksiya nervozanın etiyopatogenezi tam olarak bilinmemektedir. Literatürde yer alan çalışmalar anoreksiya nervosalı hastalarda beslenme tedavisinin ve yeniden ağırlık kazanımının intestinal disbiyoz yönetiminde yeterince etkin olmadığını göstermektedir, ancak çalışmaların sonuçları çelişkilidir. Bu derlemede intestinal mikrobiyotanın anoreksiya nervosa patofizyolojisindeki olası rolü, anoreksiya nervosalı hastalarda intestinal disbiyoza ilişkin özellikler ve intestinal mikrobiyota yönetiminde olası tedavi yaklaşımları hakkında bilgi verilmesi amaçlanmıştır.

**Anahtar Sözcükler:** Anoreksiya nervoza, mikrobiyota, disbiyoz

Anorexia nervosa is characterized by low body weight, distorted body image, and fear of gaining weight according to DSM-5 criteria and is divided into two groups as restricting type and binge eating/purging type (APA 2013). Weight loss and restriction of food intake lead to metabolic, cardiopulmonary, endocrine, gastrointestinal, and hematological complications (Cass et al. 2020). The lifetime prevalence of anorexia nervosa in women has been estimated as 1.4% and 0.6% for men (Galmiche et al. 2019). Of all eating disorders, anorexia nervosa has the highest mortality rate (Arcelus et al. 2019). The etiology of anorexia nervosa is not fully understood, but it has been suggested that biological, psychological, and social factors may involve in the development of anorexia nervosa (Erbay et al. 2016, Moskowitz et al. 2017). Genetic factors and neurobiological risk factors including personality traits such as anxiety, obsession, and perfectionism play an important role in the pathogenesis of anorexia nervosa. (Kaye et al. 2013). The development of neuroimaging techniques, epigenetic approaches, animal studies, new discovery neuropeptides, and changes in gut microbiota patterns have enabled to suggest more comprehensive models related to the pathophysiology of anorexia nervosa (Gorwood et al. 2016). It has been considered that changes in gut microbiota patterns may involve in the pathogenesis of anorexia nervosa by causing disruptions in the gut-brain axis (Di Lodovico et al. 2020). The efficacy of pharmacotherapy in the treatment of anorexia nervosa is very limited and psychotherapeutic interventions have a moderate effect (Öyekçin et al. 2011, Herpertz-Dahlmann et al. 2015, Okumuş et al. 2016). Therefore, it is essential to develop new treatment approaches in addition to pharmacotherapy and psychotherapeutic interventions. It is considered that therapeutic approaches for regulating the alterations in the gut microbiota of anorexia nervosa patients may improve treatment outcome (Carr et al. 2016, Carbone et al. 2020).

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The gut microbiota is comprised of various types of microorganisms and host specific. It evolves throughout an individual's lifetime as it is susceptible to both exogenous and endogenous modifications (Sekirov et al. 2010). Previous studies have reported that the gut microbiota is involved in the regulation of energy homeostasis and body weight and associated with eating behaviour, anxiety, and depressive disorders (De Clercq et al. 2016, Torres-Fuentes et al. 2017, Fetissov 2017, Simpson et al. 2020). Furthermore, the possible role of the gut microbiota in the pathophysiology and treatment of anorexia nervosa has received increased attention in recent studies (Herpertz-Dahlmann et al. 2017, Karakula-Juchnowicz et al. 2017, Ruusunen et al. 2019, Igudesman et al. 2019). The aim of this review is to evaluate the possible role of gut microbiota in the pathophysiology and treatment of anorexia nervosa.

