

The Future Perspective of Gut Microbiota and Autoimmune Thyroid Disease

Angela Esther Sihombing ^{a, c}, Jongky Hendro Prajitno ^{b, d}

^a angela.esther.nathaniella-2019@fk.unair.ac.id

^b jongky-h-p@fk.unair.ac.id

^c Medical Programme, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

^d Internal Medicine Department, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Abstract

The human digestive tract contains a large number of gut microbiota. Where the composition of the bacteria is influenced by various factors, ranging from geographical differences, to various other factors. The gut microbiota plays an important role not only in the stability of digestive function, but also in immune function, hormones, and metabolic homeostasis. Recent research results indicate that there is an autoimmune process that occurs after bacterial infection, where the mechanism involves molecular mimicry, epitope distribution, bystander activation, and cryptic antigens. The condition of dysbiosis has been associated with various gastrointestinal disorders and systemic disorders, one of which is in the group of autoimmune diseases. Increased intestinal permeability causes the flow of toxins, antigens, and bacterial metabolites from the intestine into the blood vessels. Where this condition is a hypothesis of the initiation process of autoimmune thyroid disease. A balance between protective reactions and tolerance is required to maintain intestinal homeostasis. Changes in this balance can cause auto-aggressive disturbances triggered by differences in the composition of the microbiota. The deiodinase enzyme is an important factor in thyroid hormone metabolism. Several microbes were identified as regulators of certain enzymes involved in iodothyronine metabolism. Autoimmune thyroid disease and gut microbiota have a potential relationship which, if further investigated, could be the future of autoimmune thyroid disease therapy.

Keywords: Autoimmune Thyroid Disorders, Gut Microbiota, Graves' Disease, Hashimoto's Thyroiditis

Introduction

The human digestive tract contains a large number of gut microbiota. The gut microbiota are bacteria, viruses, and fungi ^[1]. Where 70% of 1013 microbes throughout the human body are normal flora in the digestive tract ^[2]. Most of the bacteria living in the human intestine generally consist of Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia ^[3]. Where the composition of the bacteria is influenced by various factors, ranging from geographical differences, to various other factors, such as the condition of the fetus in the womb ^[4], birth procedures, the way the mother breastfeeds the baby ^[5], the food consumed, the use of antibiotics and others drugs, genetic factors, environmental factors, and the disease ^[6], ^[7]. The composition of the microbiota reaches a composition similar to that of adults in general at around three years of age, although the composition can still change when influenced by factors as previously mentioned ^[6].

The gut microbiota plays an important role not only in the stability of digestive function, but also in immune function, hormones, and metabolic homeostasis ^[8]. When viewed in more depth, the microbiota is the basis for

the formation of Gut Associated Lymphoid Tissue (GALT) ^[9]. Where GALT is a component of the large lymphoid system and contains more than 70% of the immune system. Recent research results indicate that there is an autoimmune process that occurs after bacterial infection, where the mechanism involves molecular mimicry, epitope distribution, bystander activation, and cryptic antigen ^[10].

Dysbiosis is a condition in which the composition of pathological intestinal microbes is excessive, the concentration of normal flora is reduced, and the variety of microbes is decreasing ^[11]. This condition has been associated with various gastrointestinal disorders and systemic disorders, one of which is in a group of autoimmune diseases, such as multiple sclerosis ^[12], rheumatoid arthritis ^[13], systemic lupus erythematosus ^[14], and type 1 diabetes ^{[15],[16]}. However, even so, the relationship between autoimmune thyroid disease and dysbiosis conditions is still rarely studied, so the aim of this article is to review various research evidence that may indicate a potential relationship between the gut microbiota and autoimmune thyroid disease.

