Casual Friday Series

Mechanics of Optimal Thyroid Function III

A BIOGENETIX CLINICAL PRESENTATION

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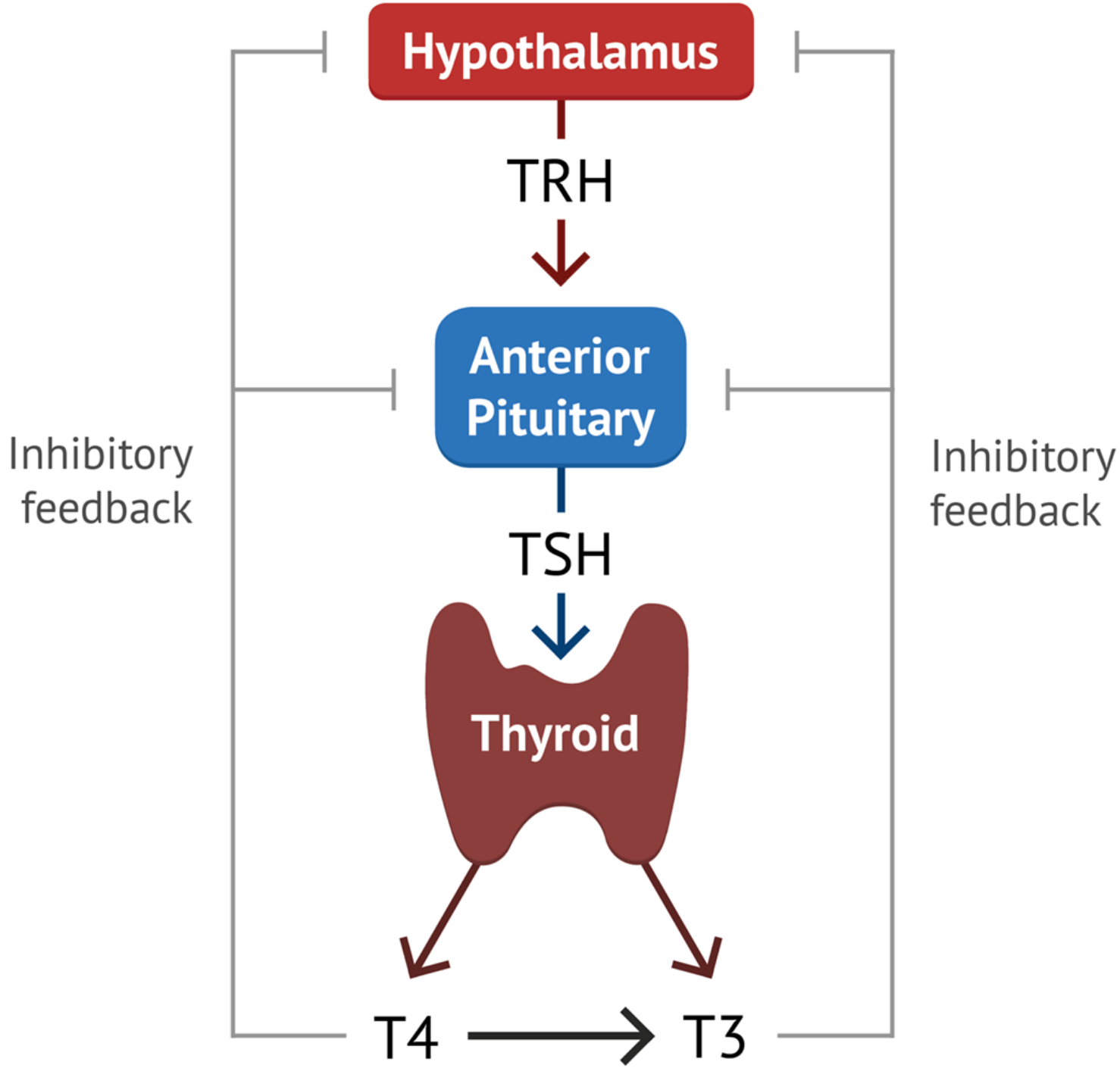
Hypothalamus
TRH
Anterior Pituitary
TSH
Thyroid
T4
T3
Inhibitory feedback
Inhibitory feedback

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Functional Lab Ranges

TSH: 1.5-2.0 / 1.8-3.0
T4: 6-12
Free T4: 1.3-1.8
T3 total: 100-180
Free T3: 3.2-4.2
T3 Uptake: 32-38 / 28-34
Reverse T3: 9-35
TBG: Path Lab Range
TPO Ab: 0
Thyroglobulin Ab: 0

* Updates are made as new and additional information becomes available.

