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REVIEW ARTICLE

Microbiome and thyroid diseases: future precision studies of the gut-thyroid axis to facilitate the adjuvant treatment

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ABSTRACT

Background and Objectives: The gut microbiome is a key determinant of overall health, impacting numerous bodily functions, such as those of the endocrine glands. The effect of the microbiota on thyroid function has become a matter of interest, more so since the revelation of the possible link between intestinal disease and autoimmune thyroid disorders (AITDs). This review aims to provide an in-depth insight into the possible link between gut microbiota and thyroid diseases and metabolism of thyroid hormones.

Materials and Methods: A set of online sources including, PubMed, Scopus, Google Scholar and CENTRAL were comprehensively searched to find the studies relevant to the topic of the review. Only reports in English were included in this review.

Results: It has been proposed that damage to the intestinal barrier is a key element in the passage of antigens from the lumen into the bloodstream and their subsequent contact with the immune system. In addition to AITDs, dysbiosis has been shown to be linked with thyroid cancers, in which higher counts of certain bacteria associated with inflammation and carcinogenesis have been identified.

Conclusion: The majority of the available literature is focused on the differences in the microbial strain composition in individuals with thyroid disorders compared to that of healthy controls. Nonetheless, the current body of evidence has implied on possible role gut microbiome in the development of thyroid diseases.

Keywords: Thyroid function; Thyroid disease; Microbiome; Dysbiosis

INTRODUCTION

The gut microbiota, also referred to as the hidden organ, comprises a vast array of bacteria, archaea and eukaryotic cells covering a total surface area of 250-400 m^2. The development and establishment of the intestinal microbiota begin at birth and evolves further through breastfeeding. Initially, the gut possesses low phyla diversity and is dominated by Actinobacteria and Proteobacteria (1, 2). A gradual shift,

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and increase in diversity occur in the first 2.5 years of life, and at age three, the microbiota has reached an initial maturation. After this stage, diet, medications and infections are the major forces impacting the microbiota composition, which may result in major changes in some instances (3). In association with the human digestive system, the microbiota also plays a role in micronutrient (e.g., choline, and short-chain fatty acids (SCFAs), vitamin K, B12, riboflavin and biotin.) and medication absorption, as well as lipid and carbohydrate metabolism (4, 5). Furthermore, the microbiota is closely linked to the integrity of the mucosal barrier, further highlighting its role in both adaptive and innate immune responses (4-7), maintenance of structural integrity of the gut mucosal barrier, and the pathogenesis of diseases (4). With this view of the microbiome in the body, researchers have studied the gut microbiota in various diseases, including metabolic diseases such as obesity and diabetes (8-10). In addition to metabolic diseases, other diseases, including the relationship between gastrointestinal cancers, inflammatory bowel disease and gut microbiome, have been studied (11, 12).

The gut microbiome enables proper thyroid function through providing selenium, iodine and iron, while also aiding the absorption of thyroid-related medications (13, 14). These elements are integral to thyroid function, with well-established correlations between thyroid dysfunction and its dysregulated homeostasis. Iodine deficiency, for instance, is etiologically linked to goiter, thyroid nodule formation, and follicular thyroid carcinoma. Conversely, excessive iodine intake can precipitate both hypothyroidism and hyperthyroidism in susceptible individuals. Iron is critical for the efficient utilization of iodine and the synthesis of thyroid hormones; thus, iron deficiency can instigate thyroid disorders (13).

Furthermore, the metabolism of thyroid hormones in the form of a hepatoenteric cycle, as well as the maintenance of the oxidative balance, are two major examples of the roles of the microbiota in maintaining thyroid health and function (4, 11, 13, 15).

Dysbiosis disrupts immune homeostasis by promoting inflammatory states and diminishing immune tolerance. This perturbation damages the intestinal epithelial barrier, increasing intestinal permeability. This state results in heightened exposure to luminal antigens and increases the risk of localized inflammation (13, 16). Furthermore, the microbiota can directly modulate thyroid hormone levels via bacterial deiodinase activity and the inhibition of thyroid-stimulating hormone (TSH), or indirectly through the disruption of microbial metabolic pathways which is related to impaired butyrate production and increases the risk of thyroid nodules development (17). Moreover, variations in the intestinal microbiome may be a key factor in the thyroid tumors' pathogenesis through its regulation of DNA damage and apoptosis, as well as its influence on inflammatory processes mediated by microbiota-derived metabolites (18). Although the importance of microbiota in the development of different pathologies including diseases is well established, research regarding their role in the development of thyroid disorders remains sparse and a limited number of original research and clinical trials have set out to utilize the microbiota in the battle against thyroid diseases.

To shed further light on the matter, this study aims to provide an in-depth review of the relationship between intestinal microbiome composition, and hypothyroidism, hyperthyroidism and thyroid cancer.

