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Commentary on the role of berberine in addition to methimazole compare to methimazole alone in the treatment of Graves' Disease

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Abstract

Graves' Disease (GD) is the most common form of hyperthyroidism. It affects 3% of female patients and 0.5% of male patients usually between the age of 30-60. It is the cause of 80% of hyperthyroid cases in the USA. The pathogenesis of the disease is complex and autoimmunity plays a key role. The antibodies stimulating the thyrotropin receptor (TRAb) lead to uncontrolled Thyroid-stimulating Hormone (TSH) overproduction of thyroid hormones from the overactive thyroid gland. The disease is frequently associated with Graves's ophthalmopathy, dermatopathy, and clubbing. It affects the whole body with deleterious effects on the Cardiovascular system, vision, bones, etc. The treatment of the disease is with anti-thyroid medications, Radioactive iodine, or thyroid surgery each one of which has its pluses and minuses. Other factors like Genetic, inflammatory, immune, environmental factors, etc. play critical roles in disease pathogenesis as well. In this article, we are discussing the newfound role of the gut-thyroid axis in the pathogenesis of GD. We are describing the role of the probiotic Berberine added to the anti-thyroid medication Methimazole in changing the gut microbiota by increasing the benefits and decreasing the deleterious bacteria in the gut. This can lead to the induction of anti-inflammatory cytokines and reduction of inflammatory ones which can regulate the immune system faster and better than with treatment with Methimazole alone. This treatment combination can eventually lead through the effect on the gut-thyroid axis to faster disappearance of the TRAb and remission and cure of GD.

Key Words: Graves' Disease; Graves Ophthalmopathy; Berberine; Methimazole; Autoimmunity; iron

1. Introduction

Graves' disease(GD) is an autoimmune disease [1, 2]. The lifetime risk in females for the disease is 3% and 0.5% in males. In iodine-sufficient areas, the disease causes 80% of hyperthyroid cases [3]. Usually, the peak of the disease is between 30- 60 years of age, with female to male ratio of 6 to 1. It is also common in patients with other autoimmune diseases and can be part of Autoimmune Polyglandular Syndrome 1,2, and 3(APS 1,2,3). Also, there might be a family history of the disease. It is not the only cause of Hyperthyroidism. Multinodular goiter, toxic adenomas, and Thyroid stimulating hormone (TSH) producing HP tumors also cause hyperthyroidism as well as activating mutations of the TSH receptor on the thyroid gland, among others. The difference between hyperthyroidism and thyrotoxicosis is that hyperthyroid patients have the endogenous increased function of the thyroid gland, while thyrotoxic patients might include hyperthyroid patients, but they also include patients who have increased release from the thyroid gland of the thyroid hormones in different forms of thyroiditis or exogenous consumption of thyroid hormones although the clinical manifestation of these diseases is similar. All hyperthyroid patients are thyrotoxic, but not all thyrotoxic patients are hyperthyroid. In this article, we will describe the accepted pathogenesis of GD and treatment while talking about new factors described recently in the genesis of GD and its treatment which are still not widely acceptable being new.

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2. Pathogenesis of GD and the role of berberine added to methimazole in the treatment of GD

The major accepted pathogenesis of GD disease is that the T lymphocytes become sensitized to some thyroid antigens and stimulate the B lymphocytes to produce the thyroid stimulating Immunoglobulin (TSI), un IG G1 antibody, and other Thyrotropin receptor antibodies(TRAb)[4] . This leads to autonomous production by the thyroid gland of excessive thyroid hormones responsible for the clinical manifestations of the disease not regulated by the TSH from the hypophyseal area. The classic manifestation of the disease includes thyroid ophthalmopathy, palpitations, weight loss, muscle weakness, thyroid acropachy, pretibial myxedema, cardiac arrhythmias, congestive heart failure, psychosis, and many others. The thyroid gland is usually diffusely enlarged, and there is a palpable thrill and audible bruit because the gland is hyper-vascularized. GD is an auto-immune-related disease. Micro RNAs, proteins, antibodies, and cytokines are upregulated in the circulatory system. The connection between all these factors and the immune system remains not very clear. Graves' disease is a classical Autoimmune, metabolic thyroid disease. Genetic, inflammatory, immune, environmental factors, stress, smoking, epigenetics, and other factors play critical roles in disease pathogenesis [5, 6, 7]. Some patients treated with radioactive iodine (RAI) for Multinodular goiter(MNG) also release thyroid antigens after treatment which stimulate the production of TSI and the development of GD.