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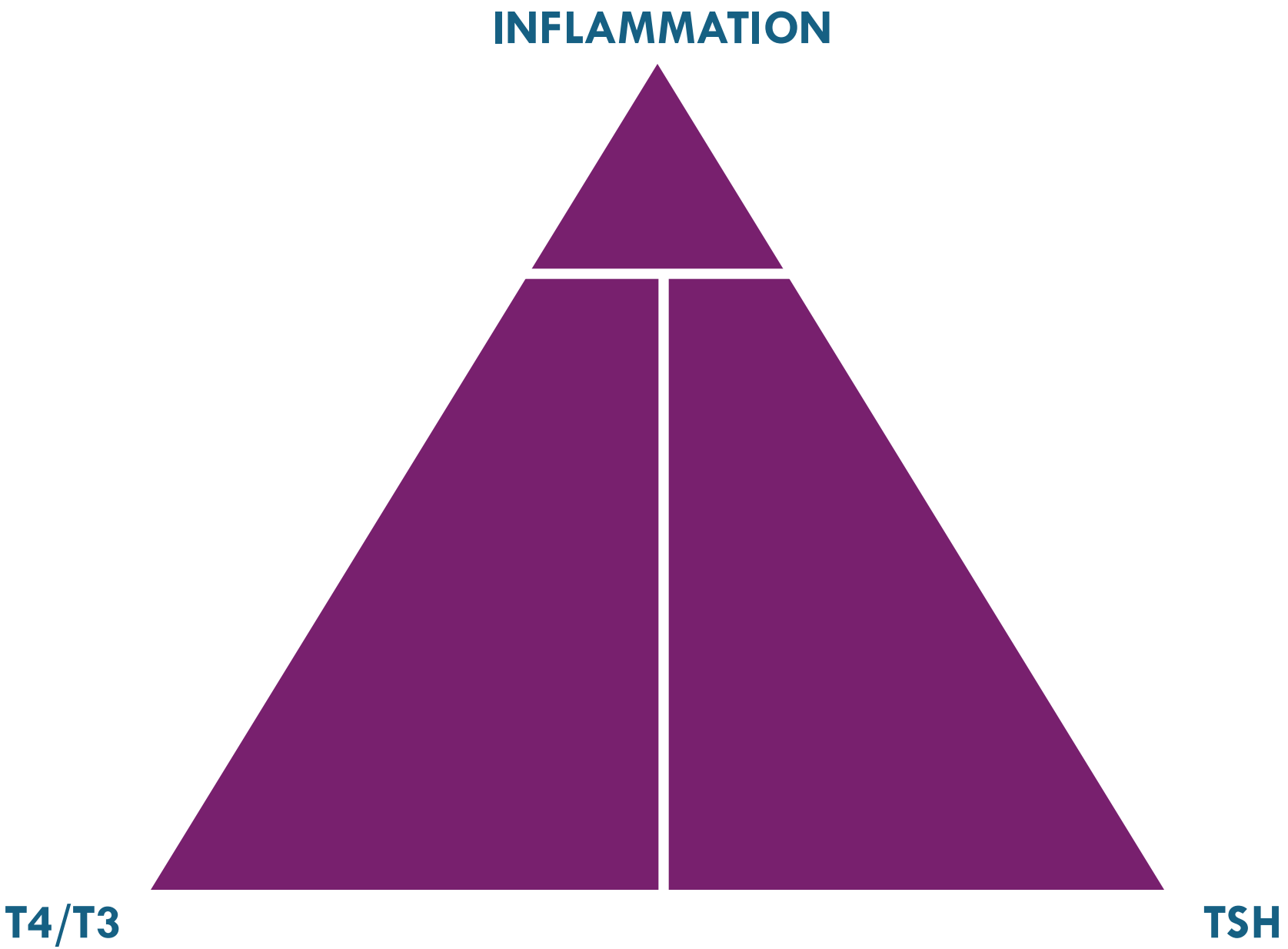
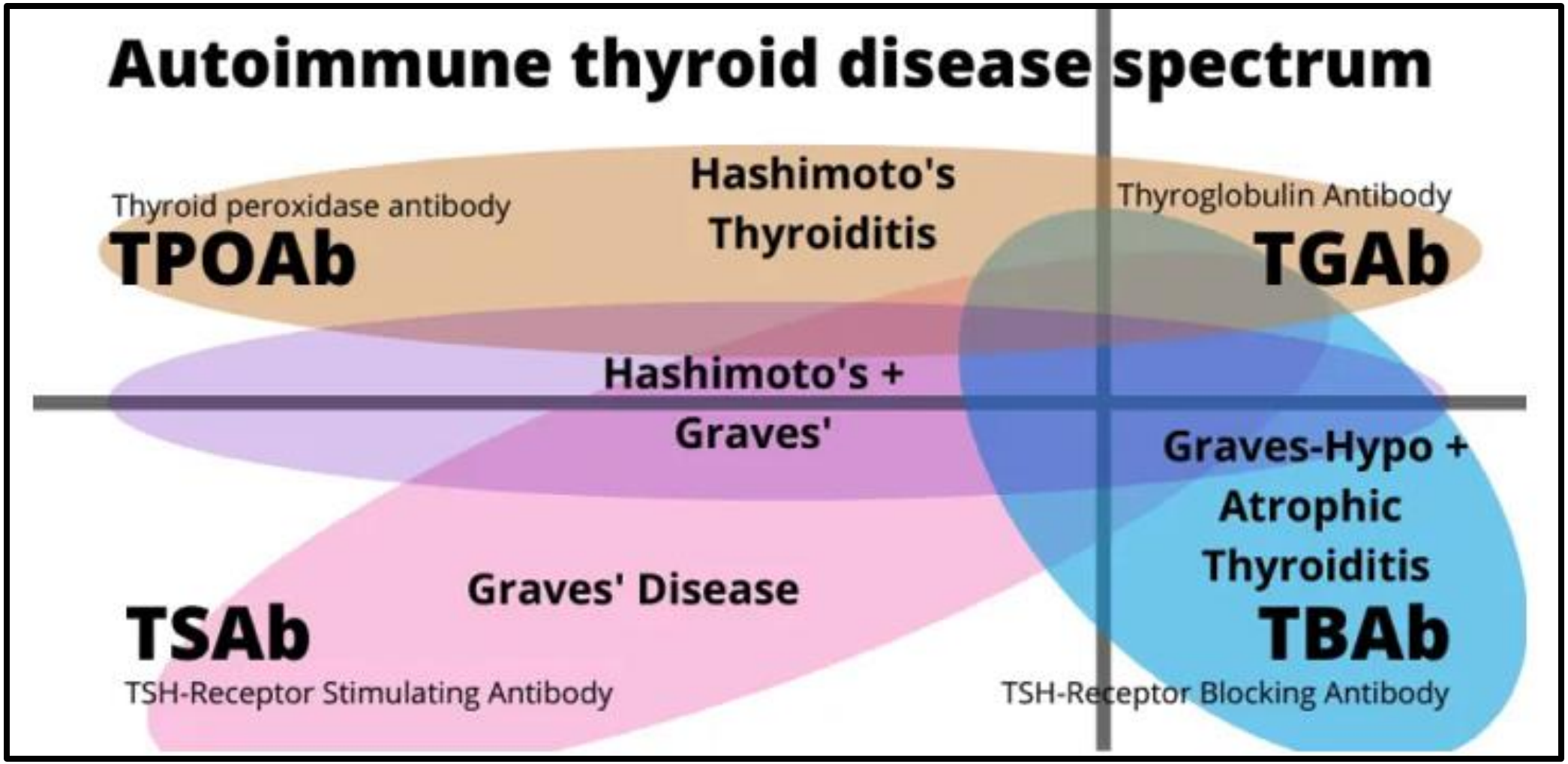
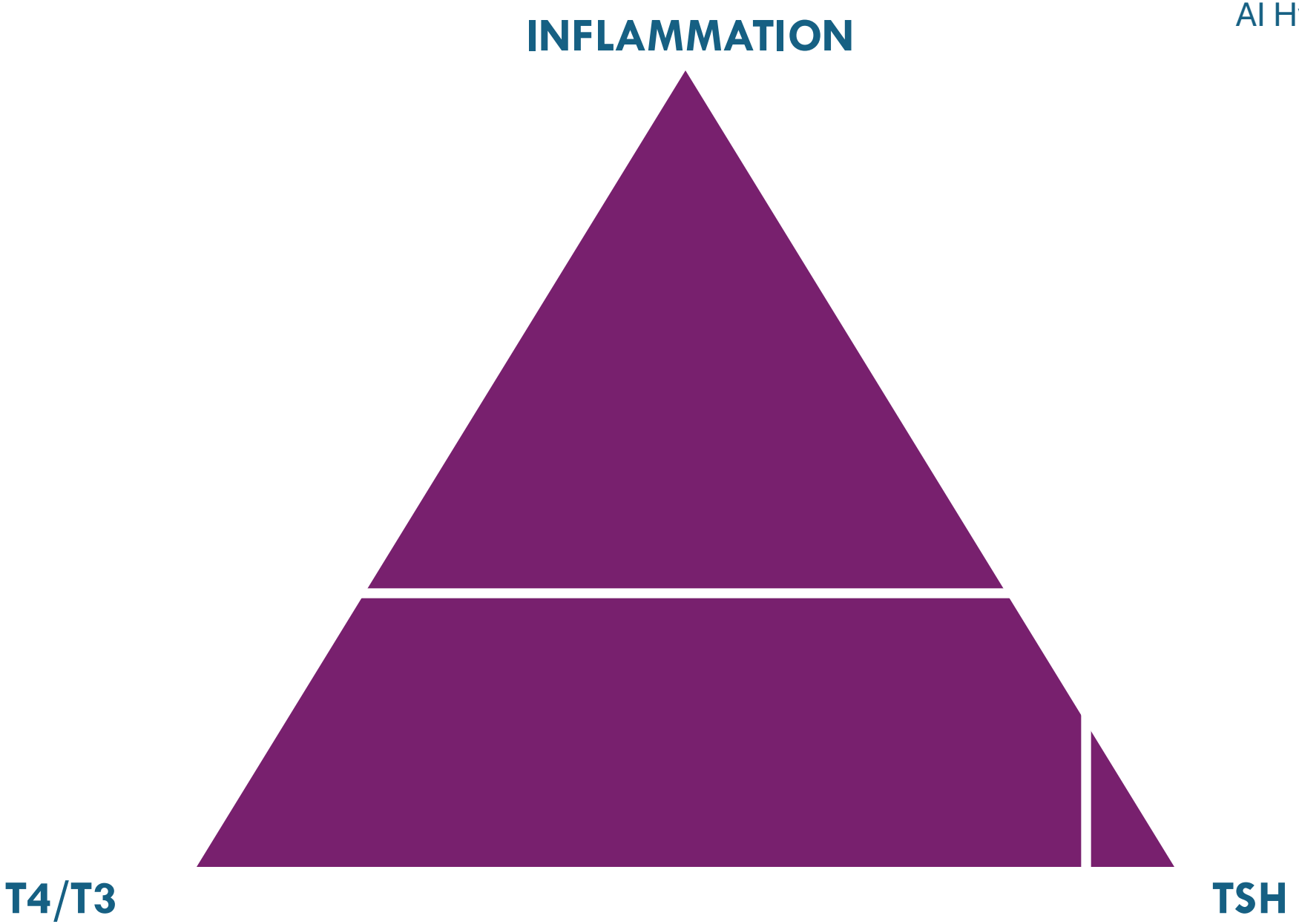
Euthyroid

