



Original Article

Acupuncture treatment for Hashimoto's thyroiditis: An exploratory randomized controlled trial

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ABSTRACT

Background: Hashimoto's thyroiditis (HT) has a high incidence rate and unresolved clinical symptoms. Although Hand Yangming Meridian Penetrating Acupuncture has been used to treat thyroid diseases in China, there is no randomized controlled trial (RCT) on HT.

Methods: This exploratory RCT aims to preliminarily evaluate the efficacy, safety, and feasibility of Hand Yangming Meridian Penetrating Acupuncture in the treatment of HT. Included subjects were randomly assigned to the acupuncture group and the waiting treatment group at a ratio of 1:1. Subjects in the acupuncture group received 16 weeks of acupuncture treatment, followed by a 16-week follow-up observation phase. Subjects in the waiting group received thyroxine supplementation for 16 weeks, followed by 16 weeks of compensation treatment. Serum thyroid peroxidase antibody (TPOab) and thyroglobulin antibody (TGAb) levels were the main indicators, and Thyroid-Related Patient-Reported Outcome short form (ThyPRO-39), MOS Item Short Form Health Survey (SF-36), and Hospital Anxiety and Depression Scale (HADS) scores were also recorded.

Results: In total, 58 subjects were included. After 16 weeks of treatment, there was no statistical difference in the changes in TPOab levels between the two groups, but the TGAb level in the acupuncture group was significantly lower than in the waiting group (difference: -141.97 [95 % CI: -222.4 to -61.5], $P = 0.011$). Moreover, the total ThyPRO-39 and SF-36 scores were statistically different between the two groups ($P_{\text{ThyPRO-39}} < 0.001$, $P_{\text{SF-36}} = 0.005$). There was no statistical difference in HADS between the two groups.

Conclusions: Hand Yangming Meridian Penetrating Acupuncture may be safe and feasible for HT hypothyroidism to improve symptoms and reduce TGAb levels.

Trial registration number: This trial was registered at Acupuncture-Moxibustion Clinical Trial Registry: AMCTR-IOR-19000308 (ChiCTR1900026830, <https://www.chictr.org.cn/searchprojEN.html>).

1. Introduction

Hashimoto's thyroiditis (HT) is one of the most common autoimmune thyroid diseases (AITDs) and the most common cause of hypothyroidism.¹ Since HT was reported at the beginning of the 20th century, its incidence rate has gradually increased. At present, the annual incidence rate is 0.3–1.5 in 1000 people, and the prevalence in women is 4- to 10-fold higher than that in men.² In China, the positive rate of the presence of thyroid antibodies is around 10 %, and the proportion of HT cases diagnosed by thyroid serum antibodies and thyroid ultrasound is about 2 %.^{3,4} The symptoms of HT are not completely dependent on abnormal thyroid hormone levels. With normal thyroid

hormone levels, HT patients may still experience clinical manifestations such as fatigue, emotional abnormalities, and neck discomfort, which are correlated with the antibody level.^{5–7} There is no treatment for the root cause of HT in modern medicine. At present, treatment of HT is based on stabilization of thyroid function.^{8,9} However, patients with stable thyroid function still require treatment to relieve their clinical symptoms and improve their quality of life. Some studies showed that levothyroxine (L-T4) treatment has no effect on various symptoms in patients with subclinical hypothyroidism (thyroid-stimulating hormone [TSH] levels, 3.5–10.0 mIU/L).¹⁰ Therapeutic effects of selenium preparations,^{11,12} vitamin D,¹³ metformin,¹⁴ diet management,¹⁵ and operative treatment¹⁶ have been preliminary observed in clinical trials, yet

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they may have some side effects after long-term usage and the clinical treatment needs have not been met. Therefore, there is an urgent need for more effective treatments.

Acupuncture is a traditional Chinese medicine treatment modality, which helps to regulate the internal environment of our bodies. It has anti-inflammatory and immunoregulatory effects and is widely used in the treatment of various diseases, including rheumatoid diseases, digestive tract diseases, and mental disorders, as well as pain management.¹⁷ Acupuncture treatment for HT has potential clinical value, in both regulating the immune system and improving clinical symptoms.^{18,19} Ancient Chinese books contain records of the use of acupuncture and moxibustion treatment for goiter disease dating back 2000 years, and the same acupoints are currently still being used in the clinical practice of acupuncture therapy and moxibustion treatment in China.²⁰ At present, clinical studies on the effects of acupuncture and moxibustion in the treatment of thyroid diseases are scarce, and the evidence level and research quality are low.¹⁸ The results of these studies show that acupuncture and moxibustion can reduce the thyroid antibody levels, stabilize thyroid function, and improve clinical symptoms.^{18,19} Among them, the application of penetration needling of the Hand Yangming Meridian is relatively common.^{20,21} A clinical study carried out in Beijing showed that penetration needling of the Hand Yangming Meridian can reduce the size of thyroid nodules.²² Although many Chinese physicians have used this method to treat different kinds of thyroid diseases, there is no randomized controlled trial (RCT) on the treatment of HT with penetrating acupuncture through the Hand Yangming Meridian, limiting the application of acupuncture in the treatment of thyroid diseases.

