MINI-REVIEW

Impact of diet on human gut microbiome and disease risk

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Abstract

The gut microbiome of humans comprises a diverse group of trillions of microorganisms including symbiotic organisms, opportunistic pathogens and commensal organisms. This microbiota plays a major role in digesting food; it also helps with absorbing and synthesizing some nutrients and releases their metabolites, which may deliver a variety of growth-promoting and growth-inhibiting factors that influence human health either directly or indirectly. The balance between microbial species, especially those responsible for the fermentation of different substrates within the microbial community, which are in the majority, depends on daily diet. Therefore, an unbalanced diet may lead to the progression and development of human diseases. These include metabolic and inflammatory disorders, cancer and depression, as well as infant health and longevity. We provide an overview of the effect of diet on the human microbiome and assess the related risk of disease development.

Keywords: Diet, diversity of microbial gut, gut microbiome, human health, metabolic disorder, unbalanced diet
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Introduction

In recent decades, it has become apparent that human health reflects the impact of nutrition. Daily diet greatly affects the microbiome of the digestive tract [1]. Dietary components that are not digested by host enzymes but remain unchanged through their passage to the gut may deliver a variety of growth-promoting and growth-inhibiting factors that influence the balance between microbial species, especially those responsible for the fermentation of different substrates within the microbial community. Meanwhile, the gut's processing of the human diet, which contains macronutrients (protein, carbohydrates and fat) and micronutrients (vitamins, minerals and trace minerals), regulates human responses to food types depending on the inhabitant's microbiome. Therefore, diet affects host health status by modulating the composition and diversity of the gut microbiome [2,3]. It has been found that normal gut microbiota can induce alteration of host physiology and affect the development of the immune system, nutrient absorption and generation of tissue, morphogenesis and bone homeostasis metabolism as well as their ability to synthesize beneficial vitamins such as folate, biotin and vitamin K [4,5]. Bacteria in the human gut microbiota can also neutralize potentially carcinogenic compounds such as pyrolysates [6].

The human gut is generally inhabited by more than trillion microbes of diverse groups, which may be considered as a metabolic organ as a result of their immense impact on human health, as well as host metabolism, physiology, nutrition and immune function. These microbes comprise diverse groups of symbiotic (Fig. 1), commensal organisms as well as opportunistic pathogens. One study classified the inhabitants of a microbiome by using an advanced molecular technique, metagenomic analysis, to provide a larger scope and provide a deep view into hundreds of microbial communities concurrently as those previously identified by 16S ribosomal RNA [7]. This classification revealed that the human gut microbiome is mostly composed of four main bacteria phyla, *Firmicutes, Bacteroidetes, Actinobacteria* and *Proteobacteria;* the rest, however, is remarkably diverse. *Bacteroidetes,* which are mostly represented in the

