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Effects of Levothyroxine Treatment on Lipid Profile in Subclinical Hypothyroidism: A Randomized Clinical Trial

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Abstract

Background: Studies demonstrated controversial results on subclinical hypothyroidism (SCH) regarding lipid profile alteration with or without Levothyroxine treatment. The purpose of this study is to investigate the effects of Levothyroxine on serum lipids in SCH.**Materials and Methods:** One hundred patients with SCH referred to Taleghani hospital in Kermanshah were recruited and randomly assigned into the intervention or the control group. Patients in intervention group received Levothyroxine 50-75 micrograms for three months. Patients in control group received the same placebo with the same dose and duration. Lipid profile was measured before and after the trial and the changes were compared between groups. (IRCT code: 138903244179N1). **Results:** Triglyceride, Total Cholesterol, LDL, HDL and Lipoprotein-A were measured before and after treatment. None of the factors showed significant difference either between or within groups, before and after the treatment ($P<0.05$). **Conclusion:** Treating with Levothyroxine does not have any clinically significant impact on lipid profile in SCH patients which indicates that we should not expect SCH patients to use Levothyroxine solely for lipid profile alternation, except those with other clinical indications for treatment.**[GMJ.2015;4(2):72-77]**

Keywords: Levothyroxine; Subclinical Hypothyroidism; Cholesterol; Lipoprotein-A; LDL; HDL

Introduction

Subclinical hypothyroidism (SCH) is defined as normal-range thyroid hormone levels (T4) with elevated serum thyroid-stimulating hormone (TSH); which is seen in 3% to 8% of the general population. It is more common in women than men; and its prevalence increases with age [1, 2].

Cardiovascular diseases (CVD) are amongst the most important issues worldwide. Smoking, high blood pressure and dyslipidemia are

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the most known risk factors for CVD through increased atherosclerosis. Several underlying diseases can also increase CVD risks. Although minimal TSH elevations are not associated with an increased risk, studies have demonstrated that TSH levels are highly associated with cardio-cerebro-vascular events [3-5].

Autopsy researches have demonstrated progressive atherosclerosis in patients with hypothyroidism. Researchers reported severe atherosclerosis in 84% of patients with myxedema, while only 40% of normal matched patients had atherosclerosis. Furthermore, prevalence of CVD is higher in SCH patients [6]. Increased cholesterol, LDL and Triglycerides (TG) are reported as the main lipid deregulation in clinical and subclinical hypothyroid patients [6-9].

There are controversial debates regarding the effect of SCH treatment with Levothyroxine on serum lipid profile. Razvi et al [10] demonstrated an association between incident coronary heart disease and related mortality in patients with subclinical hypothyroidism over 20 years of follow-up, which was attenuated after Levothyroxine treatment. Some studies demonstrated high decrease in lipoprpotein-a, total cholesterol and LDL [11-15], while some others stated otherwise [16-19]. Therefore, according to the importance of both SCH and lipid profile in cardiovascular diseases, we assessed the effect of Levothyroxine treatment on dyslipidemia in these patients.

Methods and Materials

Patients and Methods

This is a double-blind randomized placebo controlled clinical trial on 100 middle-aged (less than 60 years old) patients with SCH between March 2010 and March 2011 referred to endocrinology and metabolism out-patient clinic of Taleghani Hospital, Kermanshah, Iran. The number of patients was calculated via Altman nomogram (α= 0.05, β=0.2). Researchers as well as patients cases were blinded. Patients were aware and consent was acquired prior to study. The protocol of this research was approved by the ethical committee of Kernamshah University of Medical Sciences, Medicine Faculty (IRCT code: 138903244179N1).

All patients were diagnosed as SCH by normal range Total T4 (0.8 to 1.8 ng/L) and Free T4 (Range: 0.8 -2.8 ng/dL) and increased TSH level (higher than upper limit of 4.70 μIU/mL) [1]. All patients with history of receiving Levothyroxine, Glucocorticoid, Aspirin, Amiodarone, Lipid lowering drugs, contraceptive and dopamine agonist or antagonists such as Metochlopramide and Domperidon were not included in this study. Furthermore, patients with history of acute or severe thyroid dysfunction or diabetes, pregnant and menopaused women were abruptly excluded from the study. Demographic information such as age, gender, height, weight, smoking, physical activity and educational level were entered in a checklist.

