Original Article

Investigating the effect of levothyroxine replacement on cholesterol levels in hypothyroid patients

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Abstract

Introduction: Effects of levothyroxine therapy on the lipid profile of hypothyroid patients lead to decrease in the risk of cardiovascular diseases and mortality. **Objective:** Overt or subclinical hypothyroid dysfunction has negative effects on lipid metabolism and leads to hypercholesterolemia that in turn increases the risk of cardiovascular diseases and mortality. In this matter, several interventional studies investigated the effects of levothyroxine therapy on the lipid profile of hypothyroid patients, and conflicting results have been obtained. The current research aims to investigate the effect of levothyroxine replacement on cholesterol levels in hypothyroid patients. **Methods:** The present prospective study examined 112 patients (mean age of 43.80 ± 14.36 years) with overt hypothyroidism. To do so, 72.3% of patients were females. Levothyroxine replacement therapy was prescribed for patients, and they were examined monthly to evaluate the effects of therapy on their lipid profiles. After reaching normal thyroid stimulating hormone (TSH), the patients' laboratory parameters, including TSH, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, were surveyed. **Results:** After Levothyroxine therapy, there was a significant reduction in mean TSH (62.03 vs. 2.33 ± 1.95; $P < 0.0001$), triglycerides (145.57 ± 88.65 vs. 121.91 ± 59.52, $P = 0.002$), cholesterol (203.90 ± 53.73 vs. 166.65 ± 40.07, $P < 0.0001$), and serum LDL (123.61 ± 45.03 vs. 95.99 ± 24.20, $P < 0.0001$), but the mean value of serum HDL did not show any significant change (54.18 ± 16.60 vs. 51.59 ± 18.38, $P = 0.274$). **Conclusions:** Levothyroxine therapy has beneficial effects on lipid profile in patients with overt hypothyroidism because it decreases serum triglyceride, total cholesterol, and LDL. However, levothyroxine therapy does not significantly change HDL levels.

Keywords: Hypothyroidism, levothyroxine, lipid profile

Introduction

Overt hypothyroidism is manifested by a decrease in levels of thyroid hormones. In such medical conditions, the thyroid-stimulating hormone (TSH) level is higher, and serum level of the T4 hormone is lower than normal.[1,2] The prevalence of overt hypothyroidism is different in various studies and regions of the world depending on geographical location, diet, race, sex, and TSH range. This disease is more common in women, the elderly, and whites.[3,4] Hypothyroidism is associated with weight gain, higher body mass index (BMI), lower basal metabolism, dyslipidemia, and insulin resistance.[5,6] Overt hypothyroidism has been introduced as a risk factor for cardiovascular diseases and hyperlipidemia.[7-9] Lipid profile disorder is a common manifestation of thyroid dysfunction, so that an increase in serum TSH gradually raises the mean total cholesterol, triglyceride, and low-density lipoprotein (LDL) of serum, and hypercholesterolemia is associated with an increase in TSH level.[7]

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The primary mechanism of hypercholesterolemia in hypothyroidism is the accumulation of LDL cholesterol due to the reduction in the number of LDL recipients on the surface of cells, leading to a decrease in the catabolism of LDL. The reduction in the activity of LDL receptors has also been reported. Other mechanisms affecting serum cholesterol levels in hypothyroidism include a significant increase in LDL oxidation, lower cholesterol secretion into the bile, decreased cholesterol ester transfer, and reduced lipoprotein lipase activity.[9-11]

Synthetic thyroxine (T4, levothyroxine) is a selective treatment for hypothyroidism. Levothyroxine is a prohormone with very low intrinsic activity. This drug is deiodinated in peripheral tissues and converted to T3 (an active form of thyroid hormone).[6] In recent years, there has been an improvement in the lipid profile of hypothyroid patients during levothyroxine therapy, and some studies have found significant differences in serum lipid levels after levothyroxine therapy so that levothyroxine therapy in these patients has decreased the low-density lipoprotein levels as well as concentrations of blood LDL, thereby improving cardiovascular functions.[12-15] On the contrary, the results of a meta-analysis on the effectiveness of levothyroxine therapy on TSH hormone status and lipid profiles in patients with hypothyroidism indicated that such therapy improves the initial hypothyroidism until normal TSH. However, LDL and total cholesterol do not reach normal levels.[16]

Several studies have also investigated the effect of levothyroxine therapy on non-atherogenic lipids. Some studies indicated the inefficacy of this therapy on high-density lipoprotein (HDL),[17,18] while a study showed a positive effect of levothyroxine therapy on HDL.[19]

Since higher TSH can increase cholesterol, appropriate treatment can be an effective strategy to reduce the risk of dyslipidemia and prevent adverse cardiac outcomes in hypothyroid patients. Therefore, given the contradictory results about the effect of levothyroxine therapy on blood lipids, the present study aimed to evaluate the impact of levothyroxine therapy on lipid parameters in patients with overt hypothyroidism.

