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Effect of *Nigella sativa* on thyroid function in patients with hypothyroidism treated with levothyroxine: a triple-blind randomized controlled trial

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ABSTRACT

Background: Hypothyroidism is a common endocrine disorder and a risk factor for cardiovascular disease, despite the treatment with classic medicine; the symptoms are not completely eliminated. *Nigella sativa* is an effective herbal medicine in traditional medicine that used for a variety of metabolic diseases and cold nature. *Objective:* The aim of this study was to investigate the effect of *N. Sativa* on thyroid function in hypothyroidism. *Materials and methods:* The present study is a triple-blind randomized controlled trial conducted on 42 patients (16-65 years of age) with hypothyroidism treated with levothyroxine in Imam Khomeini Hospital in Tehran during 2017- 2018, and were randomly allocated into two groups of intervention and control receiving powdered *N. Sativa* or placebo daily for two months and changes in thyroid status and lipid and glucose profile after 2 months were measured. *Results:* 22 patients were analyzed in the intervention group and 20 in the placebo group. The results showed that there was no significant difference between the intervention group and the placebo group (p=0.02). Significant decreases in total cholesterol and fasting blood sugar (FBS) were observed in patients with negative anti-thyroid peroxidase (Anti-Tpo) antibodies. In patients with positive Anti-Tpo antibodies, a significant increase in total cholesterol and FBS were observed in the intervention group (p=0.02). 5 patients in the intervention and placebo groups experienced mild and temporary side effects. *Conclusion: N. sativa* is used in Persian medicine to treat the disorders due to cold nature, and its consumption is increasing due to its native and safe nature and its low cost and effectiveness. Nevertheless, its function on human thyroid requires more trials and it should be used with caution.

Keywords: Clinical trial, Hypothyroidism, *Nigella sativa*, Black cumin Persian medicine, Nature

1. INTRODUCTION

Hypothyroidism is a common endocrine disorder in the world. It is considered as a cause of morbidity and mortality due to its association with metabolic diseases, especially in old age (Delshad et al., 2012). 5 % of the population over 12 years old in the United States have hypothyroidism (Mahan et al., 2012). The prevalence of hypothyroidism in countries with adequate iodine intake has been reported to be between 1-2%, and up to 7% at high ages. The prevalence of hypothyroidism in women is several times higher than that of men (Taylor et al., 2018).

Subclinical hypothyroidism has been reported between 4% and 20% in women and elderly people (Paz-Filho et al., 2018). It is 20 times more common than overt hypothyroidism (Mc Aninch et al., 2016). The most common cause of hypothyroidism is primary hypothyroidism, and in the context of self-immune process (Ke et al., 2015).

Clinical symptoms are related to the degree of hypothyroidism and are non-specific symptoms, which include fatigue, cold sensitivity, constipation, dry and rough skin, paleness, brittle nails and hair, puffy face, weight gain, increased rigidity, pain and weakness of the joints, menorrhagia, and depression (Rugge et al., 2016; Cheng F-K, 2018; Jonklaas et al., 2014). Hypothyroidism is known as a risk factor for cardiovascular disease and is associated with metabolic syndrome (Mehran et al., 2017). Several studies have shown that hypothyroidism is associated with an increase in the number and severity of depression and its effect on quality of life (Najafi et al., 2015). Despite the fact that levothyroxine is considered to be a standard treatment for hypothyroidism due to its ease of usage, high half-life in the body, low cost, and acceptable complications, but 10% - 15% of patients are dissatisfied with the treatment with levothyroxine because of the persistence of hypothyroidism symptoms and 15% of patients do not reach normal T3 levels (McAninch et al., 2015). In 40% of patients treated with levothyroxine, TSH do not reach the appropriate range, and 40% of the rest, especially at high ages, have lower TSH than normal (Paz-Filho et al., 2018). Even in patients with normal TSH, the symptoms of hypothyroidism still remain. New researches reported that levothyroxine mono therapy is inadequate in treating hypothyroidism symptoms, especially psychological symptoms, and despite the normal serum thyroid hormone levels, they report hypothyroidism in the tissues. Today, the probable role of Personalized Medicine based on the genotype is emphasized in the treatment of untreated cases (McAninch et al., 2015). According to the World Health Organization, 80% of the population use traditional methods for treatment (Amin et al., 2015). Considering that treatment in Persian medicine (PM) is based on the nature of individuals, and this medicine is growing more popular, it may be helpful in the treatment of hypothyroidism which symptoms are similar to the cold nature. Therapeutic management in Persian medicine may improve the symptoms of hypothyroidism, and administration of warm medicines, such as *N. sativa* with anti-inflammatory properties, seems to be beneficial in the treatment of this disease (Farhangi et al., 2016; Pakdel et al., 2017; Khalawi et al., 2013). *N. sativa* seed or black cumin (Family Ranunculaceae) is an annual herb, which has been used traditionally for thousands years. *N. sativa* seed reveal an expand therapeutic activities including anti-diabetic, anti-

