# High-sugar diet affects immunity and metabolism by affecting gut microbiota

Jiahao Tang *

Department of food, South China Agricultural University, Guangzhou, China

* Corresponding Author Email: tangjiahao@stu.scau.edu.cn

**Abstract.** Due to the rise of global material levels and people's lack of awareness of scientific diets, high-sugar diets are gradually becoming one of the largest diet types in modern humans; some researchers believe that this diet will have negative impact on people's intestinal flora. The number of bacteria in the human body is known to be extremely large, and the intestinal flora is one of the main components. Their number roughly between 10 and 100 times as many as cells of humans. Owing to several studies, an imbalance in gut microbiota is linked to a variety of information that will support disorders. The present investigation examines the appropriate information on obesity, diabetes, and other disorders, and discusses the potential linkages among these diseases and a high-sugar diet and intestinal flora, in order to figure out if a high-sugar diet might have an unhealthy effect on human immunity and metabolism through gut microbiota. A high-sugar diet can cause excessive proliferation of intestinal Firmicutes and Proteus, disrupting intestinal flora balance, and the root causes of diabetes, weight gain, inflammation of the intestines, and non-alcoholic hepatitis, as well as the corresponding therapeutic mechanisms, are all associated to the excessive growth of certain species of bacteria in the intestines, which also means gut microbiota imbalance.

**Keywords:** High-sugar diet; gut microbiota; obesity; diabetes; inflammation.

## 1. Introduction

A high-sugar diet mainly refers to the excessive intake of fructose and glucose in food by human beings. The term "gut microbiota" relates to the numerous floras found in the intestines of a person [1]. gram-positive Firmicutes species and Gram-negative bacteria constitute the vast majority of the gut microbiota. The intestinal barrier, which includes the mucus layer, the epithelial layer, and the intestinal immune system, maintains its homeostasis. The normal formation and stability of intestinal flora are related to the body's nutritional intake in infancy [2]. Imbalances in the microbiota of the gut are believed to be associated with the rise in an assortment of non-contagious illnesses. Such as obesity, diabetes, intestinal inflammation, and non-alcoholic hepatitis, and external factors such as nutrition can disrupt the gut microbiota's homeostasis. At this time, the flora mainly affects the body through the vague nerve, microbial metabolites, and the immune system [3]. Latest study in germ-free mice has revealed that a gain of body mass can be linked to a boost in the amount of the Bacteroides polymorpha in the stomach. And Bacteroides polymorpha, which is a Gram-positive bacterium, has the same obesogenic effect as Firmicutes. At the same time, obesity is thought to be tightly related to the diabetes, the prime reason is that the imbalance of intestinal flora causes obesity and also causes the body's resistance to insulin; and there are also some researchers states that adipose tissue is one of the causes of intestinal inflammation because peristaltic fat is considered to be the main source of pro-inflammatory. For nonalcoholic hepatitis, choline deficiency due to abnormally elevated levels of Gram-negative bacteria and endogenous ethanol production triggers the disease. This article starts from the association between high-sugar diet and gut microbiota, comprehensively discussing how high-sugar diet affects gut microbiota from immune and metabolic perspectives, and expressing how the imbalance of intestinal flora affects the health of people. Obesity, diabetes, intestinal inflammation and non-alcoholic hepatitis were taken as examples [4-6].

## 2. High Sugar Diet and Gut Microbiome

### 2.1. Ecosystem and Composition

For humans, the flora of the gastrointestinal tract is colonized at birth and comes from the environment and their mothers, mainly from mother's vagina and skin. Based on data, approximately $10^{13}$ bacteria have settled in the human gastrointestinal system, which is equivalent to the amount of normal human cells; however, the genetic codes expressed by the microbiota of the gut are a hundred times more prevalent than those expressed by the human genome. Based on studies, microorganisms make up more than half of the gut microbiota. Bacteria are largely made up of two microorganisms' phyla: Gram-negative Bacteroidetes and Gram-positive Firmicutes, which together account for approximately between 85 and 90 percent of the whole intestinal microbiota. Actinomycetes, Proteus, Fusobacterium and verrucous microorganisms were relatively few. The diversity and density of gut microbiota is usually related to the distance between the intestine and stomach, the farther the distance, the richer the density and diversity [1].

