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Review

Gut Microbiota and Thyroid Diseases: A Comprehensive Review of Mechanisms and Clinical Implications

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Abstract: The interplay between gut microbiota and thyroid diseases has emerged as a cutting-edge topic in endocrinology and microbiome research. Accumulating evidence indicates that gut microbes not only influence thyroid hormone synthesis and metabolism through metabolites such as short-chain fatty acids and bile acids, but also play critical roles in immune homeostasis, thereby contributing to the pathogenesis and progression of Graves' disease, Hashimoto's thyroiditis, thyroid dysfunction, and thyroid cancer. Epidemiological and clinical studies suggest that specific microbial signatures are associated with disease risk, subtype classification, therapeutic response, and recurrence, highlighting their potential as diagnostic and prognostic biomarkers. Emerging interventions, including probiotics, dietary modulation, and fecal microbiota transplantation, have shown promising effects in animal models and preliminary clinical studies, offering new opportunities for personalized management. Nevertheless, current research faces notable challenges: causal relationships remain unclear, disease heterogeneity and population differences compromise reproducibility, and biases inherent to low-biomass samples and sequencing methodologies limit evidence strength. Future investigations should focus on standardized protocols, cross-cohort validation, multi-omics integration, and mechanistic trials to elucidate the biological basis of the "gut–thyroid axis" and accelerate its translation into clinical diagnostics, risk stratification, and therapeutic interventions.

1. Introduction

In recent years, the relationship between gut microbiota and thyroid diseases has become a major focus of both basic and clinical research. Growing evidence indicates that the composition of gut microbiota is closely associated with the onset and progression of various thyroid disorders, and that microbial dysbiosis may promote disease pathology through disrupted metabolic pathways and abnormal immune regulation [1, 2]. On this basis, the concept of the "gut–thyroid axis" has been proposed, providing a new theoretical framework for understanding the mechanisms underlying thyroid diseases and laying the foundation for exploring potential diagnostic and therapeutic strategies. At the metabolic level, gut microbiota regulate the production of short-chain fatty acids (SCFAs), thereby contributing to immune homeostasis and thyroid hormone metabolism. Studies have shown that in patients with thyroid diseases, beneficial taxa such as *Bifidobacterium* and *Lactobacillus* are markedly reduced, whereas potential pathogenic bacteria including *Bacteroides* and *Proteobacteria* are significantly increased [1, 3]. Such dysbiosis may lead to decreased SCFA levels, which in turn impair mucosal immune function, alter the inflammatory microenvironment, and further affect the synthesis, transport, and metabolism of thyroid hormones [4]. From an immunological perspective, gut microbiota modulate the differentiation and function of host immune cell subsets, thereby contributing to the development and progression of autoimmune thyroid diseases (AITD). Some studies suggest that specific gut microbes can influence the immune response in Graves' disease by altering the proportion of $CD4^+$ T cells, thereby exacerbating disease progression[3]. This effect may be indirectly mediated through the "gut–thyroid axis," in which microbial compositional changes feedback to influence thyroid hormone synthesis and metabolism[5]. In terms of clinical interventions, modulation of gut microbiota has been considered a promising approach for the management of thyroid disorders. Probiotic supplementation has demonstrated beneficial effects in improving thyroid function and alleviating clinical symptoms. For example, strains such as *Lactiplantibacillus plantarum* and *Bifidobacterium longum* have been shown to restore microbial homeostasis and improve patient outcomes when combined with conventional therapies. In addition, fecal microbiota transplantation (FMT), as an emerging strategy, has demonstrated the potential to reshape gut microbiota in both Graves' disease animal models and preliminary clinical studies. This effect may occur via the gut–thyroid–brain axis, through the regulation of immune responses and micronutrient metabolism, thereby influencing disease progression. In summary, current evidence supports a critical role for gut microbiota in the pathogenesis and progression of thyroid diseases, and highlights their potential as targets for individualized therapy and integrated management. Nevertheless, the specific mechanistic roles of distinct microbial taxa remain insufficiently characterized, and their feasibility as diagnostic, prognostic, and therapeutic tools requires further validation [2, 6].

2. Mechanistic and Clinical Evidence Linking Gut Microbiota to Thyroid Diseases

To provide an integrative overview before discussing disease-specific mechanisms, we present a schematic illustration of the gut–thyroid axis (**Figure 1**). This framework highlights how gut microbiota, including both beneficial and pathogenic taxa, influence thyroid health via microbial metabolites such as short-chain fatty acids (SCFAs), lipopolysaccharides (LPS), secondary bile acids, and indoles. These intermediates modulate key mechanistic pathways, including immune regulation, nutrient metabolism, drug handling, and barrier function, ultimately contributing to distinct thyroid disease phenotypes such as Graves' disease, Hashimoto's thyroiditis, hypothyroidism, hyperthyroidism, and thyroid cancer. The figure also underscores clinical implications, ranging from diagnostic biomarkers to therapeutic interventions such as probiotics, dietary modulation, and fecal microbiota transplantation (**Figure 2**).