The gut microbiota plays an important role in regulating the thyroid function in Graves' Disease (GD), and this is why adjusting its structure and function may produce beneficial metabolites to modulate host immunity and thus alleviate the disease. Graves' disease is a classical Autoimmune, metabolic thyroid disease. Genetic, inflammatory, immune, environmental factors, stress, smoking, epigenetics, and other factors play critical roles in disease pathogenesis. Recently described gut-thyroid axis in the regulation of thyroid function also plays a role in the disorder. There is a causal relationship between GD and the gut Microbiome. In the intestinal microbiota of GD patients, there is an increased number of pathogenic bacteria and decreased number of beneficial bacteria which might play a role in the pathogenesis and the treatment and outcome of the disease [8].

In previous studies, it has been shown that the abundance of Prevotella spp. in the gut is higher in patients with GD, as well as Bacteroides and Lactobacillus than in healthy individuals [9, 10, 11]. Those microorganisms might alter the intestinal barrier and increase the concentration of inflammatory cytokines which can change the immune status and predispose to autoimmune diseases. It has been shown that increased numbers of these gut bacteria correlate with immune activity in humans suggesting that the development of GD may be related to those gut bacteria [12].

The abundance of other pathogenic bacteria such as Streptococcus pneumoniae, Enterobacter hormaechei, and Chryseobacterium indologenes is also increased in patients with the disease and might play a role in its pathogenesis as described above [8]. These are new insights in the pathogenesis of GD underscoring the role of the Thyroid- gut axis. Prebiotics are substances that reduce the harmful strains of bacteria while increasing the healthful strains and activities.

Berberine acts on the gut microbiota as a prebiotic. It decreases the immunogenic strains of Prevotella spp. and the other harmful immunogenic microorganisms mentioned above. At the same time, it increases the healthful strains of bacteria like *Faecalibacterium prausnitzii and Lactococus lactis*. Treatment with Methimazole significantly decreases the immunogenic Prevotella spp. also, but the addition of Berberine leads to further suppression of these harmful microorganisms and increases also the healthful strains of *F. prausnitzii* and L. lactis. In some new studies, it was found that with the combination of Berberine and Methimazole significant decrement in the immunogenic strains of Prevotella spp. has been achieved beyond the effect of Methimazole alone [8]. At the same time, Berberine increased *F. prausnitzii*, and L. lactis. The new study found a significant negative correlation between increased *F. prausnitzii*, and lower levels of FT3 and FT4 and at the same time increment of the TSH due to increased

numbers of *F. prausnitzii* bacterias in the gut. This indicates a close relationship between the gut microbiota and thyroid hormones.

F. prausnitzii and L. lactis play key roles in the whole network [8] . GD has been reported to be an organ-specific autoimmune disease mediated by T lymphocytes. *F. prausnitzii* can stimulate peripheral mononuclear cells and increase the secretion of the anti-inflammatory cytokine IL-10, which can suppress autoreactive T and B cells and maintain autoimmune tolerance. The gut microbiota plays a significant role in improving or worsening the thyroid function in GD. Berberine added to methimazole adjusts further the gut microbiota which may produce beneficial metabolites to improve the host immunity and lead to faster improvement of the disease [8, 13].

Six months after berberine combined with methimazole treatment, FT4, FT3, and TSH showed significant changes compared to baseline, with FT4, FT3, and TRAb showing a decreasing trend and TSH showing an increased trend. In contrast to methimazole alone, berberine supplementation not only restored FT3 to the normal level of healthy

individuals but also restored TSH to a normal level within 6- months [8, 14]. TSH frequently in GD might be low one year after treatment of the disease only with Methimazole and this can lead to recurrence of the disease after stopping the drug. The expression of thyrotropin receptor antibodies(TRAb) although not in the normal range was much lower in combined treatment compared to the treatment with Methimazole alone. This is the most important factor for the lack of recurrence of autoimmunity and GD after stopping the medication therapy.

3. Discussion

Graves' disease is a classical autoimmune disorder, where antibodies are formed against thyrotropin receptor and stimulate its activity leading to excessive not regulated by TSH hyperfunction of the thyroid gland. The TRAb are stimulatory and they are mimicking the effect of TSH. Having another autoimmune disease increases the risk of developing GD and vice versa [15].

There are 3- major treatments nowadays for GD-anti-thyroid medications, thyroidectomy, and Radioactive iodine treatment(RAI) [16].

