International Journal of General Medicine

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REVIEW

# Significance of Gut Microbiota on Graves' Disease

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**Abstract:** Growing research proves gut microbiota and thyroid autoimmunity are linked. Graves' disease (GD), as an autoimmune thyroid disease (AITD), is attributed to the production of thyroid-stimulating hormone receptor (TSHR) autoantibodies that bind to the thyroid follicular endothelial cells. It is well known that genetic factors, environmental factors, and immune disorders count for much in the development of GD. So far, the pathogenesis of GD is not elucidated. Emerging research reveals that the change in gut microbiota composition and its metabolites are related to GD. The gut microbial diversity is reduced in GDs compared with healthy controls (HCs). Firmicutes and Bacteroidetes account for a large proportion at the genus level. It is found that phyla Bacteroidetes increased while phyla Firmicutes decreased in Graves' Disease patients (GD patients). Moreover, gut microbiota modulates the immune system to produce cytokines through bacterial metabolites. This article aims to find out the relation between gut microbiota dysbiosis and the development of GD. As more molecular pathways of bacterial metabolites are revealed, targeting microbiota is expected to the treatment of GD.

**Keywords:** Graves' Disease, gut microbiota, autoimmunity, dysbiosis, Firmicutes, bacteroidetes

## Introduction

Graves' Disease (GD) is an organ-specific autoimmune disease caused by intolerance to thyroid antigens. The exact pathogenic mechanism of GD is unclear. Anti-TSHR antibodies (TRAb) are deem as a key pathogenic factor, which is produced by the loss of immune tolerance to thyroid antigens. TRAb binds to the thyrotropin receptor and stimulates production of thyroid hormone.[1] GD occurs in genetically susceptible individuals usually triggered by the effect of the environment. Ichiro Horie et al show that how Th17 cells impact the pathogenesis of a certain autoimmune disease depends on the mouse's genetic background.[2]

The gut microbiota consists of more than 1200 species of anaerobic, aerobic bacteria, phages, viruses, and fungi,[3,4] mainly dwelling within the digestive tract, participating in nutrient metabolism, drug metabolism, prevention of colonization of pathogenic microorganisms, protecting intestinal barrier function and shaping immune development.[5] Gut microbiota has attracted much attention due to its multiple effects on the intestinal barrier, nutrient and drug metabolism, immune system, and resistance to pathogenic bacteria.[6] Increasingly studies show the relation between gut microbiota and autoimmune disease.[7–10] Changes in its composition and metabolism may affect the pathogenesis of obesity, diabetes, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and AITD.[11–13]

The gut microbiota is a huge bacterial community which consists of Firmicutes, Bacteroidetes, Verrucomicrobia, Actinobacteria, and Proteobacteria.[14,15] Research has shown that there are significant differences in gut microbiota between Graves' Disease patients (GD patients) and healthy individuals.[16] Research on high-throughput sequencing shows that the composition of gut microbiota in GD patients is different from that HCs. The diversity and the richness of the gut microbiota in GD were lower than in the controls.[17] They also thought that Bacilli, Prevotella, Megamonas, Veillonella, and Lactobacillales can distinguish between GD and healthy people, while J. Chen et al thought Ruminococcus and Lactobacillus may be novel biomarkers of GD.[18] Besides, Xinhuan Su et al proposed that

Received: 8 March 2024
Accepted: 13 August 2024
Published: 11 September 2024

Bacteroides, Alistipes, and Prevotella could discriminate GD patients from healthy individuals with 85% accuracy.[19] However, there is no unified conclusion on which species is the characteristic marker of GD.

Research has found a correlation between them, but the causal relationship is still uncertain. Dysbiosis of gut microbiota may affect the onset and progression of GD through multiple pathways.