Microbiome, Thyroid hormone and rare minerals. Microorganisms play a pivotal role in modulating thyroid hormone concentrations through their regulatory effects on iodine uptake, degradation processes, and enterohepatic circulation (19). The first step in the synthesis of thyroid hormones involves the uptake of iodine from the small intestine. Although animal studies suggest a significant association between gut microbiota and iodine uptake, human studies on patients who have undergone bariatric surgery or those suffering from short gut syndrome have failed to reach a similar conclusion (20-23). Alongside iodine, adequate amounts of iron, zinc and selenium are also necessary for thyroid hormone synthesis and the management of the significant oxidative stress resulting from the process. A recent study has shed light on the role of *Lactobacillus fermentum* in facilitating iron absorption. Selenium and selenoproteins play a significant role in maintaining the oxidative balance and numerous studies have documented an increase in anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies, as well as increased TSH and reduced free thyroxine (FT4) and free triiodothyronine (FT3) levels in the setting of Hashimoto's thyroiditis (HT) and selenium deficiency (24-27). The uptake of selenium has been documented to be influenced by certain bacteria such as *Lactobacillus* and Bacteroides (increased uptake),

Firmicutes, *Alistipes* and *Helicobacter* (decreased uptake) which further highlights the importance of microbiota balance in thyroid health and autoimmunity (28). Zinc deficiency also exhibited a similar pattern of increased oxidative stress within the thyroid gland while also increasing overall autoimmune susceptibility (29, 30). Unfortunately, we failed to find human studies evaluating the association between zinc uptake and microbiota, one animal study exhibited increased zinc uptake in the presence of *Enterococcus faecium*. Based on the available literature, the deficiency of trace elements is associated with HT more than the other presentations of autoimmune thyroid disorders (AITD).

Although the synthesis of thyroid hormones occurs within the thyroid gland itself, it only accounts for about 20% of the synthesized triiodothyronine (T3), the active thyroid hormone. The majority of the available T3 is the result of the peripheral conversion of thyroxin (T4) by deiodinase enzymes, which may either convert T4 to T3 or reverse T3 (rT3), the latter of which is biologically inactive (31). Since the intestinal mucosae retain deiodinase activity, the role of the microbiota in this conversion requires further investigation. Furthermore, Zn and Se are at the core of iodine deiodinase (D1-3) function and the gut microbiota compete with the host cells for the absorption of these trace elements, the deficiency of which will subsequently reduce the biologically active T3, as well as limit the antioxidant potential of the host (32, 33).

The mechanism behind the inactivation of thyroid hormones involves their conjugation with sulphates (sulphoconjugation) and glucuronides (glucuroconjugation), which increases water solubility and enhances their biliary and urinary clearance. A body of evidence suggests that gut microbiota, more specifically *Peptococcus* products, are capable of deconjugating these metabolites and contribute to the reabsorption of T3. This process is not only limited to endogenous thyroid hormones, but also impacts the absorption of thyroid-related medications such as levothyroxine and propylthiouracil (34-36). A reduced uptake of medication is capable of impacting the elevation of oxidative stress through the overproduction of free radicals and subsequently inflicting further damage to the thyroid. Additionally, Yao et al. reported that microbial composition in hypothyroid patients resulted in an increased requirement of prescribed L-thyroxine to maintain adequate TSH levels in hypothyroid patients compared to controls (37).

Thyroid diseases: autoimmune thyroid disease. The autoimmune disorders of the thyroid are mainly caused by hormonal, environmental, and genetic factors, which can impair thyroid function (38, 39). AITD is recognized as the most prevalent form of organ-specific autoimmunity, affecting an estimated 2-5% of the general population (40). As depicted in Fig. 1, an incompetence between the intestinal microbial composition and thyroid gland could be associated with AIDTs, such as Hashimoto's thyroiditis, goiter, thyroid nodules or cancers, Graves' disease, and transient fluctuations of the thyroid gland, such as postpartum thyroiditis, painless thyroiditis, and subacute thyroiditis.

The majority of the influence of the microbiota on the development of AITDs is exerted through the production of SCFAs, the regulation of oxidative balance, the shift of Treg/Th17 cells, and the subsequent promotion of inflammation. For instance, fecal transplant from hypothyroid patients into mice caused a significant reduction in SCFAs levels compared to controls (41).

Another key promoter of the production of autoantibodies is molecular mimicry, which may be invoked by shifts in the bacterial population and dominance of the gut microbiota (Table 1). Although the investigations into the pathophysiologic relationship between the gut microbiota and autoimmunity, and AITDs in particular, are relatively abundant, the reports are incongruent and irreproducible at times.

In a study of Egyptian patients with AITD, El-Zawawy et al. reported that although AITDs exhibited increased *Bacteroidetes* and decreased *Firmicutes* populations, no significant difference was observable between HTs and GDs (42). Furthermore, the Shanon index was significantly decreased in AITDs, indicating a decrease in richness and diversity of microbiota. Anti-TSH receptor levels were directly correlated the populations of these phylae. Also, anti-TPO exhibited a similar relationship with *Bacteroidetes*, *F. prausnitzii*, *Firmicutes* and *Prevotella*.