Therefore, we carried out this exploratory RCT to preliminarily evaluate the efficacy, safety, and feasibility of Hand Yangming Meridian Penetrating Acupuncture in the treatment of HT by evaluating the levels of thyroid antibodies and patients' quality of life. In the study design, on the one hand, HT's condition is stable and can only be observed clinically. On the other hand, the effective mechanism of this acupuncture method is not yet clear, making it difficult to set up a placebo control. Therefore, we used the waiting treatment group as the control group. Based on interviews with experienced physicians, we believe a long course of acupuncture treatment might reinforce the immune system. Therefore, the treatment period was set at 16 weeks to fully observe the effects of acupuncture treatment in HT.

2. Methods

2.1. Design and participants

This study is an exploratory, practical, randomized, blank-controlled clinical trial. The study was carried out at the outpatient department of the Department of Acupuncture and Moxibustion of Dongzhimen Hospital of Beijing University of Traditional Chinese Medicine from October 2019 to May 2021. Clinical subjects were recruited through advertisements at the outpatient department of the hospital and nearby communities, the official WeChat account of the hospital. Subjects were randomly assigned to the acupuncture group and the waiting treatment group at a ratio of 1:1. Subjects in the acupuncture group received 16 weeks of acupuncture treatment, followed by a 16-week follow-up observation phase; subjects in the waiting group received exogenous thyroxine supplementation treatment for 16 weeks, followed by 16 weeks of compensatory treatment (Fig. 1).

According to China's Guidelines for Diagnosis and Treatment of Thyroid Diseases (2008)²³ and Reviews on Autoimmunity (2014),²⁴ diffuse goiter as determined by ultrasound and positive serum thyroid peroxidase antibody (TPOAb) can be used as criteria for the diagnosis of HT. Patients aged between 18 and 70 years, diagnosed with HT, and in the stage of hypothyroidism who regularly take L-T4 and are willing to cooperate with acupuncture treatment were included in this study. TRAb-positive patients, patients with thyroid malignancies, subacute thyroiditis, or severe medical or psychiatric diseases, patients who underwent

thyroid surgery, and pregnant or lactating women were excluded. This research protocol was approved by the Ethics Committee of Dongzhimen Hospital of Beijing University of Traditional Chinese Medicine (No. 2017BL-076-01), registered in the Acupuncture Clinical Trial Registration Center (AMCTR-IOR-19,000,308, ChiCTR1,900,026,830), and published.²¹

2.2. Randomization and blinding

A random sequence was generated by an independent researcher who did not participate in the recruitment, treatment, follow-up, and data processing using SPSS 23.0 (IBM Corp., Armonk, NY, USA). The random numbers were kept in an opaque envelope. Subjects signed the informed consent form, and the clinical therapists opened the envelopes to obtain the grouping information. The subjects were randomly divided into two groups at a ratio of 1:1. Due to the application of acupuncture therapy and the setting of the blank control group, subjects and clinical therapists were not blinded, but data analysts were blinded. The data analysts collected subjects' data every 8 weeks through online questionnaires. Any form of communication between the subjects and data analysts was prohibited. The data analysts were unable to predict the grouping information from the questionnaire results, thus realizing the blind evaluation of this study.

2.3. Intervention

The acupuncture treatment plan for HT was based on ancient medical books and the experience of acupuncture experts (Supplement 1, 2). Acupoints included Sanjian (LI3), Hegu (LI4), Quchi (LI11), Binao (LI14), Jianyu (LI15), Renying (ST9), and Zusanli (ST36). The positioning of acupoints referred to the national standard (G/T12346).²⁵ The subjects were requested to stay in a supine position, and LI3 was punctured penetrating toward LI4 by a 0.25×40 mm acupuncture needle, LI11 was punctured penetrating toward LI14, and LI14 was punctured penetrating toward LI15 by a 0.30×75 mm acupuncture needle, ST9 was punctured superficially about 0.3–0.8 mm by a 0.18×40 mm acupuncture needle, ST36 was punctured perpendicularly about 25–37.5 mm, and LI15 was obliquely punctured about 25–37.5 mm deep. The needles were retained for 20 min after the manipulation of lifting, inserting, twisting, and turning to “deqi”. Subjects in the acupuncture group received acupuncture treatment for 16 weeks, two to three times in a week, followed by 16 weeks of follow-up observation. Subjects in the waiting group were treated with compensatory acupuncture after 16 weeks.