## Possible Role of Gut Microbiota in the Pathogenesis of Anorexia Nervosa

The term microbiota describes a community of commensal, symbiotic, and pathogenic microorganisms living in the human body (Lederberg et al. 2001, Çetinbaş 2017). Bacteria are the most abundant organisms residing in the normal human gut microbiota and the dominant gut microbial phyla are *Bacteroides* (~ 20-25%), *Firmicutes* (~60-65%), *Proteobacteria* (~ 5-10%) and *Actinobacteria* (~ 3%) (Rosenbaum et al. 2015). Gut microbiota plays a crucial role in the digestion and fermentation of nutrients (Rowland et al. 2018), synthesis of short chain fatty acids (Morrison et al. 2016), vitamin K and B-vitamins (thiamine, riboflavine, niacin, pantothenic acid, biotin, folate, vitamin B12) (Soto-Martin et al. 2020, Uebanso et al. 2020), xenobiotic and drug metabolism (Li et al. 2016) and development and activation of the immune system (Yoo et al. 2020). It also affects the gut-brain axis by interacting with the central nervous system, intestinal cells, and enteric nervous system through neuroendocrine and metabolic pathways (Carabotti et al. 2015, Evrensel and Ceylan 2015a). The enteric nervous system influences the composition of the gut microbiota by regulating gastrointestinal motility and secretion, mucosal transport, and blood flow (Al Omran et al. 2014). Linking the enteric nervous system to the central nervous system via the vagus nerve provides neurochemical signals from the microbiota to the brain and from the central nervous system to the microbiota (Carabotti et al. 2015).

The interaction between the brain and intestinal microbiota is quite complex, and some of the mechanisms controlling this interaction are considered regulated through neuroendocrine pathways (Lyte 2013). The intestinal microbiota affects the neurotransmitter levels of the host either directly by neurotransmitter synthesis or indirectly by microorganisms modulating the function of the adrenal cortex (Neuman et al. 2015). The gut microbiota synthesizes numerous neurotransmitters, including γ-aminobutyric acid (GABA), acetylcholine, serotonin, dopamine and histamine (Huang et al. 2019). For example, *Lactobacillus* spp. produces GABA and acetylcholine; *Bifidobacterium* spp. produces GABA; *Escherichia* spp. produces noradrenalin and serotonin; *Bacillus* spp. produces noradrenaline and dopamine; *Saccharomyces* spp. produces noradrenalin; *Candida* spp., *Streptococcus* spp., and *Enterococcus* spp. produces serotonin (Roshchina 2010). Neurotransmitters synthesized by the gut microbiota may play a role in the regulation of mood by affecting the neurotransmitter levels of the central nervous system (Farzi et al. 2018). It has been reported that the monoamine neurotransmitter levels of anorexia nervosa patients decrease, which may have negative effects on mood, food intake, and memory (Riva 2016).

Short-chain fatty acids produced by intestinal bacteria may play a role in the regulation of food intake (Byrne et al. 2015), which have anti-inflammatory effects (Tedelind et al. 2007), and activate the sympathetic nervous system (Kimura et al. 2011). In addition, animal studies have shown that butyrate may cause an antidepressant-like effect by altering the activation of cells in the blood-brain barrier (Yamawaki et al. 2012, Smith 2015). Fecal metabolite levels of anorexia nervosa patients were evaluated in previous studies and it was reported that there was a reduction in short-chain fatty acids, especially butyrate (Mack et al. 2016, Borgo et al. 2017). It has been shown that this decrease is associated with increased severity of depression and anxiety scores in patients with anorexia nervosa (Borgo et al. 2017). Furthermore, it has been considered that short-chain fatty acids may play a role in the pathophysiology of anorexia nervosa, with their effects on the host's energy metabolism and regulation of the biosynthesis of intestinal hormones that play a role in appetite control (Van de Wouw et al. 2017).

Studies of germ-free mice and rats have revealed a mutual interaction between stress and gut microbiota (Foster et al. 2017, Mackos et al. 2017). Germ-free mice displayed enhanced hypothalamic–pituitary–adrenal (HPA) response to restrained stress and substantially increased adrenocorticotropic hormone and corticosterone levels in the plasma. The exaggerated HPA stress response was normalized by colonization of germ-free mice with commensal bacteria (Nobuyuki et al. 2004). Chronic stress can activate the HPA axis leading to alterations in the composition of the gut microbiota (Bailey et al. 2011). Hyperactivity of the HPA axis may trigger cortisol synthesis and induce a proinflammatory response. Cortisol increases intestinal and the blood-brain barrier permeability resulting in enhanced interaction between gut microbiota and the central nervous system (Foster et al. 2017). It has been revealed that excessive physical activity similarly results in increased intestinal permeability (Clark et al. 2016). Chronic stress, enhanced cortisol levels, and excessive exercise are also indicated in patients with anorexia nervosa, and the results of studies evaluating the intestinal permeability of these patients differ (Monteleone et al. 2004, Mörkl et al. 2018). In a study conducted in patients with anorexia nervosa, it was reported that intestinal permeability is decreased in anorexia nervosa (Monteleone et al. 2004), while it showed no significant changes in another study (Mörkl et al. 2018). The methods used in the assessment of intestinal permeability in these two studies differ. In the first study (Monteleone et al. 2014), the lactulose/mannitol test was performed, and in the second study (Mörkl et al. 2018), serum zonulin concentrations were measured.

