10.5005/jp-journals-10045-0073

ORIGINAL ARTICLE

Impact of Levothyroxine Therapy on Lipid Profile Value in Patients with Subclinical Hypothyroidism

[1]Swapnav Borthakur, [2]Deepesh K Maurya, [3]Nitin Nyaharkar

ABSTRACT

Aim: To study the effect of levothyroxine treatment on lipid profile in patients with subclinical hypothyroidism.

Materials and methods: This study was a randomized controlled trial, prospective study conducted on 22 cases of subclinical hypothyroidism with 22 controls at Down Town Hospital, Guwahati, Assam, India. Inclusion and exclusion criteria were undertaken. Levothyroxine therapy was given and follow-up was done after 3 months with thyroid and lipid profile tests. Pretreatment and posttreatment values were compared using paired t-test using Statistical Package for the Social Sciences (SPSS), version 19.

Results: Statistical significance between pretreatment and posttreatment values was found to be in values of thyroid-stimulating hormone (TSH), cholesterol high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides ($p < 0.05$). There was no significant difference in the pretreatment and posttreatment triiodothyronine (T3) and thyroxine (T4) values. There was mild increase in value of HDL, and significant decrease in value of TSH, cholesterol, very low density lipoprotein (VLDL), and triglycerides.

Conclusion: Lipid profiles are altered in patients with subclinical hypothyroidism compared with controls. Levothyroxine therapy has beneficial effect on lipid profile in patients with subclinical hypothyroidism.

Clinical significance: Levothyroxine therapy in patients of subclinical hypothyroidism reduces TSH levels and thus prevents conversion to overt hypothyroidism and also reduces cardiac morbidity.

Keywords: Levothyroxine, Lipid profile, Subclinical hypothyroidis.

How to cite this article: Borthakur S, Maurya DK, Nyaharkar N. Impact of Levothyroxine Therapy on Lipid Profile Value in Patients with Subclinical Hypothyroidism. J Med Sci 2018;4(1):10-13.

Source of support: Nil

Conflict of interest: None

[1]Associate Professor, [2,3]Postgraduate Student

[1,3]Department of Medicine, Down Town Hospital, Guwahati Assam, India

[2]Department of ENT, Down Town Hospital, Guwahati, Assam India

Corresponding Author: Deepesh K Maurya, Postgraduate Student, Department of ENT, Down Town Hospital, Guwahati Assam, India, Phone: +919987858780, e-mail: maurya.deepesh@gmail.com

INTRODUCTION

The term "subclinical hypothyroidism" is used to describe a state where there is a raised TSH concentration with a normal concentration of T4. It is common with prevalence of 7 to 8% in women and 2 to 4% in men.[1] Patients with subclinical thyroid disease have few or no symptoms or signs of thyroid dysfunction and vary in nature, thus subclinical thyroid disease is a laboratory diagnosis. Levothyroxine therapy in mild elevation of serum TSH is generally agreed to be appropriate.[2,3] Management of patients with a serum TSH level of less than 10 mIU/L is also controversial.[4] 3-Hydroxy-3-methylglutaryl-CoA reductase (HMGCR) is the rate-limiting enzyme in cholesterol synthesis. In hypothyroid state, HMGCR mRNA levels are reduced and treatment with thyroid hormone (TH) restores it to normal level. Thyroid hormone stimulates HMGCR transcription and increases its stability.[5] The abnormality of lipid profiles in subclinical hypothyroidism may be related to gradually decreased TH levels in the serum and tissues.[6] Additionally, high TSH level stimulates HMGCR expression by stimulating the cyclic adenosine monophosphate/protein kinase a/cyclic adenosine monophosphate-responsive element binding protein (cAMP/PKA/CREB) cassette.[7] Conversion of cholesterol into bile acids is important for maintaining whole body cholesterol homeostasis. The rate-limiting enzyme in bile acid synthesis is controlled by cholesterol 7-hydroxylase, which is regulated by TH.[8]

Thus, TH also reduces cholesterol through enhancing cholesterol clearance pathway. Over time, subclinical hypothyroidism may develop to overt hypothyroidism. This study will also help patients to prevent the development of overt hypothyroidism.

