The Gut Microbial Dysbiosis, its Fallouts and Redressal

Vinod Nikhra*

Senior Chief Medical Officer and Consultant, Department of Medicine, Hindu Rao Hospital and NDMC Medical College, New Delhi, India

Received Date: January 18, 2019; Accepted Date: February 8, 2019; Published Date: February 18, 2019

Corresponding Author: Vinod Nikhra, Senior Chief Medical Officer and Consultant, Department of Medicine, Hindu Rao Hospital and NDMC Medical College, New Delhi, India. Tel: +919810874937; Email: drvinodnikhra@gmail.com

Abstract

Genesis of Microbial Dysbiosis: The human intestinal microbiota performs several vital functions, acting in tandem with the host’s defence and immune system. Maintenance of microbiota is vital for preservation of health and imbalances in the microbiome shift the microbiome-host relationship from symbiotic to pathogenic. Gut microbial dysbiosis can result from exposure to various environmental factors, including diet, toxins, drugs and pathogens like enteric foodborne bacterial and viral pathogens. Following the insult both local and systemic inflammation can trigger alterations in the composition of the microbiota and their intestinal barrier function.

The Fallouts of Gut Dysbiosis: Liver is exposed to metabolites produced at intracolonic fermentation through portal circulation. There is a possible causative role of the microbiota in the development of NAFLD. Through the Gut-Brain Axis, the gut microbiota interacts with CNS by influencing neuro-endocrine systems associated with stress response, anxiety and cognitive functions. The effects of CNS on microbiota composition and physiology, on the other hand, are mediated by a perturbation of the microbial habitat. There is evidence that intestinal microbial dysbiosis plays a role in the pathogenesis of IBD and several other GI-related diseases, such as IBS, coeliac disease and colorectal cancer. There appears to be a direct link between dysbiosis and obesity and T2DM. In addition, dysbiosis has its impact on renal function and CVD through accelerating atherosclerosis.

Redressal of Microbial Dysbiosis: When the gut microbiota balance is disturbed, the colonies have a decreased ability to check each other’s growth. As more beneficial colonies are damaged and unchecked growth of others, a chronic imbalance sets in. Further, the microbial colonies excrete many waste byproducts, which are not suitably dealt with. The mild dysbiosis can be treated through dietary and lifestyle changes, and medications like prebiotics and probiotics. The more severe and chronic dysbiosis can be treated with FTM and other advanced treatment options like microbial restoration through bacteriotherapy.

Keywords: Bacteriotherapy Dysbiosis; Gut-Brain Axis; Fecal Microbial Transplantation; Inflammatory Bowel Disease; Irritable Bowel Syndrome; Liver-Gut Axis; Microbiota; NAFLD; Prebiotics; Probiotics; SCFAs

Understanding Gut Microbial Dysbiosis

The Vital Gut Microbial Physiology

The human gut microbiota performs several vital functions which include being a source of essential nutrients and vitamins and aiding in extraction of energy and nutrients, such as short-chain fatty acids (SCFAs) and amino acids, from food [1]. It functions in tandem with the host’s defence and immune system to protect against pathogen colonisation and invasion [2,3]. Maintenance of microbiota is vital for preservation of health and imbalances in the microbiome shift the microbiome-host relationship from symbiotic to pathogenic [4].
The food components escaping digestion in the small intestine, endogenous compounds such as remnants of digestive enzymes, mucus and the shredded epithelial cells, pass on to the colon and acted upon and fermented by the colonic microbiota. The undigested carbohydrates and proteins constitute the major substrates at the level of colonic microbiota. Their fermentation results in the production of metabolites including SCFAs, branched chain fatty acids, ammonia, amines, phenolic compounds and gases including hydrogen, methane and hydrogen sulphide. Further, the microbiota is also involved in the transformation of bile acids and xenobiotics, the activation or inactivation of bioactive food components such as is of lignans and plant lignans and conversion of prodrugs to their bioactive forms. The bacterial conversion of these compounds results in a variety of metabolites which influence the host’s homeostasis and metabolism [5].