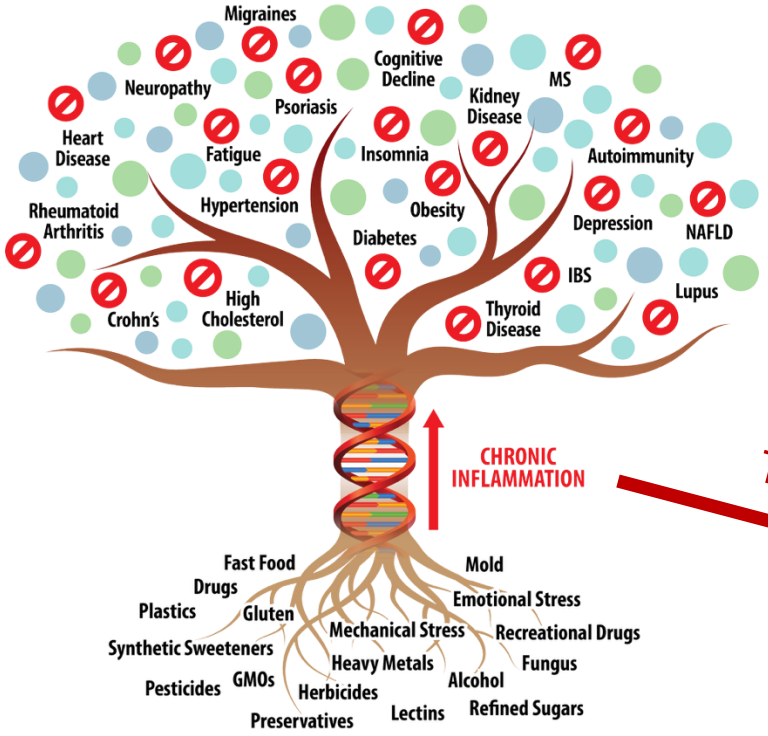




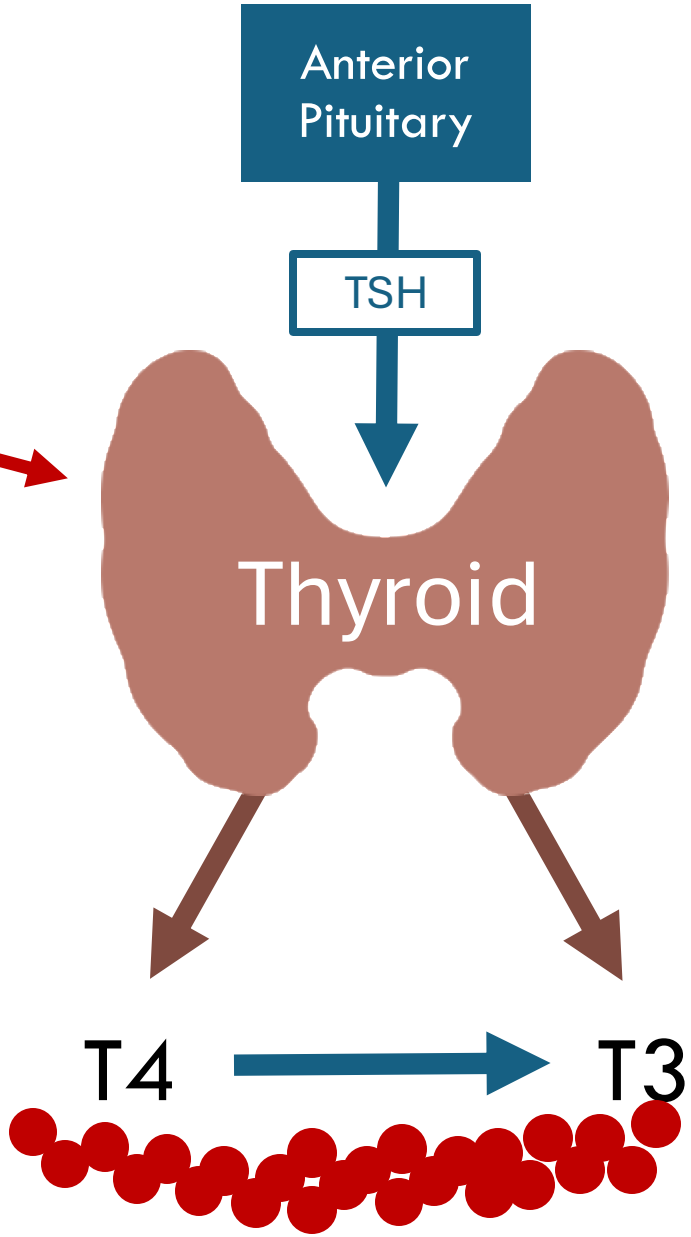
https://thyroidpatients.ca/2020/04/05/remissions-and-fluctuations-trab/


