Trends in Endocrinology & Metabolism

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REVIEWS

Review

Microbiota and Thyroid Interaction in Health and Disease

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The microbiota has been identified as an important factor in health and in a variety of diseases. An altered microbiota composition increases the prevalence of Hashimoto's thyroiditis (HT) and Graves' disease (GD). Microbes influence thyroid hormone levels by regulating iodine uptake, degradation, and enterohepatic cycling. In addition, there is a pronounced influence of minerals on interactions between host and microbiota, particularly selenium, iron, and zinc. In manifest thyroid disorders, the microbiota may affect L-thyroxine uptake and influence the action of propylthiouracil (PTU). Although it is relatively well documented that thyroid disorders are linked to the composition of the microbiota, the role of specific genera and the potential use of therapies targeting the microbiota are less clear.

Importance of the Gut Microbiome

The intestinal **microbiota** (see Glossary; Box 1) plays a prominent role in gastrointestinal homeostasis and may represent an additional contributing factor to **thyroid disorders** [1]. The influence of the microbiota on depression, neurodegenerative diseases, heart disease, obesity, diabetes, immunological disorders, inflammatory bowel diseases, and cancer appears to be established [2]. The microbiota may explain why the prevalence of goiter, which has been associated with insufficient iodine (I^-) intake, is not correlated to low iodine excretion in South India, and why in Japan hypothyroidism is more prevalent in iodine-rich than in iodine-poor areas [3,4].

Diabetes mellitus is the most common endocrine pathology encountered in clinical practice, followed by thyroid disorders. Thyroid disorders are usually linked to localized (nodules) or general (goiter) enlargement of the thyroid. The prevalence of thyroid nodules depends on the identification method, and ranges from 4% to 7% by palpation and from 20% to 76% by ultrasound in the adult population of the USA [5]. Frequencies encountered at surgery and autopsy are reported to be between 50% and 65%. In addition to genetic disposition, common risk factors for thyroid disorders are I^- insufficiency, age, and sex [6]. Severe iodine deficiency is linked to hypothyroidism, mild to moderate deficiencies cause multifocal autonomous growth of the thyroid, and excess of iodine is associated with thyroid autoimmunity [7]. Deficiency of iron and selenium are further causes for thyroid disorders, mainly hypothyroidism. Thyroid-stimulating hormone (TSH) levels increase with age, but thyroid dysfunction appears to be most prevalent in the middle-aged population [8]. Sex differences observed in the middle-aged population decrease with age. **Autoimmune diseases** (AIDs) in general, and particularly those affecting the thyroid gland, are diagnosed more frequently in women than in men. A similar imbalance in the prevalence of non-communicable diseases that cause 70% of all deaths worldwide (e.g., cardiovascular disease, cancer, chronic respiratory disease, and diabetes) has not been observed [9].

There are different levels where the microbiota could act on thyroid function (Figure 1, Key Figure). Region, diet (iodine supply), obesity, age, sex hormones, and AID influence the composition of the intestinal microbiota. Reciprocally, the microbiota has been linked to the prevalence of AID, influencing estrogen and iodine levels, and affecting obesity. Further, it influences the enterohepatic cycling

Highlights

The microbiota influences the uptake of iodine, selenium, and iron, and the microbiota may alter the availability of L-thyroxine and toxicity of PTU.

Several findings, including the altered microbiota composition in patients with thyroid disorders, the prominent metabolism of thyroid hormones by the microbiota, and that germ-free rats have smaller thyroids than normal rats, support the hypothesis that the gut microbiota also plays a prominent role in thyroid function of the host.

A variety of recent studies suggest that the gut microbiota has an enormous impact on human health and disease, and alimentary modulation of the gut microbiota by ingestion of pre, pro-, post-, and synbiotics has been advocated for a variety of diseases.

Autoimmune thyroid disorders and metaplastic atrophic gastritis are particularly linked.

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Box 1. The Gut Microbiota

It has been reported that the microbiota comprises 2 kg, representing 39 trillion bacteria, in a 70 kg person consisting of 30 trillion human cells. Its action is not limited to local effects in the gut because 20% of host blood metabolites are derived from commensal bacteria. Positive effects for the host include prevention of growth of pathogens, education of the immune system, caloric salvage, the production of short-chain fatty acids (SCFAs), vitamin E and folate, drug metabolism, and deconjugation of bile salts [56]. Schmidt *et al.* listed four main components that determine the composition of the microbiota, (i) microbiome-intrinsic factors including composition, age-dependence, disease, and stochastic effects; (ii) environmental factors comprising the local environment and vertical transmission, for example from the mother, household, and family; (iii) lifestyle including diet, medication, culture, and physical activity; and (iv) host genetics (body mass index, adaptive and innate immunity, and sex [57]).

Colonization of the gut appears to start already during intrauterine life and is determined by the type of delivery. The first composition of the infant gut resembles the microbiota of the maternal vagina (normal delivery) or skin (Cesarean section). Breast-feeding later plays an important role in the further development of the gut microbiota. The microbiota in children shows high interindividual variation and consists of a relatively low number of bacterial species. After 3 years of life the gut microbiota of the adult is fully developed, the basal composition of which is unique for the individual and remains stable throughout adulthood, with limited variations caused by diet, antibiotic treatment, and challenge with exogenous microbes. Culture-related and geographic differences in the diet appear to be linked to differences in microbiota composition. Phyla enriched in the gastrointestinal (GI) tract are Firmicutes in USA and Russia, whereas Bacteroidetes genus *Bacteroides* spp. are dominant in France, Jamaica, Spain, China, Korea, and Denmark, and Bacteroidetes genus *Prevotella* spp. in Germany, Malawi, India, Peru, and Venezuela. Actinobacteria genus *Bifidobacterium* spp. dominated in Singapore, Indonesia, Scotland, and Sweden. The list demonstrates that classification based only on geographic differences is not possible. More detailed analysis shows that age also markedly influences geographic differences. *Bacteroides* are active in the hydrolysis and fermentation of exogenous dietary fiber and endogenous mucins. The prevalence of *Bacteroides* was higher in Italy than in Germany, but differences between adults and elderly individuals within one country were also pronounced [58].

of thyroid hormones, the bioavailability of levothyroxine (L-thyroxine), and the metabolism of the antihyperthyroid drug **propylthiouracil** (PTU). The influence of the microbiota on thyroid function, dysfunction, and the treatment of thyroid diseases will be discussed in this review.

