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The Microbiome-Thyroid Link: A Review of the Role of the Gut Microbiota in Thyroid Function and Disease

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ABSTRACT

The gut microbiota has emerged as a potential regulator of thyroid homeostasis and disease. Recent studies suggest that the composition and diversity of intestinal bacteria can impact thyroid stimulating hormone levels, thyroid hormone synthesis & metabolism and the risk of thyroid conditions like hypothyroidism and autoimmune thyroiditis. However, the mechanisms through which the gut microbiota influences the thyroid remain poorly understood. This review aims to summarize the current evidence on the role of the gut-thyroid microbiome axis in thyroid physiology and pathophysiology. Studies investigating the association of gut dysbiosis with altered thyroid function and disorders like Hashimoto's thyroiditis were discussed. Potential mechanisms through which gut bacteria may influence thyroid hormone levels and autoimmunity, such as interference with autoantigen presentation, induction of inflammation, and production of metabolites were evaluated. The impact of dietary and probiotic interventions targeting the gut microbiota for managing thyroid disease is assessed. Future research directions focusing on delineating key bacteria influencing thyroid health, characterizing longitudinal microbiota changes in thyroid conditions, and identifying novel microbiota-based therapies are proposed. A deeper understanding of the gut-thyroid axis may lead to microbiota-targeted strategies for managing thyroid disorders.

Introduction

The thyroid gland plays a central role in regulating metabolism, growth, and development. Thyroid disorders like hypothyroidism and autoimmune thyroid disease are common and often difficult to manage [1]. Meanwhile, research in recent years has illuminated a surprising connection between the gut microbiota and the thyroid. Studies show that the composition and diversity of gut bacteria can impact thyroid hormone levels and the risk of developing thyroid conditions [2,3]. However, our understanding of the mechanisms linking the intestinal microbiome and the thyroid remains limited.

This review article aims to provide an overview of the current evidence on the role of the gut microbiota in thyroid function and disease. It will summarize the research on how gut bacteria may influence thyroid stimulating hormone, thyroid hormone synthesis and metabolism, and the development of hypothyroidism and autoimmune thyroiditis. The potential mechanisms through which the gut microbiome interacts with the thyroid will also be discussed. Finally, directions for future microbiome-thyroid research will be outlined to provide insight into promising avenues that could lead to novel microbiota-based therapies for thyroid disorders.

The gut microbiome and thyroid function

Several studies have found correlations between the composition of the gut microbiota and thyroid hormone concentrations [4]. In healthy individuals, higher gut bacterial diversity and levels of certain bacterial species like Bifidobacterium and Lactobacillus have been associated with higher circulating free thyroxine (T4) and triiodothyronine (T3) levels [5]. However, lower bacterial diversity and alterations in bacterial composition are seen in individuals with hypothyroidism. For example, reduced levels of Firmicutes and increased Proteobacteria and Actinobacteria have been found in hypothyroid patients [6].

Gut bacteria can influence thyroid hormone synthesis and metabolism in several ways. Certain bacterial species can interfere with the uptake of iodine, an essential component for thyroid hormone production. Bacteria can also produce thyroid hormone-metabolizing enzymes like deiodinases and beta-glucuronidases, which affect the activation and deactivation of thyroid hormones. Alterations in the gut microbiota have been linked to changes in the activity of these thyroid hormone-metabolizing enzymes [7]. The pathological mechanisms that could lead to thyroid disorders are illustrated in Figure 1.

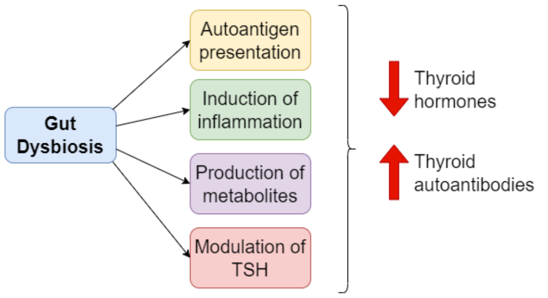

Figure 1: Potential mechanisms through which gut dysbiosis may influence thyroid function and disease

Emerging evidence suggests that gut microbiota signaling through the gut-brain axis can impact the release of thyroid stimulating hormone (TSH) from the pituitary gland. TSH levels tend to be higher in individuals with gut dysbiosis and lower bacterial diversity. It is hypothesized that bacterial metabolites and modulation of the vagus nerve may influence TSH secretion [8]. However, the precise mechanisms through which gut bacteria regulate TSH release remain unclear.

