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THE ROLE OF THYROID HORMONES ON THE PHYSICAL DEVELOPMENT AND FORMATION OF THE INTESTINAL IMMUNE SYSTEM AND THE RELATIONSHIP BETWEEN THE GUT MICROBIOME AND THE THYROID GLAND.

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ANNOTATION

In this section, we have summarized some materials dedicated to the health of the thyroid gland in its relationship with the intestinal microbiome. Despite the fact that this topic is currently less researched than, for example, microbiome-dependent intestinal health, it is already possible to draw some conclusions regarding the importance of preventing dysbiosis in endocrine health. Preparations containing propionic acid bacteria and organic iodine in a bioavailable (absorbable) form replenish iodine deficiency. The ability of dairy propionic acid bacteria to modulate the microbiota, promote intestinal absorption of micronutrients, and have an anti-inflammatory effect is particularly important in the context of existing research (as indicated below). For example, it is worth noting that P. freudenreichii promotes the growth of bifidobacteria through special bifidogenic growth stimulators, which also contribute to the growth of several lactobacilli [1, 2] and an increase in the level of butyrate [2, 3], synthesized by butyrate-producing bacteria, the levels of which (both species) are significantly reduced in thyroid cancer and nodules (as will be discussed below). Furthermore, the importance of maintaining the intestinal microbiota in a normal state arises from the fact that with increased permeability of the intestine due to dysbiosis, lipopolysaccharides from gram-negative bacteria can enter the bloodstream and contribute to the destruction of the thyroid gland. It has also been shown that SIBO (small intestinal bacterial

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overgrowth) is more commonly observed in autoimmune hypothyroidism (more on this below). All this speaks to the unquestionable importance of gut microbiome health in thyroid health.

Keywords

intestinal mycobiont, thyroxine, triiodothyronine, lactic propionic acid bacteria

Relevance. In recent years, the microbiota has been implicated in numerous chronic diseases, from obesity to inflammatory bowel disease and multiple sclerosis (1). Indeed, it should come as no surprise that it also has profound effects on endocrine organs such as the thyroid gland. The fact of disruption of the intestinal flora with subsequent dysfunction of the thyroid gland was first mentioned in the early 1900s, long before the terms "microbiota" and "microbiome" appeared (2).

Today, microbial sequencing of human fecal samples allows us to measure differences in microbiota composition. A 2014 study found that individuals with hyperthyroidism had significantly lower numbers of Bifidobacteria and Lactobacilli and significantly higher levels of Enterococcus species compared to healthy controls (3). An equivalent study has not yet been conducted on people with hypothyroidism, but given that 90 percent of hypothyroidism cases are autoimmune in nature (4) and the fact that altered microbiota has been implicated in countless other autoimmune diseases suggests that dysbiosis plays a significant role (5).

Microbes recognize a number of different host endocrine molecules, including epinephrine, norepinephrine, sex hormones, and thyroid hormones, and can even alter aspects of their metabolism and virulence in response to these signals (6). Additionally, germ-free rats, raised under sterile conditions and completely devoid of gut bacteria, have smaller thyroid glands than conventionally raised rats, suggesting a critical role for these microbes in thyroid health (7).

INTESTINAL BACTERIA AFFECT THE CONVERSION OF T4 TO T3

As stated above, inactive T4 must be converted to active T3. Approximately 20 percent of this conversion occurs in the gastrointestinal tract. Commensal gut microbes can convert inactive T4 intoT3-sulfate, which can then be restored as active T3 by an enzyme called intestinal sulfatase (8).

Bile acids represent another interesting link between gut bacteria and thyroid function. Primary bile acids are produced in the gallbladder and released into the small intestine after consuming fat. Metabolism of primary bile acids by intestinal bacteria leads to the formation of secondary bile acids. These secondary bile acids increase the activityIodothyronine deiodinase(the main enzyme that converts T4 to T3) (9).

