DOI: 10.53469/jcmp.2025.07(09).48

Exploring the Approach of Soothing the Liver and Strengthening the Spleen in Preventing and Treating Hashimoto's Thyroiditis from the Perspective of Gut Microbiota Dysbiosis

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Abstract: ***Hashimoto's thyroiditis is a significant immune disorder in modern times, and liver-stomach disharmony is a key pathogenesis in Traditional Chinese Medicine (TCM). Recent studies have found that gut microbiota dysbiosis is correlated with the onset of Hashimoto's thyroiditis, while the functional characteristics of the TCM "liver" and "spleen" share many similarities with those of gut microbiota. Research indicates that the essence of liver depression and spleen deficiency may be associated with gut microbiota dysbiosis. Clinically, the approach of soothing the liver and strengthening the spleen not only effectively alleviates symptoms of Hashimoto's thyroiditis but also regulates gut microbiota function. This paper aims to explore the mechanism of soothing the liver and strengthening the spleen in treating Hashimoto's thyroiditis from the perspective of gut microbiota dysbiosis, with the goal of providing new insights and evidence for its clinical prevention and treatment.***

Keywords: Hashimoto's thyroiditis, Liver depression and spleen deficiency, Gut microbiota**.**

1. Introduction

Hashimoto's thyroiditis (HT) is a common autoimmune thyroid disorder (AITD) characterized by thyroid enlargement or nodules. Its clinical presentation primarily progresses through transitional, hyperthyroid, and hypothyroid phases. The condition is marked by insidious onset, high incidence, and difficulty in achieving complete cure. Early clinical symptoms are often non-specific, Symptoms may include neck thickening and throat discomfort. Laboratory thyroid function tests often remain within normal ranges, while thyroid peroxidase autoantibodies (TPOAb) and thyroglobulin antibodies (TGAb) persist at elevated levels. Conventional Western medical treatment for this stage has limitations, with most patients undergoing clinical observation without definitive therapeutic interventions. In contrast, Traditional Chinese Medicine (TCM) can employ syndrome-differentiated herbal formulas or acupuncture during this phase. Guided by TCM's "preventive medicine" philosophy, such interventions aim to halt disease progression. Stress-induced gut microbiota dysbiosis may represent a key pathological mechanism in HT. Research indicates that gut microbiota can influence HT pathogenesis and thyroid function through the thyroid-gut axis [1].

Goiter falls under the category of "goiter disease" in traditional Chinese medicine. The Treatise on the Origins and Manifestations of Various Diseases: Manifestations of Goiter and Tumors first documented: "Goiter arises from the stagnation of qi caused by worry and resentment. It is also said to result from drinking sandy water, where sand enters the blood vessels with the qi, accumulating beneath the neck to form the condition." Traditional Chinese medical theory posits that the liver governs the free flow of qi, the spleen governs the transformation and transportation of food and fluids, and the stomach governs the reception and digestion of food. The spleen and stomach serve as the source of qi and blood generation and the foundation of acquired constitution in the human body. Physiologically, the liver and spleen play crucial roles in maintaining intestinal function and regulating qi circulation throughout the body. Among 60 observed HT patients, the pattern of liver qi stagnation with spleen deficiency accounted for 63.3% of cases [2]. Liver Qi Stagnation with Spleen Deficiency is not only a key pathogenesis inducing gastrointestinal symptoms but also one of the primary TCM pathomechanisms underlying HT. Research indicates that the method of soothing the liver and strengthening the spleen can significantly reverse intestinal dysbiosis and improve gastrointestinal symptoms, suggesting a close association between the liver-qi stagnation and spleen-qi deficiency pathogenesis of HT and intestinal dysbiosis [3]. This study aims to explore the mechanism of action of liver-soothing and stomach-harmonizing methods in preventing and treating Hashimoto's thyroiditis from the perspective of gut microbiota dysbiosis.

2. Intestinal Flora and HT

2.1 Intestinal Flora Dysbiosis and HT

The gut microbiota constitutes a vast community of microorganisms residing within the human gastrointestinal tract. Characterized by its immense diversity, this microbial population plays a crucial role in promoting normal metabolic processes, participating in immune regulation, and exerting significant influence on multiple systems including the digestive, endocrine, immune, and nervous systems [4]. Under normal conditions, the body maintains a dynamic equilibrium with the gut microbiota. When the human microecological system exceeds its self-regulatory capacity, gut microbiota dysbiosis may occur, leading to a series of immune-related diseases. Research indicates that patients with Hashimoto's thyroiditis exhibit significant gut microbiota dysbiosis, characterized by increased levels of

Bacteroides, Escherichia coli, and Parabacteroides, alongside reduced levels of Bifidobacteria, Lactobacillus, and Prevotella [5].