Role of the Gut Microbiota in Autoimmune Thyroid Diseases

Autoimmune thyroid diseases are the most prevalent organ-specific autoimmune diseases and affect 2–5% of the population. Microbial products, particularly short-chain fatty acids (SCFAs), can serve as an energy source for enterocytes and, together with thyroid hormones, enhance enterocyte differentiation and strengthen intercellular tight junctions [10]. An altered microbiota composition in the gut, on the other hand, promotes the development of AID by several hypothesized mechanisms including the generation of self-antigens by post-translational modification of proteins, lipopolysaccharide (LPS)-induced Toll-like receptor 4 activation, induction of a type 1 (Th1) to type 2 (Th2) T helper cell shift, reducing the integrity of intercellular junctions (leaky gut), and inducing transcriptomic, proteomic, and metabolic changes. HT and GD are the major causes of hypothyroidism and hyperthyroidism, respectively. Although both are AIDs, the involved immunological processes are different. The main immunologic features of GD are circulating antibodies against the TSH receptor. HT is characterized by the presence of autoreactive T cells and antibodies against thyroperoxidase and thyroglobulin that lead to destruction of the thyroid gland. It is therefore possible that the role of microbiota is also different. In both autoimmune thyroid diseases (AITDs) the severity of the disease is not correlated to antibody levels. Furthermore, anxiety and depression in GD are not linked to thyroid function or thyroid autoimmunity [11]. Direct effects on mood by thyroid hormones are unlikely because subclinical hyperthyroidism is associated with better mood compared to euthyroid subjects. An abundance of Actinobacter and Enterobacteriacae was noted in all mood disorders, whereas *Faecalibacterium* spp. were decreased [12] relative to the distribution of phyla (see **classification of bacteria**) in the normal gut (Box 2). In addition, the GABA-producing Lactobacillaceae and Bifidobacteria were decreased, and *Clostridium* and *Prevotella* were increased, in major depression. Because

Glossary

Autoimmune diseases (AIDs): are caused by dysregulation of the immune system triggered by bacteria, viruses, drugs, or toxins. Of the ≫80 entities, Addison disease, celiac disease, dermatomyositis, diabetes type I, the autoimmune thyroid diseases (AITDs) Graves' disease (GD) and Hashimoto's thyroiditis (HT), multiple sclerosis, myasthenia gravis, AMAG, rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus are the most common.

Autoimmune metaplastic atrophic gastritis (AMAG): synonymous with pernicious anemia, atrophic body gastritis, corpus-restricted atrophic gastritis, and type A gastritis.

Classification of bacteria: the main taxonomic classifications of bacteria comprise phylum or class (Actinobacteria, Proteobacteria, Firmicutes, and Bacteroidetes), family, genus, and species. As an example, a species in the phylum Bacteroidetes is classified as belonging to the family Bacteroidaceae, genus *Bacteroides*, and the species *Bacteroides fragilis*.

Cytochrome P450s (CYPs): these dehydrogenases are the main drug-metabolizing enzymes, and members of the CYP3A isoenzyme family are the most important contributors to pre-systemic elimination of orally administered drugs.

Dysbiosis: the term has several definitions, but is mainly used to describe a general change in the composition of the microbiota (e.g., alteration, perturbation, abnormal composition, loss of diversity), as an imbalance in composition (almost always deemed to have negative effects), and as changes to specific lineages in that composition (a change in the representation of different genera).

Inflammatory bowel disease (IBD): includes Crohn's disease and ulcerative colitis.

Iodothyronine deiodinases: type I, II, and II (D1, D2, D3) deiodinases are important selenium (Se)-containing enzymes that remove iodine residues from thyroid hormone.

Methimazol (MMI) and propylthiouracil (PTU): drugs used in the treatment of hyperthyroidism. The drugs interfere with the organification of iodine. Higher doses of PTU can also block peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3).

Key Figure

Interactions between Factors That Are Important for the Development and Treatment of Thyroid Diseases