MATERIALS AND METHODS

This was a randomized controlled, prospective study conducted on 22 cases of subclinical hypothyroidism with 22 controls at Down Town Hospital, Guwahati, Assam, India.

Inclusion Criteria

- All patients with subclinical hypothyroidism
- Patients willing to participate in the study.

Exclusion Criteria

- Patient not willing to participate in the study
- A past history of thyroid disease
- Patients on treatment for thyroid disorder
- Patient not on antidyslipidemic drugs.

This study was approved by Down Town Hospital ethical committee. Thyroid stimulating hormone, T3, T4, total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, and serum triglycerides were measured in all the patients after an overnight fasting. All patients with subclinical hypothyroidism were started with levothyroxine therapy with a daily dose of 25 to 75 µg depending on the level of T4 and the serum TSH level. Serum TSH level was then checked after 8 weeks, and the dose was adjusted. Patients were followed up after 3 months from first date of visit with a repeat lipid profile and thyroid profile tests.

Descriptive statistical analysis was carried out in the present study. Paired t-test is applied to analyze the data. The SPSS (version 19) was used to generate data.

RESULTS

Total 22 patients and 22 controls were taken in the study.

Mean age of the patients was 43.22 years, while it was 40.45 years for the controls. Female predominance of 86.36% was found among cases. Mean values of variables (Table 1) were compared with that of controls (Table 2) after levothyroxine therapy. Mean TSH value was found to be significantly higher, i.e., 7.24 than in controls, i.e., 2.67 after levothyroxine therapy ($p = 0.00091$). There was no significant change in T3 values when compared with controls ($p = 0.165746$) and also in T4 values ($p = 0.967266$). The mean total cholesterol levels were significantly higher in patients with subclinical hypothyroidism as compared with controls (372.1364 *vs* 205.5909, $p \leq 0.0001$). The mean LDL levels were reduced from 97.4545 to 85.2727, and mean VLDL values were decreased from 28.2273 to 27.8636 and was statistically significant when compared with controls ($p = 0.003102$). Mean triglyceride value decreased from 169.8636 to 166.9545 and was statistically significant when compared with controls ($p < 0.00001$). Mean HDL value increased from 34.7727 to 35.2273 and was statistically significant when compared with controls ($p < 0.00001$).

Statistical significance between pretreatment and posttreatment values was found to be in values of TSH, cholesterol, HDL, LDL, and triglycerides ($p < 0.05$; Table 3).

There was no significant difference in the pretreatment and posttreatment T3 and T4 values. There was mild increase in value of HDL, and significant decrease in the values of TSH, cholesterol, VLDL, and triglycerides.

DISCUSSION

The Colorado study, which screened 25,862 subjects, found that the mean total cholesterol and LDL cholesterol progressively increased with increasing levels of serum TSH and hypercholesterolemia was associated with mild elevations of TSH levels.[9] In this study, the mean age of patients was 43.22 years, which is similar to Rigdway et al:[10] 44 years; Bell et al:[11] 42 years; and Elder et al:[12] >40 years. Female predominance in this study (86.36%) was close to the study by Bhandopadyay et al,[13] where females constituted 78% of the study population. In this study, the mean total cholesterol levels were significantly higher in patients with subclinical hypothyroidism, as supported by Asranna et al[14] and Bandyopadhyay et al.[13] Increased levels of LDL

Table 1: Paired samples statistics of cases

		Mean	*n*	*Standard deviation*	*Standard error of mean*
Pair 1	T3-B	1.7182	22	0.23048	0.04914
	T3-A	1.7359	22	0.24325	0.05186
Pair 2	T4-B	107.3636	22	18.86934	4.02296
	T4-A	105.7727	22	27.57489	5.87899
Pair 3	TSH-B	9.9627	22	3.36084	0.71653
	TSH-A	7.2364	22	2.09433	0.44651
Pair 4	CHOL-B	384.2273	22	118.21245	25.20298
	CHOL-A	372.1364	22	122.48121	26.11308
Pair 5	HDL-B	34.7727	22	5.07029	1.08099
	HDL-A	35.2273	22	5.10771	1.08897
Pair 6	LDL-B	97.4545	22	20.63222	4.39880
	LDL-A	85.2727	22	20.82394	4.43968
Pair 7	VLDL-B	28.2273	22	6.20239	1.32235
	VLDL-A	27.8636	22	6.34932	1.35368
Pair 8	TG-B	169.8636	22	21.01767	4.48098
	TG-A	166.9545	22	19.90089	4.24288