In studies examining the correlation between gut microbiota and clinical thyroid indicators, CAYRESLCF et al. [6] found that Clostridium globosum and Clostridium globosum - Rectobacillus recti were positively correlated with TSH levels. The phyla Firmicutes and Bacteroidetes belong to the beneficial microbiota of the human body. ZHAOFY et al. [7] reported a positive correlation between the phylum Firmicutes and TPOAb and TGAb, while the phylum Bacteroidetes showed a negative correlation with these antibodies. These findings collectively indicate that the gut microbiota influences thyroid function and autoantibodies through multiple pathways and multi-targeted synergistic mechanisms.

2.2 Mechanisms of Gut Microbiota in HT Pathogenesis

2.2.1 Gut Dysbiosis Leads to Increased Intestinal Permeability

Abnormal or excessive growth of gut microbes and increased intestinal permeability can damage the intestinal mucosal barrier. This allows foreign pathogens to attack the internal environment, forming a “leaky gut,” leading to local immune activation and triggering systemic immune responses, thereby compromising the barrier function of the intestinal mucosa. A study comparing intestinal tissue of HT patients and healthy controls found thickened intestinal epithelial villi and enlarged inter-villous spaces in HT patients. The fructose/mannitol test confirmed significantly enhanced intestinal permeability in HT patients, increased intestinal permeability may lead to antigen leakage and trigger cross-immunity through molecular mimicry mechanisms [8]. Zonulin is a physiological modulator of intercellular tight junctions and regulates intestinal permeability. Gut dysbiosis can activate the Zonulin release pathway, increasing intestinal permeability in HT patients. Cayres et al. [6] assessed and found significantly elevated serum Zonulin in HT patients. Thus, damage to the intestinal mucosa caused by gut dysbiosis can further accelerate HT progression.

2.2.2 Gut Microbiota Affects Uptake of Essential Trace Nutrients for the Thyroid

Trace elements are crucial for maintaining normal thyroid function, participating in the synthesis, absorption, and metabolism of thyroid hormones. Knezevic et al. [9] first comprehensively described, through the “thyroid-gut axis” concept, how gut microbiota affects the uptake of various trace elements (such as Vitamin D, selenium, iodine) involved in thyroid hormone synthesis. Vitamin D may play a role in HT. Fu L et al. [10] found that Vitamin D can influence the Th17/Treg balance by downregulating IL-17 and upregulating IL-10, thereby reducing antibody titers in HT patients. Vitamin D supplementation can significantly lower serum TgAb and TPOAb levels [11]. Most known selenoproteins are expressed in thyroid tissue, assisting in maintaining thyroid hormone metabolic homeostasis by reducing free radical damage to the thyroid. Studies found the incidence of selenium deficiency was significantly higher in HT patients than controls, suggesting selenium deficiency may be related to HT pathogenesis [12]. Iodine is a raw material for thyroxine synthesis; both insufficient and excessive intake can cause thyroid disorders. Iodine deficiency leads to nodular goiter and hypothyroidism, while iodine excess is considered an important environmental factor in HT pathogenesis [13].

3. Relationship between Liver Depression - Spleen Deficiency and HT, Gut Microbiota

3.1 Liver Depression-Spleen Deficiency and Gut Microbiota Dysbiosis

From a modern medical perspective, beneficial bacteria dominate a healthy gut microbiota, enabling regular gastrointestinal peristalsis and promoting digestion and absorption of nutrients. Thus, gut microbiota participates in the metabolism of nutrients within the body. In TCM, the Liver is a rigid organ, substantive in form and functional in activity. It governs free coursing, prefers orderly reaching, regulates the qi dynamic and emotions, and governs the discharge of urine and feces. Normal bowel movements depend on the free flow of Liver qi. The Spleen is the official of the granary, governing transformation and transportation, receiving food and water, and transforming them into qi and blood. The Spleen is also the pivot of qi movement; when the ascent and descent of qi are orderly, Spleen and Stomach transportation and transformation function properly. From the TCM Five Elements theory perspective, the Liver belongs to Wood, and the Spleen belongs to Earth. When the Liver freely courses the qi dynamic, the Spleen benefits from this free flow, resulting in coordinated and orderly movement of qi and normal transportation and transformation functions. Conversely, emotional disorder can lead to Wood Depression overwhelming Earth or an exuberant Liver overacting on the Spleen, causing disorder in the qi dynamic. This leads to Spleen dysfunction in transportation and transformation, resulting in gastrointestinal and systemic symptoms like indigestion, abdominal distension, diarrhea, or constipation, which are highly similar to gut microbiota dysbiosis. The dynamic balance of gut microbiota reflects the normal function of the “Spleen governing transportation and transformation,” while gut microbiota dysbiosis is similar in connotation to “Spleen failing in its transporting function” [14]. The “Treatise on the Spleen and Stomach” emphasizes “internal damage to the Spleen and Stomach gives rise to all diseases,” pointing out the indispensable importance of Spleen and Stomach function in disease development, which may share similarities with the pathogenic role of gut microbiota dysbiosis. Thus, the pathogenesis of Liver Depression-Spleen Deficiency is closely related to gut microbiota dysbiosis.

