The Impact of Subclinical Hypothyroidism on Lipid Profile in Jeddah

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Abstract

Background

Patients with subclinical hypothyroidism have a high serum concentration of thyroid-stimulating hormone, whereas their serum free thyroxine concentrations are normal. Lipid metabolism is regulated in large part by thyroid hormones. It could be connected to a changed lipid profile. The purpose of the current study was to evaluate the relationship between subclinical hypothyroidism and alterations in the lipid profile.

Methods

Data of 99 patients with subclinical hypothyroidism and 109 euthyroid cases were collected from king Abdulaziz medical city, Jeddah, Saudi Arabia from 2016–2022. Patients older than 18 years, and the groups were matched in terms of gender, age, and body mass index (BMI). SCH was defined as a TSH value of 4.5 to 10 mU/L, and normal T4 as 5 to 18 µg/dL. Control cases had a normal TSH ranging from 0.45 to 4.5 mU/L. The total serum cholesterol (TCHOL), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels in both groups were examined and the results were recorded.

Result

In comparison to the control group, SCH patients had greater median HbA1C (p = 0.001) and lower median vitamin D levels (p = 0.004) prior to therapy. Before therapy, SCH patients also showed considerably lower HDL levels and significantly higher LDL and triglyceride levels (p < 0.001).

Conclusion

there is a substantial correlation between subclinical hypothyroidism and reduced HDL and vitamin D levels. It was linked to increased triglyceride, LDL, and HbA1c levels. Only vitamin D and low-density lipoproteins were pathologically high. Treatment with levothyroxine raised total and LDL cholesterol levels. Future research ought to look into how affordable treating subclinical hypothyroidism is.

Background

Subclinical hypothyroidism (SCH) is a disease characterized by the absence of distinct clinical symptoms and signs Thyroid-stimulating hormone (TSH) levels in the serum of patients with SCH were found to be high whereas serum free thyroxine concentrations were normal. TSH levels can be used to categorize SCH into mild and severe forms. Mild SCH is defined as having a TSH level less than 10 mIU/L (normal thyroxine), whereas severe SCH is defined as having a TSH level greater than or equal to 10 mIU/L[1].In
the general population, the prevalence of subclinical hypothyroidism ranges from 4–8%, and in women over 60, it can reach 15–18%[2]. 35% of 257 Saudi women who participated in a study in outpatient clinics at a Jeddah university hospital had subclinical hypothyroidism [3] Patients with SCH are typically only treated if they display related symptoms, are infertile, are pregnant, or have a high risk of developing overt hypothyroidism. SCH has a high prevalence, but the advantages and hazards of its therapy, as well as the data supporting screening for this disorder, are still up for debate [4].

Both primary and secondary hypothyroidism were frequently associated with hyperlipidemia. After receiving therapy for hypothyroidism, the lipid readings decreased. Patients with primary hypothyroidism were more likely to have type IIa hyperlipidemia than secondary hypothyroidism patients, who were more likely to have type IIb hyperlipidemia [5]. Moreover, according to a meta-analysis, patients with subclinical hypothyroidism had significantly higher serum levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and total triglycerides than people with euthyroidism with no significant deference in serum high-density lipoprotein cholesterol (HDL-C) [6]. Another systematic analysis demonstrated the significance of treating individuals with subclinical hypothyroidism by finding that levothyroxine therapy significantly reduced serum levels of thyroid-stimulating hormone (TSH), TC, and LDL-C [7].