Materials and Methods

The present intervention prospective research was conducted on overt hypothyroidism patients who were over 18 years of age and referred to the Endocrinology clinic of Golestan Hospital in Ahvaz in 2019–2020. The study was performed after obtaining the approval of the Ethics Committee of the research deputy of Ahvaz Jundishapur University (code: IR.AJUMS.REC.1398.947). Informed written consent was also received from all patients before starting the therapy. Besides, the research ethics items of the Declaration of Helsinki and the patient information confidentiality were observed at all stages of the study.

In this study, the sample size was 112, according to an article by Saxena *et al.*,[12] in which the total cholesterol was 219 ± 32.6 before therapy and 194 ± 27 after therapy, the researcher's opinion according to which a 10-unit difference was clinically important, and considering α =0.05, and β =0.1. Further, Sampling was carried out through the census method. Levothyroxine-treated patients, pregnant patients, patients with diabetes, and those treated with lipid-lowering drugs were excluded from the study.

Data collection and intervention

At the beginning of the study, basic characteristics of patients, including age, sex, height, and weight, were collected. The patient's body mass index (BMI) was calculated as weight (kg)/ by height (m^2). Moreover, to measure their LDL, HDL, triglyceride (TG), Cholesterol, and TSH, venous blood samples were taken from all patients after 12 hours of fasting. Furthermore, serum levels of glucose, cholesterol, HDL, and TG were measured through the enzymatic method and by using special kits (Pars Azmun, Iran), LDL was obtained with the Friedewald equation, and TSH was calculated by ELISA method using a monobind kit (made in Iran).

Sodium levothyroxine prescribed for patients with overt hypothyroidism is equal to1.6 μg/kg/day; however, a lower dose can be used based on TSH level. In the present research, to help absorb the drug, all patients were advised to consume levothyroxine 30-45 min before breakfast and at least 3 h after the last meal. After administering levothyroxine to all the patients, fasting blood samples were taken monthly from patients to assess the level of improvement in TSH. After reaching normal TSH level, the serum LDL level and the concentration of HDL, TG, cholesterol, and TSH were determined in patients, and the obtained values were compared with values before the intervention and treatment.

Statistical analysis

To statistically analyze the data, SPSS 22 was employed. The collected data were analyzed using descriptive statistics, including frequency, mean, standard deviation, frequency, and frequency percentage. The paired *t*-test was also used to compare the mean of variables before and after therapy. The significance level of the tests was 0.05.

Results

In this study, 112 hypothyroid patients aged from 18 to 71 years were examined. Table 1 presents the participants' basic

Table 1: Basic characteristics of hypothyroid patients

Variable	Value
Gender	Female 81 (72.3)
	Male 31 (27.7)
Age (year)	43.80±14.36 (18-71)
Weight (kg)	74.18±13.84 (46-124)
Height (cm)	164.87±7.76 (150-188)
BMI (kg/m^2)	27.70±4.89 (17.54-41.91)

The numbers are presented as frequency (%) or mean±standard deviation (minimum-maximum). BMI refers to body mass index

characteristics. Table 2 presents the results of the effect of levothyroxine therapy on the serum TSH level and lipid profiles of hypothyroid patients. As shown, the levels of triglycerides, cholesterol, and serum LDL of patients with hypothyroidism have significantly decreased after treatment with levothyroxine and reaching normal TSH B ($P < 0.05$), but the serum HDL levels of these patients do not show any significant change after levothyroxine therapy ($P = 0.274$). Furthermore, the patient's serum levels of fasting blood sugar were equal to 100.11 ± 17.02 (75-148) and 98.50 ± 18.41 (62-127) before and after levothyroxine therapy, respectively ($P > 0.05$).

Discussion

The results of the present study indicated that levothyroxine therapy remarkably decreased the mean TSH, triglyceride, total cholesterol, and serum LDL of patients with overt hypothyroidism until TSH reached normal level, but such therapy did not have any significant effect on the level of serum HDL in these patients. According to the results, levothyroxine was a therapeutic strategy that could improve the cholesterol, TG, and LDL abnormalities in hypothyroid patients, thereby reducing the risk of cardiovascular diseases.

