Thyroid Function of the Aged
as Viewed from the Pituitary-Thyroid System

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Synopsis

Functional changes of the pituitary thyroid system in healthy aged subjects ranging from 60 to 94 year olds were compared with those of healthy adults from 25 to 35 year olds.

As a result, significant decreases in triiodothyronine resin sponge uptake rate and free thyroxine index (FT4I) were observed in the aged group, while no significant change in the thyroxine levels was indicated. TSH levels in serum tended to be elevated in the aged, although no negative correlation between TSH levels and FT4I was seen. A significant difference in TSH responses between 100 µg and 300 µg doses of TRF was observed in the adult control, on the other hand, no difference was seen in the aged group. A comparison of TSH responses to relatively small doses of TRF (100 µg) was made between the adult control and the aged, and a significantly higher responsiveness was observed in the aged group. It is postulated that a higher TSH response to relatively smaller doses of TRF is characteristic in the aged probably due to a reflection of a latent hypothyroid state.

Materials and Methods

Subjects: Fifty three aged subjects ranging from 60 to 94 year olds (20 males and 33 females) showing no apparent abnormality in clinical and laboratory findings were chosen for the investigation of parallel determinations of triiodothyronine resin sponge uptake rates, serum thyroxine levels, free thyroxine indices, and TSH levels in serum. Twenty one cases of 25-35 year olds healthy male adults were selected as the control.

Among the aged subjects, 5 cases of 60-69 year olds, 8 of 70-79 year olds, 16 of 80-89 year olds, and 3 of 90-94 year olds were selected at random for the investigation of TSH response to the administration of synthetic TRF, and 16 healthy adults from the 25-35 year-old group were selected as the control.

Triiodothyronine resin sponge uptake rate (T3RSU) and thyroxine (T4) level were measured by Mallincrodt T3 and T4 kit respectively. Free thyroxine index (FT4I) was calculated by means of T3RSU and T4 concentrations.

Serum TSH level was determined by a modification of double-antibody technique according to Odell’s method (Odell et al., 1967).

Synthetic TRF (Tokyo Tanabe Pharm. Co.) was injected intravenously in the morning under fasting, and blood samples were collected before and after the injection at intervals of 15, 30, and 60 minutes.
Results

1. Thyroid function and TSH level in the aged.

Results obtained in parallel determinations of T₃RSU, T₄ levels, FT₄I, and TSH levels in the aged and adult control were summarized in Table 1.

The mean value of T₃RSU in the control was 32.55 ± 2.56%, while those in the aged groups of 60-69, 70-79, 80-89, and 90-94 year olds were significantly lower than the control.

The mean value of serum T₄ levels in the control was 9.86 ± 2.04 µg/dl. No significant difference was observed between adult control and the respective age groups.

The mean value of FT₄I in the control showed 10.54 ± 1.92. Cases which showed FT₄I less than lower limit of the control were 8 out of 53 cases in the aged group, and significant decreases of FT₄I were seen in the 60-69, and 90-94 year groups as compared with the control value.

The lower limit of TSH determination in the present study was 1.25 µU/ml as shown in Table 1, and the control levels ranged from 1.25 to 5.2 µU/ml including 3 nondetectable cases. The mean value was calculated as 3.11 ± 1.98 µU/ml (mean ± 2SD) when the value of the nondetectable cases was tentatively assumed to be 1.25 µU/ml.

Cases which showed a high TSH levels above the upper limit of the control were 13 out of 53 in the four aged groups as described in parentheses in Table 1.

The correlation between the TSH levels and the corresponding FT₄I of the same individuals was investigated in the above mentioned 13 cases with abnormally high TSH level, however, no significant correlation (r = −0.25) was seen. Correlation between low FT₄I levels and corresponding TSH levels was then investigated in 8 cases with abnormally low FT₄I, and likewise no significant correlation (r = −0.35) was observed between the two.

2. TRF stimulation test.

a) TSH responses to 100 µg and 300 µg doses of TRF in adult controls: Eight cases of adult controls (4 males and 4 females) were chosen, and a relatively small dose (100 µg) and a relatively large dose (300 µg) of TRF