L-T4 is the main substitute for primary clinical hypothyroidism and subclinical hypothyroidism. Throughout the study period, all subjects in the acupuncture group and the waiting group took levothyroxine sodium tablets (trade name: Youjiale; specification: $50 \mu\text{g} \times 100$ pieces; Manufacturer: Merck, Germany) to manage their thyroid function in an appropriate range throughout the entire study period. The prescription is once a day in the morning on an empty stomach. The target of treatment for HT with clinical hypothyroidism and subclinical hypothyroidism is to maintain the serum TSH, TT4, and FT4 levels within the normal range; for pregnant women, the goal is to maintain TSH below 2.5 mU/L. During the study period, subjects did not take other drugs that may affect the thyroid antibody level, such as selenium preparations and vitamin D.

2.4. Outcomes

2.4.1. Primary outcomes

Although the diagnosis of HT mainly depends on the level of TPOAb, thyroglobulin antibody (TGAb) also reflects the immune status of HT objectively and quantitatively and is often used as a therapeutic indicator of HT.²⁶ Therefore, TPOAb and TGAb were used as the main therapeutic indicators in this study. Hypothyroidism is a common complication and

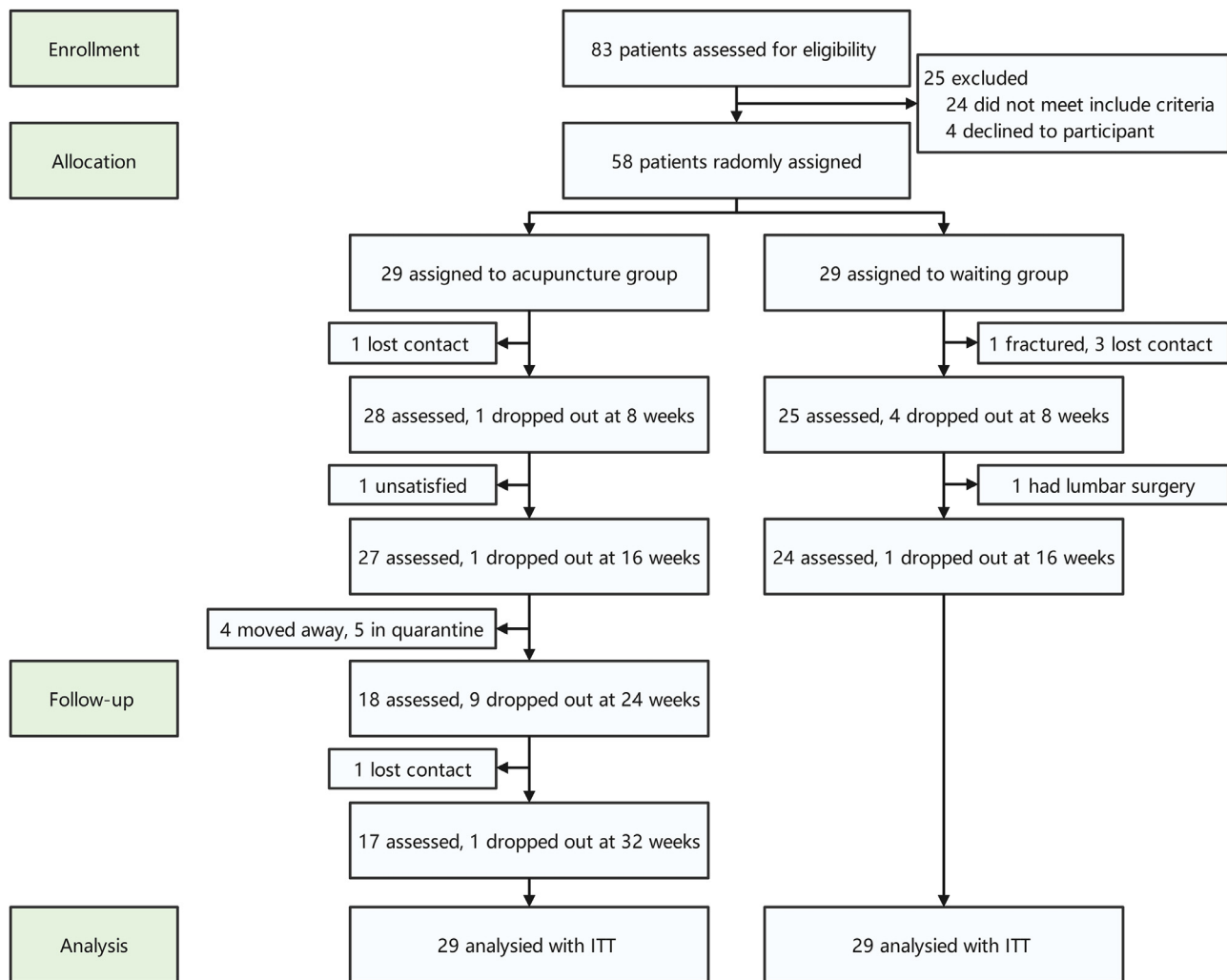


Fig. 1. Trial flow chart. ITT, Intention-To-Treat.

outcome state of HT. Therefore, HT hypothyroidism subjects taking exogenous thyroxine to maintain stable thyroid function were selected as research objects in this study, and their thyroid function was monitored to exclude the impact of fluctuations of thyroid function on antibody levels. Thyroid antibody levels and thyroid function were tested by taking peripheral blood at 0, 8, 16, 24, and 32 weeks during the study period.