Relationship between Autoimmune Thyroid Disease and Gut Microbiota

As previously mentioned, the intestinal tract is an important aspect for the homeostasis and metabolism of nutrients, molecules, drugs, and hormones related to thyroid function, such as iodothyronine, both exogenous and endogenous ^[17]. In mice as well as in humans, the intestine is a large part of the immune system, even the intestine contains more immuno-globulin secreting cells compared to lymphoid organs ^[18]. An interesting finding showed that in Hashimoto Thyroiditis patients there were ultrastructural morphological changes in the distal part of the duodenal enterocytes, where there were variations in the thickness of the microvillus and an increase in the spacing between adjacent microvilli under transmission electron microscopy ^[19]. These patients were found to have a “leaky gut” condition on gut permeability evaluation with the lactulose/mannitol test, compared to the control group ^[19]. The increase in intestinal permeability causes a flow of toxins, antigens, and bacterial metabolites from the intestine to the blood vessels. Where this condition is a hypothesis of the initiation process of thyroid autoimmune disease ^[20].

In contrast side, intestinal homeostasis requires a balance between defence mechanisms and tolerance. This ability is controlled by antigen-presenting cells, which evolved alongside with microbiota and finally established the capacity to distinguish between infections and normal flora ^[21]. In germ-free mice, the absence of microbial stimuli leads in a major immaturity of the immune system. Other cells (neutrophils, macrophages, and natural killers) similarly contribute to innate immunity, and it was shown that germ-free mice were lacking in both quantity and/or function ^[21]. In this mouse model, balance of adaptive immunity is also compromised, as shown by a substantial decrease in intestinal B cells and reduced immunoglobulin synthesis. In addition, the T-cell subsets likely to be composed of Th2 cells ^[22]. These alterations may result in auto-aggressive diseases induced by microbiota composition variations. Finding comparable physical and functional abnormalities to the intestinal barrier in individuals with type 1 diabetes ^[23] and autoimmune thyroiditis ^[19] was of special interest in humans. This supports the concept that chronic lymphocytic thyroiditis is caused by a pathogenetic process linked to alterations in intestinal permeability and dysbiosis ^[1].

In fact, the deiodinase enzyme is a crucial component of the thyroid hormone metabolic pathway. In which the function of deiodinase enzymes 2 and 3 is highly correlated with that found in the human gut. Consequently, the amounts of T3 as well as other hormones are based on intestinal circumstances, which are regulated by gut bacteria. Several microorganisms have been discovered as regulators of iodothyronine metabolism-related enzymes. Furthermore, the gut bacteria may bind thyroid hormone particularly ^{[24], [25], [1]}. The mechanisms of

glucuronide conjugation and conjugation through sulphate groups are crucial for iodothyronine metabolism within the liver. Conjugation through sulphate groups increases the quantity of deiodinase's inactive metabolite, while glucuronide conjugation generates substantial quantities of T4 that are released further into gut lumen via the biliary system [26]. The majority of glucuronidase action is produced by bacteria [27]. Through the hepatoenteric cycle [28], T4, the inactive variant of thyroid hormone, re-enters the systemic circulation and increases iodothyronine levels. That process is a major bottleneck for the balance of thyroid hormones in rats [28], but the precise function of deconjugated thyroxine is unknown.

The most prevalent form of hyperthyroidism, which is Graves' disease, with an incidence of 20 to 50 instances per 100,000 people per year, have a peak age of 30 to 50 [29]. There have been thorough descriptions of epigenetic and also genetic risk susceptibility in this condition, including susceptibility genes that include thyroglobulin and TSH receptor, which is thyroid specific genes, and other key genes that also contribute to control of the immune system [30]. Several endogenous variables, such as excess iodine, poor levels of vitamin D, smoking, medicines (α-interferon, alemtuzumab) [31],[32], also infections [31], are related with an increased chance of developing Graves' disease. In addition, Hepatitis C, *H. pylori*, and *Y. enterocolitica* have been implicated within the development of Graves' disease. Using molecular mimicry, an *in silico* research investigated the potential involvement of infection in inducing thyroid autoimmunity. The scientists discovered a significant level of similarity between the thyroid antigens and amino acid sequences of microbial proteins [33]. Several species come under the genera *Lactobacillus* and *Bifidobacterium*, including a number of commensal bacteria and even probiotics [33], have been characterized as having the potential for cross-reactivity owing to TSH receptor similarity.

