Gut Microbiota in Thyroiditis of Hashimoto

Subjects: Nutrition & Dietetics

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Since the thyroid gland is one of the organs most affected by autoimmune processes, many patients with thyroiditis of Hashimoto (TH) seek medical advice on lifestyle variance and dietary modifications to improve and maintain their hyroid function. For most TH patients, the hormone-replacement therapy with levothyroxine is indispensable. Nevertheless, an appropriate dietary regimen and ecological lifestyle can complement the standard treatment and favor remission of TH by improving the function of the thyroid gland. Other less significant parameters may be a repercussion of healthier body reactions and improvement of life quality, such as better sleep and alertness. Compliance with nutritional guidelines with a focus on the prevailing anti-inflammatory diet and controlled vitamin D dosing may help individual TH patients to reduce the need for medicines, slow down the course of the disease, and avoid relapses.

Keywords: autoimmune Hashimoto’s thyroiditis ; proinflammatory ; Gut Axis ; anti-inflammatory nutrients ; detoxification ; ecological diet

1. Introduction

The thyroid gland is the organ most affected by autoimmune processes [1]. Between 20% and 40% of American Caucasians and British citizens show lymphocytic infiltration in post-mortem specimens, while the highest percentage is typical for white females [2]. The intra-thyroidal lymphocytic infiltration induces chronic inflammation and autoimmune conditions, which most often results in autoimmune hypothyroidism or thyroiditis of Hashimoto (TH) [3]. TH development leads to scarring and destruction of the thyroid gland and is manifested by by a decrease of plasma free triiodothyronine (T3) and thyroxine (T4), elevated plasma levels of thyroid-stimulating hormone (TSH) and by the presence of antibodies to thyroid peroxidase (Ab-TPO) and thyroglobulin (Ab-Tg) [4]. It is generally accepted that the pathogenesis of TH, like other autoimmune diseases, represents the combination of environmental (i.e., lighting regimen, pollution, micronutrients, variety of physical and social factors), existential (lifestyle, hormonal status, diet, gut microbiota), as well as genetic factors that provoke immunological dysfunction and support the autoimmune destruction of the gland [4].

To treat the condition in the long term, patients with TH-associated hypothyroidism often require lifetime hormone replacement therapy with levothyroxine [5][6]. There is growing evidence of the existence of a thyroid–gut axis that controls many autoimmune disorders, and patients frequently report changes in their quality of life and thyroid function as a result of dietary modifications.

Genetic factors contribute to 70–80% of autoimmune thyroid diseases [7]. The major histocompatibility complex genes (HLA class I and II), thyroid-related genes, genes associated with thyroid peroxidase antibody synthesis (BACH2, TPO), and genes regulating immune response (CD40, CTLA4, PD1) are the common genetic factors [7][8].

From the environmental factors, a vast variety of nutrients play an important role in the onset and development of TH. High iodine intake, deficiencies of selenium and iron, inadequate intake of proteins, unsaturated fatty acids, and dietary fibers could favor TH [1][9][10]. Proinflammatory foods may induce dysbiosis and oxidative stress [11] that can cause intestinal inflammation and spread it towards different organs, including the thyroid gland [4][12][13]. The reduction and replacement of commensal microbiota caused by dietary supplementation significantly change the immune function and epithelial metabolism of the intestinal mucosa and the absorption of nutrients [11][14]. Drugs such as pembrolizumab, interferon-α, anti-retroviral therapy, and estrogens used for oral contraception or hormone replacement therapy are also crucial for TH [7][8]. Smoking and moderate alcohol consumption protect against TH, but quitting smoking may provoke this disease [8]. Immunomodulatory therapies and infections such as rubella, hepatitis C, and Epstein-Barr virus could also be responsible for the development of TH [8].

Cyanotoxins such as cylindrospermopsin (CYN) and microcystins, in addition to their general toxicity, increase the permeability of epithelial and model pseudo-epithelial layers of human intestines. They even possess the ability to affect the function of the gastrointestinal epithelium and other cell types, and thus induce “leaky gut” syndrome, inflammation,

oxidative stress, and apoptosis [15]. Furthermore, microcystins dose-dependently reduce thyroid hormone levels, and influence deiodinase activity and transcription of genes related to thyroid hormones' synthesis and metabolism [1]. Direct harmful effects of acute and chronic exposure to cyanotoxins on the hypothalamic–pituitary–thyroid (HPT) axis may lead to hypothyroidism [16][17].