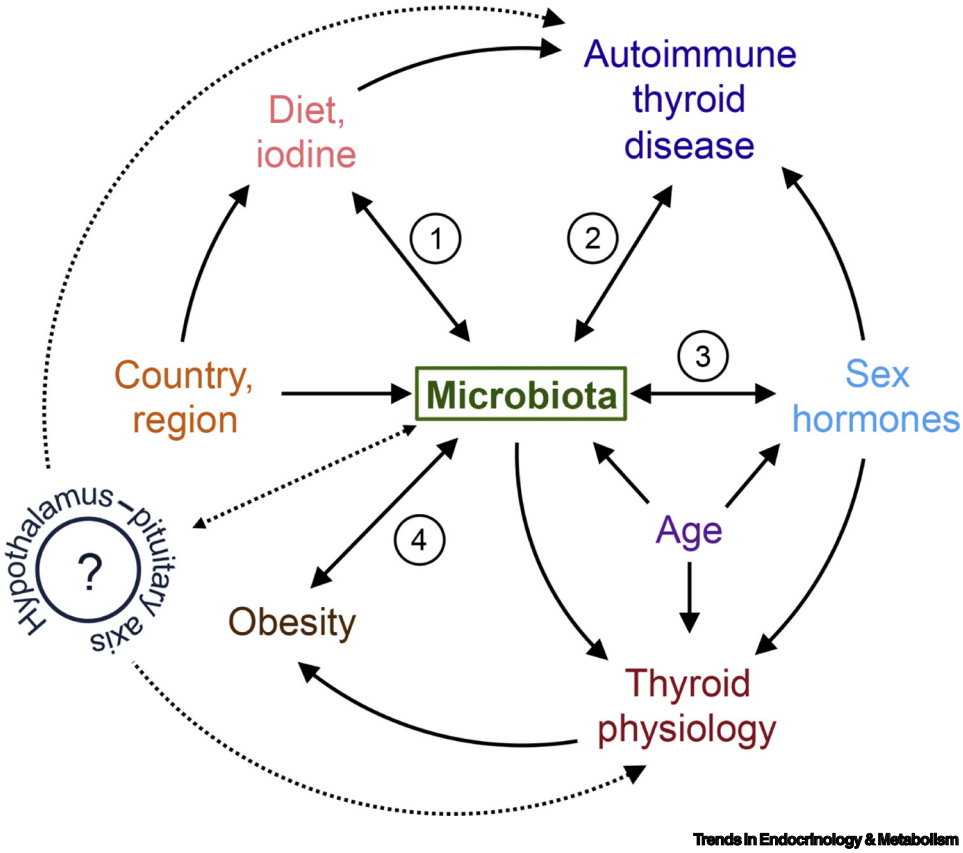


Figure 1. Thyroid physiology includes iodine uptake, hormone recycling, and drug uptake and metabolism. Interaction with the hypothalamus–pituitary axis may include dopamine, but this is speculative. Reciprocal relationships are as follows: (1) iodine may be toxic to the microbiota, and the microbiota influences iodine uptake. (2) Patients with autoimmune thyroid disease (AITD) have altered microbiota populations. Leaky gut syndrome induced by bacterial overgrowth, on the other hand, increases the prevalence of AITD. (3) The microbiota carries out estrogen recycling, and the composition of the microbiota is different in men and women. (4) Obesity leads to an altered microbiota, and fecal transplantation can change the phenotype from obese to lean.

Microbiota and microbiome: the terms microbiota (population of microorganisms) and microbiome (ecosystem, on which the microorganisms form part) are often used interchangeably. The microbiota is the newer and more correct word for what was formerly named the microflora. Descriptors of microbiota composition are the richness of species within a sample (α diversity) and differences versus a control group (β diversity).

Microbiota-targeted therapy: comprises (i) fecal microbiota transfer (FMT), the transfer of gut bacteria from healthy donors to patients, (ii) selective antibiotic therapy to eradicate specific bacterial species, (iii) probiotics, where living microorganisms are administered, (iv) prebiotics, the administration of compounds to support the growth of specific microbiota, (v) synbiotics, the combination of pro- and prebiotics, as well as postbiotics that represent non-viable microbial products to induce specific biological responses.

Thyroid disorders: also termed thyroid dysfunction and thyroid disease, these comprise conditions that affect thyroid function.

it is known that microbial metabolites act on the central nervous system, microbial products may lead to the different manifestations. A contribution of the microbiota to AITD has been proposed because transfer of microbiota from conventional to specific pathogen-free (SPF) rats increased their susceptibility to HT. Owing to molecular mimicry, *Lactobacillus* spp. and *Bifidobacterium* spp. may induce antibodies crossreacting with thyroperoxidase and thyroglobulin [13]. The composition of microbiota appears to play an important role in the susceptibility of mouse strains to GD. Several genera of *Paludibacter* and *Allobaculum*, *Limibacter*, *Anaerophaga*, and *Ureaplasma* were enriched in susceptible C57BL/6J mice compared to the less-susceptible BALB/c strain [14]. Patients with GD or HT produce anti-gliadin, anti-transglutaminase, and anti-yeast (*Saccharomyces cerevisiae*) antibodies. Studies in humans reported a higher abundance of

Box 2. Predominant Phyla of the Gut

In the human gut, Firmicutes and Bacteroidetes are the predominant phyla. In people on high-carbohydrate diets, Firmicutes dominate together with Bacteroidetes of the genus *Prevotella*. Bacteroidetes, with *Bacteroides* as the main genus, predominate when diets rich in protein and fat are ingested [59]. Use of antibiotics, chlorinated water, and non-fermented food decreases microbial diversity. Other important factors include host genetics, geographical region, physical exercise, drugs, age, and disease. The high-fat, high-sugar (Western) diet together with mainly sedentary activity result in a predominance of Firmicutes over other phyla, as well as a lower degree of diversity, compared to a low-fat, high-polysaccharide diet. Changes in microbiota composition can be induced to a substantial extent only via long-term changes in dietary habits. The Firmicutes:Bacteroidetes ratio is influenced by body mass index (BMI). Below a BMI of 33, women have lower ratios than men, whereas above BMI 33 men have higher ratios [60]. Obesity-induced changes in the microbiota may thus be suggested as an additional factor to explain the reported correlation between thyroid diseases and (central) obesity. Studies have reported a lower abundance of Bacteroidetes and a higher proportion of Firmicutes in women than in men. Males exhibit an increased abundance of *Bacteroides* and *Prevotella* compared to females. The lack of sex-related differences in microbiota composition between men and women in postmenopausal women supports a link to estrogen and progesterone levels [61].

