

ORIGINAL RESEARCH

The Effect of Thyroid Hormone Replacement on the Metabolic Control and Insulin Resistance in Patients with Subclinical Hypothyroidism

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Abstract: Introduction: Studying the treatment effect of subclinical hypothyroidism in decreasing metabolic syndrome risk factors and cardiovascular diseases is necessary and can be helpful to control future disorders. In spite of various studies, the relationship between subclinical hypothyroidism and cardiovascular diseases remain controversial. Studies which consider the effects of subclinical hypothyroidism treatment on metabolic control and insulin resistance have not been done in the Islamic Republic of Iran yet. Materials and methods: In this interventional study, 153 patients with subclinical hypothyroidism (thyroid stimulation hormone (TSH) >5, normal T3 and T4 at least 2 times) were selected from Labbafinejad endocrine clinic. Laboratory tests were performed at 8 a.m. after 12-14 hours fasting. Patients were then treated with levothyroxine (25-50 µg daily). To adjust the dose, thyroid function tests (TFT) were checked every 2 months for 6 months. Collected data was used for analysis by spss18 software. Results: After 6 months treatment of subclinical hypothyroidism mean values improved in factors such as insulin resistance profile (fasting blood sugar (FBS), 2 hours post prandial (2hPP), fasting insulin and homeostasis model assessment estimated insulin resistance (HOMA-IR index), lipid profile (total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL), decreased c-reactive protein (CRP) and weight (all had P value<0.05). Treatment did not have significant effect on triglycerides (TG), waist circumference, body mass index (BMI), uric acid and systolic/diastolic blood pressure (p values>0.05). But the number of cases with high systolic/diastolic blood pressure decreased significantly after 6 months treatment (P values=0.007 and 0.01). Conclusion: Subclinical hypothyroidism treatment is suggested according to mentioned effects, especially in cases with insulin resistance, lipid profile disturbance, obesity, and high blood pressure.

Keywords: Diabetes; Hypothyroidism; Insulin resistance

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1. Introduction

hypothyroidism is one the most common thyroid dysfunctions and has two types: subclinical hypothyroidism (SHT) and overt hypothyroidism(1-4)Subclinical hypothyroidism is characterized by high serum TSH and normal free T3 (FT3) and free T4 (FT4). (1, 5, 6) Prevalence of subclinical hypothyroidism is %3-8 in euthyroid population, it increases with age and is more common in women although after the age of 50



it becomes the same in men and women and the total prevalence increases to %10. (7)

Subclinical Hypothyroidism can lead to overt hypothyroidism and increase the risk of coronary artery disease (CAD) and other cardiovascular diseases as well as osteoporosis, change in mineral elements, anemia, depression and memory dysfunction.(2, 5, 8)Dyslipidemia and insulin resistance in patients with subclinical hypothyroidism has been reported in different studies.(2, 8-10) No correlations between serum TSH, BMI, and lipid profile has been proved in various studies.(10-13) There are no sufficient information about metabolic state and insulin resistance in patients with subclinical hypothyroidism.

Although there are various studies considering adverse effects of Subclinical hypothyroidism there are no agreement about clinical importance and profits of levothyroxine treatment especially in those %80 patients with TSH<10 mIU/L, because different TSH and SHT levels are not considered in these studies.(9, 14) The clinical importance of therapy for mild elevation of serum TSH (<10 mIU/L) (6, 15) and the exact upper limit of normal for the serum TSH level remain subjects of debate(6, 16-19). When the TSH level is above 10 mIU/L, levothyroxine therapy is generally agreed to be appropriate(6, 15, 20). However, management of patients with a serum TSH level of less than 10 mIU/L is controversial. (6, 14) Studying the treatment effect of subclinical hypothyroidism in decreasing metabolic syndrome risk factors and cardiovascular diseases is necessary and can be helpful to control future disorders. In spite of various studies, the relationship between subclinical hypothyroidism and cardiovascular diseases remain controversial. We assessed the effects of thyroid hormone replacement on metabolic control and insulin resistance in patients with subclinical hypothyroidism referred to Labbafinejad hospital endocrine clinic during 2010.