Individual characteristics such as age, lifestyle, gender, pregnancy, and certain diseases, such as allergic rhinitis, prolactinoma, and subacute thyroiditis, may serve as an important predisposition or triggers for TH [7][8]. Current treatment of TH in hypothyroid subjects includes replacement monotherapy with levothyroxine, which greatly reduces relapses of the disease and slows down the progression of thyroid damage. However, a proportion of the patients continue to experience various symptoms and deteriorating overall quality of life. Unfortunately, there are limited data on any effective concomitant treatment other than levothyroxine, which by itself does not target the autoimmune processes related to disease severity. It is already known that the diet and lifestyle of patients with TH can play a key role in the management of disease episodes, which necessitates an in-depth study of complex external and internal factors. Intensive research shows that many dietary supplements have the potential to positively affect TH symptomatology due to their anti-inflammatory and antidepressant activity, thus improving the overall sense of well-being. Among the most attractive candidates which may be able to influence the severity of clinical symptoms and improve thyroid function are vitamins from the groups A, B, C, and D, fatty acids, antioxidants, phytochemicals, but also the indole-amine melatonin [4][10].

The interest in dietary vitamin D and melatonin is based on research findings of their physiological role as regulators of the production of inflammatory cytokines and prostaglandins. The controlled dietary supplementation of vitamin D and melatonin might represent an essential strategy for treating TH via their molecular mechanisms on the cellular level. Data suggest that appropriate nutritional protocols may help to decrease the chronic inflammation in the thyroid gland, other tissues, and organs, as well as to suppress or stop the thyroid gland degradation and thus improve patients' quality of life [4][11].

2. Nutritional Factors Linked to TH Etiopathogenesis

2.1. Nutritional Deficits or Excess

The nutritional deficit or excess of some minerals and other nutrients plays an essential role in the etiopathogenesis of hypothyroidism and TH [18]. Iron and selenium participate in T3 (active hormone) and T4 (prohormone) formation, where iodine is a part of these molecules, and selenium is a cofactor of deiodinases that activates T4 by converting it into T3 or inactivates both T4 and T3 [10]. Zinc is important for T3 receptor activation and can influence thyroid function via other mechanisms [10][19]. Reduced intake of some nutrients, such as vitamins (A, B1, B5, B6, and C), proteins, and minerals (magnesium, sodium, potassium, phosphorus, chromium), may also provoke or support TH, and this is more evident in deficiencies for more than one of these nutrients [20]. Adequate intake of A, C, and E vitamins and group B is recommended in prophylaxis and prevention of thyroid diseases because of their antioxidative (for vitamins C and E), anti-neoplastic, and anti-goitrogenic protection (for vitamins A, D, and E), as well as regulation of the pituitary–thyroid axis, the iodine intake in the thyroid gland, and T3 signaling (for vitamin A) [4][10][20]. Inositol and its most abundant metabolite myo-inositol have a protective effect on the thyroid gland by improving TSH signaling and proinflammatory cytokine suppression [10].

2.2. Nutritional Elements Generating Intoxication

Some trace elements such as Se, Zn, and Fe participate in thyroid gland function, and their deficiency is critical for thyroid hormone homeostasis. Others such as lead, cadmium, chromium, manganese, and fluoride are toxic for many organs and tissues, including the thyroid gland, and may provoke or support hypothyroidism when their levels in the circulation are in excess [18][21].

2.3. Cyanotoxins and Thyroid Function

Cyanotoxins are a diverse group of toxins produced by cyanobacteria. Their amount increases exponentially during cyanobacteria bloom in sweet or salt waters. In this case, their poisonous substances achieve high concentrations that are sufficient to harm or even kill animals and humans [22][23]. Cyanotoxins microcystins, CYN, and lipopolysaccharides were linked to gastrointestinal complaints and effects on the immune system, including gastrointestinal inflammation [24]. Microcystin significantly alters the mouse gut microbiome and induces dysbiosis [25]. Microcystins are potent and specific inhibitors of protein phosphatases 1 and 2 A and can induce oxidative stress [26]. CYN can also lead to oxidative stress, either directly or indirectly linked to the reduction of glutathione formation [25]. Furthermore, CYN may reduce the viability of human gastrointestinal epithelial cells in culture and increases the permeability of intestinal epithelium [15][27].

