Subclinical Hyperthyroidism Is a Risk Factor for Poor Functional Outcome After Ischemic Stroke

Frank Arne Wollenweber, MD*; Vera Zietemann, PhD*; Andreas Gschwendtner, MD; Christian Opherk, MD; Martin Dichgans, MD

Background and Purpose—Subclinical hyperthyroidism is associated with adverse cardiovascular events, including stroke and atrial fibrillation. However, its impact on functional outcome after stroke remains unexplored.

Methods—A total of 165 consecutively recruited patients admitted for ischemic stroke were included in this observational prospective study. Blood samples were taken in the morning within 3 days after symptom onset, and patients were divided into the following 3 groups: subclinical hyperthyroidism (0.1< thyroid-stimulating hormone ≤0.44 μU/mL), subclinical hypothyroidism (2.5≤ thyroid-stimulating hormone <20 μU/mL), and euthyroid state (0.44< thyroid-stimulating hormone <2.5 μU/mL). Patients with overt thyroid dysfunction were excluded. Follow-up took place 3 months after stroke. Primary outcome was functional disability (modified Rankin Scale), and secondary outcome was level of dependency (Barthel Index). Ordinal logistic regression analysis was used to adjust for possible confounders. Variables previously reported to be affected by thyroid function, such as atrial fibrillation, total cholesterol, or body mass index, were included in an additional model.

Results—Nineteen patients (11.5%) had subclinical hyperthyroidism, and 23 patients (13.9%) had subclinical hypothyroidism. Patients with subclinical hyperthyroidism had a substantially increased risk of functional disability 3 months after stroke compared with subjects with euthyroid state (odds ratio, 2.63; 95% confidence interval, 1.02–6.82, adjusted for age, sex, smoking status, and time of blood sampling). The association remained significant, when including the baseline NIHSS, TIA, serum CRP, atrial fibrillation, body mass index, and total cholesterol as additional variables (odds ratio, 3.95; 95% confidence interval, 1.25–12.47), and was confirmed by the secondary outcome (Barthel Index: odds ratio, 9.12; 95% confidence interval, 2.08–39.89).

Conclusions—Subclinical hyperthyroidism is a risk factor for poor outcome 3 months after ischemic stroke. (Stroke. 2013;44:1446-1448.)

Key Words: acute ischemic stroke • functional outcome • subclinical thyroid dysfunction

With an estimated prevalence of ≈2%, subclinical hyperthyroidism is common in the general population, varying in frequency with age, sex, and nutrition factors. It is associated with various cardiovascular effects and conditions, including a higher heart rate, an increase of left-ventricular mass, and atrial fibrillation. Subclinical hyperthyroidism has further been shown to increase the risk for carotid plaques and prevalent stroke.

Although subclinical hypothyroidism has been associated with favorable outcome after acute ischemic stroke, the effects of subclinical hyperthyroidism on functional outcome have not been investigated. Therefore, we studied the effects of subclinical thyroid dysfunction on functional outcome 3 months after acute ischemic stroke, considering euthyroid state as a reference.

Methods

Study Population
Patients were recruited through an observational single-center cohort study following Institutional Review Board approval by the medical faculty of the Ludwig-Maximilians-Universität-München. Inclusion criterion was an acute ischemic stroke defined by a new focal neurological deficit with a corresponding lesion on MR- or delayed computed tomography scan. Exclusion criteria were known thyroid disease, biochemically defined overt thyroid disease, time since symptom onset >72 hours, and use of thyroid-affecting medication. Patients received 72-hour ECG monitoring at baseline and 12-channel ECG monitoring at follow-up.

Exposure Measurement
Blood samples were drawn between 6 and 9 AM. Serum thyroid-stimulating hormone, free thyroxine (fT4), and free tri-iodothyronine (fT3) were available at admission, and follow-up.

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(fT3) concentrations were quantified using a chemiluminescence-based immunoassay. Because clinical symptoms of mild thyroid diseases are nonspecific, thyroid state was biochemically defined using published criteria.

Outcome
The modified Rankin Scale measured 3 months after stroke was used as the primary functional outcome measure. The Barthel Index was used as a supporting measure to assess consistency in direction of effect.