INFLAMMATION
T4/T3
TSH

AI Hyperthyroid



TSI/TSAb



TSH: LOW
T4: HIGH
T3: HIGH

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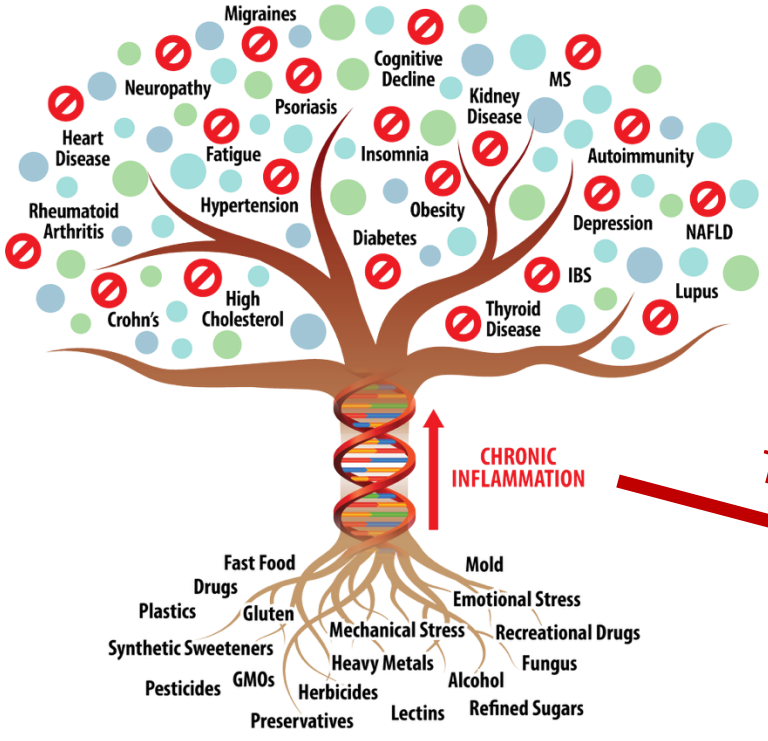
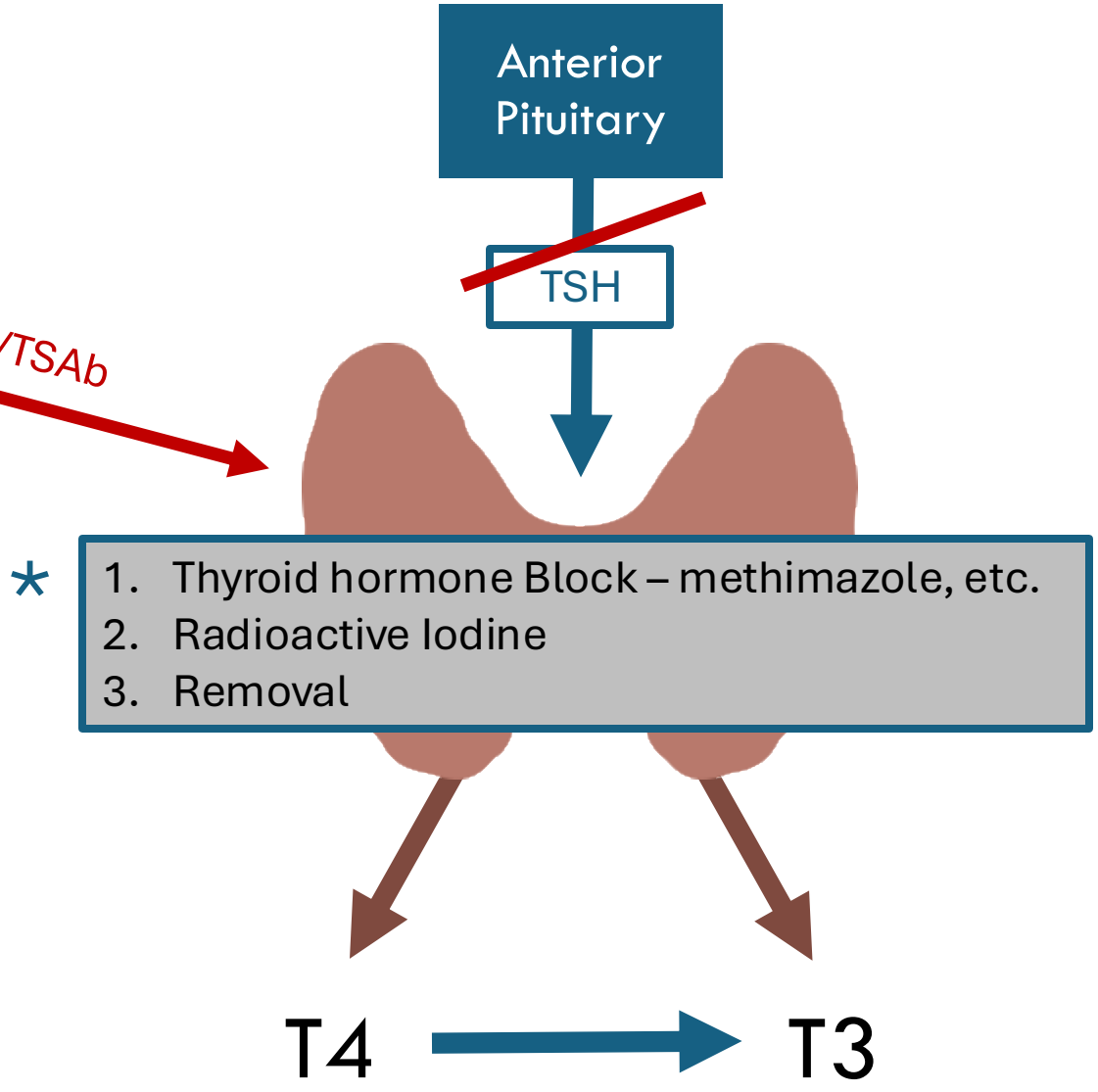


TSI/TSAb



*

TSH: LOW
T4: HIGH
T3: HIGH

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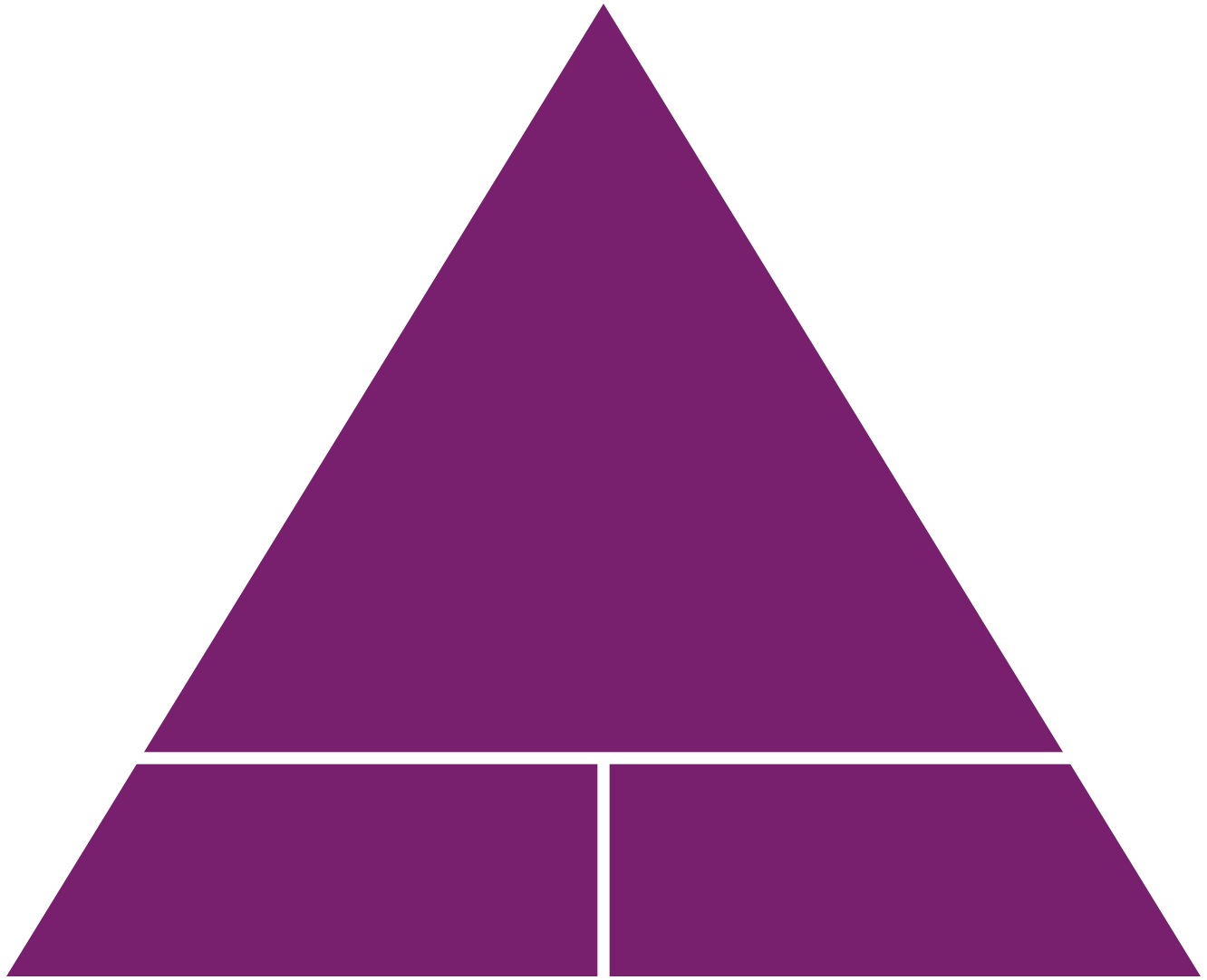
AI Hyperthyroidism
Radiate/Remove
+Medicate



