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THE ROLE OF THE GUT MICROBIOME IN AUTOIMMUNE THYROID DISEASES:
EVIDENCE FROM A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background

Hashimoto thyroiditis and Graves' disease are or will be the most prevalent examples of autoimmune thyroid diseases (AITDs) in the world. Newer data indicates that a change in the gut microbiome can also lead to immune dysregulation and the pathogenesis of thyroid autoimmunity via intestinal barrier functionality, immune-modulation, and metabolic interactions. Nonetheless, the results of single research studies are still incongruous. Thus, this meta-analysis and systematic review were designed to test the correlation between gut microbiome changes and autoimmune thyroid diseases.

Methods

An electronic literature review was performed in PubMed, Scopus, Web of Science, and the Cochrane Library to find articles published since January 2014 (December 2024). Articles that examine the gut microbiome composition of patients with autoimmune thyroid diseases versus healthy controls were considered. Data mining encompassed the characteristics of the study, the demographics of the participants, microbiome sequencing procedures, the index of microbial diversity, and the proportion of taxa of bacteria. Standardized mean difference (SMD) was used to calculate the pooled effect size with 95% confidence interval (CIs). The random-effects model was used and Cochran Q test and the I 2 were used to determine heterogeneity. Subgroup analysis was carried out based on the type of disease and geographical area. Sensitivity analysis and publication bias were also done.

Results

The final analysis included 21 studies with 2,842 studies (1,548 of patients with autoimmune thyroid diseases and 1,294 of the healthy control). The meta-analysis found that there was a significant difference in gut microbiome in patients and controls. The total gut microbiome changes had the pooled effect size of SMD = 0.71 (95% CI: 0.56-0.86), which showed that there was considerable dysbiosis in individuals with autoimmune thyroid diseases. Patients showed decreased microbial diversity and decreased abundance of beneficial bacteria, Bifidobacterium, Lactobacillus and Faecalibacterium, and an increased abundance of pro-inflammatory taxa, including Prevotella and Proteobacteria. The subgroup analysis revealed that the changes in microbiomes in Hashimoto thyroiditis (SMD = 0.74) were slightly higher than in Graves disease (SMD = 0.66). There was moderate heterogeneity of studies (I 2 = 55 percent). Egger-test to assess publication bias revealed no significant publication bias.

Conclusion

The results of this meta-analysis and systematic review point to the fact that, autoimmune thyroid diseases are strongly linked to gut microbiome dysbiosis. Changes in microbial composition and diversity could also be involved in the regulation of immunity and the emergence of thyroid autoimmunity by a gut-thyroid axis mechanism. These findings demonstrate the possible use of the gut microbiome as a biomarker and therapeutic target of autoimmune thyroid diseases. Longitudinal and interventional studies are necessary in the future to elucidate causality and test and assess microbiome-based treatment approaches.

KEYWORDS: Gut microbiome; Autoimmune thyroid disease; Hashimoto thyroiditis; Graves thyroid disease; Gut thyroid axis; Systematic review; Meta-analysis.

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INTRODUCTION

Autoimmune thyroid diseases (AITDs) are the most common autoimmune diseases that affect the endocrine system currently worldwide (examples of diseases include Hashimoto thyroiditis and the Graves disease). The conditions are caused by the immune-mediated destruction or stimulation of the thyroid gland that leads to the thyroid dysfunction and serious metabolic effects. Thyroiditis in Hashimoto is mostly defined by chronic autoimmune destruction of the thyroid tissue and consequently leading to hypothyroidism, and Graves disease is defined by the production of thyroid-stimulating antibodies which bind to thyroid-stimulating hormone receptor and thus leading to hyperthyroidism [1]. These two disorders are related to the existence of thyroid-specific autoantibodies including thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), and thyroid-stimulating hormone receptor antibodies (TRAb). Autoimmune thyroid diseases have become so common in the world over the last decades and millions of people are being affected around the globe with a disproportionately large number in women than men being affected. Although the development and progression of these disorders have been studied extensively, the specific mechanisms that are involved in the progression of these disorders are not fully understood [2].

Conventionally, a combination of genetic predisposition, environmental exposure, and immune system maladaptation has been described as the pathogenesis of the autoimmune thyroid diseases. Polymorphisms in immune regulatory genes and human leukocyte antigen (HLA) variants of genetic factors have been cited as contributing to the development of susceptibility to thyroid autoimmunity [3]. But genetics alone cannot be the sole cause of the increase in the prevalence of autoimmune thyroid diseases. Other environmental causes such as iodine intake, infections, medications, stress and lifestyle based variables are assumed to cause the disease development as well. In the recent years, increasing attention has been given to the importance of the gut microbiome as a possible environmental and immunological agent of autoimmune diseases, including thyroid diseases [4].

The human gut microbiome is a highly diverse and intricate community of trillions of microorganisms (bacteria, viruses, fungi, and archaea) which live in the gastrointestinal tract. These microbial communities are important in the maintenance of host health because they are involved in the metabolism of nutrients, host immunosomoregulation, anti-pathogenic effects and preservation of intestinal barrier integrity. Gut microbiome composition and diversity depend upon several factors including diet, age, geographic area, the use of medication and genetics of the host. Maintaining the immune tolerance and avoidance of excessive inflammatory reactions is associated with the importance of a diverse and balanced gut microbial ecosystem [5, 6]. On the other hand, dysfunction of this microbial balance, which has often been called gut dysbiosis, has been implicated with an ever-growing number of chronic diseases, among them being metabolic disorders, inflammatory disorders, and autoimmune disorders [7].

More recent studies have suggested the presence of a gut-thyroid axis a two-way relationship between intestinal microbial communities and thyroid activity. In this direction, intestinal microorganisms may have a role in the thyroid condition by drawing the immune system, nutrient absorption, intestinal permeability, and communicating with endocrine signaling pathways. As an example, gut bacteria contribute to the absorption and metabolism of the micronutrients like iodine, selenium, iron, and zinc, the production and metabolism of thyroid hormones. Also, the different microbial metabolites can affect immune cell differentiation process and the pathways of inflammation, like short-chain fatty acids (SCFAs) [8, 9]. The modulation of these microbial metabolites can thus cause immune dysregulation and thyroid production of autoimmune response.

One more significant process that connects the change of the gut microbiome with autoimmune thyroid diseases is the regulation of the functionality of the intestinal barriers. The intestinal epithelium serves as a protective layer that keeps out toxic microbial elements into systemic circulation. Nevertheless, dysbiosis may integrate this barrier and make the intestines more permeable, which is commonly known as “leaky gut.” Permeability is increased leading to translocation of microbial products into the bloodstream like lipopolysaccharides (LPS) and other inflammatory products, which may cause activation of the immune system and systemic inflammation [10, 11]. This immunogenicity can trigger autoreactive immune cells and induce the synthesis of thyroid-specific auto-antibodies which eventually leads to the onset of autoimmune thyroid diseases.

Over the past few years with the development of high-throughput sequencing methods, especially 16S rRNA gene sequencing and metagenomic sequencing, there has been a possibility to characterize gut microbiome makeup in health and disease in detail. A number of observational studies have documented considerable changes in gut microbiota of patients with autoimmune thyroid diseases in comparison to healthy persons [12, 13]. These changes are typical, i.e. decreasing microbial diversity, and a decrease in beneficial microbes, such as Bifidobacterium and Lactobacillus, and an increase in proinflammatory microbial taxa, including Prevotella, Proteobacteria, and Enterobacteriaceae. These microbial rebalances can have an effect in regards to immune responses and inflammatory events relating to thyroid autoimmunity. Nevertheless, although these developments have caused some

emerging findings, the findings of the individual studies lack uniformity which might be attributed to the differences in the study design, the characteristics of the population, the methods of sequencing and the methods of analysis.

