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Dysbiosis of the Microbiota in Anorexia Nervosa: Pathophysiological Implications

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Abstract

Anorexia nervosa (AN) is a severe and often enduring condition of which the etiology is unknown. Studies on the gut microbiota in AN have found deviations from that of healthy individuals, which may imply a relation to pathophysiology, development and maintenance of the disorder via the gut-brain axis, which has been shown in other disorders. A narrative review of the gut microbiota studies in AN is presented. Several studies point to a dysbiosis in AN which may have implications for maintenance of a low body weight, immunological changes and a severely reduced food intake. An association may be found to clinical symptoms in AN. A pathophysiological model for disease is presented implying a role of the microbiota in maintenance of AN. Dysbiosis in AN may play an important role in the development and maintenance of AN.

Keywords: anorexia nervosa, feces, microbiota, species, biomarkers

1. Introduction

Anorexia nervosa (AN) is a serious and often enduring psychiatric condition. The hallmark features of AN are a phobia for weight gain, and for intake of fattening food, disturbance in body image, and often compensatory behaviors such as excessive exercise and purging, which overall leads to a reduction of energy intake relative to energy expenditure leading to low body weight. An increased risk of suicide and frequent potential life-threatening medical complications of several body organs contribute to AN having a high standardized mortality ratio of 5.2 [3.7–7.5] [1]. This is coupled with a high risk of enduring disease [2].

The weight loss is in some patients preceded by a depression, a trauma, gastrointestinal symptoms or an infection. But in a majority of patients there is no detectable psychiatric or somatic disorder preceding the weight loss. In children and adolescents with AN, family-based treatment as described by Lock and LeGrange is recommended [3] and if treatment is started shortly after debut of the disorder, the prognosis is fairly good. However, if treatment is delayed, the prognosis becomes worse [4]. In adults, individual eating-disorder-focused therapy (CBT-ED) is recommended [5]. With this treatment, drop-out rates are high and even with optimal treatment by well-trained therapists only 50% of the patients who start CBT-ED have good effect of the therapy [6, 7].

Considering the high mortality, high chronicity and lack of knowledge on the etiology of AN, there is an immense need for an improved understanding of the etiology and pathophysiology of the disease in order to find ways to better treatments. This knowledge would preferably explain both the routes into developing the disorder and mechanisms that serve to maintain it, and proposedly involve both biological and psychological factors, such that measures and biomarkers to follow the development and recovery from of the disease could be identified. Potential further benefits with biomarkers for AN may be guidance for risk stratification, treatment and target identification for novel treatments. The last few years have seen an increase in studies on the gut microbiota and its associated microbiome which might harbor trait biomarkers for AN.

The “microbiota” refers to the cumulative microorganisms, including Bacteria, Viruses, Archaea, Protists and Fungi, which populate a number of human tissues and biofluids including the skin, lungs, oral mucosa, saliva, and gastrointestinal tract, and the “microbiome” refers to the collective genomes of the present microorganisms [8]. There are more than 1000 ‘species-level’ phylotypes that coexist in a human [9], and the majority of these phylotypes are Bacteria, with *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Bacteroides uniformis* dominating in the adult microbiota found in feces samples [10]. The composition of the phylotypes is mostly consistent across individuals, albeit there may be a large variability with regard to relative composition and diversity of the included microorganisms, intra-individually depending on anatomical site and inter-individually at the same anatomical location. In addition, there are inter-individual variations at the same anatomical site.

The gut microbiota is critical for the development of the gut mucosal immunity [11, 12], and it is also involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis [13], serotonergic neurotransmission [14], and signaling mechanisms affecting neuronal circuits involved in motor control and anxiety in mice [15]. This pathway has been named the gut-brain axis [16].

