

Thyroxine Therapy Improves Serum Lipoproteins and Some Clinical Findings In Patients With Subclinical Hypothyroidism

Kalantari S, Heidarzadeh A.

Endocrine Research Center, Razi hospital, Guilan University of Medical Sciences, Rasht, Iran.

Data on the effect of thyroxine therapy on lipid profiles and signs and symptoms of mild hypothyroid patients is controversial. This study was conducted to elucidate the issue.

Material and Methods: In a single blind placebo control clinical trial, 80 patients with sub clinical hypothyroidism (TSH > 5 m U/L on two occasions, positive anti TPO and normal FTI) were recruited and allocated into two groups by fixed block randomization (thyroxine therapy- 40 patients and placebo- 40) The patients did not have any disease, nor were they taking any medication influencing serum lipids and thyroid hormone levels. After physical examination, blood was drawn for measurement of serum TSH (IRMA), T4, T3, (RIA), and total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL) with enzymatic method by commercial kits before and after thyroxine therapy and placebo. The adequacy of thyroxine therapy was documented by a normal TSH after 3 months. Data were statistically analyzed by t-test, paired t-test and Fisher's exact test.

Results: Attrition rate was 10 percent (72 patients followed completely). The mean ages in the therapy and placebo groups were 35.82 ± 12.3 yr and

and 36.3 ± 11.5 yr and the female to male ratio in each group was 36/4 and 26/6 respectively. There was no significant difference in the BMI of the two groups (28.1 ± 5.5 vs. 25.9 ± 3.7 Kg/m² respectively). The mean of lipid profile and thyroid hormones were not significantly different in the two groups before intervention. The mean difference of total cholesterol (18.27 ± 30.7 vs. 1.5 ± 33.8 , $p = 0.019$) and LDL (22.45 ± 28.4 vs. 2.08 ± 37.0 , $p = 0.005$) before and after therapy between the two groups were significant. Triglyceride levels and HDL were not significantly changed in both groups. With regard to clinical findings, only skin dryness and fatigue were significantly improved with thyroxine therapy ($p < 0.05$).

Conclusion: There is a significant decrease in serum total cholesterol and LDL levels and improvement of some clinical findings in patients with sub clinical hypothyroidism treated with levothyroxine.

Keywords: Thyroid failure, Subclinical, Lipid profile, Levothyroxine therapy.

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Introduction

Sub clinical hypothyroidism (SCH) is defined by an elevated serum thyroid stimulating hormone (TSH) with normal free T4 con-

Correspondence: Saeed Kalantari, Endocrine Research Center, Razi hospital, University of Medical Sciences, Rasht, Iran.

E-mail: dr_skalantari@yahoo.com

centration. Sub clinical hypothyroidism is a common disorder with a prevalence ranging from 1-10% of adult population in most community based studies.¹⁻² The effects of SCH on serum lipid levels remain controversial; some cross-sectional studies have found that serum total cholesterol (TC) concentrations in patients with SCH were similar to those of normal subjects³⁻⁵ and cholesterol levels did not fall with T4 therapy.⁶⁻¹⁴ In contrast some studies have reported increased TC and low density lipoprotein (LDL) in SCH patients than euthyroid controls^{8-10,15-17} and lipid profile improvement with T4 therapy.^{8,18-21} There is also controversy about the effect of T4 therapy on clinical symptoms of SCH.^{6,7,22} To clarify this issue we conducted a single blind placebo controlled clinical trial to assess the effect of T4 therapy on lipid profile and clinical symptoms of patients with SCH.

