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VIEWPOINT

Does microbiota composition affect thyroid homeostasis?

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Abstract The intestinal microbiota is essential for the host to ensure digestive and immunologic homeostasis. When microbiota homeostasis is impaired and dysbiosis occurs, the malfunction of epithelial barrier leads to intestinal and systemic disorders, chiefly immunologic and metabolic. The role of the intestinal tract is crucial in the metabolism of nutrients, drugs, and hormones, including exogenous and endogenous iodothyronines as well as micronutrients involved in thyroid homeostasis. However, the link between thyroid homeostasis and microbiota composition is not yet completely ascertained. A pathogenetic link with dysbiosis has been described in different autoimmune disorders but not yet fully elucidated in autoimmune thyroid disease which represents the most frequent of them. Anyway, it has been suggested that intestinal dysbiosis may trigger autoimmune thyroiditis. Furthermore, hypo- and hyper-thyroidism, often of autoimmune origin, were respectively associated to small intestinal bacterial overgrowth and to changes in microbiota composition. Whether some steps of this thyroid network may be affected by intestinal microbiota composition is briefly discussed below.

Keywords Intestinal microbiota · Selenium · Thyroxine malabsorption · Autoimmune thyroiditis · Deiodinase · Dysbiosis

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Introduction

Intestinal tract contains about 800 bacteria species, both anaerobes and aerobes, and about one hundred of that characterize each human being. They are distributed in a progressive fashion in the gut being lesser represented in the stomach and duodenum, increased in jejunum and ileum, then reaching the maximum concentration in the colon. Along with bacteriophage viruses and fungal species, they constitute the intestinal microbiota [1]. Its composition is clustered in at least 3 enterotypes [2] depending on several features including genetic background, immune phenotype, dietary habits, etc. [3]. Relatively simple at birth, microbiota composition increases its complexity with time but remains substantially stable in adult life being modified, however, by long-term diet changes, drug interference (anti acid or immunosuppressive treatments), and regional or systemic pathologic conditions [1]. Microbiota is essential for the host to develop and to maintain immunologic and digestive homeostasis [4]. In fact, in germ-free (GF) rats, a model of microbiota-free animals, the lack of microbiota is associated to reduced intestinal surface areas with shorter villi, changes in mucus layer and permeability [5]. Also the immune system is compromised in GF animals with reduced B and T cells production both in the lamina propria and in lymph nodes and spleen [6]. It is not surprising that, when microbiota homeostasis is impaired and dysbiosis occurs, the malfunction of epithelial barrier may ensue and local and general disorders may develop. A pathogenetic link with dysbiosis has been described for obesity, type II diabetes, and inflammatory bowel diseases as well as autoimmune disorders like multiple sclerosis, type I diabetes, and rheumatic diseases [7]. Autoimmune thyroid disease is the most frequent autoimmune disorder and hypo- and

hyper-thyroidism, often of autoimmune origin, were associated to bacterial overgrowth [8] and to a different microbiota composition, respectively [9]. So far, the possible interference of microbiota subtype on the whole thyroid equilibrium is an intriguing issue (Fig. 1). However, thyroid homeostasis is a finely tuned multistep process which may be perturbed only when an essential step is impaired. Whether some steps of this thyroid network may be affected by intestinal microbiota composition is discussed below.

Microbiota composition and thyroid-related micronutrients

Iodine and selenium have a key role in maintaining thyroid homeostasis. Gastrointestinal absorption of these two nutrients is, as yet, incompletely understood [10, 11]. What we know is neither severe malabsorption [10] nor bariatric surgery [12], which causes a significant reduction of absorbent mucosa and a rearrangement of microbiota composition, seems to stably change urinary iodine excretion, a reliable measure of iodine intake and status. Contrasting evidence, however, indicates a significant early reduction of radioiodine uptake in kanamicin-treated rats [13]. The hierarchically arranged iodination process in the body and the paucity of data prevented from drawing conclusions. On the contrary, it has been reported that an avidity of intestinal bacteria for selenium, essential element of selenoproteins (deiodinase, glutathione peroxidase, etc.), is able to reduce the availability of selenium in the host. This, in turn, under selenium shortage, may lower the availability of selenoproteins in the host. Whether, under adequate selenium supply, such a competition has any physiologic role in humans is not known [11]. Therefore, microbiota composition appears to have very little effect, if any, on the metabolism of these nutrients.