In 2011, Bassi et al. studied the correlation between AITDs and the prevalence of *Helicobacter pylori* in fecal samples. The results showed a clear correlation between the presence of *H. pylori* (especially Cag-A positive strains) in Graves' disease, although this correlation was not significant in Hashimoto's thyroiditis (43). Völzke et al. reviewed data collected from

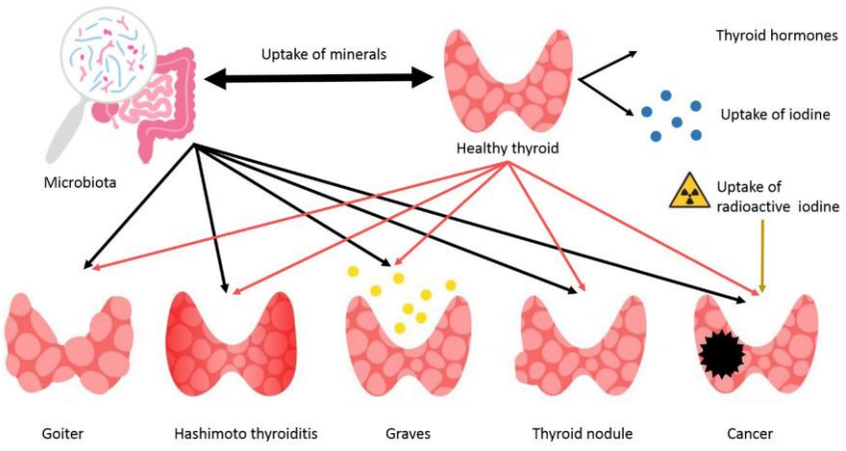

Fig. 1. Crosstalk between thyroid diseases and microbiota

Table 1. Microbial dysbiosis pattern in different thyroid pathological diseases

Thyroid Disease	Increased bacteria	Decreased bacteria
Hashimoto`s thyroiditis	*Helicobacter pylori, Blautia, Roseburia, Ruminococ-cus_torques_group, Romboutsia, Dorea, Fusicatenibacter, Eubacterium_hallii Firmicutes, Synergistetes, Ruminococcus, Lachnospiraceae incertae sedis, Lactonifactor, Alistipes, and Subdoligranulum, Roseburia Fusicatenibacter, Romboutsia, Dorea, Blautia, Phascolarctobacterium*	*Faecalibacterium,Intestinimonas, Ruminococcus Fecalibacterium, Bacteroides, prevotella, Lachnoclostridium*
Graves' disease	*Bacteroides, Bifidobacterium Bacterioides fragilis, Actinobacteria, Collinsella, Pediococcus Oribacterium, Mogibacterium, Lactobacillus, Aggregatibacter Enterobacter hormaechei, Chryseobacterium indologenes, various Bifidobacterium Fusobacterium, Sutterella, Prevotella*	*Firmicutes,Roseburia, Dorea, Dialister, Blautia, Anaerostipes, Butyricoccus, Romboutsia, Fusicatenibacter, Collineslla, Intestinibacter, Phascolarctobacterium Faecalibacterium*
Thyroid cancers (PTC, DTC)	*Prevotella , Bacteroides, Proteobacteria, Comamonas Sphingomonas, Firmicutes, Verrucomicrobia, Ruminococcaceae, Verrucomicrobiaceae, Escherichia-Shigella,Akkermansia (Eubac-terium),coprostanoligenes, Dorea, Subdoligranulum, Ruminococ-cus Escherichia coli,Fusobacterium, Alistipes, Hungatella, Phas-colarctobac-terium,Clostridiaceae, Neisseria, Streptococcus Bacteroides enterotype, Holdemanella genus, Proteobacteria, Ruminiclostridium, class Mollicutes, genus Ruminococcaceae UCG004, genus Paraprevotella, and phylum Tenericutes*	*Bacteroidaceae, Prevotellaceae, Porphy-romonadace-ae, Alcaligenaceae, Prevotella, Bacteroides, Klebsiella, Lachnospiraceae, Butyric monas, Lactoba-cillus, g_Christensenellaceae_R-7_group, g_Eubacte-rium_coprostanoligenes_group RuminococcaceaeUCG004 genus, Streptococcaceae family Faecalibacte-rium, Ruminococcaceae_UCG-002, and Phascolarctobacterium, Firmicutes, Actinobacteria*

