Serum thyroglobulin in hospitalized chronic geriatric patients: its relationship to age, non-thyroidal illness, goitre and thyroid dysfunction in a follow-up study

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The objectives were to determine whether the serum thyroglobulin (TG) level is influenced by age or by non-thyroidal illness (NTI) of the aged, to investigate the constancy of the TG level after 1- and 2-month intervals and to investigate if the TG level could help to differentiate whether a subnormal thyrotrophin (TSH) level in a geriatric patient is caused by autonomous thyroid function, by age or by NTI. Two-hundred and twenty-six non-selected, chronic hospitalized patients over 60 years old and 82 healthy adults (20–40 years) participated in the study, and TSH, thyroxine, free thyroxine, triiodothyronine and TG were estimated. In 122 euthyroid geriatric patients with normal TSH the mean TG was normal (12.18 μg/l), but elevated (> 45 μg/l) TG values occurred more often than in healthy control persons (15/122 vs 3/82; χ² = 4.54, p = 0.03). The severity of the clinical state of the euthyroid patients had no influence on the TG values. If TG was measured after 1 and/or 2 months, in only 3/123 non-selected geriatric patients was there a fluctuation between the normal and abnormal range (versus fluctuation of the corresponding TSH values in 19/123 cases; χ² = 12.78, p = 0.0012). In 28 patients with subnormal TSH, a normal TG value had a predictive value of 0.6 to exclude autonomous thyroid function. Age and NTI of the geriatric patients have no significant influence on their mean TG level but high TG levels occur more often, even in euthyroid patients. The predictive value of TG is not sufficiently high to allow a clear differentiation of whether a subnormal TSH is caused by autonomous thyroid function or by the age process or by NTI. Nevertheless, the advantage of TG estimation to be more constant than TSH could be of benefit in screening studies.

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Serum thyroglobulin (TG), mostly used in the follow-up of patients who had undergone thyroidectomy because of differentiated thyroid cancer (1), was found to be elevated also in autonomous thyroid hyperfunction caused by iodine deficiency or Graves’ disease and goitre (2–9).

Serum thyrotrophin (TSH) is diminished in about one-third of chronic geriatric patients (10), due to autonomous thyroid function and hyperthyroidism, to non-thyroidal illnesses (NTI), to the aging process itself (11–13) or to glucocorticoid and dopamine treatment (14, 15). A suppressed TSH measured by a sensitive method is more probably due to thyroid hyperfunction than to NTI (16), but cases with subnormal TSH are a diagnostic problem because the exclusion of thyroid autonomy-caused diminution of the TSH is only possible by the suppressive technetium uptake test (17). In geriatric patients, however, this test usually cannot be performed because the suppression of TSH with thyroxine for 3 weeks or more may be dangerous for the cardiovascular system of the patients. We investigated TG in the hope that TG could be the new tool in the differentiation of NTI- and autonomy-caused diminutions of TSH.

A follow-up screening study of hospitalized chronic geriatric patients was performed to see whether TG is influenced by NTI of the aged or by the age process itself and thereby to investigate if TG could be helpful in the laboratory diagnostic differentiation of autonomous thyroid function from NTI in elderly patients.

Patients and methods

Two-hundred and twenty-six hospitalized chronic geriatric patients, all over 60 years of age (90 males and 136 females) living in an iodine-deficient area, were screened for thyroid dysfunction. The patients had no known thyroid disease and did not receive any drugs having an effect on the TSH and thyroid hormone levels (i.e. steroids, dopamine, thyrostatic treatment) Serum TSH (sensitive two-site immunoradiometric assay), thyroxine (T4), free T4 (FT4) and triiodothyronine
Table 1. Serum thyroglobulin (TG) values and their connection to thyroid function and to the presence of goitre in chronic hospitalized geriatric patients.