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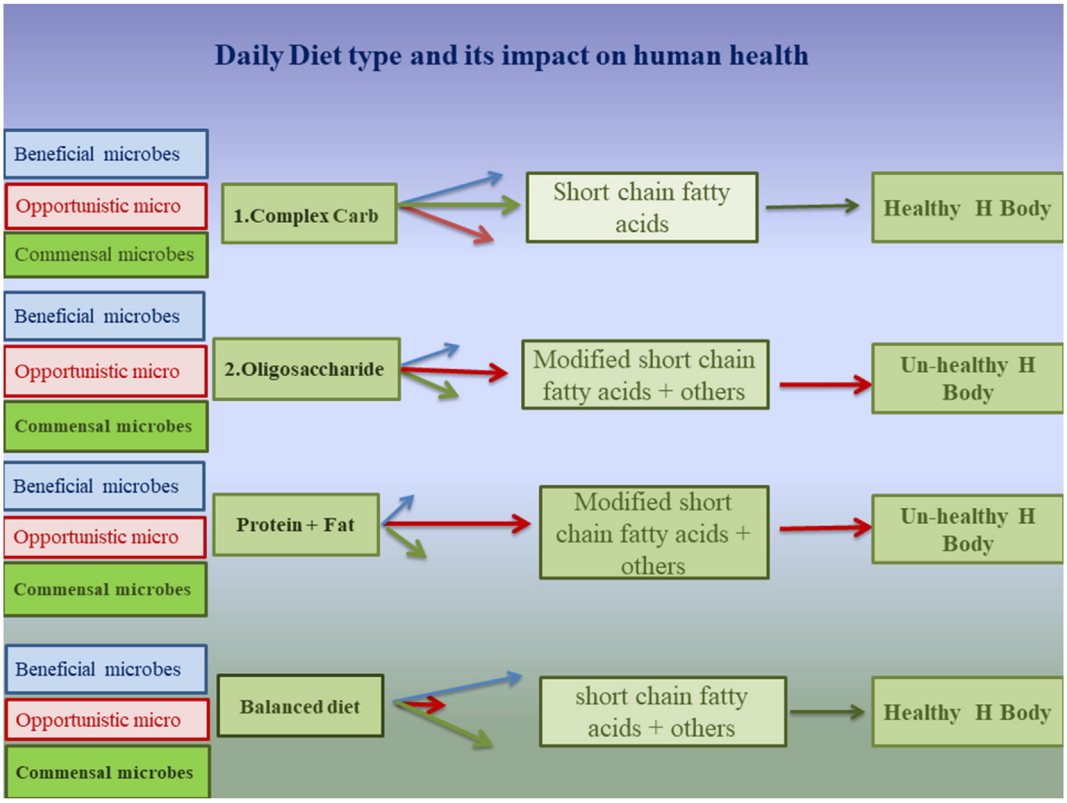

FIG. 1. Gut microbiome, type of daily diet and their interaction's impact on human health. Arrows represent approximate population of each group: beneficial (symbiotic) organisms, opportunistic pathogens and commensal microbes. Arrow lengths indicate symbol/function for microbial alterations depending on diet type.

healthy human gut (beneficial genera, or symbionts), are Gram-negative bacteria involved in complex carbohydrate digestion and immune system modulation; they export antibacterial proteins to target competing bacteria [8,9]. *Proteobacteria* and some *Firmicutes* are Gram-positive bacteria that also digest carbohydrates [10]; however, some of them are highly pathogenic opportunistic pathogens. Meanwhile, *Actinobacteria* comprise Gram-positive microbes involved in the digestion of cellulose; they play a remarkable role in maintaining microbial balance through production of antibacterial and antifungal agents [11].

As mentioned above, disturbance (dysbiosis) of these dynamic communities is greatly affected by many factors, including age, stress, lifestyle, host genetics, external microbial exposure, intake of drugs such as antibiotics and daily diet [12]. However, the consistency and diversity of these gut microorganisms can be restored by taking a daily good-quality probiotic that will help keep the gut healthy [13]. Generally, recommended probiotic therapy/products may contain more than one selected microbial strain, mostly belonging to the following genera: *Lactobacillus, Bifidobacterium and Lactococcus, Enterococcus* and *Streptococcus* [14]. Moreover, strains of Gram-positive bacteria belonging to the genus Bacillus and some yeast strains belonging to the genus *Saccharomyces* are also used in probiotic products [15]. The reaction mechanisms of these probiotic microbes may effectively inhibit the development of pathogenic bacteria such as *Clostridium perfringens, Campylobacter jejuni, Salmonella enteritidis* and *Escherichia coli* as well as various species of other pathogenic genera, such that food poisoning that escapes to the bloodstream will be prevented [16]. Additionally, probiotic microorganisms are naturally able to produce different groups of vitamin B, to increase the efficacy of immune system and to improve the absorption of vitamins and mineral compounds, which are required for synthesis of organic acids and amino acids. Probiotic microorganisms may also be able to produce antibiotics that inhibit associated bacterial pathogens, thus preventing inflammation and immunosuppressive progression [17].

Daily diet greatly affects the gut microbial balance; diet can help maintain a normal population or change its balance. Flourishing or fading of the beneficial microbiome may lead to boosting metabolites in a healthy direction or raising opportunistic genera, which may lead to a pathogenic appearance by producing certain metabolites that influence the host

physiology and gene expression, consequently resulting in the development of different diseases.

