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Original Research Article

# A Study of Dyslipidemia and Inflammatory Markers in Subclinical Hypothyroidism

**Manoj Kumar Sharma[1], Hans Raj Pahadiya[2], Priyanshu Soni[3], Ajay Mathur[4]**

[1]Senior Resident, Department of Medicine, S.M.S. Medical College and Hospital, Jaipur
[2]Assistant Professor, Department of Medicine, S.M.S. Medical College and Hospital, Jaipur
[3]Resident doctor, Department of Cardiology, S.M.S. Medical College and Hospital, Jaipur
[4]Professor, Department of Medicine, JNU Medical College and Hospital, Jaipur

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**Corresponding Author: Dr. Manoj Kumar Sharma**
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**Abstract:**

**Objective:** We aimed to investigate the association of subclinical hypothyroidism with blood lipid profile and inflammatory markers including ESR and CRP.

**Material and Method:** This was a cross-sectional study done at Department of Medicine, S.M.S. Medical College Jaipur, India, during the period of December 2017 to January 2020. Age-matched 100 patients [50 subclinical hypothyroidism (SCH) and 50 euthyroid] were recruited. SCH was defined as serum thyroid stimulating hormone (TSH) level >5 (µIU /ml) with normal free T4 and T3 levels. Thyroid profile, lipid profile, and inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were estimated by standard methods.

**Results:** SCH group had a significantly higher level of TSH as compared to the euthyroid group (8.95±1.03 µIU/ml, 2.29±1.08 µIU /ml, respectively, p<0.001). SCH group had a significantly higher serum LDL levels as compared to the ethyroid controls (117.28±28.85 mg/dl, 104.86±28.78 mg/dl, respectively, p<0.05). Serum total cholesterol levels were raised and serum HDL levels were low in the SCH group, but this difference was statistically not significant (p>0.05). Serum CRP level was 4.64±3.98 mg/l in the SCH group and this was 2.34±1.53 mg/l for the control group (p <0.001), while ESR levels were high in the SCH group (p>0.05). LDL level showed a statistically significant positive correlation with serum TSH (p-<0.001). HDL level shows a negative correlation with serum TSH, which was statistically not significant (r -0.095, p 0.345).

**Conclusion:** We concluded that SCH is associated with dyslipidemia and elevated levels of inflammatory markers, which are good indicators for atherosclerosis, and predictors of cardiovascular morbidity. Thyroid hormone screening should be recommended in dyslipidemic patients.

**Keywords:** ESR, C-reactive protein, Dyslipidemia, Subclinical hypothyroidism.



## Introduction

Thyroid diseases are one of the most common endocrine disorders worldwide.[1] The primary hypothyroidism indicates an abnormality in the thyroid gland itself, which can be subclinical or overt. Subclinical hypothyroidism (SCH) is a laboratory diagnosis that is defined as an elevated thyroid stimulating hormone (TSH) level with normal free-T4 and free-T3 levels. These patients have few or no symptoms or signs of thyroid dysfunction. [2] The SCH has a female preponderance that increases with age and has varied prevalence in various studies, ranging from 4 to 15 percent.[3-6] Over a period of time, SCH progresses to overt hypothyroidism in approximately 2–5% patients per year.[2] The rate of progression to overt hypothyroidism is proportional to baseline TSH concentration and antithyroid antibody levels. Recent literature described that overt hypothyroidism increases the risk of atherosclerotic cardiovascular diseases by altering several traditional risk factors for cardiovascular disease. These risk factors include increases in circulating levels of highly atherogenic low-density lipoprotein (LDL) cholesterol particles, increased levels of triglycerides, induction of diastolic hypertension, altered coagulability, and direct effects on vascular smooth muscle.[6] Cardiovascular disease is more frequently present in males less than 50 years of age with SCH compared to euthyroid males. The altered lipid profile in SCH leads to atherosclerosis, which is an inflammatory disorder.[7] The risk of atherosclerosis can be easily assessed by markers of inflammation, including erythrocyte