2.4.2. Secondary outcomes

Secondary outcome measurements included the Thyroid-Related Patient-Reported Outcome short form (ThyPRO-39),^{27,28} MOS Item Short Form Health Survey (SF-36),⁷ and Hospital Anxiety and Depression Scale (HADS) scores to comprehensively evaluate the quality of life and discomfort symptoms of subjects. All scores were recorded at 0, 8, 16, 24, and 32 weeks. For the clinical scales, see Supplement 3.

The TPOab and TGAb serum levels were determined by electrochemical luminescence (Roche Diagnostics GmbH, Germany) to evaluate thyroid immune function. The serum-free triiodothyronine (FT3), free thyroxine (FT4), and TSH levels were determined by immunochemiluminescence assays (Beckman Coulter, USA) to evaluate thyroid function. Blood samples were collected from fasting subjects at 7:00–9:00 a.m. in 3 ml pro-coagulant tubes. The collected blood was left to stand for 30 min and centrifuged at room temperature for 10 min (3000 rpm). The serum thyroid antibody level was determined with a Roche Cobas e immune analyzer (Roche Diagnostics, Rotkreuz, Switzerland) and serum thyroid function was analyzed with a Beckman Kurt UniCel Dxl 800 im-

mune analyzer (Beckman Kurt Co., Ltd., USA) within 8 h of the day. The normal reference ranges are TPOab, 0.0–34.0 IU/mL; TGAb, 0–115 IU/mL; FT3, 2.3–4.8 pg/mL; FT4, 0.62–1.24 ng/dL; TSH, 0.56–5.91 μ IU/mL. Thyroid antibody and thyroid function tests were performed at 0, 8, 16, 24, and 32 weeks.

At the end of the study, an anonymous questionnaire was administered to subjects who had participated in at least one acupuncture treatment to ask for their evaluation of this acupuncture program for HT. The questionnaire consisted of four questions, including “Is acupuncture treatment for Hashimoto’s thyroiditis satisfactory in improving symptoms?” “Is acupuncture treatment for Hashimoto’s thyroiditis satisfactory in improving thyroid hormone levels?” “Are you satisfied with the improvement of thyroid hormone levels in the treatment of Hashimoto’s thyroiditis by acupuncture?” and “Would you want to receive acupuncture treatment for Hashimoto’s thyroiditis in an outpatient clinic, taking into consideration the financial cost, time cost, experience of acupuncture treatment, and efficacy of the treatment?” Each question utilized a 5-point Likert scale with options including “Satisfied” “Relatively satisfied” “fair” “Somewhat dissatisfied” “Unsatisfactory”.

During the study, all adverse events were recorded in detail. According to the relationship of adverse events with acupuncture treatment, they were classified as treatment-related adverse reactions and unrelated adverse reactions. Adverse events caused by acupuncture include needle fainting, needle stagnation, needle breakage, unbearable acupuncture pain (VAS ≥ 6 points), local hematoma, infection, and other

discomfort after acupuncture, including pain after acupuncture, fatigue, palpitation, and dizziness.

2.5. Sample size

This study is a preliminary study, so the sample size was not previously calculated. As stated in the published protocol,²¹ considering the ethical requirements and feasibility, 30 subjects were recruited in each group. This study can serve as a reference for the calculation of sample size in subsequent studies.

2.6. Statistical analysis

All statistical analyses were conducted using R software (version 4.1.0). Two-sided tests were used. Differences were considered significant if $P < 0.05$. The Shapiro–Wilks test and QQ charts were used to test the normality of measurement data. Measurement data are presented as mean \pm standard deviation or as median and quartiles according to the distribution type. Count data and graded data are presented as frequencies. Demographic data and baseline data were compared by the independent sample *t*-test, Wilcoxon test, or chi-square test.

The data of all subjects in the first 16 weeks were analyzed based on intention-to-treat (ITT) analysis. Thyroid-related antibody was the main outcome indicator. The comparison between groups was based on a mixed linear model. TPOab and TGAb levels, which were tested three times in 16 weeks, were the response variables, while the baseline was the co-variate, group and time were fixed factors, and subjects were the random factor. The effect of acupuncture was determined based on the interaction between group and time. We used the lme4 and lmeTest packages in R to build this model. Due to the inaccuracy of the baseline data, missing data were not filled in. Similar analysis methods were used for secondary outcome indicators such as thyroid function (TSH, FT3, and FT4) and SF36, ThyPRO-39, and HADS scores.

In addition, to observe the long-term impact of acupuncture therapy on HT, we used a mixed-effect model to analyze the data of acupuncture groups. The model used all outcome indicators collected in 32 weeks as response variables, baseline data as co-variables, time as a fixed factor, and subjects as a random factor. The SIDAK method was used for correction in post hoc analysis.