4,256 people from 1997 to 2001 and found that there was no association between *Borrelia* exposure as defined by anti-Borrelia IgG, and the risk of AITD (44). In 2011, Kiseleva and colleagues investigated the possible role of probiotic organisms of the genus Bifidobacterium and *Lactobacillus* in AITD stimulation, and their results showed that both genera may be involved in AITD stimulation by molecular mimicry (45). However, the findings of Yang et al. contradict these reports, observing a significantly higher *Firmicutes/Bacteroidetes* ratio. In their study, *Oribacterium*, *Mogibacterium*, *Lactobacillus*, and *Aggregatibacter* were significantly more abundant in GDs compared to controls (46). Furthermore, Yan

et al. reported increased *Bacilli, alongside Lactobacillales, Prevotella, Megamonas* and *Veillonella*, as well as decreased *Ruminococcus, Rikenellaceae* and *Alistipes.* Shanon and Simpson diversity indices showed significantly reduced diversities (47). Ishaq et al. reported similar findings, alongside increased *H. Parainfluenza* (48). The results of a prospective study by Cornejo-Pareja reported an increased abundance of *Firmicutes.* They also observed that the *Pasteurellaceae* were only shared within the AITD group and not the controls. They also determined the differences in the core bacteria of AITDs (HTs: *Victivallaceae*, and *Streptococcaceae*; GD: *Prevotellaceae*) (49).

Hashimoto's thyroiditis. Hashimoto's thyroiditis is regarded as the most prevalent presentation of AITD and, in iodine-sufficient regions, is the prevailing cause of hypothyroidism with an estimated global prevalence of 5-12% (50, 51). HT is caused by the infiltration of inflammatory cells into the thyroid gland, followed by the atrophy of the thyroid tissue.

Through the production of anti-thyroid antibodies, including anti-TPO and anti-TG, the thyroid sustains gradual damage and is overtaken by fibrosis (52). In addition to environmental factors, such as excessive iodine intake, radiation, decreased selenium stores, vitamin D, viral infections and some medications, the pathogenesis of HT also includes a genetic component involving a number of genes, such as the human leukocyte antigen gene (53-56).

It has been suggested that primary hypothyroidism induces alterations in the gut microbiome. Consequently, these modifications in microbial flora may have implications for thyroid function (57).

The capacity for SCFAs production in the gut of patients with primary hypothyroidism was significantly diminished, leading to elevated serum levels of lipopolysaccharide (LPS) (57). A possible reduction in SCFAs could impact T-regulatory cells (Tregs), potentially resulting in an imbalance between Th1 and Th2 responses. This imbalance may trigger a heightened production of pro-inflammatory cytokines, including interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α). The increased immune response could lead to a loss of immune tolerance, resulting in the production of anti-TPO and anti-TG autoantibodies, which are known key features of HT (36).

Also, gut dysbiosis appears to influence the onset and progression of HT by modulating the metabolism of glutathione and arachidonic acid, particularly linked to elevated levels of specific bacterial genera, including *Ruminococcus, Flavonifractor, Moryella*, and *Anaerotruncus.* Additionally, presence of *Bacillus, Corynebacterium, Ornithinimicrobium, Brachybacterium, Nocardioides*, and the *Ruminococcus_gnavus*_group may contribute to HT by regulating the metabolism of purine and pyrimidine. Random forest analysis has indicated that *Bacillus* and *Ornithinimicrobium* might be considered possible biomarkers for differentiating normal individuals from patients with AITD (58).

Furthermore, a specific set of microbial genera, including *Blautia, Roseburia, Ruminococcus* torques group, *Romboutsia, Dorea, Fusicatenibacter, Clostridium, Enterococcus, Yersinia, Proteobacteria, Erysipelotrichia, Cyanobacteria, Desulfobacterota, Klebsiella, Peptococcaceae Ruminococcus, Actinobacteria, Veillonella, Paraprevotella, Neisseria, Rheinheimera*, and the *Eubacterium hallii* group, has been documented to have higher abundance in patients with HT (Table 1). Conversely, a reduction in the levels of *Fecalibacterium, Bifidobacteria, Bacteroides, Prevotella, Bacillaceae, Actinobacteriota, Clostridium, Megamonas,* and *Lachnoclostridium* has been observed when compared to healthy control groups (58, 59).

Su et al. also reported that variations in proliferation of *Eillonella, Paraprevotella, Neisseria*, and *Rheinheimera* could discriminate primary untreated hypothyroidism from other thyroid disorders (41). Comparative analysis of bacterial diversity and richness evaluated by Liu et al. also revealed increased *Lachnospiraceae incertae sedis, Lactonifactor, Alistipes*, and *Subdoligranulum* in euthyroid HTs, *Phascolarctobacterium* in hypothyroid HTs. and *Faecalibacterium, Intestinimonas*, and *Ruminococcus* in healthy controls (60).

Interestingly, recent studies have demonstrated significant differences in gut microbiota composition between individuals with different hypothyroidism conditions. Specifically, an increased abundance of *Lachnospiraceae_incertae_sedis, Lactonifactor, Alistipes*, and *Subdoligranulum* in hypothyroid patients characterized by euthyroidism. Conversely, *Phascolarctobacterium* was found to be more prevalent in individuals diagnosed with hypothyroidism (58, 60). Other studies further expanded upon these findings, revealing an elevation in the proliferation of

Bacilli, Lactobacillales, *Prevotella*, *Megamonas*, and *Veillonella* strains among individuals with Graves' disease; On the other hand, decline in *Ruminococcus*, *Rikenellaceae*, and *Alistipes* abundance were observed (58).