2.1. Gut Microbiota and Thyroid Hormone Metabolism

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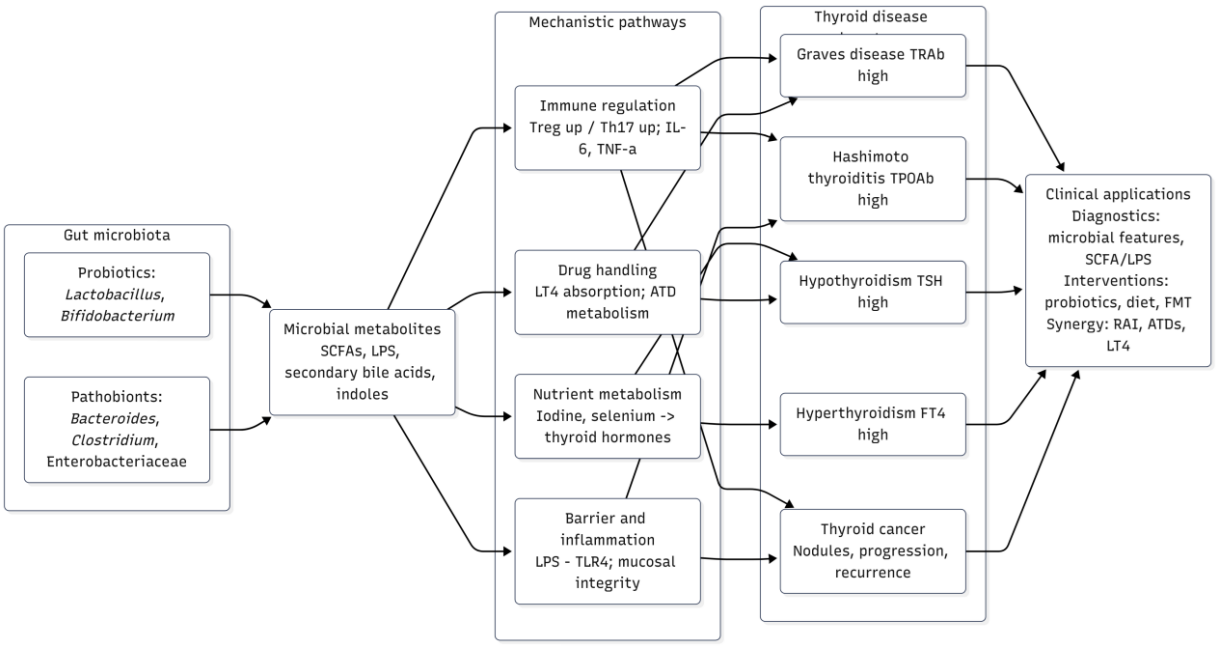

Figure 1. The gut–thyroid axis: mechanisms and clinical implications. Schematic illustration showing how gut microbiota (probiotics such as *Lactobacillus* and *Bifidobacterium*; pathobionts including *Bacteroides*, *Clostridium*, and *Enterobacteriaceae*) and their metabolites (short-chain fatty acids, LPS, secondary bile acids, indoles) influence thyroid diseases through multiple mechanistic pathways. These include immune regulation (Treg/Th17 balance, cytokines such as IL-6 and TNF-α), nutrient metabolism (iodine and selenium utilization), barrier integrity and inflammation (LPS–TLR4 signaling), and drug handling (levothyroxine absorption, antithyroid drug metabolism). The resulting alterations contribute to distinct thyroid disease phenotypes, including Graves' disease (↑TRAb), Hashimoto thyroiditis (↑TPOAb), hypothyroidism (↑TSH), hyperthyroidism (↑FT4), and thyroid cancer (nodules, progression, recurrence). These mechanistic insights highlight clinical applications in diagnostics (microbial features, SCFA/LPS profiling), interventions (probiotics, diet, fecal microbiota transplantation), and therapeutic synergy with standard treatments (radioactive iodine, antithyroid drugs, levothyroxine).

The relationship between gut microbiota and thyroid hormone metabolism has emerged as a research hotspot in recent years. As a complex microbial ecosystem of the human body, the gut microbiota not only participates in digestion and nutrient metabolism but also regulates endocrine homeostasis through multiple pathways. Emerging evidence suggests that gut microbes can directly or indirectly influence the synthesis, transport, and metabolism of thyroid hormones, thereby contributing to the development and progression of thyroid disorders. One important mechanism involves the interaction between bile acids and gut microbiota. The diversity of bile acids results from the combined activity of the host and intestinal microbes. Microbes regulate