sedimentation rate (ESR) and C-reactive protein (CRP). The increased concentration of fibrinogen during the inflammatory process causes an increased ESR level. On the other hand, CRP is an acute-phase reactant synthesized mainly in the liver, which also reflects the ongoing inflammation.[7-9] Duntas et al.[9] concluded, that SCH has been associated with increased CV mortality, especially in patients aged <65 years. Moderate SCH should be treated as it has a negative impact on various CV risk factors, while mild SCH should be closely followed up to look for the progression of diseases. In the view of scarcity of data regarding SCH, dyslipidemia, and inflammation, here we aimed to evaluate the association of SCH with dyslipidemia and inflammatory markers (ESR and CRP).

## Materials and Methods

This was a hospital based cross sectional observational study conducted at S.M.S. Medical College and attached hospitals in Jaipur, India, during the period of December 2017 to January 2020. After obtaining informed consent from the patients and clearance from the ethics committee of the medical college, 50 cases aged ≥18 years with SCH (TSH level between 5 to 10 μIU/ml with normal fT3 and fT4 levels) and 50 euthyroid cases as controls were included.

Patients who had a history of overt hypothyroidism or were taking medication for thyroid disorder or had a history of irradiation of the neck or were on antiepileptic drugs or had end stage renal disease, post myocardial infarction, congestive heart failure, diabetes mellitus, or any chronic illness were excluded from the study. Laboratory investigations, including a complete hemogram, liver function tests, kidney function tests, random blood sugar, CRP, and ESR, were done by standard methods. The lipid profile and thyroid hormone profile (fT3, fT4, TSH) were done on a fasting venous sample taken in the morning after an overnight fast. ESR was estimated by westergren's method (reference value, male: 0-20 mm/1st hour; female: 0-30 mm/1st hour) and CRP by the immunoturbidimetric method. (Reference value: <3.0 mg/L). The thyroid hormone profile was estimated by a fully automated immunoflorescence immunoassay analyzer. (reference value: fT3: 1.8–4.2 pg/ml, fT4: 0.78–2.19 ng/dL, TSH: 0.4–4.05 μIU/ml).

Total cholesterol and triglyceride were assessed by the enzymatic method (GPO-PAP) (reference value: < 200 mg/dL; male 50-165, female 40-140 mg/dL, respectively). HDL cholesterol was calculated by Burstein et al., 1970 method [10] (reference value: male 30-50, female 45-60 mg/dL). LDL cholesterol was calculated by Freidwald and Fredrickson's (1972) formula. [11] LDL = Total Cholesterol – [HDL+VLDL]. (reference value: < 130 mg/dl). VLDL cholesterol was calculated by TG/5 based on the average ratio of cholesterol in VLDL. (reference value: < 30 mg/dl) [NCEP-ATP III guideline].[12]

**Statistical analysis:** Data collected were entered in a Microsoft excel 2010 worksheet. Qualitative data was expressed in the form of percentages and proportions. The significance of the difference in proportions was assessed by the chi-square test. Quantitative data was expressed in the form of means and standard deviations. The significance of the difference in means was assessed by an unpaired t-test. Pearson's correlation coefficient (r) was calculated to determine the correlation between lipid parameters (triglycerides, total cholesterol, HDL, LDL, and VLDL) and inflammation markers (ESR, and CRP) with serum TSH level. A p-value of <0.05 was considered statistically significant.