A 2013 study by Aghili et al. examined the association between *Helicobacter pylori* and HT. presentations, and clinical findings included goiter, high TSH, normal T4 and positive anti-TPO antibody. The results showed that in the group of patients with Hashimoto's thyroiditis 46% had *H. pylori*, while in the control group this rate was reported to be 10%, marking a significant correlation between *H. pylori* and thyroid autoimmune disease (61). Other findings also, showed that *H. pylori* mimics thyroid cell surface antigens, and therefore may invoke an immune response against the thyroid (62). To that end, Bassi et al. also evaluated the role of *H. pylori* in AITD. In this study, 112 HT and GD patients were studied, of which 82% and 46% were infected with *H. pylori*, respectively. Among these, 83.7% and 89.2% were positive for Cag-A antigen, respectively. As a result, a significant correlation was observed between the presence of *H. pylori* and Graves' disease, while only CAG-A -positive *H. pylori* was found to be correlated with HT (43).

Following a study on the effect possible of *Helicobacter pylori* in prognosis and management of HT patients, Franceschi et al. compared the rate of *H. pylori* infection, regardless of Cag subtypes, in HT patients. They also investigated the chance of molecular mimicry between anti-TG or anti-TPO antibodies, with any of the *Helicobacter pylori* antigens profile. Contrary to the observations of previous studies, they did not observe any significant association between *H. pylori* infection and Hashimoto's thyroiditis (63).

Shmuely et al. evaluated the performance of *H. pylori* as a prominent environmental risk factor for the development of HT in 101 Female HT patients. The study of several factors in this study stated that *H. pylori* seropositivity was not correlated with HT and congenital thyroid defect which can independently increase the risk of HT (64).

Graves' disease. GD is a form of autoimmune hyperthyroidism that may occur as a result of the destruction of thyroid cell fibers (38, 39). GD is the underlying cause of 50-80% of all instances of hyperthyroidism and is characterized by the overstimulation of the TSH receptor through the production of autoreactive receptor antibodies (38, 65). Similar to other autoimmune disorders, women are at an increased risk of developing AITD compared to men (4-6:1) (66). Genetic predisposition, often involving helper T-cell function, is the major contributing risk factor in 71% of all GD cases. GD is characterized by tachycardia, proptosis, and goiter. Given to the autoimmune nature of the disease, it should be noted that B cells are the key component of the immune system participate in the underlying pathophysiology. Primarily these cells are activated by CD4 + T cells in thyroid cells. Activation of B cells secretes TSH-stimulating antibodies, which can lead to hyperthyroidism by proliferating thyroid cells and releasing hormones (67). Environmental risk factors such as smoking, excessive iodine intake, insufficient levels of vitamin D, selenium and zinc, as well as exposure to a number of viral pathogens such as Hepatitis C virus, comprise the remaining risk for GD development (68).

An in vivo study of GD revealed that, though the dominant genus in non-hyperthyroid subjects, *Bacteroides* and *Bifidobacterium* were significantly more abundant in hyperthyroid GD mice. *Firmicutes*, also exhibited a direct correlation with orbital-adipogenesis in TSHR-immunized mice (69). In Leaky gut syndrome, the intestinal barrier is damaged which increase the risk of host autoimmune diseases, and is identifiable through the release of intestinal fatty acid-binding protein (I-FABP), diamine oxidase (DAO), zonulin, D-lactate and lipopolysaccharide. Zheng et al. observed that GD patients exhibited significantly higher levels of all markers, with zonulin being capable of differentiating between GDs and controls. LPS was also directly correlated with more severe disease and symptomatic presentation (70). Su et al. also reported that in a subset of GD patients with systemic inflammation as evidenced by exhibited higher proinflammatory cytokines (sCD14, sCD25, IL-2, -17A, -1β, -6, -12 & -18) and lower anti-inflammatory cytokines (TGF-β and IL-10). Treg/Th17 ratio in peripheral blood samples was significantly lower compared to controls (71).

A recent investigation has identified a notable composition of the microbiome of patients diagnosed with GD. Detecting a particular microbiome, including *Lactobacillus* and *Bacteroides*, has been associated with thyroid autoimmune diseases. This association suggests a probable role of these microbiota in modulating the responses of the immune system

directed at the thyroid (58).

Additionally, in GD, immune dysregulation is associated with specific microbial shifts, notably a reduction in *Faecalibacterium* and an elevation in pro-inflammatory taxa such as *Enterobacter hormaechei*, *Chryseobacterium indologenes*, *certain Bifidobacterium* species, *Fusobacterium*, *Sutterella*, and *Prevotella*. This altered composition is implicated in the loss of self-tolerance and the pathogenesis of the disease. Also, gut metabolites, including numerous SCFAs, were found to be significantly lower in GD (18).