Recent clinical research has found a strong link between TSH and lipid metabolism as well as a number of cardiovascular illnesses. The effect of TSH on blood lipids has always been attributed in these investigations to thyroid hormone levels. Furthermore, findings from experimental trials provide substantial support to the concept that TSH directly affects lipid constituents [8]. Important physiological processes including development, growth, and metabolism are mediated by the thyroid hormone (TH). The active form of TH is intracellular triiodothyronine (T3), which binds to the thyroid hormone receptor (TR), a transcription factor that is a member of the nuclear receptor superfamily. TRα and TRβ are the two isoforms of the TR. In contrast to TRβ, which predominates in the liver, TRα is highly expressed in the heart, muscle, and adipose tissue. Significant changes in body weight, thermogenesis, and lipolysis are caused by TH; these changes are predominantly mediated by TH's effects on skeletal muscle and adipose tissue. Through its effects on the liver, TH can also control fatty acid (FA), cholesterol, and glucose balance. Thus, hepatic lipid and carbohydrate metabolism can be negatively impacted by thyroid dysfunctions, which can also lead to intrahepatic and systemic dysregulation of the metabolism of substances that are critical sources of energy for cells [9]. Thyroid hormone enhances the flow of bile acids (BA), depleting intrahepatic cholesterol while stimulating liver cholesterol synthesis and hepatic uptake of circulating cholesterol, maintaining the balance of hepatic cholesterol [10]. The study aimed to evaluate the impact of Subclinical hypothyroidism on lipid profile in adult.

Methods

This is a case control retrospective cohort study, conducted on patients followed in King Abdulaziz Medical City-Jeddah from 2016 to 2022. The study was approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (KAIMRC) (NRJ23J/228/09). The main objective was to evaluate the Impact of Subclinical hypothyroidism on lipid profile in adult patients. The secondary
objective was aimed to compare the lipid profile after they treated for more than. It consisted of 208 patients divided into 99 affected group and 109 controlled group. The inclusion criteria were patient over 18 years old and diagnosed with subclinical hypothyroidism. The exclusion criteria included patients who had previous dyslipidemia, Pregnancy, Cancer, Liver diseases, end stage kidney disease, diabetes.

**Data Analysis**

Data were collected in Excel and analyzed using R software (version 4.2.2). Normality was tested with histograms. Continuous variables were represented by mean and standard deviation, and categorical variables by frequencies and percentages.

A Wilcoxon rank sum test compared clinical characteristics and lipid profiles between subclinical hypothyroidism (SCH) and control groups. Additionally, within the SCH group, Wilcoxon signed rank tests assessed lipid profile differences before and after treatment. Statistical significance was set at $p < 0.05$.

**Definitions:**

Subclinical hypothyroidism was defined as TSH is higher than 4.5 mIU/L with normal T4 level 5–18 mcg/dl, total cholesterol > 5.18, LDL > 1.55, HDL < 1.55, and Triglyceride > 1.77 mmol/L.

**Result**

The study involved 208 participants, with a median age of 45 years, predominantly male (51%) and obese (41%). Common comorbidities included hypertension. Patients with subclinical hypothyroidism (SCH) were older and more obese than the control group (Table 1). Before treatment, SCH patients had lower median vitamin D levels ($p = 0.004$) and higher median HbA1C ($p = 0.001$) compared to the control group. Additionally, SCH patients exhibited significantly higher LDL and triglyceride levels, as well as significantly lower HDL levels before treatment ($p < 0.001$) in (Table 2).

The Wilcoxon signed rank test with continuity correction testing the difference in ranks between LDL after treatment and LDL before treatment suggests that the effect is negative, statistically significant, and very large ($W = 443.50, p = 0.001, 95\%\ CI [-0.67, -0.23]$). It also showed that the difference in ranks between HDL after treatment and HDL before treatment suggests that the effect is negative, statistically not significant, and medium ($W = 829.00, p = 0.053, 95\%\ CI [-0.50, -3.73e-03]$). The test showed that the difference in ranks between total cholesterol after treatment and total cholesterol before treatment suggests that the effect is negative, statistically significant, and very large ($W = 652.00, p < 0.001, 95\%\ CI [-0.70,-0.33]$) while the testing the difference in ranks between triglyceride before the treatment and triglyceride after the treatment suggests that the effect is positive, statistically not significant, and medium ($W = 1724.50, p = 0.114, 95\%\ CI [-0.05,0.44]$) (Table 3).

Figure 1 illustrated dyslipidemia in the SCH and control group, with high percentages of high LDL, high triglycerides, low HDL, and hypercholesterolemia compared to the control group. Figure 2 depicted
significantly lower vitamin D-25 levels and higher HbA1C levels in the SCH group before treatment compared to the control group.