In line with the present study, several research works revealed the positive effect of levothyroxine therapy on improving the lipid profile in overt hypothyroid patients. For example, in a meta-analysis by Kotwal *et al.*[13] levothyroxine therapy in overt hypothyroidism significantly increases total cholesterol. LDL-C, HDL-C, apolipoprotein B (ApoB), and lipoprotein a, but it had no significant effect on triglyceride levels. Saxena *et al.*[12] also found that levothyroxine therapy enhances dyslipidemia by reducing cholesterol, LDL, and triglycerides in patients with overt and subclinical hypothyroidism. Additionally, Gluvic *et al.*[20] observed a significant reduction in total cholesterol and LDL levels in hypothyroid patients 3 months after levothyroxine therapy. Singh *et al.*,[21] also studied the effect of levothyroxine therapy on serum lipid levels in overt and subclinical hypothyroid patients and noticed that serum levels of TSH, total cholesterol, triglyceride, and LDL significantly decreased in both groups of patients after the therapy, but the HDL-C level only showed a significant reduction in the hypothyroid group. Ito *et al.*[22] also reported the positive effect of levothyroxine therapy (until reaching the normal level of TSH) on the reduction of total cholesterol, triglyceride, and LDL in patients with overt hypothyroidism.

Packard also conducted a similar study and found that levothyroxine therapy in six hypothyroid patients normalized the level of TSH and significantly reduced LDL.[23] In another study on 15 patients with overt hypothyroidism and 14 patients with subclinical hypothyroidism, Arem *et al.*[24] found positive effects of levothyroxine therapy on total cholesterol and LDL-C. Moreover, Becerra *et al.*[25] indicated that hypothyroid patients, who had received levothyroxine therapy, showed decreased levels of LDL-C, and total cholesterol as far as thyroid hormones reached normal levels. Hylander and Rosenqvist[26] also reported that levothyroxine therapy in hypothyroid patients with abnormal LDL could improve the LDL cholesterol level until TSH reached a normal level. The above results confirm the findings of the present study.

In another study, Pazos *et al.*[27] examined 12 patients with severe hypothyroidism with hypercholesterolemia and found that levothyroxine therapy caused a rapid decrease in LDL cholesterol after a month of therapy, and the change remained for a year with the improvement of thyroid hormone status. Although the individuals with hypercholesterolemia were excluded from the present study, the results of Pazos' *et al.*[27] study was consistent with the findings of the present study. Consistent with the previous studies, the findings of the current work showed that levothyroxine therapy does not noticeably reduce HDL-C.[17,28] However, the results of a trial by Sigal *et al.*[19] indicated a significant reduction in HDL-C after levothyroxine therapy. Therefore, further studies are necessary for a definite conclusion.

Dyslipidemia and increased levels of total cholesterol and LDL are the most common changes in lipid profile in hypothyroid patients, and there are conflicting results for other parameters, including triglyceride, especially HDL-C so a meta-analysis by Li *et al.*,[18] as well as studies by Yildirimkaya *et al.*,[29] Meier *et al.*,[30] Ganotakis *et al.*,[31] and Arem *et al.*,[24] indicated that levothyroxine therapy does not significantly change levels of HDL and triglyceride. The results of the above-mentioned studies are consistent with the results of the present study, except that in the present study, the level of TG also significantly decreased after therapy.

However, some studies have indicated that levothyroxine therapy does not have any clinically significant effect on the lipid profiles of patients with overt hypothyroidism[16] and subclinical hypothyroidism.[32,33] Such a result is not consistent with the findings of the present study. The discrepancy between results could be explained by different definitions of overt and

Table 2: Comparison of different parameters before and after levothyroxine therapy

Parameter	Before therapy	After therapy	Difference between pre- and post-therapy	*P**
TSH (mlU/ml)	54.15±62.03 (7.0-360.0)	2.33±1.95 (0.5-5.5)	51.82±61.88 (6.50-358.8)	<0.0001
TG (mmol/l)	145.57±88.65 (37-706)	121.91±59.52 (44-380)	29.20±82.86 (-133-509)	0.002
TC (mmol/l)	203.90±53.73 (98-429)	166.65±40.07 (98-305)	41.46±65.82 (-53-242)	<0.0001
LDL-C (mmol/l)	123.61±45.03 (25-301)	95.99±24.20 (42-195)	21.06±58.73 (-40-193)	<0.0001
HDL-C (mmol/l)	54.18±16.60 (18-112)	51.59±18.38 (16-154)	1.45±28.41 (-89-71)	0.274

*Paired *t*-test ($P<0.05$ is significant). Numbers are presented as mean±standard deviation (minimum-maximum). The table presents levels of Thyroid-stimulating hormone (TSH), Triglyceride (TG), Total cholesterol (TC), Low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C)

subclinical hypothyroidism, and other underlying variables such as age, sex, and race in different populations. Another probable reason for differences in results is that most studies that had not confirmed the effectiveness of levothyroxine therapy on improving lipid profiles had examined subclinical hypothyroid patients. In this regard, Ito *et al.*[22] found that levels of all lipid profile parameters, including total cholesterol, triglyceride, LDL-C, and HDL-C, significantly decreased in overt hypothyroid patients three months after levothyroxine therapy, but only serum total cholesterol levels showed a significant decrease in subclinical hypothyroid patients, and levothyroxine therapy did not have any significant effect on other lipid profile parameters.

