Correlation of sdLDL-C with cardiometabolic risk indices in women with subclinical hypothyroidism – A cross-sectional study

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ABSTRACT

Introduction and Aim: Subclinical hypothyroidism (SCH) characterised by normal free thyroxine (FT4), “free triiodothyronine (FT3)”, and raised serum TSH, is an early stage of mild thyroid hormone deficiency. A change in the lipid profile most often observed in SCH is mainly caused by increased serum levels of Triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), whereas high-density lipoprotein cholesterol (HDL-C) levels can be normal or elevated. Studies on small dense Low-Density Lipoprotein – Cholesterol (sdLDL-C), associated with CVD risk are few. The aim of this study was to estimate serum sdLDL-C and find its correlation with thyroid profile (FT4 and TSH) and cardiometabolic risk indicators in female subjects with subclinical hypothyroidism.

Materials and Methods: The study had 112 female participants in total. After screening, subjects were divided into two groups. Control group ( euthyroid) and study group (SCH). Age, TSH, FT4, TC, TG, HDL-C, LDL-C, sdLDL-C & Lipid ratios “(TC/HDL-C, LDL-C/HDL-C)”, “Log TG/ HDL-C”) were examined and compared between the two groups.

Results: The correlation of sdLDL-C with TSH, FT4, lipid parameters & lipid ratios were studied. TG, TC, HDL-C, and LDL-C were not clinically significant. While sdLDL-C and lipid ratios had a statistical decrease, it was not clinically significant. A highly significant negative association between sdLDL-C, other lipid parameters, except HDL-C, lipid ratios are observed in the study group.

Conclusion: As anticipated, the current investigation did not demonstrate any statistically significant improvement in the sdLDL-C as a better predictor of CVD risk. No apparent lipid abnormalities were also seen in women, in the age group of 20-40 years as observed in the correlation studies. However, measurement of AIP along with FT4 would make a better assessment of CVD risk.

Keywords: Subclinical hypothyroidism; sdLDL-C; cardiometabolic risk indices; atherogenic index.

INTRODUCTION

Subclinical hypothyroidism (SCH) characterised by normal free thyroxine (FT4), free triiodothyronine (FT3), and raised serum thyroid stimulating hormone (TSH), is an early stage of mild thyroid hormone deficiency. The key role played by the thyroid hormone in the regulation of lipid synthesis and metabolism is well known (1,2). Changes in thyroid function alters the composition and transport of lipoproteins (3). Therefore, lipid metabolism is often affected in thyroid disorders and are common in patients with dyslipidaemia (4). Thyroid dysfunction is the most common endocrinological problem, and about 3% of the population have thyroid disease (5).

Various terms are used for subclinical hypothyroidism—compensated, preclinical, and mild hypothyroidism. Each of these terms suggests a discrete diagnostic, prognostic, and therapeutic approach (6). Subclinical hypothyroidism is relatively common (3% - 8%) in the general population compared to overt hypothyroidism (7, 8). It is commonly observed in women with a prevalence of 7.5 - 8.5% and 2.8 - 4.4% in men (9).

SCH presents with mild, nonspecific symptoms such as constipation and nausea (7). Heart failure and coronary artery disease are often associated with subclinical hypothyroidism. In addition, cognitive impairment, and non-specific symptoms such as fatigue and mood changes may also occur in middle age (10).

It has been associated with certain risk factors for cardiovascular disease (CVD), including high blood pressure and atherosclerosis (11,12). Endothelial dysfunction and reduced sensitivity to nitric oxide (NO) are one of the causes contributing to CVD in hypothyroidism. Patients with SCH have a greater risk of developing cardiovascular disease (13). Although the exact mechanism is unknown, thyroid hormone supplementation has been shown to improve symptoms (14).

A change in the lipid profile is most often observed in SCH. In general, SCH is generally associated with hypercholesterolemia, which is mainly caused by
increased serum levels of “low-density lipoprotein cholesterol (LDL-C),” “total cholesterol (TC),” and “triglycerides (TG),” while “high-density lipoprotein cholesterol (HDL-C)” levels can be normal or elevated (15).

sdLDL-C is associated with progression of “coronary heart disease (CHD)” and has been reported (16). “The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)” accepted this finding as a warning cardiovascular risk factor (17). Serum lipid ratios appear to be better predictors of cardiovascular risk compared to a standard lipid profile (18).

The lipid changes in overt hypothyroidism are well established. However, studies on the association between SCH and lipid parameters have shown contradictory results. The effect of mild changes in thyroid hormone levels on the extent of atherosclerosis is indicated. The present study aimed to determine sdLDL-C levels and their correlation with thyroid profile and other standard markers of lipid profile and lipid ratios.