Materials and methods

In this study, 80 patients referring to an endocrine clinic with SCH (TSH > 5 m IU/L on 2 occasions, and positive anti TPO with normal FTI) were recruited for the study by non probability simple sampling. The patients were allocated into two groups by fixed block randomization (group 1, therapy group, 40 patients and group 2, placebo group, 40 patients). The inclusion criteria were as follows: age >18 yr old, good general health as assessed by a medical history and physical examination by an internist. The exclusion criteria were as follows: diabetes mellitus, confirmed coronary artery disease, pituitary/hypothalamic disorders and any non thyroidal illness influencing thyroid function tests, severe hyperlipidemia which needs medication according to NCEP guidelines, being on levothyroxine or lipid lowering agents 3 months priorly to enrollment in the study. All recruited patients signed an informed consent. Levothyroxine was given in the fasting state in doses of 75-200 µg and the placebo tablets were prepared and packed

similar to the levothyroxine tablets. The study duration was 3 months. Hormone as well as serum lipid levels were assessed at the baseline visit and after 3 months at the end of the study in a qualified reference laboratory. Serum total cholesterol (TC) (normal <200mg/dl), Low density lipoprotein (LDL) (normal < 130mg/dl), high density lipoprotein (HDL, normal, 40-70 mg/dl), triglyceride (TG, normal, <150mg/dl) were assayed enzymatically by Cobaf auto analyzer. Serum TSH concentration (normal, 0.3-5 m IU/L) was measured by immunometric assay. T4 (normal, 4-12.8 µg/dl), T3 (normal, 0.8-2.1 ng/ml) were determined by radioimmunoassay with commercial kits. FTI (normal 1.2-4.4, ratio) was calculated using the related formula. All data were expressed as the mean ± sd, and analyzed statistically by the t-test, paired t-test, Fisher's exact test, logistic regression analysis and Wilcoxon rank test.

Results

Total attrition rate was 10 percent. Seventy two patients were followed completely. In the therapy group there was no attrition and all patients recruited remained in the study until the end, but in the control group we lost 8 patients because of personal reasons and the results reported are only for 32 patients. The mean ages in the therapy and placebo groups were 35.82 ± 12.3 yr and 36.3 ± 11.5 yr, female to male ratio in each group being 36/4 and 26/ 6 respectively. There was no significant difference in the BMI of the two groups (28.1 ± 5.5 vs. 25.9 ± 3.7 Kg/m² respectively). No significant differences were seen between lipid profiles or thyroid function tests (TFT), before intervention in both groups as shown in table 1.

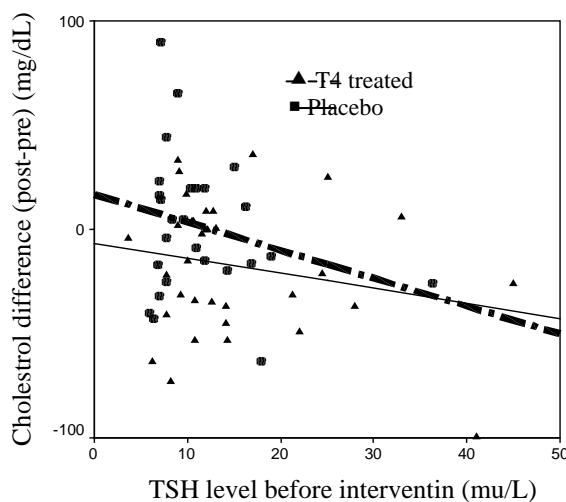
The mean lipid profiles were not significantly different in the placebo group after intervention (table 1). Free thyroxine index increased and TSH decreased significantly in the therapy group in contrast to the placebo group. There was a significant decrease in

Table 1. Comparison of laboratory parameters of subclinical hypothyroid patients before and after therapy