### 2.2. The Vital Reasons of Maintaining the Gut Microbiome

Existing research has established that early nutrition in infants can affect the colonization and growth of their gut microbiota; It has also been hypothesized that adverse effects on infants in the womb are largely responsible for increasing their risk of developing chronic diseases later in life; breast milk, infant formula, or a mix of the two is typically used as a baby's major meal after birth. Milk from humans' oligosaccharides (also called HMO) is among the most abundant elements in breast milk, but newborn youngsters are unable to absorb these oligosaccharides. Health maintenance organizations, on the other hand, may be employed as the primary carbon source for some bacterial strains due to their structural similarities to mucin glycans. (e.g., Bifidobacterium, Bacteroides). These strains are closely related to the initial colonization of the human gut microbiota, and there are numerous beneficial effects on mucosal, immune, and metabolic health in humans. Excessive fructose consumption during pregnancy has been linked to fetal programming, as well as a number of unfavorable conditions in children. Examples include high blood pressure, being overweight, having diabetes, coronary artery disease, and fatty liver caused by non-alcoholic beverages syndrome (Fig. 1) [1, 7].

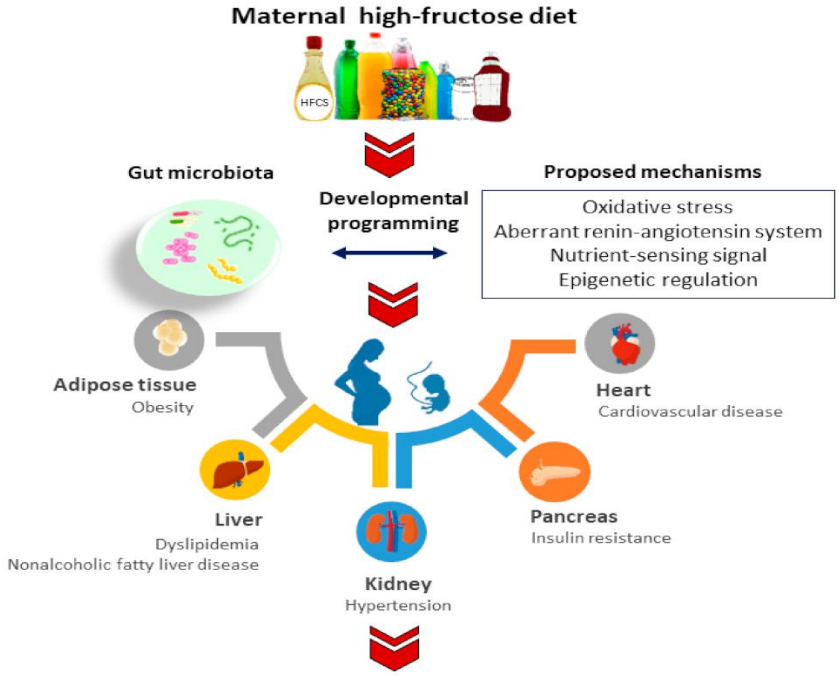


**Fig 1.** Mechanisms associated gut microbiota to maternal fructose-induced developmental programming in numerous organ systems [7].

### 2.3. Intestinal Barrier and Immune System

The mucus layer, epithelial layer, and immune system are all common components of the intestinal barrier. Proper host-microbiome interactions play a vital role in sustaining a healthy gut through existence amid these impediments. The pathogenesis in humans is determined by many factors and it is usually caused by some external or internal factors. Variations in the composition of the microbiota in the gut, nutrition, as well as antibiotic use are a few examples. These factors can interfere with one or more parts of the intestinal barrier, leading to diseases, typified by intestinal inflammation, extraintestinal autoimmune diseases, diabetes mellitus caused by metabolic disorders, and obesity [1, 8].