2. The gut-brain axis

The existence of the gut-brain axis is exemplified by irritable bowel syndrome (IBS) where more than half of the patients also suffer from mood disorders and for which antidepressants is one of the more common pharmaceutical treatments [17]. In IBS and other potential gut-brain axis disorders, cognitive alterations seem to be key features of the disorders [18]. These cognitive alterations might be induced by signal transduction from gut to the brain [18]. In addition, the existence is also shown by the effects of antibiotic exposure, which may lead to altered brain function such as anxiety, panic disorder, major depression, psychosis, and delirium which are usually described as side effects of antibiotic treatment [19]. Support for the latter comes also from studies in mice which have shown that an altered composition of the gut microbiota in adult mice, and an increased exploratory behavior including hippocampal expression of Brain Derived Nerve growth Factor (BDNF) has been found after oral administration of non-absorbable antimicrobials [20], in contrast to intraperitoneal administration, which had no effect on behavior or BDNF levels.

Another area of evidence for the gut-brain-axis stems from dietary induction of changes in gut microbiota and linked psychopathological outcomes. For example, a high fat diet has been found associated with an altered microbial diversity and diminished synaptic plasticity [21, 22] but also increased vulnerability and anxiety-like behavior in the mice [23]. In addition, a diet high in sucrose also led to an altered microbial diversity associated with impaired development of spatial bias for

long term memory, short term memory, and reversal trainings [24]. Another strong evidence for the gut-brain axis comes from a study in mice exposed to a microbiome depletion and/or transplantation paradigm where microbiota, in a first step, was isolated from donors who were provided with either in high fat diet or a controlled diet, and thereafter in a second step, transfused to mice who developed significant and selective disruptions in exploratory, cognitive, and also developed the stereotypical behavior following the high fat diet [25]. However, there are also evidence from studies where alcohol exposure, smoking habits, and disruptions in diurnal rhythm all have been shown to affect the microbiota composition.

There are also other evidence pointing to a reciprocal interaction from a study where a second generation antipsychotics, olanzapine, was exposed to rats and found to affect the composition of the microbiota, which also triggered an inflammatory response and weight gain [26, 27]. Furthermore, the exposure to antibiotics seemed to attenuate these physiological effects [28].

The microbiome has also been found to have been altered in various psychiatric conditions, or to affect its clinical expression, as well altered in rodent models for these disorders [29]. One example is major depressive disorder (MDD) where, for example, in germ-free mice (mice completely void of bacterial microbiota or derived molecules), there are both changes from comparable normal mice in the hypothalamic, pituitary, adrenal stress response, as well as altered levels of monoamines concentrations or their receptors [13–15, 20, 30]. Indirect evidence in MDD also comes from an increased serum antibody level to lipopolysaccharides that stems from Gram-negative enterobacteria, which are higher in MDD compared to controls [31], and which is associated with stress associated increased gut permeability and bacterial translocation in animal models [32, 33]. In addition, depression also altered the gut microbiota in a mouse model, in which chronic depression and anxiety-like behaviors were induced by olfactory bulbectomy [34], suggesting a feedback loop between depressive states and dysbiosis.

Furthermore, a similar type of relation between dysbiosis and psychopathogenesis is found in schizophrenia [35, 36]. For example, elevated levels of serological markers of bacterial translocation have been found to be highly correlated with systemic inflammatory markers in schizophrenia [37], and, cytokine levels in schizophrenia are correlated with the severity of symptomatology [38]. From a genetic point of view, several of the strongest associations identified between genetic risk and schizophrenia stems from genes that are linked to immunological function [57, 58]. This is particularly interesting in view of the genetic association between AN and schizophrenia [39].