Lab Test	T4 Therapy group			Placebo Therapy group				
	(n)	Before Mean \pm SD	After Mean \pm SD	P value	(n)	Before Mean \pm SD	After Mean \pm SD	Pvalue
Triglycerids (mg/dL)	(38)	150.43 \pm 71.3	149.7 \pm 69.6	NS	(28)	164.62 \pm 96.9	158.7 \pm 114	NS
Total cholesterol CH (mg/dL)	(38)	209.49 \pm 44.5	191.2 \pm 33.5	<0.001	(28)	191.46 \pm 32.23	193 \pm 36.57	NS
High Density Lipoprotein (mg/dL)	(36)	45.74 \pm 10	47.77 \pm 12.9	NS	(28)	45.88 \pm 21.2	45 \pm 12.7	NS
Low Density Lipoprotein (mg/dL)	(36)	135.6 \pm 37.6	113.14 \pm 32.9	<0.0001	(28)	116.76 \pm 34.5	118.8 \pm 34.37	NS
T4 (μ g/dL)	(38)	6.92 \pm 1.75	10.77 \pm 2.58	<0.0001	(29)	6.69 \pm 3.33	6.58 \pm 2.55	NS
T3 (ng/mL)	(34)	1.77 \pm 1.4	1.7 \pm 0.66	NS	(29)	1.33 \pm 0.48	1.75 \pm 0.62	NS
Free Thyroxin Index (ratio)	(29)	1.68 \pm 0.6	1.99 \pm 0.47	NS	(26)	1.9 \pm 0.49	3.23 \pm 0.87	NS
TSH (m IU/L)	(36)	15.74 \pm 9.6	1.44 \pm 1.66	<0.0001	(32)	11.11 \pm 5.9	10.43 \pm 7.87	NS

TC and LDL (209.49 \pm 44.58 mg/dl vs. 191.22 \pm 33.57 mg/dl P= 0.001, 135.6 \pm 37.64 mg/dl vs. 113.14 \pm 32.97 mg/dl, P= 0.0001 respectively), but no significant difference was observed in TG and HDL after thyroxine treatment in the therapy group (table 1). The mean of differences between pre and post intervention in therapy group was significant for TC (p= 0.019) and LDL (p=0.005) and was insignificant for TG and HDL. The prevalence of abnormal lipid profiles in the 2 groups is shown in table 2. In the therapy group TC and LDL were abnormal in 21 cases (52.5%) and 12 patients (30%) respectively after T4 therapy. The decrease in serum total cholesterol level in both groups after intervention was related to basal serum TSH levels, but this relation was not statistically significant (fig 1). The serum total cholesterol changes after levothyroxine therapy, were significantly related to the basal cholesterol level before intervention. The means of lipid profiles were not significantly different in the placebo group after intervention (table 1). There was a significant

decrease in TC and LDL (209.49 \pm 44.58 mg/dl vs. 191.22 \pm 33.57 mg/dl P= 0.001, 135.6 \pm 37.64 mg/dl vs. 113.14 \pm 32.97 mg/dl, P= 0.0001 respectively), but no significant difference was discernable in TG, HDL after thyroxine treatment in the first group (table1) (p=0.0001)

**Fig. 1. Relation of serum cholesterol decrease to basal TSH in both groups**

The prevalence of hypothyroid symptoms in both groups is shown in fig. 2. Clinical symptoms of skin dryness and fatigue improved ($p= 0.002$ and $p=0.007$ respectively) but there was no significant improvement in loss of memory, eye puffiness and constipa-

tion in patients, treated with levothyroxine, and no significant relation was found between serum TSH level and clinical symptoms before and after thyroxine therapy.

Table 2. Prevalences of abnormal lipid profiles in the two groups before and after intervention

Parameters	Before treatment, no (%)	After treatment, no (%)
Treatment with thyroxin:		
• Increased CH	21(52.5%)	15(37.5%)
• Increased LDL	17(42.5%)	12(30%)
• Increased TG	17(42.5%)	15(37.5%)
• Decreased HDL	10(25%)	9(22.5%)
Treatment with placebo:		
• Increased CH	13(40.6%)	10(31.3%)
• Increased LDL	12(37.5%)	11(34.4%)
• Increased TG	11(34.4%)	13(40.6%)
• Decreased HDL	12(37.5%)	12(37.5%)