Analysis of the microbiota in GD revealed comparatively fewer Firmicutes and more abundant *Bacteroidetes* counts. It has also been reported that SCFA-producing *Bacterioides fragilis* had the greatest impact on modulating Treg/Th17 ratio, while also being associated with higher TSH and anti-thyroglobulin, and lower free-T3 and -T4 and anti-TSH receptor antibodies. This is suggestive that controlling the population of *B. fragilis* may exert a significant impact on the management of GD (71). Yang et al. also reported a decreased frequency of Firmicutes and higher *Actinobacteria* at the phylum level, as well as lower plentitude of *Roseburia* and *Dialister* and higher relative abundances of *Bifidobacterium*, *Collinsella*, and *Pediococcus* (72). Jiang et al. reported a similar distribution, while also emphasizing the correlation between *Blautia* populations with Anti-TPO antibodies (73). Shi et al. also observed that decreased *Blautia*, alongside *Anaerostipes*, *Dorea*, *Butyricicoccus*, *Romboutsia*, *Fusicatenibacter*, *Collineslla*, *Intestinibacter*, and *Phascolarctobacterium*, was associated with GD (74). Prior evidence suggests that through the production of butyric acid and promotion of Treg cells, *Blautia* exerts an anti-inflammatory influence (75). Lower *firmicutes* was also found to be correlated with Graves Orbitopathy in two other human studies (74, 76). However, the findings of Yang et al. contradict these reports, since they observed a significantly higher Firmicutes/Bacteroidetes ratio. In their study, *Oribacterium*, *Mogibacterium*, *Lactobacillus*, and *Aggregatibacter* were significantly more abundant in GDs compared to controls (Table 1) (46).

Recent high-throughput sequencing analyses of the 16S rDNA from patients diagnosed with primary GD have revealed a significant increase in *Lactobacillus*, *Veillonella*, and *Streptococcus.* Following the restoration of thyroid functionality, a notable reduction was observed for *Blautia*, *Corynebacterium*, *Ruminococcus*, and *Streptococcus.* Conversely, the relative abundance of *Phascolarctobacterium* exhibited a significant increase ($P < 0.05$) (77).

Other studies revealed that the relative abundance of *Prevotellaceae*, *Pasteurellaceae* (specifically *Prevotella*), *Firmicutes*, *H. parainfluenzae*, Proteobacteria, *Y. enterocolitica* and *Actinobacteria* was significantly elevated in patients. Conversely, the abundance of *Enterobacteriaceae*, *Alistipes*, *Faecalibacterium*, *Veillonellaceae*, and *Rikenellaceae* was markedly reduced among GD patients in comparison to the control group (18).

While certain species exhibit comparable trends in patients with GD and HT, suggesting a potential shared dysbiosis of the microbiota that may contribute to the pathogenesis of both conditions, studies have indicated a correlation between *Helicobacter pylori* and GD, although this association does not extend to HT.

The findings presented by Bassi et al. indicate a significantly elevated prevalence of *Helicobacter pylori* among patients with Graves' disease, suggesting a potential role for this bacterium in the onset and/or maintenance of the condition (62).

Cancer. Microbial changes could be involved in promoting cancer progression and/or inhibiting treatment efficacy. Among thyroid disorders, thyroid cancers (TC) and thyroid nodules are more common, accounting for about 90% of thyroid cancers, including papillary thyroid cancer (78-80). In addition, thyroid carcinoma is one of the five most prevalent cancers among women, and according to studies, metabolism and intestinal microbiome compounds are also influential environmental risk factors in the pathogenesis of this type of malignancy. In 2019, Feng and colleagues examined the association between intestinal microbiome profiles and thyroid carcinoma in 30 patients and 35 healthy individuals. The results of this study showed that 21 different genera and 72 metabolites showed significant changes ($p < 0.05$). Of these, eight metabolites and 5 genera were more proficient in diagnosing TC patients (81). In a study, Yao et al. examined the impact of cefazolin on the intestinal microbiome of three patients with thyroid cancer, post-operation (82). The results showed that antibiotic treatments alone did not change the gut microbiome and that genetics, surgery, diet and environment were also effective. In general, according to this

study, the diversity of intestinal microbiota showed no significant change after surgery compared to preoperative in the patients (Table 1). But the ratio of the two dominant genera, *Prevotella* and *Bacteroides*, was significantly altered (82). Zhang et al. evaluated 20 patients with thyroid cancer, 18 patients with thyroid nodules, and 36 healthy individuals with regard to microbial diversity. The findings of this study yielded that the intestinal microbiota composition had influences on the development of thyroid cancer and thyroid nodules (80). A cross-sectional study reported a similar gut microbiome profile between cases with TC and healthy controls on the phylum level, *Proteobacteria*-types were observed in around 70% of patients with TC. Besides, a four-genera microbial signature could discriminate thyroid cancer patients with metastatic lymph nodes from those without (83).

