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Gut microbiota and thyroid diseases – summary of current knowledge

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Abstract

Introduction and purpose: The gut microbiota is a diverse collection of microorganisms that coexist in the human intestine. Disorders in its structure leads to dysregulation of huge number of organs, including the thyroid. This review summarizes the latest findings regarding the links between gut microbiota and common thyroid diseases: Hashimoto's thyroiditis, Graves' disease and thyroid cancer.

Materials and methods: This review was based on the PubMed and Google Scholar databases, using keywords: „gut microbiota AND thyroid/Hashimoto/Graves/thyroid cancer", „Graves' disease", „Hashimoto thyroiditis".

Description of knowledge: Gut dysbiosis can contribute to autoimmune thyroid diseases by influencing micronutrient availability and immune regulation. Specific bacterial species may impact Hashimoto's development by regulating neurotransmitters and hormone secretion. In Graves' disease, significant changes in gut microbiota suggest their potential role in autoimmune processes. Research on gut microbiota in thyroid cancer suggests potential diagnostic tools and implicates gut microbiota alterations in tumor development.

Conclusions: Significant gut microbiota changes are observed in Hashimoto's thyroiditis, Graves' disease, and thyroid cancer compared to healthy individuals, indicating a possible association. However, the exact mechanisms remain unclear, necessitating further research to understand how microbiota alterations contribute to these diseases.

Key words: microbiota; thyroid diseases; thyroiditis; Hashimoto disease; thyroid neoplasms; Graves disease.

Introduction

The gut microbiota is a diverse collection of microorganisms that coexist in the human intestine. It develops from birth and plays a crucial role in many life processes, such as digestion and the functioning of the immune system. This diverse population of bacteria and other microorganisms has a huge impact on both physical and mental health [1].

The thyroid is one of the organs whose pathologies coexist with an abnormal gut microbiota. The two most common autoimmune thyroid diseases - Hashimoto's thyroiditis (HT) and Graves' disease (GD) - often coexist with intestinal diseases such as celiac disease or gluten intolerance. The reason may be the easier passage of antigens that activate the immune system, caused by increased gut permeability [2].

It has also been demonstrated that there is a connection between gut microbiota and the development of thyroid cancer [3] (TC), which is the most common tumor of the endocrine organs[4]. Recent scientific research has shown that the gut microbiota and its metabolites can act on the thyroid directly or indirectly, influencing the absorption of micronutrients from the intestines, the metabolism and storage of thyroid hormones, and immune regulation [5].

The aim of this study is to present the changes in gut microbiota occurring in Hashimoto's thyroiditis, Graves' disease and thyroid cancer, as well as their impact on the development of these diseases.

Materials and methods

This review was based on articles published in PubMed and Google Scholar databases after searching for „gut microbiota thyroid", „thyroid cancer microbiota", „gut microbiota Hashimoto", „gut microbiota Grave's disease", „Hashimoto thyroiditis". Data from 41 papers were utilized, with particular emphasis on the latest publications from the years 2018-2024.

Hashimoto's thyroiditis

Hashimoto's disease is the most common autoimmune disease worldwide. It is characterized by chronic inflammation and the presence of circulating antibodies against thyroid peroxidase and thyroglobulin [6]. Typically, it progresses asymptomatically, with the most common symptom being goiter, which may or may not be accompanied by hypothyroidism. Epidemiological data indicate that the prevalence of the disease is eight times higher in women compared to men [7].

Hashimoto's disease is characterized by both local and systemic symptoms. The local symptoms are caused by compression of anatomical structures in the neck. For example, dysphonia resulting from involvement of the recurrent laryngeal nerve, dyspnea due to tracheal compression, and dysphagia caused by esophageal

compression [8]. Systemic symptoms include typical hypothyroidism symptoms such as easy fatigability, weakness, bradycardia, hypotension, constipation, and depression.

In the course of this disease, Hashimoto's encephalopathy may also occur. It can manifest in various ways, from mild symptoms to severe complications such as coma [9]. The most common symptoms include subtle cognitive impairment, behavioral changes, myoclonus, and seizures. This condition responds well to treatment with glucocorticosteroids [8].

The etiology of Hashimoto's thyroiditis (HT) remains unknown, but epidemiological studies suggest that it is caused by the interaction between genetic and environmental factors. Environmental factors that may contribute to the occurrence of this disease include excessive iodine intake; deficiencies in zinc, selenium, iron, and vitamin D; bacterial infections such as *Helicobacter pylori* and *Yersinia enterocolitica*; viral infections; smoking; as well as factors such as stress, age, and gender [10].