All patients underwent phlebotomy in an outpatient's laboratory. We took samples from antecubital vein after at least 12 h of fasting between 08:00–08:30 in the morning and stored it in standard Vacutainer (Becton Dickinson, Plymouth, UK) tubes. Samples were centrifuged at 1000x for 10 minutes at 18-21 degrees Celsius to extract plasma. Serum samples were frozen for the measurement of serum fasting blood sugar (FBS), triglycerides (TG), total cholesterol, low density lipoprotein (LDL) and high-density lipoprotein (HDL) and Lipoprotein-a as well as TSH and T4.

Before any intervention, a laboratory technician (which was not included as a researcher) assigned the patients into two groups based on a computer random number selector. Patients with odd numbers were assigned to the case group, coded as L-no (L for Levothyroxine and an identifying number) receiving 50 (in patients less than 60kg) or 75 (in patients much heavier than 60 kg) mcgr of Levothyroxine (Iran Hormone Inc., Tehran, Iran) for 3 months. Patients with even numbers were assigned to the control group, coded as P-no (P for Levothyroxine and an identifying number, receiving a size- and color-matched placebo (manufactured by the Pharmacy Faculty of Kermanshah Medical University, Iran). The patients were then followed and at the end of six-month period, the same assays were un-

dertaken. All information were then included in the checklist and the randomization technician presented blinded groups to the researchers as group A and Group B.

Serum Lipid Assays

Total cholesterol, HDL and TG were measured by photometric assay with intra- and inter-assay CVs less than 2% (Pars Azmoon®; Iran). LDL was calculated by LDL Cholesterol = Total Cholesterol, HDL, (TG/5). Lipoprotein-A was measured by biochemical kit (Bionic®, Germany) with intra- and inter-assay CVs less than 1%. TSH and T4 were also assessed by Liaison instrument using chemiluminescence method (DiaSorin LIAISON®, Italy) with intra- and inter-assay CVs of 0.2-6%.

Statistical Analysis

Results are shown as mean and standard deviation (SD). Laboratory and anthropometric data were entered in STATA, windows version 12.0 and all confounding variables were tested prior to final analysis to ensure random allocation. Kolmogorov-Simonov normality test was applied. Data were then compared using standard statistical tests such as independent samples Pearson Chi-Square, Independent samples T-test, paired samples t-test or their non-parametric equivalents such as Mann-Whitney-U test. P-values less than 0.05 were considered as significant.

Results

Demographic Data

One hundred SCH patients were enrolled in the present study; however, seven were excluded due to our criteria all at the end. 93 patients were divided into 48 cases and 45 placebo group. The male/female ratio was 11/82 and mean age was 27.7±5.7 (ranging 15 to 60) years. Furthermore, 42% of the patients had sufficient physical activity. 79% of the patients had K-12 diploma, while only 21% had academic education. As seen in table 1, no significant difference was seen in demographic data between two groups.

Disease Characteristics

All patients were documented on diagnosis of SCH. The chief complaint of patients accounted for the followings: 77% fatigue, 40% weight gain, 32% irregular menstruation, 56% hair loss, 26% constipation and 37% goiter.

In case and placebo groups, serum level of TSH decreased from 6.95 to 2.72 (mean TSH changes 4.23±1.22, p=0.01) and 6.79 to 6.12 (mean TSH change 1.4±0.67, P=0.400), respectively.

Lipid Profile

Table 2 demonstrates all information regarding TG, Total Cholesterol, LDL, HDL and Lipoprotein-A in both groups, before and after treatment. As seen, none of the factors showed significant difference either between or within groups (P <0.05).

Discussion

Our study was unable to show that treatment with Levothyroxine influence lipid profile in SCH patients. Although SCH treatment needs some indications, which were described previously, improving lipid profile has been sug-

Table 1. Demographic Data of Patients Enrolled in the Study. No Significant Difference Was Found Between Groups.

		Levothyroxine Group	Placebo Group	P Value
Female		5 (11%)	5 (10%)	0.900
Age		33.9±13.06	35.9±11.06	0.412
BMI		26.7±5.4	28.5±5.9	0.111
	K-12	75.60%	81.20%	
Education	Collage	22.20%	19.80%	0.521
	Academic	2.20%	0	
Smoking		6.70%	2.10%	0.472

Table 2. Lipid Profiles of Patients in Both Groups, Before and After Levothyroxine Treatment.