<table>
<thead>
<tr>
<th></th>
<th>Mean TG values without log transformation (µg/l)</th>
<th>TG log Mean ± sd (values after log transformation) (µg/l)</th>
<th>Occurrence of elevated (&gt; 45 µg/l) TG values</th>
<th>Occurrence of TG-ab positivity (&gt; 1 x 10^8 mU/l)</th>
<th>Occurrence of TPO-ab positivity (&gt; 1 x 10^8 mU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20–40-Year-old healthy controls</td>
<td>82</td>
<td>12.55</td>
<td>2.53 ± 0.90</td>
<td>3 (3.7%)</td>
<td>5 (6.1%)</td>
</tr>
<tr>
<td>Euthyroid geriatric patients, no goitre</td>
<td>122</td>
<td>12.18</td>
<td>2.50 ± 0.16</td>
<td>15 (12.6%)</td>
<td>11 (9%)</td>
</tr>
<tr>
<td>Geriatric patients with subnormal TSH, no goitre</td>
<td>45</td>
<td>14.43</td>
<td>2.67 ± 1.15</td>
<td>9 (20%)</td>
<td>3 (6.7%)</td>
</tr>
<tr>
<td>Geriatric patients with normal or subnormal TSH and with goitre</td>
<td>27</td>
<td>25.79</td>
<td>3.25 ± 1.62</td>
<td>10 (37%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Geriatric patients with hypothyroidism (except one all subclinical)</td>
<td>12</td>
<td>11.47</td>
<td>2.44 ± 1.57</td>
<td>2 (16.7%)</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>Geriatric patients with clinical hyperthyroidism</td>
<td>9</td>
<td>89.12</td>
<td>4.49 ± 1.81</td>
<td>6 (66.7%)</td>
<td>1 (11.1%)</td>
</tr>
<tr>
<td>Geriatric patients with subclinical hyperthyroidism</td>
<td>11</td>
<td>26.84</td>
<td>3.29 ± 1.10</td>
<td>5 (45.4%)</td>
<td>2 (18.1%)</td>
</tr>
</tbody>
</table>

\[
\chi^2 = 4.54, \ p = 0.03.
\]

Occurrence higher than in the controls: \( \chi^2 = 4.54, \ p = 0.03 \).

Occurrence higher than in euthyroid patients without goitre: \( t = 3.01, \ p < 0.001 \).

Occurrence higher than in euthyroid patients without goitre: \( \chi^2 = 6.79, \ p < 0.001 \).

Occurrence higher than in euthyroid patients without goitre: \( t = 5.13, \ p < 0.001 \).

Occurrence higher than in euthyroid patients without goitre: \( \chi^2 = 18.4, \ p < 0.001 \).

Occurrence higher than in euthyroid patients without goitre: \( t = 2.36, \ p < 0.02 \).

Occurrence higher than in euthyroid patients without goitre: \( \chi^2 = 8.68, \ p = 0.003 \).

(T₃) were measured by Corning-magic assays (Medfield, MA, USA; normal ranges: TSH = 0.5-4.0 mU/l, T₄ = 55-155 nmol/l, FT₄ = 13-27 pmol/l, T₃ = 1.3-2.9 nmol/l; interassay CV = 3.5%, 7.3%, 3.4%, 5.9%, respectively). The TSH receptor antibody was measured only in cases of clinical or subclinical hyperthyroidism (TRAK radioreceptor assay; Henning, Berlin, Germany; normal range below 9 U/l; interassay CV = 8.9%).

Thyroglobulin was measured by the DYNOnet TG two-site immunoanalytisc assay (Henning, Berlin, Germany; interassay CV = 3.5%). The sera were tested for TG antibodies in the TG assay by the recovery test, adding 100 ng of TG (normal range 50-120%). Initially we investigated 234 patients, but eight sera with abnormal recovery tests were excluded from the study (three patients had clinical or subclinical hypothyroidism and one was hyperthyroid). The presence of TG and thyroid peroxidase (TPO) antibodies (TG-ab and TPO-ab) also was investigated by the IMMUnetest anti-TG and IMMUnet anti-TPO radioligand assay (Henning, Berlin, Germany; normal range < 1 x 10^9 mU/l; interassay CV = 9.1% and 4.0%). The occurrence of TG-ab and TPO-ab positivity is shown in Table 1. Sera with TG-ab positivity but with a normal TG recovery test were not excluded from the study.