Table 1
Demographic characteristics of the participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Overall, N = 208¹</th>
<th>Affected group, N = 99¹</th>
<th>Controlled group, N = 109¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>208</td>
<td>45 (35, 60)</td>
<td>50 (35, 67)</td>
<td>43 (36, 53)</td>
</tr>
<tr>
<td>gender</td>
<td>208</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>101</td>
<td>(49%)</td>
<td>49 (49%)</td>
<td>52 (48%)</td>
</tr>
<tr>
<td>Male</td>
<td>107</td>
<td>(51%)</td>
<td>50 (51%)</td>
<td>57 (52%)</td>
</tr>
<tr>
<td>Comorbidities*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>208</td>
<td>10 (4.8%)</td>
<td>4 (4.0%)</td>
<td>6 (5.5%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>208</td>
<td>8 (3.8%)</td>
<td>6 (6.1%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Others</td>
<td>208</td>
<td>14 (6.7%)</td>
<td>7 (7.1%)</td>
<td>7 (6.4%)</td>
</tr>
<tr>
<td>BMI</td>
<td>208</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>11</td>
<td>(5.3%)</td>
<td>4 (4.0%)</td>
<td>7 (6.4%)</td>
</tr>
<tr>
<td>Healthy weight</td>
<td>57</td>
<td>(27%)</td>
<td>19 (19%)</td>
<td>38 (35%)</td>
</tr>
<tr>
<td>Overweight</td>
<td>54</td>
<td>(26%)</td>
<td>26 (26%)</td>
<td>28 (26%)</td>
</tr>
<tr>
<td>Obese</td>
<td>86</td>
<td>(41%)</td>
<td>50 (51%)</td>
<td>36 (33%)</td>
</tr>
<tr>
<td>TSH before treatment</td>
<td>208</td>
<td>208 (100%)</td>
<td>7.00 (5.61, 8.26)</td>
<td>1.36 (1.02, 2.13)</td>
</tr>
<tr>
<td>FreeT4 before treatment</td>
<td>208</td>
<td>208 (100%)</td>
<td>12.23 (11.10, 13.95)</td>
<td>12.85 (11.98, 14.00)</td>
</tr>
</tbody>
</table>

¹Median (IQR); n (%)  
*multiple answer question
### Table 2
Clinical characteristics of the participants among case and control groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Overall, N = 208(^1)</th>
<th>Affected group, N = 99(^1)</th>
<th>Controlled group, N = 109(^1)</th>
<th>p-value(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D-25 before treatment</td>
<td>117</td>
<td>56 (36, 77)</td>
<td>44 (30, 70)</td>
<td>60 (40, 86)</td>
<td>0.004</td>
</tr>
<tr>
<td>Fasting glucose before treatment</td>
<td>145</td>
<td>5.10 (4.80, 5.60)</td>
<td>5.10 (4.80, 5.80)</td>
<td>5.05 (4.80, 5.40)</td>
<td>0.10</td>
</tr>
<tr>
<td>HbA1C</td>
<td>183</td>
<td>5.20 (5.00, 5.50)</td>
<td>5.40 (5.10, 5.90)</td>
<td>5.20 (5.00, 5.30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>178</td>
<td>128 (117, 138)</td>
<td>130 (115, 142)</td>
<td>124 (118, 137)</td>
<td>0.3</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>178</td>
<td>74 (67, 80)</td>
<td>73 (69, 80)</td>
<td>75 (67, 80)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

\(^1\)Median (IQR)