The microbiota has a higher metabolic capacity than the human host, and assists in digesting resistant starch to produce a variety of compounds, mainly SCFAs. Butyrate is not only an energy source for enteric microbiota but also displays anti-inflammatory and antitumor effects in the host. The composition of the microbiota determines resistance against colonization by pathogens; thus, it is not surprising that patients suffering from IBDs possess bacterial community structures that are different from those of healthy controls. The most frequently used term to describe the changed composition of microbiota in diseased versus healthy individuals is dysbiosis. This use is under debate because the link between changes in microbiota composition and disease has only been shown in few models (obesity and IBD), and both the causes and effects of disease are called dysbiosis [62]. The link between altered microbiota composition and IBD is hypothesized to be reciprocal. Although the microbiota promotes IBD development, chronic inflammation favors an imbalance in the composition of the microbiota by altering the oxidative and metabolic environment of the intestine.

Prevotellaceae and Pasteurellaceae in patients, whereas Enterobacteriaceae, Veillonellaceae, and Rikenellaceae were significantly lower in the disease group compared to controls [15]. Compared to healthy controls, a decrease in Bifidobacteria and Lactobacillaceae, and an increase in *Enterococcus* spp., were reported in hyperthyroid patients [16].

Intestines of GD patients contain higher levels of antibodies against *Yersinia enterocolica* and *Helicobacter pylori*, greater colonization by yeast, and less colonization by *Bacteroides* compared to healthy guts. Microbiota species diversity in hypothyroid patients is higher than in healthy controls. This may be explained by effects related to the longer gastrointestinal (GI) transit time commonly seen in hypothyroid patients. Low cell turnover, low redox potential, and long transit times were proposed as main reasons for the higher diversity of microbiota in the colon [17]. Although high diversity has been interpreted as positive for human health, negative effects may also result, namely increased protein catabolism, decreased polyphenol conversion and mucus secretion, and decreased epithelial turnover. Increased tryptophan metabolism, on the other hand, promotes the formation of anti-inflammatory indole derivatives. Levels of *Bacteroides* richness and diversity similar to those of healthy subjects have also been reported for HT patients, and differences in 27 genera correlated with clinical symptoms [18]. The microbiota also influences the progression and course of the disease. Mice with Graves' ophthalmopathy (GO) had decreased levels of Bacteroidetes and increased amounts of Firmicutes in their intestines [19]. This finding mirrors the observations in GD patients. *Lactobacillus reuteri* supplementation improved thyroid function in mice by increasing free thyroxine (T_4), thyroid mass, and physiological parameters such as slimness and skin structure [10]. In broiler chickens, lactic acid bacteria supplementation also increased thyroid hormone levels [higher triiodothyronine (T_3):T_4 ratio in blood]. These findings appear to indicate that, despite considerable interspecies differences in taxonomic profiles, specific microbial species have similar functions across species.

Both HT and GD usually start before menopause, and a role for estrogen in modulating the composition of the microbiota may be considered [20]. During perimenopause, progesterone levels

Box 3. Role of the Microbiota in Therapy of Thyroid Diseases

The efficacy of oral L-thyroxine supplementation via its absorption in stomach, duodenum, and jejunum by different transporters may depend on the extent to which the microbiota degrades thyroid hormones by oxidation. Higher microbiota numbers in cases of bacterial overgrowth might require higher doses of L-thyroxine. SIBO is defined as the presence of microorganisms exceeding 10^6 colony-forming units/ml in intestinal aspirates. In hypothyroidism, where the pH of the stomach often increases and gastric motility decreases, reduced protein cleavage in the stomach and bacterial overgrowth may take place [63]. One study suggested that altered colonization of the GI with microbiota, such as due to infections with *Helicobacter pylori*, leads to the requirement for higher doses of L-thyroxine [64]. Because of the need for L-thyroxine dissolution at acid pH, it is likely that the increased pH in patients harboring *Helicobacter pylori* is the main reason for decreased absorption. On the other hand, doses of L-thyroxine therapy to normalize T_4 levels in hypothyroid patients with SIBO did not significantly differ from hypothyroid patients without SIBO [47].

Similarly to L-thyroxine in hypothyroidism, the treatment of hyperthyroidism may also be influenced by the microbiota; in fact, it is now known that more than 30 drugs are metabolized by the intestinal microbiota. However, none of the listed drugs is used in the treatment of thyroid diseases [65]. Secondary bile acids produced by the intestinal microbiota can modulate hepatic **cytochrome P450** (CYP) CYP3A expression, as shown in animal experiments where CYP3A expression levels were reduced in ciprofloxacin-treated conventionally housed mice but not in germ-free animals relative to untreated conventionally housed controls. **Methimazol** (MMI) and PTU are neither substrates of cellular transporters, nor do they undergo intense metabolism by CYP enzymes. However, metabolism of PTU by the action of flavin-dependent monooxygenase (FMO3) generates hepatotoxicants. FMOs are the most important non-CYP enzymes and represent 60% of CYP3A4, the most abundant hepatic CYP enzyme. Bacteria possess a similar enzyme, trimethylamine monooxygenase [66], which can metabolize PTU in the same way as FMO3. An evidence-based study stated that, upon PTU treatment, a higher percentage of patients had subtherapeutic drug levels than under MMI medication. It cannot be excluded that variable extent of metabolism by the gut microbiota plays a role in the less stable action of PTU [67].

decline more than estrogen levels, and the estrogen:progesterone ratio increases. Microbiota may affect estrogen levels by recycling secreted estrogens through β-glucuronidase activity and by the production of estrogenic metabolites. In addition to affecting mineral processing (iodide, selenium, iron, zinc), discussed below, the microbiota may also influence the metabolism of drugs used to treat thyroid disease (summarized in Box 3).