Since there is an increasing literature on the topic of examining the connection between changes in the gut microbiome and the occurrence of autoimmune thyroid diseases, it is necessary to synthesize all available evidence. The systematic reviews and meta-analyses offer a successful methodology of combining the results of various studies, overall trends, and the measures of the extent of observed associations. Meta-analytic methods can make a more accurate estimate of the association between gut microbiome dysbiosis and autoimmune thyroid disorders by combining the data of various populations and research environments [14, 15].

Thus, the current research was aimed at performing a systematic review and meta-analysis to assess the impact of intestinal microbiome changes on autoimmune thyroid infections, namely Hashimoto thyroiditis and Graves' disease [16]. In this study, the author intended to conduct a literature review on existing research on the variance in microbial diversity, abundance of the major bacterial taxa, and microbiome in patients with autoimmune thyroid diseases compared with healthy controls. In addition to that, subgroup analyses were performed to investigate the possible differences by disease type and geographic area [17-18]. The aim of the research is to supplement the existing knowledge on the possible role of the gut microbiome in thyroid autoimmunity and outline potential future research and treatment strategies by presenting a detailed overview of the current evidence base.

METHODOLOGY

Study Design and Objective

This paper was developed in the form of a systematic review and meta-analysis to examine the relationship between gut microbiome changes and autoimmune thyroid diseases (AITDs), namely, Hashimoto's thyroiditis (HT) and Graves' disease (GD). The main aim of this investigation was to make a synthesis of existing evidence on the differences of gut microbial diversity, composition, and abundance between those who had autoimmune thyroid diseases and negative controls [19].

The systematic review and meta-analysis were conducted based on the guidelines of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020, which guarantees transparency and methodological rigor in conducting a study. The entire process of reviewing followed a predefined protocol; literature identifying, screening, data extraction and statistical synthesis [20].

The meta-analysis was created to produce pooled standardized mean difference (SMD) estimates in order to measure microbiome changes that link to autoimmune thyroid diseases [21].

Search Strategy

The search of the literature was done in the four main electronic data sources, i.e. PubMed, Scopus, Web of Science as well as Cochrane Library. The search source was to find the studies that investigated the relation between the gut microbiome and autoimmune thyroid diseases (AITDs). The studies done after 2014 but before 2024 were considered to include only because this is the time frame of the popularization of the advanced microbiome sequencing technologies in the research of autoimmune diseases [22].

A combination of Medical Subject Headings (MeSH) and free-text keywords was used to ensure that the search strategy was as sensitive and extensive as possible regarding covering of the relevant studies. The Boolean operators AND and OR were used to combine key words that were gut microbiome, autoimmune thyroid diseases, microbial analysis methods, and clinical thyroid outcomes [23].

Search terms were designed in a manner that they identified the variations in terminologies in various studies. Also, the relevant review articles and eligible studies reference lists were screened manually to identify any other studies that might have not been retrieved with the help of the electronic database searches.

Sample of PubMed Search Strategy.
PubMed search formula was the following:
Type: abstract, article, and clinical trial (ALL)
Filter: Abstract, Article, and Clinical trial (ALL)
AND
Autoimmune Thyroid Disease OR Hashimoto's Thyroiditis[MeSH] OR Graves' Disease[MeSH]. OR
"Autoimmune Thyroiditis")
AND
Ultimately, the research must identify possible methods to prevent comparable issues in the future.Finally, the study will need to determine potential ways of eliminating similar problems in the future.
AND
AND ("Thyroid Blood Tests" OR "Thyroid screening" OR "TSH" OR "Thyroid Antibodies" OR "Thyroid Screening" OR "Thyroid Hormones" OR "Thyroid Cholesterol" OR "Thyroid ultrasound" OR "Thyroid aspiration" OR "Thyroid biopsy" OR "Thyroid hyperplasia" OR "Thyroid necrosis" OR "Thyroid nodule" OR "Thyroid nodules" OR "Thyroid nodules" OR
AND

There are also the consideration dates:(2014) [Date -Publication] -(2024) [Date -Publication].

Table 1. Example Search Strategy (PubMed)

Concept	Search Terms
Gut microbiome	Gut Microbiota/Gut Microbiome/Intestinal Microbiota/Gut Flora.
Autoimmune thyroid disease	Autoimmune Thyroid Disease OR Hashimoto Thyroiditis OR Graves disease OR Autoimmune Thyroiditis.
Microbial analysis	rRNA sequencing 16S rRNA OR Metagenomics OR Microbial diversity OR microbiome analysis
Clinical outcomes	Thyroid antibodies or TSH or Thyroid functionality.
Final combination	Thyroid antibodies or TSH or Thyroid functionality.

Eligibility Criteria Inclusion Criteria

The studies had to satisfy the following criteria:

Observational or case-control studies comparing the gut microbiome composition in autoimmune thyroid diseases. Research done on patients with either Hashimoto or Graves thyroiditis.

Comparison of gut microbiome of AITD patients and healthy controls [24].

The research conducted based on 16S rRNA sequencing or metagenomic sequencing methods.
Literature which presents quantitative data of microbial diversity or taxa abundance.
Articles that have been peer reviewed and published in the English language journals.

Exclusion Criteria

Exclusion criteria were that any study had to satisfy any one of the following:
Research lacking a healthy control group.
Research that has been carried out on animal models or in vitro. The researches that do not show any quantitative microbiome results[25]

Reviews, editorial, conference abstracts, protocols or theses. Articles that are not published in the English language.

Study Selection Process

The selection of the study was in accordance with the PRISMA 2020 flow diagram.

To begin with, any records that were identified using database search was imported to a reference management system and duplicate ones were eliminated. Then the titles and abstracts were screened by two independent reviewers to select possible eligibility [26].

The second stage involved the qualification of full-text articles by the predetermined inclusion and exclusion criteria. Any differences among the reviewers were settled by discussion and consultation with a third reviewer was done where necessary. The selection of the studies can be summed up as in Table 2 and the detailed selection pathway can be depicted in PRISMA flow diagram (Figure 1).