Cyanotoxins are also shown to facilitate the absorption of other toxins due to their inflammatory action on the gastrointestinal border [24].

Additionally, cyanotoxins may directly affect the thyroid gland. It was recently reported that microcystin-LR is able to affect the HPT, the hypothalamic–pituitary–gonadal, and the hypothalamic–pituitary–adrenal endocrine axes in rats. In regard to the HPT axis, microcystin-LR increased the concentration of TSH and decreased TRH and plasma levels of free T3 and T4 [17]. All three axes under study were influenced at the gene transcription level of the hormones and the nuclear hormone receptors. These results are in line with the effect of chronic oral administration of low doses of microcystin-LR, which leads to activation of p38/MAPK and MEK/ERK cell signaling that up-regulates type 3 deiodinase expression in mice [16].

In conclusion, drinking water and foods contaminated with cyanotoxins may indirectly influence plasma levels of free T3 and T4 via proinflammatory mucosal reaction and dysbiosis, or by a direct effect on the HPT axis and the thyroid in particular. Some of these stimuli may challenge the thyroid function and can be linked to TH.

2.4. Diets Favoring Inflammation and Gut Dysbiosis and Their Role in Thyroiditis of Hashimoto

Diet and microbiota are among the main factors in gut inflammation and proper intestinal function [11][13][28]. Foods rich in antioxidants help the body control oxidative stress and exert anti-inflammatory effects. These foods are considered healthy and good for maintaining an optimal body mass index. On the other hand, some diets are rich in proinflammatory foods and thus have a substantial impact on the inflammation in the human body. Research shows that certain foods can affect C-reactive protein (CRP) production, which is a serum marker of inflammation [29]. The consumption of some foods causes the release of inflammatory messengers that raise the risk of chronic inflammation, cancer, diabetes, metabolic syndrome, autoimmune diseases, and other chronic conditions.

The disruption of gut microbiota, also known as gut dysbiosis, is influenced by the individual genetic profile, diet, antibiotics, and inflammation. It is linked to the pathogenesis of some inflammatory diseases, such as obesity and inflammatory bowel disease [30]. Intestinal dysbiosis and increased intestinal permeability seem to favor the progress of TH as well, while no alteration in systemic cytokines could be detected within the same group of study [13]. Nevertheless, dietary modulation of the microbial gut balance affects the inflammatory environment, most probably due to the microbiota metabolites. Microbiota-derived metabolites, short-chain fatty acids, and Gram-negative bacterial lipopolysaccharides (LPS) exert anti-inflammatory or proinflammatory effects by acting on macrophages, depending on their M1 and M2 phenotypes [31]. Butyrate, a commensal microbial fermentation product, has been shown to favor the polarization and function of M2 macrophages through interleukin 4 (IL-4)-mediated STAT6 transcription, which could attenuate intestinal inflammation in mice [32].

A simulation model of interaction between thyroid follicular cells, Th1, Th17, Tregs, and gut microbiota in TH pathogenesis was recently proposed by Salazar-Viedma et al. [33]. Their model showed that increased proliferation and differentiation of Th1 and Th17 lymphocytes indirectly trigger inflammation and apoptosis of healthy thyrocytes. Furthermore, imbalanced gut microbiota composition results in a reduction of Treg cells and stimulation of Th17 lymphocytes, thus contributing to inflammation processes and apoptosis of healthy thyrocytes [33].

The impact of foods, the diversity of microbiota metabolites, and their interference with the immune cells' balance in patients with TH are scarce and require further clarification to understand the mechanisms behind the development of this disease and find nutritional strategies for its alleviation.

