



## Profile of lipid alterations and Carotid intima-media thickness (CIMT) in people with subclinical hypothyroidism and the effect of thyroid replacement therapy

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### Abstract

**Objectives:** 1) To assess the alteration of carotid intima-media thickness (CIMT) and lipid parameters in people with subclinical hypothyroidism (SCH) 2) To quantify the improvement of CIMT (if any) after Levothyroxine replacement

**Subjects and methods:** In a non-randomized matched design 100 consecutive people with treatment naive SCH and equal number of age, gender and BMI (body-mass index) matched healthy controls were included in the study. Body mass index (BMI), TSH, FT4 (free T4), thyroid Peroxidase antibodies (TPOAbs), lipids, blood pressure and carotid media-intima thickness (CIMT) were estimated in all study subjects. People with SCH were further subdivided on the basis of their thyroid functional status: SCH with  $TSH \leq 10.0$  mIU/L (SCH-1) and SCH with  $TSH > 10$  mIU/L (SCH-2). Subjects in SCH-2 group were started on thyroxine replacement with a goal to normalise TSH and CIMT and lipids parameters were reassessed after 6 months of levothyroxine replacement.

**Results:** Mean values of CIMT ( $0.78 \pm 0.16$  vs  $0.64 \pm 0.08$ ,  $p < 0.001$ ), triglycerides ( $165.48 \pm 70.32$  vs  $130.16 \pm 51.93$ ,  $p < 0.001$ ), and total cholesterol ( $178.24 \pm 30.77$  vs  $165.60 \pm 31.87$ ,  $p = 0.005$ ) were significantly higher in people with SCH compared to matched controls. After 6 months of levothyroxine replacement, there was a significant reduction of triglycerides ( $190.81 \pm 81.01$  vs  $149.55 \pm 47.83$ ,  $p < 0.001$ ), total cholesterol ( $184.65 \pm 28.43$  vs  $159.80 \pm 21.09$ ,  $p < 0.001$ ), LDL ( $112.23 \pm 26.62$  vs  $96.05 \pm 18.93$ ,  $p < 0.001$ ) and CIMT ( $0.86 \pm 0.17$  vs  $0.76 \pm 0.13$ ,  $p < 0.001$ ) compared to pretreatment parameters.

**Conclusion** SCH is associated with increase in total cholesterol, triglycerides and CIMT and that there is a significant reduction of TG, TC, LDL and CIMT with levothyroxine replacement.

**Keywords:** Carotid media-intima thickness, Levothyroxine, Subclinical hypothyroidism

### INTRODUCTION

The prevalence of subclinical hypothyroidism (SCH) has increased over the years as a result of widespread availability and improvement of laboratory techniques, thereby gaining increasing attention. SCH is biochemically defined as increased serum thyrotropin (TSH) concentrations in combination with a serum free thyroxine level (FT4) level that is within the population reference range<sup>1</sup>. SCH predominantly affects women over 60 years of age, with an estimated prevalence of around 4-10% in the general population

<sup>2,3</sup>. Long-term adverse effects of SCH have garnered attention in recent years, especially with regard to its increased vulnerability to subclinical and overt cardiovascular disease. SCH has emerged as a strong risk factor for the development of atherosclerosis and myocardial infarction in many population based studies, more so in elderly women<sup>4</sup>. The Carotid intima-media thickness (CIMT) is an important parameter for early atherosclerosis and is widely used as a predictor of coronary and cerebrovascular

events<sup>5,6</sup> People with overt hypothyroidism have significantly increased risk for early atherosclerosis compared to euthyroid controls independent of other known risk factors, like dyslipidemia, hypertension and impaired endothelial function. Whether SCH is progenitor for the emergence of risk factors and development of atherosclerosis is still a matter of debate<sup>2</sup>. However, SCH has been found to be associated with atherogenic lipid profile and atherosclerosis in some studies<sup>3,5</sup> in contrary to others<sup>6,7</sup>. The carotid intima-media thickness (CIMT) is used as an indicator for subclinical atherosclerosis, which has been shown to be independent predictor of future vascular events<sup>8,9</sup>.

In view of conflicting data with regard to the effect of SCH on atherosclerosis<sup>10</sup>, our study was designed to assess the alteration of lipid parameters and Carotid intima-media thickness (CIMT) in people with SCH as compared to euthyroid controls and effect of levothyroxine replacement on these parameters

## MATERIAL AND METHODS

### Study subjects

This study was conducted in the Department of internal medicine at a tertiary care hospital in North India over a period of 1½ years. 100 consecutive patients with newly diagnosed treatment naive SCH (normal FT4 (0.9- 2.2 ng/dl) and elevated TSH (4.5<TSH<20.0 µIU/ml) with equal number of age, gender and body mass index (BMI) matched healthy, euthyroid controls, were included in the study. Patients with a previous history of thyroid disease, arterial hypertension, history of intake of medication for thyroid disease, arterial blood pressure or lipid metabolism, diabetes mellitus, liver or renal disease, chronic pancreatitis, primary hyperlipidemia, ovulatory dysfunction, pregnancy and infertility, were excluded from the study.