Uptake of Iodide

Iodide (I^-) uptake takes place mainly via the sodium/iodide symporter (NIS), which is regulated and processed in a tissue-specific manner and shows variable cellular localization. Expression of functional NIS protein has been demonstrated in salivary gland, stomach, and breast tissue [21]. Although the NIS is localized at the apical part of the plasma membrane in GI cells, it localizes on the basolateral side in cells of all other tissues. I^--uptake by GI NIS is regulated by intracellular I^- concentrations. In the intestine the Na^+/multivitamin transporter, which is related to NIS and binds I^- with lower affinity, also transports I^-. Another mechanism to accumulate I^- involves the cystic fibrosis transporter (CFTR), which transports along a Cl^- gradient [22] but contributes to I^- transport only to a small extent.

Production of thyroid hormone is influenced by the presence of goitrogens in the food. Thiocyanate and perchlorate compete with I^- uptake by NIS through competitive inhibition [23]. Furthermore, humic acids, nitrates, fluorides, aluminum hydroxide, ferrous sulfate, and sucralfate interfere with I^- uptake, whereas soy, phenobarbital, amiodarone, phenytoin, carbamazepine, rifampicin, propranolol, and glucocorticoids interact with the organification of iodide and the metabolism of thyroid hormones. I^- uptake takes place mainly in the stomach, duodenum, and jejunum, where the microbiota population is lower than in the large intestine. Nevertheless, I^- uptake was decreased in patients with atrophic gastritis, who often present colonization by *Helicobacter pylori*, but not generally following gastric surgery [24,25]. **Inflammatory bowel disease** (IBD) is also a common reason for iodine malabsorption, suggesting that the microbiota of the upper GI tract plays a role in I^- uptake.

Role of the Gut Microbiota in Mineral Uptake and Thyroid Hormone Metabolism

It is unlikely that adverse effects on the microbiota occur at doses of iodine in regular diets, but medical application of high doses of iodide, for instance in I^--containing contrast agents, may

affect the microbiota. Toxicity may be caused by binding of I^- to the amino acids Tyr and His on the outer bacterial membrane, and by oxidation of cytoplasmic and membrane components.

Selenium (Se), iron (Fe), and zinc (Zn) are minerals that support thyroid function. The thyroid gland contains the highest amount of Se per mg tissue in the body [26]. Several proteins involved in thyroid metabolism contain Se, namely glutathione peroxidase, type I, II, and III **iodothyronine deiodinases** (D1, D2, D3), and thioredoxin reductase [27]. Thyroperoxidase contains Fe in the active center, and Zn enhances the activity of D2, the enzyme that converts T_4 to active T_3. It has been shown that thyroid dysfunction is linked to abnormal levels of these minerals. Mothers with goiter had lower iodine, Se, and Fe serum levels than healthy controls [28]. Zn deficiency reduces free T_3 and T_4 levels by 30% in animals [29]. In humans TSH, T_4, and T_3 serum levels are also decreased by Zn deficiency, hypothyroid individuals frequently present with low serum Zn levels [30]. It appears that the relationship between Zn and thyroid metabolism is reciprocal because hypothyroidism induces Zn deficiency and insufficient supplementation with Zn causes hypothyroidism.

These minerals also have prominent roles influencing the gut microbiota. Bacteria compete with the host for Se. Resident microbes of the colon metabolize the Se, which is not absorbed by the host in the upper GI tract [31]. Se increased microbial diversity in mice, with a relative increase in Bacteroidetes and a decrease in Parabacteroidetes [32]. Dietary Se is positively linked with the abundance of *Bifidobacterium adolescentis* in the gut, and Se promotes growth of this genus [33].

Iron is absorbed as Fe (II) mainly in the duodenum, where the pH is acidic (pH ~6.0). In the colon, the availability of absorbable iron is low but the microbiota can increase availability and absorption by the host by lowering the pH through the production of SCFAs. Bacteria possess several high-affinity proteins for Fe, the siderophores (mainly enterobactin), to facilitate uptake [34]. Expression of enterobactin is particularly high in pathogenic bacterial strains. Although severe Fe deficiency limits bacterial growth, a heme-rich diet decreases microbiota diversity in mice. Iron supplementation in humans increased Enterobacteriaceae and Bacteroidetes members, and decreased Lactobacillaceae and Bifidobacteria groups. This shift has been interpreted as the action of inflammation in promoting the **microbiome**, and was accompanied by decreased butyrate and propionate as well as by increased production of lactate and formate [32]. The Fe requirement of Lactobacillaceae is low, and *Bifidobacterium* spp. also do not synthesize siderophores or other iron carriers. A contribution of the microbiota to Fe supply of the host is supported by the finding that differences in microbiota in patients with IBD compared to healthy individuals are more pronounced after oral, but not intravenous, supplementation with Fe [35].

A role of Zn in modulating the composition of the microbiota has only been demonstrated in chicken, where an altered balance between Proteobacteria and Firmicutes in Zn deficiency was noted, as well as a decrease of microbial diversity. Feeding with *Enterococcus faecium* increased serum Zn levels in deficient chickens [36]. In mice, however, acute Zn deficiency did not cause any changes in microbiota phyla types. Zn supplementation in humans has positive effects in preventing diarrhea, inhibiting the growth of pathogenic *Escherichia coli*, and promoting the growth of probiotic strains such as *Lactobacillus* spp. [37]. The above-mentioned studies suggest a negative correlation between Lactobacillaceae and *Bifidobacterium* spp. with dietary iron, and a positive correlation with Se and Zn. Because these phyla are also reduced in HT and GD, it may be hypothesized that regulation of mineral levels might contribute to these diseases.