2. Materials and Methods

2.1. Study design

This Before and After Interventional Study included 159 subclinical hypothyroidism (TSH>5, normal T3 and T4) patients. Inclusion criteria of the study included men and women presented to the endocrinology clinic of Imam Hossein Hospital with the finding of an elevated TSH and normal FT4 and T3 level indicating new diagnosis of subclinical hypothyroidism. Exclusion criteria of the study included patients under treatment with levothyroxine for the past 3 months or lipid-reducing drugs for the past 6 months, any past medical history of CAD, DM, pituitary or hypothalamus disorders and any other disorders effecting lipid metabolism. Patients' serums were collected at 8 a.m. after 12-14 hours overnight fasting and was checked for lipid profile, TSH, T4, T3, serum insulin level, CRP, FBS, uric acid and 2-hour postprandial glu-

cose after breakfast. Then height, weight, BMI and blood pressure of the patients were measured, and patients undergone treatment with levothyroxine 25-50 micrograms daily. All patients were recommended to maintain their usual exercise and diet habits. Levothyroxine dose was determined after checking TSH and T4 every 2 months. Eventually after 6 months the initial laboratory tests were repeated and evaluated and the results were imported to SPSS 18 for analysis.

2.2. Patients

Subjects of this study were patients referring to Labbafinejad hospital endocrine clinic with subclinical hypothyroidism that had 2 consecutive tests showing TSH>5mIU/L and normal T3 and T4. Patients should not have been under treatment with levothyroxine for the past 3 months or lipid-reducing drugs for the past 6 months and shouldn't have had history of CAD, DM, pituitary or hypothalamus disorders and any other disorders effecting lipid metabolism.

2.3. Statistical analysis

Data collection method of this study is Non Probable & Convenience, volume of the samples was calculated 144 patients which considering %10 probable loss will come to 159 patients, after completing the study 153 patients remained until the end. Collected data was analyzed descriptively by measures of central tendency and then qualitative variables were analyzed through ANOVA and Chi2 tests and quantitative variables were analyzed through paired t-test ($\alpha=0.05$, $\beta=0.2$).

2.4. Ethical considerations

Due to Helsinki convention, name and personal information of the patients will remain confidential with the researchers and all reports will be generalized and nameless. All patients were given written consent forms to participate in the study and they were handed sufficient information about the study.

3. Results

In this interventional study 159 patients passed the entering criteria but only 153 patients remained until the end of study and the collected data from them was analyzed. These patients had an average age of 41.29 (SD=14.9), ages varied from 19-70 years old. 51 patients (%33.3) were men and 102 patients (%66.7) were women. Other factors such as TSH, T4, T3, CRP, fasting serum insulin, FBS, 2hPP, HOMA score, total cholesterol, LDL, HDL, and body weight had a significant difference before and after treatment also the number of patients with high systolic or diastolic pressure dropped clearly. On the other hand, treatment did not seem to have a significant effect on serum TG, BMI, waist circumference, mean diastolic or systolic blood pressure and uric acid. (Table 1)

4. Discussion

This is a before and after interventional study with 153 patients and %66.7 of them are women which is acceptable considering the higher prevalence in women.

4.1. Thyroid profile and inflammation

T3 and T4 levels both shown significant increase after treatment (table1). TSH levels had significant decrease after treatment (table1) which is the same result Ganie and associates (21) achieved in their studies, showing proper and adequate treatment in our patients. CRP decreased significantly after treatment (table1), studies done by Al Sayed (22) and Sharma (23) reported higher levels of CRP in SHT patients. Therefore, it seems that treatment of SHT can decrease CRP levels and treat chronic inflammations.

4.2. Blood sugar and insulin resistance

This study shows significant decrease in fasting serum insulin, FBS, 2hPP and HOMA score (Table1), in Al Sayed (22) study, fasting serum insulin was higher in SHT patients but there was no significant difference in HOMA score between SHT patients and control group so the numbers are quite similar but there is a disagreement between the studies of Al sayed(22), Dessein (24), Singh (25) and others (26, 27) which show that SHT can lead to or exacerbate insulin resistance, and studies of Ganie(21), Liu(28), Oweeki(29) and others(22, 27, 30) which indicate SHT does not have any relations with insulin resistance. Therefore, according to the findings in this study SHT treatment can decrease insulin resistance indexes.

4.3. Lipid profile

In our study LDL and total cholesterol decreased significantly and HDL showed a significant increase, TG in the other hand did not vary significantly. (Table1) Similarly in articles published by Al Sayed (22), Dessini (24), Ganie (21), Sharma (23), Iqbal (30) and Razvi (31), total cholesterol and LDL were higher in SHT patients than control group. Al sayed (22) and Kong (32) reported no statistical difference in HDL. Therefore according to our study and the others mentioned treatment of SHT improves lipid profile by effecting cholesterol but has no effect on TG.