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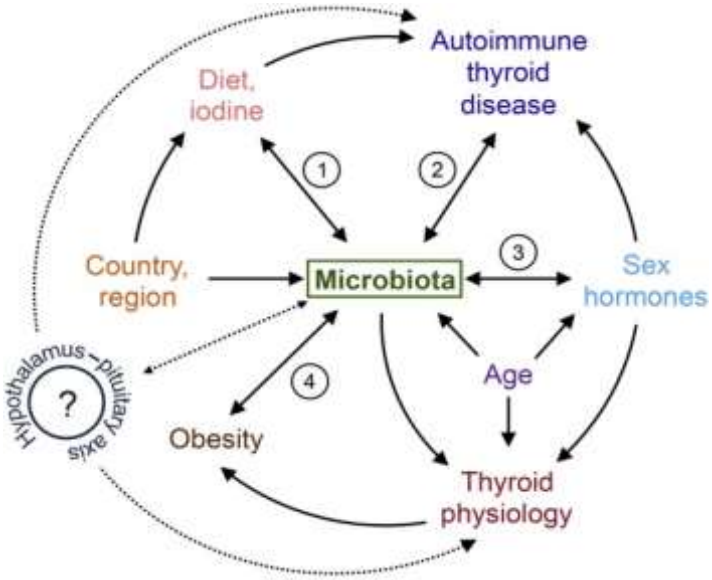
SIBO AND THYROID

Thyroid function is also closely linked to small intestinal bacterial overgrowth (SIBO). In a healthy person, most microbes are concentrated in the large intestine. In SIBO, certain bacteria and archaea are able to colonize the small intestine and multiply, causing bloating, gas, and other unpleasant symptoms.

The connection between SIBO and the thyroid gland is underappreciated. A 2007 study found that among people with a history of autoimmune hypothyroidism, 54% had a positive breath test for SIBO, compared with 5% of controls (10). It is currently unknown whether this relationship is causal.

Because thyroid hormones help stimulate intestinal motility, it is also possible that low motility and constipation provide an environment in the small intestine that is conducive to bacterial overgrowth.

Picture 1. Thyroid physiology includes iodine absorption, hormone recycling, and drug absorption and metabolism. Interactions with the hypothalamic-pituitary axis may involve dopamine, but this is just speculation. The relationships are as follows: (1) Iodine can be toxic to microbiota, and microbiota affects iodine absorption. (2) Patients with autoimmune thyroid disease (AITD) have altered microbiota populations. On the other hand, leaky gut syndrome, caused by bacterial overgrowth, increases the prevalence of AITD. (3) The microbiota recycles estrogen, and the composition of the microbiota differs between men and women. (4) Obesity results in an altered microbiota, and stool transplantation can change the phenotype from obese to lean.



ROLE OF INTESTINAL MICROBIOTA IN THE ABSORPTION OF MINERAL SUBSTANCES AND METABOLISM OF THYROID HORMONES

It is unlikely that adverse effects on the microbiota occur at doses of iodine in normal diets, but medical use of high doses of iodide, such as in contrast agents

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containing I-, may affect the microbiota. Toxicity may be caused by binding of I- to amino acidsTyrAndHison the outer bacterial membrane and 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 of tissue in the body [11]. Several proteins involved in thyroid metabolism contain Se, namely glutathione peroxidase, iodothyronine deiodinases type I, II and III (D1,D2,D3) and thioredoxin reductase (TR) [12]. Thyroperoxidase contains Fe in the active site, and Zn enhances the activity of D2, the enzyme that converts T4 to active T3. Thyroid dysfunction has been shown to be associated with abnormal levels of these minerals. Mothers with goiter had lower serum levels of iodine, Se and Fe than healthy controls [13]. Zn deficiency reduces the levels of free T3 and T4 in animals by 30% [14]. People have levelsTSH, T4 and T3 in serum are also reduced due to Zn deficiency, people with hypothyroidism often have low serum Zn levels [15]. It appears that the relationship between Zn and thyroid metabolism is reciprocal because hypothyroidism causes Zn deficiency and insufficient Zn supplementation causes hypothyroidism.