Inflammation is widely believed to be an early indicator for gastrointestinal disease as well as cancer. Inflammation in the gastrointestinal system can result in the replacement of cells lining the gut on a constant basis. And this frequent turnover may increase the possibility of cancer formation. Calprotectin is a neutrophil-derived protein which is now widely recognized as an important indicator of intestinal inflammation. Levels of this protein are frequently related with inflammation in the stomach in individuals with a condition called inflammatory bowel disease. According to study findings, an increase in cytokines (IL-6, IL-1, TNF-) in people with inflammatory bowel diseases is correlated with an increased risk of cancer. This is due to the fact that these cytokines not only stimulate cell proliferation and suppress apoptosis. Nevertheless, they additionally promote cell invasion and metastasis. The levels of CRP are inversely connected with IL-6 levels, and CRP rates tend to rise in obese and IBD patients. TNF- activation was demonstrated to activate NF-B, and fifty percent of CRC presented NF-B overexpression. Inflammation can also cause oxidative stress by causing the body to produce reactive oxygen species and nitrogen, which have been linked to carcinogenesis in the body. The gut microbiota is also linked to a key role within colorectal cancer. The researchers observed that the control group was significantly distinct from UC using 24 6-week-old male SD rats separated in two sets and developing ulcerated colitis (UC) and cancer of the colorectal (CRC). The makeup of the gut microbiota differed considerably across the CRC groups. The alteration of the dominance of bacteria such as Firmicutes may be seen in the comparison of the control group and the SD rats produced by UC and CRC: when the researchers analyzed the UC group with the CRC group, they discovered that the CRC group had larger numbers of Enterobacter, Shigella, and Proteus, while the Lactobacillus family was lower. Firmicutes Lactobacilli have been demonstrated to exhibit properties that reduce inflammation. Unbalanced microbiota in the gastrointestinal tract can produce metabolic products that accelerate the progression of UC to CRC. According to research, UC and CRC-induced rats with SD showed greater metabolic activity when Enterobacteriaceae and Proteus were involved in the metabolism of the compounds arachidonic acid as well as linoleic acid, respectively [6].

## 3. How the Gut Microbiome Influence Human

Gut flora has the potential to regulate most of the behavioral activities of the body, including but not limited to regulating the body's emotions, physical behavior, metabolic activities, based on the broad connect that exists among the microbiome-gut-brain and the microbiota of the gut, as well as the immune system's action recent studies have identified three gut flora functions and body channels: the vagus nerve, the immune system, and gut flora regulating neuroactive compounds.

There are afferent and efferent branches of the nerve that runs through the vagus (cranial nerve X) and it is important in communicating between the brain and the gut. In a mouse experiment, researchers discovered that once asymptomatic mice with no obvious immune response got infected with the intestinal pathogen Candida jejuni, the mice were more anxious than uninfected control mice; This phenomenon suggests that neurological interaction among the gastrointestinal tract and the central nervous system may occur via the vagal pathway during GI infections.

The immune system is also important in the two-way communication between the stomach and the brain. Elevated levels in the blood of cytokines that are pro-inflammatory such as cytokines such

as IL-1, IL-6, as well as TNF- are often linked with inflammation in the body. These elements are thought to be involved in human depressive disorders. Both IL-6 and IL-1 have been shown in studies to enhance the hormone that releases corticotropin CRH, and CRH is a modulator of HPA axis. When the body's innate immune receptors, such as LPS, come into contact with the gut microbiota, the immunological response frequently results in the generation of pro-inflammatory cytokines. Therefore, the intestinal flora usually affects the body's activities and emotional performance through the immune system in an inflammatory manner.

