Age-related alterations of pituitary-thyroid function in normal female subjects and in female patients with simple goitre

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Abstract. Age-related alterations in pituitary-thyroid function were studied in 173 female patients with simple goitre and in 70 normal female subjects. They were divided into 4 groups according to age: A group, less than 19 years; B group, 20 to 29 years; C group, 30 to 39 years; D group, 40 to 59 years. Serum triiodothyronine (T3) concentrations decreased progressively but insignificantly with age in female patients with simple goitre and in normal female subjects, whereas serum thyroxine (T4) concentrations remained constant throughout the studied age range. Only in female patients with simple goitre, did basal serum TSH concentrations show a tendency to increase with age. However, thyrotrophin-releasing hormone (TRH)-stimulated increase of serum TSH was progressively augmented with age both in female patients with simple goitre and in normal female subjects; the magnitude of change was greater in the former group.

As reflected by acute increases of serum T3 and T4 concentrations, thyroid responsiveness to endogenous TSH was progressively depressed with age in female patients with simple goitre and in normal female subjects. This age-related thyroidal refractoriness to TSH was more apparent when the changes were expressed as ΔT3(stimulated T3 - basal T3)/ΔTSH (maximum TSH after TRH - basal TSH), and ΔT4(stimulated T4 - basal T4)/ΔTSH. ΔT4/ΔTSH was lower in female patients with simple goitre than in normal female subjects in all age groups. However, the difference was significant only for ΔT4/ΔTSH in group A. Thyroidal responsiveness to exogenous TSH also gradually declined with age in female patients with simple goitre.

Our data indicate 1) TRH-stimulated TSH secretion increases with age probably to overcome age-related thyroidal refractoriness to TSH and 2) although the thyroid of patients with simple goitre is slightly less responsive to TSH than that of normal subjects for all age groups, the difference was significant only for young patients.

The thyroid is known to change with age (Pittman 1962). Histologically, the follicles frequently become atrophic and the parenchyma is often replaced by fibrous tissue in older subjects (McGavack & Seegers 1959). Functionally, thyroid radioiodine uptake (Oddie et al. 1960; Gaffney et al. 1962; Hansen et al. 1975) and serum triiodothyronine (T3) concentrations (Rubenstein et al. 1973; Bermudez et al. 1975; Hesch et al. 1976; Westgren et al. 1976) progressively decline with age whereas serum thyroxine (T4) concentrations are reported to remain constant (Rubenstein et al. 1973; Hesch et al. 1976; Westgren et al. 1976; Gaffney et al. 1960; Gregerman et al. 1962). Thus, most of the previous data indicate an age-related decrease of thyroid function. However, it is not entirely clear whether this decrease of thyroid function is accompanied by any change in TSH secretion from the pituitary gland (Lemarchand-Béraud & Vannotti 1969; Sawin et al. 1979). The

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age-related decrease in thyrotrophin-releasing hormone (TRH)-stimulated TSH secretion was reported in male but not in female subjects (Snyder & Utiger 1972; Azizi et al. 1975), although the number of subjects studied was limited.

TSH secretion in patients with simple goitre has not been thoroughly investigated either (Dige-Petersen & Hummer 1977). Although regression of the goitre after thyroid hormone therapy is often observed, thorough evaluation of pituitary-thyroid function in a large series of patients with simple goitre is lacking.

In the present study, we systematically re-evaluated pituitary-thyroid function in a large series of patients with simple goitre and normal subjects and found an unequivocal decline in thyroidal responsiveness to TSH in both groups.

Materials and Methods

One hundred and seventy-three female patients with simple goitre and 70 normal female subjects were investigated. The normal subjects were recruited from hospital staff, laboratory personnel, and volunteers, all in good health and with no personal or family history of thyroid disease. They had no thyroid enlargement on clinical examination and no thyroidal autoantibodies. Euthyroidism was confirmed by clinical and laboratory data such as normal serum T3, T4 and TSH concentrations before and after TRH administration. The diagnosis of simple goitre was made by the presence of a small, soft and diffuse goitre not associated with hypo- or hyperthyroidism and not due to inflammatory or neoplastic process. Patients with positive thyroidal autoantibodies (thyroglobulin or microsomal) were excluded. The subjects were divided into 4 groups according to their ages: A group, less than 19 years; B group, 20 to 29 years; C group, 30 to 39 years; D group, 40 to 59 years of age, respectively. For evaluation of the pituitary-thyroid function, serum concentrations of T3, T4 and TSH were measured before and 30, 60, 90 and 120 min after the administration of 500 µg TRH im. Serum T3 and T4 were also measured before and 2 h after injection of 10 U bovine TSH (Thytopar, Armour) in the patients with simple goitre. Serum hormone concentrations were determined by commercially available RIA kits for each hormone. Thyroidal autoantibodies (thyroglobulin or microsomal) were also checked by commercially available kits. The normal values for basal hormone concentration were 1.38–2.76 nmol/l for T3, 64.37–141.63 nmol/l for T4 and 0 to 10 mU/l for TSH.