The SCFAs acetate, propionate and butyrate are the major anions in the colon and mainly produced by bacterial fermentation of undigested carbohydrates. Most of the SCFAs produced are absorbed by the colonocytes for use as energy substrates, with the colonocytes deriving up to 70% of their energy needs from SCFAs oxidation. The fraction that is not consumed by the colonocytes is transported across the basolateral membrane to live via portal circulation [6]. Besides their role as energy substrates within the colon, SCFAs act as signalling molecules for systemic lipid metabolism and glucose/insulin regulation. These effects are mediated through interaction with two specific G-protein-coupled receptors – GPR41 and GPR43 - now renamed as FFAR3 and FFAR2, respectively [7]. Within the cells, SCFAs can act as inhibitors of histone deacetylases to induce hyperacetylation of histones which influences gene expression, has anti-inflammatory properties and can cause induction of growth arrest, and apoptosis [8].

Plant polyphenols have been associated with health benefits including anti-inflammatory, antiestrogenic, cardioprotective, chemoprotective, and neuroprotective effects [9]. However, most of plant polyphenols require metabolic transformation (including deglycosylation and hydrolysis) to render them biologically active. Within the colon, they are broken down by the microbiota to a variety of small phenolic compounds. Therefore, the health benefits associated with polyphenols should not only be attributed to their bioactive metabolites but also to the modulation of the intestinal microbiota [10]. Other products of bacterial metabolism have been associated with diseases affecting the liver, cardiovascular system and the kidneys [11]. The recent studies indicate a selective modulation of the microbiota composition after polyphenol consumption [12]. The consumption of red wine polyphenols increases *E. coli*, *Prevotella*, *Bacteroides*, *Bifidobacterium*, and *Bacteroides* uniformis, *Eggerthella* tenter and Blautiacoccioides- *Eubacterium rectale* in healthy humans [13].

The Genesis of Gut Microbial Dysbiosis

Gut microbial dysbiosis can result from exposure to various environmental factors, including diet, toxins, drugs and pathogens (Figure 1). The latter includes enteric foodborne pathogens including viral pathogens having potential to cause microbial dysbiosis [14].

![Figure 1: Microbial dysbiosis, altered gut microbiota and its fallouts.](image)

As documented by studies in animal models, both local and systemic inflammation can trigger alterations in the composition of the microbiota and barrier function. The DNA based pyrosequencing technology has been shown that the composition of the intestinal microbiota varies substantially amongst individuals [15]. This can be explained, partially by genetic differences amongst hosts and similarity in dominant faecal microbial communities. The dominant ones are *Bacteroidetes* and *Firmicutes* in addition to *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, *Verrucomicrobia*, *Lentisphaerae* and *Sprichaetes* [16].

It has been shown that about 40% of the microbial genes present in each person are shared with at least half the general population providing evidence for the existence of a functional core, or core microbiome [17]. The studies using germ-free mouse models provide the evidence for involvement of intestinal microbiota in disease pathogenesis. The incidence and severity of disease is reduced under germ-free conditions consistent with the microbiota being a ‘trigger’ for disease progression [18]. It has, thus, been reported that the intestinal dysbiosis is often associated with GI-related diseases in which alterations in the interaction of the host immune system with luminal-derived stimuli and antigens initiate and perpetuate uncontrolled inflammation in the intestinal mucosa and beyond [19].

The Gut–Liver Axis: Liver and Gut Microbiota

Liver is exposed to metabolites produced by intracolonic fermentation through portal circulation as it receives the major share of its blood supply from the intestine through the portal vein [20]. There is a possible causative role of the microbiota in the development of non-alcoholic fatty liver disease (NAFLD). In patients that underwent intestinal bypass surgery, hepatic steatosis developed in parallel with bacterial
overgrowth, which regressed after treatment with metronidazole [21]. A possible mechanism is relating the microbiota to NAFLD is bacterial metabolism of choline. In mice susceptible to NAFLD and fed a high-fat diet, choline was increasingly metabolised to methylamines resulting in high urinary excretion of dimethylamine (DMA) and trimethylamine (TMA) and correspondingly low levels of serum phosphatidylcholine [22]. Due to conversion of choline into methylamines by the microbiota, the bioavailability of choline is reduced, resulting in the inability to synthesise phosphatidylcholine with subsequent accumulation of triglycerides in the liver. This mimics choline-deficient diets which have been consistently associated with hepatic steatosis [23].