Hashimoto's thyroiditis represents the most prevalent autoimmune condition, affecting five percent of the global population [6]. The genesis of Hashimoto's thyroiditis is based on the interplay among genetic background susceptibility also both endogenous and environmental trigger factors, as described in Graves' disease. The Hashimoto's thyroiditis-related polymorphism was identified in genes encoding immune proteins implicated in particular stages [30]. The pathophysiology of Hashimoto's thyroiditis should entail environmental variables in addition to endogenous elements. These environmental variables include excessive iodine intake, α-interferon and antiretroviral medication, and infection with hepatitis C [34]. An imbalance among anti-inflammatory and also pro-inflammatory processes might initiate autoimmunity of the thyroid [35],[36].

Conclusion

Autoimmune thyroid disease and gut microbiota have a potential relationship which, if further investigated, could be the future of autoimmune thyroid disease therapy. The gut microbiota can influence the morphology of the gut itself and ultimately influence thyroid hormone function. Impaired intestinal permeability can be another cause that affects thyroid hormone function. Furthermore, the gut microbiota becomes an important factor in the development of the immune system, so that disturbances in the balance of the gut microbiota can trigger auto-aggressive disorders that lead to autoimmune thyroid disease. The deiodinase enzyme, which is an important factor in thyroid hormone metabolism, can also be influenced by the gut microbiota. Where the most common autoimmune thyroid disease, Graves' disease and Hashimoto's thyroiditis both have links with the balance of the gut microbiota.

Acknowledgement

None of the authors have any conflict of interest regarding the contents of this article