Increased colonic permeability was reported in mice using an animal model of anorexia nervosa (Jésus et al. 2014).

A recent review on the impact of starvation on the gut microbiota across both human and animal studies concluded that the directionality of this relationship remains complex and unclear (Mack et al. 2018). In spite of that, it has been considered that the gut microbiome may affect appetite, satiety, and eating behavior (Ruusunen et al. 2019). The production of short-chain fatty acids via the microbiome may facilitate the secretion of satiety hormones (peptide YY and a glucagon-like peptide) expressed by gut enteroendocrine cells (Alcock et al. 2014). Studies have indicated that anorexia nervosa induced starvation is associated with profound alterations of the gut microbiome (Kleiman et al. 2015, Mack et al. 2016, Mörkl et al. 2017).

Excessive restriction of food intake by individuals with anorexia nervosa leads to a decrease in energy, carbohydrate, and fat intake, resulting in alterations in the composition of the gut microbiota (Ruusunen et al. 2019). The gut microbiota in patients with anorexia nervosa appear to be shifted towards protein and mucin-degrading Verrucomicrobia and Firmicutes with reduced Bacteroidetes (Mack et al. 2016). Mucin degrading bacteria can feed on the mucins produced by intestinal goblet cells that line the inside of the gut wall, which further weaken the intestinal barrier and increase gut permeability (Jésus et al. 2014, Mack et al. 2016). A weakened barrier and increased permeability can trigger inflammatory and immunological reactions of the host. The passage of bacteria and bacterial contents such as lipopolysaccharides from the intestinal wall to the bloodstream activates immune cells, leading to enhanced expression of proinflammatory cytokines and production of antibodies (Kelly et al. 2016, Bambury et al. 2018). In meta-analyses, it has been reported that anorexia nervosa patients display increased proinflammatory cytokine levels compared to healthy controls (Solmi et al. 2015, Dalton et al. 2018). Mice have been immunized with caseinolytic protease B (ClpB) produced by *Enterobacteria*, such as *Escherichia coli (E. Coli)* and identified as a conformational mimetic of α-melanocyte-stimulating hormone (α-MSH) and ClpB-immunized mice produced anti-ClpB IgG crossreactive with α-MSH, influencing food intake, body weight and anxiety (Tennoune et al. 2014). Chronic intragastric delivery of *E. Coli* in mice decreased food intake and stimulated the formation of ClpB- and α-MSH-reactive antibodies. Moreover, anorexia nervosa and bulimia nervosa patients displayed increased plasma levels of anti-ClpB IgG antibodies (Tennoune et al. 2014). In another study, it has been reported that plasma ClpB concentrations of patients with eating disorders including anorexia nervosa, were elevated which was correlated with anti-ClpB and anti-α-MSH antibodies (Breton et al. 2016). These studies suggest that bacterial ClpB may play a role in the pathophysiology of anorexia nervosa.

