

## Study of serum lipid profile in subclinical hypothyroidism

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### Abstract

**Objective:** It has been known that overt hypothyroidism is associated with hyperlipidemia, replacement therapy with Levothyroxine significantly reverses lipid metabolism abnormalities. But no clear consensus has been established regarding the treatment of Subclinical Hypothyroidism subjects. This is due to the fact that there are no data from large trials on whether and to what degree Subclinical Hypothyroidism affects lipid profile. This study is aimed to provide a look at the status of Lipid Profile in the case of Subclinical Hypothyroidism.

**Materials and Methods:** Total 100 subjects were recruited and divided into 2 groups. 50 Patients with Subclinical Hypothyroidism were considered as the cases and 50 healthy people as the controls. Serum TSH was analysed by sandwich electrochemiluminescence immunoassay method. Serum cholesterol, triglyceride and HDL were estimated by enzymatic colorimetric method, LDL was calculated by using friedewald formula.

**Results:** Serum cholesterol, LDL were higher ( $P < 0.0001$ ) and HDL ( $P < 0.0001$ ) was lower in Subclinical Hypothyroid patients (mean $\pm$ SD= 199.9 $\pm$ 27.8 mg/dl, 130.0 $\pm$ 26.3mg/dl, 44.2 $\pm$ 9.1 mg/dl respectively) compared to healthy controls (mean $\pm$ SD= 170.1 $\pm$ 16.8 mg/dl, 97.3 $\pm$ 14.7 mg/dl, 54.2 $\pm$ 10.0 mg/dl respectively). A significant correlation was found between the levels of TSH and Serum Cholesterol ( $r=0.5101$ ,  $P < 0.0001$ ), LDL ( $r=0.5637$ ,  $P < 0.0001$ ) and a significant negative correlation was found between the levels of TSH and HDL ( $r=-0.4525$ ,  $P < 0.0001$ ).

**Conclusion:** Subclinical hypothyroidism is associated with elevated levels of Serum Total Cholesterol and LDL which is atherogenic in nature, and low level of HDL. This may further increase the risk of development of atherosclerosis.

**Keywords:** Subclinical Hypothyroidism, lipid profile, Total Cholesterol, LDL, HDL, dyslipidemia

### 1. Introduction

It has been proved for a while that overt hypothyroidism is associated with hyper-lipidemia. Increase in serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) may occur in hypothyroidism because of several changes in the synthesis, metabolism, and mobilization of lipids. Thyroid hormones induce the hepatic expression of hydroxymethylglutaryl coenzyme A reductase, which increases the cholesterol synthesis [1]. On the contrary, thyroid hormones also increase the expression of cell surface LDL receptors in various tissues. LDL receptor levels are regulated by negative feedback in the presence of high intracellular cholesterol levels. This may be mediated through the sterol regulatory element-binding protein-2 (SREBP-2). The SREBP-2 gene is directly regulated by T3 [2]. The decrease in LDL receptors leads to reduced clearance of LDL from the serum. Hypothyroidism may also lead to increased intestinal cholesterol absorption due to thyroid hormone

actions on Niemann-Pick C1-like 1 protein in the gut [3]. The thyroid hormone effects on LDL receptor expression and cholesterol absorption outweigh the effects of decreased hepatic cholesterol synthesis, leading to a net accumulation of serum LDL in overt hypothyroidism.

Although the overall effects of Subclinical Hypothyroidism (SH) on serum lipid levels remain unclear, it is likely that subtler manifestations of the same alterations that occur in overt hypothyroidism are present in mildly hypothyroid patients. Cholesteryl ester transfer protein (CETP) transfers cholesterol from high-density lipoprotein cholesterol (HDL) to LDL and very low density lipoprotein (VLDL). Plasma CETP concentrations are decreased in hypothyroidism and increased in hyperthyroidism, which may lead to alterations in serum HDL concentrations [4]. Thyroid hormone stimulates cholesterol efflux from macrophages to HDL via the ABCA1 transporter [5]. Lipoprotein lipase activity is increased by thyroid hormone.

Higher serum triglycerides may be observed in overtly hypothyroid individuals because of their lower lipoprotein lipase activity [6].