## Results

Our study included 50 SCH cases (mean age 38.32±11.91 years) and 50 euthyroid cases (42.88±12.62 years). Among cases and controls, more than 50% of patients belonged to the age group of 20-40 years [30(60%) and 26(52%), respectively]. The male-to-female ratio in cases was 1:2, while it was 1:3 in controls. The mean serum TSH of cases and controls was 8.95±1.03 mIU/ml, and 2.29±1.08 mIU/ml, respectively (p-value <0.001). The mean serum fT3 level of cases and controls was 2.91±0.59 pg/ml, and 2.95±0.582 pg/ml, respectively (p-value 0.778). The mean serum fT4 of cases and the control group was 1.09±0.22 ng/dl, and 1.14± 0.29 ng/dl, respectively (p-value 0.334). The cases (SCH) groups had significantly higher values of TG and LDL as compared to the control group (141.72±28.24 mg/dl vs. 113.44±26.36 mg/dl, p-value <0.001; and (117.28±28.85 mg/dl vs. 104.86±28.78 mg/dl, p-value 0.034, respectively). Table 1 depicts that the level of serum total CHOL, serum HDL, and serum VLDL did not differ significantly between both groups.

The case group had a significantly higher value of CRP as compared to the control group (4.64 ±3.98 mg/l, 2.34 ± 1.53 mg/l, respectively, p-value <0.001). The mean serum ESR was high in the case group (10.72±8.49mm/1st hr) as compared to the control group (9.90±6.23 mm/1st hr) but this difference was statistically not significant (p-value 0.583). Serum TG level showed a positive correlation with serum TSH that was statistically significant (r = + 0.485, p value <0.001).

LDL levels also had a statistically significant positive correlation with serum TSH. (r = 0.216, p-value 0.03). Total cholesterol levels also showed a positive correlation with serum TSH levels, but this was statistically not significant (r = + 0.150, p-

value 0.137). HDL and VLDL level showed a negative correlation with serum TSH, but statistically not significant [(r = -0.095, p-value 0.345); (r = -0.138, p-value 0.170), respectively]. The CRP level had a positive correlation with serum TSH. (r = + 0.381, p-value <0.001). ESR level also showed a positive correlation with serum TSH but was statistically not significant (r = + 0045, p-value 0.656) [Table 2], [figure 1].

**Table 1: Baseline characteristics of study patients**

| Parameter (Mean ± SD) | SCH Group n (%)) | Control Group n (% | P-Value* |
|---|---|---|---|
| Age | 38.32 ± 11.91 | 42.66 ± 12.62 | 0.080 |
| Sex Male/female (n/n) | 16/34 | 12/38 | 1.000 |
| fT3 | 2.91±0.59 | 2.95±0.582 | 0.778 |
| fT4 | 1.09±0.22 | 1.14± 0.29 | 0.334 |
| TSH | 8.95±1.03 | 2.29±1.08 | < 0.001 |
| Triglycerides | 141.72±28.24 | 113.44±26.36 | < 0.001 |
| Total Cholesterol | 182.70±28.55 | 173.94± 31.06 | 0.145 |
| HDL | 42.18±7.65 | 44.22±8.74 | 0.217 |
| LDL | 117.28±28.85 | 104.86±28.78 | 0.034 |
| VLDL | 23.46±8.56 | 25.18±7.78 | 0.989 |
| ESR | 10.72±8.49 | 9.90±6.23 | 0.583 |
| CRP | 4.64 ±3.98 | 2.34 ± 1.53 | < 0.001 |

Abbreviations: fT3: free T3, fT4: free T4, TSH: thyroid stimulating hormone, LDL: low density lipoprotein, HDL: high density Lipoprotein. VLDL: very low density lipoprotein, ESR: erythrocyte sedimentation rate, CRP: C - reactive protein.