<table>
<thead>
<tr>
<th>Age (y.o.)</th>
<th>Sex</th>
<th>Cases</th>
<th>T₃RSU (%)</th>
<th>T₄ (µg/dl)</th>
<th>Free T₄ Index</th>
<th>TSH (µU/ml)</th>
<th>Abnormal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-35</td>
<td>M</td>
<td>21</td>
<td>32.55 ± 2.56</td>
<td>9.86 ± 2.04</td>
<td>10.54 ± 1.92</td>
<td>1.25–5.2</td>
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</tr>
<tr>
<td>60-69</td>
<td>M</td>
<td>9</td>
<td>29.40 ± 3.45</td>
<td>9.69 ± 1.97</td>
<td>9.59 ± 2.12</td>
<td>1.25–5.7</td>
<td>(2)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>4</td>
<td>27.30 ± 3.62</td>
<td>7.75 ± 2.59</td>
<td>7.27 ± 2.30</td>
<td>1.4–19.0</td>
<td>(1)</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>9</td>
<td>28.75 ± 3.65***</td>
<td>9.09 ± 2.27 N.S.</td>
<td>8.87 ± 2.36*</td>
<td>1.25–19.0</td>
<td>(3)</td>
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<tr>
<td>70–79</td>
<td>M</td>
<td>7</td>
<td>30.17 ± 4.47</td>
<td>9.28 ± 2.14</td>
<td>9.45 ± 2.55</td>
<td>3.0–6.8</td>
<td>(1)</td>
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<tr>
<td></td>
<td>F</td>
<td>11</td>
<td>29.30 ± 5.37</td>
<td>8.44 ± 2.78</td>
<td>8.25 ± 2.26</td>
<td>1.7–17.0</td>
<td>(4)</td>
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<tr>
<td>Total</td>
<td>18</td>
<td>18</td>
<td>28.62 ± 4.91*</td>
<td>8.77 ± 2.52 N.S.</td>
<td>8.71 ± 2.38*</td>
<td>1.7–17.0</td>
<td>(5)</td>
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<tr>
<td>80–89</td>
<td>M</td>
<td>4</td>
<td>30.78 ± 3.68</td>
<td>10.25 ± 4.01</td>
<td>10.14 ± 3.40</td>
<td>2.6–26.0</td>
<td>(1)</td>
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<td></td>
<td>F</td>
<td>15</td>
<td>29.09 ± 3.31</td>
<td>9.83 ± 2.77</td>
<td>9.71 ± 2.92</td>
<td>1.8–14.0</td>
<td>(4)</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>19</td>
<td>29.45 ± 3.47***</td>
<td>9.92 ± 3.10 N.S.</td>
<td>9.80 ± 3.04 N.S.</td>
<td>1.8–26.0</td>
<td>(5)</td>
</tr>
<tr>
<td>90–94</td>
<td>F</td>
<td>3</td>
<td>28.23 ± 1.89**</td>
<td>7.77 ± 0.91 N.S.</td>
<td>7.46 ± 1.24**</td>
<td>2.8–4.4~</td>
<td></td>
</tr>
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</table>

N.S. not significant

*** p < 0.01 compared with adults between 25 and 35 years old.

** p < 0.02

* p < 0.05

# Number of cases more than mean value + 2S.D.
TRF 100 μg i.v. inj.  TRF 300 μg i.v. inj.

Fig. 1. Comparison of TSH responses to 100 μg and 300 μg doses of TRF in healthy adults.
* Significant difference from 30 min value in 100 μg doses of TRF injection.

TRH 100 μg i.v. inj.

Fig. 2. Correlation between maximum TSH increments and body weights following 100 μg doses of TRF injection.
were injected intravenously into the same subjects at more than 2 week intervals between successive injections of TRF. The maximum peak in TSH values was seen at 30 minutes after TRF injection in both TRF doses, and a significantly higher TSH response in the 300 μg TRF injected group, as compared to the 100 μg of TRF injected group, was seen at 30 min as shown in Figure 1. No significant sex-related difference was observed in TSH responses to these TRF tests.

b) Correlation between maximum TSH increments and body weight: Forty two cases in total (21 cases from the aged subjects and from the adult controls respectively) were chosen at random in order to investigate a possible correlation between maximum TSH increase and body weight. The body weights of these subjects were ranged widely from 30.5 to 75 kg. The maximum increases of TSH level after intravenous injection of 100 μg TRF were plotted against the corresponding body weight. As shown in Figure 2, no significant correlation (r = -0.20) was observed.

3. TSH response to 100 μg dose of TRF administration.

   a) Healthy adult control (Fig. 3): The mean values in 16 adult male controls at pre-injection, and 15, 30 and 60 min after the TRF injection were indicated in the figure. The maximum peak of the value was seen at 30 min after TRF administration in 12 out of 16 cases, while none of the cases showed a peak at 60 min. The mean value of 60 min was lower than that of 15 min values.

   b) 60–69 age group (Fig. 4): Five cases (3 males and 2 females) of this age group were subjected to the experiment. Significantly higher differences from the adult control were seen in 15, 30 and 60 min values.

   c) 70–79 age group (Fig. 5): Two out of 8 cases indicated abnormally high TSH levels prior to injection, and abnormally high TSH levels were also seen in 5 cases at 15 min, 4 at 30 min, and 5 at 60 min after each TRF administration. No significant difference from the adult controls, however, was seen in this age group due to the wide deviation.

   d) 80–89 age group (Fig. 6): Sixteen cases (2 males and 14 females) were subjected to the study, and the maximum mean value was observed at 60 min after the injection. Significant differences from the control were seen in pre-injection values and 30 and 60 min values.

   e) 90–94 age group (Fig. 7): Two out of 3 cases indicated abnormally high TSH levels at 15, 30 and 60 min after the injection.