SH defined as an increased serum TSH level in the setting of normal free peripheral thyroid hormone concentrations, is relatively common, occurring in 4–10% of the adult population [7, 15]. In case of overt hypothyroidism, it's been studied that replacement therapy with L-thyroxine significantly improves lipid metabolism abnormalities. A period of 4-6 weeks of thyroxine replacement therapy is usually needed to correct dyslipidemia in overt hypothyroidism. A study in newly-diagnosed hypothyroid patients showed a decrease in serum TC and LDL levels after thyroxine treatment [8]. But no clear consensus has been established regarding the treatment of SH subjects [9,10]. This is due to the fact that there are no data from large trials on whether and to what degree does SH affect lipid profile. Our study is aimed to provide a look at the status of Lipid Profile in case of SH.

## 2. Materials and Methods

In this cross sectional study, patients were enrolled from Medical O.P.D. and health check-up clinic of the affiliated hospital. Total 100 subjects were recruited, on the basis of predefined Performa, history was taken & physical examination was done thoroughly. Prior approval of Institutional Ethics Committee was taken, informed consent form of all the subjects were duly signed.

### 2.1 Sampling procedures, inclusion & exclusion criteria

Venous blood was drawn in plain vacutainer with strict aseptic precaution after 10-12 hours of fasting; serum was separated after centrifugation at 3000 rpm for 10-15 mins. Serum TSH, Serum FT4 and regular Lipid Profile were analysed on fully automated COBAS INTEGRA - 400 plus analyser & Cobas e411 Immunoassay. Serum Total Cholesterol was analysed by Colorimetric assay with CHOD-POD, triglyceride was analysed by Colorimetric endpoint GPO-PAP, serum HDL was analysed by homogenous enzymatic colorimetric, serum LDL, VLDL were calculated by using friedewald formula. Serum TSH level was analysed by sandwich electrochemiluminescence immunoassay and serum FT4 was analysed by competitive electrochemiluminescence immunoassay. 50 patients with SH defined on the basis of Serum TSH level between 4.2-10 mU/L, Serum FT4 level between 12-22 pmol/L, history & physical examination of the patients were categorized into cases & 50 Healthy people having normal TSH <4.2 mU/L were categorized as controls. Subjects having Diabetes Mellitus according to ADA guidelines [11] and overt thyroid conditions like hypothyroidism & hyperthyroidism on the basis of TSH & FT4 were excluded [12].

### 2.2 Statistical analysis

Statistical analysis was carried out in MedCalc version 14.8.1 and Microsoft Excel 2016. Student "t" test was used to find out statistical significance between various parameters. Pearson's Correlation Coefficient was used for correlation analysis. P value <0.05 was considered as statistically significant.

## 3. Results

### 3.1 Age and Gender distribution

Table 1 shows the age and gender distribution of both the case group and the control group. Total 100 subjects were enrolled and 41-50 years of age group was having higher number of subjects compared to rest of the groups. The mean age of the case group was  $49.04 \pm 10.53$  years and of the control group was  $48.96 \pm 10.11$ , the P value was 0.969 for both the groups which indicates there was no significant difference between both the groups. The female subjects were more compared to male subjects overall.

### 3.2 Mean comparison and student "t" test of various parameters

Table 2 shows means of various parameters and comparison between the case and the control groups. Student "t" test was applied between case and control groups for all parameters. It showed highly significant difference in TSH, Serum Total Cholesterol (TC), LDL, HDL, LDL/HDL and TC/HDL values between both case and control groups. All of them were having P value < 0.0001. Similarly, Triglyceride and VLDL in both groups also showed significant difference (P = 0.0003)

### 3.3 Bivariate correlation analysis between TSH and various parameters of Lipid Profile by using Pearson's Correlation Coefficient

Table 3 shows the correlation between TSH and various lipid parameters. The correlation between TSH and TC was highly significant, P value was < 0.0001 and  $r = 0.5101$  [Figure 1]. Similarly, correlation between TSH and LDL was highly significant with P value = <0.0001 and  $r = 0.5637$  [Figure 2] and between TSH and HDL, P value was <0.0001 and  $r = -0.4525$  [Figure 3] which showed highly significant negative correlation between TSH and HDL value.