INFLAMMATION

AI Hyperthyroidism
Block/Radiate/Remove
+Medicate
*Lifestyle Intervention

T4/T3

TSH

Nutrients. 2020 Jun 12;12(6):1769. doi: 10.3390/nu12061769

Thyroid-Gut-Axis: How Does the Microbiota Influence Thyroid Function?

Jovana Knezevic [1], Christina Starchl [1,*], Adelina Tmava Berisha [2], Karin Amrein [1]

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PMCID: PMC7353203 PMID: 32545596

Intestinal bacteria play a role in vitamin synthesis (vitamin K, folic acid, vitamin B2, B3, B5, B6, B7, and B12 [6,7], digestion of dietary fibers, regulation of the immune response, and mental disorders [8]. In regard to nutrition, the composition of the microbiota can be positively influenced by dietary fibers and other probiotic factors. For example, a rodent study showed that a change from a low-fat and high-fiber diet to a "Western diet" (high sugar, high fat, low fiber) made a difference in their microbiota composition after just one day [5]. David et al. illustrated changes in the microbiota in 10 participants after only five days of eating either a plant-based or animal-based diet [9]. Dietary fibers are of great importance to the intestine as their fermentation and the resulting short chain fatty acids (SCFAs) serve as an energy source for the enterocytes [5,10]. In addition, SCFAs (especially butyrate) impact the immune regulation and have anti-inflammatory effects [10,11].

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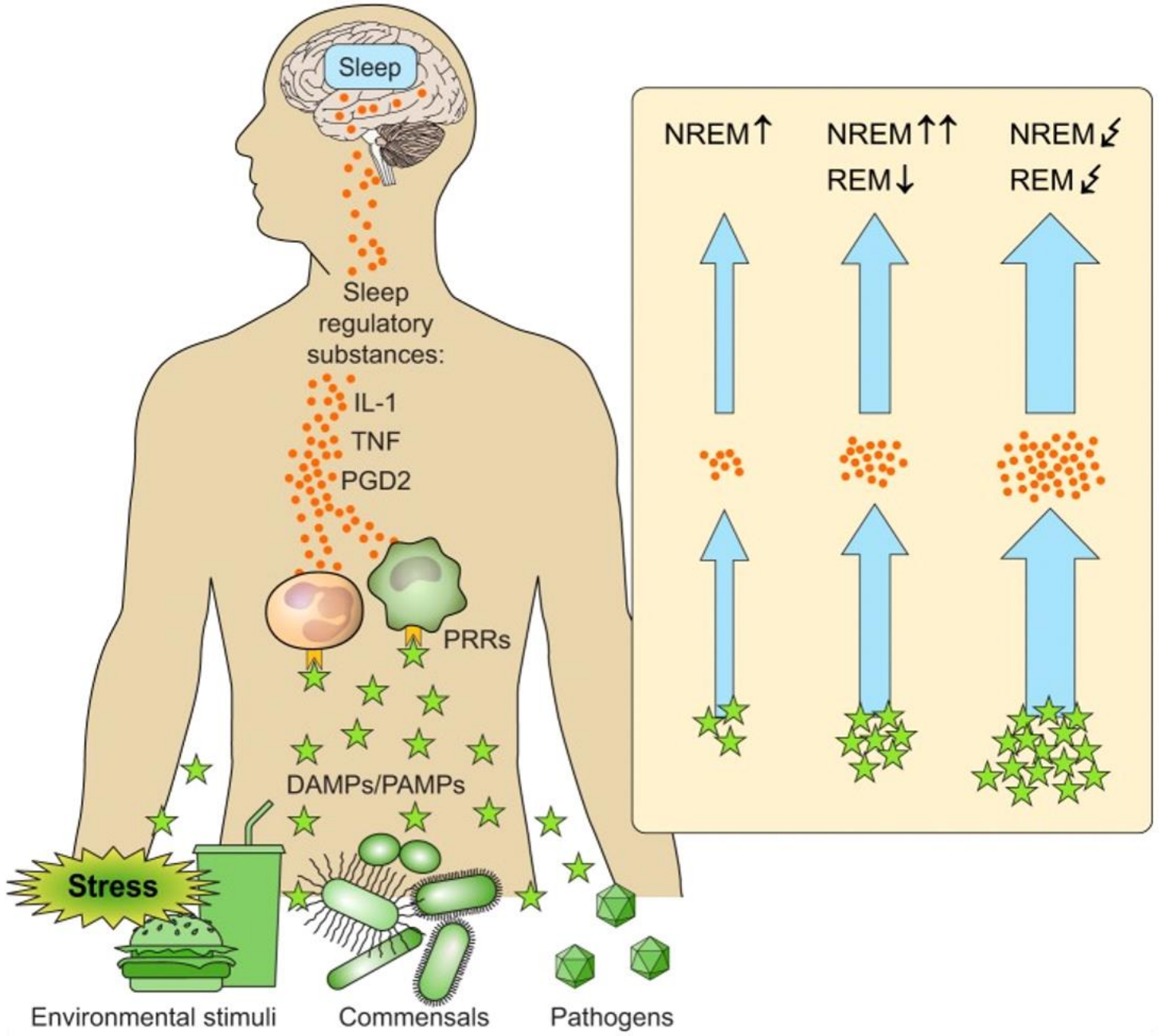
The negative influence on the immune system and the inflammatory regulation of an impaired microbiota seems to be likely to promote autoimmune diseases such as autoimmune thyroid diseases (AITD) [4]. Hashimoto's thyroiditis (HT) is the most common thyroid disorder worldwide with a general prevalence of around 10–12% and is characterized by chronic inflammation, autoantibodies against thyroid peroxidase (TPO) and thyroglobulin (TG), leading to hypothyroidism, and often, destruction of the thyroid gland [12,13]. Graves' disease (GD) has a prevalence of 1–1.5% and is marked by autoantibodies against the thyroid stimulating receptors (TSHR), causing hyperactivity of the thyroid [14,15]. The consequences of these two AITDs affect the entire metabolism of the human body. Graves orbitopathy is the most relevant extrathyroid manifestation [10,16].