The data are presented as mean ± se and analyzed by analysis of variance, or Student's t-test as indicated.

Results

Age-related changes in pituitary-thyroid function in patients with simple goitre

In 140 female patients with simple goitre, basal serum T3 concentrations decreased slightly but not significantly with age (Table 1). After administration of TRH, serum T3 concentrations increased significantly in response to an increase of TSH in all groups. However, the magnitude of increase [ΔT3(serum T3 120 min after TRH - basal T3)] was progressively less with the increasing of age. The basal T4 concentration was not significantly different between the groups. A slight but significant increase of serum T4 was found 120 min after administration of TRH. The magnitude of increase [ΔT4(serum T4 120 min after TRH - basal T4)] was least in D group (B vs D, P < 0.005). The basal concentration of TSH tended to increase with age but the difference was not statistically significant. After TRH administration, a significant increase of serum TSH was found in all groups. The increase [ΔTSH(serum maximum TSH after TRH - basal TSH)] was greater in old than in young patients, however.

To compare the relative responsiveness of the thyroid to TSH between each group, T3/T4 ratio, ΔT3/ΔTSH and ΔT4/ΔTSH were calculated. The basal T3/T4 ratio was the same in all the groups. The ratio increased significantly after TRH in all groups, but no significant difference was found between the groups (Table 2). ΔT3/ΔTSH and ΔT4/ΔTSH progressively decreased with increasing age.

Age-related changes in the pituitary-thyroid function in normal subjects

In 70 normal female subjects, age-related changes essentially similar to those in female patients with simple goitre were obtained: progressive but insignificant decreases in basal T3 with advancing age and greater TSH but a smaller T3 and T4 rise after TRH in old than in young subjects (Table 1). The T3/T4 ratio increased significantly after TRH in all groups. ΔT3/ΔTSH and ΔT4/ΔTSH also progressively decreased with age (Table 2).

However, the following points of difference between patients with simple goitre and normal subjects were noted. 1) TRH-stimulated TSH rise was greater in patients with simple goitre than in normal subjects for all age groups and the difference was statistically significant in groups C and D,
Table 1.

Effect of TRH administration on serum T3, T4 and TSH in female patients with simple goitre and in normal female subjects.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>No. of subjects</th>
<th>Serum T3 nmol/l</th>
<th>ΔT3</th>
<th>Serum T4 nmol/l</th>
<th>ΔT4</th>
<th>TSH mIU/l</th>
<th>ΔTSH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before</td>
<td>120 min after</td>
<td></td>
<td>Before</td>
<td>120 min after</td>
<td></td>
</tr>
<tr>
<td>Female patients with simple goitre</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>15 ± 1</td>
<td>15</td>
<td>1.90 ± 0.06</td>
<td>2.54 ± 0.09a</td>
<td>0.65 ± 0.08</td>
<td>113.3 ± 5.1</td>
<td>124.8 ± 5.1a</td>
<td>11.6 ± 1.3</td>
</tr>
<tr>
<td>B</td>
<td>26 ± 0.4</td>
<td>35</td>
<td>1.89 ± 0.05</td>
<td>2.48 ± 0.08a</td>
<td>0.60 ± 0.06</td>
<td>109.4 ± 3.9</td>
<td>122.3 ± 3.9a</td>
<td>12.9 ± 1.3</td>
</tr>
<tr>
<td>C</td>
<td>36 ± 0.4</td>
<td>49</td>
<td>1.86 ± 0.03</td>
<td>2.40 ± 0.06a</td>
<td>0.54 ± 0.05</td>
<td>109.4 ± 3.9</td>
<td>122.3 ± 3.9a</td>
<td>12.9 ± 1.3</td>
</tr>
<tr>
<td>D</td>
<td>50 ± 0.8</td>
<td>41</td>
<td>1.85 ± 0.05</td>
<td>2.31 ± 0.06a</td>
<td>0.46 ± 0.03c</td>
<td>112.0 ± 3.9</td>
<td>121.0 ± 3.9a</td>
<td>9.0 ± 1.3</td>
</tr>
<tr>
<td>Normal female subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>15 ± 1</td>
<td>7</td>
<td>2.22 ± 0.11</td>
<td>2.99 ± 0.12a</td>
<td>0.75 ± 0.11</td>
<td>109.4 ± 5.1</td>
<td>145.4 ± 7.7a</td>
<td>28.3 ± 9.0</td>
</tr>
<tr>
<td>B</td>
<td>25 ± 1</td>
<td>12</td>
<td>1.96 ± 0.08</td>
<td>2.60 ± 0.11a</td>
<td>0.60 ± 0.08</td>
<td>112.0 ± 5.1</td>
<td>127.4 ± 6.4a</td>
<td>15.4 ± 1.3</td>
</tr>
<tr>
<td>C</td>
<td>35 ± 0.6</td>
<td>12</td>
<td>1.96 ± 0.03</td>
<td>2.43 ± 0.09a</td>
<td>0.46 ± 0.08b</td>
<td>106.8 ± 5.1</td>
<td>122.3 ± 5.1a</td>
<td>15.4 ± 2.6</td>
</tr>
<tr>
<td>D</td>
<td>50 ± 1</td>
<td>39</td>
<td>1.85 ± 0.05b</td>
<td>2.25 ± 0.06a</td>
<td>0.40 ± 0.05e</td>
<td>109.4 ± 2.6</td>
<td>118.4 ± 3.9a</td>
<td>9.0 ± 1.3f</td>
</tr>
</tbody>
</table>