The distribution of the TG values was not Gaussian (skewness = 2.68) but became normal after logarithmic transformation (skewness = 0.08). The transformed data were used for statistical analysis. The normal range, calculated from the logarithmically transformed values of 82 20-40-year-old healthy volunteers living in the same region, was less than 45 µg/l (mean = 12.6 µg/l, median = 11.9 µg/l, 2.4-97.5% interval = 2.1-45 µg/l).

The presence or absence of goitre was investigated by palpation, and ultrasonography was done only in the presence of palpatory estimated goitre.

The geriatric patients were classified as follows:

(i) Euthyroid patients (TSH = 0.5-4.0 mU/l) without palpable goitre (N = 122). (ii) Patients with subnormal but not suppressed TSH (> 0.1 < 0.5 mU/l) without palpable goitre (N = 45). (iii) Patients with palpable goitre and normal or subnormal TSH (N = 27). The mean ultrasonographically determined (18) volume of the goitres was 37.8 ml.

(iv) Patients with clinical (N = 9) or subclinical (N = 11) hyperthyroidism (suppressed TSH, i.e. < 0.1 mU/l, elevated or normal T₄, FT₄ and T₃). Only 2/20 of these patients were positive in the TRAK assay, i.e. were suspected to have Graves' disease.

(v) One patient with clinical and 11 with subclinical hypothyroidism (TSH > 4.0 mU/l, diminished or normal T₄ and FT₄). Eight of 12 patients had anti-TG or
Table 2. Constancy of serum thyroglobulin (TG) compared to the corresponding TSH levels in hospitalized chronic geriatric patients. a

<table>
<thead>
<tr>
<th>Repeated TG and TSH measurements with 1-month interval</th>
<th>TG</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial value</td>
<td>Control value</td>
<td>Initial value</td>
</tr>
<tr>
<td>Normal ( N = 73 )</td>
<td>Normal ( N = 72 ) Elevated ( N = 1 )</td>
<td>Suppressed ( N = 3 )</td>
</tr>
<tr>
<td>Elevated ( N = 24 )</td>
<td>Elevated ( N = 23 ) Normal ( N = 1 )</td>
<td>Subnormal ( N = 17 )</td>
</tr>
<tr>
<td>Repeated TG and TSH measurements with 2-month interval</td>
<td>TG</td>
<td>TSH</td>
</tr>
<tr>
<td>Initial value</td>
<td>Control value</td>
<td>Initial value</td>
</tr>
<tr>
<td>Normal ( N = 20 )</td>
<td>Normal ( N = 19 ) Elevated ( N = 1 )</td>
<td>Suppressed ( N = 2 )</td>
</tr>
<tr>
<td>Elevated ( N = 6 )</td>
<td>Elevated ( N = 6 )</td>
<td>Subnormal ( N = 3 )</td>
</tr>
</tbody>
</table>

a Fluctuation of TG values between normal and abnormal range in 3/123 cases. Fluctuation of the corresponding TSH values in 19/123 cases. The difference is significant: \( \chi^2_{(1)} = 12.78, p = 0.0012 \).

anti-TPO positivity but this does not reflect the real occurrence of ab positivity, because three other patients (one with clinical and two with subclinical hypothyroidism) were excluded from the study owing to a low TG recovery test.

According to their clinical state, the patients were classified into four groups; their biological and psycho-social function was semiquantitated by the Katz Index of Independence in Activities of daily living (ADL) (19): I = relatively good health: not bedridden, mostly independent of nursing, no severe chronic diseases, Katz Index A-B; II = relatively poor health: pronounced chronic diseases making the patient significantly dependent on nursing, but not rendering him completely immobile, Katz Index C-D-E; III = bad health: severe chronic diseases, bedridden patient, Katz Index F; IV = very bad health: severe chronic diseases with acute complications, or acute diseases, bedridden patient completely dependent on nursing, Katz Index G.

Analysis of variance (ANOVA), t-test and the chi-squared test were used for statistical analysis. The diagnostic indices, sensitivity, specificity and predictive value also were calculated.