\(^2\)Wilcoxon rank sum test

### Table 3
Association between subclinical hypothyroidism and lipid profile of the participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Overall, N = 208(^1)</th>
<th>Affected group, N = 99(^1)</th>
<th>Controlled group, N = 109(^1)</th>
<th>p-value(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL before the treatment</td>
<td>138</td>
<td>3.42 (2.61, 4.30)</td>
<td>4.00 (3.07, 4.86)</td>
<td>2.89 (2.45, 3.63)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HDL before the treatment</td>
<td>192</td>
<td>1.17 (0.99, 1.42)</td>
<td>1.12 (0.90, 1.37)</td>
<td>1.23 (1.05, 1.48)</td>
<td>0.012</td>
</tr>
<tr>
<td>Total cholesterol before the treatment</td>
<td>202</td>
<td>4.87 (4.19, 5.55)</td>
<td>4.96 (4.20, 5.87)</td>
<td>4.72 (4.18, 5.35)</td>
<td>0.13</td>
</tr>
<tr>
<td>Triglyceride before the treatment</td>
<td>202</td>
<td>1.06 (0.75, 1.58)</td>
<td>1.32 (0.85, 1.89)</td>
<td>0.94 (0.66, 1.27)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

\(^1\)Median (IQR)

\(^2\)Wilcoxon rank sum test
Table 4
difference in lipid profile among patients with subclinical hypothyroidism before and after treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>estimate</th>
<th>Number before treatment</th>
<th>Number after treatment</th>
<th>statistic</th>
<th>p-value</th>
<th>Low 95% CI</th>
<th>High 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>-0.400</td>
<td>68</td>
<td>74</td>
<td>444</td>
<td>0.001</td>
<td>-0.649</td>
<td>-0.159</td>
</tr>
<tr>
<td>HDL</td>
<td>0.049</td>
<td>71</td>
<td>87</td>
<td>1,449</td>
<td>0.053</td>
<td>-0.00001</td>
<td>0.095</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.484</td>
<td>77</td>
<td>93</td>
<td>2,198</td>
<td>&lt; 0.001</td>
<td>0.250</td>
<td>0.775</td>
</tr>
<tr>
<td>triglyceride</td>
<td>0.119</td>
<td>77</td>
<td>93</td>
<td>1,725</td>
<td>0.114</td>
<td>-0.029</td>
<td>0.269</td>
</tr>
</tbody>
</table>

Discussion

Subclinical hypothyroidism is an asymptomatic condition that affects 10% of the population [11]. In spite of being asymptomatic, it causes metabolic derangement [12, 13] and increases all-cause mortality [14]. In this study, we found a significant association between subclinical hypothyroidism and the levels of vitamin D, HbA1c, LDL, and triglyceride. Levothyroxine treatment significantly improved lipid profile with a main effect on LDL and cholesterol.

In this study, subclinical hypothyroidism was significantly associated with a decrease in vitamin D levels. The relative homology between vit D receptor and thyroid hormone receptor was noted in 1980 [15]. Later research showed an association between vitamin D deficiency and autoimmune thyroiditis [16]. Another study found that vitamin D supplementation delays the progression of autoimmune hypothyroidism further emphasising its role in the pathogenesis [17]. The findings are not confined to autoimmune hypothyroidism as the association was shown between subclinical hypothyroidism and vitamin D in children aged 6–24 months [18]. The mechanism causing this association is yet to be investigated.

Both fasting blood glucose and HbA1c were slightly higher among patients with subclinical hypothyroidism without reaching the diabetic or prediabetic range. The difference in HbA1c level between healthy subjects and patients with subclinical hypothyroidism was statistically significant.

Hypothyroidism is more common among patients with type I and type II diabetes mellitus indicating a significant association [19, 13]. It has been reported that thyroid dysfunction complicates 12.5–51.6% of diabetes cases with subclinical hypothyroidism being the most frequently reported dysfunction [20]. It is hypothesised that hypothyroidism causes insulin resistance and plays a role in development of diabetes mellitus [21]. A recent study found a significant positive association between TSH and Homeostatic Model Assessment of insulin resistance [22]. On the other hand, a recent systematic review found no association between subclinical hypothyroidism and incident diabetes [23]. It should be noted that in spite of not reaching a diabetic level, HbA1c was significantly higher among patients with subclinical hypothyroidism in our sample. Whether this increase will later result in manifest diabetes mellitus is to be investigated.
There was no significant association between subclinical hypothyroidism and hypertension in our population. A recent meta-analysis showed that the association between subclinical hypothyroidism and hypertension is age dependent with significant association noted in the middle-age group but not in older females [24].