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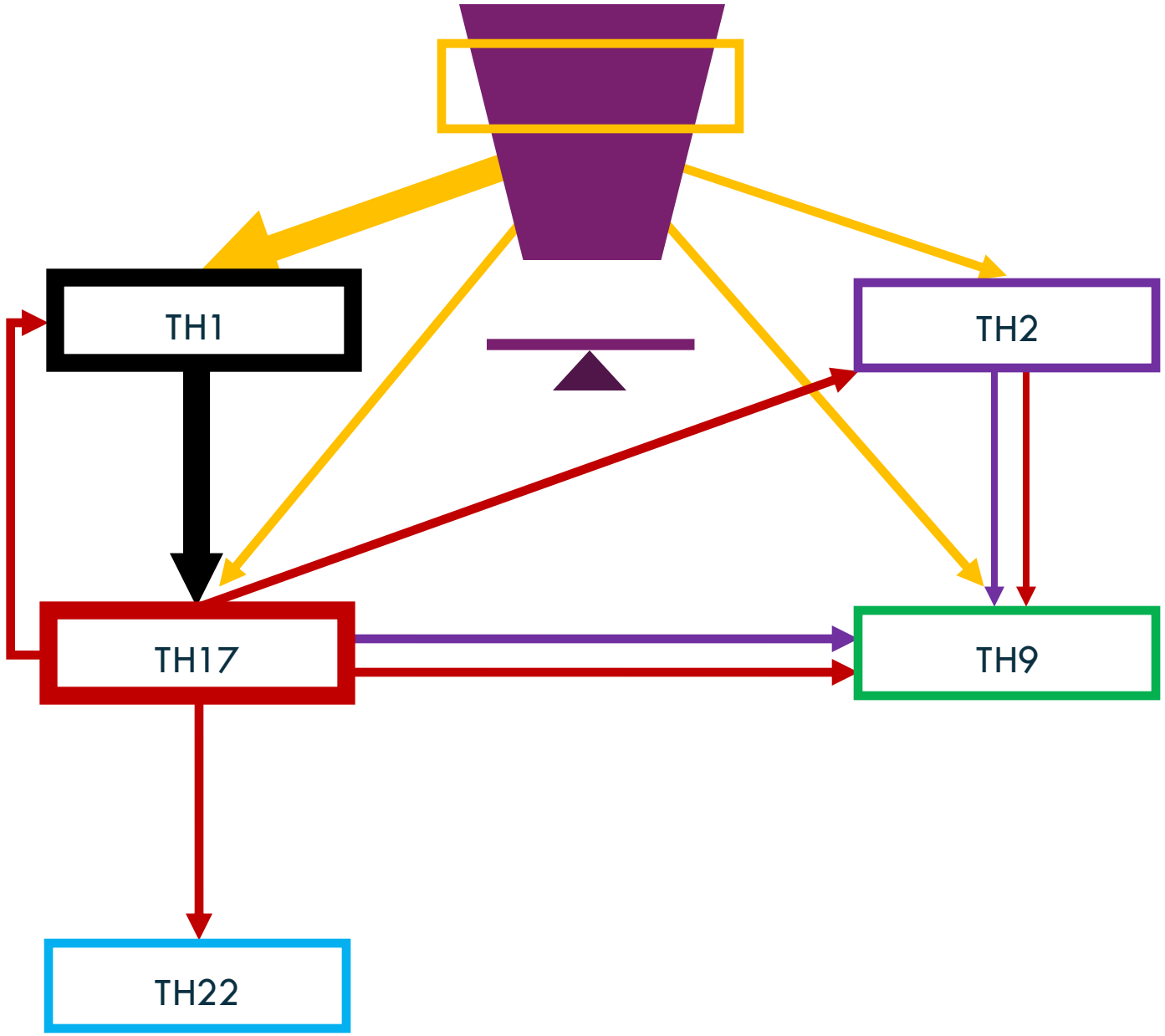
The gut microbiota largely regulates the homeostasis as well as the development of immune cells. It modulates both the innate and the adaptive immune system, even outside the gut [5], and is fundamental in the development of gut-associated lymphatic tissue (GALT), where more than 70% of the entire immune system is situated [1]. GALT plays an important role in the development of tolerance to self-antigens by controlling its toll-like receptors (TLR) in the intestinal mucosa [2].

There is a positive correlation between the short chain fatty acid butyrate concentration and the number of regulatory T-cells (TREGs), which are key mediators of immune tolerance, just as with lower concentrations of the proinflammatory Th-17 cells [10,17]. SCFAs are able to strengthen intercellular tight junctions together with thyroid hormones [4]. The immune system itself has an influence on the composition of the gastrointestinal microbiota, which underlines the symbiotic relationship. In germ-free (gf) mice, disturbed maturation of immune cells was found due to a lack of microbial stimulus to the immune system. Furthermore, shortened villi and crypts, changes in permeability and a thinner mucous membrane layer were reported in these animals [1,2,18].



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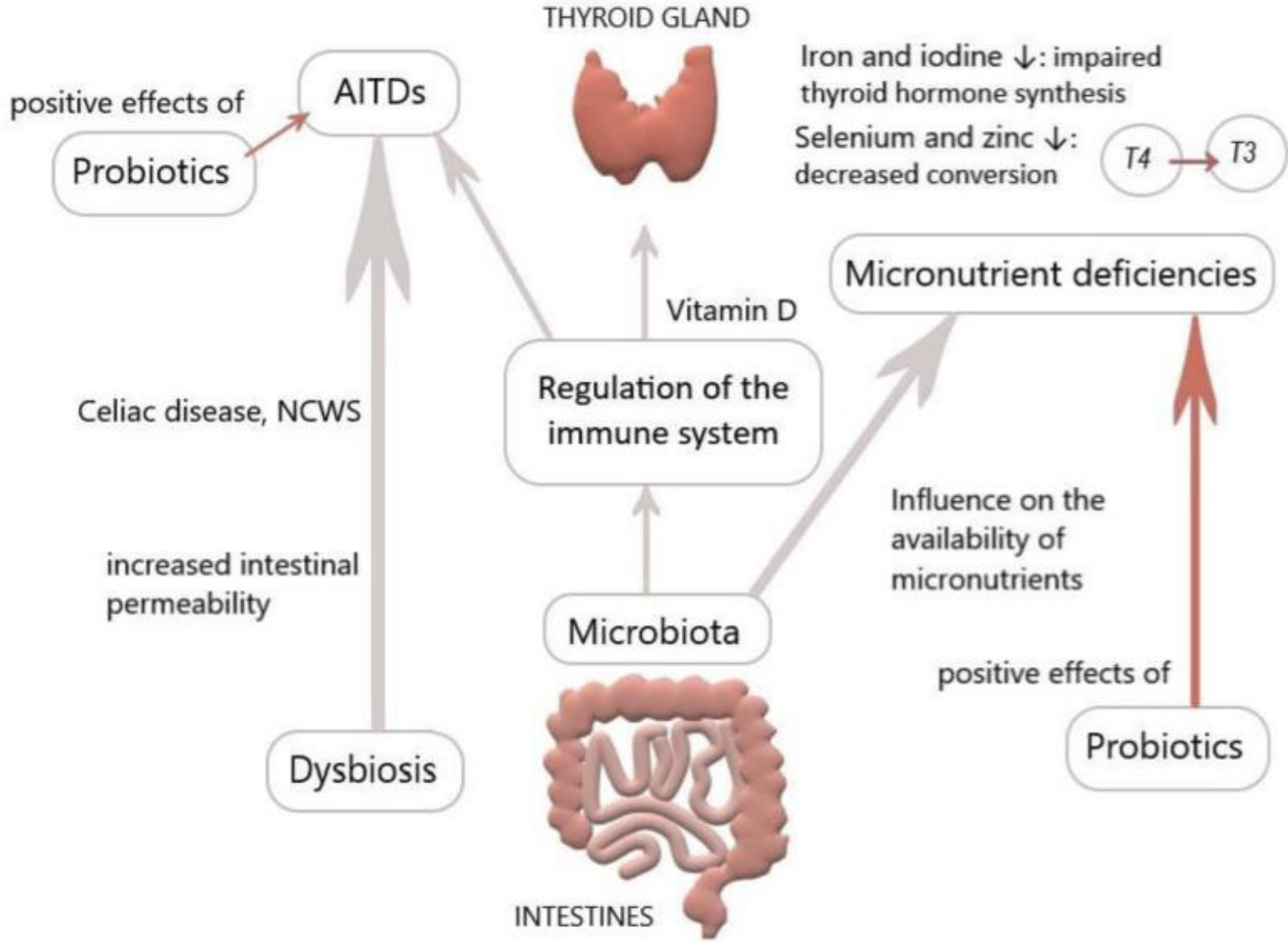
The signs of immunodeficiencies in gf mice include a reduced number of T-helper cells (specifically CD4 + Th cells), reduction of Th-17 and TREG differentiation, and reduced production, respectively [1,11]. All of these immune cells play a role in the pathogenesis of AITD like HT and GD, as well as in the intestinal autoimmune Celiac Disease (CD) and Non-celiac wheat sensitivity (NCWS) [19,20]. Even though NCWS usually does not show autoimmunity, it reveals several similarities in the pathogenesis with the autoimmune diseases mentioned above [21]. An alteration in the composition of intestinal bacteria (dysbiosis), a bacterial overgrowth increasing intestinal permeability, and a shift to proinflammatory cells are some of the factors of microbial impact on the thyroid [4,19]. Zhao et al. and Ishaq et al. investigated the microbial composition in euthyroid and hypothyroid HT patients and found a dysbiosis as well as a bacterial overgrowth in the hypothyroid patient group [22,23]. Lauritano et al. assigned the bacterial overgrowth in connection with hypothyroidism mainly to the small intestine [24].