Statistical Analysis
Associations between thyroid-stimulating hormone and functional outcomes were determined using ordinal logistic regression with euthyroid state as a reference. To avoid inappropriately small patient numbers within individual cells, modified Rankin Scale scores were categorized into 3 groups: 0 to 1, 2 to 3, and 4 to 6. Adjusted associations were calculated to investigate confounding and direct effects. All analyses were 2-sided, conducted at a 0.05 level of significance, and carried out using SAS version 9.3. Detailed Methods are described in the online-only Data Supplement.

Results
Baseline characteristics of the study population are shown in Table 1. Patients with subclinical hyperthyroidism had a lower body mass index and lower blood lipid levels compared with patients with euthyroid state. AF was more common in patients with subclinical hyperthyroidism and hypothyroidism compared with patients with euthyroid state.

Stroke recurrences occurred in 1 patient (5.3%) with subclinical hyperthyroidism, in 6 patients (4.9%) with euthyroid state, and in none of the patients with subclinical hypothyroidism. One patient with subclinical hyperthyroidism and 4 patients with euthyroid state died during follow-up (Figure). Subclinical hyperthyroidism was associated with a significantly higher risk of poor functional outcome in both statistical models (Table 2). Subclinical hypothyroidism was associated with a lower risk of poor functional outcome, although the association was not significant (Table 2).

Figure. Functional outcome assessed by modified Rankin scale 3 months after acute ischemic stroke stratified by thyroid function.
Discussion

This study demonstrates that subclinical hyperthyroidism is an independent risk factor for poor functional outcome 3 months after ischemic stroke. Our findings must be interpreted in the context of recent studies that have shown multiple effects of subclinical thyroid disease on the cardiovascular system. Subclinical hyperthyroidism increases the risk of AF and cardioembolic stroke, which has a less favorable short-term outcome than other stroke subtypes. In the current study, AF was more common in patients with subclinical hyperthyroidism than in patients with euthyroid state. However, the association with poor outcome remained significant after adjustment for AF, and AF was likewise more common in patients with subclinical hypothyroidism, which showed a favorable effect on outcome in this and in earlier studies.

Long-lasting subclinical hyperthyroidism has been associated with heart failure. None of our patients showed signs of heart failure, but cardiac function was not quantitatively assessed and therefore cannot be excluded as a contributing factor. Other mechanisms to be considered are changes in coagulation parameters and an increased sympathetic nervous system tone. Elevated concentrations of thyroid hormones are associated with an increase in energy and oxygen demand, which would be expected to impair ischemic tolerance in the brain. However, more detailed studies are required to determine the impact of thyroid function on cerebral ischemia.

Serum thyroid-stimulating hormone reference limits remain a matter of debate. This in part relates to the impact of age, sex, ethnicity, diurnal variations, and acute illnesses. In the current study, we accounted for these factors by standardized blood sampling by excluding patients with symptom onset >72 hours and by including age, sex, and time of blood sampling in our statistical models. Limitations of this study include the relatively small number of patients with subclinical thyroid disease, a potential bias toward recruitment of less severely affected patients, and that the outcome had to be assessed by telephone interviews in some patients. Also, we did not perform systematic imaging on the thyroid gland.

Our findings contribute to the growing evidence for adverse effects resulting from subclinical hyperthyroidism. Although significant for both end points, our findings require confirmation in additional cohorts.

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Disclosures

None.

References

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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/03/12/STROKEAHA.113.000833.DC1

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SUPPLEMENTAL MATERIAL

Subclinical hyperthyroidism is a risk factor for poor functional outcome after ischemic stroke

Supplementary methods

Study design and study population. Patients were recruited through an on-going observational cohort study conducted at the Interdisciplinary Stroke Centre Munich, a tertiary level hospital. Enrollment occurred between February 2011 and March 2012. Patients of both sexes aged 18 years or older with ischemic stroke were recruited through the local stroke unit. Inclusion criterion was an acute ischemic stroke defined by an acute focal neurological deficit documented by either a diffusion weighted imaging (DWI)-positive lesion on MR imaging or a new lesion on a delayed CT scan. Exclusion criteria were known thyroid disease, a biochemically detected overt thyroid disease, medication with thyroid affecting drugs, time since symptom onset of greater than 72 hours, brain tumor or brain metastasis.