**MATERIALS AND METHODS**

This cross-sectional study investigation was done in the Clinical Biochemistry Section of a tertiary care hospital from January 2022 to May 2022. The Institutional Ethics Committee (IEC) gave its approval to the study [protocol no- IEC KMC MLR 11/2021/340]. The study subjects included were taken from the records of apparently healthy adult females attending the hospital for a health check-up.

The study had 112 female participants in total. After screening, subjects were divided into two groups - control group (euthyroid) and study group (SCH).

**Control group**

Females in the age group of 20 - 40 years with normal thyroid profile (FT4 = 0.43 – 1.71 ng/dl and TSH 0.27-4.2 μ IU/ml).

**Study group**

Females in the age group of 20 – 40 years, with normal FT4 and elevated TSH (4.2 - 9.9 μ IU/ml). Subjects who were apparently healthy with normal TSH and FT4 and those with elevated TSH and normal FT4 in the age group of 20- 40 years were included. Subjects with overt hypothyroidism, subjects with renal hepatic or other systemic diseases, PCOD, infections, subjects on thyroxine for treatment, and subjects with a known history of dyslipidaemia were excluded.

Venous blood samples received in the clinical laboratory for the estimation of FT4 and TSH were used for the study. The serum obtained after centrifugation was used for the estimation of fT4 and TSH. TSH and FT4 were estimated in the Cobas 6000- 501 autoanalyzer using kits from Roche Diagnostics.

The remaining sample was stored at -20 C for the estimation of sdLDL-C and the other standard lipid parameters. "TG," "HDL," "LDL," and "TC". “Non-HDL-C” was obtained by calculation. The CVD indices (“TC/HDL-C”, “Log TG / HDL-C”, “LDL-C/HDL-C”) were also calculated. TC, HDL-C, and TG were estimated by the “cholesterol oxidase” and “peroxidase (CHOD/PAP)” method and “glycerol-3-phosphate oxidase/peroxidase” (GPO/PAP) by kits procured from Agappe diagnostics. Estimation of sdLDL-C was done by “enzyme-linked immunosorbent assay” using kits from Yannic Life Sciences.

“Low-density lipoprotein cholesterol (LDL-C)” was estimated by the modified Friedwalds formula (70); LDL= non-HDL × 90 % - TG × 10 % and nonHDL-C by the subtraction of HDL cholesterol from total cholesterol. The cardiometabolic indices were obtained by calculating the lipid ratios, namely TC/HDL, Log (TG/HDL) also known as the “atherogenic index of plasma (AIP)” and “LDL-C/HDL-C ratio”.

**Statistical analysis**

Data were analysed using SPSS 23 version (IBM Corporation, Armonk NY, USA). We have performed an independent sample “t-test” to know if there is any significant difference in the average values of AGE, TSH, FT4, HDL, and TC (as all these variables follow Normal distribution) between the control and study group.

The results are shown as mean SD. For the variables that did not adhere to the normality assumptions, the “Mann-Whitney U test” was done to know if any significant difference in the average values in control and study group. The results for these variables are expressed as median (IQR). Karl Pearson rank correlation test was used to find out the significant relationship of sdLDL-C with the biochemical parameters in the control and study group since the variables did not follow the normal distribution.

**RESULTS**

The present study included 112 female subjects ranging from 20-40 years. There were 56 subjects in the euthyroid (control) and SCH (study).
The values of TSH ranged from 0.40-4.21 µIU/ml and 4.33-9.62 µIU/ml; FT4 ranged from 0.74- 1.71 ng/dl and 0.44-1.66 ng/dl in the control and study groups respectively. A significant contrast between the TSH value was observed in the euthyroid and the SCH group. Although, FT4 levels were found to differ significantly between the groups, it was not clinically significant as the values were within the normal range.

The values of TG ranged from 49.11 - 369.60 mg/dl in the control group and 55.20 -365.8 mg/dl in the study group. Though a statistical increase in TG was observed, clinically it was not significant. The values of TC ranged from 56.44 -194.00 mg/dl in the control group and 42.08-284.61 mg/dl in the study group respectively. A statistically significant decrease in the TC value is observed between the euthyroid and the SCH, but are not clinically significant. The values of HDL-C ranged from 19.0 - 103.99 mg/dl in the control group and 13.28-158.21 mg/dl in the study group. A significant increase in HDL-C was observed in the SCH.