Here we discuss the effect of diet on the human microbiome and the related risk of disease development.

Human diet

The human diet generally consists of different food varieties including protein, fat and carbohydrates, with a good balance among them necessary. The type and quantity of these diet constituents are greatly influenced by the community and diversity of the gut microbiome. The digestion of these constituents leads to variability in the end products, which play a key role in the prevention, management and treatment of certain diseases such as cancer and diabetes [18–20]. Degradation of the protein in diets normally occurs at the distal end of the colon, where the conditions are suitable for the secretion of proteolytic bacteria. The usual end products of protein degradation are amino acids, ammonia, amines and short-chain fatty acids. High concentrations of ammonia are related to the development of malignant growths [21]. However, a diet containing fat alteration in gut microbial composition has been reported in which a decrease in *Bacteroidetes* and an increase in both *Firmicutes* and *Proteobacteria* were frequently occurring [22,23]. In addition, several genera of the class *Gammaproteobacteria* also recorded an increase in their abundance with other specific genera, leading to an alteration in microbial population and diversity [24]. These changes result in a lowering of the microbial production of short-chain fatty acids and antioxidants. Consequences of the metabolites' changes include signs of disease risk and the potential for disease.

Regarding diets containing carbohydrates, studies have shown that carbohydrates promote cell survival in cancer via the upregulation of fatty mass– and obesity-associated gene expression levels [25,26]. Diets containing complex carbohydrates derived from plant tissue are slowly digested by the gut microbiome, especially those existing in the distal part of the intestine. Digestion of plant fibers increases the symbiotic microbiota that leads to increasing short-chain fatty acids, which play a role in energy supply and therefore in human health. Complex carbohydrates exert beneficial effects on body weight, food intake, glucose homeostasis and insulin sensitivity [27]. Studies have demonstrated a significant correlation between a higher-fiber diet intake and a reduction of risk of irritable bowel syndrome, inflammatory bowel disease, cardiovascular disease, diabetes and colon cancer [25,28].

Diseases that may occur as a result of microbiome alteration

Disturbance or imbalance of the gut microbiome, or dysbiosis, may occur as a result of many possible reasons, including stress, illness, overweight, overuse of antibiotics or eating a poor-quality diet. Indeed, daily diet is the most important factor affecting the composition of the human gut's microbiome. Consuming a diet composed of energy-dense and highly processed foods, as well as emulsifiers and artificial sweeteners, appears to compromise the barrier lining the human gut. If the gut barrier is weakened, then tiny particles like bacteria or digested food are able to escape into the bloodstream, where they are marked as introducers and trigger the immune system to act. This can be a factor for disease. Continuous immune activation and the inflammation that goes with it can lead to a range of diseases.

The human diet not only supplies vital nutrients but also influences the life span [29] and physiologic state of many organs; it also contributes to the development of many diseases [30]. Diseases that develop as a function of alteration of human microbiome that are greatly affected by daily high-fat and/or high-carbohydrate diets, especially in a susceptible host; the results include inflammatory diseases, cardiovascular diseases, obesity, type 2 diabetes and several cancers [31].

Inflammatory bowel disease

A variety of factors contribute to the development of inflammatory bowel disease (IBD). These factors may be environmental, genetic, immunologic or microbial (i.e. inhabiting the digestive system); all contribute to the development of IBD [32]. Although the exact aetiology of IBD remains unclear, it is believed to be the result of complex, unusual immune responses to all the abovementioned factors separately or in sequence. Research has focused on the intestinal microbiome, especially with genetically susceptible hosts. There is growing evidence that imbalances in gut microbial populations and their diversity can be associated with many diseases, including IBD [33,34]. It has been proven that the intestinal microbiota is a source of many proinflammatory components such as lipopolysaccharide or capsule-derived compounds (peptidoglycans, lipoproteins, flagellins) that are able to activate innate inflammatory pathways, leading to the development of a chronic inflammatory state. IBD is identified as comprising a group of inflammatory conditions of the small intestine and colon. The main types of IBD are Crohn disease and ulcerative colitis.

