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Major influences of the gut microbiota on thyroid metabolism: a concise systematic review

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Abstract

The objective was to discuss the influence of the gut microbiota on the functions of the thyroid gland, elucidating the main aspects of rebalancing intestinal function and its importance in the regulation of thyroid functions. The present study followed a systematic review of the literature in periodicals published between 2010 and 2023. The microbiota of the healthy gastrointestinal system presents around 800 species of bacteria, and a hundred of these microorganisms together with bacteriophage viruses and fungi species characterize each human being, with maximum concentration in the colon. In the presence of dysbiosis, the malfunction of the epithelial barrier leads to intestinal and systemic disorders, mainly immunological and metabolic. The functions of the gut microbiota are fundamental and determinant in the metabolism of nutrients, drugs, and hormones, including exogenous and endogenous iodothyronines, as well as micronutrients involved in thyroid homeostasis. The state of the art of effects of the gut microbiota on the regulation of thyroid functions has not been fully elucidated. The intestinal tract is of great importance for the balance of exogenous and endogenous thyroid hormones, but the analysis of the composition of the microbiota is not an easy task. A recent study revealed that individuals with hyperthyroidism had significantly lower levels of Bifidobacteria and Lactobacilli and significantly higher levels of Enterococcus species compared to healthy controls.

Keywords: Gut microbiota. Dysbiosis. Thyroid Diseases. Autoimmune disease.

Introduction

The microbiota of the healthy gastrointestinal system has around 800 species of bacteria, and a hundred of these microorganisms together with bacteriophage viruses and fungal species characterize every human being, with maximum concentration in the colon **[1]**. This composition is organized into at least three enterotypes depending on various characteristics, including genetic background, immune phenotype, dietary habits, etc **[1,2]**.

The human microbiome has about 3 million genes in the gastrointestinal tract, corresponding to 150 times more than the human genome. The combination of bacterial cells and genes with host cells and genes leads to the conception of a "superorganism". This depends on appropriate interactions between the gut microbiota and the host to achieve and maintain health **[1]**.

In this scenario, the gut microbiota (GM) is essential for the host to ensure digestive and immunological homeostasis **[2,3]**. However, in the presence of dysbiosis, the malfunctioning of the epithelial barrier leads to intestinal and systemic disorders, mainly immunological and metabolic. GM functions are fundamental and determinant in the metabolism of nutrients, drugs, and hormones, including exogenous and endogenous iodothyronines, as well as micronutrients involved in thyroid homeostasis. Thus, there is an important lack of information about the interaction of thyroid metabolism and GM **[2-4]**.

Furthermore, autoimmune thyroid disease is the most frequent autoimmune disorder, and hypo- and hyperthyroidism, often of autoimmune origin, have been associated with bacterial overgrowth and altered

microbiota composition, respectively. Linked to this, thyroid homeostasis is a process that has several steps and may suffer deviations when an essential step is impaired **[5]**.

In this context, the main bacteria that make up the enteric microbiota are beneficial and/or probiotic and pathogenic. As an example of probiotics, there are Bifidobacteria and Lactobacilli (*Bacteroides spp., Bifidobacterium spp., Lactobacillus spp.*, and for the pathogenic ones, Enterobacteriaceae and *Clostridium spp*. are also found in the enteric microbiota, *Eubacterium spp., Fusonbacterium spp., Peptostreptococcus spp., Ruminococcus spp.* **[1,6,7]**.

Because of this, the present study aimed to present the influence of the GM on the functions of the thyroid gland, elucidating the main aspects of rebalancing intestinal function and its importance in the regulation of thyroid functions.

Methods

Study Design

The present study followed a systematic literature review model of publications in journals. The studies followed the systematic review rules – PRISMA (Transparent reporting of systematic reviews and meta-analyses-http://www.prisma-statement.org/).

Search Strategy

A bibliographic search was carried out using search sources made up of electronic resources in the following databases: Latin American and Caribbean Literature in Health Sciences (LILACS), Health Information from the National Library of Medicine (Medline), Web of Science, Scopus, Pubmed and in the Scientific Electronic Library Online (SciELO) published from 2010 to 2023. A total of 45 scientific articles were found, and 27 articles were selected for analysis and composition of the present work. The descriptors used were G*ut microbiota. Thyroid. Metabolism. Thyroiditis. Dysbiosis. Autoimmune disease*. The aforementioned descriptors were found in Health Sciences Descriptors (DECS).