**Table 2: Correlation of TSH with lipid profile and inflammatory markers in SCH**

| Parameters | Pearson's Correlation coefficient (r) | P-Value |
|---|---|---|
| Triglycerides | 0.485 | < 0.001 |
| Total Cholesterol | 0.150 | 0.137 |
| HDL | -0.095 | 0.345 |
| LDL | 0.216 | 0.030 |
| VLDL | -0.138 | 0.170 |
| ESR | 0.045 | 0.656 |
| CRP | 0.381 | < 0.001 |

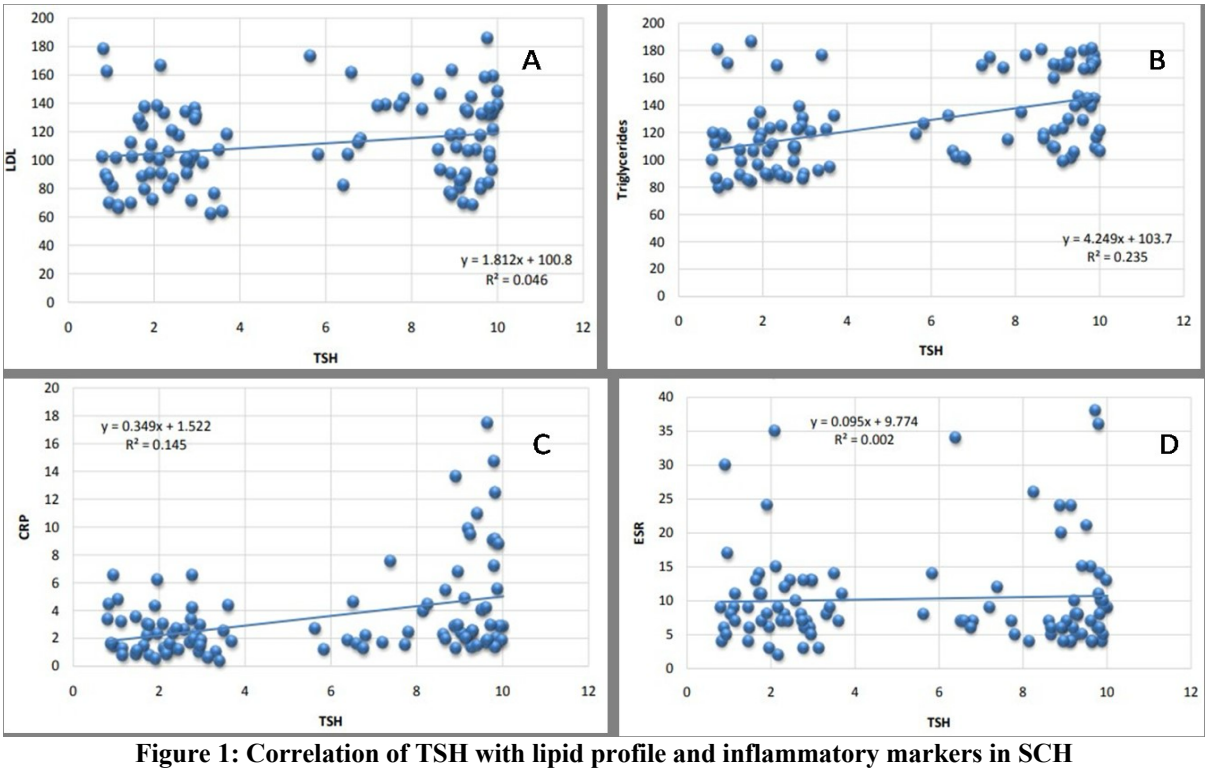


**Figure 1: Correlation of TSH with lipid profile and inflammatory markers in SCH**

## Discussion

The underlying pathophysiological mechanism of dyslipidemia in SCH is multi-factorial and less obvious. Dyslipidemia in hypothyroidism occurs due to disturbed or altered lipid synthesis, absorption, metabolism, and fat mobilization. [13,14]