3. How is the effects in the gut-brain axis mediated?

The mechanism behind the gut brain axis may be multifaceted involving neural signal transduction in nervus vagus, neurotransmitters, immunological mechanisms, and mechanisms related to metabolism and energy utilization [40]. One of the strongest links from a mechanistic point of view, stems from research on serotonin and the microbiota. Enterochromaffin (EC) cells provides approximately 95% of the total body content of serotonin [41] of which the majority exists in plasma. Multiple levels of evidence links disturbances in the serotonergic system and several psychiatric disorder such as depression, anxiety, and borderline personality disorder. For example, the metabolism of tryptophan, a precursor of serotonin, is potentially regulated by the gut microbiota thereby enabling it to influence brain function [42]. Tryptophan is an essential amino acid derived from the diet [43], and tryptophan that is absorbed from the gut into the bloodstream passes the

blood-brain barrier to contribute to serotonin synthesis in situ [43]. The availability of tryptophan is strongly affected by the gut microbiota, and several studies have indicated that bacteria such as streptococcus, Escherichia, enterococcus species and *Bifidobacterium infantis*, and especially indigenous spore-forming bacteria may modulate serotonin levels by increasing plasma tryptophan [44]. An example of this is studies in germ free mice that have found that they exhibit an increased plasma tryptophan concentration [14, 15], which after post weaning colonization can be normalized [14]. The serotonergic neurotransmission may thereby be influenced by the availability of tryptophan for serotonin production [45]. There are studies have found that a depletion of tryptophan influences mood, anxiety and borderline personality traits, for example, in AN and bulimia nervosa [46–49].

There are also other evidences that link the gut microbiota with psychiatric conditions such as MDD. For examples, a recent publication by Seng et al. [50] provides three additional levels of evidences: (a) that germ free mice lacks gut microbiota and display depression like features in forced swimming test compared to conventionally raised healthy control mice; (b) that the gut microbiota composition of MDD patients differ from that of healthy controls; and (c) and that transplantation of MDD microbiota to germ free mice led to the development of depression like behaviors. In addition, Seng et al. found that mice that were harboring the microbiota from MDD patients primarily exhibited disturbances of microbiome genes and host metabolism which thereby suggests that the depression-like behavior was mediated through the host metabolism [50].

Another neurotransmitter that is produced by the microbiota and that may influence host behavior is gamma aminobutyric acid (GABA) which is the main inhibitory neurotransmitter in the CNS. GABA produced by the probiotic *Lactobacillus rhamnosus* was administered to mice and led to an alteration in the expression of GABA receptors in different CNS regions, associated with reduced anxiety and depression-like behaviors [51].

Another mechanism for interaction between the microbiome and the CNS is at the level of the blood-brain barrier (BBB). The vascular BBB is comprised of specialized brain endothelial cells acts as a regulatory interface between brain and blood that prevent the unrestricted transfer of molecules into the CNS. Disruption of the tight junctions of the BBB can expose the CNS, and has also been linked to CNS disorders [52]. A dysbiotic microbiome could possibly interact with the BBB in several ways: bacterial factors and immune-active molecules released from peripheral sites influenced by the microbiome can cross the BBB, alter BBB integrity or change BBB transport [53]. In germ-free mice, it has been shown that the BBB has increased permeability compared to pathogen-free mice with a normal gut flora. The increased permeability was associated with reduced expression of the tight junction proteins. Exposure of germ-free adult mice to a normal gut microbiota decreased BBB permeability and up-regulated the expression of tight junction proteins [54]. Metabolic products such as short-chain fatty acids (SCFAs) are produced through the fermentation of dietary fibers by the gut microbiota [55] and can cross the BBB to affect brain function. A low production of SCFAs could lead to increased BBB permeability and SCFAs has been shown to be able to improve a dysfunctional BBB in germ-free mice [54]. Another example is that antibiotics are able to modify barrier integrity and alter behavior in mice [56] and alterations to the microbiome composition in mice in favor of, for example, probiotic bifidobacteria spp. through food supplement with prebiotics showed impact on neuroinflammation and were accompanied with changes in the expression of tight junction proteins [57]. Furthermore, leptin, a key hormone for the control of appetite and weight gain, is normally restricted by the BBB but has been shown in mice with a deficit in leptin transport to the brain to enhance the sense of food reward [58].