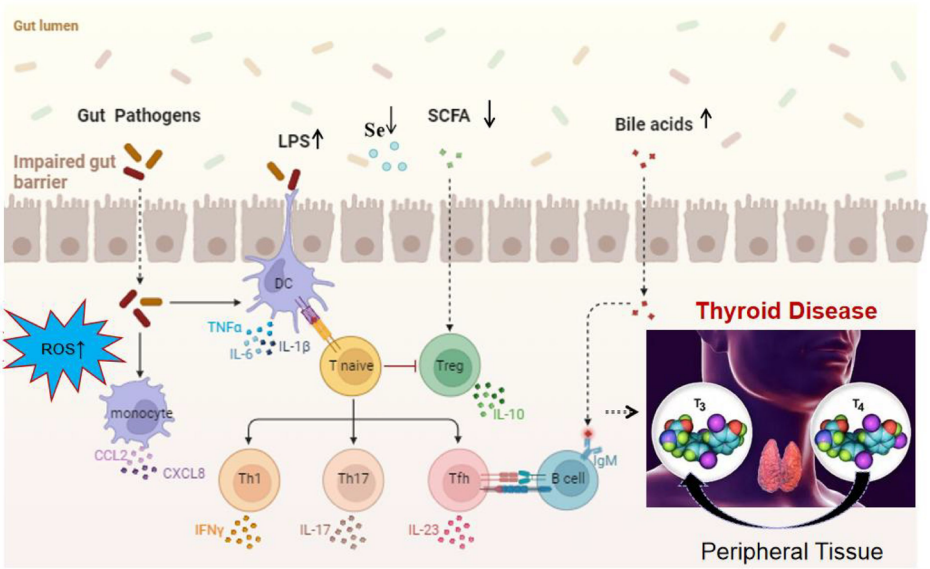

Figure 2. Mechanistic overview of the impact of gut microbiota on thyroid function[1] (licensed under CC BY 4.0.).

bile acid deconjugation, transformation, and recirculation, while bile acid composition in turn shapes microbial diversity and stability. This bidirectional interaction has been implicated in diseases such as inflammatory bowel disease, colorectal cancer, hepatocellular carcinoma, type 2 diabetes, and polycystic ovary syndrome[7]. Given that bile acids influence the activity of thyroid hormone-binding proteins and metabolic pathways, the microbiota–bile acid axis may indirectly affect thyroid hormone homeostasis by modulating gut stability and immune responses. Gut dysbiosis has also been associated with primary hypothyroidism. Compared with healthy individuals, patients with hypothyroidism exhibit significant differences in both α- and β-diversity of

gut microbiota. Specific genera such as *Veillonella*, *Paraprevotella*, *Neisseria*, and *Rheinheimera* were found to distinguish untreated hypothyroidism patients from healthy controls with high accuracy[8]. These structural changes may reduce the capacity for short-chain fatty acid (SCFA) production while increasing serum lipopolysaccharide (LPS) levels, thereby inducing systemic inflammation and impairing thyroid hormone synthesis and function. Further evidence arises from studies on the interplay among nutrition, gut microbiota, and thyroid hormones. Iodine and selenium are essential micronutrients for thyroid hormone synthesis and activity, and the gut microbiota plays a critical role in their bioavailability and metabolism. Certain probiotics, such as *Lactobacillus* and *Bifidobacterium*, enhance the bioavailability of selenium metabolites and thereby indirectly support thyroid hormone synthesis. In contrast, dysbiosis may reduce nutrient absorption efficiency and exacerbate thyroid hormone imbalance[9]. Moreover, microbial metabolites themselves may modulate thyroid hormone activity. For example, SCFAs can affect the activity of deiodinases, thereby influencing the conversion of thyroxine (T4) into triiodothyronine (T3). Other metabolites such as indole derivatives and secondary bile acids may interfere with thyroid hormone metabolism indirectly by binding to nuclear receptors including FXR and PXR[10]. In summary, gut microbiota influence thyroid hormone metabolism through multiple levels of regulation, including bile acid modulation, dysbiosis-associated hypothyroidism risk, nutrient metabolism, and microbial metabolite-mediated control of hormone conversion. These findings not only provide new insights into the pathophysiology of thyroid disorders but also highlight the microbiota as a potential therapeutic target. Future studies should leverage longitudinal cohorts and multi-omics analyses to clarify the role of specific taxa and metabolic pathways in thyroid hormone regulation, thereby advancing the development of personalized intervention strategies.