*Mean ± se. Before: before administration of TRH. 120 min after: 120 min after administration of TRH.
Serum T3, T4, TSH: a: P < 0.001 as compared to before TRH.
Serum T3, T4, TSH: b: P < 0.05. c: P < 0.02, d: P < 0.01. e: P < 0.005. f: P < 0.001 as compared to A of simple goitre or normal subjects.
2) \( \Delta T_4/\Delta TSH \) was invariably smaller in patients with simple goitre. However, a statistically significant difference was obtained only in group A (Table 2).

### Table 2.

Age-related loss of responsiveness of the thyroid to an increase of TSH in response to TRH.

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>( T_3/T_4 ) (nmol/nmol \times 100) Before</th>
<th>120 min after</th>
<th>( \Delta T_3/\Delta TSH ) (nmol/l)</th>
<th>( \Delta T_4/\Delta TSH ) (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female patients with simple goitre</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>15</td>
<td>1.72 ± 0.091(^1)</td>
<td>2.08 ± 0.11***</td>
<td>0.0494 ± 0.0081</td>
<td>0.849 ± 0.129</td>
</tr>
<tr>
<td>B</td>
<td>35</td>
<td>1.76 ± 0.05</td>
<td>2.07 ± 0.07***</td>
<td>0.0488 ± 0.0463</td>
<td>1.017 ± 0.129</td>
</tr>
<tr>
<td>C</td>
<td>49</td>
<td>1.76 ± 0.06</td>
<td>2.01 ± 0.07***</td>
<td>0.0275 ± 0.0027b</td>
<td>0.811 ± 0.129</td>
</tr>
<tr>
<td>D</td>
<td>41</td>
<td>1.68 ± 0.05</td>
<td>1.96 ± 0.05***</td>
<td>0.0229 ± 0.0022b</td>
<td>0.463 ± 0.013b</td>
</tr>
<tr>
<td>Normal female subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>7</td>
<td>1.90 ± 0.18</td>
<td>2.06 ± 0.07**</td>
<td>0.0506 ± 0.0089</td>
<td>1.892 ± 0.644d</td>
</tr>
<tr>
<td>B</td>
<td>12</td>
<td>1.80 ± 0.10</td>
<td>2.09 ± 0.14**</td>
<td>0.0451 ± 0.0064</td>
<td>1.248 ± 0.257</td>
</tr>
<tr>
<td>C</td>
<td>12</td>
<td>1.87 ± 0.09</td>
<td>2.02 ± 0.11**</td>
<td>0.0294 ± 0.0046a</td>
<td>1.145 ± 0.219</td>
</tr>
<tr>
<td>D</td>
<td>39</td>
<td>1.74 ± 0.05</td>
<td>1.94 ± 0.05***</td>
<td>0.0222 ± 0.0024c</td>
<td>0.618 ± 0.013c</td>
</tr>
</tbody>
</table>

\(^1\) Mean ± SE.

Statistical analysis: a: \( P < 0.05 \), b: \( P < 0.005 \), c: \( P < 0.001 \) as compared to A of simple goitre or normal. d: \( P < 0.05 \) as compared to \( A \) of simple goitre.

* \( P < 0.05 \), ** \( P < 0.005 \), *** \( P < 0.001 \) as compared to before.