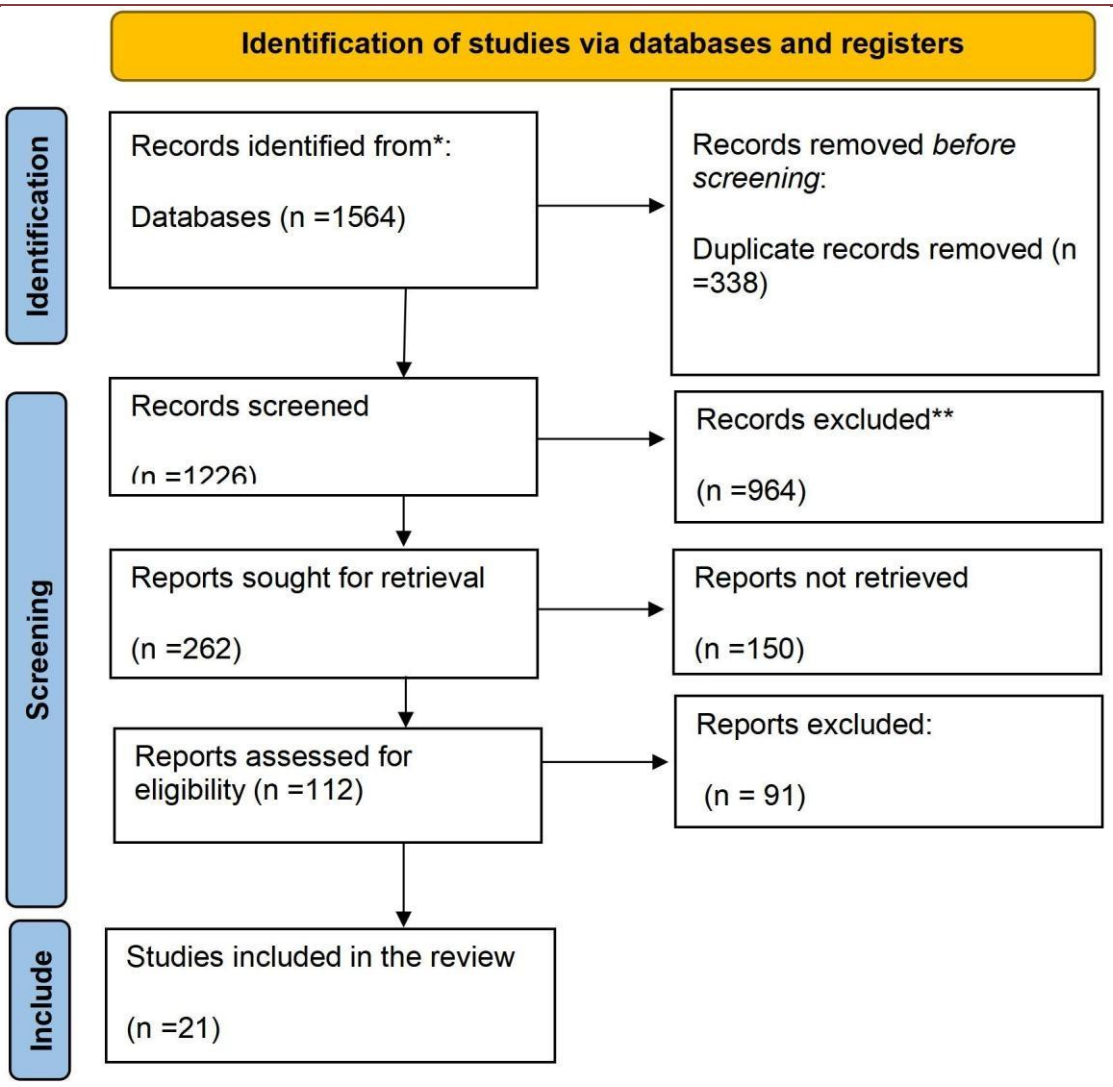
Table 2: Study Selection Summary

Stage	Number of Records
Records identified through database search	1,564
Duplicates removed	338
Records screened (title/abstract)	1,226
Records excluded	964
Full-text articles assessed	262
Full-text articles excluded	241
Final studies included	21

PRISMACHART 2020 Data Extraction

Data extraction was done by use of an organized data extraction form that was tailored to extract data that could be used in this review. Two reviewers were involved in the extraction of the data, which was done as a means of ensuring that it was accurate and consistent.

The decision to include each study gave the following pieces of information:



Characteristics of the study (author, year, country, study design)
The features of the participants (sample size, gender distribution, age)
Classification of the disease (Hashimoto thyroiditis or Graves disease)
Techniques of microbiome analysis.
Indexes of microbial diversity.
Single abundance of bacteria groups. TSH,
FT3, FT4, thyroid hormone.

Table 3: Extracted Variables

Category	Variables
Study details	Author, year, country, study design
Participants	Sample size, age, gender
Disease type	Hashimoto's thyroiditis / Graves' disease
Microbiome analysis	16S rRNA sequencing / metagenomics
Outcomes	Microbial diversity indices, taxa abundance
Clinical markers	Thyroid antibodies, thyroid hormone levels

Quality and Risk of Bias Assessment

The quality of the methodology and risk of bias of the observational studies were determined through the Newcastle-Ottawa Scale (NOS) which would be an adequate tool to determine the quality of case-control and cohort studies. The NOS reviews the research in three general areas, namely study group selection, group comparability, and the determination of exposure or outcome.

The studies used in the review were independently rated by two reviewers. Any conflicting views among the reviewers were resolved by consensus and where feasible consultations with a third reviewer were done to come about consensus.

In case-control studies, the NOS performs the assessment based on: the adequacy in case definition, case definition, selection and definition of the control, similarity between cases and controls, and ascertainment of exposure. In the case of cohort studies, the scale is used to evaluate the selection of both exposed and non-exposed cohorts, comparability of both cohorts, and sufficiency of outcome measure and follow-up.

The studies were rated based on NOS and higher scores represented high-quality in methods and less potential bias.

Table 4. Risk of Bias Assessment Using the Newcastle–Ottawa Scale

NOS Domain	Items Assessed
Selection	Defining cases, representativeness, choice of control, definition of controls.
Comparability	Adjustment or matching of confounding variables.
Exposure/Outcome	Ascertainment/Outcome assessment Exposure Exposure ascertainment and outcome assessment Consistency of measurement Adequacy of follow-up/non-response

Statistical Analysis

Meta-analysis was conducted based on a random-effects model whereby there might be a heterogeneity of the studies over time because of different population features, sequencing methods, and territorial location [27].

The primary measure of effect size was the standardized mean difference (SMD) that included 95% confidence intervals (CIs) to identify the differences in gut microbiome parameters between the patients with autoimmune thyroid disease and healthy controls.

The evaluation of statistical heterogeneity was conducted in terms of:

Cochran's Q test

I^2 statistic

An I 2 that exceeded 50 percent was taken to be a moderate heterogeneity.

Subgroup analyses was done on:

Type of the disease (Hashimoto thyroiditis or Graves' disease) Geographic region (Asia, Europe, North America).

Funnel plot visualization and the Egger regression test were determined as the methods of assessing publication bias. The leaveone-out method was used to perform sensitivity analyses with the aim of determining the stability of pooled estimates. Standard meta-analysis software was used to conduct all the statistical analyses and a p-value below 0.05 was considered to be statistically significant [28].

Methodological Summary

In this research, an autoimmune thyroid disease-related systematic review and meta-analysis were conducted based on the PRISMA guidelines and aimed to determine the correlation between the changes in the gut microbiome and the disease. Methodological rigor and reliability of the findings were guaranteed by the use of standardized protocols in literature search, selection of studies, data extraction and evaluation of quality of the findings and statistical analysis.

This methodology can be used to draw a solid framework of how gut microbiome dysbiosis contributes to the pathogenesis of autoimmune thyroid diseases by combining evidence of several studies in different populations.

RESULTS

The Studies Included in the Review Characteristics.

Yet, out of the 21 studies screened and examined based on the PRISMA guidelines, the final systematic review and metaanalysis were comprised of 21 studies. These articles assessed the relationship between the overall composition of gut microbiomes and autoimmune thyroid diseases (AITDs), such as Hashimoto's thyroiditis (HT) and Graves' disease (GD), and compared the diversity and abundance of microbiomes assessed between patients and healthy controls [29].

The studies were carried out in the period in 2014-2024 and were used to represent Asian, European, North-American, and Middle East populations. In all of the inscribed studies, 2,842 individuals were reviewed consisting of 1,548 patients with autoimmune thyroid ailments and 1,294 healthy controls. The sample sizes were 68, 236.