2.2. Gut Microbiota and Graves' Disease: Mechanisms and Clinical Evidence

Graves' disease (GD) is one of the most common autoimmune thyroid disorders, characterized by limited treatment efficacy, high relapse rates, and frequent adverse effects. Increasing evidence suggests that gut microbiota play an important role in its pathogenesis. Clinical studies have shown that gut microbial diversity is markedly reduced in GD patients, with a significant decrease in *Firmicutes* and an increase in *Bacteroidetes*[11, 12]. These compositional shifts are closely associated with immune dysregulation, indirectly supporting the concept of the gut–thyroid axis. Beyond disease onset, gut microbiota also demonstrate diagnostic potential. High-throughput sequencing has identified microbial signatures strongly associated with GD, which can differentiate GD from other conditions (e.g., Parkinson's disease) with high specificity and predictive value [13]. Such noninvasive microbial biomarkers may enable earlier detection and individualized management. Importantly, the microbiota–GD relationship appears bidirectional. Bidirectional Mendelian randomization analyses indicate that certain taxa may act as risk factors for GD, whereas others may exert protective effects [14–16]. This dual causality underscores the complexity of the gut–thyroid axis in GD pathogenesis. Compelling experimental evidence comes from microbial intervention studies. A recent investigation in a GD mouse model evaluated the effects of the commensal bacterium *Bacteroides fragilis* and its metabolite propionate. Oral supplementation with either *B. fragilis* or propionate significantly reduced serum inflammatory cytokines, total thyroxine (TT4), and TSH receptor antibody (TRAb) levels, while decreasing circulating Th17 cells and increasing regulatory T cells (Tregs). These changes alleviated systemic inflammation, hyperthyroidism, and TSHR autoimmunity. Histological analysis further revealed reduced proportions of M1 macrophages and increased M2 macrophages in thyroid tissue, accompanied by decreased inflammation and thyroid size. Notably, the combination of *B. fragilis* or propionate with methimazole (MMI) produced synergistic effects, ameliorating pathological damage while reducing the required MMI dose and minimizing drug-related adverse effects. This study provided the first experimental evidence that gut microbiota and their metabolites can serve as effective adjuvant strategies for GD, offering a microbiota-based rationale for personalized interventions [17]. In summary, current research highlights multiple roles of the gut microbiota in GD, spanning dysbiosis, immune dysfunction, diagnostic potential, and therapeutic efficacy. Future studies should clarify the causal contributions of specific taxa and evaluate the clinical feasibility of microbiota- and metabolite-based interventions to establish more comprehensive and precise strategies for GD management.

2.3. Gut Microbiota and Hashimoto's Thyroiditis: Mechanisms and Clinical Evidence

The relationship between gut microbiota and Hashimoto's thyroiditis (HT) has attracted increasing attention in recent years. Evidence indicates that the gut microbiota plays a pivotal role in host immune regulation and is closely linked to the pathogenesis of multiple autoimmune diseases. HT, the most common autoimmune thyroid disorder, arises from a multifactorial etiology involving both genetic and environmental factors. Growing evidence shows that the composition and abundance of gut microbiota in HT patients differ significantly from healthy controls, suggesting that microbial alterations may influence disease onset and progression through specific mechanisms[18]. Multi-omics studies have further revealed characteristic microbial signatures in HT. Integrated metagenomic and host transcriptomic analyses demonstrated reduced microbial diversity, with early HT patients showing increased abundance of *Bacillota_A* and *Spirochaetota*, along with significant differences across 24 genera and 67 species[19]. Functional analyses indicated altered activity of immune- and infection-related pathways, providing new insights into the molecular mechanisms of HT[20]. Such changes may disrupt peripheral thyroid homeostasis, thereby promoting autoimmune responses and disease progression[21]. Moreover, interactions between the microbiota and host transcriptome were found to involve metabolic, immune, and cancer-related pathways, further reinforcing the role of the gut–thyroid axis in HT[2]. Clinical and experimental data also support this association. A case–control study reported that butyrate-producing bacteria were markedly reduced in HT patients, while opportunistic pathogens such as *Escherichia/Shigella* were enriched. This imbalance correlated with elevated pro-inflammatory cytokines and higher titers of anti-thyroid antibodies[22]. In an animal model, oral supplementation with Lactobacillus reuteri significantly lowered thyroiditis scores and anti-thyroid peroxidase antibody (TPOAb) levels, while promoting regulatory T cell (Treg) differentiation, thereby restoring immune homeostasis[23]. Collectively, these findings suggest that gut microbiota contribute to HT pathogenesis by modulating immune and metabolic pathways, and may also represent promising targets for future therapeutic interventions.

2.4. Gut Microbiota and Thyroid Cancer: Mechanisms and Clinical Evidence

In recent years, increasing attention has been paid to the relationship between gut microbiota and thyroid cancer. Studies indicate that microbial dysbiosis is not only closely associated with thyroid cancer development but also with thyroid nodules and several thyroid function indices. In a cohort of 74 participants, thyroid tumor patients exhibited significantly lower gut microbial diversity compared with healthy controls, with elevated *Neisseria* and *Streptococcus* and reduced *Butyricimonas* and Lactobacillus abundance[24]. These alterations suggest that dysbiosis may disrupt immune homeostasis and local metabolic environments, thereby promoting tumorigenesis. Further evidence links specific microbial compositions to thyroid cancer risk. Metagenomic sequencing revealed enrichment of *Prevotella* and *Fusobacterium* in papillary thyroid carcinoma (PTC), while butyrate-producing genera such as *Faecalibacterium* and *Roseburia* were depleted, with abundance shifts correlating with tumor markers and tumor size[25]. Microbial metabolites are also implicated: short-chain fatty acids (SCFAs) promote regulatory T cell differentiation and suppress inflammation, whereas lipopolysaccharides (LPS) activate chronic inflammation via the TLR4 pathway, thereby enhancing tumor-related immune responses[26]. In PTC patients, serum propionate and butyrate levels were reduced, while LPS levels increased, correlating positively with disease progression [27]. Microbiota may also modulate immune checkpoint regulation in thyroid cancer. A clinical study reported that *Bacteroides* abundance was elevated in PD-1/PD-L1–positive patients, while probiotic genera were depleted, suggesting that dysbiosis may shape the tumor immune microenvironment and influence immunotherapy response[28]. Moreover, in patients with concurrent thyroid dysfunction, elevated *Bacteroides* and reduced *Lactobacillus* abundance were associated with prolonged disease course and poorer prognosis[29]. Nutritional metabolism provides another link, as gut microbiota can influence iodine absorption and utilization, which are critical for thyroid hormone synthesis. In animal models, high-iodine diets combined with dysbiosis significantly accelerated tumor growth and follicular cell proliferation[30]. Thyroid cancer is also frequently accompanied by metabolic syndrome features such as obesity and insulin resistance. Patients exhibited gut microbiota profiles partially overlapping with those of diabetes, with *Ruminococcus* abundance correlating with the degree of insulin resistance, suggesting that metabolic disturbances may accelerate carcinogenesis via the gut–thyroid axis[31]. Inflammation represents an additional mechanism. A Chinese cohort study found elevated *Escherichia coli* abundance in PTC patients, which correlated with serum IL-