There is considerable evidence indicating that the development of HT is favored by gut dysbiosis, increased permeability, and bacterial overgrowth. The composition of the gut microbiota affects the availability of micronutrients necessary for the synthesis of thyroid hormones, such as iodine, iron, and copper. Micronutrients such as selenium and zinc are essential for the conversion of T4 to T3. Vitamin D helps regulate the immune response. Deficiencies in these micronutrients are often observed in autoimmune thyroid diseases (AITDs), leading to thyroid dysfunction [2]. The gut microbiota can also influence thyroid hormone levels by controlling their absorption and degradation. It also affects the bioavailability of levothyroxine. Another way in which the microbiota plays a role in thyroid disorders is its influence on neurotransmitters, the hypothalamic-pituitary axis, dopamine production, and consequently TSH secretion [11].

The gut microbiota is also a source of secondary bile acids in the colon, which exert systemic effects and influence the level of TSH [12]. In animal models, depleted microbiota in rats treated with antibiotics led to a decrease in thyroid function when evaluated using radioactive iodine uptake [13]. Significant increases in *Bacteroides* species and decreases in *Bifidobacterium* were observed in stool samples from patients with HT. Patients using oral levothyroxine had lower levels of *Lactobacillus* compared to individuals without hormonal replacement therapy [10].

Some gut microbiota metabolites, including short-chain fatty acids (SCFAs), may serve as an energy source for enterocytes and, together with thyroid hormones, increase the tightness of intercellular connections and enhance the differentiation of intestinal epithelial cells. In an analysis by Jilai Liu and colleagues, the most common 5 species at the phylum level were: *Firmicutes*, *Bacteroidota*, *Actinobacteriota*, *Proteobacteria*, and *Fusobacteriota*, while the five most common species at the genus level were: *Bacteroides*, *Blautia*, *Faecalibacterium*, *Bifidobacterium*, and *Escherichia-Shigella* [14].

Ishaq et al. investigated a significant disparity between the gut microbiota of patients with Hashimoto's disease and healthy individuals. Patients showed elevated levels of *Actinobacteria*, *Enterobacteriaceae*, and *Alcaligenaceae*. Conversely, the levels of *Prevotellaceae* and *Veillonellaceae* were lower in the patient group compared to healthy individuals. Additionally, *Bifidobacterium* and *Lactobacillus* were less abundant in patients with HT [15].

Study	Increases	Decreases
Zhao et al., 2018	*Firmicutes*/*Blautia*, *Roseburia*, *Ruminococcus_torques_group*, *Romboutsia*, *Dorea*, *Fusicatenibacter*, *Eubacterium_hallii_group*	*Bacteroidetes*/*Faecalibacterium*, *Bacteroides*, *Prevotella_9*, *Lachnoclostridium*
Cayres et al., 2021	*Bacteroides*	*Bifidobacterium*
Ishaq et al., 2017	-	*Bifidobacterium*, *Lactobacillus*, *Dialister*
Liu et al., 2020	*Phascolarctobacterium (HT with hypothyroidism)* *Lachnospiraceae_incertae_sedis, Lactonifactor, Alistipes, Subdoligranulum (HT with euthyreosis)*	-

Table 1. Alterations in gut microbiota abundance in patients with Hashimoto’s thyroiditis.

Graves' disease

Graves' Disease is an autoimmune disorder in which the thyroid is stimulated by antibodies directed against the thyrotropin receptor [13]. The interaction between the antibody and the receptor leads to excessive secretion of thyroid hormones, resulting in hyperthyroidism. It is the most common cause of hyperthyroidism in the population [16].

Symptoms of the disease can vary from mild to severe and include nervousness, increased sweating, tachycardia, palpitations, easy fatigability, heat intolerance, heart palpitations, eye symptoms, emotional instability, and

frequent bowel movements. In older individuals, symptoms may be milder and less typical, often dominated by fatigue, weight loss, depression, or atrial fibrillation [17].

Recent studies have demonstrated that gut dysbiosis, caused by factors such as improper diet, antibiotic use, toxins, smoking, or stress, affects the production of cytokines and other metabolites. This leads to disruption of immune homeostasis and loss of tolerance in Graves' disease [18].

Several studies have also shown the influence of gut microbiota on the development of thyroid diseases by affecting the secretion of thyrotropin-releasing hormone by the hypothalamic-pituitary axis [11].