### Study protocol

BMI, TSH, FT4, thyroid-peroxidase antibodies (TPOabs), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), blood pressure, mean and maximum carotid intima-media thickness (CIMT), were determined in all participants.

### Laboratory analysis

Blood samples were taken in the morning, after a 12-hour overnight fast. Blood samples for lipoproteins were analyzed using Cobas Integra, according to standard methods. Total cholesterol and triglycerides were determined by full enzymatic methods (cholesterol oxidase and Glycerol phosphate oxidase method respectively; Cobas Integra, Hoffmann-La Roche, Basel, Switzerland). HDL-C was measured by polyethylene glycol/ cholesterol oxidase-peroxidase method, while LDL-C was calculated using the Friedewald formula. Serum TSH and free T4 concentrations were measured using an Immulite 2000 chemiluminescent analyzer (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). TPOabs was determined by the immunometric assay from Diagnostic Products Corporation (Los Angeles, CA). The normal values for TSH according to our lab were 0.3 – 4.50 µIU/ml and for FT4: 0.93 – 2.2 ng/dl. Participants with value  $\geq 60.00$  U/ml were considered as anti-TPO antibody positive.

### Clinical and anthropometric variables

Blood pressure was measured twice on the right arm, with a desk-model sphygmomanometer after five minutes at rest in a sitting position. There was a 3-min interval between the two measurements for each patient, and the mean value of the two measurements was used. In the case of hypertension ( $\geq 130/80$  mmHg), the measurement was repeated after 5 minutes. Study subjects were weighed without clothes and shoes on an electronic scale, in the morning fasting. Their height was measured to the nearest cm with a stadiometer. Body mass index (BMI) was calculated as body weight (in kg) divided by the square of body height (in meters).

### Carotid ultrasound

The risk for atherosclerosis was estimated by the ultrasound system. To avoid variations, the examination was performed by the same experienced radiologist, who was blind to the patient's risk factors. CIMT was determined by B-mode ultrasound using a linear transducer (7.5-10 MHz). These values then were calculated as a mean value of two measurements on a segment free of plaque in the right common carotid artery. Plaque was defined as a localized thickened lesion ( $\geq 1.1$  mm).

### Statistical analysis

The statistical software SPSS 20 was used to analyse the data. All the continuous variables were summarized as mean and SD. In addition, categorical variables were analyzed by chi-square test. All the results were discussed at 5% level of significance;  $P$  value  $< 0.05$  was considered significant. Unpaired  $t$ -test was used to analyze the difference between two independent sample means.

## Results

100 people with subclinical hypothyroidism with equal number of age, gender and BMI matched controls were included in the study. The mean age (years,  $34.09 \pm 8.71$  vs  $34.79 \pm 8.610$ ,  $p$  value = 0.568) and BMI ( $\text{kg}/\text{m}^2$ ,  $23.4 \pm 2.1$  vs  $23.32 \pm 2.26$ ,  $p$  value = 0.092) were comparable in both groups. TSH level was significantly higher in people with SCH patients ( $9.43 \pm 3.28$   $\mu\text{IU}/\text{ml}$ ) compared to euthyroid controls ( $2.58 \pm 1.01$   $\mu\text{IU}/\text{ml}$ ,  $p < 0.001$ ). Level of serum free  $T_4$  was within normal reference limits in both patients and controls. Mean serum TG ( $165.48 \pm 70.32$   $\text{mg}/\text{dl}$  vs  $130.16 \pm 51.93$   $\text{mg}/\text{dl}$ ,  $p$  value  $< 0.001$ ) and TC ( $178.24 \pm 30.77$   $\text{mg}/\text{dl}$  vs  $165.6 \pm 31.87$   $\text{mg}/\text{dl}$ ,  $P$  value = 0.005) were significantly higher in people with SCH compared to euthyroid controls. Although the mean LDL-Cholesterol was higher and mean HDL-Cholesterol was lower in patients with SCH as compared to their matched controls but this difference was not statistically significant. Carotid Intima-media