2.5. Proinflammatory Nutrients Favoring Clinical Manifestation of Endocrine and Metabolic Disease

Some foods can be described as proinflammatory or anti-inflammatory depending on their content—proinflammatory or anti-inflammatory nutrients. A diet rich in too many proinflammatory nutrients may increase the risk of chronic inflammation and could accelerate the inflammatory disease process. Therefore, it is essential to not only recognize foods which can elicit inflammation, but also the inflammatory nutrients that are present in the food.

Some foods associated with weight gain and an increased risk for chronic diseases such as heart disease and type 2 diabetes are also linked to elevated inflammatory reactions. Again, it is because some of the food ingredients or nutrients may have independent effects on inflammation.

3. The Role of Thyroid–Gut Axis and the Influence of Gut Microbiota on TH

There is mounting evidence for the existence of a robust thyroid–gut axis. It is reflected by a significant influence of the intrinsic bacterial microflora in the gut on the immune system reactivity and the thyroid function [34]. Furthermore, the concomitance of thyroid- and gut-related disorders is common, such as TH/Graves' disease and celiac disease/non-celiac wheat sensitivity. Thyroid diseases are frequently associated with dysbiosis.

Dysbiosis may significantly impair the immune system and compromise inflammatory control, causing autoimmune illnesses such as autoimmune thyroid diseases [14][34]. Moreover, microbiota influences the intake of thyroid-related minerals such as iodine, selenium, zinc, and iron. They all have a role in thyroid function, and there is a definite correlation between thyroid disease and changed amounts of these minerals in the body [34].

Aside from that, it appears that Lactobacillaceae and Bifidobacterium spp. have a negative association with dietary iron and a favorable correlation with selenium and zinc. Since these bacteria are reduced in TH and Grave's disease, it has been assumed that gut composition and mineral regulation may play a role in both disorders [14].

Furthermore, Lactobacillaceae and Bifidobacteriaceae are frequently decreased in hypo- and hyperthyroidism. Supplementation with *Lactobacillus reuteri* improved thyroid function in rats by increasing free T4, thyroid gland mass, and physiological indices, such as more dynamic behavior. This result might be caused by interleukin-10, which is known to enhance the T-regulatory cells [35].

Symbiotic supplementation is a mixture of pro- and pre-biotics that has been shown in a study to benefit individuals with hypothyroidism by considerably lowering TSH, levothyroxine dosage, and exhaustion, while raising fT3. However, no effect on anti-TPO or blood pressure was demonstrated [36].

It has not been determined whether bacterial infections can cause autoimmune thyroid diseases or influence therapy efficacy and prognosis [37].

Considering the numerous possible effects of microbiota and micronutrients on thyroid functions and medicines, innovative treatment methods for the management of thyroid illnesses might be developed and tailored to individuals based on their gut flora composition. Future detailed research in humans is of particular importance to delineate the influence of gut microbiota on thyroid function and disease.

References

1. Hu, S.; Rayman, M.P. Multiple Nutritional Factors and the Risk of Hashimoto's Thyroiditis. Thyroid 2017, 27, 597–610.
2. Okayasu, I.; Hara, Y.; Nakamura, K.; Rose, N.R. Racial and age-related differences in incidence and severity of focal autoimmune thyroiditis. Am. J. Clin. Pathol. 1994, 101, 698–702.
3. Krysiak, R.; Szkróbka, W.; Okopień, B. The Effect of Gluten-Free Diet on Thyroid Autoimmunity in Drug-Naïve Women with Hashimoto's Thyroiditis: A Pilot Study. Exp. Clin. Endocrinol. Diabetes 2019, 127, 417–422.
4. Ihnatowicz, P.; Drywień, M.; Wątor, P.; Wojsiat, J. The importance of nutritional factors and dietary management of Hashimoto's thyroiditis. Ann. Agric. Environ. Med. 2020, 27, 184–193.
5. Caturegli, P.; De Remigis, A.; Rose, N.R. Hashimoto thyroiditis: Clinical and diagnostic criteria. Autoimmun. Rev. 2014, 13, 391–397.
6. Subekti, I.; Pramono, L.A. Current diagnosis and management of Graves' disease. Acta Med. Indones. 2018, 50, 177–182.
7. Wiersinga, W.M. Clinical Relevance of Environmental Factors in the Pathogenesis of Autoimmune Thyroid Disease. Endocrinol. Metab. 2016, 31, 213–222.
8. Weetman, A.P. An update on the pathogenesis of Hashimoto's thyroiditis. J. Endocrinol. Investig. 2021, 44, 883–890.
9. Rayman, M.P. Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease. Proc. Nutr. Soc. 2019, 78, 34–44.
10. Benvenga, S.; Ferrari, S.M.; Elia, G.; Ragusa, F.; Patrizio, A.; Paparo, S.R.; Camastra, S.; Bonofiglio, D.; Antonelli, A.; Fallahi, P. Nutraceuticals in Thyroidology: A Review of in Vitro, and in Vivo Animal Studies. Nutrients 2020, 12, 1337.
11. Ceballos, D.; Hernández-Camba, A.; Ramos, L. Diet and microbiome in the beginning of the sequence of gut inflammation. World J. Clin. Cases 2021, 9, 11122–11147.

