Multi-center study on the prevalence of hypothyroidism in patients with hypercholesterolemia

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Abstract. Hypercholesterolemia is one of the most representative disorders of the common diseases. To evaluate the prevalence of hypothyroidism in the population of adult hypercholesterolemia, we prospectively examined the thyroid function in patients with untreated or treated hypercholesterolemia as a multi-center survey. Subjects were the patients who were treated with some antilipemic agents or the untreated patients whose total cholesterol (TC) was over 220 mg/dL and/or LDL-cholesterol (LDL-C) over 140 mg/dL. Among 737 cases recruited, 725 cases (300 males and 425 females) participated in the survey including the thyroid function test. The patient’s backgrounds include hypertension (51%), diabetes mellitus (49%), fatty liver (17%), smoking (15%), and habitual drinking (10%). The 72% of the patients were treated with some antilipemic agents and the mean values of TC, LDL-C, triglyceride (TG), HDL-cholesterol (HDL-C), and LDL-C/HDL-C ratio were 204.5 mg/dL, 119.6 mg/dL, 144.4 mg/dL, 60.7 mg/dL and 2.25, respectively. The primary hypothyroidism was seen in 27 cases (3.7%) (11 males, 16 females) with subclinical hypothyroidism in 17 cases (2.4%) and overt hypothyroidism in 10 cases (1.4%). The central hypothyroidism was seen in 4 cases (0.6%). The prevalence of hypothyroidism was 4.3% in patients with hypercholesterolemia. Taking account of the large number of patients with dyslipidemia and importance of avoiding unnecessary administration and associated adverse effects, evaluation of the thyroid function could be warranted in patients with dyslipidemia although cost-benefit issues waits further investigation.

Key words: Hypercholesterolemia, Dyslipidemia, Subclinical hypothyroidism
priced levothyroxine promptly improves cholesterol metabolism and, consequently, prevents these events [3, 4]. Although the prevalence of hypothyroidism in the population with dyslipidemia has been investigated in several previous studies, most of them are the cross-sectional and/or retrospective studies and the details remain unclear [5-10].

Subclinical hypothyroidism is defined as serum free thyroxine (FT4) and free triiodothyronine (FT3) levels within their respective reference ranges in the presence of mildly elevated serum thyroid stimulating hormone (TSH) concentrations. Increasing evidences indicate that subclinical hypothyroidism is also related to dyslipidemia and T4 treatment of this condition may improve the lipid profile of the patients [11, 12]. Consequently, subclinical hypothyroidism is associated with an increased risk of coronary heart disease [13, 14] and with increased coronary heart disease events and cardiovascular deaths [15].

In order to avoid unnecessary administration of antilipemic agents and associated adverse effects, appropriate diagnosis of hypothyroidism is essential in patients with hypercholesterolemia. Although some surveys performed in limited areas, the reported prevalence of hypothyroidism in patients with hypercholesterolemia seems to differ among countries. In the present study, to evaluate the prevalence of hypothyroidism in the population of hypercholesterolemia, we prospectively examined the thyroid function in the patients with untreated or treated hypercholesterolemia as a multi-center survey in Japan.