Results and discussion

Based on literary findings on the participation of the gut microbiota (GM) in mechanisms that favor health or disease, dietary patterns interfere with the composition of the microbiota and have relevance in the metabolic modulation and regulation of thyroid functions, for example **[1,2]**. In this sense, the highest proportion of Firmicutes (64%) concerning Bacteroidetes (23%) is related to metabolic disorders. In this context, the proportions between the phyla and the variability of microorganisms are relevant in the physiopathogenesis of diseases **[8]**.

Thus, the identification of genera and species in different experimental models has made it possible to expand knowledge about the metabolic effects of the microbiota **[2,9,10]**. Microorganisms that colonize the intestine can alter gene expression in intestinal mucosal cells and also alter gastrointestinal function. Therefore, diet is a determining factor for healthy colonization **[9]**.

Furthermore, a recent study characterizing the GM in patients with Hashimoto's Thyroiditis (HT) confirmed that patients with HT have altered GM and that the gut microbiota is correlated with clinical parameters, suggesting that microbiome composition data could be used for the diagnosis of the disease **[2,11]**.

In this intestinal condition, it is strongly associated with thyroid function. Hypothyroidism can lead to heartburn, dysphagia, vomiting, dyspepsia, intestinal motility disorder, and constipation. In turn, hyperthyroidism may be associated with diarrhea. In addition, Graves' disease, which is Nonthyroidal illness syndrome (NTIS), is a condition characterized by clinical euthyroidism with low triiodothyronine (T3), total thyroxine (T4), and normal or low stimulating hormone thyroid TSH concentration **[12]**.

In this context, the biomolecule lipopolysaccharide (LPS) stands out, which is part of the cell wall of Gram-negative bacteria and is a trigger of septic shock. It was stated that LPS "is no less endotoxin than an exo-hormone", showing that LPS has similarities to human hormones, for example, LPS has its exposure dependent on endogenous reserves (commensals, Gram-negative bacteria of the gastrointestinal tract), has a transporter protein, interacts with the specific cell receptor, its signaling is specifically modulated by endogenous mechanisms, and the LPS signal interferes with endogenous hormone pathways **[13]**.

Thus, Gram-negative bacteria carrying LPS may participate in the pathogenesis of thyroid function by several mechanisms. In one way, endotoxin together with cytokines inhibits hepatic type I iodothyronine deiodinase (D1), which converts T4 to T3 and induces type II iodothyronine deiodinase (D2) in the mid-basal hypothalamus and anterior pituitary gland [14]. The induction of D2, which converts T4 into T3, in the central nervous system can cause suppression of TRH (thyrotrophic hormone) and TSH (thyroid-stimulating hormone) **[14,15]**.

These effects are limited by excess cytokines. Signaling pathways by IL1, IL 6 (interleukins) and tumor necrosis factor (TNFα) include NF-kB (nuclear factor kappa B) and AP-1 (activator protein 1), which interact with SRC-1 (steroid receptor coactivator-1), thus

decreasing its availability for other pathways. In this sense, SRC-1 in healthy individuals increases the expression of the hepatic D1 gene and its deficit decreases D1 activity **[2,3]**. Furthermore, the thyroid changes observed after combined administration of IL-1α, TNFα, IL-6, and IFNγ (interferon-gamma) are less after LPS administration. Another mechanism responsible for NTIS during infection is the influence of LPS on the thyroid hormone (TR) receptor in the liver. LPS decreases RXR and TR expression in liver extracts by reducing RXR/TR DNA binding **[7]**.

In addition, the Na+/I- symporter (NIS) (Sodium/Iodide symporter) plays an important role in thyroid physiology, participating in the absorption of iodide, which is the limiting factor in the rate of thyroid hormoneogenesis. Thus, the hormone TSH induces the expression of NIS and stimulates its transport to the basolateral membrane of thyrocytes. In turn, iodine inhibits NIS expression and increases NIS protein turnover, which contributes to the reduction of thyroid hormone levels after treatment with large amounts of iodine (Wolff-Chaikoff effect) **[4]**.