Gut dysbiosis and thyroid disease

Association between altered gut microbiota and hypothyroidism: Several studies have found that hypothyroid patients have altered gut microbiota composition compared to healthy individuals. These changes include:

- Reduced bacterial diversity and richness [9]
- Lower levels of "healthy" bacteria like Bifidobacterium and Lactobacillus [10]
- Increased levels of opportunistic pathogens like Proteobacteria and Fusobacteria [11]

These gut microbiota alterations have been linked to the severity of hypothyroidism and inadequate response to Levothyroxine treatment. Hypothyroidism itself may also promote dysbiosis by slowing gastrointestinal mobility and altering the gut environment. Gut microbiota changes in Hashimoto's thyroiditis [12]

Gut microbiota changes in Hashimoto's thyroiditis

Similar gut dysbiosis has been observed in patients with Hashimoto's thyroiditis, an autoimmune disorder causing hypothyroidism. Changes include:

- Reduced abundance of short-chain fatty acid producing bacteria like Faecalibacterium [12]
- Increased levels of facultative anaerobic bacteria belonging to Enterobacteriaceae family [13]
- Overall reduction in bacterial diversity and richness [14]

Such shifts in the gut microbiota composition are thought to contribute to the pathogenesis of Hashimoto's by enhancing intestinal permeability and promoting immune system abnormalities.

Intestinal bacteria as a risk factor for autoimmune thyroid disease

Several studies have found that individuals with autoimmune thyroid disease like Hashimoto's thyroiditis tend to have gut dysbiosis even before the onset of clinical symptoms [3,12]. This suggests that alterations in the gut microbiota may act as a risk factor for developing autoimmune thyroid conditions.

Specific bacterial species have been proposed to drive thyroid autoimmunity through mechanisms like molecular mimicry, modulation of autoantigen presentation and regulation of immune cells involved in thyroid inflammation [15]. However, larger prospective studies are needed to establish a definitive link between gut dysbiosis and autoimmune thyroid disease risk.

Growing evidence indicates that gut dysbiosis characterized by reduced bacterial diversity and shifts in microbial composition are associated with both hypothyroidism and Hashimoto's thyroiditis [12]. Further research is warranted to determine whether manipulating the gut microbiota could help manage or prevent these thyroid conditions.

Interference with thyroid autoantigen presentation

One proposed mechanism is that altered gut microbiota can promote autoimmune thyroid diseases by interfering with the presentation of thyroid autoantigens to the immune system.

Certain bacteria may enhance the permeability of the intestinal epithelium, allowing thyroid autoantigens to gain access to gut immune cells [16]. This can trigger an aberrant immune response against thyroid autoantigens, leading to the production of thyroid autoantibodies and thyroid inflammation.

Induction of inflammation

An imbalanced gut microbiota characterized by reduced bacterial diversity and overgrowth of opportunistic bacteria can induce chronic low-grade inflammation. This inflammation can spill over from the gut and influence the immune system at distant sites like the thyroid gland [17]. Gut bacteria-induced inflammation may contribute to thyroid autoimmunity by activating immune cells that attack the thyroid and by disrupting regulatory pathways that maintain self-tolerance.

Production of bacterial metabolites affecting thyroid function

Gut bacteria produce several metabolites like short-chain fatty acids and inflammatory mediators that can influence thyroid physiology. For example, some bacterial metabolites have been shown to interfere with thyroid hormone synthesis by competing for iodine uptake or inhibiting thyroid peroxidase activity. Other metabolites may alter thyroid hormone metabolism and clearance [18]. Changes in the levels and types of bacterial metabolites due to gut dysbiosis could therefore impact thyroid function.

Gut bacteria appear to influence the thyroid through direct interference with auto-antigen presentation, induction of local and systemic inflammation and production of metabolites that disrupt thyroid hormone homeostasis. Further studies are needed to identify the specific bacterial species and mechanisms mediating these effects [5]. Elucidating how the gut microbiota communicates with the thyroid immune system could point to new microbiota-based therapeutic approaches.

Effect of high-fiber diets on gut bacteria and thyroid health

Studies have found that high-fiber diets rich in plant-based foods can beneficially modulate the gut microbiota and impact thyroid function. Fiber serves as fuel for beneficial bacteria while restricting the growth of pathogenic species [8].

High-fiber diets have been shown to:

- Increase gut bacterial diversity
- Promote the growth of short-chain fatty acid producing bacteria like Faecalibacterium and Bifidobacterium [19]
- Improve thyroid hormone levels and reduce thyroid antibodies in patients with autoimmune thyroid disease [20]

These findings suggest that increasing fiber intake through diets high in fruits, vegetables and whole grains could help maintain a healthy gut microbiota and optimize thyroid health. The recommendations for dietary and lifestyle modifications that promote gut microbiota are listed in Table 1.