Iodothyronine-deiodinases play an important role in the conversion of thyroxine (T4) to its active form triiodothyronine (T3) or reverse T3 (rT3), its inactive form [4]. Deiodinase activity has also been found in the intestinal wall and could contribute to total T3 body levels. A study conducted in rats showed binding of thyroid hormones by gut bacteria and even competing with albumin [1,25].



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2.2. Non-Celiac Wheat Sensitivity (NCWS)

NCWS is defined as a non-allergic, non-autoimmune disease in which gluten consumption can lead to symptoms similar to those of celiac disease without specific immunologic findings (21). However, NCWS also has immune-related origins, indicating activation of the innate immune system. This can be shown by an increased expression and activation of toll-like receptors (TLRs), such as TLR 2 and TLR 4, and TNF-α [21,29]. The symptoms, which typically occur shortly after the consumption of gluten-containing foods, include intestinal disorders such as those found in CD, fatigue, anemia, and brain fog. It is more and more taken into consideration that gluten does not seem to be the only cause of discomfort in wheat-sensitive patients [29]. Other grain proteins, such as amylase trypsin inhibitors (ATI), may also act as triggers [31]. For this reason, instead of "non-celiac gluten sensitivity", the more appropriate term appears to be "non-celiac wheat sensitivity" [32].

Multiple studies showed a higher prevalence of coexisting AITDs in CD [33,34], as well as in NCWS [35,36] patients and vice versa. Different hypotheses connect these diseases by discussing (I) shared cytokines in pathogenesis pathways [37,38,39], (II) cross-reaction of antibodies (molecular mimicry) [19,40], (III) malabsorption of essential micronutrients for the thyroid [41] (e.g., iron, vitamin D, and selenium [42,43,44] in CD, and (IV) increased intestinal permeability (IP) as a result of damaged intestinal intercellular junctions [45,46].

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In further consequence, harmed tight junctions (TJ) lead to penetration and exposure of pathogens to the immunoreactive sub-epithelium, promoting inflammation and autoimmunogenesis [45,46]. Zonulin, a protein that when triggered by gluten or certain bacteria, can be secreted by the small intestine and modulate the integrity and permeability of intercellular junctions. When gluten induces zonulin release, it weakens the connection between the tight junctions and breaks the intestinal barrier. In general, zonulin expression is increased in autoimmune diseases [47]. Paterson et al. compared a zonulin peptide inhibitor AT1001 with placebo in a randomized clinical trial including 21 patients with CD. The results revealed that the permeability increased by 70% in the placebo group and the proinflammatory cytokine release decreased by 28% in the AT1001 group [48]. Some of the cytokines involved in inflammatory processes due to increased pathogen exposure to the intestinal immune cells are TNF-α und INF- γ [46,49]. Among others, these can also be involved in the pathogenesis of HT, GD, CD, and NCWS [21,37,38,39].

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The local inflammation adds to the issue by increasing the intestinal permeability itself [46]. The intestinal permeability is influenced by various factors. Drugs (e.g., proton-pump inhibitors, non-steroidal anti-inflammatory drug), stress, alcohol, bacteria, cytokines, reactive oxygen species, and microbial dysbiosis have a negative effect on TJ integrity [50]. In contrast, glutamine [51], polyphenols (contained in turmeric, green tea, citrus fruits, etc.) [52], and vitamin D help to maintain TJ function [49,50,53]. Kong et al. showed increased mucosal damage in vitamin D receptor knockout mice, implicating a protective effect of vitamin D on the intestinal mucosa [54]. Probiotics also seem to support the intestinal barrier function positively [45].

Iodine

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The amount of iodine in soil determines the iodine content of food, resulting in regional differences. Seafood and seaweed, especially from saltwater, are a rich iodine source. Thus, regions near to the ocean and cultures with high seafood consumption, like the Japanese, [58] are more likely to be iodine sufficient. However, iodine fortification of salt and milk products attempts to ensure better overall global access to iodine sources [59].

Iodine deficiency can lead to goiter, probably thyroid nodules, and even thyroid cancer. On the other hand, papillary thyroid cancer seems to be more common in areas with high iodine intake, suggesting complex relations between iodine levels and adverse outcomes [63,64]. Iodine—at least when applicated during medical procedures in high doses—on the opposite, has been proven to influence the gut microbiota. Administering iodine containing contrast agents can have noxious effects on the microbiota by binding to the amino acids tyrosine and histidine on the bacterial membrane, as well as by oxidation of cytoplasmic and membrane components [4].

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Excess intake of iodine triggers the Wolff-Chaikoff effect, a transient reduction of thyroid hormone synthesis for around 24 h after ingestion of a high iodine load [65]. High iodine intake additionally can either induce hypothyroidism in susceptible patients, such as those with autoimmune thyroid disease, antithyroid drug therapy, or patients with higher intake of goitrogens, but it can also cause hyperthyroidism in patients at risk, e.g., with diffuse nodular goiter or latent Grave´s disease [66].