3.2 Liver Depression-Spleen Deficiency and HT

“Goiter is formed by qi binding.” The “Jisheng Fang · Treatise on Goiter and Tumor Treatment” states: “Goiter and tumor mostly arise from failure to restrain joy and anger, or excessive worry and contemplation.” Hashimoto’s thyroiditis often originates from emotional stagnation and Liver Qi Stagnation. The Liver governs free coursing, its core physiological function. Normal coursing allows Liver qi to flow freely, enabling the qi of all organs and meridians to

operate normally, i.e., overall "qi regulation". The Spleen governs transportation and transformation. The "Records of Traditional Chinese and Western Medicine in Combination" states "the Liver and Spleen are organs that assist each other's function." Dysfunction of Wood (Liver) coursing can overact on Earth (Spleen), leading to Spleen dysfunction in transportation and transformation. This weakens the function of transforming food and essence, resulting in stagnation of dampness and phlegm, which congeal in the neck region causing disease. Patients may exhibit anterior neck swelling, throat discomfort, sensation of a foreign object in the throat, distending pain in the hypochondrium, and reduced food intake. Liver Depression-Spleen Deficiency is the root, while Qi Stagnation, Blood Stasis, and Phlegm Obstruction are the branch. Clinical treatment should emphasize soothing the Liver and strengthening the Spleen. The "Suwen · Jin Gui Zhen Yan Lun" states: "The East Wind arises in spring, the disease is in the Liver, and the transport point is in the neck." This means the East Wind as a pathogenic factor can damage the Liver, and the disease manifestation appears externally at the neck. Similarly, dysfunction of the Liver can lead to pathological products lodging in the neck region, causing anterior neck swelling. Although the "Inner Canon" does not specifically record goiter, it documents that the meridians of the Liver, Spleen, and Stomach all traverse the throat area (where the thyroid is located), pass through the umbilicus, connect the head and feet, and network the entire body. Professor Lin Lan [15] believed the thyroid is an "extraordinary fu-organ that can assist the Liver in coursing and the Kidney in generating Yang." Liver Depression-Spleen Deficiency and Spleen-Kidney Yang Deficiency are important pathogeneses of HT. Clinical findings [16] indicate that HT patients are particularly prone to Spleen deficiency symptoms, such as spiritlessness, fatigue, and poor appetite, even during the euthyroid phase with insignificant clinical symptoms, further emphasizing the importance of strengthening the Spleen in clinical HT treatment.

4. Applying the Method of Soothing the Liver and Strengthening the Spleen to Regulate Gut Microbiota and Improve HT

The Liver Depression-Spleen Deficiency pattern is one of the common clinical patterns in HT. Applying the method of soothing the Liver and strengthening the Spleen through acupuncture, herbal medicine, and other means to regulate the gut microecology can prevent and improve HT.

4.1 Chinese Herbal Medicine - Gut Microbiota - HT

Liu J [17] found that the method of soothing the Liver and strengthening the Spleen, represented by Tongxie Yaofang (Painful Diarrhea Formula), can regulate the enteric nervous system (ENS), repair the intestinal mucosal barrier, and improve gut microbiota dysbiosis. Xiaoyao San (Free Wanderer Powder), from the "Tai Ping Hui Min He Ji Ju Fang" of the Song Dynasty, is another representative formula for soothing the Liver and strengthening the Spleen. Meta-analysis and trial sequential analysis confirmed [18] that modified Xiaoyao San is more effective than conventional Western medicine for irritable bowel syndrome with fewer adverse reactions. Modified Xiaoyao San can increase the abundance of probiotics producing short-chain fatty acids and reduce genera that stimulate intestinal inflammation, thereby inhibiting inflammation and promoting repair of the intestinal mucosal barrier [19]. Xiaoyao San modified granules, by coursing Liver qi, strengthening the Spleen, and resolving stasis, treat HT. A study [20] found that compared to selenium yeast tablets alone, Xiaoyao San modified granules combined with external herbal application more effectively reduced TSH levels and improved thyroid function in HT patients. Xiaoyao Bushen Formula (Soothing Liver and Tonifying Kidney Formula) [21] can downregulate pro-inflammatory bacteria like Enterobacteriaceae and Helicobacteraceae in EAT rats, and upregulate Coprococcus to produce large amounts of butyrate, inhibiting inflammatory responses, improving oxidative stress status, regulating TSH, TPOAb, and TgAb levels, and thereby modulating immune responses. Wang Y [22] proposed a modified version of Chaihu Jia Longgu Muli Tang (Bupleurum Plus Dragon Bone and Oyster Shell Decoction) by removing minium and rhubarb, and adding Chinese angelica, selfheal fruit spike, forsythia fruit, stir-fried white peony root, and honey-fried licorice. This new formula showed significant efficacy in treating HT with anxiety state of the Liver Depression-Spleen Deficiency, Heart Spirit Disquietude type. Ruanjian Xiaoying Granules (Softening Hardness and Dissipating Goiter Granules) contain ingredients like bupleurum root, white peony root, citrus peel, Chinese angelica, white atractylodes rhizome, poria, sargassum, and thallus laminariae. It has the effects of soothing the Liver, strengthening the Spleen, and dissipating goiter and nodules. Dong T [23] proposed that this formula can regulate the abundance of Firmicutes, Proteobacteria, Clostridia, Gammaproteo bacteria, Escherichia coli, etc, thereby regulating gut microbiota dysbiosis, improving TgAb and TPOAb levels and autoimmune status, inhibiting the destruction of thyroid cells by related cytokines, and exerting a therapeutic effect on HT.