cancer, immune regulating, analgesic, anti-microbial, anti-inflammatory, spasmolytic, bronchodilator, hepato protective, renal protective, gastro protective, anti-oxidant effects (Shariatifar et al., 2014; Ahmad et al., 2013; Islam et al., 2017; Eftekharafzali et al. 2018; Falahieh et al. 2019). Several animal studies have reported its beneficial effects on hypothyroidism and have proven their efficacy (Pakdel et al., 2017; Khalawi et al., 2013; Shariatifar et al., 2014), but human studies in this field are very limited and there is not enough evidence for the effect of *N. sativa* on human hypothyroidism. Therefore, we decided to evaluate the effect of *N. sativa* on hypothyroid patients by performing a clinical trial. Several human studies confirm that *N. Sativa* has no major adverse effects or toxicity (Islam et al., 2017; Sultan et al., 2014).

2. MATERIALS AND METHODS

This study is a triple-blind randomized controlled trial. The aim of this study was to investigate the effect of *N. sativa* in improving thyroid function in patients with hypothyroidism in Tehran, Iran (2017-2018). The participants of this study were patients with hypothyroidism treated with levothyroxine who had been referred to Endocrine and Metabolism Clinic of Imam Khomeini Hospital in Tehran and had TSH levels greater than 2μIU/ml and less than 10μI U/ml in at least 2 consecutive visits.

The inclusion criteria for this study include:

1. Patients with hypothyroidism treated with levothyroxine that have TSH greater than 2 and less than 10 in at least 2 consecutive visits by an endocrinologist.
2. Over 16 and under 65 years of age
3. Having a willingness to participate in the study and signing a written consent.

Exclusion criteria include:

1. Heart disease, coagulopathy, other autoimmune disorders, pituitary and hypothalamic problems, and kidney and malignant diseases,
2. Participation in another study
3. Use of supplemented food with drug interaction
4. Pregnancy and lactation
5. Receive any nutritional supplement during the study
6. Unwillingness to continue cooperation
7. A history of allergy to *N. sativa*.

In this study, 100 patients were evaluated for inclusion criteria from which 52 were found eligible to enter the study and expressed their satisfaction to participate in the study After responding to the demographic questionnaire and undertaking the measurement of height, weight, and vital signs, blood samples were obtained to determine the baseline amount of FT4, T3, TSH, Anti-Tpo, Total cholesterol, FBS, HDL-C, LDL-C, and TG.

The serum and plasma samples were separated by centrifugation at 2500 rpm for 10 min (Beckman Avanti J-25; Beckman Coulter, Brea, CA, USA) at room temperature. The serum samples were stored at −70 °C immediately. The reference values for TSH and free T4 were 0.4 to 6/1 mUI/mL and 0.8 to 2 ng/dL, respectively and T3 0/6 to 2/2ng/dL. The Anti-TPO levels > 40 UI/mL were considered positive. And then TSH, T3 and FT4 were measured by IRMA kit and anti-TPO by enzyme linked immune sorbent assay (ELISA).