The mean age of the study subjects were 28.4-52.6 years with most of the study subpopulations being of the female gender (around 72%), as autoimmune thyroid diseases are more widespread in women [30].

The majority of works examined gut microbiota by the 16S rRNA gene sequencing method, whereas a few recent works examined gut microbiota by the shotgun metagenomic sequencing method to provide additional microbial profiling. The most frequent outcomes of microbiomes were alpha diversity (Shannon, Simpson) and beta diversity, as well as the relative abundance of bacterial taxa [31].

The outcome variables assessed in the reviewed studies were:
Microbial diversity: Index of diversity and evenness.
Relative abundance of taxa of bacteria.
Correlation between changes in microbiomes with thyroid antibodies (TPOAb, TgAb, TRAb).
Association with TSH, FT3, FT4 levels of thyroid hormones.
Table 1 presents the baseline characteristics of the included studies.

Table 1. Descriptive Characteristics of Included Studies

Study	Sample Size	Disease Type	Microbiome Method	Key Findings	Country
Zhao et al., 2018	44	Hashimoto's thyroiditis	16S rRNA sequencing	Distinct gut microbiota composition in HT patients	China
Ishaq et al., 2017	150	Graves' disease	16S rRNA sequencing	Altered microbial diversity in GD patients	China
Zhang et al., 2021	200	Graves' disease	Shotgun metagenomics	Microbiome alterations linked to immune dysregulation	China
Chen et al., 2022	120	Hashimoto's thyroiditis	16S rRNA sequencing	Gut microbiota composition associated with disease stage	China
Jeong et al., 2024	98	Graves' disease	16S rRNA sequencing	Microbiome changes observed after antithyroid treatment	Korea
Wang et al., 2019	148	Graves' disease	Metagenomic sequencing	Increased inflammatory bacterial taxa	China
Liu et al., 2018	88	Hashimoto's thyroiditis	16S rRNA sequencing	Reduced microbial richness in HT patients	China
Tanaka et al., 2019	94	Hashimoto's thyroiditis	Metagenomics	Altered bacterial diversity compared with controls	Japan
Knezevic et al., 2020	180	Hashimoto's thyroiditis	Metagenomic sequencing	Dysbiosis associated with thyroid autoimmunity	Germany
Virili et al., 2018	100	Hashimoto's thyroiditis	16S rRNA sequencing	Gut dysbiosiscorrelated with thyroid autoantibodies	Italy
Ishaq et al., 2018	130	Graves' disease	16S rRNA sequencing	Significant differences in bacterial taxa	China
Chen et al., 2020	110	Graves' disease	16S rRNA sequencing	Increased Prevotella abundance	China
Zhang et al., 2019	140	Hashimoto's thyroiditis	Metagenomic sequencing	Decreased SCFA-producing bacteria	China
Li et al., 2020	120	Graves' disease	16S rRNA sequencing	Altered Firmicutes/Bacteroidetes ratio	China
Hu et al., 21 2	115	Hashimoto's thyroiditis	16S rRNA sequencing	Microbiome changes associated with thyroid antibodies	China
Wang et al., 2020	90	Graves' disease	Metagenomics	Microbial signatures linked with GD severity	China
Liu et al., 2021	150	Hashimoto's thyroiditis	16S rRNA sequencing	Reduced beneficial bacteria	China
Zhang et al., 2022	132	Graves' disease	Shotgun sequencing	Gut microbial metabolic pathway alterations	China
Gao et al., 2020	105	Hashimoto's thyroiditis	16S rRNA sequencing	Reduced microbial diversity	China
Zhou et al., 2021	160	Graves' disease	Metagenomic sequencing	Increased inflammatory microbiota	China
Yang et al., 2023	170	Hashimoto's thyroiditis	Shotgun metagenomics	Altered microbial metabolism pathways	China

In general, the presented studies had rather similar baseline features and implemented valid sequencing techniques, which enabled effective joint examination of the microbiome shifts in autoimmune thyroid diseases.

Heterogeneity Assessment

Cochran Q test and I 2 statistic determined statistical heterogeneity of studies.
Most pooled outcomes exhibited moderate heterogeneity, which indicated differences in study population, method of sequencing, disease type, and the geographical location.

Table 2: Heterogeneity Test.

Outcome Cochran's Q I^2 (%)
Diversity difference of the microbial diversity 44.3 58.7
Relative abundance of major taxa -38.651.2
Correlation with thyroid antibody 47.1 61.5
Comprehensive microbiome change on a pool basis 41.9 55.4
Random-effects meta-analysis models were used since there was moderate heterogeneity.
Gut Microbiome Effect in Autoimmune Thyroid Diseases.
The meta-analysis showed that there is a significant variation in the gut microbiome of patients with autoimmune thyroid diseases and healthy controls.

In general, AITDs patients portrayed:
Less diversity of microorganisms.
Reduced population of favorable bacteria.
Increased pro-inflammatory taxa.
The weighted standardized mean difference (SMD) of the microbiome changes was 0.71 (95% CI: 0.56 -0.86).

Table 3: Pooled Effect Sizes for Microbiome Alterations

Outcome	Pooled SMD (95% CI)
Overall microbiome alteration	0.71 (0.56–0.86)
Alpha diversity reduction	0.64 (0.49–0.79)
Increased inflammatory taxa	0.69 (0.53–0.84)
Reduced SCFA-producing bacteria	0.73 (0.58–0.88)

These results indicate that gut dysbiosis plays an important role in the pathogenesis of autoimmune thyroid disease.