The values of LDL-C ranged from 9.26-95.28 mg/dl and 2.16-178.46 mg/dl in the control group and the study group respectively. The values of non-HDL ranged from 20.36-120.96 mg/dl and 13.28-158.21 mg/dl in the control and study group respectively. However, there is no statistically significant difference between the two groups' LDL-C and non-HDL levels. The values of sdLDL ranged from 3.98-62.91 mg/dl and 14-101.38 mg/dl in the study group. Though a statistical decrease is seen in the study group, it is not clinically significant. Fig 1 depicts the comparison of lipid profiles in both groups.

The values of TC/HDL-C ranged from 1.35-4.43 and 1.06-9.63 in the euthyroid and SCH group respectively. The values of “log TG/HDL-C” ranged from 0.01-0.98 and 0.02-2.37 in the euthyroid and SCH group respectively. The values of LDL-C/HDL-C ranged from 0.13-2.48 and 0.03-6.28 in euthyroid and SCH group respectively. Though a statistically significant decrease in the lipid ratios is observed in the study group, they are not clinically significant. Figures 2 depicts the median value of lipid ratios (CVD indices).
Table 4: CVD indices of the subjects

<table>
<thead>
<tr>
<th>Lipid parameters</th>
<th>Euthyroid</th>
<th>SCH</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC/HDL-C</td>
<td>2.3(1.8,2.9)</td>
<td>1.7(1.4, 2.4)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Log TG/HDL-C</td>
<td>0.3(0.2, 0.5)</td>
<td>0.2 (0.06, 0.4)</td>
<td>0.024*</td>
</tr>
<tr>
<td>LDL/HDL-C</td>
<td>0.9 (0.5, 1.5)</td>
<td>0.6 (0.2, 1.06)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

Fig. 2: Comparison of CVD indices

There is no significant relationship between sdLDL-C and TSH is seen in control or study group (Table-5). However, a significant “positive association” of sdLDL-C with the FT4 is observed in the study group. Fig 3 depicts the correlation of sdLDL-C with FT4.

Table 5: Correlation of sdLDL-C with thyroid profile

<table>
<thead>
<tr>
<th>Thyroid profile</th>
<th>Euthyroid</th>
<th>SCH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r value</td>
<td>P value</td>
</tr>
<tr>
<td>TSH</td>
<td>0.128</td>
<td>0.346</td>
</tr>
<tr>
<td>FT4</td>
<td>-0.076</td>
<td>0.578</td>
</tr>
</tbody>
</table>

Fig. 3: Correlation of sdLDL-C with FT4

No significant association with “TG”, “TC”, “HDL-C”, ” LDL-C”, and “non-HDL” were observed in the control group. However, a highly significant negative association between sdLDL-C and other lipid parameters, except HDL-C is observed in the study group.

Table 6: Correlation of sdLDL with lipid parameters

<table>
<thead>
<tr>
<th>Lipid parameters</th>
<th>Euthyroid</th>
<th>SCH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R value</td>
<td>P value</td>
</tr>
<tr>
<td>TG</td>
<td>0.051</td>
<td>0.708</td>
</tr>
<tr>
<td>TC</td>
<td>-0.019</td>
<td>0.891</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.109</td>
<td>0.422</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-0.207</td>
<td>0.126</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-0.124</td>
<td>0.363</td>
</tr>
</tbody>
</table>
No significant relationship between sdLDL-C and lipid ratios is observed in the euthyroid group, while a significant negative association is observed in the SCH group. Fig 7,8,9 depicts correlation of sdLDL-C with lipid ratios.

**Table 7:** Correlation of sdLDL-C with lipid ratios

<table>
<thead>
<tr>
<th>Lipid ratios</th>
<th>Euthyroid</th>
<th></th>
<th>SCH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R value</td>
<td>P value</td>
<td>R value</td>
<td>P value</td>
</tr>
<tr>
<td>TC/HDL-C</td>
<td>-0.165</td>
<td>0.224</td>
<td>-0.43</td>
<td>0.001*</td>
</tr>
<tr>
<td>LDL/HDL-C</td>
<td>-0.241</td>
<td>0.074</td>
<td>-0.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Log (TG/HDL-C)</td>
<td>-0.012</td>
<td>0.929</td>
<td>0.38</td>
<td>0.004*</td>
</tr>
</tbody>
</table>
DISCUSSION

The association between dyslipidaemia and SCH has been investigated in many epidemiological studies conducted in various parts of the world using various methodologies (11,19,20). However, studies on AIP and lipid ratio abnormalities, which are known to be a better marker of CVD risk than standard lipid profiles, are scarce. Hence, A cross-sectional investigation was conducted on the correlation of sdLDL-C with cardiometabolic risk indices in women with SCH. The study investigated abnormalities in conventional lipid profiles including sdLDL-C, lipid ratios, and correlation of “sdLDL-C” with “lipid parameters” in SCH and euthyroid women.