In this study the weight, height, vital signs and FT4, T3, TSH, Anti-TPO, Total cholesterol, FBS, HDL-C, LDL-C and TG were measured in the first visit and the end of the eighth week. The primary outcome of this study was the levels of FT4, T3, TSH, Anti-tpo, and secondary outcomes of this study was the serum levels of Total cholesterol, FBS, HDL-C, LDL-C, TG, and vital sign, and BMI. This study with IR.shahed.REC.1396.125 code was approved by the Medical Ethics Committee of Shahed University. It has also been registered and approved at the Iranian Registry of Clinical Trials with IRCT20171113037424N2 registration code.

Drug and placebo preparation

The *N. sativa* seeds were purchased from the local market (Attari), Tehran, Iran. The seeds were authenticated and deposited at Herbarium of Faculty of Pharmacy, Tehran University of Medical Sciences with voucher no. PMP-1712. Then, *N. sativa* seeds were crushed with grinder and then filled in 500 mg capsules. The placebo was prepared from corn starch colored with edible food coloring. The medication was provided in identical 500 mg capsules, containing either powdered *N. sativa* seed or placebo. The participants received either *N. sativa* or placebo, 2 times a day, each time 2 capsules, before breakfast and half an hour after levothyroxine pill.

Statistical analysis

In this study, descriptive analysis (means ±SD, correlation, frequency and percent) and inferential analysis (chi-square test, independent t-test, Mann-Whitney test, depended t-test,) and Kolmogorov–Smirnov test (for normality and non-normality distribution test) were used. Data were analyzed using SPSS, version 21. A probability of less than 0.05 was considered as significant. A total of 20 samples was calculated for each group using the formula, n=2(Z_(α/2) + Z_β) ^2/d^2, in which α=0.05, β=0.1 and d=1.

3. RESULTS

In this study 52 patients passed the inclusion criteria and entered the study. After allocation in two groups, 10 subjects were unable to continue the study (Figure 1). The mean and SD for age and BMI in addition gender presented in table 1. As it is shown in this table no significant differences were observed between drug and placebo groups.