4.4. Body indexes

This study shows significant decrease in body weight but no statistical difference in BMI and waist circumference after treatment. (Table1) Al Sayed (22) studies show higher weight in SHT patients than control group. In Razvi (31) and Luboshitzky (33) studies SHT patients had higher waist circumference and it is indicated that treatment of SHT can significantly decrease waist circumference. Overall, this study and the others show that treatment of SHT can lead to weight loss

but has no significant effect on BMI, also waist circumference can be lowered through the treatment but this has not been shown by this study.

4.5. Blood pressure

According to this study SHT treatment has no significant effect on average SBP or DBP (table1), Ganie (21) studies also indicates this. Article published by Erkan (34) F on the other hand shows that treatment could lead to decrease in blood pressure. Overall, this study shows no effect of the treatment on average blood pressure but can significantly decrease the quantity of those patients with high SBP or DBP.

There were some limitations to this study including the poor cooperation of patients and discontinuing the treatment for resolving this problem %10 more patients were added to the study. Generalization to all the patients cannot be concluded and cannot be resolved with available facilities.

5. Conclusion

Considering this study and the similar published studies 6 months treatment of SHT can improve lipid and insulin resistance profile and decrease in CRP and body weight but has no effect on TG, waist circumference, BMI, uric acid, and blood pressure, it can however help patients with high SBP and DBP. According to these benefits, therefore, treatment is suggested especially in patients with insulin resistance, dyslipidemia, obesity and systolic or diastolic hypertension.

6. Appendix

6.1. Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

6.2. Funding and support

None.

6.3. Author's contributions

All the authors had the same contribution.

6.4. Acknowledgement

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Table 1: Test results in patients before and after treatment with levothyroxine.

Factor	Mean value before treatment (SD)	Mean value after treatment (SD)	Minimum value before treatment (after)	Maximum value	P-value
TSH mIU/L	9.95±(2.96)	2.97±(2.21)	5.2 (0.2)	15.8 (5)	<0.001
T4 µg/dl	6.83±(1.22)	8.85±(1.46)	4.4 (6.3)	9.3 (12.2)	<0.001
T3 µg/dl	0.8±(0.29)	1.36±(0.53)	0.2 (0.3)	1.55 (2.5)	<0.001
CRP mg/l	4.04±(3.63)	2.95±(2.67)	1.2 (0.1)	14.7 (10.7)	0.03
Fasting serum insulin mIU/L	10.52±(3.06)	7.92±(3.03)	2.5 (1.5)	15.8 (15.5)	0.035
FBS mg/dl	97.6±(10.96)	93.54±(10.17)	74 (67)	125 (111)	<0.001
2hPP mg/dl	110.63±(24.69)	95.88±(16.67)	72 (66)	167 (136)	0.018
HOMA score	2.42± (2.6)	1.93± (0.78)	0.67 (0.46)	4.14 (3.7)	<0.001
TG mg/dl	117.52±(48.39)	119.3±(41.26)	50 (43)	223 (190)	0.45
Total cholesterol mg/dl	195.64±(37.3)	186.97±(29.66)	143 (137)	296 (254)	0.015
LDL mg/dl	119.5±(23.9)	103.4±(19.4)	82 (57)	180 (137)	<0.001
HDL mg/dl	47.19±(12.11)	53.64±(16.38)	26 (33)	74 (95)	0.04
Body weight kg	73.19±(9.11)	71.08±(9.12)	52 (51)	97 (96)	0.047
BMI kg/m ²	27.1±(2.66)	26.3±(2.7)	20.7 (20.3)	30.4 (30)	0.56
Waist circumference cm	98.9±(7.4)	98.3±(7.6)	81 (80)	115 (115)	0.09
Systolic BP mmHg	126.12±(16.4)	115.01±(13.3)	92 (92)	167 (147)	0.81
Patients with SBP > 140mmHg	23	8	-	-	0.007
Diastolic BP > 90mmHg	78.34±(8.3)	71.6±(10.22)	62 (42)	97 (87)	0.88
Patients with DBP	11	0	-	-	0.01
Uric acid mg/dl	6.48±(1.81)	5.7±(1.9)	3.2 (1.5)	10.4 (9.3)	0.053

Table 2: Baseline characteristics.

Characteristics	Total participants	Men	Women	Mean age (SD)	Minimum age	Maximum age
Value	153	51(%33.3)	102(%66.7)	41.29± (14.9)	19	70