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Iron

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Dietary non-heme iron (Fe^{3+}) absorption is improved by acidic pH and mainly occurs in the proximal duodenum by divalent metal ion transporter 1 (DMT1), after being reduced by duodenal cytochrome b to Fe^{2+} [4,67]. On the contrary, heme iron Fe^{2+}, an important source for both the human and the intestinal microbiota, is directly absorbed by heme/folate transporter 1 (HCP1) in the host and by siderophores like enterobactin in bacteria. Particularly pathogenic strains grow well in heme-rich conditions, due to their efficient heme capturing ability [68]. Many enteric gram-negative bacteria, including *Salmonella*, *Shigella*, and pathogenic *E. coli* require iron for their virulence and colonization [69,70]. Beneficial commensal gut bacteria from genera *Lactobacillus* and *Bifidobacterium* on the other hand require less or no iron [71]. In mice, Constante et al. demonstrated that a heme-rich diet decreases microbial diversity and increases the abundance of *Proteobacteria,* namely *Clostridiales and Lactobacilales.* A heme-rich intestinal environment may favor bacteria-coding genes linked to heme uptake [72].

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On the one hand, iron is essential for bacterial growth and iron availability influences the composition of the microbiota because some bacteria have developed better heme-catching mechanisms. On the other hand, microbiota are able to increase iron bioavailability in the colon through lowering of pH via the production of short chain fatty acids. Bacteria possess siderophores, such as enterobactin, which are high-affinity proteins for iron that acquire Fe^{3+}, especially in iron-poor environments. Humans developed a defense protein called lipocalin-2 to sequester siderophores and limit microbial growth [4,68,73].

Administration of iron supplements (due to incomplete absorption of around 20%) increases colonic iron, leading to adverse effects and altering the microbiota. In vitro and in vivo studies proposed that through oral iron, the beneficial barrier of commensal gut bacteria is decreased and the abundance of enterobacteria such as enteropathogenic *Escherichia coli* is increased, implicating gut inflammation [74].

Iron is essential for efficient iodine utilization and thyroid hormone synthesis. Iron deficiency is a common finding in hypothyroidism and is diagnosed in up to 60% of these patients [75]. It does not appear to correlate with the severity of the disease and it may be caused by celiac disease, autoimmune gastritis, or other malabsorption disorders [75,76,77].

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Iron deficiency may contribute to compromised thyroid hormone synthesis, storage, and secretion due to decreased oxygen transport or by impairing heme-dependent thyroid peroxidase despite adequate iodine intake. Thyroid iodine peroxidase (TPO) is located at the apical membrane of the thyrocyte and catalyzes two crucial steps in thyroid hormone synthesis: Iodination of thyroglobulin and coupling of iodotyrosine molecules. Activity of this iron-dependent enzyme can be negatively affected by iron deficiency, resulting in low thyroid hormone levels in plasma, thus increased TSH secretion and enlarged thyroid [75,78]. In 1998, Beard et al. reported significantly lower plasma T3 concentrations and a lower T4 plasma pool and T4 disposal rate in ID rats [79].

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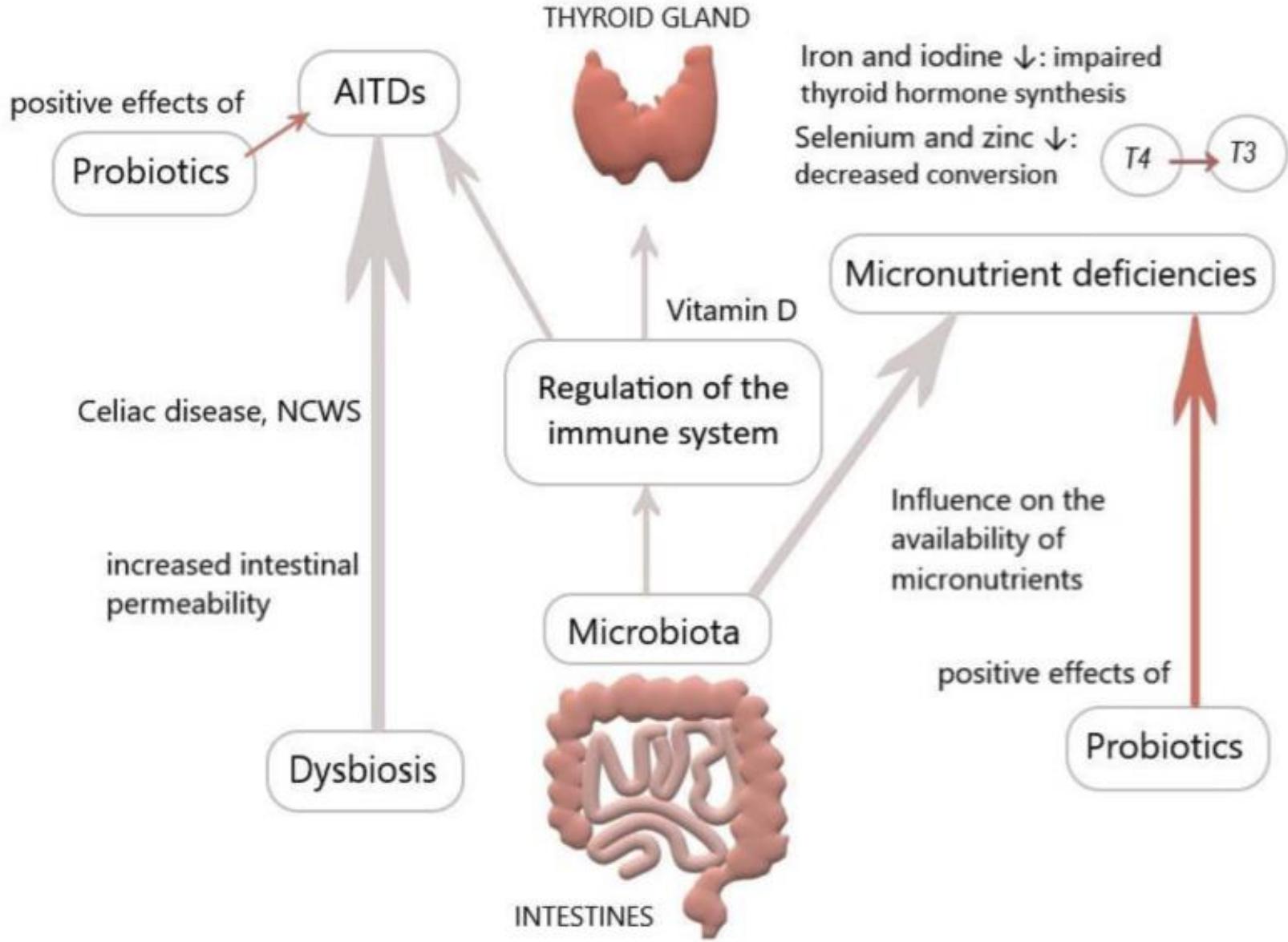
transporter (CFTR); however, only to small extents [4,55,56]. In inflammatory bowel disease (IBD), a reduction in the diversity of gut microbiota and a lower abundance of *Firmicutes* and *Bacteroidetes* have been observed. Iodine malabsorption is a common consequence of IBD and vice versa, suggesting a reciprocal relationship. Chronic inflammation promotes changes in the composition of the microbiota due to alterations in the oxidative and metabolic environment of the intestine [4,57].

The amount of iodine in soil determines the iodine content of food, resulting in regional differences. Seafood and seaweed, especially from saltwater, are a rich iodine source. Thus, regions near to the ocean and cultures with high seafood consumption, like the Japanese, [58] are more likely to be iodine sufficient. However, iodine fortification of salt and milk products attempts to ensure better overall global access to iodine sources [59].



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