Crohn disease

Crohn disease targets the mucosa and submucosa tissues, which leads to regional ileitis, Crohn disease's old name. Crohn disease affects the small and large intestines as well as the mouth, esophagus, stomach and anus. Intestinal microbiota seems to play an important role in the pathogenesis and causes of this Crohn disease. Microbial shifts have been associated with IBD, in which a relative increase in the abundance of *Enterobacteriaceae*, including *Escherichia coli* and *Fusobacterium, Serratia marcescens* and fungal species like *Candida tropicalis,* compared to their healthy relatives. These shifts will lead to an alteration of metabolic pathways, including an increase in the occurrence of oxidative stress pathways and a decrease in basic metabolism and short-chain fatty acid production [35].

Ulcerative colitis

Ulcerative colitis tends to occur in the colon and distal ileum, which contain the highest intestinal bacterial concentrations. It targets the mucosa tissue only. It causes long-lasting inflammation and ulcers in the digestive tract. It primarily affects the innermost lining of the large intestine (colon) and rectum. Symptoms usually develop over time rather than suddenly. In patients with ulcerative colitis, a higher incidence of *Enterobacteriaceae* and *Bacteroides fragilis* is evident compared to patients' healthy relatives [15].

Irritable bowel syndrome

Irritable bowel syndrome is a common disorder that affects the large intestine. Signs and symptoms include cramping, abdominal pain, bloating, gas, and diarrhoea, constipation or both. There is no cure, but changing the type of diet often helps to control or even remove the pain associated with this disease. In patients with irritable bowel syndrome, the microbial communities record an alteration whereby the *Proteobacteria* and *Firmicutes* phyla flourish while *Actinobacteria* and *Bacteroidetes* are diminished compared to healthy controls [36]. According to 16S recombinant DNA sequences, the family *Lachnospiraceae* within the phylum *Firmicutes* is recorded in greater abundance [36].

Diabetes and obesity

Type 2 diabetes (T2D) is considered to be a metabolic disorder primarily caused by obesity-linked insulin resistance. There has been much debate regarding the involvement of the gut microbiome as a causative agent in developing such disease; indeed, studies performed to explore the correlation between the gut microbiome and T2D have noted the importance of gut microbiota in the pathophysiology of T2D [37,38]. Generally, some beneficial bacteria, such as butyrate producers *Faecalibacterium* sp. and *Roseburia*, might be important in the efficacy of improvements in diabetes and obesity disorder [37]. Further studies and more scientific evidence are needed to elucidate and confirm the correlation of microbial composition and these metabolic disorders.

For gut microbiome and obesity, evidence of a fundamental link between them comes primarily from germ-free mouse models; such animals are resistant to a high-fat diet that induces obesity as a result of a lack of fermenting bacteria that can process complex carbohydrates. In a sequential step, reduction in short-chain fatty acids will occur [39]. Colonization of these germ-free mice with fermenting bacteria such as *Bacteroides* spp., together with organisms that promote the fermentation process, results in increased body weight and obesity. This process is significantly dependent on the activation of the GPCR41 receptor of short-chain fatty acids [40].

Cardiovascular disease

Cardiovascular diseases (CVD) are the primary cause of death worldwide. The existence of a gut microbiome characterized by high population and diversity has been positively implicated in human health and disease, and CVD are no exception. Microbiome dysbiosis has been proved to be involved in the progression and pathogenesis of CVD, including atherosclerosis, hypertension and heart failure. Production of trimethylamine-*N*-oxide (TMAO) as a net product derived from specific dietary nutrients reflects the close relationship between gut microbe and future cardiovascular events [41]. Suzuki *et al.* [42] found that elevated blood TMAO levels were directly linked to patients with CVD such as coronary artery disease and acute and chronic heart failure. Several studies have been conducted to demonstrate the microbial alteration and genera involved in the incidence and progression of CVD [43–45], which report a lower abundance of the phylum *Bacteroidetes* and a higher abundance of the order *Lactobacillales,* in particular *Enterococcus* sp., in patients with CVD compared to non-CVD patients with coronary risk factors.