In this study, subclinical hypothyroidism was significantly associated with impaired lipid metabolism. Both LDL and triglyceride were significantly higher among patients with subclinical hypothyroidism. While HDL was significantly lower in the same group. However, only LDL reached a pathological level. The association between hypothyroidism and dyslipidemia is widely studied in literature [25–27]. A newly published meta-analysis showed a significant association between hypothyroidism and altered lipid profile in the adult population [28]. The decrease in the activity of lipoprotein lipase in adipose tissue and hepatic lipase is hypothesised to be the cause of elevated triglycerides level in subclinical hypothyroidism [29]. The high level of LDL may be attributed to decreased transcription of LDL receptor gene [30]. Interestingly, it was suggested that dyslipidemia itself increases the risk of hypothyroidism [31]. On the other hand, the association between hypothyroidism and dyslipidemia is not universal and lack of association is reported in the literature [32, 33]. Dyslipidemia plays a role in increased cardiovascular disease in patients with subclinical hypothyroidism [34]. The benefit of treating subclinical hypothyroidism is debated in literature and current guidelines suggest individualised decisions [14, 35, 36]. In our study, we used levothyroxine to treat patients with subclinical hypothyroidism. The aim of the treatment was to investigate its effect on lipid profile and indeed it improved LDL and cholesterol level emphasizing the role of thyroid hormone in lipid metabolism [37].

We should acknowledge that the available data limited our investigations. We couldn't account for the severity of subclinical hypothyroidism and thyroid antibodies and we recommend future studies to consider them.

**Conclusion**

Our study showed that subclinical hypothyroidism was significantly associated with lower levels of vitamin D and HDL. It was associated with higher levels of HbA1c, LDL and triglyceride levels. Only LDL and vitamin D fell within the pathological level. Levothyroxine treatment improved LDL and total cholesterol levels. Future studies should investigate the cost effectiveness of treating subclinical hypothyroidism.

**Limitation**

Since our study was retrospective, it had all the drawbacks and restrictions associated with such research. Since all patients were included in this single-center study, it is not possible to extrapolate the findings to a wider population. Our sample was reduced by certain files that were difficult to add or had incomplete data. Further studies are also required to determine how subclinical hypothyroidism affects the glucose profile.
Abbreviations

SCH
Subclinical Hypothyroidism
HDL
High Density Lipoprotein
LDL
Low Density Lipoprotein
TG
Triglyceride
TSH
Thyroid Stimulating Hormone
T3
intracellular triiodothyronine
TSH
Thyroid Stimulating Hormone
TC
Total Cholesterol
KAMC
King Abdulaziz Medical City

Declarations

Ethics approval and consent to participate

This study acquired the scientific approval from King Abdullah International Medical Research Center (KAIMRC), and ethical approval was obtained from the Institutional Review Board (IRB) (approval number: NRJ23J/228/09)

Availability of data and materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not require any funding.

Authors' contributions
MA conceived, planned and conceptualized the study. AA executed analysis. AG, BA, LA, AA, OB, AA wrote the manuscript and participated in the data collection. All authors critically reviewed and edited the manuscript and approved the final version as submitted.

**Ethics approval and consent to participate:**

We certify that every procedure was followed in compliance with all applicable rules and regulations. As this was a retrospective chart review research, participant permission was not required. The King Abdullah International Medical Research Center's (KAIMRC) Institutional Review Board (IRB) gave the study approval. Since no patient data will be identified in this retrospective analysis, the Institutional Review Board of King Abdullah International Medical Research Center waived the requirement of informed consent for participation. This decision was made in accordance with local regulations in our hospital, King Abdulaziz Medical City, and was deemed unnecessary.

**References**


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Figures
Figure 1

Distribution of dyslipidemia among subclinical hypothyroidism group and control group
Figure 2

Median of vitamin D-25 and HbA1C among subclinical hypothyroidism group and control group