In a study by Hafiz Muhammad Ishaq et al., the amount of *Prevotellaceae* and *Pasteurellaceae* bacteria was significantly higher in patients with Graves' disease, while *Enterobacteriaceae*, *Veillonellaceae*, and *Rikenellaceae* were significantly lower in the patient group compared to controls. At the genus level, a significant increase in the number of *Prevotella_9* and *Haemophilus* genera was observed in the patient group. There was a significantly decreased number of *Alistipes* and *Faecalibacterium* genera in the patient group, and a higher amount of *H. parainfluenzae* [19].

In a study by Chen et al., differences in bacterial species were mainly observed at the genus level. The amount of *Lactobacillus*, *Veillonella*, and *Streptococcus* bacteria was significantly higher in individuals with Graves' disease [20].

Similarly, in a study by Wen Jiang in 2021, patients with Graves' disease had a significantly higher percentage of *Bacteroidetes* ($p = 0.002$) and a significantly lower percentage of *Firmicutes* ($p = 0.008$) compared to controls at the phylum level. At the genus level, patients showed an increased number of *Bacteroides* and *Lactobacillus* genera and a decrease in *Blautia*, *[Eubacterium]_hallii_group*, *Anaerostipes*, *Collinsella*, and *Dorea*.

The authors suggest that *Lactobacillus* bacteria may play a key role in the pathogenesis of autoimmune thyroid diseases [21].

Study	Increases	Decreases
Chang et al., 2021	*Bacteroidetes*, *Actinobacteria*/*Bacteroides*, *Prevotella_9*	*Firmicutes*/*Faecalibacterium*, *Lachnospiraceae_NK4A136_group*
Chen et al., 2021	*Lactobacillus*, *Veillonella*, *Streptococcus*	*Proteobacteria*, *Synergistetes*
Ishaq et al., 2018	*Prevotella_9*, *Haemophilus*	*Alistipes*, *Faecalibacterium*, *Dialister*, *Bifidobacterium*,

		Lactobacillus
Jiang et al., 2021	*Bacteroidetes*/*Bacteroides*, *Lactobacillus*;	*Firmicutes*/*Blautia*, *Eubacterium_hallii_group*, *Anaerostipes*, *Collinsella*, *Dorea*,
Yan et al., 2020	*Bacilli, Lactobacillales, Prevotella, Megamonas, Veillonella*	*Ruminococcus, Rikenellaceae, Alistipes*
Yang et al., 2022	*Actinobacteria/Bifidobacterium, Collinsella, Pediococcus*	*Firmicutes/Roseburia, Dialister*

Table 2. Alterations in gut microbiota abundance in patients with Graves' disease.

Relation between thyroid cancer and gut microbiota

Thyroid cancer is the most common malignancy of the endocrine organs worldwide, with its incidence increasing over the past few decades [22]. Its etiology is multifactorial, and the precise mechanism of its initiation and progression remains incompletely understood [23]. However, known risk factors for the development of this cancer include exposure to ionizing radiation in childhood, as well as genetic and environmental factors (such as iodine levels) [24,25]. In recent years, evidence has emerged suggesting possible associations between gut microbiota and thyroid cancer, highlighting the role of the gut-thyroid axis in the development of this malignancy [26]. In patients with thyroid cancer, significant changes occur in the composition of the gut microbiota.

Sun et. al. demonstrated that Phylum *Verrucomicrobia*, Family *Christensenellaceae, Family Victivallaceae,* Genus *Subdoligranulum, Genus Methanobrevibacter* and *Genus Ruminococcus2* exhibited a positive correlation with the risk of thyroid cancer, whereas *Class Betaproteobacteria, Family XI* and *Genus Sutterella* could be correlated with reduced risk of TC [27].

Patients with thyroid cancer exhibit a comparatively elevated presence of *Proteobacteria* in their gut [3,28]. They are considered as a signature of microbial dysbiosis [29]. However, some studies found that *Betaproteobacteria*, one of the five classes constituting *Proteobacteria*, is characterized by a relative decrease in abundance in the gut flora of

patients with thyroid cancer [27]. The abundance of bacteria in this class in the gut microbiota demonstrates a strong protective effect against the development of thyroid cancer.

Zhou et. al. suggest that other groups of bacteria in the gut microbiota that may act as protective factors against the development of thyroid cancer include genera *Odoribacter*, *Anaerofilum* and *Sutterella*, as well as *Family XI*, but the strongest protective effect have *Betaproteobacteria*. The study revealed that potential factors in the gut microbiota that may be significant in the progression of thyroid cancer include the families *Victivallaceae* and *Christensenellaceae*, as well as the genera *Ruminococcus2*, *Methanobrevibacter*, and *Subdoligranulum*, emphasizing that *Subdoligranulum* may have the greatest importance in the development of this cancer [26].