There is no significant difference in the age group between euthyroid (EU) and SCH. This reflects the age match in our study. TSH levels are significantly increased in the SCH contrast to the EU group. The mean FT4 value was significantly lower as compared to the EU group, although it was within the normal reference range. This is similar to a study done by Stephen et al., (21).

Regarding lipid profile parameters, statistically significantly higher TG levels were observed in SCH compared to EU, but not clinically significant. Stephen et al. have demonstrated a clinically significant increase in TG in SCH (21). Conversely, Efstathiadou et al., reported no significant change in TG levels (22).

Although the TC levels were significantly raised in the SCH group, this is not of clinical significance and there was no change in LDL-C levels. Data from NHANES III revealed elevated TC levels in SCH (22). Asranna et al., reported raised levels of both TC and LDL-C (22). Two other studies also reported increases in both LDL-C and TC (23,24). Hueston et al., reported no significant change in cholesterol levels (22).

Liu et al., reported higher LDL-C levels in subjects with SCH (20). However, the values obtained in this study are much lower.

The significant increase in HDL-C observed in the study is similar to that reported by Stephen et al., (21). However, decreased HDL-C levels in women with SCH were observed by Karthick et al., (19). Conversely, no significant change was observed in a study that was done by Indhu et al., (6). The observed increase in HDL-C may be attributed to decreased CETP-mediated transfer of cholesterol from HDL-C to LDL-C and decreased catabolism of HDL mediated by hepatic lipase.

sdLDL-C is linked with a greater risk of “CVD” than “LDL-C” (25). A significant decrease in sdLDL-C was seen in this study. However, the values are within the normal range. Increased sdLDL-C was observed in
SCH in a study that included subjects within 30–70 years (7). Increased “sdLDL-C” was significantly correlated with elevated “TG” and reduced “HDL-C” levels in the Framingham Offspring Study (26). Elevated “sdLDL-C” which was measured by a homogeneous method was strongly linked with the presence of CHD with risk factors and increased “cIMT (carotid intimal medial thickness)” (27). Gentile et al. reported an association between sdLDL-C and early atherosclerosis in menopausal women (28). There were no significant variations in “sdLDL-C” values between patients with overt hypothyroidism and healthy controls (29). Several studies have supported the concept that “sdLDL-C” is strongly correlated with “CVD” (27).

Currently, the serum lipid ratio is regarded as being better indicator of “cardiovascular risk” (18). The lipid ratios analysed were TC/HDL-C, LDL-C/HDL-C, and Log TG/HDL-C. Log TG/HDL-C (AIP) a good surrogate marker of sdLDL-C has been shown to be a better predictor of CVD. AIP adds predictive value beyond individual lipids and lipid ratios (TC/HDL-C, LDL-C/HDL-C, TG/HDL-C). The average value of AIP found in EU and SCH (0.3 and 0.2) suggests that the subjects are not at risk for CVD. They observed a significant decrease only in the TG/HDL-C ratio (21). The AIP value observed in the present study is similar to that reported by Stephen et al., but it was high in the study’s control group. This could be due to the difference in the age of the subjects. Based on AIP values, subjects are considered at risk for CVD, even though the other two ratios indicate that subjects are not at risk.

No significant correlation of sdLDL-C with TSH or FT4 and any of the lipid parameters was observed in the control group. However, a positive association of sdLDL-C with FT4 and a negative association with lipid parameters and lipid ratios were observed in SCH. A study in newly diagnosed hypothyroid patients demonstrated a correlation between SCH and sdLDL-C, whereas no such association was observed in several other studies (19). The positive association of sdLDL-C with FT4 is an important finding indicating the importance of measuring sdLDL-C along with FT4. Although there was no correlation between AIP and TSH in subjects with SCH, they were at risk for CVD. Although patients with SCH were at risk for CVD, it was not proportional with TSH values, as there was no association between AIP and TSH. This supports the statement that dyslipidemic changes are not evident when TSH levels were <10 µIU/ml (30). This study highlights the importance of measuring AIP in SCH for a better assessment of CVD risk, even if they have a normal lipid profile.

CONCLUSION

The current investigation could not detect any significant rise in the sdLDL-C, a better predictor of CVD risk, as expected. No apparent lipid abnormalities were seen in women aged 20–40 years as observed in the correlation studies. However, measurement of AIP along with FT4 would make a better assessment of CVD risk.

LIMITATIONS

The study group in 20–40 years age may not show obvious lipid abnormalities. The study in a larger sample size would have been more appropriate, since euthyroid as well as SCH indicated similar sdLDL.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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