Although the gut microbiota can produce a variety of neurotransmitters (serotonin, dopamine, noradrenaline, GABA), cortisol, and GI hormones (ghrelin, leptin, glucagon-like peptide 1), *de novo* synthesis of thyroid hormones has not been demonstrated. T_4 is the main secretion product

from the thyroid gland, and can be metabolized in different ways (Figure 2). Apart from deiodination by the action of D1 and D3, T_4 can be conjugated to sulfate (T_4S) or glucuronide (T_4G), and levels of T_4S are low in plasma, urine, and bile because degradation by D1 takes place rapidly. T_4G is rapidly secreted into the bile and can be deconjugated by the microbiota and subsequently reabsorbed by the host. Alternatively, T_4G may bind to bacteria for storage and release at a later time-point. Non-conjugated T_4 can also bind to bacteria in the rat intestine [38]. Similarly to T_4, T_3 is also conjugated and excreted as sulfate and as glucuronide derivatives. T_3S is proposed to serve as a reservoir for iodothyronines, particularly in fetal tissues, and excreted T_3S may be recovered by the action of bacterial sulfatases in the intestine [39]. Microbes, for instance *Escherichia coli,* may serve as reservoir for T3 owing to strong binding to bacterial thyroid-binding protein [40]. An intestinal reservoir may prevent fluctuations of thyroid hormone levels and reduce the need for T_4 supplementation. A study on probiotics showed that application of the probiotic VSL#3® – a mixture of four *Lactobacillus* spp., three *Bifidobacterium* spp., and *Streptococcus thermophilus* – reduced the number of L-thyroxine dose adjustments compared to the control group without probiotics, whereas mean L-thyroxine doses were similar [41]. It was concluded that there is a positive role for probiotics in averting serum hormone fluctuations. However, it must be taken into consideration that the existence of enterohepatic cycling of thyroid hormones after deconjugation and storage in the gut has only been demonstrated in rats. Nonetheless, something similar in humans appears likely. Furthermore, the microbiota possesses an activity comparable to the mammalian deiodinases [42].

The microbiota influences neurotransmitters, for example dopamine, in the brain and regulates the hypothalamus–pituitary axis (HPA) [43]. Because dopamine inhibits TSH secretion, thyroid function may also be affected. It has been reported that germ-free rats have 25% higher TSH levels than controls, and germ-free mice have lower luminal dopamine concentrations [44]. Dopa-

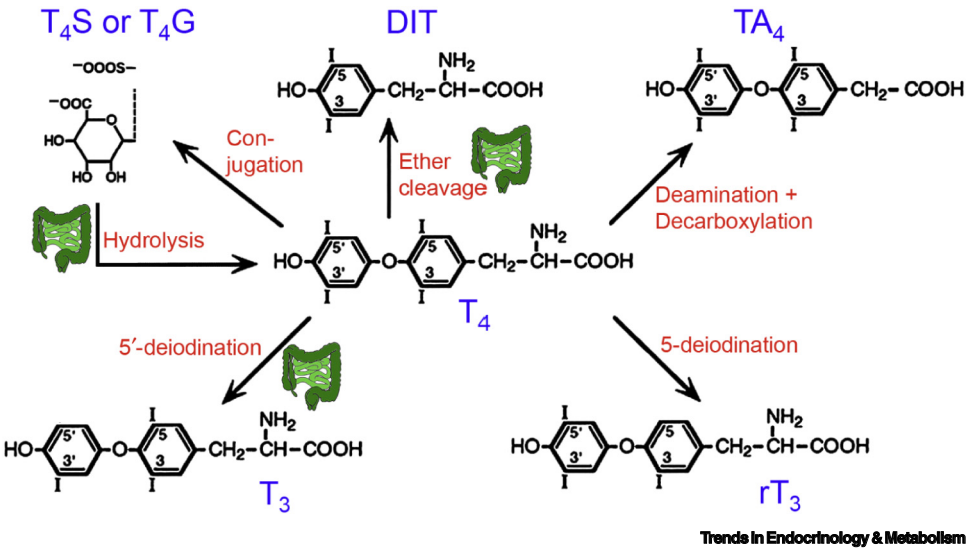
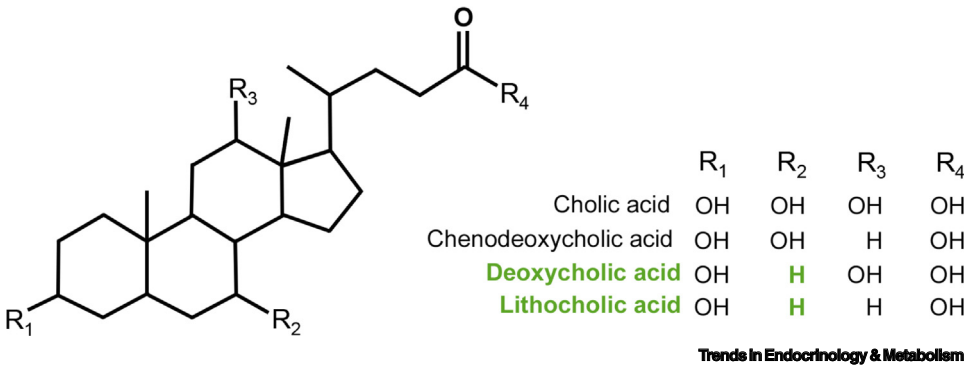


Figure 2. Deiodination by the Action of Type I and Type II Iodothyronine Deiodinases (D1 and D2) on the Outer Ring Activates Thyroxine (T_4) to Triiodothyronine (T_3), the Bioactive form of Thyroid Hormone in the Body. Deiodination by D1 and D3 of the inner ring produces biologically inactive 3,3′,5′-triiodothyronine (reverse T_3). Further deiodination of T_3 or reverse T_3 results in 3,3′-diiodothyronine (T_2). Deamination of T_4 or T_3 by L-amino oxidase and thyroid hormone deaminotransferase produces the acetate analogs tetraiodothyroacetic acid (TA_4) and triiodothyroacetic acid (TA_3). The analogs are devoid of thyroid hormone activity in healthy individuals, but TA_3 is active in patients with thyroid hormone resistance. Reactions that can be performed by the gut microbiota are indicated by the gut pictogram. Abbreviations: DIT, diiodotyrosine; rT_3, reverse T_3; T_4G, T_4 glucuronide; T_4S, T_4 sulfate.



