Prevalence of hypercholesterolemia in hypothyroidism compared with euthyroid controls: effects of levothyroxin replacement therapy

Abstract

Background: Hypothyroidism (HT), a relatively common condition among general population is associated with lipid profile abnormalities. The present study was designed to determine the contributive role of HT in the development of hypercholesterolemia (HCh).

Methods: One hundred thirty six consecutive patients with HT and 272 euthyroid controls entered the study. Serum total cholesterol (CH) level was determined before and after treatment of HT and compared with controls. Frequency of subjects with HCh defined as plasma total CH level ≥240 mg/dl, were determined and compared between hypothyroid patients and sex - age-matched controls. The contributive role of HT in the development of HCh was determined by the comparison of pre-treatment and post-treatment CH levels. HT-induced HCh was regarded as restoration of HCh (reduction of CH level to less than 240 (mg/dl) after achievement of euthyroid state with thyroid hormone.

Results: The mean ages of patients and controls were 43±13 and 44±13 years, respectively. In HT patients the frequency of HCh and mean level of CH were significantly higher compared with sex and age-matched euthyroid controls. Replacement therapy of 44 HT patients resulted to a significant reduction of CH level from baseline by 22% (p<0.0001) in the whole number of patients, and reduction of 32.2% (p<0.0001) along with the restoration of HCh in 22(50%) patients. Whereas, in 22 patients after achievement of euthyroid state, despite a significant reduction of CH from baseline (12%, p<0.05), HCh persisted and CH levels remained ≥240mg/dl.

Conclusion: The results show contributive role for HT in the development of HCh. Two different populations of HCh with different responses to replacement therapy is recognizable in HT.

Key words: Hypothyroidism, Hypercholesterolemia, Treatment, Prevalence.


Hypothyroidism (HT) is known to influence lipoprotein metabolism and result to hyperlipidemia (1-3). HT has been shown to affect lipids profile and management. A high prevalence rate of overt or subclinical HT has been demonstrated in patients attending to lipid clinics (4-6). Patients with hypothyroidism are at increased risk of developing coronary heart disease. This may in part be related to lipid abnormalities such as hypercholesterolemia (HCH) and hypertriglyceridemia (1,4,7-10). HT and HCH are common among general population. Both conditions are associated with increased risk of cardiovascular diseases (11,12). The effect of thyroid hormone replacement therapy on lipoprotein concentrations were shown in a number of previously published studies. In these studies, the efficacy of hormone was more evident in patients with the initially elevated cholesterol levels, or in patients with obvious HT rather than the patients with the normal lipid levels or subclinical HT (1,6,13,14). Until now, the relationship between HT and HCh as well as the contributive role of HT in the development of HCh has not been clarified. In addition, it has not been cleared what proportion HCh can be attributed to HT itself. Since the coexistence of HT and HCh may not be uncommon among general population, augmentation of CH levels is expected to be observed in patients with HCh in which HT takes place.
Therefore, the treatment of hypothyroid patients is anticipated to restore only hypothyroid induced HCH or previously superimposed portion of total cholesterol (CH) levels. The purpose of this study was to determine the frequency of HCH in patients with HT compared to sex and age-matched euthyroid controls, and to investigate the efficacy of thyroid hormone on the levels of CH.

**Methods**

Patients with HT attending to an outpatient medical clinic were entered in the study. Diagnosis of HT was confirmed by the determination of plasma TSH and T4 level assessed by radioimmunoassay. Fasting plasma CH was measured by standard methods at entry. HCH was confirmed by fasting total plasma CH level of ≥240 mg/dl. The primary objective of this study was to determine the frequency of HCH as well as the levels of plasma CH in patients compared to sex and age-matched euthyroid controls. The secondary objective was to assess the effect of levothyroxin replacement therapy on CH by comparison of CH levels before and after achievement of euthyroid state with levothyroxine replacement therapy.

The effect of thyroid hormone on cholesterol level was assessed in 44 hypothyroid patients who had HCH. These patients were treated with levothyroxin in a stepwise fashion until reaching to euthyroid state defined as clinical improvement along with normal serum T4 and TSH achievement (less than 5 Mic Iu/ml). The CH level was measured at least two months after the achievement of euthyroid state without any changes in diet. Serum T4 and TSH levels were determined before and after the treatment for confirmation of diagnosis as well as to confirm achievement of euthyroid state with treatment.

The control groups were selected among subjects who attended to the same clinic and did not have HT or other systemic diseases by history and clinical examination. The controls were matched with respect to age, sex, and BMI. Patients with secondary HT, pregnancy, diabetes, chronic diseases and those taking thyroid hormones, anti-lipid agents and diet were excluded from the study.

Statistical analysis was performed using SPSS and Chi square, paired t-test and Student's t-test were used when appropriate.

**Results**

One Hundred thirty six consecutive hypothyroid patients (78% females) with mean±SD age of 43±13 years and 272 controls (79% females) with mean age of 44±13 years were analysed. Characteristics of patients and controls are shown in table 1.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients</th>
<th>Controls</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>136</td>
<td>272</td>
<td></td>
</tr>
<tr>
<td>Females (%)</td>
<td>108(78)</td>
<td>212(79)</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>43(13)</td>
<td>44(13)</td>
<td></td>
</tr>
<tr>
<td>Age distribution</td>
<td>&lt;30yrs</td>
<td>23(17)</td>
<td>29(11)</td>
</tr>
<tr>
<td></td>
<td>30-39</td>
<td>37(27)</td>
<td>69(25)</td>
</tr>
<tr>
<td></td>
<td>40-49</td>
<td>37(27)</td>
<td>99(36.4)</td>
</tr>
<tr>
<td></td>
<td>50-59</td>
<td>20(15)</td>
<td>38(14)</td>
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<tr>
<td></td>
<td>60+</td>
<td>19(14)</td>
<td>37(14)</td>
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</tbody>
</table>

