Thyroid function and internal carotid artery stenosis in ischemic stroke

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Abstracts. Thyroid dysfunction has been known to be closely associated with increased vascular events. The aims of the present study included determining the prevalence of subclinical thyroid disease and relationships between normal ranges of thyroid function and internal carotid artery steno-occlusion (ICS) in patients with ischemic stroke. From March 2007 to February 2008, 382 consecutive patients with ischemic stroke referred to the neurovascular ultrasound laboratory were analyzed. ICS was defined as greater than 50% luminal narrowing or complete obstruction in at least 1 internal carotid artery. Subclinical thyroid disease was determined by free thyroxine (fT4) and thyroid stimulating hormone (TSH) measurements. After the exclusion of patients with abnormal levels of thyroid hormones, normal ranges of fT4 were classified into 3 groups: low-normal (fT4, 11.0~12.3 pmol/L), mid-normal (12.4~15.4), and high-normal (15.5~24.0) thyroid groups. There were 17 patients (4.5%) with subclinical hypothyroidism and 6 (1.6%) with subclinical hyperthyroidism. There were 301 patients (78.8%) with normal fT4 and TSH levels, and among them, 67 patients (22.3%) had ICS. There was a significantly higher percentage of ICS in the low-normal thyroid group than in the other groups. By multivariate regression analysis, the low-normal fT4 group had an OR of 2.80 (95% confidence interval, 1.39-5.66) for ICS compared to the mid-normal group. In patients with ischemic stroke, the prevalence of subclinical thyroid disease was similar to the general population, and in euthyroid patients, low-normal thyroid function was independently associated with a higher percentage of ICS.

Key words: Free thyroxine, Internal carotid artery stenosis, Stroke, Subclinical thyroid disease
thyroid disease and the relationship between normal ranges of free T4 (fT4) and ICS in patients with ischemic stroke. In order to achieve these aims, the authors compared fT4 and TSH levels to establish a definition of subclinical thyroid disease in Korean patients with ischemic stroke. In addition, after the exclusion of patients with abnormal levels of fT4 and/or TSH, normal ranges of thyroid hormones were examined for an association with ICS, taking into consideration potential confounding variables.

Subjects and Methods

Study population

From March 2007 to February 2008, all patients with ischemic stroke who had been referred to the Neurovascular Ultrasound Laboratory of the Stroke Centre of Chonbuk National University (CNU) Hospital were recruited. Detailed explanations about the study design were reported previously [15]. In brief, all patients who were referred and underwent neuroradiology examinations were included for the present study. Among them, patients with ischemic stroke were defined as those who had a history of cerebral infarction with evidence of an acute focal neurological dysfunction lasting more than 24 h. Evidence was based on signs and symptoms thought to be due to cerebral ischemia diagnosed on brain imaging (computed tomography and/or magnetic resonance imaging). Ischemic strokes were categorized into 5 groups using the diagnostic criteria of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) study, as follows: large artery atherosclerosis (LAA), cardioembolism (CE), small vessel occlusion (SVO), and stroke of other determined etiology (SDE) or, undetermined etiology (UDE) [16]. All participating patients gave written informed consents, and this study was performed with the approval of the institutional ethics committee.

Assessments for risk factors and biochemical measurements

Data collected from consecutive patients included history of previous CVD, type 2 diabetes mellitus (DM), hypertension, dyslipidemia, and medication usage. Smoking status was classified into 3 categories: current smokers, exsmokers, and nonsmokers. Patients with persistent elevation of blood pressure (i.e., ≥ 140/90 mmHg) or taking antihypertensive medications were classified as hypertensive according to the criteria defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [17]. Subjects with type 2 DM were those who reported having been told by a physician that diabetes was present, or those with a fasting blood glucose of greater than 6.9 mmol/L (126 mg/dL) determined on more than 2 occasions, according to the criteria defined by the American Diabetic Association [18]. Dyslipidemia was defined as recommended [19], which is total cholesterol greater than 6.2 mmol/L (240 mg/dL), triglycerides greater than 2.3 mmol/L (200 mg/dL), or LDL cholesterol greater than 4.1 mmol/L (160 mg/dL).