Age-related refractoriness of the thyroid to exogenous TSH in patients with simple goitre

Thirty-three patients with simple goitre were divided into 3 groups depending on age (none was less than 20 years). Administration of 10 U bovine TSH produced unequivocal increases in serum \( T_3 \) and \( T_4 \) in all age groups. However, the magnitude of increase (\( \Delta T_3 \), \( \Delta T_4 \)) was progressively depressed with age (Table 3).

**Discussion**

One plausible cause for an age-related decrease of thyroid function (Pittman 1962) would be age-related decrease of pituitary secretion of TSH as reported in male subjects (Snyder & Utiger 1972; Azizi et al. 1975). If this is the case in female subjects, age-related thyroid hypofunction may be more apparent in female patients with simple goitre since some participatory role of TSH in the maintenance of goitre is indicated by the regression of goitre that sometimes follows the administration of suppressive doses of thyroid hormone (Greer & Astwood 1953). Thus, our first attempt was to compare serum \( T_3 \), \( T_4 \) and TSH and \( T_3/T_4 \) ratios under basal conditions throughout a wide age range in normal female subjects and female patients with simple goitre. The well-documented age-related decrease of serum \( T_3 \) was found in normal female subjects and in female patients with simple goitre. However, \( T_3/T_4 \) ratios and serum \( T_4 \) levels were not different between the two groups throughout the studied age range. As compared to normal female subjects, basal TSH increased slightly but progressively with age in female patients with simple goitre, but these changes were too small to interpret. Thus, we failed to find a significant age-related decrease of pituitary TSH secretion and resultant thyroid hypofunction in normal female subjects and female patients with simple goitre under basal conditions.

Our second attempt was to stimulate the thyroid to enhance a possible age-related decrease of thyroid function. After administration of TRH, we found an age-related decrease of thyroid function in two respects. First, the increase of serum TSH in
response to TRH increased progressively with age in normal female subjects. This age-related increase of TSH suggested age-related primary failure of the thyroid. By using a small dose of TRH (100 µg) and a limited number of older subjects (female and male), Ohara et al. (1974) reported that pituitary response to TRH was greater in older subjects than in young controls. Our finding is in contrast with that of Azizi et al. (1975) who failed to find a difference in TSH response after TRH between young and old normal female subjects. The reason for their failure to find such a difference might be the limited number of subjects studied or the large dose of TRH (2 mg) used. We also found an age-related increase of TSH in response to TRH in female patients with simple goitre. Interestingly, the TSH increase was larger in female patients with simple goitre than in normal female subjects for all age groups studied. This suggested an important participatory role of TSH in the maintenance of goitre in female patients with simple goitre. Second, thyroidal responsiveness to TSH decreased progressively with age in normal female subjects as evidenced by age-related decrease of ΔT₃, ΔT₄, ΔT₃/ΔTSH and ΔT₄/ΔTSH. A similar age-related fall was also found in ΔT₃, ΔT₄, ΔT₃/ΔTSH and ΔT₄/ΔTSH after administration of TRH in female patients with simple goitre. In contrast, Faber et al. (1976) failed to find an age-related thyroidal loss of responsiveness to TSH. However, exact comparison with our data is not possible because they used relatively old subjects (80–89 years) of both sexes when compared with our study (female 40 to 59 years). At any rate, we found that ΔT₄/ΔTSH was less in female patients with simple goitre than in normal female subjects throughout the studied age range. This suggested that thyroidal refractoriness to TSH was more pronounced in female patients with simple goitre than in normal female subjects, and that this refractoriness is somewhat related to the development of simple goitre. A similar age-related thyroidal refractoriness to TSH was also found in the mouse (Studer et al. 1978; Eleftheriou 1975).

Since the proportion of the large molecular weight form of immunoreactive TSH, which is probably biologically less active, is reported to increase with age in experimental animal (Klug & Adelman 1977), our final attempt was to exclude the possibility that age-related thyroidal refractoriness to TSH was due to an age-related decrease in biological activity of TSH. As was the case with
endogenous TSH, exogenous TSH was less effective in stimulating the thyroid in older patients with simple goitre. Thus, it can be concluded that thyroidal refractoriness to TSH in aged female patients with simple goitre was due to primary thyroid failure. It is not known whether thyroidal failure is produced by an age-related histological abnormality such as follicular atrophy and parenchymal fibrosis (McGavack & Seegers 1959) or by an age-related functional abnormality such as thyroglobulin or endocytosis (Studer et al. 1978).

Since we studied pituitary-thyroid interplay in female but not in male, and since pituitary-thyroid interplay may differ between the sexes (Azizi et al. 1975; Christianson et al. 1981), further studies are required to assess a possible age-related decrease of thyroid function in the male.

References


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