## Gut Dysbiosis in Patients with Anorexia Nervosa

Dysbiosis ***is*** characterized by a decrease in microbial diversity and some beneficial strains and an increase in pathogenic strains. Studies have indicated that dysbiosis is associated with inflammatory bowel disease (IBD) (Sartor 2008, Bajer et al. 2017), irritable bowel syndrome (IBS) (Rajilić–Stojanović et al. 2011), asthma (Barcik et al. 2020), obesity (Walters et al. al. 2014, Yüksel Altuntaş et al. 2017, Tekin et al. 2018), and various neuropsychiatric disorders (Morita et al. 2015, Castro-Nallar et al. 2015, Keshavarzian et al. 2015, Jiang et al. 2015, Aizawa et al. 2016, Alagöz 2017, Borgo et al. 2017, Strati et al. 2017, Vogt et al. 2017, Schwarz et al. 2018, Pulikkan et al. 2018). Role of the gut microbiota in modulating the stress response and stress-related behaviors related to psychiatric disorders such as anxiety and depression has become an important research area in recent years (Cryan et al. 2012). Colonization of germ-free mice with microbiota from various bacterial strains alters the composition of the microbiota and plays a role in inducing anxiety and depressive behavior (Bercik et al. 2011, Bravo et al. 2011, Neufeld et al. 2011). Studies conducted with anorexia nervosa patients have shown that these patients have significant alterations in the gut microbiota composition (Gorwood et al. 2016, Borgo et al. 2017). It has been reported that these patients have higher intestinal Methanobrevibacter smithii archaeon concentrations (Armougom et al. 2009). On the other hand, it has been indicated that anorexic patients had significantly lower amounts of total bacteria and obligate anaerobes including those from the *Clostridium coccoides* group, *Clostridium leptum* subgroup, and *Bacteroides fragilis* group than control group (Morita et al. 2015). Also, it has been considered that there were no significant differences in gut microbial composition between patients with restrictive (ANR) and Binge eating/purging (ANBP) types of anorexia nervosa. In another study, it has been reported significant differences in gut microbial structure between ANR and ANBP types (Mack et al. 2016). It is thought that the reason ANR patients need more kilocalories than ANBP patients for gaining the same amount of weight is due to the difference in gut microbiota composition which plays an important role in energy extraction from the same amount of food (Krajmalnik-Brown et al.2012, Marzola et al. 2013). In a study, the low microbial diversity and differences in taxa abundance in patients with anorexia nervosa were associated with gut dysbiosis. In addition, in this study, it was shown that gut dysbiosis is associated with depression and eating disorder psychopathology. (Kleiman et al. 2015). In another study, it has been shown significant differences in the gut microbiota composition of patients with anorexia nervosa compared to the control group. In addition, it has been highlighted the lower *Bacteroidetes/ Firmicutes* ratio in AN patients (Mack et al. 2016). In almost all reviewed studies, the intestinal microbiota diversity and composition of AN patients are different from healthy individuals and overweight/obese control groups (Armougom, et al. 2009, Million et al. 2013, Morita et al. 2015, Mack et al. . 2016, Borgo et al. 2017, Mörkl et al. 2017, Hanachi et al. 2019) (Table 1).

## Microbiota Management (Modification) in Patients with Anorexia Nervosa

It is thought that gut dysbiosis plays an important role in the etiology of eating disorders. Therefore, the investigation of

treatment methods aiming to regulate the composition of the intestinal microflora has great importance for the treatment of these diseases (Lam et al. 2017). A multidisciplinary team approach consisting of a doctor, a dietitian, and a mental health professional is required for diagnosis, treatment, and follow-up patients with eating disorders like anorexia nervosa (Jeffrey et al. 2020). The role of the dietitian in the treatment of eating disorders is to determine nutritional status and identify irregular eating habits and factors like wrong beliefs about food and eating that prevent attainment and maintenance of optimal nutrition status (McMaster et al. 2021). In nutritional therapy; a dietitian is responsible to design an individual meal plan, establish a healthy relationship between food and eating, correct nutrient deficiencies, provide nutritional education to build healthy and regular eating habits for gaining body weight of AN patients (Zipfel et al. 2015, McMaster et al. 2021). It has been reported that weight gain is not effective in recovering microbial perturbations and dysbiosis in patients with AN (Mack et al. 2016). The composition of the gut microbiota can be modified by probiotic and prebiotic supplementation and fecal microbiota transplantation.