Blood samples were drawn in the morning after a 12-hour overnight fast, and assessed using a Hitachi 7600-110 analyzer (Hitachi High-Technologies Corporation, Tokyo, Japan). The concentration of plasma total homocysteine (tHcy) was measured by fluorescence polarization immunoassay (AxSYM, Abbott Laboratories, Abbott Park, IL), on the third day after the onset of acute ischemic stroke. Daily quality control of the above measurements made on the Hitachi analyzer was carried out by duplicate measurements with a commercially available control material (Bio-Rad Laboratories, Hercules, CA).

Measurements of free T4 and thyroid function categorization

Free T4 and TSH serum concentrations were determined by electrochemiluminescence immunoassays using Elecsys 2010 system (Roche Diagnostics, GmbH, Mannheim, Germany), usually after one night of admission during the acute stage of ischemic stroke. Chemiluminescent emission was measured by a photomultiplier, and T4-specific antibody and biotinylated T4 were used as reagent and control, respectively. Results were determined by a calibration curve which was instrument generated using 2-point calibration and a master curve provided by the reagent barcode.

Euthyroidism was defined as TSH (reference range: 0.2 ~ 4.0 mIU/L) and fT4 (reference range: 11.0 ~ 24.0 pmol/L) serum concentrations falling within the normal reference ranges. Patients with abnormal TSH and/or fT4 values or taking any thyroid medication were excluded from the present study. TSH and fT4 values were natural log- (ln) transformed, because the frequency distributions of fT4 and TSH were positively skewed, and lnT4 values were categorized into quartiles. The lowest quartile was designated as low-
Thyroid function and ICA stenosis

was used to determine the statistical differences between continuous variables, and a chi-square test was used for categorical variables. The associations between ICS and stratified ln fT4 values were analyzed using regression analyses, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Three categories were considered to be explanatory variables, with mid-normal fT4 values as a reference category and ICS as a dichotomous outcome variable. Interaction terms for ICS between ln fT4 and other independent variables were entered separately and their significances were assessed by likelihood ratio tests. All statistical analyses were conducted using SPSS software version 17.0 (SPSS, Chicago, IL).

Results

In total, 391 patients with ischemic stroke were referred to the Neurovascular Ultrasound Laboratory in the CNU hospital during the 1-year study period. Free T4 and TSH serum concentrations were determined in 382 patients (97.7%), who were not receiving any thyroid medication, as shown in Fig. 1. Of the 22 patients with TSH values greater than 4 mIU/L, 17 patients had normal ranges of fT4 (subclinical hypothyroidism), both the second and third quartiles as mid-normal, and the fourth quartile as high-normal.

Measurement of ICA stenosis and categorization

The extent of ICS was determined for each patient. ICA stenosis was defined as greater than 50% luminal narrowing (de novo) in at least 1 ICA, according to the criteria defined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [20]. ICA occlusion was defined as complete obstruction of 1 or both ICAs, and both ICA stenosis (> 50%) and occlusion were designated as ICS. All extracranial and intracranial carotid arteries were examined using computed tomography, magnetic resonance angiography, or invasive cerebral angiography, and images obtained from such examinations were interpreted by 2 neuroradiologists who were blinded to each other’s report. When the 2 neuroradiologists did not agree, a case conference was held to discuss the discrepancy and the final conclusion was based on mutual agreement.

Statistical analysis

Descriptive data for the major characteristics were expressed as means ± standard deviations (SDs) or percentages, as appropriate. An independent $t$-test was used to determine the statistical differences between continuous variables, and a chi-square test was used for categorical variables. The associations between ICS and stratified ln fT4 values were analyzed using regression analyses, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Three categories were considered to be explanatory variables, with mid-normal fT4 values as a reference category and ICS as a dichotomous outcome variable. Interaction terms for ICS between ln fT4 and other independent variables were entered separately and their significances were assessed by likelihood ratio tests. All statistical analyses were conducted using SPSS software version 17.0 (SPSS, Chicago, IL).
rroidism), resulting in prevalence of 4.5%. All of the 6 patients with TSH values less than 0.2 mIU/L had normal ranges of fT4 (subclinical hypothyroidism), for a prevalence of 1.6%. The total prevalence of subclinical thyroid disease was 6.0% in the stroke patients of this study.