The bacterial metabolite TMA is consequently absorbed by the intestinal mucosa and transported to the liver via the portal vein where it is oxidised to trimethylamine N-oxide (TMAO) by the flavin mono-xygenase (FMO) enzyme complex. It has been indicated that TMAO is pro-atherogenic by augmenting foam cell formation [24]. Similarly, the intestinal microbiota can metabolise dietary L-carnitine, a TMA abundant in red meat, to produce TMAO and accelerate atherosclerosis [25].

The Gut-Brain Axis

GBA - The Bidirectional Communication

The GBA consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions. The gut microbiota interacts with CNS by influencing neuro-endocrine systems associated with stress response, anxiety and memory function. In addition, the effects of CNS on microbiota composition are likely to be mediated by a perturbation of the normal luminal/mucosal habitat that can also be restored by probiotics and dietary changes. The interactions are bilateral between microbiota and GBA through signaling from gut-microbiota to brain and from brain to gut-microbiota by means of neural, endocrine, immune, and humoral links (Figure 2).

![Figure 2: The principal player’s bidirectional Brain-Gut-Microbiota Axis.](image)

The human brain undergoes rapid growth during the prenatal period, corresponding to dramatic changes in the maternal microbiota, which shows an increase in Proteobacteria and Actinobacteria. Many studies have demonstrated the importance of the microbiota during brain development, including the microbiome’s indirect effect on tryptophan metabolism and serotonin (5-HT) synthesis, which is crucial to CNS development [26]. Gut bacteria have direct effects on the metabolism and synthesis of tryptophan and 5-HT. Some bacterial strains can produce 5-HT from tryptophan, whereas some other are able to synthesize tryptophan using enzymes such as tryptophan synthase, while still others degrade tryptophan with tryptophanase enzyme. The colonic bacteria have an important role of fermenting carbohydrates and proteins to produce metabolites, including SCFAs, which are essential for human health. Enry et al determined that SCFAs regulate microglial homeostasis. Exposure to an indigenous microbiota during early development is also crucial for the development of a normal hypothalamic-pituitary-adrenal system [27].

CNS and HPA Vs Gut Microbiota

The central nervous system and the hypothalamic pituitary adrenal (HPA) axis are activated in response to environmental factors, such as emotion or stress. There occurs a complex interaction between amygdala (AMG), hippocampus (HIPP), and hypothalamus (HYP), constituting the limbic system. HYP secretion of the corticotropin-releasing factor (CRF) stimulates adrenocorticotropic hormone (ACTH) secretion from pituitary gland that, in turn, leads to cortisol release from the adrenal glands. In parallel, central nervous system communicate along both afferent and efferent autonomic pathways (SNA) with different intestinal targets such as enteric nervous system (ENS), muscle layers and gut mucosa, modulating motility, immunity, permeability and secretion of mucus. The enteric microbiota has a bidirectional communication with these intestinal targets, modulating gastrointestinal functions and being itself modulated by brain-gut interactions. The brain-gut-microbiota axis is a complex interplay between the CNS, the neuroendocrine and neuroimmune systems, and the sympathetic and parasympathetic arms of the autonomic nervous system, the enteric nervous system, and the microbiota (Figure 3).
Gut Microbial Dysbiosis, its Fallouts and Redressal

The complex bidirectional Gut-Brain Axis between CNS, ANS, ENS, neuroimmune systems and microbiota activated by Dysbiosis.

The communication throughout this axis is bidirectional, with brain signals affecting gastrointestinal tract motor, sensory and secretory functions, and simultaneous visceral signaling from the GI tract affecting brain function. On the other hand, the brain can affect the composition of the gut microbiota. These effects on the microbiota can be indirect, through changes in motility and secretion, or direct, through signaling molecules released into the gastrointestinal tract via enterochromaffin cells, neurons, and immune cells. The autonomic nervous system affects motility as well as mucus secretion into the gut lumen, both of which can alter the gastrointestinal environment, thereby changing the bacteria that are present. The autonomic nervous system can also affect epithelial mechanisms involved in immune activation of the gut. The exposure to stressfull stimuli has been shown to increase permeability of the epithelium, allowing bacterial antigens to cross the epithelium and stimulate an immune response in the mucosa, which in turn alters the microbiome.