These minerals also play an important role in the gut microbiota. Bacteria compete with the host for Se. Colonic resident microbes metabolize Se, which is not absorbed by the host in the upper gastrointestinal tract [31]. Se increases microbial diversity in mice, with a relative increase in Bacteroidetes and a decrease in Parabacteroidetes [32]. Dietary Se is positively associated with the abundance of Bifidobacterium adolescentis in the gut, and Se promotes the growth of this genus [16].

Iron is absorbed as Fe(II) primarily 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 host availability and absorption by lowering the pH through the production of SCFAs. Bacteria possess several high-affinity proteins for Fe, siderophores (mainly enterobactin) that promote uptake [17]. Enterobactin expression is particularly high in pathogenic bacterial strains. Although acute iron deficiency limits bacterial growth, a heme (iron)-rich diet reduces microbiota diversity in mice. Iron supplementation in humans increased the abundance of Enterobacteriaceae and Bacteroidetes and decreased the abundance of Lactobacillaceae and Bifidobacteria. This shift was interpreted as the action of inflammation in promoting the microbiome and was accompanied by a decrease in butyrate and propionate, as well as an increase in lactate and formate production [18]. Fe requirement is low in Lactobacillaceae, while Bifidobacterium spp. siderophores or other iron carriers are not synthesized. The contribution of the microbiota to iron supply to the host is supported by the fact that differences in the

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microbiota in patients with IBD compared with healthy individuals are more pronounced after oral, but not intravenous, administration of Fe [19].

The role of Zn in modulating microbiota composition has only been demonstrated in chickens, where changes in the balance between Proteobacteria and Firmicutes have been noted with Zn deficiency, as well as a decrease in microbial diversity. Feeding Enterococcus faecium increased serum Zn levels in deficient chickens [20]. However, in mice, acute Zn deficiency did not cause any changes in microbiota types. Zn supplementation in the human body has a positive effect on preventing diarrhea, inhibiting the growth of pathogenic E. coli and promoting the growth of probiotic strains such as Lactobacillus spp. [21]. The above-mentioned studies indicate a negative correlation between Lactobacillaceae and Bifidobacterium spp. with dietary iron and a positive correlation with Se and Zn. Since these types are also decreased in HT and GD, it is conceivable that regulation of mineral levels may contribute to these diseases.

Although the gut microbiota can produce various neurotransmitters (serotonin, dopamine, norepinephrine, GABA), cortisol, and GI hormones (ghrelin, leptin, glucagon-like peptide 1), de novo synthesis of thyroid hormones has not been demonstrated. T4 is the major secretion product from the thyroid gland and can be metabolized in different ways (Figure 2). In addition to deiodination by D1 and D3, T4 can be conjugated to sulfate (T4S) or glucuronide (T4G), and T4S levels are low in plasma, urine, and bile because degradation of D1 occurs rapidly. T4G is rapidly secreted into bile and can be deconjugated by the microbiota and then reabsorbed by the host. Alternatively, T4G may bind to bacteria for storage and release at a later time point. Unconjugated T4 can also bind to bacteria in the intestines of rats [22]. Like T4, T3 is also conjugated and excreted as sulfates and glucuronide derivatives. It is assumed that T3S serves as a reservoir for iodothyronines, especially in fetal tissues, and the released T3S can be restored by the action of bacterial sulfatases in the intestine [23]. Microbes, such as Escherichia coli, can serve as a reservoir for T3 due to strong binding to bacterial thyroid binding protein [24]. The intestinal reservoir can prevent fluctuations in thyroid hormone levels and reduce the need for T4 supplementation. Probiotic research has shown that the use of VSL#3® probiotic is a mixture of four Lactobacillus spp., three strains of Bifidobacterium spp. and Streptococcus thermophilus - reduced the number of L-thyroxine dose adjustments compared to the no-probiotic control group, while mean L-thyroxine doses were similar [25]. It was concluded that probiotics have a beneficial role in preventing fluctuations in serum hormone levels. However, it should be taken into account that the existence of enterohepatic cycles of thyroid hormones after deconjugation and accumulation in the intestine has only been demonstrated in rats. However, something similar in humans seems

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likely. In addition, the microbiota has activity comparable to mammalian deiodinases [26].