After patients with abnormal levels of thyroid hormones were excluded, there were 301 patients (77.0%) with normal values of fT4 and TSH who were analyzed for association with ICS. There were no significant differences between the included and excluded patients groups seen for age (65.7 ± 11.8 versus 66.1 ± 12.2 yrs, p=0.793, respectively) and percentages of women (40.2 versus 42.9%, p=0.651, respectively). According to categories of lnfT4, the low-normal fT4 group had fT4 levels of 11.0–12.3 pmol/L, the mid-normal had 12.4–15.4, and the high-normal had 15.5–24.0 pmol/L, as shown in Table 1. The high-normal fT4 group had significantly lower values of TSH (1.2 ± 0.9 mIU/L) than the other 2 groups (p=0.012).

Among the included 301 patients, 67 (22.3%) had greater than 50% ICA stenosis or total obstruction, fulfilling the definition of ICS. The mean age was significantly higher and the proportion of women was lower in stroke patients with ICS than in patients without ICS, as shown in Table 2. Plasma tHcy was slightly higher in the ICS group, with a borderline significance. LAA ischemic stroke was the most common among the subtypes of ischemic stroke, and in patients without ICS, SVO (26.5%) and SDE (11.1%) were next in frequency after LAA (52.6%). The mean serum lnfT4 value was slightly lower in stroke patients with ICS, but was not statistically significant. According to the categories of lnfT4, the percentage of patients with ICS in the low-normal fT4 group showed the highest value (33.3%) compared with the other 2 groups (high-normal and mid-normal fT4 groups, 20.3% and 17.8%, respectively, p=0.012 for trend). The percentages of ICS in the patients with subclinical hypothyroidism (n = 17) and those with low values of fT4 (< 11 pmol/L, n = 58) were similar to that of the low-normal fT4 group, at 29.4 and 32.8%, respectively.

As shown in Table 3, multivariate logistic regression analyses demonstrated that the low-normal fT4 group was independently more highly associated with ICS. Compared to the mid-normal fT4 group, the low-normal fT4 group had an OR of 2.80 (95% CI, 1.39-5.66), even after adjusting for potential confounders like age, sex, TSH, tHcy, vascular risk factors, and TOAST classifications. Interaction terms between the lnfT4 categories and independent variables like age, sex, tHcy, and TOAST classifications that showed associations with ICS of more than borderline significance were all non-significant (p values > 0.5).

**Discussion**

The prevalence of subclinical thyroid disease was 4.5% for subclinical hypothyroidism and 1.6% for subclinical hyperthyroidism in the stroke patients of this study. Previous studies of the general population have reported the prevalence of subclinical hypothyroidism to be between 4 and 10%, and subclinical hyperthyroidism between 0.5 and 2% [21-23]. In this study, the prevalence of subclinical thyroid disease in patients with ischemic stroke appears to be similar to the prevalence in the general population. Considering the significantly higher mortality rates in subjects with subclinical thyroid disease than in those with euthyroid status, which was seen in a long-term follow-up study [24], these groups should be carefully considered for regular monitoring (with/without replacement therapy) of both thyroid function and cardiovascular risk factors [6, 25].

In euthyroid subjects who had normal ranges of fT4 and TSH, the study patients in the low-normal fT4 group (fT4; 11.0–12.3 pmol/L) had a significantly higher prevalence of ICS than the other normal thyroid groups. And compared to the mid-normal thyroid group, the low-normal fT4 group had 2.8 times higher association with ICS, independent of potential confounders. To our best knowledge, there has been no previously published report presenting the prevalence of subclinical thyroid disease and associations between normal thyroid function (fT4) and ICS in patients with ischemic stroke.