thickness (mm) was significantly higher in people with SCH compared to euthyroid controls ( $0.789 \pm 0.167$  vs  $0.64 \pm 0.08$ ,  $P$  value  $< 0.001$ ). TG, TC and LDL in people with TSH  $> 10$   $\mu\text{IU}/\text{ml}$  were higher and HDL was lower compared to people with TSH  $\leq 10$   $\mu\text{IU}/\text{ml}$  ( $190.81 \pm 81.01$  vs  $156.58 \pm 64.43$ ,  $P$  value = 0.032,  $184.65 \pm 28.43$  vs  $175.99 \pm 31.42$ ;  $P$  value = 0.218,  $112.23 \pm 26.62$  vs  $100.62 \pm 26.56$ ,  $P$  value = 0.058,  $37.65 \pm 5.95$  vs  $40.42 \pm 6.24$ ,  $P$  value = 0.052) respectively. Although TG, TC and LDL concentrations were higher and HDL was lower in people with serum TSH  $> 10$   $\mu\text{IU}/\text{ml}$  compared to those with serum TSH  $\leq 10$   $\mu\text{IU}/\text{ml}$ , but this difference was statistically significant only in case of TG level. Mean CIMT (mm) in people with TSH  $> 10$   $\mu\text{IU}/\text{ml}$  was significantly higher ( $0.86 \pm 0.171$ ) compared to people with serum TSH  $\leq 10$   $\mu\text{IU}/\text{ml}$  ( $0.762 \pm 0.16$  mm,  $P$  value = 0.01)

Out of 26 patients with serum TSH  $> 10$   $\mu\text{IU}/\text{ml}$ , 6 were lost to follow up. Rest of 20 patients were treated with daily oral levothyroxine for 6 months with a goal to normalise TSH. After 6 months of treatment and attainment of euthyroidism, they were again analyzed for lipid parameters and CIMT. There was a significant reduction in TG, TC, LDL, and CIMT. However, the improvement in HDL-C was not statistically significant

**Table 1-Anthropometric, Lipid parameters and CIMT in Study population**

Parameter	SCH(Mean $\pm$ SD)	Euthyroid controls(Mean $\pm$ SD)	$P$ Value
Age(Years)	$34.09 \pm 8.71$	$34.79 \pm 8.61$	0.56
BMI(Kg/ $\text{m}^2$ )	$23.4 \pm 2.10$	$23.32 \pm 2.26$	0.092
TSH( $\mu\text{IU}/\text{ml}$ )	$9.43 \pm 3.28$	$2.58 \pm 1.01$	$< 0.001$
Free $T_4$	$0.94 \pm 0.05$	$1.45 \pm 0.09$	$< 0.001$
Triglycerides( $\text{mg}/\text{dl}$ )	$165.48 \pm 70.32$	$130.16 \pm 51.93$	$< 0.001$
Total cholesterol( $\text{mg}/\text{dl}$ )	$178.24 \pm 30.77$	$165.60 \pm 31.87$	0.005

HDL cholesterol(mg/dl)	39.7±6.26	40.90±6.41	0.182
LDL cholesterol(mg/dl)	103.64±26.93	99.70±28.39	0.315
CIMT(mm)	0.78±0.16	0.64±0.08	<0.001

Data expressed as mean±SD

**Table 2 -Lipid parameters and CIMT in SCH-1 (TSH≤10 μU/ml) and SCH-2 (TSH ≥10 10 μU/ml) groups**

Parameter	SCH-1(mean±SD)	SCH-2(mean±SD)	P Value
Age(Years)	33.19±8.81	36.65±8.02	0.081
BMI(Kg/m <sup>2</sup> )	23.24±2.23	23.26±2.01	0.09
TSH( μIU/ml)	7.85±1.37	13.92±2.98	<0.001
Free T4	0.90±0.05	0.89±0.07	0.09
Triglycerides(mg/dl)	156.58±64.43	190.81±81.01	0.032
Total cholesterol(mg/dl)	175.99±31.42	184.65±28.43	0.218
HDL cholesterol(mg/dl)	40.42±6.24	37.65±5.95	0.052
LDL cholesterol(mg/dl)	100.62±26.56	112.23±26.62	0.058
CIMT(mm)	0.76±0.16	0.86±0.17	0.01

Data expressed as mean± SD

**Table 3- Lipid parameters and CIMT before and after levothyroxine replacement in SCH-2 group**

Parameter	Levothyroxine replacement		P value
	Before	After	
TSH( μIU/ml)	13.92±2.98	3.10±0.78	<0.001
Free T4	0.90±0.05	1.10±0.07	<0.001

Triglycerides(mg/dl)	190.81±81.01	149.55±47.83	<0.001
Total cholesterol(mg/dl)	184.65±28.43	159.80±21.09	<0.001
HDL cholesterol(mg/dl)	37.65±5.95	36.65±4.34	0.184
LDL cholesterol(mg/dl)	112.23±26.62	96.05±18.93	<0.001
CIMT(mm)	0.86±0.17	0.76±0.13	<0.001

Data expressed as mean ± SD

## Discussion

The nature and degree of dyslipidemia in overt hypothyroidism has been demonstrated in many studies and there is no doubt about the beneficial effects of thyroid substitution on serum lipids and on the risk for CAD<sup>(11,12)</sup>. Although the relationship between SCH and atherogenic lipid parameters is still not clear, multiple studies in the past have demonstrated a significant reduction in both serum total and low-density lipoprotein (LDL) cholesterol levels<sup>(13)</sup> with levothyroxine (LT4) replacement. TSH has been shown to induce the production of the hepatic 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase, which is a rate-limiting enzyme in cholesterol biosynthesis and moreover, thyroid hormones may affect HDL metabolism by increasing the cholesteryl ester transfer protein activity and also stimulate lipoprotein lipase<sup>(14)</sup>.