	Levothyroxine Group			Placebo Group			Changes between Groups p[1]
	Before	After	P[2]	Before	After	P[2]	
TG	121.2±59.9	124.4±60.5	0.391	134.8±68.4	141.3±56.1	0.636	0.800
Cholesterol	182.4±37.4	184.6±38.2	0.792	191.1±47.5	190.3±41.2	0.587	0.611
LDL	97.7±24.6	104.8±32.5	0.792	99.5±28.5	98.6±24.6	0.049	0.101
HDL	44.9±11.3	45.2±14.3	0.144	44.5±8.6	50.4±25.9	0.860	0.313
Lip-A	33.4±4.7	39.7±7.5	0.080	39.7±5.9	28.3±3.6	0.292	0.050

p[1]: from Student's t-test, p[2]: From Paired t-test

gested in recent years and some studies have demonstrated significant differences in lipid serum levels after treatment. However, in our study, all serum TSH in patients of case group dropped in normal range as compared to the placebo group, in which TSH remained high; therefore, our results cannot be linked to inadequate Levothyroxine dosages.

Furthermore, all assays were done by a single operator in a single laboratory. Thus, there are no inter-assay errors. In addition, patients with normal lipid profile had no obligation on their diets and maybe used more food in lipid groups than normal that may alter the results, except Lipoprotein-A which is not susceptible to one's diet [20]. However, p-value for Lipoprotein was marginal (p=0.08) which may become significant by higher sample sizes; though, does not help the patients to improve lipid profile.

Before any implication of the results, we have to clarify that not all SCH patients necessarily have dyslipidemia. There are controversial studies regarding this issue. In the largest study in this regard, Canaris et al [6] calculates a 9.5% prevalence of SCH in a 25862 natural population, which demonstrates higher TG and LDL. Mansourian et al [7] and Kung et al [8] both represented similar results. On the other hand, Vierhapper et al [22] (a study on 700 patients) demonstrated that there was no significant difference in lipid profile between SCH and normal populations. Our study has also shown no significant difference. Therefore, there is no common outcome to conclude. This is perhaps due to different types of SCH definition and other underlying variables such as age, sex and race among study populations.

Decrease in total cholesterol and LDL levels was the most frequent change in lipid profile reported in other studies. Other parameters had paradoxical changes. In Yildirimkaya et al [11], Meier et al [12] (33 patients in each group) and Ganotakis et al [13] studies, no changes in TG and HDL were seen; while other lipids decreased significantly. However, in Canturk et al [16] study (which was performed on 35 SCH patients and 30 healthy individuals) LDL and Lipoprotein-A, in Carracio et al [17] study (performed on 49 SCH patients and 33 normal subjects), TG, HDL and lipoprotein-A, and in Arem et al study [18] (14 patients followed only for 4 months), HDL demonstrated no significant change.

In Tzotzas et al [19] study, as our study demonstrates, no significant difference was seen in lipid profile in both groups, both before and after treatment. However, this study demonstrated that lipoprotein-A decreased by 14.5% in patients with clinical hypothyroidism. In the 5th study of Tromso [14], mean cholesterol and LDL were higher in SCH patients. In the second phase of the study, 64 SCH patients were treated with Lecothyroxine and placebo (such as our study), total cholesterol, TG, LDL and Apo Lipoprotein-B decreased significantly; however, no significant changes were seen in HDL and Apo lipoprotein-A.

As far as we could study, there are only two similar studies in Iran. Kalantari et al [14] (80 patients in 2 groups) demonstrated LDL and total cholesterol decrease in the case group and Moradi et al [22], which was performed only on 10 SCH patients and 13 controls showed that patients in the placebo group had insignificant increase in their lipid profiles. Our study did not demonstrate any increase

or decrease in lipid profile, except Lipoprotein-A; which changes in both groups (increase in case group and decrease in placebo group); which in authors' opinion is an accidental finding and could not be explained.
As compared to other studies, our study had a larger sample size. In addition, it seems that 3-month treatment is a sufficient time for providing enough hormones to ensure lipid changes [11-19]; however, increasing sample size and longer hormone treatment may be an option for further studies.
In conclusion, our study suggested that treating with Levothyroxine did not have any clinically significant impact on lipid profile among SCH patients indicating that we should not expect SCH patients to use Levothyroxine solely for lipid profile alternation, except those with other clinical indications for treatment. Therefore, using Levothyroxine might not help SCH patients to have lower probability of CVDs. Further studies are recommended.

Conclusion

Although this study did not find associations between drug abuse and risk of traffic injuries, the prevalence was higher just for tramadol in drivers involved in road accident than drivers transferred to the emergency ward due to non-traumatic reasons. Therefore, tramadol increased the risk of traffic accidents.
Furthermore, our results confirm that opium continues to be the most illicit drug frequently consumed in Iran and demonstrate the high proportion of illicit drug abuse in Iranian drivers. In addition, this study indicated that most of drug abusers were male and more than half of drug abuser drivers consumed more than one drug. More health education and policies are necessary to steadily decrease drug abuse in the community.

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Conflict of Interest

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

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