On the one hand, the gut microbiota and its specific metabolites participate in the body's immune response, such as short chain fatty acids (SCFAs) and tryptophan (Trp),[20] which not only affect genetic and epigenetic regulation, but also affect the metabolism of immune cells (including immunosuppressive cells and inflammatory cells).[21] The immune system is shaped by gut microbiota through regulating immune cells such as regulatory T (Treg) cells and T-helper 17 (TH17) cells,[22] which conversely affects the composition and metabolism of microbiota in the intestine.[4] Gut microbiota metabolites mediate the interaction between epithelial cells and immune cells. Xinhuan Su et al find that the incidence rate of GD in the model mice is increased after transferring the GD patients' gut microbiota to them.[19] In immune homeostasis, the immune system tolerates beneficial symbiotic bacteria. Tolerance is broken when an immune disorder occurs and genetically susceptible individuals will suffer from immune diseases.[23] When the gut microbiota is imbalanced, it may disrupt the integrity of the intestinal mucosal barrier, leading to increased permeability and the entry of gut microbiota and metabolites into the bloodstream, triggering abnormal activation of the immune system and triggering an autoimmune response. For example, patients with autoimmune thyroiditis have a high incidence rate of celiac disease(CD).[24] Research has shown that patients with CD are exposed to a large amount of foreign antigens after intestinal epithelial destruction, which in turn promotes the occurrence of autoimmune reactions.[25] In addition, studies have found that specific strains of Bifidobacterium and Lactobacillus, due to their structural homology with the amino acid sequences of human TPO and Tg, can induce AITD through a cross antigen molecular simulation mechanism.[26] 16S rRNA sequencing analyzed the fecal microbiota of 45 GD patients and 59 healthy controls, and found that the abundance of lactobacilli in TPOAb positive GD patients was significantly higher than that in TPOAb negative GD patients.[27]

On the other hand, gut microbiota can affect the absorption of thyroid related minerals, including iodine, selenium, zinc, and iron.[28] Research has found the presence of deiodinase in the intestinal wall, which helps convert thyroxine (T4) into its active form triiodothyronine (T3).[29] The changes in gut microbiota may affect the absorption and metabolism of iodine, thereby affecting the synthesis and release of thyroid hormones, exacerbating the condition of GD patients. Continuous stimulation of TSH receptor antibodies (TRAb) in GD patients leads to an increase in the production and release of thyroid hormones, and this metabolic state change may further affect the composition and function of gut microbiota.

Current research indicates a correlation between gut microbiota and its metabolites with GD, but the specific mechanism is still unclear.[16] This article is written to review the latest studies on the relationship between gut microbiota and GD, focusing on the impact of gut microbiota composition, metabolism, and immune mechanism on GD, which is helpful to understanding the possible pathogenesis of GD and provide some ideas for new effective treatment methods.

# Correlation Between Gut Microbiota and GD

## Changes in Gut Microbiota

Changes in gut microbiota composition and intestinal environment may affect the immune state of the human body. GD often co-occurs with CD,[30,31] which can be interpreted that the increased intestinal permeability following an impaired intestinal barrier allowing easier passage of antigens and activation of the immune system. Additionally, bariatric surgery to remove part of the digestive tract may lead to insufficient absorption of these micronutrients in the context of reduced overall nutrient absorption, and further reduce thyroid-stimulating hormone (TSH) levels.[32] Conversely, thyroid hormones also affect intestinal levels. Triiodothyronine (T3) may be involved in the development and differentiation of intestinal mucosal cells.[33] Recently, several studies sequence the gut microbiota in patients with GD, showing changes in diversity, richness, and composition in Table 1. The α diversity of GD patients is decreased in most studies[17–19,27,34,35] while increased after treatment.[18] Lower α diversity is related to an inflammatory response that results from the decline of host immune function.[27]