4. Microbiota findings in AN studies

Dysbiosis has been proposed in AN and through the long periods of starvation associated with the core psychopathology of AN, a considerable adaptation in gut microbiota could occur in individuals with AN. A systematic review by Schwennsen et al. [59] found some evidence of dysbiosis in AN, such as the abundance of the gut microbiota in AN, which was described as either normal [60, 61], reduced [62] or altered in AN [63]. In addition, the diversity of the gut microbiota in AN was described as normal [61, 63], or reduced (alpha, i.e., within-sample diversity) [64] both in the acute stage and after weight restoration.

Common microbiota findings in the acute stages of AN were low levels of phylum Bacteroidetes [61, 64], while the phylum Firmicutes was increased in AN in three studies [61, 64, 65] however decreased in a fourth [63]. Furthermore, the genus *Methanobrevibacter* and specifically, the species *M. smithii*, has been found increased in AN patients in several studies [60, 61, 63, 65]. It is important to remember the presence or lack of a specific bacterial spp. identified by their 16rRNA gene is not the same as the presences or lack of certain metabolic functions or microbiota steady-state dynamic. The state of knowledge of the microbiota in AN is in its infancy and more studies are needed.

4.1 The microbiota and relation to clinical symptoms in AN

This systematic review [59] identified two studies describing an association between the microbiota and clinical symptoms in AN. In one study, ClpB protein concentrations were significantly correlated with several subscales on the Eating Disorder Inventory-2 (EDI-2) for patients with eating disorders and the Montgomery-Åsberg Depression Rating Scale (MADRS) total score and specifically the anhedonia score for AN patients ($p < 0.05$) [66]. In another study, an association between alpha diversity and depression and eating disorder psychopathology was found in AN [64]. Should further studies find further support for that the microbiota drives the symptoms of AN, this would strengthen targeting the microbiota as a primary level of treatment of AN.

5. How is the gut-brain axis involved in AN? Breakdown of organic material in the gut and its exposure in plasma

A potential mechanism through which the microbiota indirectly influences the pathophysiology and symptoms of AN is through the breakdown of organic material in the gut and the transfer of metabolites into the blood stream. One of the microbiota that has been described in AN is *M. smithii*, which is involved in the breakdown of polysaccharides from vegetable sources and the finding of this specific Archaeon could illustrate an adaptation to a typical diet rich in vegetables and fruits in persons with AN. In addition, methanogenic Archaea, such as *M. smithii*, have also been linked to constipation, a common complaint in patients with AN, which statins have been shown to alleviate by suppressing the growth of methanogens [65, 67–69]. The evidence of *M. smithii* in feces from constipated patients necessitate further investigation of whether this finding in AN patients is only related to constipation or also related to AN psychopathology as a potential biomarker.

The gut microbiota is involved in both weight gain and weight loss as well as with energy extraction from the diet in both humans and animals [70, 71]. Differences in the composition of the gut microbiota between obese and lean individuals have been consistently described, potentially illustrating differences in energy extraction

efficiency between obese and lean individuals [72, 73], and specific gut dysbiosis could predispose to the drive toward negative energy balance in AN. With regard to the effect of weight gain on the fecal microbiota, Firmicutes has been found increased after weight restoration in two studies in AN [61, 64].

6. AN comorbid disorder as evidence of microbiota influence

Intestinal dysbiosis has previously been associated with psychological function and mental health including depression and anxiety, both of which are commonly comorbid with AN [40]. AN patients often present with comorbid anxiety (75% lifetime prevalence of anxiety disorder) [74] and depression (more than 34% lifetime prevalence of depression) [75, 76]. These findings provide further support for a role of dysbiosis in the pathophysiology of AN.