3. Results

3.1. Participants enrollment and characteristics

In total, 83 subjects were screened between October 2019 and October 2020, and a total of 60 subjects were initially included. One subject in the experiment group and one subject in the control group met an exclusion criterion, and they were excluded, so in total, 58 subjects were included (29 in the acupuncture group and 29 in the waiting group). During the treatment period, two cases in the acupuncture group withdrew, and a total of 27 subjects completed the treatment. In the waiting group, five subjects were lost to follow-up, so this group comprised 25 subjects. In the acupuncture group, 18 subjects completed the 24th week of follow-up and 17 subjects completed the 32nd week of follow-up. Table 1 shows the demographic data and the baseline data of the two groups. There was no significant difference between the two groups.

3.2. Effects of acupuncture on outcomes

3.2.1. Primary outcomes

After 16 weeks of treatment, there was no statistical difference in the changes in TPOab levels between the acupuncture group and the waiting group ($P = 0.389$), and there was no statistically significant difference between baseline data and the 16-week follow-up data within each group (each $P > 0.05$). However, after 16 weeks of treatment, the TGAb level was significantly lower in the acupuncture group

than in the waiting group (difference: -141.97 [95 % CI: -222.4 to -61.5], $P = 0.011$). A significant difference in antibody level was found between baseline data and the 16-week follow-up data within the acupuncture group, showing the antibody level was reduced (corrected $P_{\text{week 1 vs. week 16}} = 0.049$), and the effect lasted more than 8 weeks after the end of treatment (corrected $P_{\text{week 1 vs. week 24}} = 0.0072$). The TPOab level was increased after 16 weeks (corrected $P_{\text{week 1 vs. week 32}} = 0.481$). During the study, thyroid function of the subjects was stable, and there was no statistical difference between groups and within groups (each $P > 0.05$) (Fig. 2. & Supplement 4.).

3.2.2. Secondary outcomes

With respect to quality of life, we selected two scales to explore the clinical value of acupuncture from multiple points of view. In general, the total ThyPRO-39 and SF-36 scores were statistically different between the two groups ($P_{\text{ThyPRO-39}} < 0.001$, $P_{\text{SF-36}} = 0.005$). At the 16th week, the total ThyPRO-39 score in the acupuncture group was 3.81 points lower (95 % CI: -5.47 to -2.14) than in the waiting group, and the total score of SF-36 was 5.70 points higher (95 % CI: 2.597 to 8.81) than in the waiting group. According to the analysis of each subscale of ThyPRO-39, acupuncture is effective in relieving goiter ($P = 0.001$) and hypothyroidism ($P = 0.001$). The statistical differences shown by the ThyPRO-39 composite scale are similar to the results of the SF-36 scale. According to the SF-36 scale analysis, acupuncture treatment can improve the physical ($P = 0.002$), vitality ($P = 0.024$), mental health ($P = 0.010$), and other dimensions. Within group comparison showed that the effect of acupuncture on the quality of life in HT was mainly statistically significant at the 16th week. Within group comparison revealed a significant difference in the total ThyPRO-39 score and its composite scale at the 24th week (week 24: $P_{\text{ThyPRO-39}} = 0.003$, $P_{\text{Composite scale}} = 0.003$). The effect decreased and faded after the treatment was ceased for 16 weeks (each corrected $P_{\text{week 1 vs. week 32}} > 0.05$) (Fig. 2. & Supplement 5, 6).

Although emotional fluctuation is a common symptom of HT, the subjects in this study showed no or mild anxiety and depression according to the HADS score. Although analysis of the SF-36 scale showed improvement in the mental health dimension after acupuncture treatment, there was no statistical difference in the comparison of HADS scores between groups ($P_{\text{HADS-A}} = 0.538$, $P_{\text{HADS-D}} = 0.928$). Within group comparison revealed a statistical difference in HADS-A score at week 8 in the acupuncture group, but the difference was no longer significant after correction (week 1 vs. week 8: uncorrected $P = 0.019$, corrected $P = 0.177$) (Supplement 7.). Therefore, we speculate that the emotional state of the HT patients is close to normal, and the total score of HADS is difficult to sensitively reflect the characteristics of emotional changes of HT patients.

3.2.3. Patient evaluation

In terms of subjects' willingness to be treated by acupuncture, questionnaires were distributed to 29 subjects in the acupuncture group and 14 subjects in the control group who had received acupuncture compensation treatment. A total of 43 questionnaires were distributed and 38 were validly answered with a return rate of 88.4 %. In terms of the improvement of symptoms by acupuncture treatment, 19 (50.0 %) were satisfied and 9 (23.7 %) were relatively satisfied; in terms of the improvement of thyroid function by acupuncture, 13 (34.2 %) were satisfied and 14 (36.8 %) were relatively satisfied; in terms of the improvement of thyroid antibodies by acupuncture, 13 (34.2 %) were satisfied, 14 (36.8 %) were more satisfied; in terms of acceptance of acupuncture for HT, 25 (65.8 %) indicated acceptance and 8 (21.1 %) indicated a tendency to accept it. The results are detailed in Supplement 8.