CHOL: Cholesterol; TG: Triglyceride

Table 2: Paired samples statistics of controls

		Mean	*n*	*Standard deviation*	*Standard error of mean*
Pair 1	Control T3-B	1.8455	22	0.33684	0.07182
	Control T3-A	1.8532	22	0.34295	0.07312
Pair 2	Control T4-B	108.0455	22	22.91283	4.88503
	Control T4-A	108.0909	22	22.80541	4.86213
Pair 3	Control TSH-B	2.6782	22	1.25158	0.26684
	Control TSH-A	2.6782	22	1.25158	0.26684
Pair 4	Control CHOL-B	205.1818	22	25.52429	5.44180
	Control CHOL-A	205.5909	22	26.05426	5.55479
Pair 5	Control HDL-B	47.3636	22	7.41649	1.58120
	Control HDL-A	47.2273	22	7.52730	1.60482
Pair 6	Control LDL-B	72.1818	22	28.20273	6.01284
	Control LDL-A	72.6364	22	27.99583	5.96873
Pair 7	Control VLDL-B	22.6364	22	4.59343	0.97932
	Control VLDL-A	22.5909	22	4.66659	0.99492
Pair 8	Control TG-B	112.2727	22	27.64086	5.89305
	Control TG-A	112.2727	22	27.64086	5.89305

CHOL: Cholesterol; TG: Triglyceride

Table 3: Paired samples statistics of pretreatment and posttreatment values

		Paired differences							
					95% confidence interval of the difference				
		Mean	Standard deviation	Standard error of mean	Lower	Upper	t-value	df	p-value
Pair 1	T3-B–T3-A	−0.00955	0.02663	0.00568	−0.02135	0.00226	−1.681	21	0.108
Pair 2	T4-B–T4-A	−1.04545	22.02915	4.69663	−10.81263	8.72172	−0.223	21	0.826
Pair 3	TSH-B–TSH-A	2.72636	2.13675	0.45556	1.77898	3.67375	5.985	21	0
Pair 4	CHOL-B–CHOL-A	12.09091	11.93199	2.54391	6.80056	17.38126	4.753	21	0
Pair 5	HDL-B–HDL-A	−0.45455	0.59580	0.12703	−0.71871	−0.19038	−3.578	21	0.002
Pair 6	LDL-B–LDL-A	12.18182	4.87595	1.03956	10.01994	14.34369	11.718	21	0
Pair 7	VLDL-B–VLDL-A	0.36364	0.58109	0.12389	0.10600	0.62128	2.935	21	0.008
Pair 8	TG-B–TG-A	2.90909	4.12783	0.88006	1.07891	4.73927	3.306	21	0.003

CHOL: Cholesterol; TG: Triglyceride; df: Degree of freedom

and hypertriglyceridemia have been shown to increase the risk of cardiovascular disease. In this study, the mean LDL, VLDL, and triglyceride levels were reduced after levothyroxine therapy, but only decreased values of VLDL and triglyceride were statistically significant ($p < 0.05$). There was reduction in LDL value, but this might be due to the presence of confounding factors like low-fat diet intake. Subclinical hypothyroidism is associated with raised LDL levels and thus had larger cardiovascular risk,[15] and reduced levels were seen with levothyroxine therapy.[16] Value of triglycerides is reduced after levothyroxine therapy in this study, which is statistically significant. Similar reversal of changes following treatment are shown by Atthans et al,[17] and Monzani et al.[18] Mild increase in HDL value is also observed, which is statistically significance.

There is increasing prevalence of cardiovascular morbidity. Even small decrease in levels of total cholesterol, LDL, and triglyceride levels results in substantial reductions in cardiovascular morbidity.

