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Gut Health and Eating Disorders School: DPS Faridabad

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ABSTRACT

Eating disorders(EDs) are a growing issue in the lives of many in recent years with the number of adolescents with EDs soaring extremely high without any proper implications for treatment. Research suggests that the alteration in the normal microbial composition, called dysbiosis, may contribute to the development of EDs when associated with a specific genetic susceptibility, and several putative mechanisms have already been identified. Since the knowledge on the topic gut microbiota and its connection to eating disorders is very limited due to small number of cases, we aim to understand, through research, the reason behind the same and explore the various treatment options

1. sINTRODUCTION

According to the DSM-5, eating disorders are severe mental illnesses that occur on a continuum with behaviours shared across syndromes that negatively influence cognitive, physiological, and social functioning. While most point to negative body image and/or concerns with body weight as the primary etiology of eating disorders (and thus they are classified as mental illnesses), evidence for disturbed appetitive and feeding pathways suggest that eating disorders may also be biologically-driven. Whatever the cause(s) may be, it typically leads to controlled eating, and when this pursuit becomes an obsessive focus in life, patients pursue extreme dietary restriction, binge eating, and compensatory behaviours[1]. The most prevalent EDs are anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED), with a lifetime prevalence of 0.48%, 0.51%, and 1.12%, respectively[9]. Avoidant/Restrictive Food Intake Disorder (ARFID), and Other Specified Feeding or Eating Disorders (OSFED) are some other eating disorders [10]

These eating disorders are driven, in part, by non-homeostatic eating, including chronic underconsumption of calories in anorexia nervosa AN and intermittent binge eating in bulimic syndromes including BED and BN [5]. While AN is often defined by chronic caloric restriction, other core features include increased physical activity, an intense fear of weight gain, endocrine alterations, disturbance of body image, and low body weight, at the other end of the spectrum, bulimic syndromes are characterised by binge eating, which involves the recurrent consumption of objectively large amounts of food in a discrete period of time that is accompanied by a loss of control over eating. Intermittent binge eating is a core feature of multiple bulimic syndromes, including BED, BN, and the binge–purge subtype of AN. As such, a greater understanding of the biological mechanisms underlying binge eating in particular could advance the identification, prevention, and treatment of a range of eating disorders[5]. In recent years, medical research has increasingly focused on the intricate relationship between gut health and mental health, particularly exploring how gastrointestinal issues and eating disorders influence each other. This bidirectional link suggests that problematic eating behaviours can lead to gastrointestinal disturbances. Conversely, existing

gut issues may also make someone more susceptible to these mental health challenges. Through studying the gut-brain axis—the communication pathway between the gut's microbial inhabitants and the brain—researchers are uncovering how disruptions in this system, known as dysbiosis, contribute to both physical and psychological symptoms. In our research paper, we will delve into the nuances of the gut-brain connection, exploring how gut health intricately links to eating disorders. We aim to analyse this complex relationship to better understand and develop integrated treatment strategies that address both the psychological aspects and gastrointestinal health.

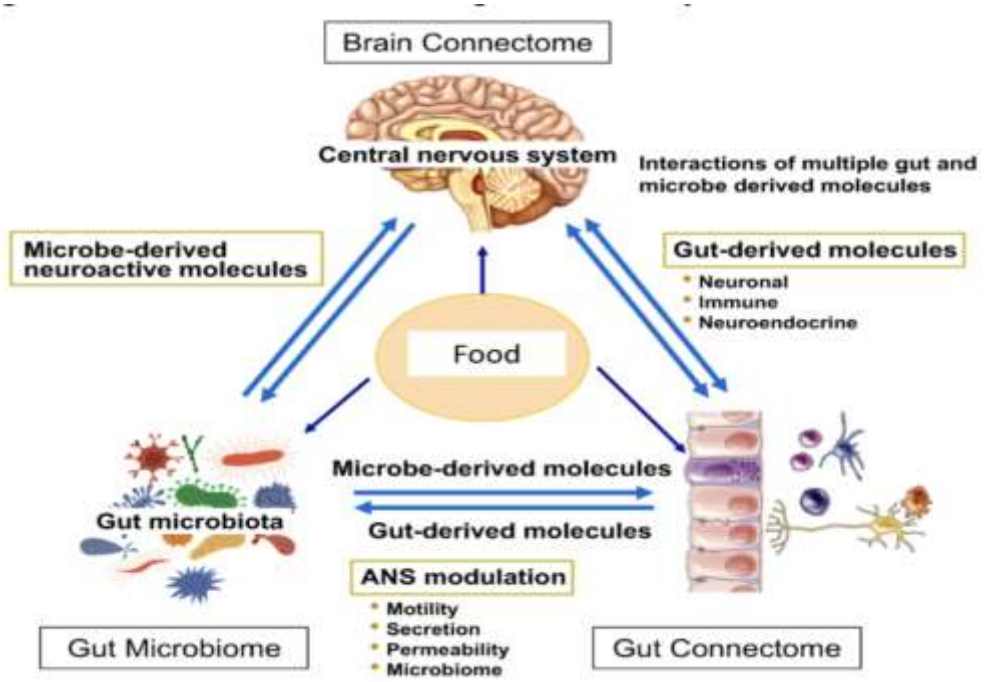
1.1 Gut Microbiota: A Missing Piece in Eating Disorders