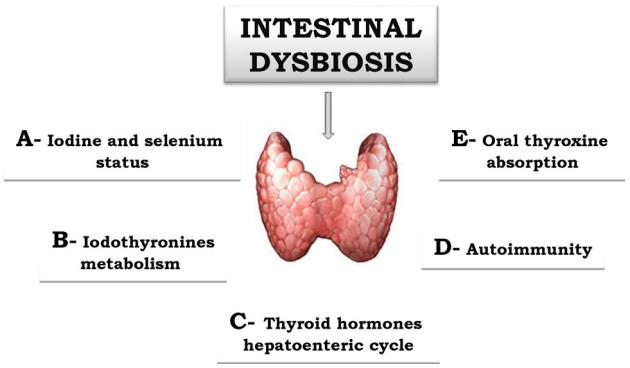

Fig. 1 How the dysbiosis may influence the fate of endogenous and exogenous iodothyronines: *A–C* affecting iodothyronines synthesis, metabolism, and catabolic pathways, *D* triggering thyroid autoimmunity, *E* interfering with oral thyroxine absorption rate

Microbiota composition and metabolism of iodothyronines

Iodothyronines are metabolized via different interrelated pathways. The most important metabolic pathway of iodothyronines is represented by deiodinating isoenzymes. Deiodinases, asymmetrically distributed in all peripheral tissues, warrant peripheral thyroid homeostasis. Type 2- and 3-deiodinase activities have been detected on rat intestinal wall, being higher in rat fetuses than in adults, possibly because of the inhibition exerted by the resident intestinal microflora [14]. Deiodinase activity was next identified in the human intestine [15], and authors suggested that owing the large surface, its contribution to the whole body triiodothyronine (T3) pool may be relevant. Even alternative metabolic pathways may be influenced by intestinal microbiota. In the liver, glucuronoconjugation and sulfoconjugation play a major role in iodothyronine metabolism. Sulfoconjugation increases the rate of deiodination to inactive metabolites, whereas glucuronoconjugation provides a significant amount of conjugated T4 which is secreted into the intestinal lumen through the biliar flow [16]. On this site, bacterial action may deeply affect the enzymatic activity and thus microbiota composition may be involved in a crucial path of thyroid homeostasis. In rats and humans, it has been proven that fecal suspensions hydrolyze significant amounts of iodothyronines conjugates because of the presence of obligate anaerobic intestinal bacteria, normal constituents of intestinal microflora [17]. In fact, most of glucuronidase activity is of bacterial origin [17]. The amount of deconjugated T4, which is the naive form of the hormone, re-enters in the general circulation and contributes to the iodothyronines pool through the hepatoenteric cycle [18]. This mechanism seems to be a limiting factor for thyroid hormones homeostasis in rats [18], while in humans, the exact role of deconjugated thyroxine was never quantitatively ascertained. Intestinal bacteria may also specifically bind thyroid hormones and may even compete with albumin in a study in rats [19]. It is intriguing that, using a mathematical model, slow and fast exchanging compartments were identified; the location of the fast compartment has been recognized in liver and kidneys T4 and T3 pools, whereas the slow exchange T4 and T3 pool may be represented by the intestine [20]. The authors conclude that the amount of intestinal exchangeable T3 or T4 in rats is the second reservoir of iodothyronines, just after the thyroid gland [20]. Due to the overwelming role of deiodinases [21] and glucuronidase activities on the iodothyronine economy, the

role of resident intestinal bacteria (inhibitor of deiodinase activity and source of glucuronidase activity) may represent an unexplored regulator of human thyroid metabolism. In this view, the dysbiosis might substantially affect thyroid hormone metabolism, but this assumption awaits further evidence.

Microbiota and thyroid autoimmuniuty

In mice and humans, the intestine houses a large part of the immune system, and the gut possesses more immunoglobulin-secreting cells than any other lymphoid organ [22]. The surface of the intestinal mucosa is the contact site for dietary antigens, pathogenic bacteria, and mutualistic microflora as well and its integrity prevents environmental agents from entering sub mucosa [22]. Exposure of sub mucosal immune cells to unrecognized antigens, may lead to the development of inflammatory and even autoimmune disorders [23]. Therefore, a balance between protective reactions and tolerance is required to maintain intestinal homeostasis. This ability is driven by intestinal antigen-presenting cells which, having co-evolved with microbiota, are able to distinguish between pathogens and normal intestinal flora [24]. Microbiota also modulate dendritic cells which maintain oral tolerance through the induction of specific integrin and chemokine receptors [25], whose role in thyroid autoimmunity is well known [26]. The lack of microbial stimuli as in germ-free animals leads to substantial immaturity of immune system. Other cells (neutrophils, macrophages, and natural killer), involved in the so-called innate immunity too, seem to be deficient in number and/or function in germ-free mice [24]. The immune adaptive homeostasis also appears to be impaired in this mice's model: gut-associated B cells are significantly reduced, also showing an impaired immunoglobulin production. Similarly, the balance between the T cells subsets is preferentially directed toward the Th2 response [6]. These alterations may enable autoaggressive disorders allegedly triggered by different microbiota compositions. In fact, altered microbiota has been reported in patients with inflammatory bowel disease and/or type 1 diabetes [7] whose autoimmune origin is widely accepted. Interestingly, in humans, a morphological and functional damage of the intestinal barrier was similar in patients bearing type 1 diabetes [27] and with autoimmune thyroiditis [28]. This suggests a pathogenetic mechanism related to the alteration of intestinal permeability and dysbiosis for chronic lymphocytic thyroiditis. In non-obese diabetic mice with thyroiditis, a polarization toward a prevalent Th1 and/or Th17 pathway [29, 30] has been reported. An activation of Toll-like receptors in the development of thyroiditis [31] as well as a protective inhibitory effect of Treg cells [32] have been also reported in this model. However, whether a similar mechanism (i.e., CD4+ Th pathways imbalance) can even initiate an autoimmune thyroiditis in humans requires more investigations [25].