Gut microbial metabolites have the ability to affect nearly every aspect of human physiology: 1. Immune system regulation 2. Metabolic process 3. Having an impact on human mood and conduct. It has been demonstrated that the gut microbiota can generate or ingest a variety of vertebrate neurological chemicals such as norepinephrine and dopamine and GABA. These metabolites might operate locally in the intestinal tract or aggregate in the blood and organs, influencing the body's functions. They can act locally in the intestines or accumulate in serum and organs before acting. According to study findings, the intestines-brain network for nutrient-sensing transmission makes it possible the gastrointestinal system to tell the cerebral cortex of every occurrence as well as the food that was consumed. An disproportionate eating habits, such as an excessive fat and sugar intake as well as a lack of fiber in the diet over a period of time, may result in an imbalance of intestinal flora, increased permeability of the intestinal mucosa, and an impairment in digestive defenses, glucose, along with the metabolism of lipids. The most prevalent organisms are easily changed at this point in time, resulting in the occurrence of related diseases [3].

## 4. The Negative Impact Caused by High Sugar Diet

The intake of high-sugar and high-fat foods and the lack of dietary fiber are important factors that cause intestinal flora disturbance; These effects are mainly reflected in the change of intestinal permeability, and also lead to the replacement of dominant species in the intestinal flora and the decline of the abundance of some species; According to research, compared with high-fat diet, high-sugar diet is more likely to increase the permeability of intestinal mucosa, damage the intestinal barrier and lead to intestinal infection; At the same time, the high permeability of the intestinal tract will make it easier for the bacteria invading from the outside to transfer and spread, which is not conducive to the later treatment.

The gut microbiota is significant in obesity and insulin resistance, as revealed by researchers like Gordon. They demonstrate variations in the percentage of Gram-negative Bacteroides and Gram-positive Firmicutes in genetically obese mice, confirming the Firmicutes' dominance in obese humans and mice fed a high fat diet. A high-fat, high-sugar diet (HFHS) also alters the bacteria in the gut and increases intestinal permeability. Furthermore, research have demonstrated that transplanting microbiota from obese human donors into germ-free mice induces weight gain and insulin resistance in animals. Consequently, illustrating that particular microbial strains separated from individuals and implanted within rats without germs trigger the desired phenotypes found in the original hosts (thin or fat), which includes Enterobacter cloacae B29 (obesity-inducing), Pseudostrand Bifidobacterium C95 (improves hypoglycemia), and Myxophila Akkermansia (improves hypoglycemia) (improves glucose tolerance and body weight) (Fig. 2) [3, 9].