The human gastrointestinal tract harbours an abundant and diverse microbial ecosystem, defined as the gut microbiome, forming an evolutionary-driven symbiotic relationship important in maintaining host homeostasis.[3]There are now over 2000 microbial species known to inhabit the human gut, and each individual has a "personal" combination of approximately 500 species with a total weight of over 1 kg. The major influencing factor that affect this combination of species is nutrition, while genetics, current illnesses, medication, stress, exercise and past experiences (such as mode of birth, having been breastfed, past illnesses and lifetime use of antibiotics) also appear to contribute[7]. Many digestive functions are thought to have been "delegated" to the gut microbiome over the course of evolution. In this symbiotic relationship, certain gut microbes break down food to supply the host with essential vitamins, fatty acids and other nutrients that the host would otherwise be unable to extract. However, the role of the gut microbiome extends well beyond digestion: the community of microbes is in continuous exchange with the cells of the gut wall and beyond, informing our immune system and affecting intestinal permeability, hormones and inflammation. Mechanisms involved in the gut-brain axis that directly influence the brain and behavior are not well understood, but seem to include direct vagal nerve signalling, immune cell migration to the brain, antibodies, cytokines and hormones[6].Host–microbe interactions are equally manifold; as human evolution took place in a world full of microbes, symbiotic partnerships provided evolutionary advantages to both the microbes and host.[7] Recently, research has focused on the microbiota and its composition, with 100 trillion microbial cells residing in different human body areas. The two phyla "Bacteroidetes" and "Firmicutes" represent about 90% of the bacterial populations identified, whereas the remaining 10% is mainly composed of Actinobacteria and Proteobacteria. The phylum Firmicutes is represented by more than 200 different genera: Lactobacillus, Bacillus, Enterococcus, Ruminococcus, and Clostridium. Bacteroidetes essentially consists of two predominant genera, the Bacteroides and the Prevotella. Bifidobacterium belongs to the Actinobacteria. A preponderance of Lactobacilli has been detected in the area of the stomach and duodenum and Streptococci at the jejunal level, whereas the ileocolic regions show a profound heterogeneity of bacterial species, including Lactobacilli, Escherichia coli, and other Enterobacteria, Enterococci faecalis, Bacteroides, Bifidobacteria, Peptococci, Petostreptococci, Ruminococci, and Clostridia.[8]

1.2. Communication pathways between the gut microbiome and the brain

There is emerging evidence of important links between the gut microbiome and the CNS, which might be depicted as "a gut feeling for the brain". Humans sustain a symbiotic relationship with the microbiome in their gut, which consists of approximately 10^14 cells; thus, there are ten times more bacteria than cells in the average human body. The highest bacterial concentrations are found in the colon, with approximately 10^12 per gram. We supply our microbiota with food, and they compensate us with important health benefits in relation to digestion, growth, and defense against pathogens [2]. The last few years have led to a growing recognition that both the gut microbiome and the immune system are involved

in a number of psychiatric illnesses, including eating disorders. Moreover, the important roles that diet composition and caloric intake play in terms of regulating microbiome and immune function have spurred further interest in studying these biological systems in the context of dysregulated eating behaviour. The gut microbiota influences somatic effects, such as energy extraction from food and body weight gain, as well as appetite, gut permeability, inflammation, and complex psychological behaviors, such as depression or anxiety, all of which play important roles in AN [5]. There is a strong association between the microbial signature and brain function. The gut microbiota includes the phyla Firmicutes (including Lactobacillus, Enterococcus, and Clostridium genera) and Bacteroidetes (including Bacteroides genus), which represent more than 90% of the intestinal community in healthy adults, as well as Actinobacteria and Proteobacteria. Alterations of gut microbiota decrease the intake of calories from the diet, altering the immunological response. The innate immune system is activated under dysbiosis by the increase of bacterial lipopolysaccharides (LPS). These endotoxins trigger the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in plasma, and downregulate synaptic proteins through the subdiaphragmatic vagus nerve [9].