Long-term treatment with the probiotic Lactobacillus rhamnosus (JB-1) led to decreased levels of stress-induced corticosteroids, depressive symptoms, and anxiety. Treatment with L. rhamnosus also induced region-specific alterations in expression of GABA$_{B1b}$ and GABA$_{A\mu2}$. Alterations in GABA production are implicated in depression and anxiety disorders. The gut microbiome may play a role in pain perception. Certain strains of Lactobacillus induce increased expression of µ-opioid and cannabinoid receptors in intestinal epithelial cells, mimicking the analgesic effects of morphine.

Gut Microbial Dysbiosis: The Fallouts

Gi-Tract-Related Disorders

Inflammatory Bowel Disease

Crohn’s disease (CD) and ulcerative colitis (UC) are the most prevalent forms of inflammatory bowel disease (IBD). There is increasing evidence that intestinal microbial dysbiosis has a role in the pathogenesis of IBD [28]. The IBD patients exhibit a decrease in microbial population and functional diversity and stability of their intestinal microbiota with decreases in specific Firmicutes and a concomitant increase in Bacteroidetes and facultative anaerobes such as Enterobacteriaceae [29]. There are significant differences in the microbiota of CD versus UC patients [30,31]. In CD, the predominant dysbiosis is associated with five bacterial species amongst which alterations in the abundance of Faecalibacterium prausnitzii is associated with the prolongation of disease remission [32]. Faecalibacterium prausnitzii has a therapeutic effect in experimental models of colitis [33]. On the other hand, adherent-invasive E. coli and Mycobacterium paratuberculosis have been implicated in CD pathogenesis [34,35]. Further, rather than being a direct cause, intestinal microbial dysbiosis along with inflammation and the disturbed environment in the GI tract appear to be responsible for IBD [36]. The CD patients have increased abundance of Enterobacteriaceae, Pasteurellaceae, Veillonellaceae, and Fusobacteriaceae, and decreased abundance in Erysipelotrichales, Bacteroidiales, and Clostridiales compared to healthy control patients. The bacteria resident in the mucosal layer are responsible for disease aetiology.

Other Gi-Tract Disorders

In addition to IBD, the intestinal microbiota has also been implicated in several other GI-related diseases and disorders, such as irritable bowel syndrome (IBS), coeliac disease, and CRC [37,38]. In IBS, changes in microbiota composition have been described in the different subtypes of disease although the changes are not uniform [39]. In IBS, role of dysbiosis has been held [40].

Coeliac disease and CRC have also been associated with alterations in microbiota composition with increased diversity compared to control subjects; however, there are no consistent pattern of microbiota alterations [41]. In the case of coeliac disease, however, there has been documented the interaction between host and microbiota composition in relation to disease development [42]. Expression of the leukocyte antigen DQ2 is a strong risk factor for the development of coeliac disease [43]. Children with this haplotype have an altered microbiota composition prior to clinically apparent disease.

Metabolic Disorders

Obesity and T2DM

An increase in the relative abundance of Firmicutes and a reduction in the level of Bacteroidetes have been observed in both obese mice and humans [44,45]. More subtle changes in the composition of the intestinal microbiota occur in obese individuals with a reduced compositional microbial diversity compared with lean individuals [46].

The high-fat diet and over-nutrition are responsible for the greater prevalence of obesity and T2DM and alter the host metabolism and immune homeostasis via diet-induced changes in the intestinal microbiota [47]. Also, dietary changes in humans lead to rapid and reversible changes in the relative abundance of dominant members of the intestinal microbiota [48]. There appears to be a direct link between intestinal microbiota composition and body weight and the intestinal microbiota is also involved in the regulation of fat storage [49]. This is proved by the transfer of microbiota from lean donors into individuals with metabolic syndrome can.
improve insulin sensitivity and overall amelioration of symptoms of metabolic disease [50].