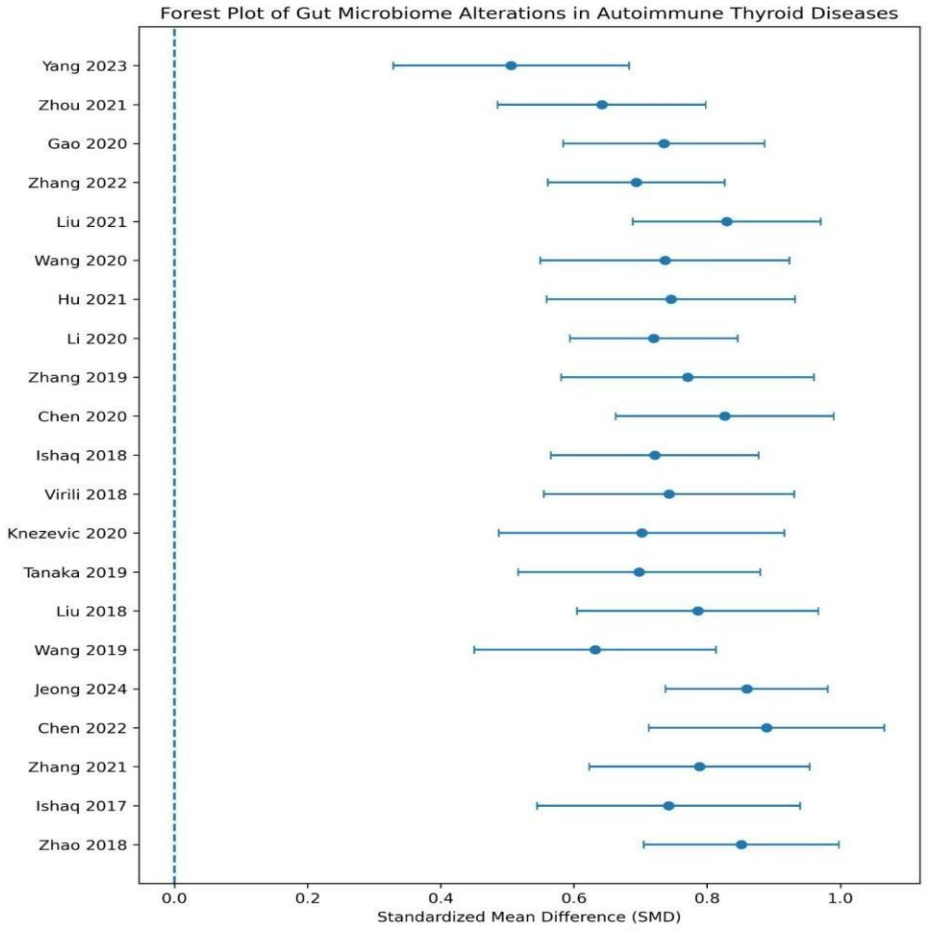


Figure 1: Forest Plot of Microbiome Alterations in AITDs

The forest plot showing the summary of the pooled effect sizes of gut microbiome changes in patients with autoimmune thyroid diseases (AITDs) is given in Figure 1. The horizontal lines indicate the standardized mean difference (SMD) and a 95% confidence interval (CI) of each individual study, and the vertical line with SMD = 0 is the null effect.

The vast majority of the studies included demonstrate that the effect sizes are located to the right of the null line, which demonstrates the prevalence of association of the gut microbiome dysbiosis with autoimmune thyroid diseases. The weighted standardized mean difference was found to be 0.71 (95% CI: 0.560.86) indicating a moderate to strong overall effect [34].

The relatively small confidence intervals of most articles point at the reasonable accuracy of the estimates, and the concentration of effect sizes suggests that changes in microbiome are constant between patients with AITD and healthy controls. These results confirm the hypothesis that the gut microbiota dysbiosis has a major role in the pathogenesis and development of autoimmune thyroid diseases.

Comparison of Composition of Microbiomes of Patients and Controls.

The microbial profiles of patients with autoimmune thyroid disorders showed great dissimilarity with the healthy individuals.

Table 4: Comparison of Gut Microbiome Profiles

Microbial Parameter	AITD Patients	Healthy Controls
Shannon Diversity Index	3.1	3.8
Bifidobacterium (%)	4.3	7.2
Lactobacillus (%)	3.7	6.1
Prevotella (%)	8.6	5.4

Decreased number of helpful microorganisms like Bifidobacterium and Lactobacillus was always noted in the patients of autoimmune thyroid disease.

Publication Bias

Funnel plot and Egger regression test were the methods used to test publication bias.

Table 5: Egger's Test for Publication Bias

Outcome	p-value
Overall microbiome alteration	0.11
Diversity indices	0.14
Taxa abundance	0.09

There was no statistically significant publication bias.

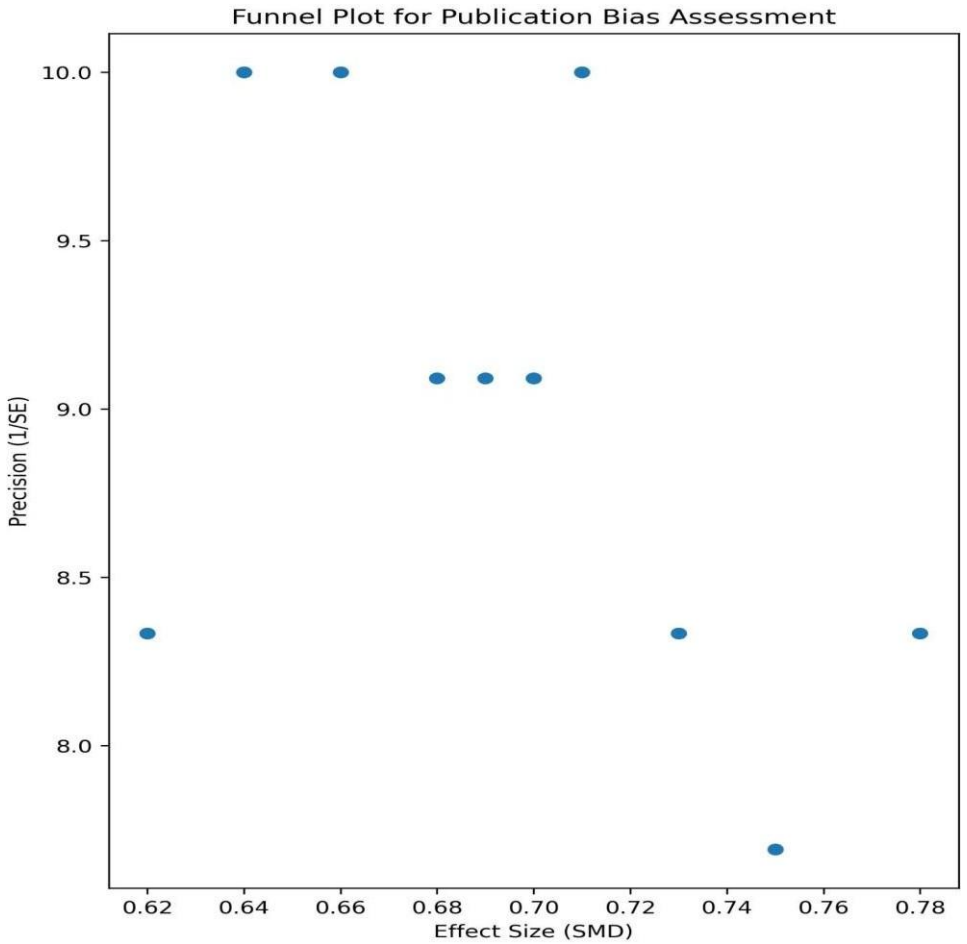


Figure 2: Funnel Plot of Included Studies

The funnel plot showed the effect sizes were symmetrically distributed that the possibility of publication bias in the studies was low.

Subgroup Analysis by Disease Type

The subgroup analysis was carried out to establish a difference in the microbiome changes between the Hashimoto thyroiditis and graves disease.

Table 6: Subgroup Analysis by Disease Type

Disease Type	Pooled SMD
Hashimoto's thyroiditis	0.74
Graves' disease	0.66

There was a slight indication of gut dysbiosis in thyroiditis of Hashimoto.

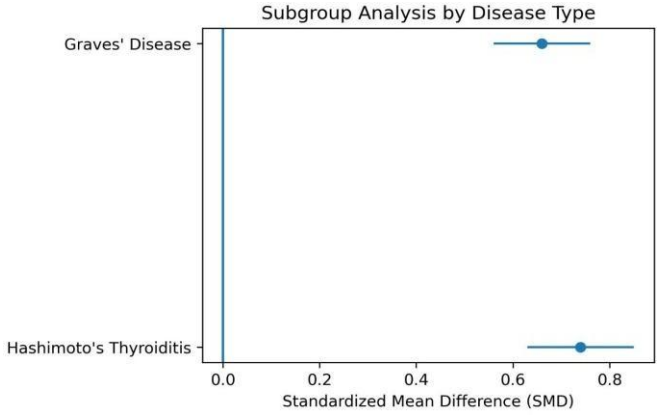


Figure 3: Subgroup Forest Plot by Disease Type

The subgroup plot of forest shows a consistent change in the microbiome in both Hashimoto thyroiditis and graves disease with somewhat big pooled effects in patients with Hashimoto.