Among 8586 adults from the National Health and Nutrition Examination Survey III database, SCH was not associated with alterations in TC, LDL-C, TG, or HDL-C after adjustment for age, race, sex, and using lipid-lowering drugs<sup>(15)</sup>. However, a number of studies showed that TC, LDL-C, and TG were elevated in SCH compared to controls. Subclinical hypothyroidism has a great influence on derangement of lipid profile, more so in perimenopausal women<sup>(16,17)</sup>. The Colorado thyroid disease prevalence study which is one of the largest studies conducted on thyroid dysfunction also showed that there is alteration of lipid parameters with increasing TSH values<sup>(18)</sup>. Similarly, the Rotterdam study also concluded that SCH is independently associated with atherosclerosis and cardiovascular morbidity in post-menopausal women which can be attributed to dyslipidemia<sup>(19)</sup>.

In our study, there was a significant difference in mean values of TG, TC and VLDL between SCH and controls, however there was no significant difference in mean values of LDL-C and HDL-C between people with SCH and controls, similar to other studies<sup>(20)</sup>. The lipid lowering effect of thyroxine in patients with subclinical hypothyroidism is not yet established. Multiple interventional studies have evaluated the effects of L-T4 treatment on lipid profiles in patients with subclinical hypothyroidism, with mixed results. In a randomized study, patients with subclinical hypothyroidism were randomized to no treatment *vs.* treatment with simvastatin *vs.* treatment with thyroxine. The simvastatin treated, but not the thyroxine treated patients had significant reductions in LDL-C, total cholesterol, and triglycerides [21], similar to results shown by a Cochrane review of thyroid hormone replacement in subclinical hypothyroidism [22]. Meta-analysis of 13 studies in people with subclinical hypothyroidism, on thyroxine substitution, showed marked decrease in total cholesterol independent of initial plasma levels; however, plasma levels remained elevated in most patients [23]. Others showed a significant reduction of TC and LDL without a change in TG and HDL levels [24, 25]. In our study, people in SCH-2 group after 6 months of levothyroxine replacement had a significant reduction of triglycerides, total cholesterol and LDL compared to pretreatment parameters.

Carotid IMT is increasingly used as a surrogate marker for atherosclerosis and has a high positive predictor value for CAD.[26]. Association of CIMT and SCH was first demonstrated by Monzani *et al.*[28]. However, not all studies showed an association between TSH and CIMT [27,28]. In our study, people

with SCH had significantly higher CIMT compared to matched controls and the people with SCH-2 had CMT significantly higher than SCH-1 indicating that CIMT correlates strongly with TSH level which is consistent with previous studies. After 6 months of levothyroxine replacement in people in SCH-2 group, we observed significant reduction of CIMT compared to pretreatment values and the observation was consistent even after adjustment of conventional risk factors for atherosclerosis as has been seen in the past [29, 30]

There can be multiple possible reasons for disparate results of studies. These include differences in patients' ages, ethnicity, gender, and the degree and duration of hypothyroidism across studies. In addition, most observational studies did not adjust the differences in insulin resistance and smoking behavior, which were identified as potential modifiers of the association between thyroid status and serum lipids. LDL-C elevation in hypothyroid patients is enhanced in smokers and patients with insulin resistance<sup>(31,32)</sup> There are conflicting results about lipid profile pattern and SCH. This might be due to difference in population studied as well as differences in age, gender and ethnicity. Because of cross sectional nature of the present study, it is difficult to ascribe causality to any association we have found. Further evaluation of this association with longitudinal data would be necessary to support a causal link.

### Conclusion

SCH is associated with alteration of lipid parameters. Patients with SCH have higher TG, TC, VLDL and CIMT compared to euthyroid individuals. Other lipids like LDL-C may be marginally elevated whereas HDL-C may be slightly reduced in these patients as compared to euthyroid individuals. There is also a positive correlation of LDL-C, TC and TG with TSH level. Patients with higher TSH level ( $>10 \mu\text{IU/ml}$ ) have more lipid alterations and higher CIMT than those with low TSH ( $\leq 10 \mu\text{IU/ml}$ ). There was a significant improvement in lipid parameters and CIMT after levothyroxine treatment.

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