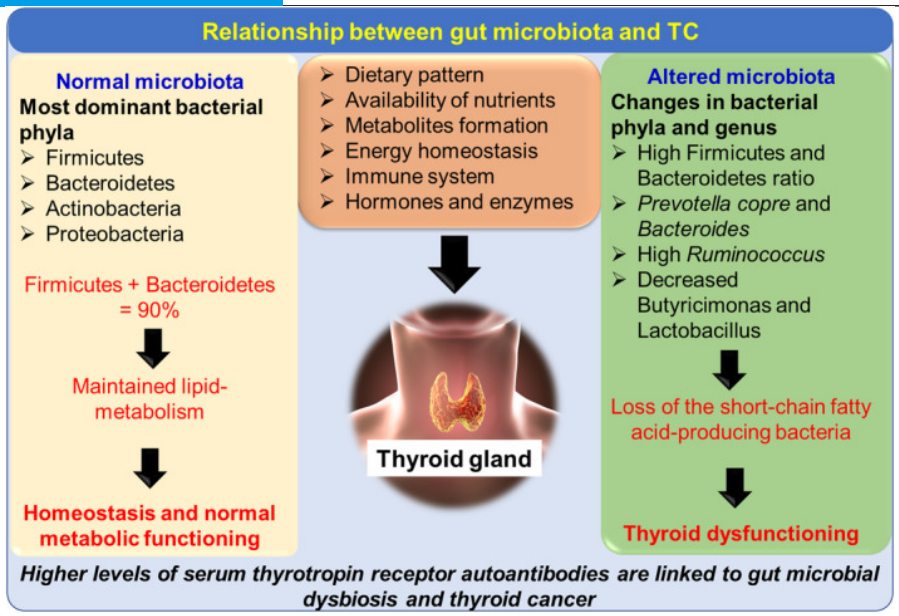

Figure 3. The influence of different gut microbes on thyroid gland function and complications associated with TC[33] (licensed under CC BY 4.0.).

6, TNF-α levels, and tumor stage, supporting a role of chronic inflammation in tumor aggressiveness[32]. Longitudinal follow-up further showed that patients with recurrence had distinct microbial profiles, with reduced *Clostridium* cluster XIVa abundance strongly associated with increased recurrence risk[33]. These findings also highlight the diagnostic and classification potential of microbial features. One study proposed a "microbiota risk score" to predict thyroid cancer risk, which outperformed some traditional biochemical markers in differentiating benign nodules from PTC[34]. Intervention studies have shown promise as well: animal experiments demonstrated that probiotic supplementation partially restored microbial homeostasis and reduced thyroid tissue inflammation[35]. Microbiota-targeted strategies, combined with immunotherapy or radioactive iodine therapy, may represent future directions for personalized management. In summary, gut microbiota plays multifaceted roles in the initiation, progression, and prognosis of thyroid cancer, involving immune modulation, metabolic alteration, nutrient absorption, and inflammatory pathways (**Figure 3**). Identification of specific taxa and metabolites not only deepens mechanistic understanding but also provides new opportunities for risk stratification, diagnosis, and individualized therapeutic intervention.