ICS can be directly associated with the acute onset of stroke [14], but ICS can also be detected incidentally by diagnostic neuroimaging work-ups. Whether or not ICS is symptomatic, it affects the entire cerebrovascular system with moderate to severe hemodynamic disturbance [15]. The ICA is a large artery with a diameter usually greater than 0.4 cm [26], and ICS represents much more advanced atherosclerosis than increased carotid intima-media thickness (IMT), which has been used as a hallmark of generalized atherosclerosis. Clinically, ICS should be managed carefully with appropriate medications, or even with surgi-
### Table 1  Values of free T4 (fT4) and TSH in stroke patients with euthyroidism*

<table>
<thead>
<tr>
<th>Degrees of ln fT4</th>
<th>Number</th>
<th>Free T4, pmol/L</th>
<th>TSH, mIU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Min</td>
</tr>
<tr>
<td>High normal</td>
<td>74</td>
<td>17.7 ± 2.1</td>
<td>15.5</td>
</tr>
<tr>
<td>Mid normal</td>
<td>152</td>
<td>13.8 ± 0.9</td>
<td>12.4</td>
</tr>
<tr>
<td>Low normal</td>
<td>75</td>
<td>11.7 ± 0.4</td>
<td>11.0</td>
</tr>
<tr>
<td>Total</td>
<td>301</td>
<td>14.3 ± 2.5</td>
<td>11.0</td>
</tr>
</tbody>
</table>

TSH; thyroid stimulating hormone, SD; standard deviation.

* Euthyroidism was defined as having both normal TSH (0.2 ~ 4.0 mIU/L) and fT4 levels (11.0 ~ 24.0 pmol/L).

† p<0.05 by analysis of variance (ANOVA), compared with high normal ln fT4 (Bonferroni comparisons).

### Table 2  Demographics of stroke patients with euthyroidism according to internal carotid artery (ICA) status

<table>
<thead>
<tr>
<th>ICA steno-occlusion (ICS)</th>
<th>No (n = 234)</th>
<th>Yes (n = 67)</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.7 ± 12.1</td>
<td>69.2 ± 10.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Women, %</td>
<td>43.6</td>
<td>28.4</td>
<td>0.025</td>
</tr>
<tr>
<td>Smoking, current and ex-, %</td>
<td>21.9</td>
<td>25.8</td>
<td>0.508</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>52.1</td>
<td>61.2</td>
<td>0.190</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, %</td>
<td>15.8</td>
<td>22.4</td>
<td>0.209</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>36.2</td>
<td>37.9</td>
<td>0.803</td>
</tr>
<tr>
<td>Total homocysteine, μmol/L</td>
<td>12.0 ± 4.3</td>
<td>13.3 ± 5.6</td>
<td>0.079</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>39.7 ± 5.7</td>
<td>39.9 ± 4.4</td>
<td>0.831</td>
</tr>
</tbody>
</table>

Stroke classification by TOAST criteria, %

- Large artery atherothrombosis: 52.6 vs 77.6
- Small vessel occlusion: 26.5 vs 4.5
- Cardioembolism: 8.5 vs 4.5
- Undetermined etiology: 11.1 vs 9.0
- Determined etiology: 1.3 vs 4.5

| TSH, mIU/L               | 1.5 ± 0.9 | 1.6 ± 1.0 | 0.565 |
| lnTSH                    | 0.19 ± 0.71 | 0.23 ± 0.72 | 0.677 |
| Free T4 (fT4), pmol/L    | 14.4 ± 2.6 | 13.8 ± 2.1 | 0.132 |
| ln fT4                   | 1.11 ± 0.05 | 1.10 ± 0.05 | 0.150 |

<table>
<thead>
<tr>
<th>Degrees of ln fT4, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High normal</td>
<td>25.2</td>
<td>22.4</td>
</tr>
<tr>
<td>Mid normal</td>
<td>53.4</td>
<td>40.3</td>
</tr>
<tr>
<td>Low normal</td>
<td>21.4</td>
<td>37.3</td>
</tr>
</tbody>
</table>

Mean ± SD or percentages were expressed. TOAST; Trial of Org 10172 in Acute Stroke Treatment.

† ICS was defined as greater than 50% stenosis or total obstruction in at least 1 ICA.