Modern pharmacological studies have also found that many Chinese herbal medicines can regulate gut microbiota, promote probiotic proliferation, modulate the composition of gut microbiota, and maintain microbial balance to treat HT. Mu Y et al. [24] experimentally found that total glucosides of paeony (from white peony root) can reduce the diversity and abundance index of gut microbiota in EAT rats, decrease the relative abundance of Firmicutes, and increase the relative abundance of Lactobacillus. The main extracts of bupleurum root [25], such as bupleurum polysaccharides and saikosaponins, can lower TGAb and TPOAb levels, regulate T lymphocytes and related subsets to maintain homeostasis, and control TLRs pathways, NF-kB, TGF-β pathway, MAPK/NF-κB pathway, etc., to collectively improve the immune system. Alginate polysaccharide is a dietary fiber extracted from seaweed. Multiple studies indicate seaweed has significant efficacy in treating HT [26]. Huang J et al. [27] found that fucoidan can regulate the disordered gut microbiota in immunocompromised mice, increase Lactobacillus quantity, alleviate intestinal mucosal damage, and effectively enhance immune function in these mice.

4.2 Acupuncture - Gut Microbiota - HT

Acupuncture can not only regulate the body's endocrine, nervous, and immune systems but also influence gut microbiota, thereby improving clinical symptoms in HT

patients. Studies indicate [28] that acupuncture at Zusanli (ST36) and Guanyuan (CV4) has a beneficial regulatory effect on the structure and richness of gut microbiota. It can reduce serum levels of TSH, TgAb, TPOAb, IL-6, and IL-12 in HT model rats, improve metabolic disorders, inhibit inflammatory responses, and control disease progression. This suggests that acupuncture at the strengthening points Zusanli and Guanyuan can improve clinical symptoms in HT patients by regulating gut microbiota. SUN J et al. [29] found that electroacupuncture and moxibustion can balance the Th17/Treg axis by regulating the composition and abundance of gut microbiota, restore normal immune responses, reduce the release of inflammatory factors, and repair intestinal mucosal damage. Currently, research on acupuncture regulating gut microbiota to intervene in HT is limited. However, regulating qi and freeing collateral networks is a strength of acupuncture therapy. By stimulating acupoints, it smoothes the qi dynamic, harmonizes yin and yang, allows smoother operation of the thyroid-gut axis, and stabilizes the immune macroenvironment through intestinal microecological stability.

5. Summary

In summary, gut microbiota, as a key link in the microbe-gut-thyroid axis, is closely related to the endocrine-immune system and is an important target for HT research. In recent years, research on the interconnection and mechanisms between gut microecology and HT has gradually intensified, ranging from basic molecular experiments to clinical observations, and from single targets to gene prediction, involving complex and intertwined mechanisms. Based on the holistic concept of TCM and the principle of "soothing the Liver and strengthening the Spleen," this article discusses regulating gut microecological homeostasis and restoring physiological balance through acupuncture, herbal medicine, and other means, hoping to provide ideas and evidence for the clinical prevention and treatment of HT based on pattern differentiation. However, exploring the microbiological mechanisms of the method of soothing the Liver and harmonizing the Stomach in treating HT still requires further validation through extensive animal experiments and clinical trials. Combined with analysis of HT subtypes, it could provide a basis for precise treatment of refractory HT. This research direction holds significant scientific value and clinical importance and is worthy of in-depth exploration.

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