Microbiota influences neurotransmitters such as dopamine in the brain and regulates the hypothalamic-pituitary axis (HPA) [43]. Because dopamine inhibits TSH secretion, thyroid function may also be impaired. It has been reported that germ-free rats have 25% higher TSH levels than control animals, and germ-free mice have lower luminal dopamine concentrations [27]. Dopamine suppresses the activity of the anterior pituitary gland, which leads to a decrease in TSH secretion. Even if the absorption of dopamine from the gut is generally small, this small amount may have a regulatory function. Decreased luminal dopamine levels may result in decreased uptake and lack of inhibition of TSH secretion by the pituitary gland in germ-free animals.

Bacterial metabolites circulating in the bloodstream include secondary bile acids produced by the microbiota from bile salts (glycine and taurine-conjugated primary bile acids) secreted by the host (Fig. 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 Clostridium are considered the most active.Deoxycholic acidhas a greater antimicrobial effect thancholic acid, thanks to its excellent cleaning properties. It is hypothesized that the production of antimicrobial agents by the microbiota is a mechanism to prevent bacterial overgrowth. Secondary bile acids are passively absorbed from the colon and cause systemic effects. Bile acids regulate energy metabolism through changes in TSH levels, and total blood bile acid levels were reduced in patients with subclinical hypothyroidism [28]. The prevalence of primary and secondary bile acids in the blood was different in hypo- and hyperthyroidism [29]. In hypothyroidism, the predominant secondary bile acid is deoxycholic acid, while in hyperthyroidism, the predominant bile acid ischenodeoxycholic acid. Levels returned to normal with medication. Higher levels of secondary bile acids in hypothyroidism may be a consequence of the fact that patients with hypothyroidism often have small intestinal bacterial overgrowth (SIBO) [31]. Another study confirmed the prevalence of chenodeoxycholic acid in patients with hyperthyroidism. The authors reported an increase in the level of this bile acid, while the level of cholic acid remained unchanged and the level of deoxycholic acid decreased [32]. In addition, secondary bile acids are able to regulate intestinalD2, ALPSinhibits intestinal D2 and hepaticD1, and also reduces the expression of thyroid hormone receptors in the liver [33].

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Conclusions. The gut microbiota has important influences on human health and disease, and altered gut microbiota composition has been identified as a contributing factor to HT and GD. Microbiota can influence I-uptake and the enterohepatic cycle of thyroid hormones. In addition, there is a pronounced influence of minerals on the interaction between host and microbiota, especially Se, Fe and Zn. In overt thyroid disease, the microbiota may influence L-thyroxine uptake and influence the efficacy and toxicity of PTU. The preferential association of AITD and AMAG may be due to cross-reacting antibodies due to their common endodermal origin. It is also possible that the individual composition of the host microbiota, which differs in different parts of the gastrointestinal tract, contributes to the development of AITD, raising the possibility that probiotics and other microbiota-targeted therapies may be beneficial in thyroid disease. Data on the causative role of the microbiota, on the other hand, are scarce, even in diseases with an established link between microbiota changes and disease (eg, metabolic disease, obesity). To obtain more detailed information about the contribution of the microbiota to AITD, it is necessary to initiate clinical studies by determining the composition of the microbiota directly in the feces of GD patients with various manifestations of psychiatric symptoms, patients with hyperthyroidism under the influence of PTU drugs (in combination with determination of plasma PTU levels), and also HT and GD patients treated with probiotics. Additionally, there is no clear definition of a healthy microbiota composition yet, because many people may have Clostridium difficile in their gastrointestinal tract without experiencing any problems. Pregnant women in the 3rd trimester have a similar microbiota composition to patients with metabolic syndrome. The findings suggest that in AITD, as in many other diseases, Lactobacillaceae and Bifidobacteria spp. may have positive effects. A potential role in the enterohepatic cycle of iodothyronines can be postulated for lactobacilli, but data on the content of β-glucuronidase activity in these bacteria are contradictory [34]. In conclusion, it is worth noting that research on cause-and-effect relationships within the framework of the topic under consideration should be intensified to better justify microbiota-targeted therapy.

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