An analysis of tumor samples and neighboring normal tissue in 30 patients with TC has been shown that the combination of *Comamonas* and *Sphingomonas* could be biomarkers for distinguishing the two tissues. Furthermore, the increased proliferation of *Sphingomonas* was correlated with lymph node metastasis (Table 1) (84). In 2022, Ishaq etal reported that *Firmicutes*, *Verrucomicrobia*, *Ruminococcaceae* and *Verrucomicrobiaceae* at the phylum level, *Escherichia-Shigella*, *Akkermansia (Eubacterium)_coprostanoligenes*, *Dorea*, *Subdoligranulum*, and *Ruminococcus* genera at the genus level and *Escherichia coli* at the species-level, had lower growth rates in healthy subjects in comparison to the TC patients with normal thyroid function, while a considerable decrease in *Bacteroidaceae*, *Prevotellaceae*, *Porphyromonadaceae*, *Alcaligenaceae*, *Prevotella*, *Bacteroides* and *Klebsiella* were observed in TC, group (85).

Research further indicates dysregulation of lipid metabolism and steroid synthesis pathways in TC patients, highlighting the imbalance in intestinal microbiota and related disorders and lipid metabolism may be key player to thyroid carcinogenesis (18).

Zhang et al., employing high-throughput sequencing, demonstrated a correlation between thyroid carcinoma, thyroid nodules, and microbiota, revealing a diminished abundance of SCFA-producing bacteria (e.g., *Lachnospiraceae* and *Butyricimonas*) in thyroid cancer patients (80). SCFAs are immunomodulatory; their depletion may disrupt the immune microenvironment, promote cell death and proliferation, and thereby elevate cancer risk.

Another study noted reductions in SCFA-producing genera such as *Faecalibacterium*, *Ruminococcaceae_UCG*-002, and *Phascolarctobacterium*. A separate, larger cross-sectional survey identified specific microbiota—*Fusobacterium*, *Alistipes*, *Hungatella*, and *Phascolarctobacterium*—as potential biomarkers associated with lymph node metastasis in thyroid cancer (86).

Microbiome profiles in thyroid cancer are characterized by a marked depletion of bacteria crucial for lipid metabolism homeostasis, including *g_Christensenellaceae_R-7_group*, *Firmicutes*, and *g_Eubacterium_coprostanoligenes_group* (87). In contrast, growth in abundance of Bacteroides enterotype may promote TC development or highlight the presence of TC in patients (88). Consistently reported changes include decreases in taxa like the *Ruminococcaceae UCG004* genus and *Streptococcaceae* family, and increases in the *Holdemanella* genus and Proteobacteria phylum (89).

Furthermore, TC cohorts exhibit a significantly higher relative abundance of *Clostridiaceae*, *Neisseria*, and *Streptococcus. Clostridiaceae* are implicated in carcinogenesis, while Streptococcus is associated with increased risk of adenomas and carcinomas. Conversely, *Lactobacillus* is significantly depleted. This genus is important for the bioavailability micronutrients like selenium, which confers antioxidative and thyroid-protective effects; its absence may contribute to elevated oxidative stress in the thyroid gland (13).

A previous report provided evidence for possible role of intestinal microbiome in emergence of differentiated thyroid carcinoma (DTC), identifying explicit compositional alterations. A decreased abundance of the phylum *Actinobacteria* was in correlation with reduced risk of DTC, whereas a raised proliferation in genera such as *Ruminiclostridium* and *Ruminococcaceae UCG004*, the class *Mollicutes*, genus *Paraprevotella*, and *phylum Tenericutes* imposed a surge in the chance of DTC development, suggesting microbiome-mediated effects on thyroid function and immune modulation (90).

Additionally, papillary thyroid carcinoma (PTC) treatment efficacy can also be improved or repressed through microbiota alteration. It has been shown that, resistance to radioiodine (RAI) could be mediated by gut microbiome through different mechanisms which were associated with sodium/iodide (Na^+/I^-) symporter alterations (79). Altogether, the current body

of evidence showed that the microbiota might be a key player in the development and progression of TC. More investigations are required to explain the possible associations between specific microbial genera and TC subtypes.

The gut microbiota has been shown to be a prognosis parameter in management of PTC patients. A common signature in TC involved a considerable decline in *Firmicutes*, particularly *Faecalibacterium*, *Lachnospira*, and *Ruminococcaceae*, alongside a mere surge in *Bacteroidetes* and *Proteobacteria*, which might lead to worse outcomes in TC patients and change the effectiveness of treatments, such as response to radioactive iodine therapy (18).

In PTC patients' post-radioactive iodine (^{131}I) therapy, compositional variations were detected in the gut microbiome. The *Firmicutes*, including genera *Faecalibacterium*, *Lachnospira*, and the *Lachnospiraceae NK4A136* group, were shown to have relatively lower abundance. On the other hand, *Bacteroidetes*, mainly the families of *Prevotellaceae* and *Veillonellaceae* and the genus *Prevotella_9* had increased abundance. These patterns may inform predictive models for ^{131}I therapy response (91).