7. A leaking gut in AN?

During starvation, some of the gut bacteria will have insufficient nutrient supply for survival. Slowly growing bacteria or bacteria able to feed on the mucus lining the gut wall will survive for a longer period of time [77]. The competition between bacteria with different growth capacities to survive and proliferate in the gut has probably taken place for millions of years. Thus, it is reasonable to expect that various mechanisms for survival and proliferation have emerged among gut bacteria including the capacity to release of substances inhibiting food intake of the host. Alterations in gut permeability has been linked to a number of intestinal diseases, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), but also to extraintestinal disease as depression, anxiety and autism specter disorders [78, 79]. Increased gut permeability may also facilitate signal transduction from the gut to the brain via the vagus nerve and blood [80], possibly in synergy with interaction with increased BBB permeability. In addition, in animal and human studies, the experience of stress is also linked to an increase in permeability of the intestinal barrier. This increase in permeability seems to be mediated through, among other factors, hypothalamic hormones, especially corticotropi-releasing hormone (CRH) [77]. Increased mucin degrading bacteria has been demonstrated in AN [81] indicating that decreased food intake induce overgrowth of bacteria able to feed on the mucus layer and thereby increase gut permeability.

An example of a possible biomarker species is the bacterium *Akkermansia muciniphila* which is abundant in humans and rodents and has been inversely correlates with body weight and is associated with metabolic syndromes and auto-immune diseases [82]. *A. muciniphila* is a symbiotic bacterium of the mucus layer, can utilize mucin as its sole carbon, nitrogen, and energy source and is able to produce certain SCFAs [83, 84]. In mice, it has been shown that the abundance of *A. muciniphila* decreased in obese and type 2 diabetic mice and that administration of the bacterium increased the intestinal levels of endocannabinoids that control inflammation, the gut barrier, and gut peptide secretion [82]. In a single AN patient case story, it has been shown that one treatment with a fecal matter transplant from a healthy donor led to weight gain and an increase in *A. muciniphila* and SCFAs blood levels [85]. *A. muciniphila* is an example of a complex interaction where the bacterium simultaneously degrade the mucin for energy, but also at the same time induces higher mucus production from the host. This could in turn improve protection of the gut wall from interaction with harmful molecules from other gut bacteria and leakage into the blood.

Furthermore, in an activity based mouse model of AN Jésus et al. demonstrated increased permeability in the colon, that is, “gut leakiness”, in anorexic mice,

however the authors also found that the gut leakiness was more related to malnutrition than exercise [86]. Although there may be conflicting studies [87], yet another study examining the role of exercise on gut permeability, found that exercise increases intestinal permeability measured with the lactulose and rhamnose differential urinary excretion test [88].

Another support for a leaking gut wall in AN comes from a study by Breton et al. [66], who found an increase in ClpB protein concentrations in plasma in eating disorder patients compared to plasma of controls, and furthermore, that ClpB protein concentrations correlated positively with alpha-Melanocyte Stimulating Hormone-(alpha-MSH)-reactive IgG for all patients with eating disorders. ClpB protein is produced by *Enterobacteriae* such as *Escherichia coli* and has been found as a conformational mimetic of alpha-MSH, which is thought to be involved in satiety and anxiety [89]. The study adds evidence to the potential role of ClpB protein produced by *Enterobacteriae* in the gut and its impact on the brain and psychopathology in eating disorders.

The potentially altered gut permeability in AN may underlie the low-grade inflammation and increased risk of autoimmune diseases found in eating disorders [90]. Moreover, starvation has a significant impact on the gut microbiota, and a diet based on animal products used for re-nutrition, may stimulate the growth of bacteria that trigger inflammation [91].

8. A model for the pathophysiology of AN

The initial reduction of food intake induces alterations in the gut microbiota. These alterations in gut microbiota induce increased gut permeability. Due to this