References

- [1] C. Virilli and M. Centanni, "Does microbiota composition affect thyroid homeostasis?," *Endocrine*, vol. 49, pp. 583-587, 2015.
- [2] E. Thursby and N. Juge, "Introduction to the human gut microbiota," *The Biochemical Journal*, vol. 474, no. 11, pp. 1823-1836, 2017.
- [3] M. Arumugam, J. Raes, E. Pelletier, D. Le Paslier, T. Yamada, D. R. Mende, G. R. Fernandes, J. Tap, T. Bruls, J.-M. Batto, M. Bertalan, N. Borruel, F. Casellas, L. Fernandez, L. Gautier, T. Hansen, M. Hattori, T. Hayashi, M. Kleerebezem, K. Kurokawa, M. Leclerc, F. Levenez, C. Manichanh, H. B. Nielsen, T. Nielsen, N. Pons, J. Poulain, J. Qin, T. Sicheritz-Ponten, S. Tims, D. Torrents, E. Ugarte, E. G. Zoetendal, J. Wang, F. Guarner, O. Pedersen, W. M. de Vos, S. Brunak, J. Doré, MetaHIT Consortium, J. Weissenbach, S. D. Ehrlich and P. Bork, "Enterotypes of the human gut microbiome," *Nature*, vol. 473, pp. 174-180, 2011.
- [4] S. Rautava, R. Luoto, S. Salminen and E. Isolauri, "Microbial contact during pregnancy, intestinal colonization and human disease," *Nature Reviews Gastroenterology & Hepatology*, vol. 9, pp. 565-576, 2012.
- [5] E. Fröhlich and R. Wahl, "Microbiota and Thyroid Interaction in Health and Disease," *Trends in Endocrinology and Metabolism*, vol. 30, no. 8, pp. 479-490, 2019.
- [6] C. Virilli, P. Fallahi, A. Antonelli, S. Benvenga and M. Centanni, "Gut microbiota and Hashimoto's thyroiditis," *Reviews in Endocrine & Metabolic Disorders*, vol. 19, no. 4, pp. 293-300, 2018.
- [7] C. R. Mackay and K. M. Maslowski, "Diet, gut microbiota and immune responses," *Nature Immunology*, vol. 12, pp. 5-9, 2011.
- [8] I. Franks, "Functional ectopic liver tissue in the lymph nodes of mice with lethal liver disease," *Nature Reviews Gastroenterology & Hepatology*, vol. 8, p. 182, 2011.
- [9] K. Suzuki, S. Kawamoto, M. Maruya and S. Fagarasan, "GALT: organization and dynamics leading to IgA synthesis," *Advances in Immunology*, vol. 107, pp. 153-85, 2010.
- [10] A. M. Ercolini and S. D. Miller, "The role of infections in autoimmune disease," *Clinical and Experimental Immunology*, vol. 155, no. 1, pp. 1-15, 2009.
- [11] M. Levy, A. A. Kolodziejczyk, C. A. Thaiss and E. Elinav, "Dysbiosis and the immune system," *Nature Reviews Immunology*, vol. 17, pp. 219-232, 2017.
- [12] L. Boussamet, E. Montassier, J.-P. Soulillou and L. Berthelot, "Anti α 1-3Gal antibodies and Gal content in gut microbiota in immune disorders and multiple sclerosis," *Clinical Immunology*, vol. 235, 2022.
- [13] A. Pianta, S. L. Arvikar, K. Strle, E. E. Drouin, Q. Wang, C. E. Costello and A. C. Steere, "Two rheumatoid arthritis-specific autoantigens correlate microbial immunity with autoimmune responses in joints," *The Journal of Clinical Investigation*, vol. 127, no. 8, pp. 2946-2956, 2017.
- [14] A. Hevia, C. Milani, P. López, A. Cuervo, S. Arboleya, S. Duranti, F. Turrone, S. González, A. Suárez, M. Gueimonde, M. Ventura, B. Sánchez and A. Margolles, "Intestinal dysbiosis associated with systemic lupus erythematosus," *mBio*, vol. 5, no. 5, pp. e01548-14, 2014.
- [15] C. T. Brown, A. G. Davis-Richardson, A. Giongo, K. A. Gano, D. B. Crabb, N. Mukerjee, G. Casella, J. C. Drew, J. Ilonen, M. Knip, H. Hyöty, R. Veijola, T. Simell, O. Simell, J. Neu, C. H. Wasserfall, D. Schatz, M. A. Atkinson and E. W. Triplett, "Gut microbiome metagenomics analysis suggests a functional model for the development of autoimmunity for type 1 diabetes," *PLoS One*, vol. 6, no. 10, p. e25792, 2011.
- [16] U. Uusitalo, X. Liu, J. Yang, C. A. Aronsson, S. Hummel, M. Butterworth, Å. Lernmark, M. Rewers, W. Hagopian, J.-X. She, O. Simell, J. Toppa, A. G. Ziegler, B. Akolkar, J. Krischer, J. M. Norris, S. M. Virtanen and TEDDY Study Group, "Association of Early Exposure of Probiotics and Islet Autoimmunity in the TEDDY Study," *JAMA Pediatrics*, vol. 170, no. 1, pp. 20-8, 2016.
- [17] V. Fernandez-García, S. González-Ramos, P. Martín-Sanz, J. M. Laparra and L. Boscá, "Beyond classic concepts in thyroid homeostasis: Immune system and microbiota," *Molecular and Cellular Endocrinology*, vol. 533, 2021.
- [18] R. P. Oliveira, A. F. Santiago, S. M. Ficker, A. C. Gomes-Santos and A. M. C. Faria, "Antigen administration by continuous feeding enhances oral tolerance and leads to long-lasting effects," *Journal of Immunological Methods*, vol. 421, pp. 36-43, 2015.
- [19] F. C. Sasso, O. Carbonara, R. Torella, A. Mezzogiorno, V. Esposito, L. Demagistris, M. Secondulfo, R. Carratu, D. Iafusco and M. Carteni, "Ultrastructural changes in enterocytes in subjects with Hashimoto's thyroiditis," *Gut*, vol. 53, no. 12, pp. 1878-80, 2004.
- [20] Q. Mu, J. Kirby, C. M. Reilly and X. M. Luo, "Leaky Gut As a Danger Signal for Autoimmune Diseases," *Frontiers in Immunology*, vol. 8, p. 598, 2017.
- [21] H.-J. Wu and E. Wu, "The role of gut microbiota in immune homeostasis and autoimmunity," *Gut Microbes*, vol. 3, no. 1, pp. 4-14, 2012.
- [22] A. J. Macpherson and N. L. Harris, "Interactions between commensal intestinal bacteria and the immune system," *Nature Reviews Immunology*, vol. 4, no. 6, pp. 478-85, 2004.