As displayed in figure e-1 1008 patients were seen at the recruiting stroke unit during the enrollment phase. 843 were not included in the analysis. 540 of them did not meet the inclusion criterion. Another 67 patients were excluded because of a stroke going back more than 72-hours at time of admittance and 71 patients could not be contacted during their hospital stay. The remaining 330 patients were asked to participate in the study. 142 patients were not willing or able to participate for various reasons (e.g. severe impairment with inability to participate into the interview, lack of German language skills). 188 patients agreed to participate in the study. 18 patients were excluded from analysis because of thyroid-affecting medication use before stroke (n=14) or overt thyroid dysfunction (n=4). Of the 170 patients that were available for baseline-assessment 70% had been admitted within 12 hours after symptom onset, 82% within 24 hours, and 96% within 48 hours.
Outcome measures were obtained at 3 months after stroke (median time: 90 days, interquartile range [IQR] 81-99 days), conducted by a structured interview via telephone or face to face depending on the patient’s feasibility to return to the study center. The interview was performed with the patient or, if not possible, with a close relative. 160 patients completed the 3 months follow-up. Five patients died within 3 months and 5 were lost to follow-up (figure e-1). Statistical analyses were performed on the 165 patients with known functional outcome after 3 months. The representativeness of the 165 analyzed and 303 not analyzed patients with acute ischemic stroke is shown in table e-1.

**Standard protocol approvals, registrations, and patient consent.** The study was conducted according to the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained by patient or legal guardian prior to study participation.

**Data collection.** Information on demographic variables, living situation, functional pre-stroke outcome, lifestyle habits, health history as well as medication before stroke was provided by the patient or the closest relative at baseline examination. Stroke severity was assessed using the National Institutes of Health Stroke Survey (NIHSS) by a certified study clinician. Stroke etiology was determined according to the criteria of the TOAST and ASCO classification. Patients received a continuous 72h-ECG recording at baseline and a 12-channel ECG at the follow-up. Furthermore all patients received complete two-dimensional (2D) and Doppler echocardiography, however left atrial diameter, ejection fraction and premature atrial contractions were not quantitatively assessed. All examinations were performed and interpreted by an independent observer who was unaware of the clinical data.

**Exposure measurement.** Blood samples were drawn in the morning between 6 and 9 am to minimize variations caused by circadian rhythm. They were taken within 3 days after symptom onset and adjusted for time differences in multivariable analyses. Serum thyroid-stimulating hormone (TSH), free thyroxin (fT4) and free tri-iodothyronine (fT3) concentrations were quantified using a chemiluminescence-based immunoassay implemented
on a fully automated immunoanalyzer system (ADVIA Centaur TSH, Siemens Healthcare Diagnostics, Tarrytown NY, USA).\(^2\)

In the recent literature different reference-limits have been proposed for hypothyroidism: Akhoundi et al.\(^3\) defined subclinical hypothyroidism as serum TSH level in the range of 2.5-10mIU/L, Baek et al.\(^4\) defined subclinical hypothyroidism as TSH >5μU/mL. In the current study we adopted the lower cut point of 2.5 to be comparable with the more recent work of Akhoundi et al.\(^3\) For hyperthyroidism we adopted the cut point used by Cappola et al.\(^5\), who determined the relationship between baseline thyroid status and incident atrial fibrillation. Thus, euthyroid state was defined by a serum TSH-level between 0.44 and 2.5 μU/ml, subclinical hyperthyroidism was defined by a serum TSH-level between 0.11 and ≤0.44 μU/ml plus normal fT4 and fT3 and subclinical hypothyroidism was defined by a serum TSH-level between ≥2.5 and <20 μU/ml plus normal fT4 and fT3.\(^3\),\(^5\) Reference values for fT4 were 0.9-1.8 ng/dl and for fT3 2.3-4.2 pg/ml. All measurements were performed by laboratory staff unaware of the patients’ clinical characteristics.

**Outcome measurement.** The modified Rankin Scale (mRS) was used as the primary functional outcome measure after 3 months follow-up as recommended in the literature.\(^6\) The Barthel Index (BI) was used as a supporting scale to assess consistency in direction of effect.\(^6\) Both outcome measurements were determined by trained raters who were unaware of the laboratory results.