The exact role of these changes in thyroid hormone metabolism is not yet established. Some authors postulate that NTIS should be treated with levothyroxine, despite clinical euthyroidism **[16]**. Also, the low concentration of T3 may be associated with lower energy expenditure and be beneficial in severe infections. Therefore, the reaction of the thyroid gland to bacterial LPS may be an adaptive change and an adequate physiological reaction to bacterial invasion **[16]**.

The influence of thyroid hormone on intestinal function depends on its action on enterocytes. Thus, T3 induces intestinal alkaline phosphatase (IAP) and represses lactase gene transcription in these cells **[17]**. SCFAs produced by the microbiota residing in the gut lumen may accompany T3 in these processes. SCFAs (butyrate, propionate, acetate) are used by enterocytes as an energy source and are involved in the regulation of host appetite and glucose level **[17]**.

These SCFAs are mainly produced by Clostridium sp., which belongs to the Gram-positive phylum of Firmicutes bacteria. Most of its effects are exerted via free fatty acid receptors (FFAR) 2 and 3 (formerly G protein-coupled receptors (GPR) 43 and 41), located in the colon **[17]**. Furthermore, they stimulate the release of incretins, Glucagon-like peptide-1 (GLP-1), and tyrosine peptide (PYY) by intestinal L cells. However, SCFAs are absorbed into the bloodstream and are detected by the receptors that are expressed also in immune cells, adipose tissue, and the peripheral nervous system **[6]**.

Furthermore, T4 and T3 sulfation in the liver significantly facilitates deiodination by D1 into inactive rT3 and T2 derivatives **[18]**. In some conditions, such as propylthiouracil treatment, fetal development, selenium deficiency, or NTIS when D1 activity is low, sulfoconjugates can be hydrolyzed to bioactive T4 and T3 due to the expression of sulfatases in different tissues and intestinal bacteria **[19]**.

About 20% of serum T3 is of intestinal origin and T3-sulfate (T3S) is a reservoir that can be recovered by sulfatases. Likewise, the main metabolite of T3 excreted in the biannual pathway - the T3-glucuronide - can be hydrolyzed by the microflora, which enables the enterohepatic cycle (EHC) of thyroid hormone **[5,6]**. Thus, the intestine may be an important site for the production of bioactive thyroid hormones. However, intestinal dysbiosis can reduce the conversion of T3S to T3, causing dysfunction of the enterohepatic cycle in T3. One study suggests that intestinal bacteria are even capable of deiodination of thyroid hormones **[20-23]**.

In maintaining thyroid homeostasis, iodine, and selenium play a key role. What causes a significant reduction in the absorption of these nutrients seems to be related to the rearrangement of the composition of the GM **[24,25]**. In this sense, it was reported that intestinal bacteria for selenium, an essential element of selenoproteins (deiodinase, glutathione peroxidase, etc.), can reduce the availability of selenium in the host. As a corollary of the above, selenium shortage, may decrease the availability of selenoproteins in patients **[26,27]**.

Microbiological Metabolism of Iodothyronines

Iodothyronines are metabolized through different routes. The most important metabolic pathway of iodothyronines is represented by the isoenzymes. Also called deiodinases, they are asymmetrically distributed in all tissues, offering peripheral thyroid homeostasis, and their contribution to the production of triiodothyronine (T3) is relevant **[1,2,19]**.

Furthermore, alternative metabolic pathways may be influenced by the GM. In the liver, glucurono conjugation and sulfo conjugation play an important role in iodothyronine metabolism. Sulfo conjugation increases the rate of deiodination to inactive metabolites, while glucurono conjugation provides a significant amount of conjugated T4 that is secreted into the intestinal lumen via bile flow **[3]**. In this location, bacterial action can interfere with enzymatic activity, therefore the composition of the microbiota influences thyroid homeostasis. In this sense, in humans, it has been proven that fecal suspensions hydrolyze significant amounts of iodothyronine conjugates due to the

presence of anaerobic intestinal bacteria [4].

In this context, the amount of deconjugated T4 enters the general circulation and contributes to the formation of iodothyronines through the enterohepatic cycle [19]. Additionally, gut bacteria can specifically bind to thyroid hormones. Furthermore, due to the excessive role of deiodinases and glucuronidase activities in the economy of iodothyronine, the resident intestinal bacteria (inhibitor of deiodinase activity and source of glucuronidase activity) function as regulators of human thyroid metabolism. Therefore, the occurrence of dysbiosis can substantially affect the metabolism of thyroid hormones [19].