**Table 1** Some Researches on the Sequencing of the Gut Microbiota in GD Patients and Healthy Controls

| Author Year | Subjects | Bacterial richness | Bacterial α diversity | Phyla level |
|---|---|---|---|---|
| Hafiz Muhammad Ishaq[34] 2018 | 27GD+11HC | ↓ | ↓ | Bacteroidetes↑, Actinobacteria↑, Proteobacteria↑ Firmicutes↓ |
| Wen Jiang[27] 2021 | 45GD+59HC | ↓ | ↓ | Bacteroidetes↑ Firmicutes↓ |
| J Chen[18] 2021 | 15GD+14HC | ↓ | ↓ | not statistically significant |
| Xinhuan Su[19] 2020 | 58GD+63HC | ↓ | ↓ | Bacteroidetes↑ Firmicutes↓ |
| Shih-Cheng Chang[36] 2021 | 55GD+48HC | Not statistically significant | - | Bacteroidetes↑, Actinobacteria↑ Firmicutes↓ |
| Isabel Cornejo-Pareja[37] 2020 | 9GD +9 HT +11HC | ↓ | ↓ | No differences |
| Hui-Xian Yan[17] 2020 | 39GD+17HC | ↓ | ↓ | - |
| Mengxue Yang[35] 2019 | 15GD+15HC | ↓ | ↓ | Firmicutes↑, Proteobacteria↑, Actinobacillus↑ Bacteroidetes↓ |
| Chaiho Jeong[38] 2024 | 29GD+230HC | ↓ | ↓ | Firmicutes↓ Bacteroidota↑ |

**Abbreviations**: GD, Graves' disease; HC, healthy control; HT, Hashimoto thyroiditis;↑, increase; ↓, reduce.

Members of the genus Bacteroides account for a major fraction of the microbiome in the gastrointestinal tract. Bacteroides can secrete antimicrobial proteins, packed in an outer membrane vesicle (OMV).[39] Bacteroides may cause disease in the host through OMVs,[40,41] by which toxicity factors can be stored and conveyed over long distances.[42] Then the target cells may be equipped with virulence factors from OMV, which promote the pathogenesis of extraintestinal organs.[43] The abundance of Bacteroidetes is higher while Firmicutes is lower than in controls at the Phyla level (Table 1). Studies in Table 1 show that the level of Bacteroidetes is increased except the one is decreased.[35] Bacteroides is recognized to be linked to inflammatory bowel disease as a pro-inflammatory bacterium.[44,45] Colonization of Bacteroides thetaiotaomicron can cause a systemic and local immune response, as seen by elevated serum IgA and IgG levels.[46]

Between the lumen and the mucosal surface of the gut, there is an axial difference. While Bacteroides, Bifidobacterium, and Streptococcus are the most common luminal bacteria, Lactobacillus is one of the most common mucosa and mucus-associated bacteria.[47] Despite the fact that Lactobacillus is typically thought to be nonpathogenic, some clinical case reports show that the genus Lactobacillus can cause endocarditis, bacteremia, and peritonitis, as well as liver abscesses and localized soft-tissue infections.[48–52] According to Miettinen et al, Lactobacillus directly triggered the NF-κB signaling pathway.[53] Studies show that Lactobacillus had a greater number than controls,[27,35] suggesting that Lactobacillus may relate to the occurrence of GD by activating the NF-κB signaling pathway.

It is generally believed that Prevotella has co-evolved with humans until new researches show that Prevotella is associated with inflammatory disorders. The genus Prevotella may be clinically relevant pathobionts that induce chronic inflammation and contribute to disease incidence. Studies show that the abundance of Prevotella members is increased,[34,54] which may associate with augmented T helper type 17 (Th17)-mediated mucosal inflammation.[55] Prevotella also stimulates epithelial cells to promote mucosal Th17 immune responses and neutrophil recruitment by producing cytokines like IL-8 and IL-6.[55]

Univariate correlations between the number of specific gut microbiota and thyroid autoimmune markers have been reported,[18,27] like thyroid-stimulating immunoglobulin antibody (TSI-ab)(positive correlation with Lactobacillus and Pasteurellaceae and negative correlation with Faecalibacterium).[37] Chen, J et al find that there is a positive correlation between changes in the level of TRAb and the abundance of Lactobacillus.[18] If a marker flora can be found based on a large number of studies, the level of immune response and prognosis of patients may be inferred.