	R_1	R_2	R_3	R_4
Cholic acid	OH	OH	OH	OH
Chenodeoxycholic acid	OH	OH	H	OH
Deoxycholic acid	OH	**H**	OH	OH
Lithocholic acid	OH	**H**	H	OH

Figure 3. Composition of the Most Important Primary and Secondary Bile Acids Involved in the Intestinal Regulation of Thyroid Hormone Metabolism. After deconjugation and decarboxylation, deoxycholic acid and lithocholic acid are formed from cholic acid and chenodeoxycholic acid, respectively. Bacterial products and modifications are indicated in green.

mine inhibits the activity of the anterior pituitary gland, leading to decreased TSH secretion. Even if uptake of dopamine from the gut in general is low, the small amount could have a regulatory function. Decreased luminal dopamine levels could lead to decreased uptake and lack of inhibition of TSH secretion by the pituitary gland in germ-free animals.

Bacterial metabolites that circulate in the blood may include secondary bile acids produced by the microbiota from bile salts (glycine and taurine-conjugated primary bile acids) secreted by the host (Figure 3). Many of the dominant genera in the human gut (*Bacteroides*, *Eubacterium*, *Bifidobacterium*, *Rumicoccus*, *Peptostreptococcus*, *Propionibacterium*, *Clostridium*, *Lactobacillus*, *Escherichia*, *Streptococcus*, and *Methanobrevibacter*) produce secondary bile acids, but clostridia are assumed to be the most active. Deoxycholic acid has a greater antimicrobial action than cholic acid owing to its superior detergent properties. It is hypothesized that the production of antimicrobial agents by the microbiota is a mechanism to prevent bacterial overgrowth. Secondary bile acids are absorbed passively from the colon and cause systemic effects. Bile acids regulate energy metabolism via changes in TSH levels, and total bile acid levels in blood were decreased in patients with subclinical hypothyroidism [45]. The prevalence of primary and secondary bile acids in blood was different in hypo- and hyperthyroidism [46]. In hypothyroidism the secondary bile acid deoxycholic acid dominated, whereas in hyperthyroidism chenodeoxycholic acid was the predominant bile acid. Levels returned to normal under medication. The higher levels of secondary bile acids in hypothyroidism may result from the fact that small intestinal bacterial overgrowth (SIBO) is common in patients with hypothyroidism [47]. Another study confirmed the prevalence of chenodeoxycholic acid in hyperthyroid patients. The authors reported increased levels of this bile acid, whereas the levels of cholic acid were unchanged and those of deoxycholic acid were decreased [48]. Secondary bile acids are furthermore able to regulate intestinal D2, and LPS inhibits intestinal D2 and hepatic D1, and also decreases thyroid hormone receptor expression in the liver [49].

Linking Gastrointestinal and Thyroid Disorders

A link between the GI tract and the thyroid, termed 'thyrogastric syndrome', had already been postulated in the 1950s [50]. Later, the identification of anti-thyroid antibodies in patients with pernicious anemia, synonymous with **autoimmune metaplastic atrophic gastritis** (AMAG), was reported. The coincidence of both diseases may be explained by the common embryonic origin of thyroid follicular cells and gastric mucosal cells because the thyroid gland develops from primitive gut cells [51]. Both cells also share the ability to take up I^- and they express similar peroxidases (gastric peroxidase

and thyroperoxidase). On the other hand, a specific composition of the microbiota could predispose individuals to both diseases. The specific composition could be reduction of Lactobacillaceae and Bifidobacteriaceae or the lack of only one genus of a family. To verify the preferential coincidence of the two diseases, the prevalence of AID in the general population and in individuals affected by an AID was compared. The tendency to develop another AID in patients who already had an AID was estimated as ~25% [52]. Prevalence of AITD in the general population in different countries varies between 0.32 and 3.5% [53]. This worldwide study indicated a prevalence of 0.12–0.8% for rheumatoid arthritis (RA), 0.3–0.57% for type I diabetes mellitus (T1DM), and 0.02–0.11% for ce-

Table 1. Overview of the Prevalence of Autoimmune Disorders (AIDs) in the General Population and in Groups of Patients with Coexisting AID to Identify Associations between AIDs

AID[a]	Prevalence in general population (%)	Patient group with AID[a]	Prevalence (%)	Change of prevalence (fold) compared to general population	Refs
AITD	0.32–3.5	N.a.[b]		1	[53]
		RA	9;24	**35.9**[c]	[68,69]
		T1DM	0.4	0.9	[70]
		CD	2.6; 5.4; 2–7	9.3	[70–72]
		AMAG	30; 9.6	**3.0**	[70,73]
RA	0.12–0.8			1	[53]
		AITD	30	15.7	[74]
		T1DM	1.83	4.2	[75]
		CD	1.12; 2–7	6.2	[72,75]
		AMAG	≪5–28	N.a.	[76]
T1DM	0.3–0.57	N.a.		1	[53]
		AITD	15–30; 20.1	11.8	[77,78]
		RA	2	4.3	[78]
		CD	4–9; 2–11	**28.9**	[72,77]
		AMAG	6–10; 5–10	2.4	[73,77]
CD	0.02–0.11; 0.77; 0.5–8	N.a.		1	[53,79,80]
		AITD	10.3; 26	9.5	[72,81]
		RA	0.5	1.1	[82]
		T1DM	2.9	6.7	[82]
		AMAG	N.a., correlated	N.a.	[83]
AMAG	2–11; 2	N.a.		1	[84–86]
		AITD	40.1; 41.7; 36.2	**21.4**	[54,87,88]
		RA	6.1	13.3	[88]
		T1DM	4	**9.2**	[88]
		CD	9.1	20.2	[88]