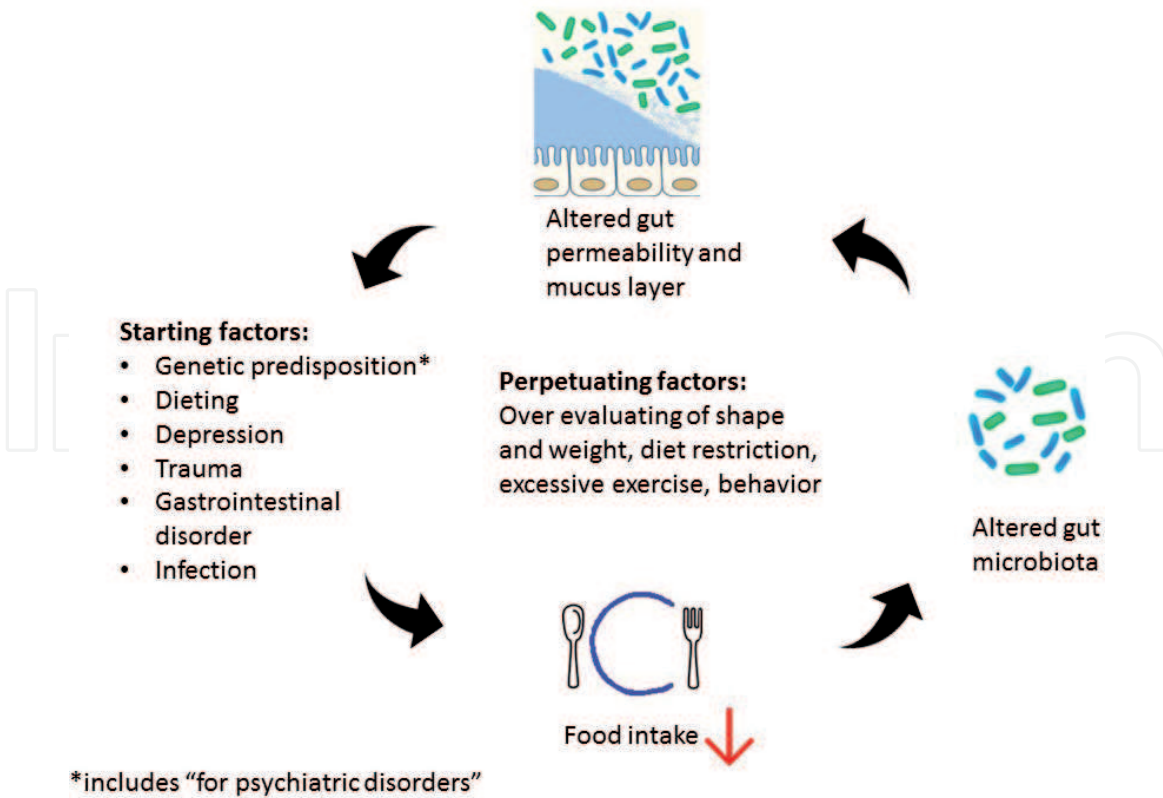


Figure 1.
The initial reduction of food intake induces alterations in the gut microbiota. These alterations in gut microbiota induce increased gut permeability. Due to this altered microbiota and increased gut and in addition, increased blood-brain barrier permeability, neurohormonal signals interfering with food intake are transferred to the brain, influencing brain functions, for example, cognition. This contributes in creating a vicious circle which subserves maintaining in the mechanisms associated with AN.

altered microbiota and increased gut and in addition, increased blood-brain barrier permeability, neurohormonal signals interfering with food intake are transferred to the brain, influencing brain functions, for example, cognition. This contributes in creating a vicious circle which subserves in maintaining the mechanisms associated with AN (**Figure 1**).

9. Conclusions

There are a lot of evidence linking dysbiosis and inflammatory and psychiatric disorders and although there are only a few studies that have examined the microbiota in AN, several of these point to a dysbiosis also in AN. The effects of this dysbiosis is mediated through the gut-brain axis, and leakage through the gut and potentially also the BBB, provide pathways for neurohormonal signals to induce and maintain psychiatric disorders such as AN. The evidence in AN will need confirmation and further clarification in larger, randomized and controlled studies. We propose a model for disease development and maintenance in AN where a dysbiosis is a key component. Future studies will need to clarify the pathophysiology of AN.

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Conflict of interest

The authors declare no conflict of interest.

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