Table 1: Recommendations for dietary and lifestyle modifications that can optimize the gut microbiota and thyroid health

Dietary/Lifestyle Recommendations	Rationale
Increase fiber intake [21] Example: Whole grains, Fruits, Vegetables, Legumes	**High fiber diet:** ▪ Promote growth of beneficial bacteria ▪ Produce short-chain fatty acids to support gut health ▪ May improve thyroid hormone levels and reduce antibodies
Limit saturated fat intake [22] Example: Red meats, Full-fat dairy, Processed foods	**High-fat diets have been linked to:** ▪ Unhealthy changes in the gut microbiota ▪ Insulin resistance that interferes with thyroid function
Consume fermented foods [20,22,23] Example: Yogurt, Kimchi, Sauerkraut, Miso	**Fermented foods provide:** ▪ Beneficial bacteria to repopulate the gut microbiome ▪ Prebiotics to feed existing healthy bacteria
Limit sugar intake [24] Example: Sweets, Soft drinks, Fruit juices	**High-sugar diets can cause:** ▪ Dysbiosis by promoting pathogenic bacteria ▪ Insulin resistance and inflammation - risk factors for thyroid disease
Stress management [24] Example: Yoga, meditation, Social support programmes	**Stress has been associated with:** ▪ Alterations in the gut microbiota ▪ Impaired thyroid function

Role of prebiotics and probiotics in modulating thyroid function

Supplementation with prebiotics and probiotics aim to selectively modulate the gut microbiota. Some studies have found that:

- Prebiotics like inulin and galacto-oligosaccharides can increase beneficial bacteria and improve thyroid function in hypothyroid and autoimmune thyroid patients [23]
- Probiotics containing Lactobacillus and Bifidobacterium species may enhance thyroid

hormone levels, reduce thyroid antibodies and inflammation in autoimmune thyroiditis [20]

However, the evidence for the thyroid benefits of prebiotics and probiotics remains limited and inconsistent. Larger trials are needed to establish their efficacy and identify the most effective strains and dosages. The list of clinical trials that shed light on the importance of probiotics and prebiotics on thyroid function is shown in Table 2.

Table 2: Clinical trials investigating the effect of probiotics and prebiotics on thyroid function

Study Intervention	Participants	Outcomes Measured	Key Findings
Smith et al. (2015) Lactobacillus casei Shirota probiotic (10^8 - 10^{10} CFU/day) for 12 weeks [25]	30 patients with Hashimoto's thyroiditis	FT4 and FT3; TSH; Thyroid peroxidase antibodies; Lipid peroxidation levels	Increased FT4 and FT3; Decreased TSH and antibodies; Reduced oxidative stress
Lee et al. (2019) Synbiotic containing Bifidobacterium breve and inulin-FOS prebiotic (1.5g/day) for 8 weeks [26]	20 patients with hypothyroidism	FT4 and FT3; TSH; Intestinal permeability; Fecal Bifidobacterium	Increased FT4 and FT3; Decreased TSH; Improved gut barrier function; Increased Bifidobacterium
Szajewska et al. (2022) VSL#3 probiotic mixture (450 billion CFU/day) for 6 months [27]	40 patients with Hashimoto's thyroiditis	FT4, FT3 and TSH; Thyroid antibodies; Thyroid ultrasonography; Inflammatory markers	Increased FT4; Decreased antibodies; Reduction in thyroid volume; Decreased inflammation

Therapeutic potential of manipulating the gut microbiome

If a definitive link between gut dysbiosis and thyroid disease is established, manipulating the gut microbiota through diet, prebiotics, probiotics or fecal microbiota transplants could emerge as a therapeutic strategy.

However, significant research gaps exist in understanding how exactly the gut microbiota influences thyroid health at the molecular level, which bacteria are most influential and how to optimally correct dysbiosis [10,28]. Addressing these gaps will be critical to develop effective microbiota-based therapies for thyroid disorders.

Overall, adopting a high-fiber diet and strategically manipulating the gut microbiota shows promise as an adjunct treatment for thyroid conditions. But large, well-designed trials are still needed to substantiate current findings and establish the gut microbiota as a viable therapeutic target.