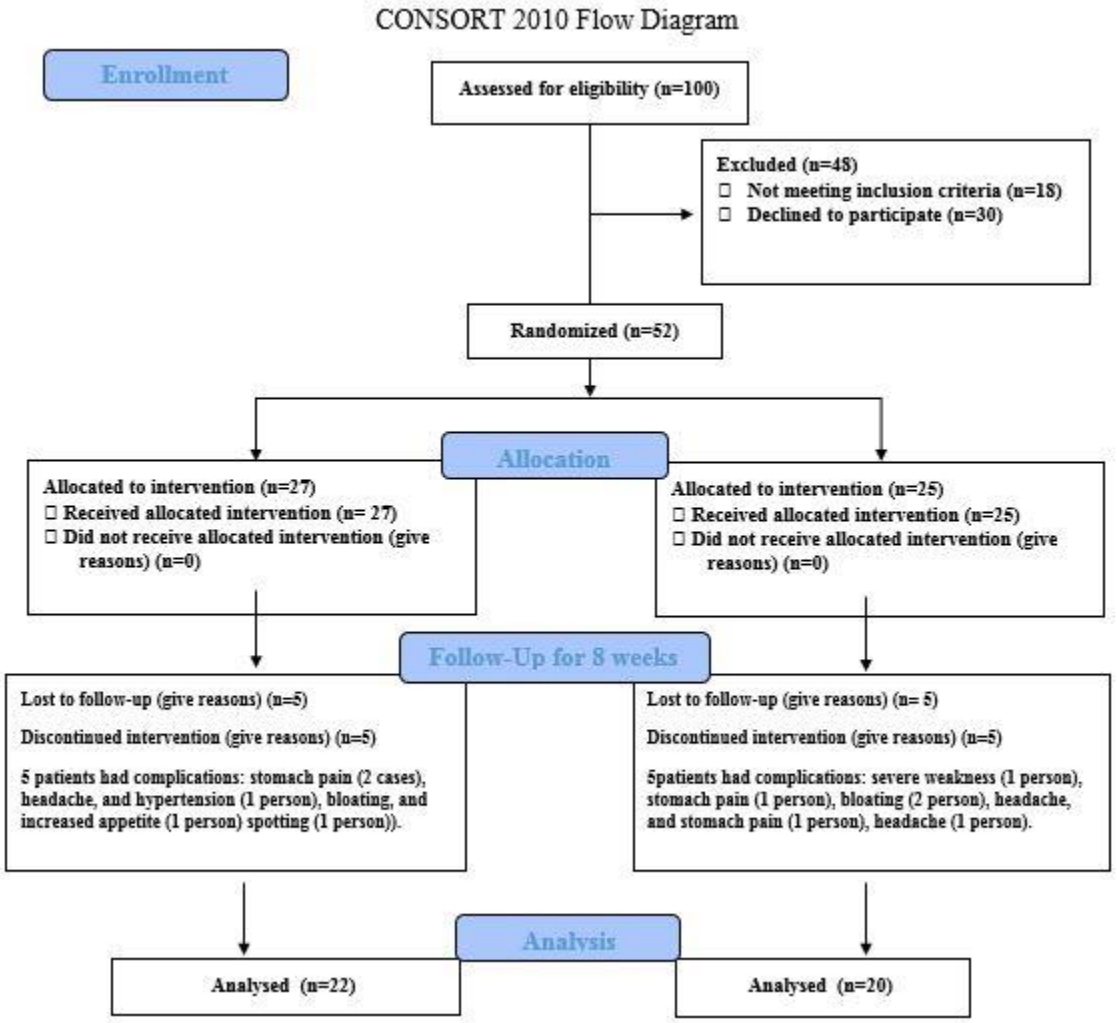

Figure 1 Follow up diagram

Table 1 The mean and SD of age and BMI according to the two groups

		Group				
		Placebo		Drug		P-value
		n	%	N	%	
Anti Tpo<40	Female	3	100.0%	7	100.0%	>0.999
	Male	0	.0%	0	.0%	
Anti Tpo>40	Female	9	90.0%	11	91.7%	>0.999

	Male	1	10.0%	1	8.3%	
		Mean	SD	Mean	SD	
Anti	Age	40.67	12.42	46.00	9.87	0.485
Tpo<40	BMI	31.14	1.17	33.28	5.85	0.560
Anti	Age	42.70	11.33	43.42	10.24	0.878
Tpo>40	BMI	30.78	6.33	30.54	4.44	0.918

SD: Standard Deviation,

P-value base on chi-square test for categorical variable and T-test or Mann-Whitney U test for continues variables

The results showed that in patients who had Anti-Tpo <40 at the beginning of the study: TSH in the placebo group showed a significant increase (+0.74, p value <0.001). In patients with Anti Tpo >40, Log Anti-Tpo variable increased and decreased significantly in the intervention group (+0.06, p value = 0.02), and the placebo group (-0.04, p value = 0.015), respectively. Also, TG increased significantly in the placebo group (+18.2, p value = 0.019) and Chol T, LDL-C, HDL-C, and FBS had no significant change in the two groups (Table 2 and Figure 2).

Table 2 The Mean and SD of variable before and after of study according to the groups