2.5. Gut Microbiota and the Impact on Thyroid Drug Therapy

The role of gut microbiota in thyroid pharmacotherapy is receiving growing attention. Increasing evidence suggests that the intestinal microenvironment not only affects thyroid hormone metabolism and homeostasis but may also directly modulate drug absorption, transport, and efficacy, thereby serving as a critical determinant of personalized treatment. Levothyroxine (LT4) absorption is closely linked to gut microbiota. Clinical studies have shown that reduced abundance of probiotics such as *Lactobacillus* and *Bifidobacterium* lowers intestinal LT4 absorption efficiency, whereas enrichment of *Bacteroides* may indirectly influence drug solubility and bioavailability through alterations in bile acid metabolism[36]. In some patients, such dysbiosis manifests as inadequate response to standard LT4 dosing. Similarly, the metabolism of antithyroid drugs such as methimazole and propylthiouracil is influenced by gut microbes. Certain enzyme-producing strains can alter drug conversion rates and the distribution of metabolites within the intestinal lumen, thereby modulating therapeutic efficacy and adverse effects[37, 38]. Gut microbiota also indirectly affect drug responses by regulating micronutrient absorption. Iodine and selenium are essential for thyroid hormone synthesis and antioxidant defense, and their bioavailability depends on gut microbial balance. Dysbiosis may impair selenium absorption, thereby reducing the metabolic stability of LT4 and weakening its therapeutic effect[39]. Additionally, chronic inflammation driven by abnormal microbial composition may increase LT4 dosage requirements; studies have linked this phenomenon to elevated proportions of Gram-negative bacteria and higher serum LPS levels[40]. Probiotic interventions have shown clinical potential in addressing these challenges. Specific strains such as *Lactiplantibacillus plantarum* and *Bifidobacterium longum* have been demonstrated to improve thyroid function, shorten TSH recovery time, and enhance drug efficacy[41]. Meanwhile, fecal microbiota transplantation (FMT) has been explored as an emerging strategy to improve antithyroid drug tolerance and efficacy. Animal experiments indicate that FMT can restore SCFA levels, modulate immune responses, and rebalance gut–thyroid axis signaling pathways, thereby enhancing therapeutic outcomes[42]. Overall, the influence of gut microbiota on thyroid pharmacotherapy is multifaceted, encompassing drug absorption, metabolism, immune regulation, and micronutrient utilization. Future strategies combining probiotics, dietary modulation, or FMT may further improve the efficacy and safety of thyroid medications and advance the development of personalized treatment.

3. Gut Microbiota as Diagnostic and Prognostic Biomarkers in Thyroid Diseases

In recent years, increasing evidence has suggested that gut microbiota and their metabolites are not only associated with the onset of thyroid diseases but may also serve as potential diagnostic and prognostic biomarkers. Their functional roles involve immune regulation, inflammatory pathways, and metabolic networks, with several studies proposing specific microbial signatures as indicators for disease stratification or risk prediction. Thyroid cancer has yielded the most consistent and clinically translatable findings. Elevated abundance of *Neisseria* and *Streptococcus* has been strongly linked to tumorigenesis, and their combined pattern effectively discriminates patients with cancer from healthy individuals, suggesting potential value in early diagnosis[43]. In addition, changes in gut microbiota–derived metabolites such as reduced short-chain fatty acids (SCFAs) and elevated lipopolysaccharides (LPS) have been associated with tumor stage and inflammatory status[44], reflecting both disease progression and immune microenvironmental disruption. Other reports have shown that high abundance of *Clostridium* correlates with lymph node metastasis in papillary thyroid carcinoma (PTC), while loss of *Ruminococcus* is more frequent in early-stage disease, offering clues for staging and invasion assessment[45]. Long-term follow-up further revealed that patients with persistent high levels of *Streptococcus* but lacking *Lactobacillus* after surgery were at significantly higher risk of recurrence[46], highlighting microbiota features as potential predictors of relapse. In autoimmune thyroid diseases (AITD), characteristic microbial signatures have also been observed. In Graves' disease, *Prevotella* abundance was significantly correlated with thyrotropin receptor antibody (TRAb) levels, suggesting its value as an indicator of disease activity[3]. In HT, reduction of butyrate-producing bacteria was closely associated with elevated serum TSH and increased thyroid parenchymal destruction, suggesting a potential marker of disease severity. In thyroid dysfunction, primary hypothyroidism has been linked to impaired SCFA production and elevated LPS levels, which not only correlate with thyroid hormone deficiency but also serve as sensitive metabolic

markers for distinguishing patients from controls[47]. In hyperthyroidism, enrichment of *Clostridium* was positively correlated with serum FT4 levels and proposed as an auxiliary diagnostic indicator[48]. Microbial features may also predict treatment responses. Studies have shown that patients with poor levothyroxine absorption often present with Lactobacillus depletion and impaired intestinal barrier function, highlighting microbiota features as indicators of reduced drug bioavailability[49]. In Graves' disease, responsiveness to antithyroid drugs has been associated with microbial structure, where the abundance of specific taxa could identify patients at risk of relapse[50]. Moreover, restoration of microbial balance following probiotic supplementation correlated positively with TSH improvement, supporting its role as a potential marker for therapeutic monitoring[51]. Overall, existing studies provide quantifiable diagnostic and prognostic insights based on microbial structure, functional metabolites (SCFAs, LPS), and clinical outcomes (treatment efficacy, recurrence risk). Among these, thyroid cancer–related findings demonstrate the greatest translational potential, with the prospect of microbiota-based multidimensional models enabling early detection, staging evaluation, and recurrence monitoring. Nevertheless, large-scale, prospective studies remain necessary to validate their reliability and generalizability. Future work should focus on integrating microbial biomarkers into clinical decision-making pathways and testing their utility in combination with molecular and imaging approaches, in order to accelerate their translation into precision medicine for thyroid diseases.