Limitations of current research

While research suggests an important link between the gut microbiota and thyroid function, existing studies have several limitations:

- Most studies are observational and cross-sectional in nature. They cannot determine causation or examine changes over time [3]
- Studies have small sample sizes and vary widely in design, making it difficult to compare findings across studies [9]
- Studies often do not account for other factors that can influence both the gut microbiota and thyroid health, like diet, medications and lifestyle [4]
- The specific bacterial species and mechanisms responsible for the gut-thyroid communication remain poorly understood [23]

Promising avenues for future microbiome-thyroid studies

Moving forward, future microbiome-thyroid studies should aim to:

- Conduct well-designed prospective cohort studies to establish causality and examine temporal changes [29]
- Identify key bacterial species that impact thyroid health using metagenomic and metabolomic analyses [30]
- Characterize longitudinal microbiota shifts in thyroid conditions to determine their role in pathogenesis [31]
- Evaluate the efficacy and safety of manipulations like prebiotics, probiotics and fecal transplants in placebo-controlled clinical trials [5]
- Elucidate the molecular mechanisms through which gut bacteria influence thyroid function and disease [32]
- Explore the potential of microbiota-targeted therapies either as standalone or adjunct treatments for hypothyroidism and autoimmune thyroid disease [33]

The future directions of research around gut microbiome and thyroid homeostasis is shown in Figure 2.

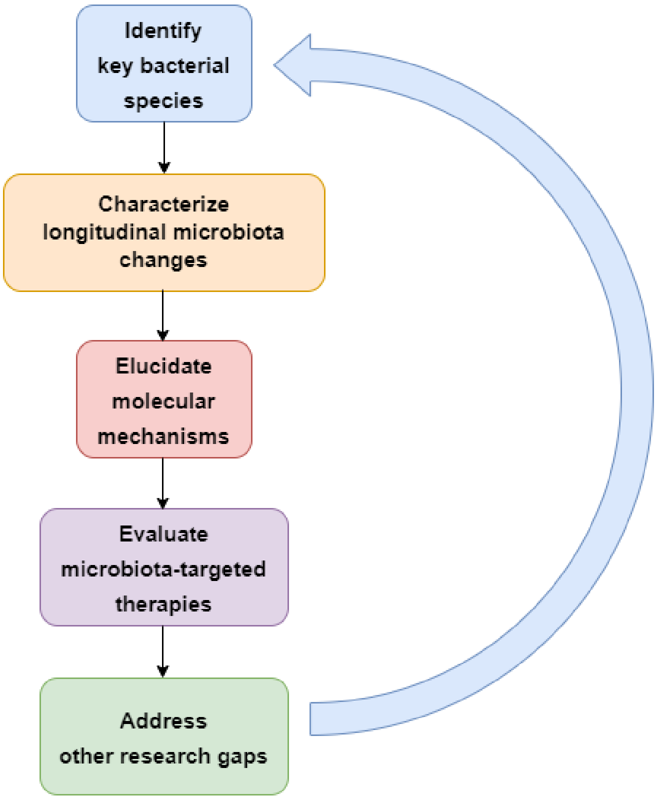

Figure 2: Future research directions to better elucidate the role of the gut microbiota in thyroid health

Table 3: Knowledge gaps and open questions regarding the gut-thyroid axis

Research Area	Open Questions regarding the gut-thyroid axis
Identifying key bacterial players [26,34]	Which specific gut bacterial species have the largest impact on thyroid function and disease risk? What are the predominant bacterial metabolites involved?
Characterizing temporal changes [35]	Do longitudinal shifts in the gut microbiota composition precede or follow the development of thyroid disease? Are certain microbiota changes associated with treatment response or disease progression?
Clarifying interaction mechanisms [36]	How exactly does the gut microbiota influence thyroid hormone synthesis, metabolism and autoimmunity? Which mechanisms - molecular mimicry, immune modulation or bacterial metabolites - play a larger role?
Evaluating interventions [37]	What doses, strains and duration of probiotic interventions are most effective for thyroid health? Do prebiotics and fecal transplants provide comparable benefits to probiotics for thyroid patients?
Addressing impact of confounding factors [17]	How do other lifestyle and environmental factors influence both the gut microbiota and thyroid health? How can their effects be distinguished from those of the gut microbiota?
Determining clinical implications [22]	Can treatments targeting gut dysbiosis help manage or even prevent thyroid conditions in the long term? Which thyroid patients are likely to benefit the most from microbiota-modifying interventions?

Properly addressing these knowledge gaps through high-quality studies holds promise for advancing our understanding of the gut-thyroid axis and developing novel microbiota-based therapies for thyroid disorders (Table 3).

Conclusion

Several studies suggest that the gut microbiota plays an important role in thyroid health and disease. However, the mechanisms underlying the microbiome-thyroid connection remain unclear. While modifying the gut microbiota through diet and probiotics shows some promise for optimizing thyroid function, high-quality evidence is still lacking. Future research identifying key bacterial influences, temporal microbiota changes and interaction mechanisms could establish the gut microbiota as a viable therapeutic target for managing thyroid disorders. However, more substantiating evidence is needed before microbiota-based therapies can be validated and implemented. Addressing knowledge gaps of the gut-thyroid axis holds potential for improving treatment of thyroid conditions but warrants further investigation to clarify this emerging relationship.

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