## Gut Microbiota and Thyroid Hormones

The gut microbiota can effectively influence the permeability and integrity of the gut barrier, further affecting the metabolism of thyroid hormones.[54] Germ-free (gf) mice with shortened villi and reduced intestinal crypts[56] affect the metabolism of thyroid hormones in the gut. In humans and rats, conjugated iodothyronine can be hydrolyzed in fecal suspensions.[57] The hydrolysis of bound T4 in the gastrointestinal tract facilitates the re-entry of the hormone into the circulation through the enterohepatic circulation, accelerating the metabolism of thyroid hormones.[58] Moreover, studies show that the regulation of thyroid hormone metabolism by gut microbiota may be achieved by inhibiting deiodination and glucuronidation activities.[15,59] The level of TRAb in GD patients is positively correlated with the relative abundance of Lactobacillus and Lactococcus,[18] and it can be speculated that the increased level of Lactobacillus and the increased level of TRAb in GD patients are correlated.

## Gut Microbiota and Graves' Orbitopathy(GO)

Graves' orbitopathy (GO) is the most common manifestation outside the thyroid. There is increasing evidence that the change in the gut microbiome may be related to the development of GO. A cross-sectional study by Shi, TT et al show that the gut microbiota diversity is significantly decreased in GO patients. At the phyla levels, the proportion of Bacteroidetes is increased, while significant differences were observed in the bacterial profiles at the genus and species levels.[60] The changes at the level of the door are consistent with the study by Y Li et al[61] who found that Bacteroidia in the gut microbiota of GD/GO rats was increased compared to the control group. Masetti, G. et al established a GD/GO model using two different sources of mice for a 2-center study, one of which show reduced gut flora diversity, while the other group is not obvious,[62] the clinical manifestations induced in this group are not as obvious as the former may explain this problem. The decreased diversity is consistent with direct observation of gut microbiota changes in GD/GO patients. Furthermore, in TSHR-immunized mice, Masetti, G.et al discovered a substantial positive connection between the presence of Firmicutes and orbital-adipogenesis, offering the possibility of utilizing the gut microbiota for the treatment of prominent orbital contents in GO. Study in experimental mice models of GD and GO developed by human thyrotropin receptor (hTSHR) A subunit plasmids show that mice's gut microbiome has altered after induction of mouse GD/GO models, proving the relationship between thyroid disease and the composition and function of intestinal microbiota.[63]

## Immune Mechanism

### Leaky Gut

The gut barrier is a complex barrier containing epithelial, chemical, and immune components. Tight junction (TJ) proteins hold intestinal epithelial cells together to separate the host and the microbiota,[64] simultaneously supported by cytokines, antibacterial molecules, mucins, and immunoglobulins.[65] The change in the intestinal permeability by drugs or diet cannot prevent harmful substances from passing through the barrier, known as the "leaky gut"[65] Bacteroides can produce Short-chain fatty acids (SCFAs) including succinate, propionate, and acetate, which cannot induce mucin synthesis. Hence, intestinal tight junctions are weakened and intestinal mucosal permeability is increased. Table 1 shows that Bacteroides are increased in GD patients,[19,27,34,36] from which we can speculate that increased Bacteroides may weaken the intestinal barrier. Then gut microbiota and their metabolites can migrate into the systemic circulation, interacting with immune cells and leading to the breakdown of immune tolerance.[23,66] Moreover, on the cellular level, the microbiota may mediate the shift of immune cells outside the intestine.[67]

### SCFAs

SCFAs are important fuels for intestinal epithelial cells (IECs), regulating IEC proliferation, differentiation, and function of subpopulations through different mechanisms, affecting intestinal motility and enhancing intestinal barrier function as well as host metabolism.[68] Indigestible oligosaccharides by Bacteroides can be fermented into SCFAs to provide energy sources for the host.[69,70] Reducing dietary fiber intake will reduce the proliferation of gut microbiota, resulting in reduced production of SCFAs.