(Image One: https://www.nature.com/articles/s41398-022-01922-0)

1.3. DYSBIOSIS IN AN PATIENTS

The gut microbiota is essential for normal physiological function, and deviations from the healthy microbial profile, known as dysbiosis, can increase the risk of various diseases. The composition of microbiota is not stable during life: it presents rapid changes from early childhood, stabilises in adulthood, and then deteriorates in old age. Research suggests that the alteration in the normal microbial composition, called dysbiosis, may contribute to the development of EDs when associated with a specific genetic susceptibility, and several putative mechanisms have already been identified [8]. The growing body of literature on the effects of the gut microbiota on host health, ranging from nutrient and energy metabolism to brain function, has led to the consideration of this "forgotten organ" in the aetiology and pathophysiology of eating disorders. Given the established gut–brain and gut–diet interactions, the gut microbiota may well be the critical mechanistic link between psychological and biological factors in these illnesses. More importantly, compensatory behaviours, e.g., purging and laxative abuse, and conventional

treatment (nutritional rehabilitation) would be expected to impact on the gut microbiota, and this change may feed back to modify the disease progress further [1].Evidence is now growing that AN-induced starvation is associated with profound alterations of the gut microbiome, which is of critical interest given its important interactions with the host metabolism in terms of weight regulation, hormonal, immunologic, and inflammatory processes, directly influence our brain and behavior ("gut-brain axis") [6]. As nutrition is one of the main factors that influence the gut microbiota, nutritional restriction and selective eating in AN are likely influencing factors [7]. An emerging avenue of AN research involves the gut microbiome, which is increasingly being acknowledged as a key interface for gene-environment interaction, with important implications for both health and disease. Over the past decade, advances in metagenomic sequencing technologies and proteomics have enabled the in-depth interrogation of the composition and function of these microbial communities. Compelling evidence supports the involvement of intestinal bacteria in core features of AN, including appetite and weight regulation, as well as in its comorbid symptoms, such as altered mood and gastrointestinal symptomatology, through a variety of immune, neuroendocrine, and metabolic pathways [3]. Because of EDs , in Germany and the UK, the number of hospitalised children and adolescents has risen substantially during the last decade , and the age of onset has decreased. In an 18-year follow-up study, 25% of the subjects with previous adolescence AND were unemployed because of a mental disorder[6]. The COVID-19 pandemic has increased these percentages, as demonstrated by a recent meta-analysis conducted in the general population and in healthcare workers, showing a prevalence for anxiety of 30% and 23.2%, respectively [9] Despite having the highest mortality rate of all psychiatric disorders the development of effective, evidence-based treatments has been hindered by a poor understanding of its etiology, which likely involves a complex interplay between genetic and environmental factor[3]. Mood disturbance and metabolic dysfunctions further contribute to physical and psychosocial morbidity. Reduced income and employment, heavy carer burden, and elevated health care cost see eating disorders not only impact negatively on an individual but also on a societal level[1]

1.4. NEUROTRANSMITTERS AND GUT HEALTH

The altered neural mechanisms in eating disorders (EDs) are primarily linked to the reward, behavioral control, and decision-making pathways. Current literature indicates that the amygdala, hippocampus, and medial prefrontal cortex are functionally compromised in anxiety disorders. These brain regions are crucial for the generation and regulation of emotions and fear. In anorexia and bulimia nervosa (BN), there is increased connectivity between the insula, orbitofrontal cortex, and ventral striatum, but decreased connectivity from the orbitofrontal cortex and amygdala to the hypothalamus. In binge eating disorder (BED), there is reduced activity in the ventromedial prefrontal cortex, inferior frontal gyrus, and insula, which are areas involved in self-regulation and impulse control. Additionally, alterations in the dopamine pathway significantly contribute to the development of EDs. In anorexia and BN, harm avoidance mechanisms related to serotonin receptor availability and dopamine receptor binding are also altered. Moreover, neuropeptides that signal hunger (ghrelin) and satiety (leptin) interact with the mesolimbic dopamine system and are altered in EDs. Leptin, an anorexigenic peptide released from adipose tissue, is diminished in anorexia nervosa (AN). Ghrelin, an orexigenic peptide, is elevated in AN and does not respond correctly after food intake. Insulin sensitivity (an anorexigenic pancreatic hormone) is also increased in AN. Stress, hyperactivity, and appetite are modulated by the cortisol awakening response of the hypothalamic-pituitary-adrenal (HPA) axis, which is imbalanced in anxiety and AN. The gut-brain axis refers to the bidirectional interaction between the gut microbiota and the central nervous system (CNS). This interaction has gained increasing interest in recent years due to the harmful effects of