Probiotic supplementation is one of the approaches that play a role in the modulation of the intestinal microbiota (Karatay 2019, Wieërs et al. 2020). Studies have been shown that probiotic supplementation regulates bowel function in patients with functional and inflammatory bowel diseases (Ni et al. 2017, Currò et al. 2020). Additionally, it has been determined that the use of probiotics can reduce abdominal pain in patients and improve the patient's adaptation to a therapeutic diet. (Didari et al. 2015, Sato et al. 2015). A systematic review and meta-analysis study evaluating the efficacy of probiotic and prebiotic supplementation in the treatment of depression and anxiety revealed that probiotic supplementation can be considered as a possible approach in the treatment of depression and anxiety, but they emphasized that more randomized controlled clinical studies are needed (Liu et al. 2019). It is thought that probiotics may have therapeutic potential, taking into consideration their effects on immunity and brain function, the regulation of appetite, and the psychopathology of eating behavior disorders, as well as modulation of the microbiome (Foster et al. 2017). These results pointed out that probiotic supplementation can be considered as a supportive therapy in addition to the standard therapy in the treatment of anorexia nervosa. It was indicated that probiotics such as *Roseburia*, which play a role in butyrate synthesis, can be applied in the treatment of anorexia nervosa in the future. (Mack et al. 2016, Mack et al. 2018).

Another potential strategy for regulating gut microbiota composition and preventing dysbiosis in anorexia nervosa is fecal microbiota transplantation (FMT), which was recently investigated by two case report studies (Evrensel and Ceylan 2015b, Ünal 2016, De Clercq et al. 2019, Prochazkova et al. 2019). In the study of De Clercq et al., a woman with anorexia nervosa underwent a fecal transplant from a healthy donor and the results showed an increase in body weight and body fat percentage over time, and a decrease in resting energy expenditure despite stable energy intake. Additionally, significant changes in the gut microbiota composition of the patient and a remarkable increase in fecal acetate and butyrate levels were observed after transplantation (De Clercq et al. 2019). In this study, increased production of short-chain fatty acids has been associated with weight gain, which can be explained by the increased levels of *Verrucomicrobia*. It is thought that short-chain fatty acids increase energy extraction from food, which might clarify the weight gain despite unchanged dietary intake in the patient during the follow-up period. (De Clercq et al. 2019). In the other study, fecal microbiota transplantation was implemented for a patient with severe and enduring anorexia nervosa and diagnosed with small intestinal bacterial overgrowth syndrome (SIBO). In this study, the AN patient's intestinal barrier function, microbiota composition, and the level of microbial metabolites were investigated (Prochazkova et al. 2019). A decrease in the patient's *Bacteroidetes* phylum and an increase in the *Firmicutes* phylum have been observed after transplantation. In addition, improvement in intestinal barrier function and increased total fecal short-chain fatty acid levels have been reported. However, a downward trend in the fecal serotonin levels of the patient and no sign of improvement in her clinical condition was observed (Prochazkova et al. 2019). This study reveals that a comprehensive fecal microorganism analysis of the donor should be performed and the most appropriate fecal donor should be selected. Although these studies show that fecal transplantation can be considered as a new treatment approach in patients with anorexia nervosa, further studies are needed. In addition, it has been reported that there are no side effects of fecal transplantation treatment in these case reports, but it should be taken into account that fecal microbiota transplantation can be associated with adverse effects such as diarrhea, constipation, and infection (Agrawal et al. 2016). However, the limited number of study results in this review point out that probiotic supplementation and fecal transplantation may play an important role in the treatment of patients with anorexia nervosa, randomized controlled clinical studies are required to determine the effectiveness of these treatments.

## Conclusion

The gut microbiota composition of patients with anorexia nervosa differs from normal and overweight or obese individuals; however, more research is needed to determine whether these differences are a cause or consequence of anorexia nervosa. Restoration of weight and improving nutritional status are essential components of nutritional therapy in increases anorexia nervosa patients. A limited number of studies reported that nutritional therapy and weight regain in patients with anorexia nervosa did not improve the gut microbiota composition. However, the fact that current nutritional therapy procedures cannot provide the desired changes on the gut microbiota, the need for new therapeutic approaches. To promote the optimal AN treatment that can play a role in modulating the gut microbiota, it is more important to have detailed information about the diets of patients with anorexia nervosa before the nutritional treatment,