At the *Phylum* level, patients with thyroid cancer also exhibit a relative increase in the abundance of *Firmicutes* and a decrease in *Bacteroides* [28]. The ratio of these bacteria (*F/B*) indicates gut dysbiosis and serves as a marker for various diseases, with this ratio increasing in thyroid cancer compared to healthy individuals [30]. A higher *F/B* ratio is also associated with colorectal cancer and breast cancer [31,32].

At the *Family* level, species enriched in TC patients included *Lactobacillaceae*, *Clostridiaceae_1*, *Christensenellaceae* and *Enterobacteriaceae*, whereas *Acidaminococcaceae*, *Prevotellaceae* and *Bacteroidaceae* were predominant in the health control group.

Significantly higher abundances of species such as *Escherichia-Shigella*, *Clostridium_sensu_stricto_1*, *Klebsiella* and *Lactococcus* etc. occur in the TC group compared to the health control group, whereas the abundance of *Prevotella_9*, *Roseburia*, *Bacteroides* and *Megamonas* was greater in the health group than in TC patients. Feng et. al. demonstrated that among the changes in genera abundances, the set of 6 related genera (*Roseburia*, *Megamonas*, *Bacteroides*, *Prevotella_9*, *Lactococcus* and *Christensenellaceae_R-7_group*) effectively distinguished TC patients from health control group with high precision, suggesting that the identified microbial signature could serve as a potent tool for disease prediction [28].

Yu et. al. deduced that diminishment of SCFA-producing bacteria may promote the development of TC [3]. These bacteria include *Phascolarctobacterium* and

Ruminococcaceae_UCG-002, whose levels in the gut microbiota are relatively reduced in patients with thyroid cancer, as well as *Faecalibacterium*, the reduced levels of which may lead to gut microbiota dysbiosis both before and after the onset of thyroid cancer. This hypothesis is based on reports that SCFAs may induce apoptosis or damage to colorectal cancer cells [33]. However, Yu et. al. suggest that further studies on a larger cohort are needed to confirm it [3].

Ruminococcus2 is a bacteria that holds a significant position among the dominant genera in gut microbiota ,serving as both a symbiotic bioindicator of human health and a producer of short-chain fatty acids (SCFAs) [34]. Interestingly, TC may lead to a reduction in the abundance of *Genus Ruminococcus2*. Due to the possible association between promoting thyroid cancer development and the decrease in the quantity of bacteria producing SCFAs it is plausible to hypothesize that a reduced abundance of *Ruminococcus2* could disrupt the balance of the gut microbial ecosystem, either preceding or following the development of TC. Furthermore, probably there is a dynamic interaction between the incidence of TC and the level of *Ruminococcus2* [27].

Ishaq et al. demonstrated that compared to healthy groups, the abundance of *Subdoligranulum*, *Verrucomicrobia*, and *Ruminococcus2* was significantly increased, while the abundance of *Prevotella9*, *Bacteroides*, and *Klebsiella* was significantly decreased in the thyroid cancer group, further emphasizing microbial differences [35].

The reduced prevalence of *Prevotella* in thyroid cancers aligns with other studies [28,36]. It has been suggested that *Prevotella* is among the predominant microorganisms in the human gut, particularly in individuals adhering to a plant-based diet [37]. The diminished presence of *Prevotella* in thyroid cancer patients may hence imply a connection between the consumption of animal-derived foods and the development of thyroid carcinoma [3].

Other interesting bacterial groups that are abundant in the gut microbiota of thyroid cancer patients include *Neisseria*, *Streptococcus*, and *Clostridiaceae*. *Neisseria* and *Streptococcus* are also abundant in thyroid nodules [2,36]. Considering that *Streptococcus* is associated with an increased risk of adenomas and cancers [38], *Clostridiaceae* likely act carcinogenically [39], and *Neisseria* are linked to pancreatic diseases and inflammatory conditions, these three bacterial groups may play an important role in the pathogenesis of thyroid cancer [40,41].

Table 3. summarizes the changes in the abundance of various gut microbiota groups in patients with thyroid cancer.