Patients and Methods

Patients

The subjects were adult patients (over 19 yr) who were treated with some antilipemic agents or the untreated patients where his/her TC was over 220 mg/dL and/or LDL-C was over 140 mg/dL. Although some patients especially with diabetes mellitus initiated antilipemic agents as of his/her LDL-C was over 120 mg/dL as recommended by Japan atherosclerosis society (http://jas.umin.ac.jp), such cases were also evaluated as hypercholesterolemia. From 2006 to 2008, 737 patients from 23 outpatient clinics of 20 participating institutions throughout Japan were enrolled in the study and followed prospectively. The patients already having thyroid disease including apparent goiter were excluded. The patients, who had thyroid function tests when their hyperlipidemia was discovered and they were normal at that time, were also excluded. The patients who had complications or conditions that affect lipid metabolism such as malignant tumor, chronic hepatic disease, uncontrolled diabetes mellitus, nephrotic syndrome, or pregnancy were excluded. After the written informed consent was obtained from each patient, the patient was counseled to abstain iodine-rich food such as kelp. At the next visit, patients were assessed their thyroid function. When the TSH value was between 4.20 and 15.00 mU/L, the thyroid function was reevaluated 2 weeks later to exclude transient hypothyroidism. A diagnosis of hypothyroidism was based on the Japan Thyroid Association’s guidelines for the diagnosis of primary and central hypothyroidism (http://www.thyroid.umin.ac.jp/). Briefly, decrease in serum FT4 and increase in serum TSH for primary hypothyroidism and normal or low level of serum TSH in the presence of decreased serum FT4 for central hypothyroidism. After the diagnosis of hypothyroidism, the anti-thyroid peroxidase (TPO) antibodies and anti-thyroglobulin (Tg) antibodies were measured to diagnose Hashimoto thyroiditis, based on the Japan Thyroid Association’s guidelines for the diagnosis of Hashimoto thyroiditis (http://www.thyroid.umin.ac.jp/). The scheme of the study design is shown in Fig. 1.

The study was conducted in accordance with the...
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Statistical analysis

The Dunnet test was performed to investigate the difference between overt or subclinical hypothyroidism and euthyroidism. Similarly, the Tukey-Kramer HSD test was applied to compare among the 3 groups. All analyses were performed using a statistical software, JMP version 7 (SAS Institute, Cary, NC, USA).

Results

Total 737 cases were enrolled to the study and 725 cases (male 300, female 425) were subjected to assessment of thyroid function. Reasons of twelve dropout patients included revocation of the consent (n=4), inability of the trace (n=6), and complications (n=2). The patient’s backgrounds include hypertension (51%), diabetes mellitus (49%), fatty liver (17%), smoking (15%), and habitual drinking (10%). The excessive iodine intake, such as overeating of seaweeds, was found in 5% of the patients by the interview. The family histories of thyroid disease, dyslipidemia and coronary heart disease were found 3%, 15% and 16%, respectively.

The baseline profile is summarized in Table 1. The recruitment was done in each lipid clinic without gender selection. Twelve subjects were excluded due to exclusion criteria.

Laboratory evaluation

The levels of TC, TG, LDL-C and HDL-C were measured by enzyme assays. Various biochemical parameters such as aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, urea nitrogen, creatinine, sodium, potassium and chloride were assessed by standard laboratory methods. Serum concentrations of TSH (normal, 0.27-4.20 mU/L), FT4 (normal, 1.0-1.8 ng/dL) and FT3 (normal, 2.3-4.0 pg/mL) were determined by electro-chemiluminescence immunoassay (ECLIA, Roche Diagnostics, Tokyo, Japan). The anti-TPO antibodies and anti-Tg antibodies were measured with commercial radiimmunoassays (RIA) (TPOAb and TgAb, Cosmic Corp., Cardiff, UK), when the patient was hypothyroidism.

<table>
<thead>
<tr>
<th>Table 1 The characteristics, lipid profiles and thyroid functions in patients with dyslipidemia</th>
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<td><strong>Total (n=725)</strong></td>
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Values are expressed as the mean ± SD. Ranges are shown in parenthesis.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Ethical Guideline of the Japanese Ministry, Health, and Labor for the clinical study. The study was approved by the ethical committee of the National Hospital Organization Kyoto Medical Center as well as of individual institution (UMIN Clinical Study ID 000000657). After each physician obtained written informed consent from each patient, enrollment and data collection were done into the analysis center, which is completely independent of all the participating institutions.
individual TSH values in primary hypothyroid patients were shown in Fig. 3. Differences of the characteristics, lipid profiles among overt hypothyroid, subclinical hypothyroid and euthyroid patients are summarized in Table 2. Although there was no statistically significant difference in BMI between subclinical and overt hypothyroid patients, the BMI of patients with subclinical hypothyroidism was significantly higher than euthyroid patients. There were no statistical differences among these 3 groups in serum biochemical data such as aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, urea nitrogen, creatinine, sodium, potassium and chloride (data not shown).