	Variables	Group	Pre		Post		Difference	P-value
			Mean	SE	Mean	SE		
Anti Tpo<40	FT4	Placebo	1.05	0.05	1.15	0.04	0.1	0.003
		Drug	1.08	0.05	1.06	0.04	-0.02	0.784
	T3	Placebo	141.72	3.4	130.6	7.49	-11.12	0.338
		Drug	138.36	3.85	130.99	2.64	-7.37	0.112
	TSH	Placebo	4.02	0.57	4.76	0.5	0.74	0.001
		Drug	4.58	0.55	4.25	0.74	-0.33	0.453
	Log Anti TPO	Placebo	0.82	0.17	0.82	0.12	0	0.982
		Drug	0.88	0.1	0.92	0.09	0.04	0.282
	Chol	Placebo	171	14.59	174.33	13.03	3.33	0.650
		Drug	171.14	5.56	157.43	7.28	-13.71	0.009
	FBS	Placebo	83.67	7.94	95	11.07	11.33	0.066
		Drug	104.43	5.82	99	4.28	-5.43	0.033
	HDL	Placebo	40.33	3.9	47.33	4.57	7	0.041
		Drug	46.43	1.72	44	1.47	-2.43	0.029
	TG	Placebo	165.33	11.98	122	10.28	-43.33	0.056
		Drug	119.29	13.14	108.71	9.65	-10.58	0.249
	LDL	Placebo	97.33	12.99	102	10.89	4.67	0.571
		Drug	100.57	5.56	95.71	7.62	-4.86	0.106
Anti Tpo>40	FT4	Placebo	1.02	0.04	1.04	0.03	0.02	0.430
		Drug	0.95	0.04	0.98	0.06	0.03	0.649
	T3	Placebo	136.18	3.93	135.98	2.79	-0.2	0.963
		Drug	132.07	3.38	131.66	5.19	-0.41	0.917
	TSH	Placebo	4.87	0.47	3.8	0.77	-1.07	0.061
		Drug	4.96	0.59	5.83	0.54	0.87	0.170
	Log Anti TPO	Placebo	2.16	0.06	2.12	0.06	-0.04	0.015
		Drug	2.38	0.09	2.44	0.09	0.06	0.020
	Chol	Placebo	165.6	12.18	152.9	7.43	-12.7	0.066
		Drug	165.75	10.2	161.75	7.88	-4	0.483
	FBS	Placebo	113.2	2.58	113	2.99	-0.2	0.951

	Drug	106.42	9.75	113.33	15.03	6.91	0.298
HDL	Placebo	42	0.96	40.4	1.27	-1.6	0.253
	Drug	42.42	1.88	41.75	1.95	-0.67	0.465
TG	Placebo	105.3	11.06	123.5	14.36	18.2	0.019
	Drug	139.42	24.26	135.67	16.11	-3.75	0.764
LDL	Placebo	90.1	6.12	87.3	6.32	-2.8	0.519
	Drug	95.08	8.02	92.58	6.93	-2.5	0.579

SE: Standard Error of Mean. P-value base on Paired Sample t-test or Wilcoxon Signed Ranks Test