12. Kochman, J.; Jakubczyk, K.; Bargiel, P.; Janda-Milczarek, K. The Influence of Oxidative Stress on Thyroid Diseases. Antioxidants 2021, 10, 1442.
13. Cayres, L.C.F.; de Salis, L.V.V.; Rodrigues, G.S.P.; Lengert, A.V.H.; Biondi, A.P.C.; Sargentini, L.D.B.; Brisotti, J.L.; Gomes, E.; de Oliveira, G.L.V. Detection of Alterations in the Gut Microbiota and Intestinal Permeability in Patients With Hashimoto Thyroiditis. Front. Immunol. 2021, 12, 579140.
14. Fröhlich, E.; Wahl, R. Microbiota and Thyroid Interaction in Health and Disease. Trends Endocrinol. Metab. 2019, 30, 479–490.
15. Chichova, M.; Tasinov, O.; Shkodrova, M.; Mishonova, M.; Sazdova, I.; Ilieva, B.; Doncheva-Stoimenova, D.; Kiselova-Kaneva, Y.; Raikova, N.; Uzunov, B.; et al. New Data on Cylindrospermopsin Toxicity. Toxins 2021, 13, 41.
16. Chen, J.; Bian, R.; Li, J.; Qiu, L.; Lu, B.; Ouyang, X. Chronic exposure to microcystin-LR reduces thyroid hormone levels by activating p38/MAPK and MEK/ERK signal pathway. Ecotoxicol Environ. Saf. 2019, 173, 142–148.
17. Chen, L.; Shi, T.; Wang, Y.T.; He, J.; Zhao, X.; Wang, Y.K.; Giesy, J.P.; Chen, F.; Chen, Y.; Tuo, X.; et al. Effects of acute exposure to microcystins on hypothalamic-pituitary-adrenal (HPA), -gonad (HPG) and -thyroid (HPT) axes of female rats. Sci. Total Environ. 2021, 778, 145196.
18. Błażewicz, A.; Wiśniewska, P.; Skórzyńska-Dziduszko, K. Selected Essential and Toxic Chemical Elements in Hypothyroidism-A Literature Review (2001–2021). Int. J. Mol. Sci. 2021, 22, 10147.
19. Baltaci, A.K.; Mogulkoc, R.; Baltaci, S.B. Review: The role of zinc in the endocrine system. Pak. J. Pharm. Sci. 2019, 32, 231–239.
20. Kawicka, A.; Regulska-Ilow, B. Metabolic disorders and nutritional status in autoimmune thyroid diseases. Postepy Hig. Med. Dosw. 2015, 69, 80–90.
21. Azami, M.; Parizad, N.; Sayehmiri, K. Prevalence of hypothyroidism, hypoparathyroidism and thefrequency of regular chelation therapy in patients with thalassemia major in Iran: A systematic review and meta-analysis study. Iran. J. Ped. Hematol. Oncol. 2016, 6, 260–275.
22. Meriluoto, J.; Spoof, L.; Codd, G.A. (Eds.) Handbook of Cyanobacterial Monitoring and Cyanotoxin Analysis; John Wiley & Sons: Chichester, UK, 2017.
23. Mills, M.C.; Evans, M.V.; Lee, S.; Knobloch, T.; Weghorst, C.; Lee, J. Acute cyanotoxin poisoning reveals a marginal effect on mouse gut microbiome composition but indicates metabolic shifts related to liver and gut inflammation. Ecotoxicol. Environ. Saf. 2021, 215, 112126.
24. Kubickova, B.; Babica, P.; Hilscherová, K.; Šindlerová, L. Effects of cyanobacterial toxins on the human gastrointestinal tract and the mucosal innate immune system. Environ. Sci. Eur. 2019, 31, 31.