The prevalence of primary hypothyroidism increased with age in men and women (Fig. 4). The male: female ratios were 7:10 in subclinical and 2:3 in overt hypothyroidism. The omission criteria or drop out, 713 patients were assessed for thyroid function. Seventy-two percents of the patients were treated with some antilipemic agents. Among them, 90% were treated with statins and 5% were with fibrates. The residual 5% were treated with other agents such as probucol, colestimide and icosapentate.

The primary hypothyroidism was seen in 27 cases (11 men and 16 women) with 17 cases of subclinical hypothyroidism (2.4%) and 10 cases of overt hypothyroidism (1.4%). The central hypothyroidism was seen in 4 cases (0.6%). The thyroid dysfunction other than hypothyroidism, such as thyrotoxicosis or inappropriate secretion of TSH, was seen in 22 patients and the others were euthyroid (Fig. 2). In consequence, total prevalence of hypothyroidism was 4.3 % in cases of hypercholesterolemia, with 3.8% of primary hypothyroidism and 0.6% of central hypothyroidism. The individual TSH values in primary hypothyroid patients were shown in Fig. 3.

Differences of the characteristics, lipid profiles among overt hypothyroid, subclinical hypothyroid and euthyroid patients are summarized in Table 2. Although there was no statistically significant difference in BMI between subclinical and overt hypothyroid patients, the BMI of patients with subclinical hypothyroidism was significantly higher than euthyroid patients. There were no statistical differences among these 3 groups in serum biochemical data such as aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, urea nitrogen, creatinine, sodium, potassium and chloride (data not shown).

The prevalence of primary hypothyroidism increased with age in men and women (Fig. 4). The male: female ratios were 7:10 in subclinical and 2:3 in overt hypo-

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**Fig. 2** Classification of thyroid function.

**Fig. 3** Individual TSH values in primary hypothyroid patients at the two time points. A, overt hypothyroidism. B, subclinical hypothyroidism. When the TSH value was between 4.20 and 15.00 mU/L, the thyroid function was reevaluated 2 weeks later to exclude transient hypothyroidism.
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One female case had a weak TgAb (0.4 IU/mL) without TPOAb and other positive cases had both of antibodies. There was also no difference between overt hypothyroidism and subclinical hypothyroidism in the incidence of these antibodies.

Discussion

Dyslipidemia is one of the most common metabolic disorders associated with hypothyroidism [16]. Thyroid hormone decreases serum cholesterol concentration by the removal of cholesterol from the liver via the increased LDL receptors [17, 18] and serum TG concentration by enhancing lipoprotein lipase and hepatic lipase activities [19-21]. Thus, a higher population of hypothyroid subjects had a higher incidence of dyslipidemia [22]. The odds ratios relating hypothyroidism to high TC and high LDL-C were 8.0 and 5.3, respectively [23]. Therefore, we expected the higher prevalence of hypothyroidism among the subjects with dyslipidemia. The prevalence of hypothyroidism in our study was 3.7% (1.4% overt and 2.4% subclinical). The prevalence of hypothyroidism in the general population was estimated as 4.6% (0.3% overt and 4.3% subclinical) in the Unites States (NHANES III)[24]. On the other hand, the prevalence of hypo-