SCFAs can strengthen the tight junctions between cells together with thyroid hormones.[29] Gf mice exhibit reduced villi and crypts, thinning mucosal layers, and altered permeability, indicating that immune cell development is disrupted owing to a lack of microbial activation of the immune system.[14,71,72] Decreased numbers of helper T cells (particularly CD4+Th cells), reduced Th-17 and Treg differentiation, and reduced production are all signs of immunodeficiency in gf mice.[14,73] In the etiology of AITD, all of these immune cells play a role.[74] The amount of Tregs, which are essential mediators of immunological tolerance, is favorably linked with the quantity of the short-chain fatty acid butyrate.[75,76]

### Molecular Mimicry

In genetically vulnerable populations, molecular mimicry between microbial and human antigens can turn protective immune responses into autoimmune. The triggering effect and its pathogenic mechanism have been studied and demonstrated in autoimmune diseases. A study on Multiple sclerosis (MS) proved that viral transmission of a Haemophilus influenzae epitope causes autoimmune illness in the central nervous system through molecular mimicry.[77]

One study finds that some Bifidobacteria and Lactobacillus share structural homology with human TPO and thyroglobulin (TG), suggesting that these bacteria may bind TPO and TG antibodies selectively through a "molecular-mimicking mechanism" and then induce AITD.[26] Studies have pointed out that there is a large amount of homology in the amino acid sequence between microproteins and thyroid antigens,[78] which might cause autoimmune thyroid disorders through the molecular mimicry process.

### Th17 and Tregs

Th17 and Tregs cells are subsets of T helper cells. Tregs secrete inhibitory cytokines including IL-10 and TGF-β, while Th17 cells release IL-17 and other pro-inflammatory cytokines. Loss of the balance of pro- and anti-inflammatory cytokine milieu in the gut environment may induce B lymphocytes to produce anti-thyrotropin receptor antibodies (TRAb) which bind to TSH receptors and then mimic the effects of TSH,[79] leading to elevated levels of thyroid hormones.

Th17 cells and Tregs have been reported to play important roles in autoimmune disease, and gut microbiota functions to regulate them.[80–82] However, it is unknown the involvement of Th17 and Tregs in the pathophysiology of GD. A study on Inflammatory Bowel Disease by Graham J. Britton et al reveals that gut microbiota can regulate Tregs and Th17 cells in the intestinal mucosa and gastrointestinal-associated lymphoid tissues.[83]

Tregs can suppress the inflammatory responses, which are induced by Clostridia and Bacteroides fragilis.[84,85] Decreased Tregs may be involved in GD, while increased Th17 lymphocytes are related to GO.[86] Lactobacillus abundance is greater in patients with GD than in the control group, which researchers believe is linked to Th17 cells.[35] Xinhuan Su et al propose similar results that propionic acid produced by Bacteroides could increase the Tregs numbers while decreasing the Th17 cell numbers.[19] Yukihiro Furusawa et al show that Butyrate stimulates Tregs differentiation in the colonic lamina propria.[87] It's possible that alteration of the gut microbiota causes aberrant Th17 and Tregs secretion, contributing to the development of GD. Disturbed gut microbiota might cause aberrant Th17 and Tregs expression, which impacts the onset and progression of GD.

## Outlook

Evidence on the relationship between gut microbiota and GD continues to emerge, and imbalances in gut microbiota can directly or indirectly affect immune regulation. Dysbiosis of gut microbiota and its specific metabolites may lead to GD through various pathways, such as altering the metabolism of iodine and thyroid hormones and affecting the absorption of thyroid related trace elements. However, the causal relationship between gut microbiota and GD is not yet clear, and the molecular mechanisms by which specific microbiota trigger GD are poorly understood. Therefore, in the future, it is necessary to explore the relationship between gut microbiota and thyroid through multi omics analysis, animal and cell

experiments, and other methods that utilize dominant microbiota. With the clarification of the mechanism, fecal microbiota transplantation, gut microbiota and their specific metabolites are expected to be used for the diagnosis, treatment and prevention of GD.

## Funding

This study was supported by the National Natural Science Foundation of China (82071006), Natural Science Foundation of Hunan Province (2020JJ4129).

## Disclosure

The authors report no conflicts of interest in this work.

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