**Statistical analysis.** Data are given as means (SD) for normally distributed interval variables, as medians (IQR) for skewed data or scores, and as frequencies (percentage) for categorical variables. Associations between TSH and functional outcomes 3 months after stroke were determined using ordinal logistic regression with euthyroid state as reference because an ordinal analysis is statistically more powerful and avoids the difficulty of choosing one cut point.\(^6\),\(^7\) We performed score tests to test the proportionality hypothesis. To avoid inappropriately small
patient numbers within individual cells outcome measures were categorized into 3 groups: mRS: 0-1, 2-3 and 4-6; BI: ≤85, 86-95 and >95 (table e-2).

Adjusted associations were calculated to investigate confounding and direct effects. Model 1 was adjusted for the possible confounder age, sex, and smoking status as smoking is known to influence the TSH-level\(^8\) and was found to be associated with TSH-levels in our data set. Model 2 furthermore included known risk factors for functional outcome after stroke (NIHSS, TIA and serum CRP) as well as variables previously reported to be affected by thyroid function (intermediate variables) such as AF, total cholesterol and body mass index (BMI). LDL cholesterol, medication before stroke for dyslipidemia and mRS at baseline was not included in the multivariable models to avoid multicollinearity. All models were adjusted for the time between symptom onset and blood sampling. Continuous variables were categorized into quartiles to account for nonlinear relations with the outcome. Odds ratios (OR) were reported with 95% confidence intervals (CI). All analyses were two-sided, conducted at a 0.05 level of significance and carried out using SAS version 9.3 (SAS Institute Inc., Cary, NC).
Figure e-1. Study profile (enrollment between February 2011 and March 2012)

1008 patients admitted to the hospital

No final diagnosis of acute ischemic stroke: n=540 (54%)

468 patients with acute ischemic stroke*

- Time since symptom onset >72h or time unknown: n=67 (14%)
- Patient could not be contacted: n=71 (15%)

330 patients contacted

- Patient refused: n=62 (19%)
- Patient rapidly transferred / not reached for interview: n=6 (2%)
- Patient could not be informed & no informant available: n=17 (5%)
- Patient in bad condition & no informant available: n=9 (3%)
- Patient does not speak German good enough: n=11 (3%)
- Patient is living too far away: n=16 (5%)
- Others: n=21 (6%)

188 patients recruited

Patient excluded because of:
- thyroid affecting medication use before stroke: n=14 (7%)
  (amiodarone: n=1; carbimazole: n=1; levothyroxine: n=12)
- overt thyroid dysfunction: n=4 (2%)
  (TSH-level >20 μU/ml: n=1; TSH-level <0.1 μU/ml: n=3)

170 patients with baseline-data

Patient lost to follow-up after 3 months because:
- patient could only be interviewed >9 months after baseline: n=2 (1%)
- relative discontinued interview because of poor health status of the patient: n=1 (1%)
- patient alive but could not be contacted (information from the registry office): n=2 (1%)

165 patients included in analysis

* defined by a new focal neurological deficit with a corresponding lesion on a MR or CT scan
Table e-1. Representativeness of the cohort with acute ischemic stroke

<table>
<thead>
<tr>
<th></th>
<th>Patients analyzed (N=165)</th>
<th>Patients with ischemic stroke not entering the analysis (N=303)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: %</td>
<td>43</td>
<td>46</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>37</td>
<td>37</td>
</tr>
</tbody>
</table>

Table e-2. Functional outcome 3 months after acute ischemic stroke

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Subclinical hyperthyroidism</th>
<th>Euthyroid state</th>
<th>Subclinical hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Scale: n (%)</td>
<td>109</td>
<td>9 (47)</td>
<td>83 (68)</td>
<td>17 (74)</td>
</tr>
<tr>
<td>≤1</td>
<td>(66)</td>
<td>5 (26)</td>
<td>31 (25)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>2-3</td>
<td>41 (25)</td>
<td>5 (26)</td>
<td>9 (7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>15 (9)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

| Barthel Index: n (%)          |                |                               |                 |                           |
| >95                           | 125            | 10 (53)                       | 96 (78)         | 19 (83)                   |
| 86-95                         | (76)           | 3 (16)                        | 13 (11)         | 3 (13)                    |
| ≤85                           | 19 (11)        | 6 (31)                        | 14 (11)         | 1 (4)                     |
|                               | 21 (13)        |                               |                 |                           |
References