Positive correlation with TC	Negative correlation with TC
Phyla *Firmicutes* *Verrucomicrobia* *Proteobacteria* *Actinobacteria*	**Phyla** *Bacteroidetes*
Families *Ruminococcaceae* *Verrucomicrobiaceae* *Enterobacteriaceae* *Lachnospiraceae* *Rikenellaceae* *Clostridiaceae_1* *Lactobacillaceae* *Peptostreptococcaceae* *Streptococcaceae* *Christensenellaceae* *Victivallaceae*	**Families** *Bacteroidaceae* *Prevotellacea* *Acidaminococcaceae*
Genera	**Genera**

Escherichia-Shigella	*Bacteroides*
[Eubacterium]_coprostanoligenes	*Klebsiella*
Subdoligranulum	*Prevotella_9*
Ruminococcus_2	*Phascolarctobacterium*
Butyrivibrio	*Olsenella*
Fusicatenibacter	*Lachnoclostridium*
Oscillospira	*[Ruminococcus]_gnavus_group*
Terrisporobacter	*Megamonas*
Streptococcus	*Ruminococcaceae UCG004*
Lactococcus	*Anaerofilum*
Lactobacillus	*Odoribacter*
Blautia	*Sutterella*
Christensenellaceae_R-7_group	
Clostridium_sensu_stricto_1	
Methanobrevibacter	

Table 3. Correlation between abundance of different groups of bacteria in gut microbiota and thyroid cancer patients.

In patients with thyroid cancer and lymph node metastasis (N1) compared to those without lymph node metastasis (N0), there is no difference in gut microbiota diversity between these groups. However, different bacterial genera are more abundant in each of these groups. A model utilizing four genera (*g__Alistipes* and *g__Fusobacterium*, which are more abundant in the N1 group, *g__Hungatella*, and *g__Phascolarctobacterium*, which are more abundant in the N0 group), developed through back-forward stepwise logistic regression, might be the most appropriate for differentiating thyroid carcinoma patients with metastatic lymphadenopathy from those without metastatic lymphadenopathy. These four genera may contribute to promoting metastasis [3].

Higher abundance in N0 patients	Higher abundance in N1 patients
g__Phascolarctobacterium	*g__Ruminococcaceae_UCG_005*
g__ Hungatella	*g__Ruminococcaceae_UCG_013*
g__Lachnoclostridium	*g__Alistipes*
g__Escherichia-Shigella	*g__Fusobacterium*
g__Flavonifractor	*g__Megamonas*

Table 4. Significant differences in gut microbiota genera between thyroid cancer patients with lymph node metastasis (N1) and those without metastatic lymphadenopathy (N0).

Studies on whether the abundance of gut microbiota in thyroid cancer patients is greater or smaller than in healthy individuals present conflicting conclusions, therefore, studies on a larger study group are needed [3].

The controversial bacterial genus suspected of being associated with the development of thyroid cancer is *Lactobacillus*. Some studies suggest that the abundance of these bacteria increases in the gut microbiota of TC patients, while others indicate that their abundance decreases. These relationships should be clarified by further studies involving larger groups of patients [28].

Conclusions

Epidemiological studies suggest that Hashimoto's disease results from interactions between genetic and environmental factors, including excessive iodine consumption, micronutrient deficiencies, and bacterial and viral infections. Gut dysbiosis, increased intestinal permeability, and alterations in gut microbiota composition may contribute to the development of autoimmune thyroid diseases by affecting micronutrient availability, thyroid hormone conversion, and immune regulation. The diversity of gut microbiota composition, as well as the presence of specific bacterial species such as *Bifidobacterium* and *Lactobacillus*, may significantly influence the

development of Hashimoto's disease through the regulation of neurotransmitters, TSH secretion, and secondary bile acid production [12,15]. The gut microbiota composition may regulate the secretion of thyroid-stimulating hormone by the hypothalamic-pituitary axis, suggesting a comprehensive role of microorganisms in the pathogenesis of these disorders [11].

Studies on gut microbiota composition in patients with Graves' disease have shown significant changes in the number and type of bacteria, particularly increased presence of *Prevotellaceae*, *Pasteurellaceae*, and *Lactobacillus*, suggesting their potential role in the autoimmune process in thyroid diseases [19,20].

On the other hand, research on the role of gut microbiota in thyroid cancer suggests the potential use of two tools in distinguishing patients with thyroid cancer from healthy individuals presented by Feng et al.: the set of 6 species and the *F/B* ratio [28], as well as the set of 4 species developed by Yu et. al, enabling differentiation of thyroid cancer patients with lymph node metastasis from TC patients without lymph node involvement. Reduction in gut bacterial flora producing SCFAs may be associated with promoting thyroid cancer development [3], while increased abundance of other gut microbiota may stimulate tumor development [26,35].

The precise mechanisms by which alterations in gut microbiota can lead to these diseases remain incompletely understood. This highlights the necessity for additional research to elucidate the pathomechanisms through which changes in the microbiota contribute to the onset of Hashimoto's thyroiditis, Graves' disease, and thyroid cancer. Conducting multicenter, randomized clinical trials on large patient cohorts is recommended to elucidate these associations.

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