Microbiota interference with thyroxine absorption

Bioavailability of a drug greatly depends on its ability to cross the intestinal barrier whose integrity and function is influenced by microbiota composition. Intestinal barrier is mainly constituted by enterocytes and the mucus layer as well as lymphoid tissue represented by a quite complex network of immune cells [1]. Mucus layer, produced by goblet cells, may vary in composition, fluidity, and electric properties [5]. The pivotal role of mucus thickness and composition in protecting the intestinal barrier has been described [33]. Some authors also consider microbiota as a part of intestinal barrier which modulates not only the gathering of tight junctions and intestinal permeability but also the shape of enterocytes and the mucus composition [5]. This role is evident in germ-free mice in which enterocytes turnover is slowed and villi are shorter with reduced intestinal crypts leading to a reduction of total intestinal surface area [5]. In this animal model, altered permeability with impaired traffic of macromolecules and modified ions secretion leads to a variation of mucus composition and thickness [33]. The mutualistic alliance of these co-evolved components, thus, seems to modulate nutrients and drugs absorption.

Oral thyroxine is considered a low permeability drug from Biopharmaceutics classification system [34] mainly absorbed and possibly reabsorbed from the hepatoenteric cycle into circulation in the upper intestinal tract [19]. The intestinal absorption of thyroxine is linear in the first hour after ingestion [35] and ranges between 62 and 82 % of the ingested dose [19]. The ability to cross the cell membrane is key for the pharmacokinetics of thyroxine. Although thyroid hormones are considered lipophylic molecules, the presence of an alanine side chain is a barrier to the efficient passage through the central part of the double hydrophobic lipid status [34]. Thyroxine, in fact, is taken up by target cells through different mechanisms: (a) by specific transporters; (b) by multispecific transporters (which also transports aromatic amino acids and steroids); and (c) by passive diffusion [36]. However, whether all these mechanisms are operating and what may be their contribution to intestinal thyroxine transport is not well established. It is well known, however, that some disorders of the upper intestinal tract are associated to different microbiota profiles [37] and concurrently to an increased need for thyroxine [38–41]. Patients with celiac disease (CD) have fewer lactobacilli and bifidobacteria as compared to

controls, and some bacterial species belonging to the genera Lactobacillus and Bifidobacterium may protect epithelial cells from gliadin-dependent damage [37]. Whether an altered microbiota profile is the cause or the consequence of CD in these patients is still unclear. An important role for colonic metabolism of lactose in patients with lactose intolerance (LI) has been also claimed [42]. Despite the absence of studies dealing with the absorption of thyroxine in subjects with different microbiota profile, the T4 malabsorption clearly shown in CD and LI [38, 39] may recognize a different microbiota composition as a pathogenic cofactor. Recently, an intestinal dysbiosis has been shown in hypochlorhydric patients [43]. This is potentially relevant in that an increased need for thyroxine has been described in patients with gastric atrophy [44]. Although the increased T4 dose in these patients is mainly due to the altered biochemical status of the hormone at higher gastric pH, dysbiosis may represent an additional source of thyroxine malabsorption.

Concluding remarks

The state of art of microbiota effects on thyroid economy is far from being fully clarified. As described above, the upper intestinal tract is crucial for the whole balance of both exogenous and endogenous thyroid hormones but, at this level, the analysis of microbiota composition is not an easy task. However, some experimental evidence as well as association studies, chiefly about autoimmunity processes and iodothyronines metabolism, seems to be promising of further achievements. Owing to microbiota's distribution and function, the outbreak of studies on this subject may offer a tool for the understanding of some pathogenetic processes in patients with thyroid disorders.

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