3.2.4. Evaluation of safety

During the treatment, 25 subjects in the acupuncture group experienced bruising of the upper limbs or neck at least once, and the bruising subsided after 3–14 days; four subjects had a sense of distension after

Table 1
Subjects demographic and baseline characteristics.

Variable	Acupuncture	Waitlist	P
Age, mean ± SD, years	48.55 ± 14.51	42.52 ± 12.50	0.095
Female, n (%)	26 (89.66)	26 (89.66)	1.000
Race, n (%)			1.000
Han	27 (93.10)	28 (96.55)	
Minorities	2 (7.90)	1 (3.45)	
BMI, mean ± SD, kg/m ²	22.11 ± 2.79	21.47 ± 2.05	0.319
Duration of disease, median (IQR), years	5.00 (2.00, 10.00)	4.00 (3.00, 7.00)	0.754
Dosage, median (IQR), mg	50.00 (25.00, 50.00)	50.00 (50.00, 50.00)	0.119
Grade of goiter, n (%)			0.277
0	1 (3.45)	1 (3.45)	
1	16 (55.17)	20 (68.97)	
2	11 (37.93)	8 (27.59)	
3	1 (3.45)	0 (0.00)	
TPOab, median (IQR), IU/mL	274.40 (114.00, 336.00)	114.30 (57.70, 402.80)	0.513
TGAb, median (IQR), IU/mL	373.70 (237.60, 495.60)	540.30 (283.70, 1000.50)	0.148
FT3, median (IQR), pg/mL	3.24 (2.92, 3.42)	3.44 (3.10, 4.30)	0.104
FT4, median (IQR), ng/dL	0.94 (0.88, 1.03)	1.01 (0.85, 1.24)	0.355
TSH, median (IQR), μIU/mL	2.98 (1.62, 5.03)	2.71 (1.87, 3.47)	0.514
ThyPRO-39			
Total score	23.23 ± 12.28	22.13 ± 9.09	0.700
Goiter symptoms	16.67(0.00, 25.00)	16.67(8.33, 25.00)	0.698
Hyperthyroid symptoms	18.75(12.50, 31.25)	18.75(12.50, 31.25)	0.615
Hypothyroid symptoms	36.64 ± 18.73	32.33 ± 14.85	0.336
Eye symptoms	35.06 ± 26.48	40.52 ± 28.15	0.450
Cosmetic complaints	8.33(0.00, 41.67)	8.33(0.00, 25.00)	0.737
Composite scale	36.53 ± 21.08	35.67 ± 15.53	0.860
SF-36			
Total score	66.51 ± 16.84	65.75 ± 16.81	0.864
Physical functioning	90.00(80.00, 95.00)	90.00(80.00, 95.00)	0.771
Role-physical	75.00(0.00, 100.00)	100.00(25.00, 100.00)	0.279
Bodily pain	76.38 ± 18.22	76.72 ± 17.34	0.941
General health	52.41 ± 17.37	56.14 ± 17.61	0.421
Vitality	59.83 ± 20.24	60.69 ± 18.84	0.867
Social functioning	80.00(70.00, 90.00)	90.00(60.00, 90.00)	0.787
Role-emotional	100.00(33.33, 100.00)	66.67(33.33, 100.00)	0.253
Mental health	58.62 ± 17.15	59.72 ± 17.20	0.808
Health transition	50.00(25.00, 100.00)	50.00(25.00, 75.00)	0.334
HADS			
Anxiety	5.28 ± 3.56	5.17 ± 3.58	0.913
Depression	6.83 ± 2.92	7.14 ± 2.81	0.682

FT3, free triiodothyronine; FT4, free thyroxine; HADS, Hospital Anxiety and Depression Scale; SF-36, MOS Item Short From Health Survey; TGAb, serum thyroglobulin antibody; ThyPRO-39, Thyroid Related Patient Reported Outcome short form; TPOab, serum thyroid peroxidase antibody; TSH, thyroid stimulating hormone.

acupuncture at the Hegu point, which was relieved within 3 days; one subject experienced tremor at the paroxysmal triceps muscle bundle, which disappeared after 5 days and did not recur. In both groups, no adverse reactions or adverse events related to L-T4 drug usage were reported. None of the subjects withdrew from the clinical study due to adverse reactions.