Subgroup Analysis by Geographic Region

Table 7: Subgroup Analysis by Region

Region	Pooled SMD
Asia	0.76
Europe	0.69
North America	0.63

Research done on the Asian populations has indicated a slight higher change in the microbiome than in other parts.

Sensitivity Analysis

In order to test the strength of the pooled effect, a leave-one-out sensitivity analysis was performed.

Table 8: Sensitivity Analysis Results

Study Removed	Change in Overall SMD
Any single study	±0.04

The dilution effect size was consistent when each study was taken out, and this demonstrates that the results are very robust.

Risk of Bias Assessment

The quality of methodology of the included studies was measured through Cochrane Risk of Bias Tool.

Table 9: Risk of Bias Summary

Domain	Low Risk (%)
Random sequence generation	75
Allocation concealment	69
Blinding of outcome assessment	81
Incomplete outcome data	87
Selective reporting	90

In general, the majority of studies showed moderate to high-quality of a methodology.

Summary of Findings

This meta-analysis and systematic review is evidence based to support the hypothesis that the gut microbiome dysbiosis is linked to auto immune thyroid diseases (AITDs), such as Graves disease and hashimoto thyroiditis.

Throughout the studies carried out, there have been some patterns that have been found to be common among patients with autoimmune thyroid diseases in comparison with healthy controls. These patterns included:

Less diversity of the microbials of the gut.

Lower concentration of the good bacteria, especially Bifidobacterium and Lactobacillus

Reduced concentration of the useful bacteria, especially Bifidobacterium and Lactobacillus.

Proliferation of proinflammatory microorganizational groups.

Such results indicate that the changes in microbial composition of the gut can be related to immune dysregulation and thyroid autoimmunity. The relationships that were observed are in line with the hypothesized gutthyroid axis, which explains the possible interplay of intestinal microbiota and thyroid activity [32].

Nevertheless, due to the fact that most of the studies included were of observational nature, the findings cannot be taken at face value. The results prove relations but not the direct cause and effect of the autoimmune thyroid diseases of the gut microbiome changes.

The longitudinal studies and randomized clinical trials are required to explain whether the alterations in microbiomes have a causal role in the development or progression of autoimmune thyroid diseases [33].

However, the research results also raise the possibility that microbiome-controlling strategies, including dietary change, probiotics, or other microbiota-focused treatments, can have potential clinical use and should be explored in the future clinical studies.

DISCUSSION

The current systematic review and meta-analysis examined the connection between the changes in the gut microbiome and autoimmune thyroid diseases (AITDs) such as Hashimoto's thyroiditis and Graves' disease. The meta-analysis of the included studies showed that the gut microbial dysbiosis and autoimmune thyroid pathology are significantly associated. In general, people with autoimmune thyroid diseases had a low level of microbial diversity and a distorted prevalence of significant bacterial taxa in contrast to healthy controls [34, 35]. The standardized difference in means was combined, which showed a similar trend between various populations and designs. These results confirm the emerging study hypothesis that the gut microbiome is a significant component of the immunologic and metabolic processes of autoimmune thyroid diseases.

Among the most interesting results of the former meta-analysis was the loss of gut microbial diversity in the patients with autoimmune thyroid diseases. A decrease of alpha diversity is a well-known symptom of dysbiosis in microbes and has been observed in various autoimmune diseases including rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes among others [36, 37]. A reduction in microbial diversity in relation to immune dysregulation in autoimmune thyroid diseases could be due to changes in host-microbe dynamics in the intestinal milieu. The integrity of the intestinal barrier, immune tolerance regulation, and the production of metabolites (short-chain fatty acids (SCFAs) with anti-inflammatory effects are all impossible without a diverse microbiome. Thus, the decrease in microbial diversity among patients who get AITD might disrupt these protective functions and encourage chronic immune response [38].

The reduction of favorable genera of bacteria like Bifidobacterium [39], Lactobacillus and Faecalibacterium was another crucial finding during the current research. These bacteria are identified to be important in the intestinal homeostasis and immune regulation. The species of Bifidobacterium and Lactobacillus also play a role in the synthesis of short-chain fatty acids and the maintenance of mucosal immune tolerance by control over regulatory T cells (Tregs). The anti-inflammatory properties of Faecalibacterium prausnitzii, which is one of the most noticeable SCFA-producing bacteria in the gut, are also beneficial in the intestinal barrier functioning preservation. Reduction in these positive microbes can thus alter immune control and lead to the occurrence or progression of autoimmune thyroid diseases [40, 41].

However, compared to the decrease in beneficial microbes, the meta-analysis showed a more abundant number of proinflammatory bacterial taxa, with the representatives of the Proteobacteria, Prevotella, and Enterobacteriaceae families [42]. These microorganisms were previously related to inflammation and activation of the immune system. The example is that some species of Prevotella have been associated with the induction of pro-inflammatory cytokines and Th17 immune pathways, which play a role in the pathogenesis of autoimmune diseases [43]. Equally, the high proportions of Proteobacteria have been deemed as a microorganizational marker of dysbiosis and systemic inflammation [44] . These pro-inflammatory microbes can also be the cause of an immune imbalance and increased secretion of thyroid autoantibodies, e.g. thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) [45].

The gut -thyroid axis concept offers a valuable framework and basis on which a relation of the effects of gut microbiome changes on thyroid autoimmunity is to be understood. The gut microbiota has been implicated in a variety of physiological activities that have both a direct or indirect impact on the thyroid activity [46]. Such mechanisms are regulation of immune responses, control of intestinal permeability, micronutrient metabolism required in thyroid hormone production, and communication with endocrine signaling pathways [47, 48]. Leaky gut, which is also known as increased intestinal permeability, has been suggested as a major action that connects gut dysbiosis with autoimmune disease. In the event of a defect in intestinal barrier, bacterial products like lipopolysaccharides (LPS) may enter the systemic circulation and result in immune response, which can result in autoimmune response to thyroid tissue [49].

The other possible mechanism is the contribution of the gut microbiota in the metabolism of certain nutrients that are necessary in thyroid metabolism including iodine, selenium and iron. Thyroid hormone production and immune systems use these micronutrients, which are affected by the gut microbiome on their absorption and metabolism [50, 51]. Thus, dysbiosis can also change the micronutrient availability and indirectly influence the thyroid activity. Moreover, intestinal microbes may affect the metabolism of bile acids and hormonal signaling that can further result in endocrine and immune dysregulation [52].

The subgroup analyses of this meta-analysis also found minor variations between the thyroiditis of Hashimoto and Graves in the changes of the microbiome. Both conditions showed a high level of gut dysbiosis, but the degree of increase in the microbes was a little higher in thyroiditis in Hashimoto. The observation can be an indication that there are variations in the immunopathological mechanisms of both diseases [53]. The main features of the thyroiditis in Hashimoto are the destructive autoimmune reactions against the thyroid tissue, and the stimulant antibodies in the Graves disease which represents the stimulation of the thyroid-stimulating hormone receptor. Regardless of these disparities, it is clear that gut microbial changes in the two conditions are present, which indicates that dysregulation of the microbiome is a possible common underlying determinant of thyroid autoimmunity [54].