Acceleration of carcinogenesis

Alteration of the gut microbiome has been highlighted by many studies of the involvement of the gut microbiome in the progression of cancer and has been marked as something that accelerates carcinogenesis [46,47]. **C**ancer represents the second leading cause of death worldwide; its multifactorial pathology has resulted in much research that assesses the ability of the gut microbiome to produce several metabolites and bioproducts necessary to protect host and gut homeostasis. However, an unbalanced diet, which is one factor among others, can permit expansion of some opportunistic microbes to the detriment of the beneficial one, thereby producing high levels of toxins that in turn are capable of triggering

inflammation and/or tumorigenesis. The organ most affected by an alteration in gut microbes is the digestive system itself, resulting in what is termed 'GI cancers', specifically esophageal, gastric, colorectal, liver and pancreatic cancers [48,49]. The simplest mechanism that leads to carcinogenesis is when the host gut microbiome is impaired and the host immune system fails to restore homeostasis of the lining tissues. In such a setting, the microbiota may influence carcinogenesis by (a) altering host cell proliferation and death, (b) disturbing the function of host immune system and (c) negatively influencing metabolism within a host by induction of selective enumeration of certain members of the microbiota, especially pathobionts. For colorectal cancer, an impaired microbiome permits the flourishing of entering toxigenic *Bacteroides* and pathobionts *Fusobacterium* and *Campylobacter* [50,51]. Similarly, Rutkowski [52] found that if the gut microbiome of animal models is altered, their hormone receptor–positive breast cancer turned more aggressive.

Neurodegenerative disease

Various studies have noted that intestinal health greatly affects neurodegeneration, despite the anatomic distance between the gut and the brain [53]. Epidemiologic data have shown that humans with neurodegenerative diseases have concurrent intestinal lesions and histopathologic changes in the gastrointestinal tract. Gut microbiome alterations have been reported in many neurodegenerative diseases, including Parkinson diseases and Alzheimer disease, as well as inflammatory central nervous system diseases.

Carabotti *et al.* [54] similarly found that the gut–brain axis interacts with intestinal cells and the enteric nervous system, as well as with the central nervous system, through neuroendocrine and metabolic pathways. Furthermore, enteric nervous system function can be influenced by the gut microbiota when they locally produce neurotransmitters, including γ-aminobutyric acid (GABA), amino acid derivatives (serotonin, melatonin and histamine) and fatty-acid derivatives (acetylcholine [55]) or biologically active catecholamines (dopamine and norepinephrine) in the gut lumen [53,56]. Therefore, metabolites resulting from dysbiosis of the gut microbiome may stimulate the sympathetic nervous system [57,58], with downstream effects on learning and memory that lead to Alzheimer disease [59,60]. Other studies have shown that certain bacteria belonging to *Bacteroidetes* (*Porphyromonas gingivalis*) was detected in brain and may be involved in neurodegenerative disease, particularly for Alzheimer disease [54,61]. However, for Parkinson disease, metabolites of the imbalanced gut microbiome, in particular Gram-negative pathogens, are the trigger for the loss of dopaminergic neurons and mitochondria dysfunction [62,63].

Conclusion

A healthy daily diet plays an important role in the gut microbiome, leading to normal distribution of and balance between different groups of gut microorganisms. Any disturbance caused by an unbalanced diet or nutrient intake could lead to a flourishing of pathogenic groups of the gut microbiome and a decrease in other beneficial groups. As a result of this alteration, toxic metabolite molecules and pathogenic microbes may disturb the intestinal barrier and reach the bloodstream, which in turn may affect human organs and cause mild disease, which will be accelerated as a result of the accumulation of these toxins, causing severe disease. Therefore, keeping the gut microbiome unaltered, including avoiding an unbalanced diet, will help maintain human health.

Conflict of interest

None declared.

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