dysbiosis on brain function. Gut bacteria interact with the CNS by synthesizing neurotransmitters such as serotonin, dopamine, gamma-aminobutyric acid (GABA), acetylcholine, and glutamate, and they respond to hormones. Furthermore, gut microbial diversity is associated with appetite dysregulation due to its ability to influence intestinal satiety pathways [9]. Distinct microbial profiles, characterized by elevated levels of Anaerostipes, Bifidobacterium, and Roseburia, and reduced levels of Akkermansia, Desulfovibrio, and Intestinimonas, have been identified in BED patients. Notably, antibiotic usage in BED patients suggests existing dysbiosis. Additionally, the concentration of ClpB, a product of enterobacteria, is implicated in the production of autoantibodies against α-MSH, associated with specific psychological traits in BED. Probiotic interventions, particularly employing Lactobacillus and Bifidobacterium strains, show promise in reducing binge eating symptoms. BN is linked with sustained periods of food restriction, impacting the gut microbiota. Studies reveal alterations in the relative abundances of specific bacterial strains in BN patients, including increased Bifidobacterium and decreased Odoribacter (Fetissov & Hökfelt, 2019). ClpB, produced by Escherichia coli, correlates with the severity of BN symptoms. Ghrelin, an appetite stimulant, may also play a role in BN. Probiotic and antibiotic interventions, along with fecal microbiota transplantation, emerge as potential therapeutic modalities for BN (Herman & Bajaka, 2021). The gut microbiome in AN is characterized by changes in bacterial abundances, with elevated Methanobrevibacter smithii and reduced anaerobes such as Clostridia and Bacteroides. Short-chain fatty acids (SCFAs), crucial for weight gain, are diminished in AN patients [10].

1.5. Implications For Treatment

higher body mass index (BMI) at the end of treatment correlates with a better overall outcome and that a normalization of body weight is necessary to prevent severe somatic sequelae such as osteoporosis and infertility . Moreover, it is well-established that weight gain is a potent agent against comorbid mental disorders of AN, especially depression[2]

Currently, closely monitored nutritional rehabilitation and weight restoration is considered the gold standard treatment for AN, surpassing pharmacological interventions and psychotherapy

Since diet is one of the primary influences on gut microbial composition in both the short (David et al. 2014) and long term (Wu et al. 2011), it is likely to be of relevance in AN. Further, the gut microbiome plays an important role in regulating mood (Slyepchenko et al. 2017), behaviour (Dinan et al. 2015), appetite (van de Wouw et al. 2017), gastrointestinal symptomology (Guinane and Cotter 2013), and metabolism (Mithieux 2017)[4]

Fecal microbiota transplantation shows promise in improving microbiota species richness and SCFA levels, correlating with increased body weight. Exposure-based Cognitive Behavioural Therapy and Family Therapy are proposed interventions, considering the intricate relationship between gastrointestinal conditions, eating behaviour challenges, and gut-brain interactions. treatment approaches, including Enhanced Cognitive Behavioral Therapy (CBT-E) and nutritional therapy [10]

Conclusion

Given our current understanding of how the gut microbiome functions in metabolic diseases and the expected changes in how the host interacts with microbes in eating disorders, it is reasonable to conclude that the gut microbiota likely plays a significant role at different stages of these conditions, thus showing that Eds might not only be psychologically but also biologically driven. However, more research is necessary in this emerging field to deepen our understanding of how gut microbes affect the human body

under the unique conditions present in eating disorders. This particularly involves the generation of detailed longitudinal metagenomic data to analyse the structure and functions of the gut ecosystem.

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