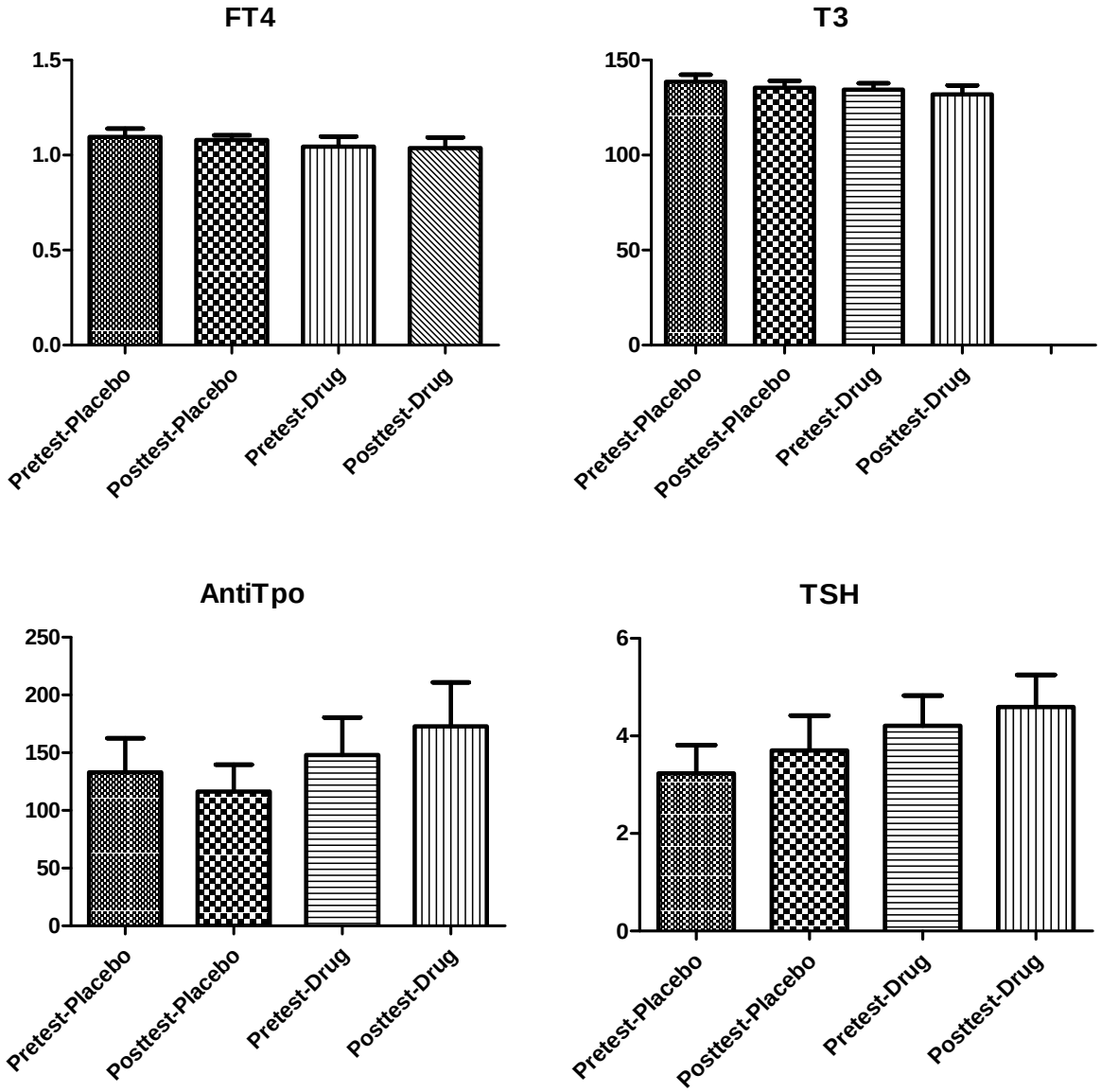

Figure 2 The Mean of variable before and after of study according to the groups

In the *N. sativa* group, five patients had complications (stomach pain (2 female), headache, and hypertension (1 female), bloating, and increased appetite (1 female) spotting (1 female). Also in the placebo group, five patients had complications: severe weakness (1 female), stomach pain (1 female), bloating (1 female), headache, and stomach pain (1 female), headache (1 female).

4. DISCUSSION

The present study showed that use of *N. sativa* along with levothyroxine for 8 weeks in hypothyroid patients had no significant effect on thyroid function and in patients with positive Anti-Tpo marker led to a significant increase in inflammatory marker compared to the control group.

Despite the fact that most animal studies in recent years reported the positive effect of *N. sativa* on thyroid function in hypothyroidism (Pakdel et al., 2017; Khalawi et al., 2013; Shariatifar et al., 2014), this study contrasted with the findings of previous studies and for the first time demonstrated the effect of *N. sativa* on increasing thyroid inflammatory markers in humans. It is probably opposed to studies that recommended the use of *N. sativa* as an anti-inflammatory drug (Hayatdavoudi et al., 2016; Butt and Sultan, 2010; Arjumand et al., 2019; Bashir et al., 2014; Al-Ghamdi et al., 2001) and a protector of thyroid against anti-thyroid drugs. The effects of fasting blood glucose and blood cholesterol reduction in the patient with negative anti-tpo in the *N. sativa* group compared to the control group were in agreement with the study of Amini and Hadi and others (Kaatabi et al., 2012; Sharif et al., 2012; Heshmati and Namazi, 2015; Pelegrin et al., 2019). Farhangi et al. reported a beneficial effect of *N. sativa* on Hashimoto's Thyroiditis (Farhangi et al., 2016). However, in the present study, not only Hashimatho patients but also all patients with negative and positive anti tpo hypothyroidism entered the intervention.