[a]Abbreviations: AID, autoimmune disease; AITD, autoimmune thyroid disease; AMAG, autoimmune metaplastic atrophic gastritis; CD, celiac disease; RA, rheumatoid arthritis; T1DM, type 1 diabetes mellitus
[b]N.a., not analyzed.
[c]Maximal increase of a given AID caused by the coexistence of another AID is indicated in bold font.

liac disease (CD). In Western countries, a higher prevalence of AITD (5–15%) has been described [54]. AMAG is reported to affect 2–11% of individuals. Data on the prevalence of the most common AIDs in the general population and in patients with coexisting AID were collected (Table 1). It can be seen that coexisting AITD increases the prevalence of RA and of AMAG more than other coexisting AIDs. The preferential co-occurrence of AITD and AMAG is consistent with a thyrogastric syndrome. Although **dysbiosis** is a known predisposing factor for AIDs in general, colonization with *Helicobacter pylori* has been linked only to AMAG and GD, and disparate reports of an association between *Helicobacter pylori* and HT have been published [51].

Concluding Remarks and Future Perspectives

The gut microbiota has important effects on human health and disease, and an altered composition of the gut microbiota was identified as a factor contributing to HT and GD. The microbiota may influence I^- uptake and enterohepatic cycling of thyroid hormones. Furthermore, there is a pronounced influence of minerals on interactions between host and microbiota, particularly Se, Fe, and Zn. In manifest thyroid disorders, the microbiota may affect L-thyroxine uptake and influence the efficacy and toxicity of PTU. The preferential association of AITD and AMAG may be due to crossreacting antibodies because of their common endodermal origin. It is also possible that the individual microbiota composition of the host, which differs in different parts of the GI tract, favors the development of AITD, raising the prospect that probiotics and other **microbiota-targeted therapies** might be of benefit in thyroid disease (Box 4).

Data on a causative role of the microbiota, on the other hand, are scarce even in diseases with an established link between microbiota changes and disease (e.g., metabolic disease, obesity). To obtain more information on the contribution of the microbiota to AITD, clinical studies need to be initiated with determination of microbiota composition directly in feces of GD patients with different manifestations of psychiatric symptoms, of hyperthyroid patients under PTU medication (in combination with determinations of plasma PTU levels), and of HT and GD patients treated with probiotics. Furthermore, there is no healthy or pathological composition of microbiota because many people can have *Clostridium difficile* in their GI tract but do not experience any problems. Pregnant women in the 3rd trimester have a similar microbiota composition to patients with

Box 4. Microbiota-Targeted Therapy

Changing an altered microbiota composition may be a useful approach for treating or supporting the treatment of not only intestinal but also extraintestinal pathologies. The therapy of sepsis, neuropsychiatric disorders, asthma, and metabolic disorders can benefit from probiotics, prebiotics, symbiotics, postbiotics, and FMT. It has been reported that the effects of metformin in humans, not only in mice, are partly caused via changes in the microbiota [89]. Probiotics, in general containing *Bifidobacterium* spp. and *Lactobacillus* spp., however, did not change susceptibility or improve hypothyroidism in HT patients [41]. The authors studied interactions among probiotics, levothyroxine (LT4) therapy, and pituitary–thyroid axis, and concluded that probiotics are unlikely to be of utility in the treatment of HT patients. The lack of effect is surprising because significantly lower levels of *Lactobacillus* spp. were identified in patients with thyroid nodules and thyroid cancer, suggesting a link between lack of this genus and thyroid disease [90]. It is possible that the duration (2 months) of probiotic treatment in the study by Spaggiari *et al.* [41] was too short to obtain a significant change in the composition of the microbiota. Furthermore, a suboptimal composition of the applied probiotics may explain the observed lack of therapeutic efficacy. In addition to probiotics, FMT has been suggested for the treatment of HT [91]. The influence of dietary changes on the microbiota, on the other hand, is variable, affects only specific individuals, and becomes smaller with increasing time after the switch. Individuals with low microbial diversity profited from a fiber-rich low-calorie diet, whereas individuals with high microbial diversity experienced no change [92]. The authors reported that there was no association between BMI and taxonomic composition, and that dietary supplements including prebiotics, probiotics, and postbiotics have only minimal beneficial effects. In general, it is not clear in which time frame changes of microbiota composition could be expected. Fiber, polyphenols, tryptophan, and glucosinolates (vegetarian diet) increase SCFAs and favor population with Bifidobacteria, whereas carnitine, choline, and fat (animal protein-rich diet) increase the production of secondary bile acids [93]. Although diet-induced changes in the composition of the microbiota take only 1 day in mice, the majority of studies reported changes in a limited number of bacterial genera only after several weeks. A small study, including only 10 volunteers, however, reported dramatic changes after 5 days [94].

Outstanding Questions

Is there a causative link between microbiota composition and thyroid disorders?

Is there also a role for fungi, viruses, and mites in thyroid disorders?

Why are microbiota alterations reported more frequently in HT than in GD?

Do changes in gut microbiota induced by drugs, diet, or supplementation influence the manifestation and progression of thyroid disorders?

Could supplementation with *Lactobacillus* spp., which induce high lactose production and absorption in the gut, cause adverse effects in humans?

metabolic syndrome [55]. The data suggest that for AITD, as with many other diseases, Lactobacillaceae and Bifidobacteria spp. can have positive effects. Current data do not support the hypothesis of a microbiota composition specific for thyroid diseases. A potential role in enterohepatic cycling of iodothyronines may be postulated for Lactobacillaceae, but data on the content of β-glucuronidase activity in these bacteria are conflicting [41]. Until causal relationships have been shown, the benefit of microbiota-targeted therapy appears questionable.

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