Anti-thyroid medications prevent the biosynthesis of thyroid hormones. Methimazole is the most frequently used. It has a long half-life, immunosuppressive properties, and fewer side effects than Propylthiouracil(PTU). PTU has been recently linked to fatal hepatotoxicity. Also, it has to be taken 3- times a day. The minor side effects of the anti-thyroid medications are fever, rash, and arthralgia, and changing from one to the other anti-thyroid medication in these situations is sufficient. The major side effects although which are very serious with using Methimazole and PTU are agranulocytosis with fatal infections, hepatotoxicity – mainly with PTU, cholestatic Jaundice with Methimazole and pancreatitis due to methimazole which necessitates stopping of the drugs. Also in the first trimester of pregnancy, PTU is preferred because of changes in the fetus- aplasia cutis, etc. associated more often with Methimazole. Methimazole can cause during pregnancy premature delivery also. These major side effects necessitate stopping not changing of the anti-thyroid medications. This is why finding a drug that can affect the autoimmune mechanism of the disease and stop the pathogenic process is of vital importance. In general, it is recommended that anti-thyroid drugs are stopped after 12-24 months when the thyroid hormone levels normalized and there is a conversion to negative TRAb. The faster this happens the best is the outcome of the GD patients. If after stopping the anti-thyroid medication the patients have a recurrence of the GD a choice of having surgery or treatment with radioactive iodine(RAI) or to continue the anti-thyroid medications belongs to them after discussion with the physicians treating them. It has been shown that the longer the patients with GD who were being treated with Methimazole the remission rates of the GD after 2- years of treatment are between 15-50% of patients but after 7-8 years of treatment with antithyroid medications up to 85% of patients might have a remission. This is a long time with potentially subjecting the patients to the side effects of the anti-thyroid drug.

The RAI therapy uses radioisotope I-131. The isotope destroys the cells that produce thyroid hormones and leads to permanent hypothyroidism in 100% of patients necessitating treatment with L- Thyroxin and thus changing one drug with another. This occurs months to years after RAI treatment, but sometimes within 6- months. Also, it can cause worsening of Graves' ophthalmopathy(GO) and is contraindicated in a moderate or severe GO. The release of thyroid antigens after RAI treatment might lead to GD rarely also.

The third available treatment is surgery- thyroidectomy. It can cause hypothyroidism, hypoparathyroidism, and recurrent nerve palsy depending on the experience of the surgeon and the patient's anatomy. Thyroidectomy reduces the known complications of GD congestive heart failure(CHF) and arrhythmias by 80% based on some studies, RAI- reduces arrhythmias by 50%, with little effect on CHF and anti-thyroid medications reduce the risk of CHF and arrhythmias by 41-67% [17].

Obviously from the above discussion if we can alter the autoimmune nature of the disease and achieve earlier remission the results will be best. Finding out the role of Berberine as a probiotic which when added to the anti-thyroid medication Methimazole decreases the time to normalization of TSH, FT3 and decreases the major pathogenetic mechanism of the disease- the TRAb significantly more than Methimazole alone. The mechanism as discussed lies in the gut- Thyroid axis. Berberine and Methimazole in combination decrease more than Methimazole alone the harmful gut bacteria as discussed above like Prevotella spp etc. This decreases the permeability of the gut and induction of proinflammatory cytokines which dysregulate the immune system and lead to autoimmunity. As evidence of benefit is the lower TRAb in GD patients treated with both drugs compare to Methimazole alone and normalized FT3 and TSH to the level of healthy individuals within 6- months compare to Methimazole alone. Also, Berberine increases the production in the gut of beneficial bacteria like L.lactis and F.prausnitzii. As discussed *F. prausnitzii* increases the secretion of the anti-inflammatory cytokine IL-10, which can suppress the autoreactive T and B cells and maintain immune tolerance which

can help the remission/cure of GD. All of these results suggest that berberine combined with methimazole modulates host immunity in GD by affecting the gut microbiota.

Another interesting phenomenon observed in some studies is the positive correlation and normalization of TSH and the number of *F. Prausnitzii* bacteria in the gut as well as the increased secretion of enterobactin. In particular, berberine upregulates the synthesis of enterobactin. Enterobactin is essential for the iron uptake by the patients and the maintenance of normal thyroid function depends on iron levels of the people. Iron deficiency can cause thyroid function to decline. Upregulating by berberine of the synthesis of enterobactin may further help the thyroid function to improve in patients with GD [17].