Regarding the increasing prevalence of cardiovascular morbidity, even a slight reduction in levels of total cholesterol, LDL, and triglyceride can significantly reduce the morbidity in cardiovascular diseases. According to the results of the present study, as well as most similar studies, hypothyroidism therapy with levothyroxine replacement and reaching a normal TSH level has beneficial effects on lowering blood cholesterol; thus, the proper treatment of hypothyroidism can help reduce the risk of cardiovascular diseases in this group of patients.

The most important strengths of the present study were its large sample size and its prospective nature. Even though the sample size of the present study was larger than other studies, larger sample size, and longer treatment, in future studies can help confirm the results. The limitation of the present study, however, included lack of evaluation of patients with subclinical hypothyroidism and lack of comparison of results with hypothyroid patients who did not reach normal levels of TSH after levothyroxine therapy.

Conclusion

The results of the present study indicated that although levothyroxine has beneficial therapeutic effects on atherogenic lipid profiles, including decreasing serum triglyceride, total cholesterol, and LDL in patients with overt hypothyroidism, it does not significantly change HDL-C. The results indicated that appropriate treatment of hypothyroidism in hypothyroid patients is of high importance to reach a normal level of TSH, thereby improving lipid profile. Finally, prospective studies with larger sample sizes are recommended to evaluate the effects of levothyroxine therapy on cardiovascular events in hypothyroid patients.

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Conflicts of interest

There are no conflicts of interest.

References

1. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet 2017;390:1550-62.
2. Longhi S, Radetti G. Thyroid function and obesity. J Clin Res Pediatr Endocrinol 2013;5:40-4.
3. Mammen JS, McGready J, Ladenson PW, Simonsick EM. Unstable thyroid function in older adults is caused by alterations in both thyroid and pituitary physiology and is associated with increased mortality. Thyroid 2017;27:1370-7.
4. Asvold BO, Vatten LJ, Bjøro T. Changes in the prevalence of hypothyroidism: The HUNT Study in Norway. Eur J Endocrinol 2013;169:613-20.
5. Duntas LH, Brenta G. The effect of thyroid disorders on lipid levels and metabolism. Med Clin 2012;96:269-81.
6. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, *et al.* Guidelines for the treatment of hypothyroidism: Prepared by the American thyroid association task force on thyroid hormone replacement. Thyroid 2014;24:1670-751.
7. Walsh JP, Bremner AP, Bulsara MK, O'leary P, Leedman PJ, Feddema P, *et al.* Thyroid dysfunction and serum lipids: A community-based study. Clin Endocrinol (Oxf) 2005;63:670-5.
8. Udovcic M, Pena RH, Patham B, Tabatabai L, Kansara A. Hypothyroidism and the heart. Methodist Debakey Cardiovasc J 2017;13:55-9.
9. Duntas LH, Brenta G. A renewed focus on the association between thyroid hormones and lipid metabolism. Front Endocr 2018;9:511-5.
10. Jin T, Teng X. Update on lipid metabolism and thyroid disorders. J Endocrinol Diabetes Obes 2014;2:1043-8.
11. Ross DS, Cooper DS, Mulder JE. Lipid abnormalities in thyroid disease. Topic 7857 Version 11.0. 2024.
12. Saxena A, Kapoor P, Saxena S, Kapoor A. Effect of levothyroxine therapy on dyslipidemia in hypothyroid patients. Int J Med Update J 2013;8:39-49.
13. Kotwal A, Cortes T, Genere N, Hamidi O, Jasim S, Newman CB, *et al.* Treatment of thyroid dysfunction and serum lipids: A systematic review and meta-analysis. J Clin Endocr Metab 2020;105:dgaa672. doi: 10.1210/clinem/dgaa672.
14. Haghi AR, Solhjoo M, Tavakoli MH. Correlation between subclinical hypothyroidism and dyslipidemia. Iran J Pathol 2017;12:106-11.
15. Javed Z, Sathyapalan T. Levothyroxine treatment of mild subclinical hypothyroidism: A review of potential risks and benefits. Therapeutic advances in Endocrinology Metab 2016;7:12-23.
16. McAninch EA RK, Miller CH, Bianco AC. Systemic thyroid hormone status during levothyroxine therapy in hypothyroidism: A systematic review and meta-analysis. J Clin Endocrinol Metab 2018;103:4533-42.
17. Maurya DR, Borthakur S, Nyaharkar N. Impact of levothyroxine therapy on lipid profile value in patients with subclinical hypothyroidism. J Med Sci 2019;5:39-42.
18. Li X, Wang Y, Guan Q, Zhao J, Gao L. The lipid-lowering effect of levothyroxine in patients with subclinical