**Table 1. Changes in the gut microbiota of patients with anorexia nervosa**

| Reference | Study population | Purpose | Measurments and Assesment | Fecal Sample Collection Time | Results |
|---|---|---|---|---|---|
| Armougoum 2009 | 9 AN (BMI 12.7 ± 1.6 kg/m2)<br>20 HC (BMI 20.7 ± 2.0 kg/m2)<br>20 Obese Control (BMI 47.1 ± 10.7 kg/m2) | To identify the relative abundance of taxonomic orders of gut MB using PCR test | -Copy number/g feces<br>- Number of individuals with concentrations greater than of certain bacterial spieces.<br><br>qPCR | AN patients recently hospitalized | - ↓ Lactobacillus species in AN patients compared to obese controls<br>-↑ Archeon Methanobrevibacter smithii,<br>-Firmicutes, Bacterioidetes and Lactobacillus similar to HC |
| Million 2013 | 15 AN (BMI 13.5 kg/m2)<br>76 HC (BMI 22.4 kg/m2)<br>38 Overweight control(BMI İ 27.1 kg/m2)<br>134 Obese control (BMI 40.0 kg/m2) | To evaluate correlation between bacterial concentration and BMI | - Bacterial prevalence in each group<br>-Determining the concentration of each species (log10 copies DNA/ml) in feces<br><br>qPCR | Hospitalized patients and outpatients at the Nutrition Unit. Fecal sample collection time is not available. | - ↓ Lactobacillus reuteri species compared to HC<br>- ↑ Escherichia coli and ↑ Archeon Methanobrevibacter smithii compared to obese control<br>-↑L. reuteri'nin dışkı konsantrasyonu, correlated with ↑BMI<br>-↑ B. animalis, M. smithii and E. Coli, correlated with ↓ BMI |
| Morita 2015 | 25 AN (BMI 12.8 ± 1.3 kg/m2)<br>21 HC (BMI 20.5 ± 2.1 kg/m2) | To compare the fecal MB of AN patients with age- and sex-matched HC. | -Bacterial count (log10 cells/g feces)<br><br>16Sor23S rRNA–targeted–qPCR | Hospitalized patients or patients visited outpatiens section. Fecal sample were collected into two tubes (~1.0 g/tube) by the participants or hospital staff. Fecal sample collection time is not available. | - ↓Total bacteria and obligate anaerobes (Clostridium coccoides gp, Clostridium leptum subgroup ve Bacteroides fragilis group, Streptococcus, Lactobacillus plantarum subgp) compared to HC.<br>- ↓SCFs (acetic and propiyonic acid) in feces compared to HC |
| Kleiman 2015 | 16 inpatient admission AN (T1) (BMI 16.2 ± 1.5 kg/m2)<br>10 discharge AN (T2) (BMI 17.7 ± 1.4 kg/m2)<br>12 HC (BMI 21.5 ± 1.9 kg/m2) | - To measure MB changes of patients with AN after weight restoration.<br>- To compare MB of AN patients with age- and sex-matched HCs. | -α-Diversity: (Chao1 index)<br>-β- Diversity: (Unifrac distance)<br>- Operational Taxonomic Units<br><br>16 s rRNA Sequencing (V1-V3) | After admisson (before starting treatment) and before discharge (samples were taken by nurses trained in collection protocols) | - ↓ α-Diversity in AN patients (T1, T2), compared to HC<br>-↑ Bacilli, ↑ Coriobacteriales↓ Filogenetik bolluk,↓ Clostridia and ↓ Faecalibacterium,↓Anaerostipes in AN(T1) patients compared to HC<br>- Significant changes between T1 and T2 in taxa abundance and β- Diversity. ↑α-Diversity in T2 compared to T1 patients. |
| Mack 2016 | 55 inpatient admission AN (T1) (BMI 15.3 ± 1.4 kg/m2)<br>44 discharge AN (T2) (BMI 17.7 ± 1.4 kg/m2)<br>55 HC (BMI İ 21.6 ± 2.0 kg/m2) | -To compare the fecal MB and SCFA in AN patients (at T1 and T2) and age and sex matched HCs.<br>-To evaluate dietary intake and gastrointestinal complaints in AN T1 and T2 patients and HCs. | - Differences in microbial composition between AN and HC.<br>- Relative proportion of bacterial phyla between AN patients (T1 and T2) and HC.<br>-α- Diversity: (Chao1 index, Shannon index).<br>-β- Diversity<br>- Operational Taxonomic Units<br><br>16 s rRNA sequencing (V4) | As soon as possible after the beginning of inpatient stay and before discharge | - ↑ Mucin-degraders, I, XI and XVIII Clostridium clusters and Bifidobacterium<br>↓ Roseburia spp, Coprococcus, Dorea and XIVa Clostridium clusters in AN patients compared to HC<br>-↑ BCFA concentration in AN patients<br>---Perturbations in intestinal MB and SCFA profiles and gastrointestinal symptoms did not recover after weight gain (T2 patients) |