REFERENCES

1. Albon LM, Franklyn JA. The thyroid: non-malignant disease. In: Michael G, editor. Scott-Brown's otolaryngology, head and neck surgery. 7th ed. Great Britain: Edward Arnold Publishers Ltd; 2008. p. 357.
2. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004 Jan;291(2): 228-238.
3. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT; American Association of Clinical Endocrinologists; American Thyroid Association; Endocrine Society. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. Thyroid 2005 Jan;15(1):24-28.
4. Chu JW, Crapo LM. The treatment of subclinical hypothyroidism is seldom necessary. J Clin Endocrinol Metab 2001 Oct;86(10):4591-4599.
5. Ness GC, Chambers CM. Feedback and hormonal regulation of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase: the concept of cholesterol buffering capacity. Proc Soc Exp Biol Med 2000 May;224(1):8-19.
6. Ito M, Takamatsu J, Sasaki I, Hiraiwa T, Fukao A, Murakami Y, Isotani H, Miyauchi A, Kuma K, Hanafusa T. Disturbed metabolism of remnant lipoproteins in patients with subclinical hypothyroidism. Am J Med 2004 Nov;117(9):696-699.
7. Tian L, Song Y, Xing M, Zhang W, Ning G, Li X, Yu C, Qin C, Liu J, Tian X, et al. A novel role for thyroid-stimulating hormone: up-regulation of hepatic 3-hydroxy-3-methylglutaryl-coenzyme A reductase expression through the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein pathway. Hepatology 2010 Oct;52(4):1401-1409.
8. Hashimoto K, Cohen RN, Yamada M, Markan KR, Monden T, Satoh T, Mori M, Wondisford FE. Cross-talk between thyroid hormone receptor and liver X receptor regulatory pathways is revealed in a thyroid hormone resistance mouse model. J Biol Chem 2006 Jan;281(1):295-302.
9. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000 Feb;160(4):526-534.
10. Ridgway EC, Cooper DS, Walker H, Rodbard D, Maloof F. Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. J Clin Endocrinol Metab 1981 Dec;53(6):1238-1242.
11. Bell GM, Todd WT, Forfar JC, Martyn C, Wathen CG, Gow S, Riemersma R, Toft AD. End-organ responses to thyroxine therapy in subclinical hypothyroidism. Clin Endocrinol (Oxf) 1985 Jan;22(1):83-89.
12. Elder J, McLelland A, O'Reilly DS, Packard CJ, Series JJ, Shepherd J. The relationship between serum cholesterol and serum thyrotropin, thyroxine and tri-iodothyronine concentrations in suspected hypothyroidism. Ann Clin Biochem 1990 Mar;27(Pt 2):110-113.
13. Bhandopadyay SK, Basu AK, Pal SK, Roy P, Chakrabarti S, Pathak HS, Murmu BK. Study of dyslipidemia in subclinical hypothyroidism. J Indian Med Assoc 2006 Nov;104(11):622-626.
14. Asranna A, Taneja RS, Kulshreshta B. Dyslipidemia in subclinical hypothyroidism and the effect of thyroxine on lipid profile. Indian J Endocrinol Metab 2012 Dec;16(Suppl 2): S347-S349.
15. Bakker SJ, ter Maaten JC, Popp-Snijders C, Slaets JP, Heine RJ, Gans RO. The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. J Clin Endocrinol Metab 2001 Mar;86(3):1206-1211.

16. Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR, Drewe J, Huber P, Herzog R, Müller B. TSH controlled L-Thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab 2001 Oct;86(10):4860-4866.
17. Atthans BU, Staub JJ, Ryff-De-Lechel A, Oberhänsli A, Stähelin HB. LDL/HDL changes in subclinical hypothyroidism: possible risk factor for coronary heart disease. Clin Endocrinol (Oxf) 1988 Feb;28(2):157-163.
18. Monzani F, Caraccio N Kozakowa M, Dardano A, Vittone F, Virdis A, Taddei S, Palombo C, Ferrannini E. Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo-controlled study. J Clin Endocrinol Metab 2004 May;89(5):2099-2106.