**Table 1: Age and Gender distribution**

Age (years)	Cases		Controls	
	Male	Female	Male	Female
25-40	3	7	2	8
41-50	7	11	11	10
51-60	7	6	3	7
61-70	4	5	5	4
Total	21	29	21	29

**Table2: Mean comparison and student “t” test of various parameters**

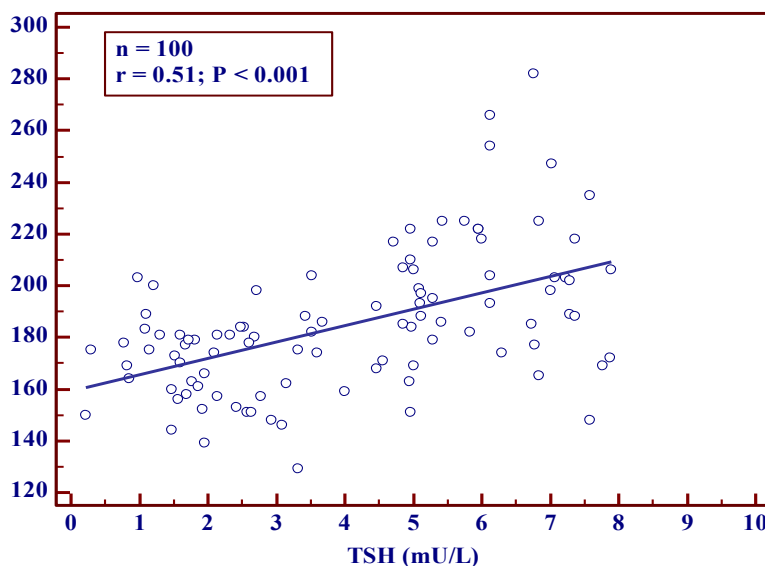
Parameter	Cases (Mean ± SD)	Control (Mean ± SD)	P Value	95% CI of difference
AGE (Years)	49.04 ± 10.53	48.96 ± 10.11	0.969	-4.1780 to 4.0180
Serum TSH(mU/L)	6.01 ± 1.05	2.10 ± 0.93	< 0.0001	-4.3019 to -3.5143
TC (mg/dL)	199.9 ± 27.8	170.1 ± 16.8	< 0.0001	-38.9346 to -20.6254
Triglyceride (mg/dL)	128.6 ± 59.6	93.0 ± 27.7	0.0003	-54.0783 to -17.0017
H D L (mg/dL)	44.2 ± 9.1	54.2 ± 10.0	< 0.0001	6.2765 to 13.8835
L D L (mg/dL)	130.0 ± 26.3	97.3 ± 14.7	< 0.0001	-41.2276 to -24.2764
V L D L (mg/dL)	25.7 ± 11.9	18.6 ± 5.5	0.0003	-10.8157 to -3.4003
TC/HDL	4.67 ± 0.95	3.24 ± 0.66	< 0.0001	-1.7590 to -1.1062
LDL/HDL	3.05 ± 0.82	1.87 ± 0.52	< 0.0001	-1.4520 to -0.9064

P value <0.05 was considered as statistically significant

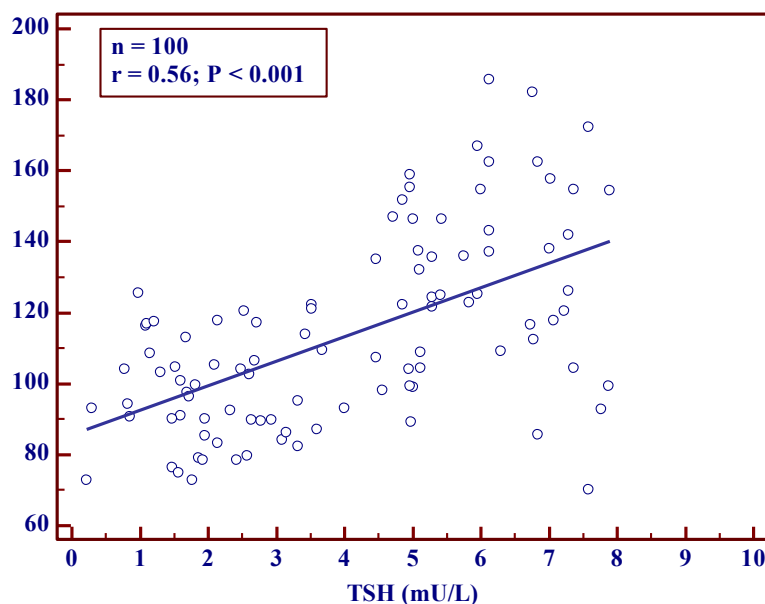
**Table 3: Pearson’s Correlation Coefficient between TSH and various lipid parameters**