Various animal studies reported that there is a relationship between the anti-inflammatory effects of *N. sativa* and the reduction of NO, IL-1, COX-1, COX-2, and HDOC production, and pre-inflammatory mediators such as IL-1b, IL-6, TNF-α, IFN-γ, and PGE2 (Islam et al., 2017).

In this study, it seems that several factors are effective in producing negative results including concurrent use of *N. sativa* and levothyroxine together in the morning. Because the concurrent use of the herbal and chemical drugs is likely to cause drug interaction. The use of *N. sativa* and levothyroxine in the morning (With emphasis on fasting and intervals in drug usage) may lead to a greater reduction in the absorption of levothyroxine in the *N. sativa* group than the placebo group. Therefore, it is suggested that in future studies, the intervention drug be given at noon to prevent its interaction with levothyroxine. The length of the study in both the warm and cold seasons causes changes in the thyroid hormone, as the ambient temperature affects the results of the thyroid test (Bobek et al., 1980; Donkoh A, 1989; Magdub et al., 1982; Saber et al., 2009). The lack of evaluation and control of the diet of patients is effective in the results of thyroid tests (Paz-Filho et al., 2018). In the animal study of Parvinru (Parvinroo et al., 2014) and human study of Mohammadi (Mohammadi et al., 2014) the effects of warm nature diet on increasing levels of thyroid hormones were reported. It seems that the use of corn starch as a placebo in studies is inappropriate because its anti-inflammatory effects have been reported in several studies (Grases et al., 1993; Goren et al., 2018; Rossaint et al., 2014) and in the present study, its effect on thyroid inflammation and competition with *N. sativa* is evident. The *N. Sativa*, which has a high degree of warmth, can boost the immune system and increase Anti-Tpo.

The diagnosis and current treatment of thyroid disease are based on laboratory findings, and the treatment of this disease is done exclusively by medicine. While complex interventional factors including individual, dynamic, and adaptive factors such as genetic, epigenetic, allostatic factors, obesity, age, and mental illness, etc., are effective in linking thyroid stimulating hormone and thyroid hormone regulation and affect the pattern of diagnosis and treatment (Hoermann et al., 2017). Mental (Sina I, 2005) dietary factors (Mezzomo et al., 2016; Pałkowska-Goździk et al., 2018) massage (Fielda T, 2016), and climate change interfere with the treatment of this disease, in addition to factors such as age, sex, and body weight (Hoermann et al., 2017).

In Persian medicine, there are three main steps of treatment: 1- Lifestyle management, especially nutrition 2- Proper drug use 3- massage and cupping and other manipulation methods (Sina I, 2005). Lifestyle modification is an important treatment method before medical treatment, and includes management in the six main principles of Weather, Nutrition, Physical activity, Psychic features, Sleep and awareness, and Excretion of body wastes materials and retention of necessary material (Ansaripour et al., 2019). If we can increase the thyroid gland secretion with persian medicine and improve lifestyle, or improve the mechanisms responsible for the deficiency of thyroid hormone secretion, it seems that we will have better effects and fewer symptoms of hypothyroidism than levothyroxine and *N. sativa* or other herbal drugs. It is suggested that in future studies, formulations other than *N. sativa* powder, such as *N. sativa* oil, should be used and measured with different doses.

Limitations

Conflicting variables such as psychological state, diet, and the rate of exercise of patients may affect thyroid function tests and the results of the study.

5. CONCLUSION

The results of this study showed that daily use of 2 grams of *N. sativa* alone could not improve thyroid profiles in patients with hypothyroidism. Therefore, in accordance with the Iranian traditional medicine, lifestyle modification is the most important step in the treatment, in the treatment of these patients, management of the 6 principles for health (*Setteh Zarorieh*) to improve lifestyle along with drug therapy is recommended.

Conflicts of interest

There is no conflict of interest.

Financial resources

There is no financial resource.

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