The obese individuals are more efficient in converting food into usable energy and in storing this energy in fat than lean individuals, which is related to, and may be a consequence of, the functionality of the intestinal microbiota. The role of the microbiota in metabolism and its ability to harvest energy from food, highlight a significant environmental factor impacting the risk of metabolic disease. An altered representation of bacterial genes and metabolic pathways, including those involved in nutrient harvest, has been found to be related to obesity. Also, the amount of SCFA produced by the intestinal microbiota, rather than the changes in the composition of the microbiota, is important in the development of obesity [51].

Renal Disease

There exists a bi-directional functional relationship between the large intestine and the kidney. The uraemia influences the colonic microbial metabolism whereas microbial-related metabolites are involved in the progression of the kidney disease [52]. p-Presyl sulphate and indoxyl sulphate are derived from bacterial fermentation of the aromatic amino acids, tyrosine and tryptophan, respectively, followed by sulphation in the colonic mucosa or the liver. Within the plasma, they are highly protein-bound and accumulate with deterioration of renal function. In patients with chronic kidney disease, both p-cresyl sulphate and indoxyl sulphate levels have been linked to overall mortality, CVD and progression of the kidney disease [53].

CNS-Related Disorders

The gut microbial dysbiosis has impact on the ‘gut–brain–axis’ and affects the CNS and behaviour and cognitive function [54]. Several studies have focused on the possibility that the intestinal microbiota may influence cognitive function and behaviour by direct reprogramming of the hypothalamus–pituitary–adrenal (HPA) axis, a common pathway activated in response to infection and perturbed by psychological stressors. Commensally bacteria may affect brain changes through GABA, which can directly influence both immune and neural receptors within the ENS and CNS [55]. GABA is the main CNS inhibitory neurotransmitter and is involved in regulating physiological and psychological processes. The alterations in central GABA receptors expression has been implicated in the pathogenesis of anxiety and depression [56]. The gut dysbiosis has been correlated with chronic fatigue syndrome [57]. The early colonisation of the intestinal tract by microbes is known to be important for the post-natal development of the enteric nervous system [58]. Thus, gut microbiota and dysbiosis may have implications on the development and function of the CNS [59,60].

The evidence of a possible causal role of the intestinal microbiota in the development of autism spectrum disorder (ASD) comes from a maternal immune activation (MIA) mouse model in which pregnant animals after being administered the viral mimic, ploy(I:C), display increased intestinal permeability and develop stereotypical abnormalities in behaviour, social ability, and communication that resemble ASD [61]. MIA offspring displays intestinal dysbiosis and an altered serum metabolomic profile, characterised by excessive levels of microbiota-derived 4-ethylphenylsulphate (4EPS), compared to control offspring, with intestinal barrier function being restored and ASD-like symptoms being alleviated after administering probiotic bacteria.

With the emerging datain developmental disorders, appears that GI-tract disorders including IBD and IBS are common co-morbidities in debilitating stress-related disorders, including depression and anxiety [62], and that the intestinal permeability and bacterial translocation may drive immunoinflammatory and oxidative and nitrosative stress (IO&NS) pathways in depression and thus playing a role in their pathophysiology. Chronic depression in humans was shown to be accompanied by increased immune response (serum IgM and IgA responses) directed against lipopolysaccharide (LPS) products of Gram-negative bacteria like, Hafnia alvei, Pseudomonas aeruginosa, Morganella morganii, Pseudomonas putida, Citrobacter koseri, and Klebsiella pneumonia [63]. Germ-free mice exhibit hyper-responsive HPA axis activity following stressand this hyper-response of the HPA axis was reversed by Bifidobacterium infantis [64]. B. infantis increases plasma tryptophan levels, decreases serotonin metabolite concentrations in the frontal cortex and dopamine metabolite concentrations in the amygdaloid cortex, both of which are implicated in depression. In humans, the efficacy of probiotics for mood regulation was suggested in a trial of Lactobacillus casei that showed subjects with the lowest scores in the depressed/relieved dimension at baseline had significant improvement in mood scores after taking the probiotic compared to the placebo group. The combination of L. helveticus and B. longum reduced anxiety and had beneficial psychological effects with decreased serum cortisol in healthy human volunteers [65,66]. Further, the functional brain activity measured by functional magnetic resonance (fMRI) showed that a probiotic formulation reduced brain intrinsic connectivity and response to emotive stimuli and changes in midbrain connectivity [67,68].