4. Gut Microbiota Interventions in the Management of Thyroid Diseases

In recent years, the potential value of gut microbiota–targeted interventions in thyroid disease management, particularly thyroid cancer, has gained increasing attention. Both clinical and experimental studies suggest that modulation of the microbiota not only influences the development of thyroid dysfunction but may also improve therapeutic efficacy and prognosis. For example, probiotic supplementation has been shown to alleviate constipation, fatigue, and metabolic disturbances induced by thyroid hormone withdrawal (THW) after thyroidectomy, while reducing serum and fecal LPS levels, thereby improving intestinal barrier function and immune homeostasis[52]. In Graves' disease, probiotic intervention has been associated with reductions in thyrotropin receptor antibody (TRAb) levels, indicating an immunomodulatory potential that may help lower relapse risk[53]. Diet represents another important means of microbiota modulation. High-fiber diets promote the production of short-chain fatty acids (SCFAs), improve inflammatory status, and may enhance the metabolic stability of thyroid hormones[54]. In contrast, high-fat diets have been linked to expansion of pro-inflammatory taxa and increased risk of thyroid tumor progression[55]. Micronutrients such as selenium and zinc also influence microbial diversity and antioxidant pathways, potentially improving immune responses and treatment tolerance in patients with thyroid dysfunction[56]. Although direct evidence for fecal microbiota transplantation (FMT) in thyroid disease is limited, its demonstrated ability to enhance responses to immune checkpoint inhibitors in other cancers[57] provides a rationale for exploring its application in thyroid cancer, particularly for overcoming resistance and improving prognosis. Prognostic associations between microbiota and clinical outcomes are increasingly recognized. Gut microbial composition has been correlated with responses to radioactive iodine therapy[58]; depletion of Lactobacillus has been linked to poor levothyroxine absorption and drug intolerance, serving as a predictor of therapeutic outcomes[59]; reduced microbial diversity following surgery or radiotherapy has been associated with increased recurrence risk[60]; and probiotic supplementation has been reported to restore microbial balance and coincide with TSH recovery, supporting its role as a potential monitoring tool[61]. Furthermore, FMT has already demonstrated efficacy in improving checkpoint inhibitor responses in melanoma[62], suggesting translational potential for thyroid cancer. Overall, evidence from microbial composition, functional metabolites (SCFAs, LPS), and clinical endpoints (treatment response, recurrence risk) highlights the promise of microbiota-based interventions. These findings suggest that targeted modulation of gut microbiota holds significant potential for precision stratification and personalized management of thyroid cancer, though large-scale prospective studies are needed to validate their clinical utility. Future efforts should aim to integrate microbiota-based biomarkers into standardized clinical workflows and explore synergistic strategies combining microbiota modulation with conventional and novel therapies, in order to translate mechanistic insights into tangible benefits for patients.

5. Controversies and Challenges: Causality, Heterogeneity, and Insufficient Evidence

Despite increasing links between gut microbiota and thyroid diseases, the translational pathway from correlation to clinical application still faces three major challenges: unclear causality, substantial heterogeneity, and methodological limitations with insufficient levels of evidence. These issues are not unique to thyroid cancer (TC) but also apply to autoimmune thyroid diseases (AITD, including Graves' disease and Hashimoto's thyroiditis) and thyroid dysfunction (hyper- and hypothyroidism).

5.1. Unclear causality and unaddressed confounding

Most studies are cross-sectional or rely on postoperative samples, making it difficult to distinguish whether dysbiosis is a causal factor or a secondary effect of disease and treatment[63]. Hyperthyroidism accelerates intestinal transit and hypothyroidism delays motility, both independently altering fecal microbiota and complicating the attribution to "primary microbial effects"[64]. Perioperative factors, radioactive iodine (RAI), levothyroxine replacement, antithyroid drugs, proton pump inhibitors, and antibiotic use can all disrupt the microbiota through bile acid and mucosal immune pathways[65, 66]. Without sensitivity analyses or instrumental variable approaches to account for drug exposures, dietary intake (iodine, selenium, fiber), and lifestyle factors, statistical models are prone to overestimating microbiota–outcome associations[67]. Prospective inception cohorts, time-series sampling, and causal inference approaches (including Mendelian randomization and intervention–response studies) are needed to clarify directionality[68].

5.2. Dual heterogeneity across populations and disease subtypes

Within thyroid cancer, molecular pathways, immune microenvironments, and treatment responses vary considerably across papillary, follicular, medullary, and anaplastic subtypes; pooled analyses risk signal dilution and poor reproducibility[69]. AITD also shows heterogeneity in antibody profiles (TRAb, TPOAb, TgAb) and disease activity, while metabolic states, body composition, and comorbidities (obesity, type 2 diabetes) can systematically shift microbiota in hyper- and hypothyroid patients[70]. Cross-regional and ethnic differences in diet and lifestyle (e.g., iodine/selenium intake, fermented foods, cereal fiber) further reduce biomarker stability across external cohorts[71]. Subtype-specific modeling and cross-center validation are therefore prerequisites for clinical utility[72].