4. Conclusion

In conclusion, in searching the ways to faster achieve remission in patients with GD the combination of Methimazole and the probiotic berberine can play an important role compared to the treatment of GD with Methimazole alone. This additional beneficial effect of berberine might be achieved by changing the gut microbiota. It increases the beneficial gut bacteria and decreases the deleterious ones. This leads to a decrease in the permeability of the gut which stimulates the decrement of the proinflammatory cytokines in the blood and, increases the anti-inflammatory ones, which leads to normalization of the immune dysregulation in patients with GD faster than with the treatment of Methimazole alone. This intervention on the gut-thyroid axis can be used in the future treatment endeavors of GD for faster achieving of immune and hormonal remission of the patients with this disease by combining Methimazole with Berberine rather than treating GD with Methimazole alone.

Compliance with ethical standards

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References

[1] Frohlich E, Wahl R. Microbiota and Thyroid Interaction in Health and Disease. Trends Endocrinol Metab (2019) 30(8):479–90. doi: 10.1016/j.tem.2019.05.008

[2] Zimmermann MB, Boelaert K. Iodine Deficiency and Thyroid Disorders. Lancet Diabetes Endocrinol (2015) 3(4):286–95. doi: 10.1016/S2213-8587(14)70225-6

[3] Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado Thyroid Disease Prevalence Study. Arch Intern Med (2000) 160(4):526–34. doi: 10.1001/archinte.160.4.526

[4] Barbesino G, Tomer Y. Clinical Review: Clinical Utility of TSH Receptor Antibodies. J Clin Endocrinol Metab (2013) 98(6):2247–55. doi: 10.1210/jc.2012-4309

[5] Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al.. Global Epidemiology of

[6] Villanueva R, Greenberg DA, Davies TF, Tomer Y. Sibling Recurrence Risk in Autoimmune Thyroid Disease. Thyroid (2003) 13(8):761–4. doi: 10.1089/105072503768499653

[7] Vaidya B, Kendall-Taylor P, Pearce SH. The Genetics of Autoimmune Thyroid Disease. J Clin Endocrinol Metab (2002) 87(12):5385–97. doi: 10.1210/jc.2002-020492

[8] Han Z, Cen C, Ou Q, Pan Y, Zhang J, Huo D, et al. The potential prebioticberberine combined with methimazole improved the therapeutic effect of graves' diseasepatients through regulating the intestinal microbiome. Front Immunol (2021) 12826067.doi: 10.3389/fimmu.2021.826067

[9] Bongers G, Pacer ME, Geraldino TH, Chen L, He Z, Hashimoto D, et al.. Interplay of Host Microbiota, Genetic Perturbations, and Inflammation Promotes Local Development of Intestinal Neoplasms in Mice. J Exp Med (2014) 211(3):457–72. doi: 10.1084/jem.20131587

[10] Jiang W, Yu X, Kosik RO, Song Y, Qiao T, Tong J, et al. Gut microbiota may play asignificant role in the pathogenesis of graves' disease. Thyroid (2021) 31(5):810–20. doi:10.1089/thy.2020.0193

[11] Wang Y, Ma XM, Wang X, Sun X, Wang LJ, Li XQ, et al. Emerging insights intothe role of epigenetics and gut microbiome in the pathogenesis of graves'ophthalmopathy. Front Endocrinol (Lausanne) (2021) 12788535. doi: 10.3389/fendo.2021.788535

[12] Cao, J et al. A cause-effect relationship between Graves' disease and the gut microbiome contributes to the thyroid-gut axis: A bidirectional two-sample Mendelian Randomization study. Frontiers in Immunology, 2023, Published 14 February 2023,doi:10.3389/fimmu.2023.977587

[13] Yang M, Zheng X, Wu Y, Zhang R, Yang Q, Yu Z, et al. Preliminary observation ofthe changes in the intestinal flora of patients with graves' disease before and aftermethimazole treatment. Front Cell Infect Microbiol (2022) 12794711. doi: 10.3389/fcimb.2022.794711

[14] Chen J, Wang W, Guo Z, Huang S, Lei H, Zang P, et al. Associations between gutmicrobiota and thyroidal function status in Chinese patients with graves' disease. J Endocrinol Invest (2021) 44(9):1913–26. doi: 10.1007/s40618-021-01507-6

[15] Kahaly GJ. Management of Graves thyroidal and extrathyroidal disease: An update. J Clin Endocrinol Metab. 2020;105(12):3704-3720.doi:10.1210/clinem/dgaa646

[16] Vargas-Uricoechea H. Molecular mechanisms in autoimmune thyroid disease. Cells.2023;12(6).doi:10.3390/cells12060918

[17] Issa PP, Hussein M, Omar M, et al. Cardiovascular health by Graves' disease management modality - Surgery versus radioactive iodine versus anti-thyroid medications: A network meta-analysis. J Surg Res. 2023;283:266-273.doi:10.1