Results

Euthyroid geriatric patients without goitre \( (N = 122) \) had a normal mean TG value, without gender differences, but we found a slightly increased incidence of high \( (> 45 \mu g/l) \) values compared to the young controls (Table 1). The patients were classified according to their age (60–69 years old = 31; 70–79 years old = 45 and > 80 years old = 46) and clinical condition (Katz ADL. I = 38; II = 41; III = 18; IV = 21—four cases were not classified). Neither the age of the euthyroid patients nor their clinical condition had any influence on the mean TG level or on the occurrence of high values, as analysed by ANOVA and the chi-squared test.

Patients without goitre but subnormal TSH (caused more probably by the age process or by NTI than by thyroid hyperfunction) had normal mean TG values, and the cases with high TG were not significantly more than in the euthyroid group. To the contrary, geriatric patients with goitre or with clinical or subclinical hyperthyroidism showed a higher mean TG and an increased incidence of elevated values as compared to the euthyroid geriatric patients without goitre (Table 1.). A more precise distinction, whether a subnormal TSH was caused by age or NTI or by thyroid hyperfunction, was not done because an isotope scanning under thyroxine suppression could have been dangerous for the geriatric patients.
In 123 non-selected geriatric patients, the TG estimation was repeated after 1 and/or 2 months. The relative constancy of the serum TG level in chronic geriatric patients as compared also to the corresponding TSH values is shown in Table 2. In this group, 28 patients initially had a subnormal but not suppressed TSH: TSH remained subnormal after 1 or 2 months in 7/8 cases with elevated TG level, whereas TG became normal (thus, making thyroid autonomy unlikely) in 12/20 cases with normal TG. This means that in chronic geriatric patients with subnormal TSH, a normal TG had a predictive value of 0.6 to exclude thyroid autonomy.

Discussion

Earlier investigations showed that TG did not differ in healthy old subjects (20). There is a rising incidence of thyroid nodularity with age (21), and in a non-selected elderly population the goitre size correlated with the TG value (22). Neither the TG levels in chronically ill hospitalized geriatric patients nor their connection with age, NTI and thyroid function and their fluctuation over a longer time period have been investigated so far, although especially in this subpopulation of geriatric patients the high occurrence rate but masked clinical appearance of clinical and subclinical thyroid disorders should justify a general screening for thyroid dysfunction (23, 24).

Apart from a slightly elevated occurrence of elevated TG levels in our euthyroid patients with no palpable goitre, which could be explained by clinically non-detectable nodularity of the thyroid, our results show neither an influence of age per se nor of NTI on the serum TG level. This suggests that TG measurements could assist in the differentiation of age and NTI-dependent decreases in serum TSH values from subnormal TSH caused by thyroid hyperfunction. The more pronounced constancy of the TG values as compared to TSH shown in our long-term follow-up study of geriatric patients also could be of benefit in this respect.

At the same time, surprisingly, an elevated TG was seen in about only half of the geriatric patients with subclinical and in two-thirds of patients with clinical hyperthyroidism, although it is the general view among thyroidologists that TG usually is elevated in thyrotoxicosis unless it is iatrogenically or self-induced (5-7). The presence of TG-ab could be an explanation for this observation but TG-ab were detected only in three cases (one with elevated and two with normal TG level) and in all three cases the TG recovery test was normal. (One hyperthyroid patient with a low value in the TG recovery test initially was excluded from the study.) Thyrotropin receptor antibody positivity was found in only 2/20 of the patients, showing that most cases of hyperthyroidism were of non-immune origin. Anyway, TG seemed not to be sensitive enough for detection of thyroid hyperfunction in the hospitalized and chronically ill geriatric population. Neither was its predictive value sufficiently high to allow a clear differentiation of autonomy-dependent subnormalities of the TSH value from diminutions caused by the age process or by NTI. To clarify the cause of a subnormal TSH level in a chronic geriatric patient, the clinical investigation of the patient (searching for goitre) and a follow-up with sensitive TSH estimation alongside with thyroxine measurement is necessary. Yet, the advantage of TG estimation being more constant than TSH estimation could be of benefit in screening studies of chronic hospitalized elderly subject, especially in cases with subnormal TSH levels.

References


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