Variable 1	Variable 2	Correlation coefficient ‘r’	P Value	95% CI for r
TSH	TC	0.5101	<0.0001	0.3486 to 0.6422
TSH	LDL	0.5637	<0.0001	0.4130 to 0.6843
TSH	HDL	-0.4525	<0.0001	-0.5960 to -0.2811

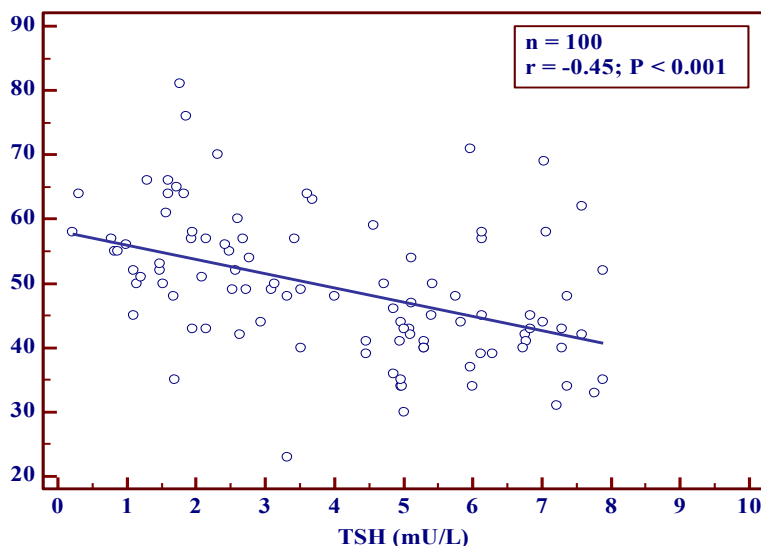
P value <0.05 was considered as statistically significant



**Figure 1: Pearson’s Correlation Coefficient between TSH and TC**



**Figure 2: Pearson’s Correlation Coefficient between TSH and LDL**



**Figure 3: Pearson's Correlation Coefficient between TSH and HDL**

#### 4. Discussion

In our study, we found that in SH, TC and LDL levels were increased while HDL level was decreased. Increased levels of TC and LDL and decreased level of HDL are known risk factors for various Cardiovascular disorders. [13,14]

Major cross sectional studies have shown direct relationship between TSH level and Total Cholesterol and LDL [15]. Many other studies have reported similar findings. Yildirimkaya *et al* [16] have found the increase in TC, LDL, Apolipoprotein B100 & Lp(a) levels and in SH& also found after giving thyroid replacement therapy, these levels were decreased. But they also found that there is no significant change in HDL levels in SH which disputes with our findings.

A prospective study, Shiro *et al* [17] suggested that LDL significantly increased in patients with subclinical hypothyroidism, after levothyroxine replacement therapy in SH patients; decrease in serum LDL level was seen. Kung *et al* [18] found that SH is associated with elevated LDL levels and low HDL levels which match with our findings. Valdemarsson *et al* [19] found similar results for TC & LDL; they also found that TG was not increased much in SH.

Lam *et al* [6] found increased concentration of TC and decreased concentration of HDL in case of SH which matches with our findings, when these patients became euthyroid after treatment, TC and HDL levels became normal. A population based study conducted by Bauer *et al* [20] found that high TSH is associated with deleterious changes in serum lipids, particularly HDL, LDL, and the ratio of LDL to HDL cholesterol in older white women.

Not all study advocated the use of levothyroxine as a replacement therapy in SH. Efstathiadou [21] found out increased levels of the atherogenic lipid parameters in SH which strengthen our findings but suggested that thyroid substitution therapy does not seem to significantly improve dyslipidemia in the whole group of patients which contradicts

many other studies. Similarly, Fatourech *et al* [9] and Biondi *et al* [10] suggest no thyroid replacement treatment for SH.

Because of the cross sectional nature of our study, we couldn't confirm the effect of thyroid replacement on SH patient, as replacement is not given to SH patients so far, a prospective study with replacement therapy is required to know the exact effect of replacement therapy on lipid profile in SH patients.