5.3. Technical and methodological biases

Low-biomass samples (thyroid tissue, blood) are highly vulnerable to environmental or reagent contamination; without negative controls, decontamination, and absolute quantification (e.g., exogenous standards or qPCR), false-positive microbial signals may occur[73]. Differences in resolution and functional inference between 16S rRNA sequencing and metagenomics, as well as variability in DNA extraction protocols, sequencing platforms, batch effects, and bioinformatics pipelines (OTU/ASV construction, host-read removal), can introduce systematic error[74]. Many models with apparently high AUCs rely only on internal cross-validation and lack preregistration or multicenter replication, raising concerns about clinical generalizability[75].

5.4. Incomplete mechanistic chains

Most evidence in TC and AITD remains "structural associations" without integrated demonstration across the full continuum: microbiota → metabolites (SCFAs, secondary bile acids, indoles) → host pathways (deiodinase activity, FXR/PXR, Treg/Th17 balance) → clinical phenotypes, within the same cohort[76]. Reversibility and dose–response data are also limited; whether targeted supplementation of butyrate producers or *Akkermansia* can consistently increase metabolite levels and improve imaging or pathological endpoints remains to be tested in randomized controlled trials[77]. In AITD, stratified assessment of "microbiota modulation–antibody titers–relapse/remission" over time is required; in thyroid dysfunction, distinguishing the marginal contribution of "hormone correction" versus "microbiota intervention" is essential[63, 68].

5.5. Clinical benefit and safety margins remain uncertain

On diagnosis, some fecal microbial features improve discrimination of benign versus malignant nodules or PTC staging, but the incremental benefit over fine-needle aspiration cytology (FNAC) and molecular assays (BRAF/TERT) has not been systematically quantified; most models lack joint evaluations with imaging or molecular tools[78]. On prognosis, recurrence models that omit stage, RAI dose, TSH suppression intensity, and molecular subtype may exaggerate the "independent effect" of microbiota[64, 74]. On interventions, although probiotics, diet, and FMT have shown efficacy in improving immunotherapy responses across other cancers, these findings cannot be

directly extrapolated to TC, where surgery and RAI remain the mainstay. Moreover, risks of FMT—including infection, transfer of antibiotic resistance genes, and immune-related adverse events—must be carefully considered in vulnerable groups such as AITD or thyroid storm patients[79].

5.6. Toward clinical translation

Future research should advance along three parallel lines: (i) methodology—developing standardized SOPs (sampling, storage, sequencing, analysis), implementing negative controls and absolute quantification, multicenter preregistration, and decision curve analyses to report true clinical gain[67, 71]; (ii) causality and mechanisms—prospective inception cohorts with multi-omics (metagenomics, metabolomics, immunomics, serum iodine/selenium), combined with MR and small-scale "mechanistic RCTs" targeting butyrate producers or *Akkermansia* to test reversibility and dose–response[80]; (iii) clinical embedding—nested designs in AITD remission/relapse, hyper- and hypothyroidism dose adjustments, and perioperative/RAI contexts in thyroid cancer, using translatable endpoints (recurrence-free survival, RAI sensitivity, antibody titers/TSH dynamics), integrated with cost–benefit analyses to confirm real-world clinical value[81].

In summary, these challenges do not negate the role of gut microbiota in thyroid diseases but emphasize that its integration into clinical practice requires filling causal gaps, addressing heterogeneity and methodological biases, and demonstrating incremental value beyond current standards across real-world endpoints. This consensus applies broadly to thyroid cancer, AITD, and thyroid dysfunction.

6. Conclusion

With the expanding depth of gut microbiota research, evidence increasingly indicates that microbial communities are critically involved in the onset, progression, and management of thyroid diseases. Beyond their associations with thyroid hormone metabolism, autoimmune responses, and inflammatory pathways, particular attention is now turning to their potential roles in thyroid cancer initiation and progression. Microbiota-derived signatures and metabolites may provide not only diagnostic and prognostic biomarkers but also mechanistic insight into tumor development and therapeutic responsiveness. Nevertheless, most current findings are derived from cross-sectional studies, limiting causal inference and leaving clinical translation in its infancy. Future priorities include establishing longitudinal, multicenter cohorts to clarify how microbial profiles shape the natural history of thyroid cancer and autoimmune thyroid disorders; integrating multi-omics with functional validation to delineate microbial metabolite–tumor–immune interactions; and advancing interventional trials in real-world settings to test strategies such as probiotics, dietary modulation, and fecal microbiota transplantation (FMT). Persistent challenges—uncertain causal chains, inconsistent findings across populations, and insufficient mechanistic evidence—remain, but these gaps define clear opportunities for progress. Ultimately, bridging mechanistic research and clinical application in a reproducible, translatable manner will determine whether microbiota-based biomarkers and interventions can be fully incorporated into precision medicine for thyroid cancer and related thyroid diseases.

Conflicts of Interest

The authors declare no conflict of interest.

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Author Contributions

All authors read and approved the final manuscript.

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