4. Comparison of TSH responses to 100 μg and 300 μg doses of TRF in the aged.

TSH responses to 100 μg and 300 μg of TRF were compared with each other in six cases of the aged (3 males and 3 females). As shown in Figure 8, the maximum response values were seen at 30 min value in both TRF administration doses as well as the adult control, however, high responsivenesses were still retained
Fig. 4. TSH response to TRF (100 μg) in 60–69 year-old aged group. The shadowed area indicates range of adult control (mean ± 2 SD).

* and ** indicate significant differences (p < 0.05 and p < 0.01) from adult control.

at 60 min in contrast to the adult control. It was noteworthy that no significant difference in TSH responses between 100 μg and 300 μg of TRF was observed in the aged group. In a comparison run on the TSH responses between the aged and the control, significantly higher responses in the aged were seen at 30 min and 60 min after the injection of 100 μg of TRF, while no significant differences were seen at 30 and 60 min after injection of 300 μg of TRF administration. It might be said that higher TSH responsiveness to relatively small doses of TRF is characteristic in the aged with regard to sex difference.
Discussion

Regarding the thyroid function in the aged subjects, a latent hypofunctional state was suggested in a few reports (Stoffer et al., 1961; Gaffney et al., 1962; Gregerman et al., 1962), and an increasing tendency of TSH levels in serum was also reported (Lemarchand-Béraud and Vannotti, 1969).

In the present study, decreases in both T₃RSU and FT₄I, and a tendency of increase of TSH level were observed in the aged group coinciding with those described in the literatures, although results opposite in part have been published (Braverman et al., 1966). As to a cause of latent hypofunction of the thyroid, there may be a possibility of occurrence of subclinical autoimmune thyroiditis in the aged, although their autoimmune-antibodies were
In our study, 25-35 year old healthy males were selected as the control, since no significant sex-related differences in healthy adults were reported in thyroid hormone levels except T₃RSU (Braverman et al., 1967) and in TSH response to TRF (Snyder and Utiger, 1972b).

As to an increasing tendency of TSH levels in serum, no significant negative correlation was observed between FT₄I and TSH levels in the aged, contrary to the results of the distinct negative correlation in the hyperthyroid and hypothyroid states as reported in the previous paper (Ohara et al., 1972). Thus, it was suggested that the thyroid function in senescence might not be too far decreases as in cases with

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**Fig. 6.** TSH response to TRF (100 μg) in 80-89 year-old aged group. The shadowed area indicates range of adult control (mean ± 2 SD).

M: male  F: female
* and ** indicate significant differences (p < 0.05 and p < 0.01) from adult control.
significant increases of TSH due to the diminution of the negative feedback mechanism.

TSH response to relatively small doses of TRF (100 μg) was then investigated in order to clarify whether higher responsiveness would be expected in the aged or not, and the results showing higher responsiveness in the aged were obtained as compared with those in adult control.

Snyder and Utiger reported a significant decrease of TRF-TSH response in parallel with aging in male (Snyder and Uniger, 1972a), and not in female (Snyder and Utiger, 1972b), by administration of maximum stimulating doses of TRF (400 μg), and Sakoda et al. (1972), on the other hand, found that no significant dif-
Comparison of TSH responses to 100 µg and 300 µg doses of TRF in the aged.

* Significant differences from respective TSH responses to 100 µg and 300 µg doses of TRF in adult control.

Values in the aged between 100 µg and 300 µg doses of TRF were not significant.

Accordingly, the largest causative factor of the difference between the result obtained by Snyder and by ours is surmised to be the differences of doses of TRF administered. In fact, Snyder et al. did not examined TSH responsiveness to a relatively small dose of TRF. In our study, however, no difference of responsiveness of TSH to TRF doses between 100 µg and 300 µg was observed in the aged group, contrary to the significant difference of TRF dose response in the adult control.

These findings suggest that the elevated responsiveness of TSH to relatively small doses of TRF in the aged may be probably due to a reflection of latent hypothyroid condition. Various workers have reported a progressive slowing of peripheral turnover of T₄ in senescence suggesting a progressive change in the binding of T₄ in extracellular fluid (Gregerman et al., 1962), diminution of the amounts of metabolically active tissue (Gaffney et al., 1962), or changes in the cellular uptake or
metabolism of the hormone per se (Braverman et al., 1966). These suggestions also seem to support our findings obtained here.

References