#### 5. Conclusion

There is no clear consensus whether SH patients should be treated with thyroid replacement therapy or not, the major hurdle is lack of data from major trial regarding the effect of SH on lipid profile in various population and also there is no availability of data regarding the outcome of the replacement therapy in SH patients. Our study confirms in our targeted population that in patients with SH, levels of lipid parameters are increased which are known to be atherogenic in nature. If thyroid replacement therapy decreases the levels of atherogenic lipids, thyroid replacement therapy may be advisable in SH and it may further avoid the harmful effects of the atherogenic lipids.

#### References

- [1] Choi JW, Choi HS The regulatory effects of thyroid hormone on the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase. *Endocr Res* 2000;26:1-21
- [2] Shin DJ, Osborne TF. Thyroid regulation and cholesterol metabolism are connected through sterol regulatory element-binding protein-2 (SREBP-2). *J Biol Chem* 2003; 278:34114-34118.
- [3] Gaïman C, Bonde Y, Matasconi M, Angelin B, Rudling M. Dramatically increased intestinal absorption of cholesterol following hypophysectomy is normalized by thyroid hormone. *Gastroenterology*2008; 134:1127-1136.
- [4] Tan KC, Shiu SW, Kung AW. Plasma cholesteryl ester transfer protein activity in hyper- and hypothyroidism. *J Clin Endocrinol Metab* 1998; 83:140-143

- [5] Boone LR, Lagor WR, MoyaMde L, Niesen MI, Rothblat GH, Ness GC. Thyroid hormone enhances the ability of serum to accept cellular cholesterol via the ABCA1 transporter. *Atherosclerosis* 2011; 218: 77–82
- [6] Lam KS, Chan MK, Yeung RT. High-density lipoprotein cholesterol, hepatic lipase and lipoprotein lipase activities in thyroid dysfunction-effects of treatment. *Q J Med* 1986; 59:513–521.
- [7] Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey(NHANES III). *J Clin Endocrinol Metab* 2002; 87: 489-99.
- [8] Abbas JM, Chakraborty J, Akanji AO, Doi SA. Hypothyroidism results in small dense LDL independent of IRS traits and hypertriglyceridemia. *Endocr J* 2008; 55: 381-9.
- [9] Fatourech V. Subclinical hypothyroidism: an update for primary care physicians. *Mayo Clin Proc* 2009; 84: 65-71.
- [10] Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 2008; 29: 76-131.
- [11] American diabetic association standards of medical care in diabetes 2014, *Diabetes Care* 2014; 37 (Suppl 1).
- [12] Carl Burtis, Edward Ashwood, David Bruns. Tietz textbook of Clinical Chemistry and Molecular Diagnostics. 4<sup>th</sup> edn 2005 Elsevier.
- [13] De Backer G, Ambrosioni E, Borch-Johnsen K et al., European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of eight societies and by invited experts). Executive summary. *Eur Heart J* 2003; 24: 1601–10.
- [14] Adult Treatment Panel III. Executive summary of the third report of the National Cholesterol Education Program (NECP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *J Am Med Assoc* 2001; 285: 2486–97.
- [15] Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med.* 2000; 160:526–34.
- [16] Yildirimkaya M, Ozata M, Yilmaz K, Kilinc C, Gundogan MA & Kutluay T. Lipoprotein (a) concentration in subclinical hypothyroidism before and after levo-thyroxine therapy. *Endocrine Journal* 1996 43 731–736.
- [17] Miura S, Itaka M, Yoshimura H, Kitahama S, Fukasawa N, Kawakami Yet al. Disturbed lipid metabolism in patients with subclinical hypothyroidism: effect of L-thyroxine therapy. *Internal Medicine* 1994 33 413–417.
- [18] Kung AW, Pang RW & Janus ED. Elevated serum lipoprotein (a) in subclinical hypothyroidism. *Clinical Endocrinology* 1995 43445–449.
- [19] Valdermarsson S, Hanson P, Hedner P & Nilsson-Ehle P. Relations between thyroid function, hepatic and lipoprotein lipase activities, and plasma lipoprotein concentrations. *Acta Endocrinologica* 1983104 50–56.
- [20] Bauer DC, Ettinger B & Browner WS. Thyroid function and serum lipids in older women: a population-based study. *American Journal of Medicine* 1998 104 546–551.
- [21] Efstathiadou Z, Bitsis S, Milionis HJ, Kukuvtis A, Bairaktari ET, Elisaf MS, et al. Lipid profile in subclinical hypothyroidism: is L-thyroxine substitution beneficial? *Eur J Endocrinol.* 2001 Dec; 145(6):705-10.