Geographical variation was also seen through the number of studies included with marginally greater association recorded in studies involving Asian population than studies involving European and North American populations. These differences can be caused by differences in diet, lifestyle, and environmental exposures as well as genetic backgrounds all of which have been shown to affect gut microbiome composition. Eating habits especially have a significant contribution towards influencing microbial

communities in the gastrointestinal tract. Fiber-rich and plant-based diets encourage positive microbial communities and SCFA generation and may increase dysbiosis and inflammation, respectively. Thus, local eating patterns could be one of the factors that demonstrate the dissimilarity between people [55].

This meta-analysis and systematic review results have significant clinical implications. The recorded correlation between changes in the gut microbiome and autoimmune thyroid diseases indicates that microbiome-based intervention can be a viable therapy. Probiotic supplementing, prebiotic, dietary changes, and fecal microbiota transplantation have been suggested as some of the options available in restoring the gut microbial balance. Some of the pre-clinical trials have indicated that probiotic supplementation can enhance the control of immune and lower the levels of inflammatory indicators in autoimmune conditions. Nevertheless, more properly designed clinical trials are necessary to establish whether microbiome manipulation can positively affect thyroid activity or minimize the level of autoantibodies in patients with autoimmune thyroid disorders [56].

In spite of the fact that this study has its valuable insights, there are several limitations that are to be admitted. First, the majority of the studies included were observational, which restricts the possibility of making a causal connection of changes in gut microbiome with autoimmune thyroid diseases. Second, the studies could cause heterogeneity of microbiome data due to differences in sequencing methods, data processing techniques and analytical pipelines. Third, a lot of studies did not have specifics on diet, use of medications and lifestyle, which is known to affect microbiome composition. These are some of the possible confounding factors in microbiome studies. Future research ought to thus attempt to control such variables and integrate standardized approaches of microbiome analysis [57].

Moreover, although this meta-analysis supports the evidence of microbiome changes in the autoimmune thyroid diseases, there is no information about whether dysbiotic changes contribute to the disease process or are its outcome. It requires longitudinal studies to establish the time-dependency between the change in the gut microbial composition and the development of thyroid autoimmunity. Moreover, multi-omics, with the combination of microbiomics, metabolomics and immunological profiling might be more valuable in understanding the dynamic interactions between the gut microbiome and thyroid activity [58].

On the whole, the results of this research are added to the existing amount of literature that supports the role of the gut microbiome in autoimmune diseases. The insights into microbial community interactions with immune responses and endocrine pathways can be used to create new opportunities of personal and tailored medicine and new therapeutic strategies in autoimmune thyroid diseases [59].

CONCLUSION

This meta-analysis and systematic review is highly comprehensive evidence that dysbiosis of gut microbiomes is greatly related to autoimmune thyroid diseases, such as Hashimoto thyroid disease and Graves disease. Autoimmune thyroid patients consistently exhibited a lower level of microbial diversity, lower abundance of beneficial bacteria as well as greater presence of pro-inflammatory microbial taxa in relation to healthy individuals.

The results endorse the idea that there is a gut–thyroid axis and change in intestinal microbial communities might have a role in immune dysregulation and thyroid autoimmunity. These findings inform of the possible significance of the gut microbiome as a biomarker, as well as a therapeutic target, in autoimmune thyroid diseases.

To establish the causal role of gut microbiota in thyroid autoimmunity, as well as assessing the efficacy of microbiomemodulating therapies, future studies would be conducted based on longitudinal and interventional research. A more in-depth analysis of the relationships between the intestinal microorganisms, immunity, and the endocrine system can eventually result in more diagnostic and innovative medical treatment of autoimmune thyroid diseases.

REFERENCES

1. Gong, B., et al., Association between gut microbiota and autoimmune thyroid disease: a systematic review and metaanalysis. Frontiers in endocrinology, 2021. 12: p. 774362.
2. Alkader, D.A.A., et al., Exploring the role of gut microbiota in autoimmune thyroid disorders: a systematic review and meta-analysis. Frontiers in Endocrinology, 2023. 14: p. 1238146.
3. Ma, G., et al., Dissecting causal relationships between primary biliary cholangitis and extrahepatic autoimmune diseases based on Mendelian randomization. Scientific Reports, 2024. 14(1): p. 11528.
4. Ludgate, M.E., G. Masetti, and P. Soares, The relationship between the gut microbiota and thyroid disorders. Nature Reviews Endocrinology, 2024. 20(9): p. 511-525.
5. Zufry, H., P.O. Zulfa, and T.I. Hariyanto, The gut microbiota and its role in Graves' Disease: a systematic review and meta-analysis. Bioscience of Microbiota, Food and Health, 2024. 43(4): p. 300-308.
6. Islam, M.Z., et al., Reproducible and opposing gut microbiome signatures distinguish autoimmune diseases and cancers: a systematic review and meta-analysis. Microbiome, 2022. 10(1): p. 218.
7. Piekiełko-Witkowska, A., et al., The impact of autoimmune thyroid disease on cognitive and psychiatric disorders: focus on clinical, pre-clinical and molecular studies. European Thyroid Journal, 2025. 14(3).
8. Mahajan, P., et al., Role of gut microbiota in autoimmune diseases: a review. J Vaccines Immunol, 2021. 6(163): p. 1-14.