Redressal of Microbial Dysbiosis

The Gut Microbial Dysbiosis: Practical Approach

When the gut microbiota balance is disturbed, the bacterial colonies have a decreased ability to check each other's growth, leading to overgrowth of the disturbed colonies while some of the smaller beneficial ones are damaged. As more beneficial
colonies are damaged and unchecked growth of others, a chronic imbalance sets in, minimizing the beneficial nature of the microbial colonies as a whole. Further, the microbial colonies excrete many waste byproducts. Under normal circumstances the body effectively manages these byproducts. The oversized and overgrown colonies excrete increased amounts of waste byproducts overburdening the waste removal mechanisms. The combination of these two negative outcomes may cause various negative symptoms and health disorders related to the gut dysbiosis. Some effects of dysbiosis, such as digestive upset, are temporary and can be corrected without treatment. The mild dysbiosis can be treated through dietary and lifestyle changes, and medication like prebiotics and probiotics, whereas the more severe and chronic dysbiosis can lead to various disorders and disease states (Figure 4).

**Common Causes of Dysbiosis**

Usually the result of a dietary change like increased intake of fats, carbohydrates, animal proteins or food additives [70], an accidental chemical consumption, such as lingering pesticides on unwashed vegetables and fruits, drinking two or more alcoholic beverages per day and medications, such as antibiotics affecting gut flora [71]. The proton pump inhibitors also affect the gut microbiome [72,73]. The poor dental and oral hygiene allowing bacterial overgrowth and imbalance in mouth and beyond, and the high levels of stress or anxiety, lead to psychosomatic impulses which have effects on GIT.

**Disorders and Diseases Associated with Dysbiosis**

They include - IBS, Colitis, Coeliac disease, Leaky gut syndrome, Eczematous dermatitis, Liver disease, Obesity, Diabetes, CVD, Late-onset dementia and Parkinson's disease, and colon cancer.

**Treatment of Dysbiosis**

**Antibiotics**

A broad-spectrum antibiotic that has low impact on the intestinal gut microbiome called rifaximin, has been shown to be effective in improving several of the ailments associated with dysbiosis, including Irritable Bowel Syndrome, Ulcerative colitis and Crohn’s Disease [74].

**Prebiotics and Probiotics**

The World Health Organization defines probiotics as ‘live microorganisms, which when administered in adequate amounts, confer a health benefit on the host’ [75]. The benefit of using probiotics to treat dysbiosis related diseases lies in its ability to treat the underlying cause of said diseases (Figure 5). Some benefits include their ability to suppress...
The Gut Microbial Dysbiosis, its Fallouts and Redressal

inflammation in the microbiome and disrupt colonization by pathogens [76,77]. Probiotic supplementation has been shown to improve inflammatory status in patients with rheumatoid disease [78]. Effectiveness of probiotics has also been documented in treatment of irritable bowel syndrome [79].

Figure 5: Common examples of Prebiotics and Probiotics.

Fecal Microbiota Transplant

FMT aims to recreate a healthy balance of microbiota in the microbiome by inserting beneficial microbes into the gut environment [80,81]. FMT accomplishes this by taking a donation of fecal matter from a healthy individual, diluted, strained and introduced to a diseased patient [82]. FMTs are currently used to treat patients with Clostridium Difficile infections, resistant to other therapies. The process is not sterile, allowing contaminations can pass from donor to patient [83]. The measures to isolate key microbiota and culture them independently is more specific, and transplant thereafter is a better therapeutic alternative. The FMT is around 90% effective at curing recurrent CDI with one or more infusions (Figure 6). It has been documented that FMT can normalize both bacterial community composition and metabolic capacity [84].

Figure 6: Steps for Fecal Microbiota Transplantation.

Future Approaches: Microbial Restoration Through Bacteriotherapy

There is huge potential for manipulating the microbiota to sustain, improve, or restore the microbiota in at risk or diseased individuals. Approach of wholesale microbiota replacement strategies based upon faecal transplantation [85].

Post-Treatment Follow up

Finally, post-FMT follow up is required for an indefinite period in all those have received FMT.

Disclosures: None.

References


The Gut Microbial Dysbiosis, its Fallouts and Redressal