25. Arman, T.; Clarke, J.D. Microcystin Toxicokinetics, Molecular Toxicology, and Pathophysiology in Preclinical Rodent Models and Humans. Toxins 2021, 13, 537.
26. Zhang, Q.; Wang, L.; Chen, G.; Wang, M.; Hu, T. Cylindrospermopsin impairs vascular smooth muscle cells by P53-mediated apoptosis due to ROS overproduction. Toxicol. Lett. 2021, 353, 83–92.
27. Sazdova, I.; Keremidarska-Markova, M.; Chichova, M.; Uzunov, B.; Georgiev, G.; Mladenov, M.; Schubert, R.; Stoyneva-Gärtner, M.; Gagov, H.S. Review of Cyanotoxicity Studies Based on Cell Cultures. J. Toxicol. 2022, 2022, 5647178.
28. Passali, M.; Josefsen, K.; Frederiksen, J.L.; Antvorskov, J.C. Current Evidence on the Efficacy of Gluten-Free Diets in Multiple Sclerosis, Psoriasis, Type 1 Diabetes and Autoimmune Thyroid Diseases. Nutrients 2020, 12, 2316.
29. Sproston, N.R.; Ashworth, J.J. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front. Immunol. 2018, 9, 754.
30. Wang, K.; Wei, H.; Zhang, W.; Li, Z.; Ding, L.; Yu, T.; Tan, L.; Liu, Y.; Liu, T.; Wang, H.; et al. Severely low serum magnesium is associated with increased risks of positive anti- thyroglobulin antibody and hypothyroidism: A cross-sectional study. Sci. Rep. 2018, 8, 9904.
31. Forbes, J.D.; Chen, C.Y.; Knox, N.C.; Marrie, R.A.; El-Gabalawy, H.; de Kievit, T.; Alfa, M.; Bernstein, C.N.; Van Domselaar, G. A comparative study of the gut microbiota in immune-mediated inflammatory diseases-does a common dysbiosis exist? Microbiome 2018, 6, 221.
32. Ji, J.; Shu, D.; Zheng, M.; Wang, J.; Luo, C.; Wang, Y.; Guo, F.; Zou, X.; Lv, X.; Li, Y.; et al. Microbial metabolite butyrate facilitates M2 macrophage polarization and function. Sci. Rep. 2016, 6, 24838.
33. Salazar-Viedma, M.; Vergaño-Salazar, J.G.; Pastenes, L.; D'Afonseca, V. Simulation Model for Hashimoto Autoimmune Thyroiditis Disease. Endocrinology 2021, 162, bqab190.

34. Knezevic, J.; Starchl, C.; Tmava Berisha, A.; Amrein, K. Thyroid-Gut-Axis: How Does the Microbiota Influence Thyroid Function? Nutrients 2020, 12, 1769.
35. Virili, C.; Fallahi, P.; Antonelli, A.; Benvenga, S.; Centanni, M. Gut microbiota and Hashimoto’s thyroiditis. Rev. Endocr. Metab. Disord. 2018, 19, 293–300.
36. Talebi, S.; Ghaedi, E.; Sadeghi, E.; Mohammadi, H.; Hadi, A.; Clark, C.C.T.; Askari, G. Trace Element Status and Hypothyroidism: A Systematic Review and Meta-Analysis. Biol. Trace Elem. Res. 2020, 197, 1–14.
37. Docimo, G.; Cangiano, A.; Romano, R.M.; Pignatelli, M.F.; Offi, C.; Paglionico, V.A.; Galdiero, M.; Donnarumma, G.; Nigro, V.; Esposito, D.; et al. The Human Microbiota in Endocrinology: Implications for Pathophysiology, Treatment, and Prognosis in Thyroid Diseases. Front. Endocrinol. 2020, 11, 586529.