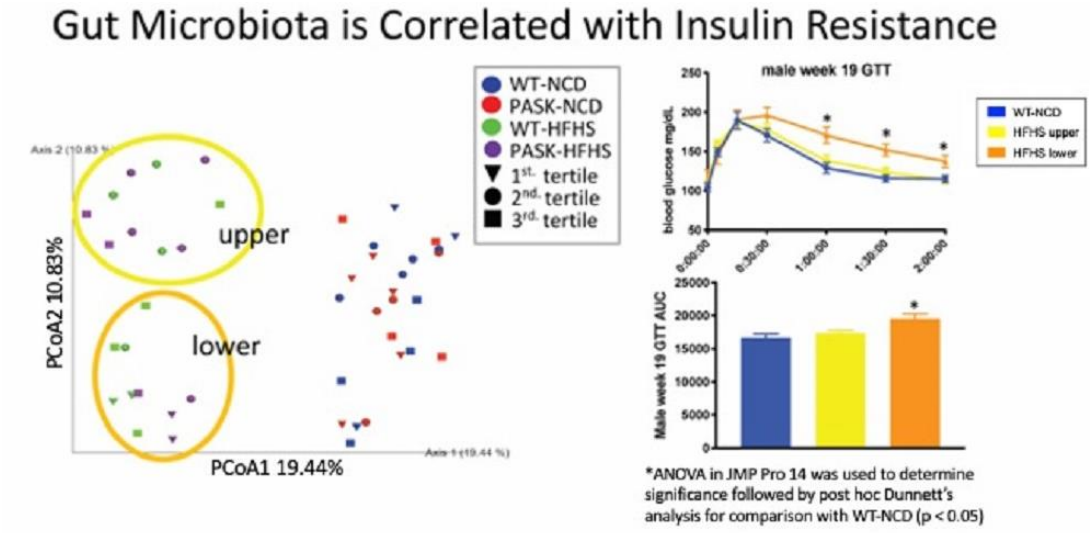


**Fig 2.** The connection between the gut microbiota and resistance to insulin [3]

### 4.1. Obesity

Being overweight is presently a worldwide epidemic, and the incidence of it is expanding. In 2016, more over 1.9 billion people were overweight, according to World Health Organization data. 650 million of those who were overweight were obese. Moreover, roughly 38 million youngsters were obese in 2019. The prevalence of overweight and obese children and adolescents increased considerably from 4% in 1975 to more than 18% in 2016. Since 2016, the global prevalence of obesity has climbed around threefold. Obesity is a complex condition that has been scientifically connected with an assortment of health problems, which includes coronary artery disease and diabetes, which is type 2 diabetes. (T2DM), high blood pressure, and several cancers. Obesity is mainly brought on by the buildup of unnecessary fat within the organs of the body. Obesity is caused by a variety of factors, including genes and hormones, but environmental factors are the most important. (bad lifestyle, eating disorders). A high-sugar, high-fat diet has been identified as the major cause of obesity and obesity-related metabolic disorders in several studies. If a high-sugar, high-fat diet is combined with a lack of exercise lifestyle, it will lead to a further imbalance between the body's calorie intake and energy expenditure, thereby forming a positive energy balance. And a long-term positive energy balance will lead to hypertrophy of fat cells, which will lead to hypoxia and compression of body cells, it also will further trigger an inflammatory response and makes fat cells dysfunction. Fat cells that are dysfunctional will produce more free fatty acids (FFA). As a consequence of rising lipid synthesis and reduced lipolysis, fat gathers in the liver, heart, intra-abdominal region (visceral tissue), muscles of the skeleton, and around the pancreas. Weight gain is believed to be linked to shifts within the intestinal microbiota's composition. Obese adults had a lower relative number of gut bacteria and a less diverse array of the microbiota in their intestines when compared to normal individuals. According to one study, genetically obese mice had 50% less Bacteroidetes and 50% more Firmicutes in their feces than lean mice. Furthermore, a study of the fecal microbiota of 12 obese persons found a higher proportion of Firmicutes as to Bacteroidetes. As a consequence, it may be deduced that the fraction of bacterial species in the gut microbes of obese organisms declines and improves with weight loss. The microbiota in the intestines of obese adults, with the exception of Firmicutes and Bacteroidetes, included less verrucous microorganisms and a greater amount of Actinobacteria. At the same time, whereas Firmicutes increased overall in obese humans and mice, Faecalibacterium in the Firmicutes phylum dropped. And the Faecalibacterium prausnitzii was associated with obesity, diabetes, and a reduction or elimination of mild inflammation. Faecalibacterium, an intestinal microorganism about properties that reduce inflammation, seems the most prevalent type in healthy individuals as well as the primary bacteria that generate butyrate within the intestines. Nevertheless, inconsistent findings concerning Faecalibacterium in obesity have been reported in the literature, with

some study organizations claiming that it causes obesity and others claiming that it reduces obesity. It is uncertain what caused this contradicting finding. Though adipocyte dysfunction has been identified as the primary root about being overweight, some research suggests that variations in the intestinal bacteria might play a role. Turnbaugh and colleagues observed that the intestinal microbial community regarding obese mice absorbed greater amounts of energy from food than the microbiota of non-obese mice, and that when the obese mice's microbiota was transplanted into germ-free mice, the germ-free animals gained significant weight. This shift shows that obese animals have a distinct gut microbiota makeup, which may be linked to a high-fat diet (Fig. 3) [10].