Thyroid function is also closely related to small intestinal bacterial overgrowth (SIBO). In a healthy individual, most microbes are concentrated in the large intestine. In SIBO, certain bacteria and Archaea can colonize the small intestine and proliferate, causing gas and distention, among other troublesome symptoms [25].

In this context, a 2007 study showed that, among people with a history of autoimmune hypothyroidism, 54.0% had a positive breath test for SIBO, compared to 5.0% of controls [24]. As thyroid hormones help to stimulate intestinal motility, it is also possible that poor motility and constipation provide an environment in the small intestine that is conducive to bacterial overgrowth. This may be one of many examples of bidirectional interaction between the host and its resident microbes [24].

Microbiota, Thyroid Autoimmunity, and Thyroxine Uptake

A substantial part of the immune system is concentrated in the intestine, which has more immunoglobulin-secreting cells than any other lymphoid organ [2]. The surface of the intestinal mucosa is the contact site for food antigens and pathogenic and mutualistic bacteria. In this context, exposure to unrecognized antigens can develop inflammatory processes and autoimmune disorders. In addition, the microbiota also modulates cells that maintain tolerance through the induction of specific integrin and chemokine receptors, whose role in thyroid autoimmunity is well known [2].

Thus the lack of microbial stimuli leads to substantial immaturity of the immune system. These alterations may allow auto-aggressive disorders allegedly triggered by different microbiota compositions. Indeed, altered microbiota has been reported in patients with inflammatory bowel disease and/or type 1 diabetes whose autoimmune origin is widely accepted [23]. Added to this, morphological and functional damage to the intestinal barrier was similar in patients with type I diabetes and autoimmune thyroiditis. This suggests a pathogenic mechanism related to altered intestinal permeability and dysbiosis for chronic lymphocytic thyroiditis. However, whether CD4+ pathway imbalance can initiate autoimmune thyroiditis in humans requires further investigation [23].

The bioavailability of a drug depends on its ability to cross the intestinal barrier, which is strongly influenced by the composition of the microbiota. The intestinal barrier consists mainly of enterocytes and the mucus layer, as well as lymphoid tissue [1]. Some authors consider the microbiota to be part of the intestinal barrier, which modulates not only tight junction collection and intestinal permeability, but also enterocyte shape and mucus composition. The intestinal absorption of thyroxine is linear in the first hour after ingestion and varies between 62.0 and 82.0% of the ingested dose. The ability to cross the cell membrane is critical to the pharmacokinetics of thyroxine, as thyroid hormones are lipophilic molecules [1].

In this sense, some disorders of the intestinal tract are associated with different microbiota profiles and an increased need for thyroxine [2]. Therefore, patients with celiac disease (CD) have fewer lactobacilli and bifidobacteria compared to controls, and some bacterial species belonging to the genera Lactobacillus and Bifidobacterium may protect epithelial cells from gliadin-dependent damage [17].

Despite the absence of studies on thyroxine absorption in individuals with different microbiota profiles, T4 malabsorption clearly shown in CD may recognize a different microbiota composition as a pathogenic cofactor [6]. One study demonstrated the occurrence of intestinal dysbiosis in patients with hypochlorhydria. This is potentially relevant in that an increased need for thyroxine has been described in patients with gastric atrophy [18]. Although the increase in T4 dose in these patients is due to the altered biochemical status of the hormone at higher gastric pH, dysbiosis may be responsible for thyroxine malabsorption [2].

Conclusion

The state of the art of effects of the gut microbiota on the regulation of thyroid functions has not yet been fully clarified. The intestinal tract is of paramount importance for the balance of exogenous and endogenous thyroid hormones, but the analysis of the composition of the microbiota is not an easy task. However, some experimental evidence, as well as association studies, mainly on autoimmunity processes

and iodothyronine metabolism, seems to be promising for other achievements. In this sense, microbial sequencing of human fecal samples allows us to measure compositional differences in the microbiota. Thus, a recent study revealed that individuals with hyperthyroidism had significantly lower numbers of Bifidobacteria and Lactobacilli and significantly higher levels of Enterococcus species compared to healthy controls. No equivalent study has been carried out in individuals with hypothyroidism, given that a significant percentage of cases of hypothyroidism are autoimmune and an altered gut microbiota (dysbiosis) is strongly related to this fact.

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