### Table 3  Multivariate logistic regression analyses for ICS

<table>
<thead>
<tr>
<th>Degrees of ln fT4</th>
<th>ICS</th>
<th>Number, (%)</th>
<th>Odds Ratio</th>
<th>95% confidence intervals</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid normal (reference)</td>
<td>27 (17.8)</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High normal</td>
<td>15 (20.3)</td>
<td>1.23</td>
<td>0.57-2.66</td>
<td>0.598</td>
<td></td>
</tr>
<tr>
<td>Low normal</td>
<td>25 (33.3)</td>
<td>2.80</td>
<td>1.39-5.66</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, sex, TSH, smoking, total homocysteine, hematocrit, hypertension, type 2 DM, dyslipidemia, and TOAST classifications.
cal intervention, to prevent stroke [27]. Considering the clinical importance of ICS, the independent association between low-normal thyroid function and ICS warrants the screening of thyroid status and consideration of optimal ranges of thyroid hormone serum concentrations. Although there has been no sound evidence for a direct relationship between acute cerebrovascular disease and thyroid dysfunction [25], most studies have focused on overt thyroid disease of low incidence, not paying much attention to normal thyroid status.

Thyroid hormones are known to have vasodilating effects [7, 8]. Both overt and subclinical hypothyroidism can cause hypercholesterolemia, diastolic hypertension, and cardiac dysfunction, thus conferring an elevated risk of atherosclerosis and vascular diseases [28]. However, some studies showed conflicting results about the association between (subclinical) hypothyroidism and atherosclerotic parameters [29, 30]. Even though, for normal ranges of thyroid hormones, previous reports showed the significant relationships between them (normal ranges of thyroid hormones) and inflammatory markers [9], mitral annular calcification [31], and carotid IMT [10, 11]. The present study has provided more evidence and extended the clinical significance of low-normal thyroid function to include an advanced atherosclerotic condition like ICS. As Dullaart et al. has postulated, there could be mechanisms other than intermediate cardiovascular outcome variables, and systemic hemodynamic factors per se might also be involved in the relationship between thyroid hormone status and elevated risk of atherosclerosis [11].

A previous ICS association study reported a significant relationship between higher concentrations of tHcy and ICS [32], and another reported that both high hemoglobin A1c and 2-h post-load plasma glucose were independently associated with ICS [33]. In the present study, the higher concentration of tHcy was also associated with ICS, showing borderline significance (Table 1); however the higher prevalence of type 2 DM in the stroke patients with ICS was not statistically significant.

This study has some important limitations. First, it was performed as a cross-sectional study in patients with ischemic stroke, which means that it is unclear whether measurement of thyroid hormones like fT4 and TSH would be useful for predicting the progression of carotid stenosis in patients with ischemic stroke. Second, thyroid hormone levels were not measured sequentially, and thyroid autoantibodies were not investigated. Free T4 levels can be variable and subclinical thyroid disease can be persistent or transient [34]. Therefore, the findings in this study, which are based on a single measurement of thyroid hormones, cannot conclusively determine if thyroid disease is present. Third, the thyroid status of 53 (13.9%) patients with fT4 values less than 11 pmol/L and normal TSH concentration was not properly defined.

Changes within the HPT axis can occur in non-thyroidal illnesses and are typically associated with low levels of T3, T4, and even TSH [35]. Previous studies have also reported that variable changes are seen in neuroendocrine function (especially TSH) in patients with acute stroke [36, 37]. Some patients with acute ischemic stroke in the present study might show abnormalities in TSH and fT4, depending on the severity of stroke as well as general physical conditions. According to the design of this study, these patients with abnormal fT4 values were simply excluded because of the confounding effect of non-thyroidal illness on thyroid function.

In conclusion, the present study found that the prevalences of subclinical hypothyroidism (4.5%) and subclinical hyperthyroidism (1.6%) in Korean patients with ischemic stroke were similar to the prevalences in the general population. In addition, low-normal fT4 values in the patients were independently and more highly associated with ICS than mid-normal fT4 values.

Acknowledgments

Authors’ contributions: J.Y.S. participated in data collection and reviewed the manuscript. H.S.N. performed statistical analyses and reviewed the manuscript. H.K.P. conceived the study design, reviewed and edited the manuscript. S.K.J. participated in data collection, drafted and reviewed the manuscript. All authors read and approved the final manuscript.

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Conflicts of interests: None declared.
References