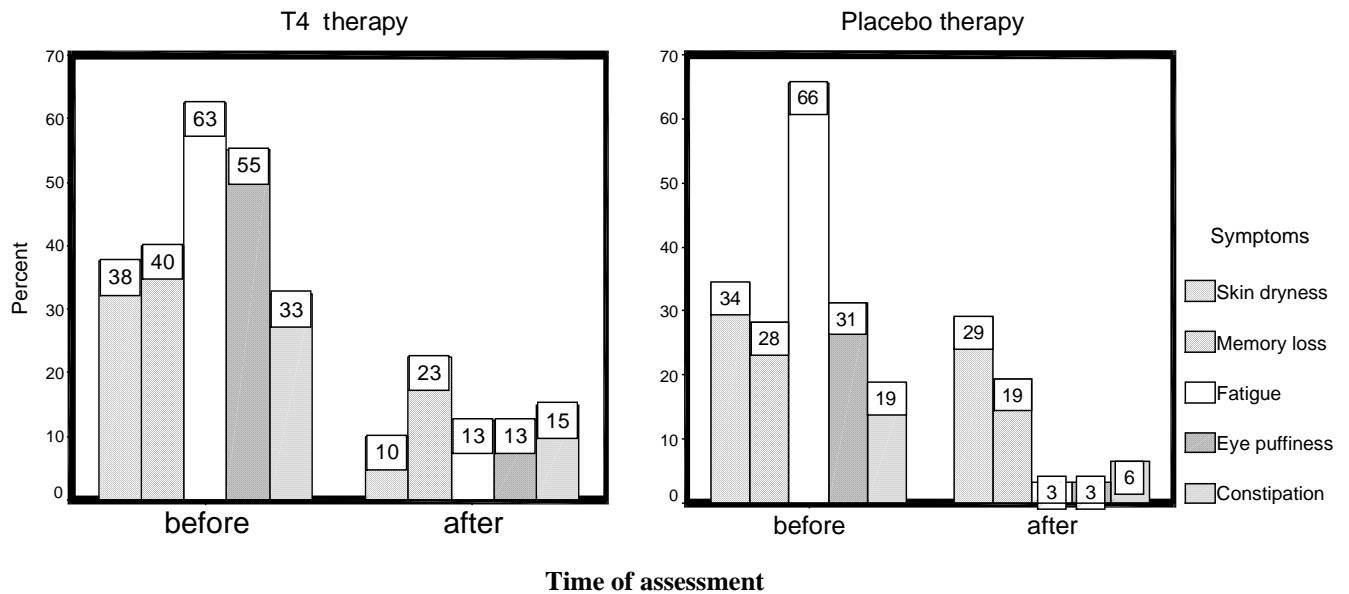


Fig. 2. The prevalence of symptoms in the two groups before and after intervention

Discussion

The overall prevalence of SCH ranges from 1-10% in the adult population in most community studies.^{1,2} In two population based studies, the prevalence of SCH was 7.5 to 8.5% in women and 2.8 to 4.4% in men.^{23,24} SCH occurs in about 15% of women over the age of 60 years²³⁻²⁵ and in about 8 % of elderly men.²⁵ There is no consensus regarding lipid profile changes and also the effect of thyroxine therapy on lipids in patients with SCH.²⁶⁻²⁷ In keeping with some studies,^{8,18,19,21,28-30} there was a significant decrease in TC and LDL in SCH patients treated with thyroxine in our study, which was contradictory to other investigations, indicating no fall in TC levels after T4 therapy.⁶⁻¹⁴ In accordance with other studies^{8,18,19,21} serum levels of HDL and TG remained unchanged with levothyroxine treatment, in our study.

According to some surveys,²⁸ patients with higher basal serum total cholesterol levels had greater reductions in cholesterol after thyroxine therapy. Some studies have suggested that patients whose serum TSH levels are less than 10 m IU/L may have no reduction in cholesterol level with thyroxine re-

placement,^{31-34,48,49} but we could not find a significant relation between basal serum TSH level and serum total cholesterol reduction after treatment with thyroxine. In accordance with our study, some trials indicate that hypothyroid symptoms in SCH patients have improved significantly,^{6,7,35-43} whereas others showed no benefits of therapy.^{22,37,44} In contrast to some studies,⁴⁵⁻⁴⁷ there was no significant relation between serum TSH level and clinical symptoms before and after thyroxine therapy.

Conclusion

A significant decrease in serum total cholesterol and LDL levels was seen; some clinical findings improved in patients with subclinical hypothyroidism, treated with levothyroxine.

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