hypothyroidism: A systematic review and metaanalysis of randomized controlled trials. Clinic Endocr 2017;87:1-9. doi: 10.1111/cen. 13338.

19. Sigal GA, Medeiros-Neto G, Vinagre JC, Diament J, Maranhão RC. Lipid metabolism in subclinical hypothyroidism: Plasma kinetics of triglyceride-rich lipoproteins and lipid transfers to high-density lipoprotein before and after levothyroxine treatment. Thyroid 2011;21:347-53.
20. Gluvic Z, Sudar E, Tica J, Jovanovic A, Zafirovic S, Tomasevic R, *et al*. Effects of levothyroxine replacement therapy on parameters of metabolic syndrome and atherosclerosis in hypothyroid patients: A prospective pilot study. Int J Endocrinol 2015;2015:147070. doi: 10.1155/2015/147070.
21. Singh S, Dey Sarkar P. Serum lipids, tHcy, hs-CRP, MDA and PON-1 levels in SCH and overt hypothyroidism: Effect of treatment. Acta Biomed 2014;85:127-34.
22. Ito M, Arishima T, Kudo T, Nishihara E, Ohya H, Kubota S, *et al*. Effect of levo-thyroxine replacement on non-highdensity lipoprotein cholesterol in hypothyroid patients. J Clin Endocrinol Metab 2007;92:608-11.
23. Packard CJ, Shepherd J, Lindsay GM, Gaw A, Taskinen MR. Thyroid replacement therapy and its influence on postheparin plasma lipases and apolipoprotein-B metabolism in hypothyroidism. J Clin Endocrinol Metab 1993;76:1209-16.
24. Arem R, Escalante DA, Arem N, Morrisett JD, Patsch W. Effect of L-thyroxine therapy on lipoprotein fractions in overt and subclinical hypothyroidism, with special reference to lipoprotein (a). Metabolism 1995;44:1559-63.
25. Becerra A, Bellido D, Luengo A, Piedrola G, De Luis DA. Lipoprotein(a) and other lipoproteins in hypothyroid patients before and after thyroid replacement therapy. Clin Nutr 1999;18:319-22.
26. Hylander B, Rosenqvist U. Time course effect of thyroxine on serum lipoprotein concentrations in hypothyroid subjects. Acta Med Scand 1982;211:287-91.
27. Pazos F, Alvarez JJ, Rubiés-Prat J, Varela C, Lasunción MA. Long-term thyroid replacement therapy and levels of lipoprotein(a) and other lipoproteins. J Clin Endocrinol Metab 1995;80:562-6.
28. Danese MD, Ladenson PW, Meinert CL, *et al*. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: A quantitative review of the literature. J Clin Endocrinol Metab 2000;85:2993-3001.
29. Yildirimkaya M, Ozata M, Yilmaz K, Kilinc C, Gundogan MA, Kutluay T. Lipoprotein(a) concentration in subclinical hypothyroidism before and after levo-thyroxine therapy. Endocr J 1996;43:731-6.
30. Meier C, Stavis JJ, Roth CB. TSH controlled T4 therapy reduced cholesterol levels and clinical symptoms in subclinical hypothyroidism: A double blind placebo controlled trial. J Clin Endocrinol Metab 2001;86:4860-4.
31. Ganotakis ES, Mandalaki K, Tampakaki M, Malliaraki N, Mandalakis E, Vrentzos G, *et al*. Subclinical hypothyroidism and lipid abnormalities in older women attending a vascular disease prevention clinic: effect of thyroid replacement therapy. Angiology 2003;54:569-76.
32. Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M. Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. Thyroid 2000;10:803-8.
33. Anagnostis P, Efstathiadou ZA, Slavakis A, Selalmatzidou D, Poulasouchidou M, Katergari S, *et al*. The effect of L-thyroxine substitution on lipid profile, glucose homeostasis, inflammation and coagulation in patients with subclinical hypothyroidism. Int J Clin Pract 2014;68:857-63.