4. Discussion

In this study, over 93 % of subjects in acupuncture group completed up to 8 weeks of acupuncture treatment and no serious adverse events over the 8-week treatment period. From the results of the subject questionnaire, this acupuncture scheme has a high level of acceptance. Therefore, acupuncture treatment may be safe and feasible, and the subjects had high compliance. In terms of efficacy indicators, no significant changes of TPOab level in HT was observed, but the TGAb level was reduced after 16 weeks of acupuncture treatment, and the effect even remained for 8 weeks after the treatment ended. Moreover, acupuncture therapy relieved the discomfort symptoms of HT subjects and improved their quality of life. In terms of safety, the main adverse reaction of acupuncture therapy was bruising at the acupuncture site, but proficient acupuncture doctors can significantly reduce the occurrence of bruising. In general, the adverse reactions of acupuncture therapy were

mild, and the subjects showed high tolerance to acupuncture therapy. Acupuncture treatment for HT may be safe and effective in improving the immune status and discomfort symptoms of HT.

To the best of our knowledge, no RCTs of acupuncture for HT have been published before. However, a few clinical studies have shown that moxibustion intervention can reduce the level of thyroid-related antibodies in HT. A multi-center RCT showed that indirect moxibustion reduced TGAb and TPOab levels in hypothyroidism subjects after 12 weeks.²⁹ In other study³⁰ showed that acupuncture reduced TGAb levels and TPOab levels.

Although TPOab has a higher specificity and diagnostic value for HT,³¹ there are also studies that suggest that TGAb may have higher sensitivity in the diagnosis of HT when immunofluorescence is used to detect thyroid antibodies.³² A cohort study³³ showed that there was a correlation between TPOab and TGAb levels in newly diagnosed hypothyroidism patients, but the correlation coefficient was only 0.11. Caturegli²⁴ believes that TPOab and TGAb represent two aspects of the thyroid autoimmune response. TGAb reflects the initial immune response, while TPOab reflects the adaptive immune response in the later stage, which is an amplification of the immune response. The effect of acupuncture on TGAb levels observed in this study may reflect the regulatory effect of acupuncture on the non-specific immune response, rather than a thyroid-specific immune response.