1. Thyroid hormones stimulate the expression of HMG-CoA reductase in the liver and increase cholesterol synthesis. Thus, a thyroid hormone deficient state leads to decreased hepatic cholesterol synthesis. However, a few other collateral mechanisms supersede this effect.[15]
2. There is an increase in intestinal cholesterol absorption mediated by the Niemann-Pick C1-like 1 protein. [16)
3. Thyroid hormone increases hepatic expression of LDL receptors; in hypothyroidism decrease in cell surface LDL-cholesterol receptors, possibly via T3-mediated effects on the sterol regulatory element-binding protein-2 (SREBP-2), leading to reduced plasma LDL-cholesterol clearance and increased apo-B lipoproteins. [17]
4. Hypothyroidism also decreases lipoprotein lipase levels, which further decreases plasma triglyceride clearance, and it also decreases cholesterol excretion.
5. In hypothyroid states, plasma cholesteryl ester transfer proteins (CETPs), shifting cholesterol from HDL-C to LDL-C, and VLDL are reduced in hypothyroid states.[18]

The cumulative effect of the above-mentioned mechanism is an increase in total cholesterol and LDL levels and a slight increase in HDL and triglyceride levels.

The dyslipidemia in SCH is associated with atherosclerosis risk and subsequently increases the risk of CVD. The literature search showed that inflammatory markers including ESR and CRP, are significantly elevated in SCH patients as compared to healthy controls.[19-21] Elevated inflammatory markers indicate the underlying pro-inflammatory process of atherosclerosis and are established as a good predictor of coronary artery disease, and possess a cardiovascular risk. The coexistence of other systemic inflammatory diseases like myocardial infarction, rheumatoid arthritis, and overt hypothyroidism can contribute to the rise of CRP levels and further precipitation of CAD risk.[22,23]

Our results demonstrated that dyslipidemia occurs more commonly in SCH groups as compared to euthyroid individuals. Serum triglycerides and LDL were elevated significantly, while HDL was low but statistically insignificant. Few studies found significantly elevated levels of serum cholesterol, LDL, and triglycerides with significantly low HDLc levels in SCH cases as compared to the euthyroid group.[21,22] Furthermore, studies done by Maleki N et al.[23], Guntaka M et al.[24], and Tuzcu Aet al.[19], noticed dyslipidemia with a significantly higher level of mean LDL, while triglyceride levels were not significantly higher in the SCH group. Hueston WJ et al.[25] showed SCH patients had a significantly higher occurrence of elevated cholesterol levels (74.2% vs. 63.9%, p-value 0.002 and mean cholesterol of 226 vs. 217 mg/dL, p-value 0.003 respectively) but, the difference in LDL and HDL levels was statistically not significant.

SCH does not appear to be associated significantly with abnormalities in serum cholesterol and triglyceride levels when adjusted for confounding variables including age, gender, race, and use of hypolipidemic drugs. Few other studies did not find any significant difference in the mean plasma lipids values when comparing patients and controls. These results can be altered due to the inclusion of patients who were being treated with hypolipidemic drugs upon sampling. Differences in disease duration, smoking habits, and insulin resistance could be other contributing factors. These could induce a higher cholesterol increase in the presence of hypothyroidism. [26-30]

Dyslipidemia and low-grade inflammation are responsible for SVI, which could be responsible for cardiovascular (CV) morbidities in overt as well as subclinical forms of hypothyroidism.[31] Viewing the high prevalence of SCH in the general population and the association between dyslipidemia and TSH, screening patients with dyslipidemia for thyroid dysfunction may be justifiable before starting hypolipidemic drug therapy.

A Literature search showed many controversial views regarding the treatment of SCH, and still, it is not clear whether SCH should be treated or not. Asrana et al.[32] found that achieving euthyroid status with thyroxine has a favorable effect on the lipid profile.

## Conclusion

The presence of increased inflammatory markers along with dyslipidemia in SCH patients can increase the future risk of further development of cardiovascular disorders. SCH has a high prevalence in the general population and has a strong kinship with dyslipidemia. Notably, we found significantly elevated levels of inflammatory markers in SCH patients, which could be responsible for developing dyslipidemia. Hence, it is worth noting to do a lookover of inflammatory markers and lipid profiles in SCH patients. It might be warranted to start thyroxin replacement therapy in SCH patients to halt CV mortality.

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