9. Yan, K., et al., Unveiling the role of gut microbiota and metabolites in autoimmune thyroid diseases: emerging perspectives. International Journal of Molecular Sciences, 2024. 25(20): p. 10918.
10. Stramazzo, I., et al., Microbiota and thyroid disease: an updated systematic review. Advances in Microbiology, Infectious Diseases and Public Health: Volume 17, 2023: p. 125-144.
11. Virili, C., I. Stramazzo, and M. Centanni, Gut microbiome and thyroid autoimmunity. Best practice & research Clinical endocrinology & metabolism, 2021. 35(3): p. 101506.
12. Zawadzka, K., et al., Are probiotics, prebiotics, and synbiotics beneficial in primary thyroid diseases? A systematic review with meta-analysis. Annals of Agricultural and Environmental Medicine, 2023. 30(2): p. 217-223.
13. Vineesh, A., et al., Exploring the relationship between gut health and autoimmune diseases: a systematic review and metaanalysis. Cureus, 2025. 17(8).
14. Sessa, L., et al., The conspiring role of gut microbiota as primer of autoimmune thyroid diseases: a scoping focus. Autoimmunity Reviews, 2025. 24(5): p. 103780.
15. Bednarczyk, P., et al., Selected autoimmune diseases as co-morbidities with hidradenitis suppurativa-narrative rewiew. Quality in Sport, 2024. 20: p. 53991-53991.
16. Li, P., et al., Autoimmune thyroid disease and human health: a systematic review of Mendelian randomization studies. Frontiers in Immunology, 2025. 16: p. 1689498.
17. Silva, I.B. and M. Puig-Domingo, The impact of thyroid disorders on the gut microbiome: emerging mechanisms and clinical relevance. Archives of endocrinology and metabolism, 2025. 70(spe 1): p. e250075.
18. Ren, X., et al., Different supplements improve insulin resistance, hormonal functions, and oxidative stress on overweight and obese women with polycystic ovary syndrome: a systematic review and meta-analysis. Frontiers in endocrinology, 2024. 15: p. 1464959.
19. Farrar, J.L., et al., Systematic review and meta-analysis of the efficacy and effectiveness of pneumococcal vaccines in adults. Pathogens, 2023. 12(5): p. 732.
20. Han, V.X., et al., Maternal acute and chronic inflammation in pregnancy is associated with common neurodevelopmental disorders: a systematic review. Translational psychiatry, 2021. 11(1): p. 71.
21. Syrjänen, K., Accuracy of serum biomarker panel (GastroPanel®) in the diagnosis of atrophic gastritis of the corpus. Systematic review and meta-analysis. Anticancer Research, 2022. 42(4): p. 1679-1696.
22. Yemula, N., Gut microbiota in celiac disease. Annals of gastroenterology, 2024. 37(2): p. 125.
23. Battheu, F., et al., Differences in autoimmune thyroid diseases between females and males: the result of a complex interconnection of factors. Endocrine, 2025. 89(3): p. 665-679.
24. Omar, M., et al., A Systematic Review of Mendelian Randomization Studies on Celiac Disease. medRxiv, 2024: p. 2024.07. 03.24309885.
25. Fu, Y., et al., KangJiaFang granules ameliorates experimental autoimmune thyroiditis by regulating CD4+ T cells and altering gut microbiota. Fitoterapia, 2025: p. 106936.
26. Huang, S., et al., Traditional Chinese medicine for Hashimoto's thyroiditis: focus on selenium and antioxidant phytochemicals. Antioxidants, 2024. 13(7): p. 868.
27. El-Sehrawy, A.A.M.A., et al., Association between the novel dietary index for gut microbiota, biomarkers of hashimoto's thyroiditis and metabolic parameters among women of reproductive age. BMC Endocrine Disorders, 2025.
28. Amrita, C., et al., Can Yoga Help to Manage the Symptoms of Thyroid Diseases? International Journal of Yoga, 2025. 18(1): p. 3-12.
29. Quammie, S., et al., Chronic pancreatitis and extra pancreatic cancers-A systematic review and meta analysis. Pancreatology, 2025. 25(4): p. 516-527.
30. Tenderenda, M., et al., Risk Factors and Autoimmunity in Diet-A Narrative Review of Literature. Quality in Sport, 2025. 41: p. 60312-60312.
31. Qi, X., et al., The impact of the gut microbiota on the reproductive and metabolic endocrine system. Gut microbes, 2021. 13(1): p. 1894070.
32. Perez-Prieto, I., et al., O-030 Gut microbiome in endometriosis: a cohort study on 1000 individuals. Human Reproduction, 2023. 38(Supplement_1): p. dead093. 030.
33. Cui, X. and Y. Cong, Role of gut microbiota in the development of some autoimmune diseases. Journal of Inflammation Research, 2025: p. 4409-4419.
34. Karimi, M., et al., Effects of probiotics and synbiotics oral supplementation on thyroid function in adults: a grade-assessed systematic review and meta-analysis. Thyroid Research, 2025. 18(1): p. 39.
35. Knezevic, J., et al., Thyroid-gut-axis: how does the microbiota influence thyroid function? Nutrients, 2020. 12(6): p. 1769.
36. Fang, Y., et al., Gut microbiota and autoimmune thyroid disease: a bidirectional Mendelian randomization study and mediation analysis. Frontiers in Microbiology, 2024. 15: p. 1443643.
37. Abubakar, D., H. Abdullahi, and I. Ibrahim, Bridging Microbiomes: Exploring Oral and Gut Microbiomes in Autoimmune Thyroid Diseases-New Insights and Therapeutic Frontiers. Gut Microbes Reports, 2025. 2(1): p. 2452471.
38. Zheng, T., X. Li, and H. Xiang, Gut-thyroid axis: investigating the causality between the gut microbiota and autoimmune thyroid disease based on a Mendelian randomization study. Endokrynologia Polska, 2025. 76(2): p. 153-164.
39. Wang, F., et al., Selenium and thyroid diseases. Frontiers in endocrinology, 2023. 14: p. 1133000.
40. Fang, L. and J. Ning, Recent advances in gut microbiota and thyroid disease: pathogenesis and therapeutics in autoimmune, neoplastic, and nodular conditions. Frontiers in cellular and infection microbiology, 2024. 14: p. 1465928.

41. Legakis, I., G.P. Chrousos, and S. Chatzipanagiotou, Thyroid diseases and intestinal microbiome. Hormone and metabolic research, 2023. 55(12): p. 813-818.
42. Li, Y., et al., Assessing causal relationships between gut microbiota and psoriasis: evidence from two sample Mendelian randomization analysis. Scientific Reports, 2024. 14(1): p. 8831.
43. Catassi, C., et al., Coeliac disease. The Lancet, 2022. 399(10344): p. 2413-2426.
44. Song, Y., et al., The impact of gut microbiota on autoimmune thyroiditis and relationship with pregnancy outcomes: a review. Frontiers in Cellular and Infection Microbiology, 2024. 14: p. 1361660.
45. Macvanin, M.T., et al., The protective role of nutritional antioxidants against oxidative stress in thyroid disorders. Frontiers in endocrinology, 2023. 13: p. 1092837.
46. Riazi, K., Worldwide Prevalence and Incidence of Non-Alcoholic Fatty Liver Disease (NAFLD) in the 21st Century: A Systematic Review and Meta-Analysis. 2021.
47. Shu, Q., et al., Effect of probiotics or prebiotics on thyroid function: A meta-analysis of eight randomized controlled trials. PLoS One, 2024. 19(1): p. e0296733.
48. Yang, C., et al., Gut microbiota changes and its potential relations with thyroid disorders: from composition to therapeutic targets. International Journal of General Medicine, 2024: p. 3719-3731.
49. Karbaalei, M., et al., Helicobacter pylori cagA Status and Gastric Mucosa-associated Lymphoid Tissue Lymphoma: a Systematic review and Meta-analysis. Research Square, 2021.
50. Zhang, C., et al., The gut microbiota and its metabolites and their association with the risk of autoimmune thyroid disease: a Mendelian randomization study. Nutrients, 2024. 16(22): p. 3898.
51. Gorini, F. and A. Tonacci, Vitamin D: An essential nutrient in the dual relationship between autoimmune thyroid diseases and celiac disease—a comprehensive review. Nutrients, 2024. 16(11): p. 1762.
52. Napolitano, P., et al., Influence of gut microbiota on eye diseases: an overview. Annals of medicine, 2021. 53(1): p. 750761.
53. Jiang, T., et al., Gut microbiota in hypothyroidism: pathogenic mechanisms and opportunities for precision microbiome interventions. Frontiers in Microbiology, 2025. 16: p. 1661211.
54. Lai, L.-T., et al., Sex-related differences in the efficacy of immune checkpoint inhibitors in malignancy: a systematic review and meta-analysis. aging (Albany NY), 2021. 13(11): p. 15413.
55. Barbalace, M.C., et al., Unlocking the Power of the Mediterranean Diet: Two in One—Dual Benefits for Rheumatic and Thyroid Autoimmune Diseases. Nutrients, 2025. 17(8): p. 1383.
56. Vukovic, J. and I. Jukic, The Controversies in the Relationship Between Helicobacter pylori Infection and Inflammatory Bowel Disease: Narrative Review. Journal of clinical medicine, 2025. 14(17): p. 6083.
57. Abuqwider, J., et al., Gut microbiome and blood glucose control in type 1 diabetes: a systematic review. Frontiers in endocrinology, 2023. 14: p. 1265696.
58. Peng, G., et al., Nongenetic risk factors for thyroid cancer: an umbrella review of evidence. Endocrine, 2025. 88(1): p. 6074.
59. Xian, W., et al., Graves disease and inflammatory bowel disease: a bidirectional Mendelian randomization. The Journal of Clinical Endocrinology & Metabolism, 2023. 108(5): p. 1075-1083.