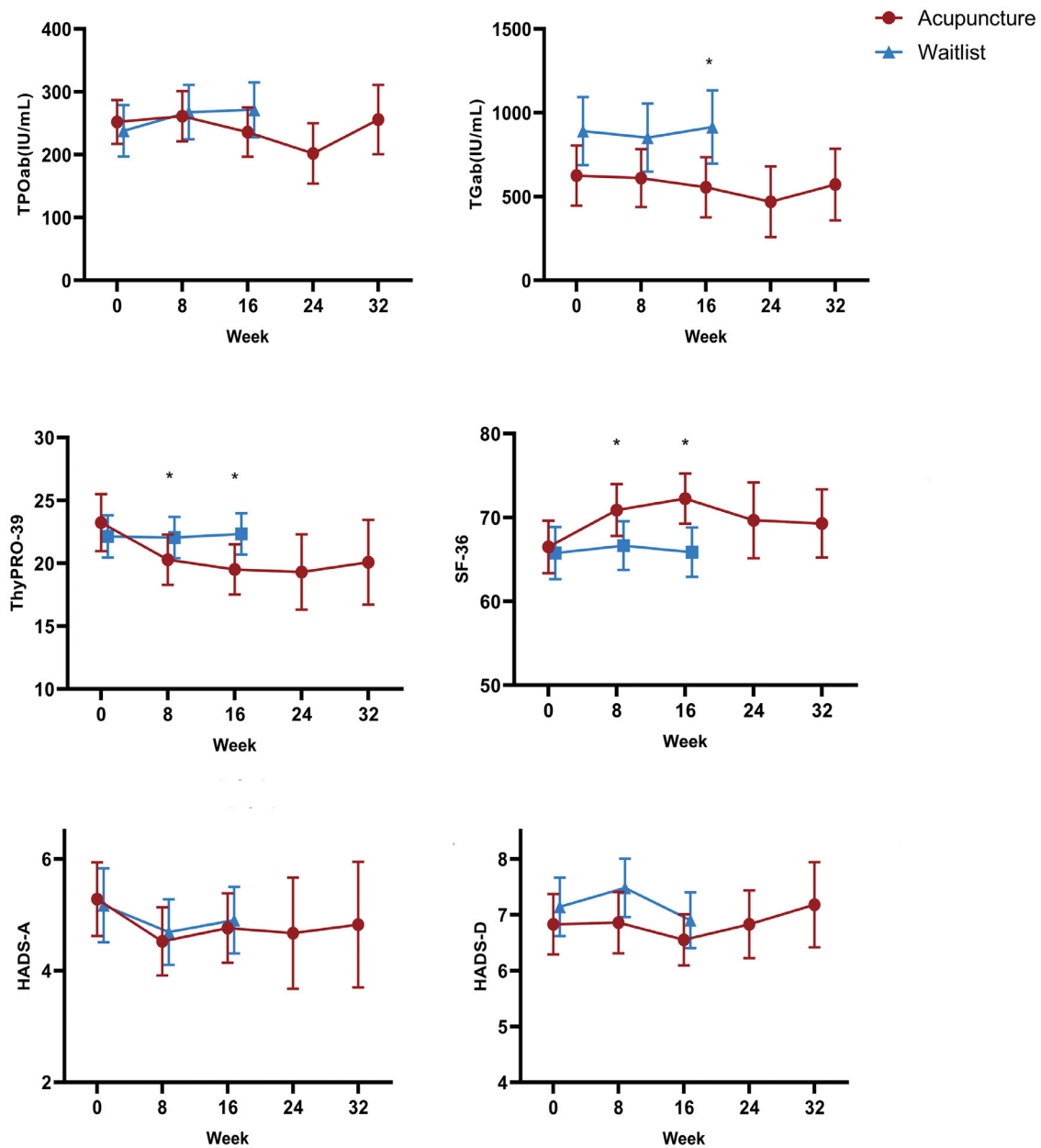


Fig. 2. Outcome measurements during study (bars indicate standard error).

HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression; SF-36, MOS item short form health survey; TGab, serum thyroglobulin antibody; ThyPRO-39, Thyroid related patient reported outcome short form; TPOab, serum thyroid peroxidase antibody. * There is a statistical difference between groups, $P < 0.05$.

The clinical symptoms of HT are caused by thyroid dysfunction, goiter, and immune disorders. Even with stable thyroid function, patients may still suffer from a variety of symptoms. Dardano³⁴ believed that HT, as an autoimmune disorder, could cause discomfort. Many studies have shown that the level of thyroid-related antibodies in HT patients is correlated with discomfort symptoms and quality of life.^{6,35} In addition, the thyroid of HT patients is generally normal in size, but compression symptoms in the neck are quite common.⁵ The discomfort of the neck may also be related to the inflammatory infiltration of the thyroid. Therefore, the effect of acupuncture on clinical symptoms may be related to the improvement of the immune state of the body. The small clinical effect size of acupuncture observed in this study may be because the severity of the overall symptoms is relatively low. For patients with serious symptoms, acupuncture may have higher clinical value in the treatment of symp-

toms such as neck compression, fear of cold, fatigue, and poor mental health.

As this study included a waitlist control, this may cause a confounding factor about changes in eating habits. A low-iodine diet is highly emphasized in health education. Subjects in the acupuncture group may be more likely to form dietary habits that are good for HT disease due to closer contact with clinical researchers. For example, a low iodine diet. Studies^{36,37} have shown that excessive iodine intake is related to the positive rate of thyroid antibodies, and iodine intake can increase the antigenicity of thyroglobulin. However, the influence of iodine intake on the two thyroid antibodies and TSH is the same, and in this study, the level of TGab is the only indicator that was decreased after treatment in the acupuncture group, so we speculated that the change in TGab is not only caused by the difference of iodine intake but also mainly due to the acupuncture treatment.

According to this clinical trial, patients in the clinic who have discomfort symptoms such as neck discomfort or fatigue, or who have a subjective requirement to lower their thyroid antibody levels, may try to receive acupuncture treatment. In the future, we can optimize the treatment scheme based on this study, to promote the development and standardization of acupuncture in clinical practice. And future confirmatory RCT to further validate acupuncture treatment for HT to reduce Tgab with a calculated sample size of at least 152 cases per group based on the results of this study, using two independent samples *t*-test. In addition, the feasibility of providing acupuncture therapy to reduce the dosage of L-T4 in HT hypothyroidism can be further explored on the basis of this study.

Our study has several limitations. First, the waitlist control may introduce the confounding factor of doctor-patient relationship, and the acupuncture group had multiple communications between doctors and patients during the treatment process, which may indirectly affect the results by enabling the subjects to have a better lifestyle. For future studies, reasonable and feasible control should be explored. Second, the inclusion criteria were relatively broad, and the sample size was small, which led to a large range of antibody levels. The next step is to carry out cohort study for specific populations who have higher treatment needs, to further observe the clinical value of acupuncture therapy. Finally, all subjects were treated with thyroxine, and no attempt was made to reduce the drug dosage during this study due to the need to control variables. A semi-standard prescription needs to be considered for future clinical studies to better conform to the clinical reality.

5. Conclusion

Compared with the waiting group, the Hand Yangming Meridian Penetrating Acupuncture scheme may be safe and feasible for HT to improve symptoms and reduce antibody levels.

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CRediT authorship contribution statement

Shanze Wang: Investigation, Writing – original draft. **Chao Yang:** Investigation, Formal analysis, Writing – original draft. **Weimei Zeng:** Data curation, Writing – original draft. **Hongfang Tian:** Writing – original draft. **Shihao Du:** Data curation, Writing – original draft. **Jiping Zhao:** Investigation, Writing – original draft.

Declaration of competing interest

The authors declare that there are no known financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical statement

This study was approved by the Ethics Committee of Dongzhimen Hospital of Beijing University of Traditional Chinese Medicine (No. 2017BL-076-01). This study was conducting by following the Declaration of Helsinki's ethical principles.

Data availability

The original data can be obtained by contacting the author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.imr.2024.101023](https://doi.org/10.1016/j.imr.2024.101023).

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