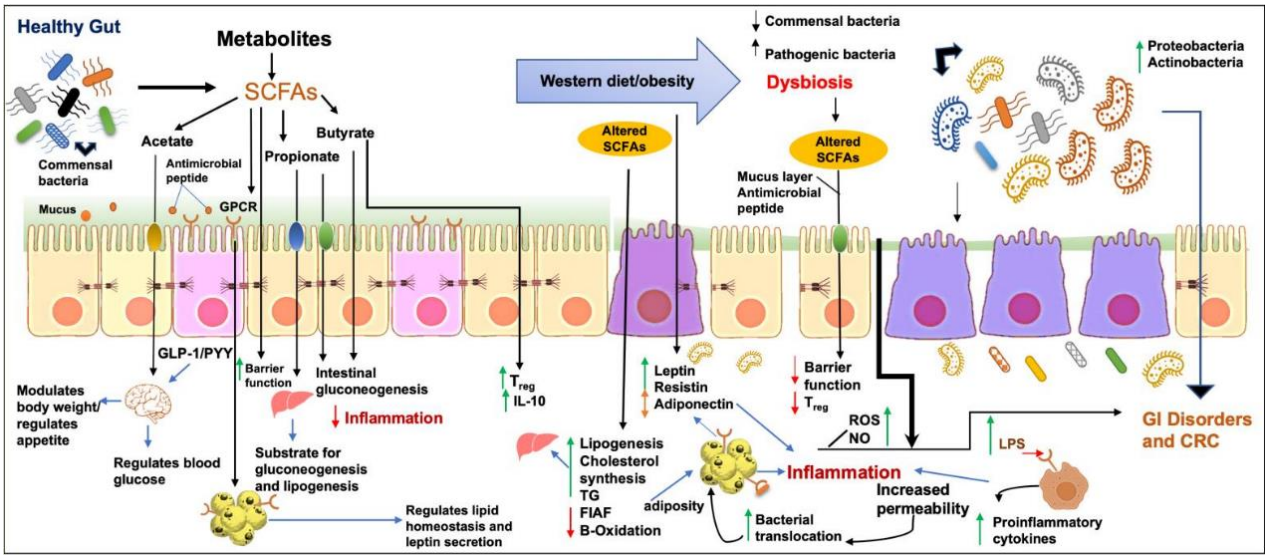


**Fig 3.** How the gut microbiota influences the obese [10]

### 4.2. Diabetes

Type 1 prediabetes and type 2 diabetes are both related to the imbalance of intestinal flora or the replacement of dominant flora; A recent study showed that prediabetic patients tend to have significantly different microbiomes compared with healthy controls. One of these was a decrease in microbial diversity in prediabetic patients; Specific explanations include greater the bacterium Rum and Streptococcus rates and lower Clostridium levels in prediabetic individuals. The findings of the present investigation are congruent with those of another experiment in mice: there is a relationship between Clostridium butyricum and blood sugar levels, insulin resistance, CRP, hemoglobin A1C levels and BMI. The researchers also found that when diabetic mice were treated with a strain of Clostridium butyricum. It can improve its blood sugar level, reduce insulin resistance and inflammatory markers, increase mitochondrial metabolism, and generally restore the balance of the intestinal flora ecology. Clostridium butyricum is known to upregulate butyrate levels in the body. Therefore, the researchers speculate that the reason why Clostridium butyricum can alleviate the symptoms of diabetes in mice is related to the increase in butyric acid levels. At the genetic level, a metagenomic-wide analysis showed that when one categorizes genes likely to be associated with diabetes into a metagenomic linkage group (MLG), then, based on the sequencing results, they were compared with the bacteria in the intestinal flora of healthy people and diabetic patients. The results showed that most of the MLG from healthy people came mainly from bacteria that can produce butyrate, and the MLG from people with diabetes is mainly from opportunistic bacteria; Based on this, it can be explained that the absence of butyrate-producing bacteria in the intestinal flora of the body is undoubtedly a phenomenon and one of the causes of diabetes; In addition, Faecalibacterium prausnitzii is also an important butyrate producer in the body. Compared with obese individuals, fecal samples from leaner subjects had a higher abundance of Faecalibacterium, and it was even lower in obese diabetic patients [5].