- [23] E. Bosi, L. Molteni, M. G. Radaelli, L. Folini, I. Fermo, E. Bazzigaluppi, L. Piemonti, M. R. Pastore and R. Paroni, "Increased intestinal permeability precedes clinical onset of type 1 diabetes," *Diabetologia*, vol. 12, pp. 2824-7, 2006.
- [24] E. Fröhlich and R. Wahl, "Microbiota and Thyroid Interaction in Health and Disease," *Trends in Endocrinology and Metabolism*, vol. 30, no. 8, pp. 479-490, 2019.
- [25] C. Virili, G. Bassotti, M. G. Santaguida, R. Iurio, S. C. Del Duca, V. Mercuri, A. Picarelli, P. Gargiulo, L. Gargano and M. Centanni, "Atypical Celiac Disease as Cause of Increased Need for Thyroxine: A Systematic Study," *The Journal of Clinical Endocrinology & Metabolism*, vol. 97, no. 3, pp. 419-422, 2012.
- [26] S.-Y. Wu, W. L. Green, W.-S. Huang, Choper and I. J. Chopra, "Alternate pathways of thyroid hormone metabolism," *Thyroid*, vol. 15, no. 8, pp. 943-58, 2005.
- [27] M. P. Hazenberg, W. W. de Herder and T. J. Visser, "Hydrolysis of iodothyronine conjugates by intestinal bacteria," *FEMS Microbiology Letters*, vol. 54, no. 1, pp. 9-16, 1988.
- [28] M. T. Hays, "Thyroid hormone and the gut," *Endocrine Research*, vol. 14, no. 2-3, pp. 203-24, 1988.
- [29] T. J. Smith and L. Hegedüs, "Graves' Disease," *The New England Journal of Medicine*, vol. 375, no. 16, pp. 1552-1565, 2016.
- [30] H. J. Lee, C. W. Li, S. S. Hammerstad, M. Stefan and Y. Tomer, "Immunogenetics of autoimmune thyroid diseases: A comprehensive review," *Journal of Autoimmunity*, vol. 64, pp. 82-90, 2015.
- [31] J.-L. Wémeau, M. Klein, J.-L. Sadoul, C. Briet and F.-L. Vélayoudom-Céphise, "Graves' disease: Introduction, epidemiology, endogenous and environmental pathogenic factors," *Annales d'Endocrinologie*, vol. 79, no. 6, pp. 599-607, 2018.
- [32] L. Scappaticcio, M. Castellana, C. Virili, G. Bellastella, M. Centanni, S. Cannavò, A. Campenni, R. M. Ruggeri, L. Giovannella and P. Trimboli, "Alemtuzumab-induced thyroid events in multiple sclerosis: a systematic review and meta-analysis," *Journal of Endocrinological Investigation*, vol. 43, no. 2, pp. 219-229, 2020.
- [33] S. Benvenega and F. Guarneri, "Molecular mimicry and autoimmune thyroid disease," *Reviews in Endocrine & Metabolic Disorders*, vol. 17, no. 4, pp. 485-498, 2016.
- [34] F. Ragusa, P. Fallahi, G. Elia, D. Gonnella, S. R. Paparo, C. Giusti, L. P. Churilov, S. M. Ferrari and A. Antonelli, "Hashimoto's thyroiditis: Epidemiology, pathogenesis, clinic and therapy," *Best Practice & Research. Clinical Endocrinology & Metabolism*, vol. 33, no. 6, p. 101367, 2019.
- [35] M. G. Santaguida, S. Nardo, S. C. Del Duca, E. Lococo, C. Virili, L. Gargano, L. Lenti and M. Centanni, "Increased interleukin-4-positive lymphocytes in patients with Hashimoto's thyroiditis and concurrent non-endocrine autoimmune disorders," *Clinical and Experimental Immunology*, vol. 165, no. 2, pp. 148-54, 2011.
- [36] C. Virili, I. Stramazzo, M. Centanni, "Gut microbiome and thyroid autoimmunity", *Best Practice & Research Clinical Endocrinology & Metabolism*, vol. 35, no. 3, pp. 1-15, 2021.