Frequency of HCH in cases and controls are shown on table 2.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients</th>
<th>Controls</th>
<th>pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>108</td>
<td>212</td>
<td>0.0001</td>
</tr>
<tr>
<td>No of patients with HCH</td>
<td>68(63)</td>
<td>69(32.5)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of patients</td>
<td>28</td>
<td>60</td>
<td>0.0001</td>
</tr>
<tr>
<td>No of patients with HCH</td>
<td>21(75)</td>
<td>7.0(11.6)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of patients</td>
<td>136</td>
<td>272</td>
<td>0.0001</td>
</tr>
<tr>
<td>No of patients with HCH</td>
<td>89(65.4)</td>
<td>76(28)</td>
<td></td>
</tr>
</tbody>
</table>

HCH in patients was significantly higher than the controls (65.4% vs 28%, p<0.001). The mean CH level in patients with HCH was significantly higher than the euthyroid controls with HCH (289±38 vs 270±24 mg/dl, 

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**Table 1: Characteristics of study patients with Hypothyroidism and age-sex matched euthyroid controls.**

**Table 2: Frequency of Hypercholesterolemia (HCH)* in male and female hypothyroid patients and age-matched controls.**
p<0.05). Plasma CH≥300 mg/dl was observed in 50% of patients and 19.7% of controls (p<0.0001). After thyroid hormone substitution therapy in the whole number of treated patients, the mean serum T4 levels increased from 2.2±1.2 to 9.15±2.9 µg/dl and serum TSH levels decreased from 67±29 to 2.07±0.9 µIU/ml. Mean plasma CH levels in the whole treated patients decreased significantly from 293±44 at baseline to 229±47 mg/dl after achievement to euthyroid state (p<0.0001). The Replacement therapy of 44 HT patients with HCH resulted to significant reduction of CH level from baseline by 22% (65±58 mg/dl, p<0.0001) and reduction of 32.2% (91±51 mg/dl, p<0.0001) along with restoration of HCH and decline of CH level to less than 240 mg/dl in 22 (50%) patients (complete responder group). In this group the mean CH level decreased to 191±30 mg/dl after treatment.

Whereas, in the remaining 22 patients despite a significant reduction of CH from the baseline (12%) (37±53 mg/dl, p<0.05), HCH persisted and the mean CH level remained close to the mean CH of euthyroid controls with HCH (268±23 vs 270±24 mg/dl, P=NS) (partial responder group). The TSH and T4 levels in both groups reached to normal levels without significant differences (T4 at 10.3±2.6 vs 9.3±3.1 and TSH at 1.9±vs 2.3±1.05 respectively). As shown in table 3, the two groups of responders and partial responders, are not similar regarding mean age and baseline CH values but represent two various populations of hypothyroid patients who demonstrated different responses to treatment.

Discussion

The findings of the present study demonstrated an increased prevalence rate of HCH and greater plasma levels of CH in HT compared with euthyroid controls that improved after achievement euthyroid state with thyroid hormone replacement therapy. In this study after treatment, the prevalence of HCH decreased from 65.4% at the baseline to 50% and the mean of CH level decreased by 22% compared with the baseline values. However, plasma CH levels in half of the treated population remained elevated. In an analysis of published studies, the effect of thyroid substitution therapy in patients with overt HT, was highly dependent on pre-treatment level of total Ch Thyroid hormone therapy in patients with HCH that resulted to reduction of CH level, but plasma levels remained elevated in most patients (13). In the present study with regard to endpoint CH values and response to levothyroxine therapy, two different populations of HCH was recognizable among hypothyroid patients of this study which are different from mean age as well as response to treatment. The responder group which is supposed to be HT induced HCH was younger and demonstrated a reversible HCH which was restored with treatment, whereas, the second population of HCH was presumed to be an augmentation of previously elevated CH due to occurrence of HT. In this group, thyroid hormone was possibly effective only to a portion of CH concentration which had been superimposed to previously elevated plasma CH. Persistence of HCH after euthyroid achievement indicated that HCH was unrelated to HT but likely a coexistence of HT with other types of HCH. This issue has not been described before and requires further studies.

The effect of thyroid substitution therapy on lipid levels in hypothyroid patients has been demonstrated in several previously published studies (6, 13-17). With regard to earlier studies, the effect of thyroid hormone was more evident in overt HT, or in subclinical HT with high pretreatment lipoprotein levels (1,14,15). In hypothyroid patients in particular subclinical HT who had normal lipids levels no significant changes in serum lipid profiles were observed (1,5). However, in previous studies the magnitude of response to thyroid hormone treatment and distinction of patients with regard to treatment response has not been reported. Furthermore, the percentage of patients with HCH who had been restored with treatment were not defined in earlier studies.

In this study, the contributive role of HT in the development of HCH was shown by comparison of pretreatment and post-treatment CH levels with euthyroid controls. The result of this study is limited with lack of lipid profile assessment in patients and controls to demonstrate HT, associated changes in lipoproteins. However, assessment of CH level is very informative and elevated CH is common in HT and comprises the most common lipoprotein abnormalities as expected to be observed in hypothyroidism and even it may be an indicator of HT. The excess risk of coronary heart disease observed with HT has been thought to be due to, at least in part to the characteristics lipid abnormalities including high LDL. However, in a study of 295 hypothyroid patients, the HCH was the most common lipids abnormalities which was
References
1. Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M. Change in lipoprotein (a) levels in overt and subclinical hypothyroidism before and during treatment. Thyroid. 2000; 10: 803-8.