<table>
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<th>Table 2 Differences of the characteristics, lipid profiles among hypothyroid, subclinical hypothyroid and euthyroid patients</th>
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<td><strong>Euthyroidism</strong> (n=672)</td>
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Values are expressed as the mean ± SD. aP<0.05, bP<0.01, cP<0.0001 vs. euthyroidism by Dunnett analysis, dP<0.05 vs. overt hypothyroidism by Tukey-Kramer’s HSD analysis BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Fig. 4 The prevalence of primary hypothyroidism in each age group.
thyroidism in the population with dyslipidemia was reported as 1.4-13.3% [5-10]. Series et al. [5] measured TC in 2250 people from Glasgow, Scotland and TSH was measured in the 90 individuals who had hypercholesterolemia. Four (4.4%) had overt hypothyroidism and 8 (8.9%) had subclinical hypothyroidism. Diekman et al. [8] performed retrospective study in 1509 consecutive referrals for severe dyslipidemia in Netherlands and the prevalence of hypothyroidism was 2.6% (0.7% overt hypothyroidism and 1.9% subclinical hypothyroidism). Pirich et al. [10] screened 1922 clinically healthy, middle-aged population of employees in Austria. The prevalence of subclinical hypothyroidism was 0.8% in normocholesterolemic and 1.4% in hypercholesterolemic subjects, and no case of overt hypothyroidism was diagnosed. There are some other reports that studied in smaller number of patients with dyslipidemia and reported 6.8% (2.2% and 4.6%, overt hypothyroidism and subclinical hypothyroidism, respectively) in United Kingdom [6], 7.8% (2.5% and 5.3%) in United States [7], and 7.2% (2.8% and 4.4%) in Greece [9]. Thus, the percentage in our study was comparable to previous studies in the subjects with dyslipidemia, but not as high as that in the studies recently reported in Japanese population [25, 26]. Several reasons can be described. First of all, we performed multi-center study whose institutions distribute all over Japan, whereas Nagasaki [25] or Suita [26] is a single city. In addition, there are some resources to obtain the clinically important frequency of subclinical hypothyroidism in our study. The subjects who had had thyroid disease were excluded in our study. When the TSH value was less than 15 mU/L, the thyroid function was reevaluated 2 weeks later to exclude transient hypothyroidism. The patients were counseled to abstain iodine-rich food such as kelp to exclude iodine-induced mild hypothyroidism. As a result, although the frequency may have decreased, we could know the population who really need to be treated with levothyroxine.

The association between subclinical hypothyroidism and serum cholesterol levels has been studied in several studies. Higher serum cholesterol levels are found in subjects with high-normal TSH levels [27]. There was a significant positive correlation between serum TSH and serum TC and LDL-C levels in men and women [28]. There are also several studies about the effects of T4 replacement therapy of subclinical hypothyroidism on dyslipidemia. Among eight studies done with double-blind placebo controlled, TC and LDL-C but not HDL-C improved in the four studies [29-32] but unchanged in the remaining four studies [33-36]. We are currently following up the patients with overt and subclinical hypothyroidism treated by T4 replacement to elucidate its effects on the lipid profile. Interestingly, the BMI of patients with subclinical hypothyroidism was significantly higher than euthyroid patients. The serum levels of TSH were higher in obese patients in some studies [37-41] but not in others [42, 43]. The reason is still unclear because the BMI of patients with overt hypothyroidism was not different from the others also in our study. It is necessary to evaluate in the larger population whether BMI is a risk factor of subclinical hypothyroidism in the patients with dyslipidemia.

Because the population with dyslipidemia is very large, we also have to consider the cost-benefit issue of thyroid function test. However, as mentioned in the introduction, life-long treatment with statins could be much higher in cost than that with levothyroxine.

Although the present study was performed prospectively, there are some possible limitations. Because the survey was performed in Japan where iodine intake is relatively in excess, the results of this study cannot be applied to the global population. However, as mentioned in the introduction, life-long treatment with statins could be much higher in cost than that with levothyroxine.
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In conclusion, the prevalence of hypothyroidism was 4.3% (1.4% primary overt hypothyroidism, 2.3% subclinical hypothyroidism and 0.4% central hypothyroidism) in the population with dyslipidemia in Japan. It is necessary to evaluate thyroid function before starting antilipemic agents to the patients with dyslipidemia by taking account of the large population of dyslipidemia, because many of these patients have no specific clinical complaints or signs of hypothyroidism. A misdiagnosed hypothyroidism may increase the risks of treatment with antilipemic agents such as statins in hypercholesterolemic patients, which could be a further reason to diagnose hypothyroidism early in these patients.

Acknowledgments

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