**Table 1 (Continued). Changes in the gut microbiota of patients with anorexia nervosa**

| Reference | Study population | Purpose | Measurments and Assesment | Fecal Sample Collection Time | Results |
|---|---|---|---|---|---|
| Borgo 2017 | 15 AN (BMI 13.9 ± 2.1 kg/m2)<br>15 HC (BMI 22.1 ± 2.6 kg/m2) | To combine MB data with clinical and psychological characteristics to explain the relationship between nutritional status and MB-gut-brain axis in AN patients. | -α-Diversity,<br>-β Diversity ,<br>- Operational Taxonomic Units ,<br>- Relative abundance of microbial taxa<br><br>16 s rRNA Sequencing (V1-V2) | Fecal sample collection time was not available. | -↑ Enterobacteriaceae and M.smithii.<br>-↓ Roseburia, Ruminococcus and Clostridium.<br>-↓ Fecal butyrate, and propionate.<br>- Butyrate concentrations are inversely correlated with anxiety levels.<br>- Propionate directly correlated with insulin levels and with the relative abundance of Roseburia inulinivorans<br>-BMI had negative correlation with Bacteroides uniformis and with psychopathological scores<br>- BMI was the best predictor for gut dysbiosis and metabolic alterations |
| Mörkl 2017 | 18 AN (BMI 15.2 ±1.3 kg/m2)<br>20 Athlete (BMI 22.1 ±1.8 kg/m2)<br>26 HC (BMI 21.9 ±1.7 kg/m2)<br>22 Overweight control (BMI 27.0 ±1.1 kg/m2)<br>20 Obese control (BMI 34.5 ± 4.4 kg/m2) | -To compare intestinal MB in AN and other groups.<br>- To investigate the relationship between intestinal MB with anthropometric measurements, total body fat and fat distribution, depression scales, serum lipids and CRP. | -α-Diversity : (Chao1 index, Shannon index).<br>-β- Diversity : (unweighted and weighted Unifrac distance)<br>-LDA score.<br><br>16 s rRNA Sequencing (V1-V2) | Fecal samples were collected 10.61 ± 13.01 (SD) days after hospital admission. | - ↓α-Diversity in AN patients and obese control compared with other groups<br>- ↑ α-Diversity in athletes<br>- ↑ Coriobacteriaceae (LDA score > 3.5) in AN patients |
| Hanachi 2019 | 33 AN (BMI 11.7 ±1.5 kg/m2)<br>22 HC (BMI 21.0 ±1.5 kg/m2) | To evaluate the relationship between functional intestinal disease severity and intestinal dysbiosis in severe AN patients receiving enteral nutritional support. | -α- Diversity ,<br>-β- Diversity,<br>- Operational Taxonomic Units ,<br>- Relative abundance of microbial taxa.<br><br>16 s rRNA Sequencing (V3-V4) | Approximately 2 g fecal sample was collected 10 days after receiving enteral nutrition | -↓ β-Diversity and distinct dysbiosi in AN patients<br>↑ Klebsiella, Turicibacter, Ruminococcus and Salmonella,<br>↓Eubacterium, Roseburia, Anaerostipes and Peptostreptococcaceae.<br>↓ Peptostreptococcaceae family<br>↑ Dialister, Robinsoniella and Enterococcus |

*AN:Anoreksia Nervosa, HC: Healthy Control, BMI: Body Mass Index, MB: Mikrobyota, CRP: C-Reactive-Protein, LDA: Linear Discriminant Analysis

to evaluate the intestinal microbiota composition at different times during the nutrition treatment, and to try different treatment strategies such as fecal microbiota transplantation and probiotic supplementation.

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