### 4.3. Non-Alcoholic Fatty Liver Disease

Unhealthy lifestyles such as high-sugar and high-fat diets will cause negative changes in intestinal flora, significantly affecting liver immunology and internal ecological balance. This change is one of the causes of non-alcoholic hepatic cirrhosis. Numerous investigations involving humans and animals provide evidence that the microbiota of the gut acts a significant part within the progression of free of alcohol hepatic disease.; among them, modifications to the composition of the microbiota in the intestines can significantly affect the liver, the balance between carbohydrate and lipid metabolism in the gut, and pro-inflammatory and anti-inflammatory effects, thus affecting alcohol-free disease of the liver. Recent studies have shown that a diet high in fat and sugar will interact with the intestinal flora and produce active metabolites, facilitating the initiation and further disease progression of non-alcoholic liver disease. It is known that the intestine and liver are connected through the portal vein, and have a close anatomical relationship and communication with various physiological functions. This connection is called the gut-liver axis, this axis can transport the active components after the reaction of diet and microorganisms from the intestinal tract to the liver to affect its various physiological indicators, and the liver can also secrete factors such as orthocholic acid that affect intestinal homeostasis. One study showed that imbalances caused by overgrowth of Gram-negative bacteria in the gut microbiota promote insulin resistance and endogenous ethanol production. At the same time, it can also induce choline deficiency in the body and cause non-alcoholic liver disease. In addition, according to one study. Certain microbe-derived compounds, which include fatty acids that are free, trimethylamine, added cholic acid as well as ethanol, may trigger damage to liver cells and death, as well as fibrosis and genomic instability, predisposing the body to cirrhosis and cancer of the hepatocellular carcinoma. [6].

## 5. Conclusion

The imbalance of intestinal flora is caused by the general relationship between the axis of the gut to the brain, the host, as well as the flora, and it has a negative impact on one's health via three channels: the vague nerve, the immune system, and the neuroactive compounds of the intestinal flora. The main changes in the intestinal tract accompanied by the imbalance of flora are the development of permeability in the intestinal tract and the deterioration about intestinal barrier. A high-sugar diet can cause a flora discord in the intestine, that is, a change in the proportion of bacterial species: Firmicutes and Proteus increase, while the number of Bacteroides decreases.

For the disease of obesity, the composition of the intestinal flora of obese patients is relatively different from that of lean people, which has been proved in experiments in mice. In obese patients, the range and proportions of the intestinal microorganisms are low. Also, the proportion of Firmicutes to Bacteroidetes and Actinobacteria to verrucous microbes was greater. But Faecalibacterium in Firmicutes was decreased. For diabetes, the gut microbiota of patients with type 1 and type 2 prediabetes were found to be high in Ruminococcus and Streptococcus, and low in Clostridium, accompanied by the absence of butyrate-producing bacteria; and available data indicates that boosting the amount of butyrate-producing bacteria in the gut microbiota (such as Faecalibacterium) is a good therapy option. In relation to intestinal inflammation, metabolites produced by an imbalanced gut microbiota can promote the progression of ulcerative colitis to colorectal cancer, Firmicutes phylum Lactobacilli have been demonstrated to have anti-inflammatory effects. For nonalcoholic liver disease, the high proportion of Gram-negative bacteria in the intestinal flora and the high-sugar diet lead to the release of active metabolites from the intestinal flora will affect the liver through the gut-liver axis, inducing non-alcoholic liver disease; At the same time, the liver will also affect the intestinal tract with factors such as orthocholic acid through this pathway, which will further unbalance the intestinal flora.

Through the observation and summary of the three diseases, the article finds that the cause of these diseases is the gastrointestinal flora discord caused by the high proportion of one or more bacteria in the intestinal flora. The treatment of the corresponding disease is mostly related to transplanting a

certain missing flora or regulating the proportion of intestinal flora as a whole; and the high-sugar diet is an important reason for disrupting the balance of intestinal flora. Finally, the gut flora-based associations of these four diseases providing a reference for later researchers.

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