It should also be noted that among patients with anaplastic thyroid cancer who received pembrolizumab as a treatment, revealed a notable growth in gut microbiome alpha diversity was revealed after treatment commencement, highlighting the probable role of intestinal microbiota on efficacy of PD-1-targeted therapies (92).

Probiotics as an adjuvant treatment. Given the multifaceted influence of the microbiota and micronutrients on thyroid function and pharmacotherapy, novel, patient-specific therapeutic strategies based on individual gut microbiome composition could be developed. Probiotics, defined as live, non-pathogenic microorganisms conferring host health benefits, may influence thyroid function by enhancing intestinal barrier integrity, repressing systemic inflammatory reactions, mediating the hypothalamic-pituitary-thyroid axis, and enhancing the absorption micronutrients like selenium, zinc, and iodine (13, 93).

The current body of evidence suggests the probiotics as an adjunctive therapy may enhance the clinical outcomes patients by refining the thyroid function and changing the microbiota into more favorable composition. Specific strains, such as *Lactiplantibacillus plantarum 299v* and *Bifidobacterium longum*, showed promising effects in augmenting conventional treatments and restoring microbial balance. Probiotic supplementation has been associated with reduced oral levels of *Prevotella*, *Fusobacterium*, *Haemophilus*, and *Lautropia*, and increased gut levels of *Holdemanella*, *Coprococcus*, and *Enterococcus*. Prebiotics like mannooligosaccharides can trigger the abundance of thyroid-relevant *Lactobacillus* and *Bifidobacterium* (18, 94).

Probiotics represent a potential adjuvant therapy for thyroid diseases. Nonetheless, current evidence predominantly derives from animal models. It was seen that the aberrant thyroid function is closely linked to declined *Lactobacillaceae* and *Bifidobacteriaceae* (95). Supplementation with *Lactobacillus reuteri* in animal models improved thyroid function, raised the level of free T4 and thyroid mass, and enhanced activity levels, potentially via an interleukin-10-mediated increase in regulatory T-cells (96). While probiotics could serve as an adjuvant therapy, well-designed clinical trials are necessary to fully capture the depths of the thyroid-gut axis and therapeutic potential of microbiome modulation.

A double-blind, randomized trial in women with Hashimoto's thyroiditis found that treatment with a symbiotic, combining several *Lactobacillus* and *Bifidobacterium* strains with fructo-oligosaccharides, led to improvements in blood pressure and quality of life, but produced no significant changes in depressive symptoms or TSH concentrations (97). Another report yielded that synbiotic supplementation improved fatigue and thyroid function in hypothyroid patients (98).

A pooled analysis of nine clinical trials involving 395 patients with various thyroid conditions found that probiotic and synbiotic supplementation significantly reduced TSH and increased free T3 and free T4 levels, with patients exhibiting heightened responsiveness (93).

Probiotics like *Bifidobacterium longum* are being investigated for microbiota modulation and symptom amelioration (18). A 6-month clinical trial in Graves' disease (GD) patients found that adding *B. longum* to the methimazole regimen enhanced thyroid hormone levels and significantly decreased thyrotropin receptor antibody (TRAb) levels to normal ranges, suggesting a therapeutic role via the gut-brain and gut-thyroid axes (99).

The plant alkaloid berberine, acting as a prebiotic, modulates the gut microbiota by overgrowing bene-

ficial *Lactococcus lactis* and decreasing pathogenic *Enterobacter hormaechei* and *Chryseobacterium indologenes*. Combined with methimazole, it improves outcomes in GD patients and upregulates enterobactin synthesis, facilitating iron uptake and potentially restoring normal thyroid function (100, 101).

Dietary prebiotic has long been known as an efficient intervention to modulate the composition of the gut microbiota, which may improve thyroid function, reduce thyroid cancer risk, and influence ^{131}I therapy responsiveness. Caution is warranted in extrapolating from animal studies due to interspecies microbiota differences. While microbial-based cancer therapies hold promise for tumor reduction, the microbiome can also adversely affect prognosis through bacterial production of oncogenic toxins and metabolites.

CONCLUSION

The variations in composition of gut microbiotas can considerably impact the thyroid hormones metabolisms and can lead to presence of thyroid-related diseases. This influence is so wide which may eventually cause AITD, carcinogenesis and thyroid cancer progression.

The precise causal links connecting the gut microbiota to thyroid pathologies, along with the detailed mechanisms through which specific bacterial taxa or core microbial communities instigate disease, remain inadequately defined. Future elucidation will necessitate large-scale cohorts, integrated multi-omics investigations, and validation through in vitro and in vivo experimental models.

Given the multifactorial etiology of thyroid disorders, interventional studies and clinical trials are warranted to further elucidate the thyroid-gut axis. Modulation of the gut microbiota to correct established dysbiosis represents an emerging strategy for the prevention and management of these conditions. Current nutritional interventions aimed at modifying the gut microbiome in humans primarily involve the use of probiotics, prebiotics and synbiotics to enhance thyroid function.

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