NOTE

Serum Thyroglobulin (Tg) Concentration in Healthy Subjects: Absence of Age- and Sex-related Differences

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Abstract

Serum concentrations of thyroglobulin in healthy subjects were measured by a solid-phase immunoradiometric assay. The mean concentration of serum thyroglobulin in 53 healthy males was 5.0 ng/ml (1.0-25.9 ng/ml) and that of 57 healthy females was 5.2 ng/ml (1.0-27.7 ng/ml). Neither sex-related nor age-related change in the serum thyroglobulin level was observed.

Thyroglobulin (Tg) is known to circulate in the serum of virtually all subjects. Several previous studies (Van Herle et al., 1973; Izumi and Larsen, 1978; Gardner et al., 1979; Pacini et al., 1980) have demonstrated varying degrees of elevated levels of serum Tg in thyroid diseases such as Graves' disease and subacute thyroiditis. In patients with thyroid carcinoma, Tg is a useful marker for their follow-up (Van Herle and Uller, 1975; Pacini et al., 1980), since the levels of serum Tg after thyroidectomy are low or undetectable in patients with complete remission, whereas elevated serum Tg indicates metastasis and/or recurrence of carcinoma.

In spite of many recent reports concerning the clinical usefulness in the measurement of serum Tg, there is still controversy as to the sex-related (Pacini et al., 1980; Gardner et al., 1979) and age-related (Feldt-Rasmussen et al., 1979; Pacini et al., 1980) changes in serum Tg levels in healthy subjects.

In this study, we examined the effects of sex and age on the serum Tg levels in healthy subjects using appropriate statistical analysis.

Materials and Methods

1) Subjects

Serum samples were obtained in the morning from 53 males and 57 females between ages 20-78 who visited Gifu Health Care Center (Gifu Kenritsu Kenkohin) for a regular check-up as previously reported (Kojima et al., 1983). All subjects were in good health and were without a history of chronic medication or diseases, including thyroid disorders. Samples were quickly separated and stored at -20°C until assayed.

All subjects showed normal blood chemistry (transaminase (GOT, GPT), lactic dehydrogenase, alkaline phosphatase, γ-glutamyltranspeptidase, total proteins, albumin, choline esterase, zinc sulfate turbidity test, total bilirubin, blood urea

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nitrogen, creatinine, uric acid, cholesterol, Ca, and P) and normal levels of T3, T4, TSH, and TBG (Kojima et al., 1983). They had neither anti-Tg antibodies as measured by hemagglutination test (Fuji Zoki, Japan) or radioimmunoassay (Eiken Immunochemical, Japan), nor antimicrosomal antibodies measured by the hemagglutination method (Fuji Zoki, Japan).

2) Tg assay
All samples were analyzed in duplicate in the same assay. Serum Tg was measured by a solid-phase, sandwich-type, immunoradiometric assay (Human Thyroglobulin Immunoradiometric Assay Kit, CIS). Briefly, Tg in the sample was bound to polystyrene tube coated with anti-human Tg IgG and then quantitated by its binding of 125I-labelled specific fraction of the same IgG. For values of 3.5, 13.8, 353, 733 ng/ml, the intra-assay variations were 9.5, 4.8, 12.0, 9.5%, respectively.

3) Statistical analysis
Statistical analysis was performed using Student's t-test after the logarithmic transformation of the Tg levels. The Mann and Whitney U test was also performed using the native values of Tg. Differences were considered to be significant if p was less than 0.05. Data were expressed as the mean value with a range of ±2SD which was calculated from the levels of log Tg.

Results
Figure 1 shows the frequency distribution of serum Tg levels before and after the logarithmic transformation. The distribution after the logarithmic transformation could be adequately approximated to a normal distribution.

Serum concentrations of Tg in a total of 110 healthy subjects ranged between 1.0 and 26.6 ng/ml with a mean level of 5.1 ng/ml.

In males, the serum concentration of Tg in the third decade, the youngest one studied, was 4.5 ng/ml (0.7–27.7 ng/ml) and this value was not significantly different up to the eighth decade (Table 1). In females, the concentration of Tg in the third decade was 4.1 ng/ml (0.7–23.1 ng/ml) and no significant differences were observed up to the eighth decade.

There was no significant difference in serum Tg levels between males (mean value; 5.0 ng/ml, range 1.0–25.9 ng/ml) and females (mean value; 5.2 ng/ml, range 1.0–27.7 ng/ml). No significant sex-related difference was observed in any decade either.

Neither age-related nor sex-related change in the serum Tg level was observed, even when the Mann and Whitney U test was used for statistical analysis.

Discussion
Tg is a glycoprotein with a M.W. of approximately 670,000 which is synthesized only in the thyroid gland. Formerly, Tg was not thought to circulate in the blood. It is now well known, however, that a small amount of Tg is continuously released into the circulation and can be detected by radioimmunoassay (RIA) in most healthy subjects.

In our present study, the serum concentration of Tg in healthy subjects ranged between 1.0 and 26.6 ng/ml. This range is similar to that reported by Izumi and Larsen (1978) (<2–27 ng/ml), Ikekubo et al. (1980) (4–25.7 ng/ml), and Pacini et al. (1980) (<1.25–27 ng/ml), but lower than that of several other workers such as Torrigiani et al. (1969) (10–150 ng/ml), Ochi et al. (1975) (10–180 ng/ml), and Bodlaender et al. (1978) (2–61 ng/ml).

The diversity of normal values in Tg seems to be related to the use of different assay systems and/or the differences in the population studied.

The Tg molecule is heterogenous with respect to its iodine and carbohydrate content. When an antibody with relatively high affinity for the Tg molecule rich in iodine is used for a RIA, the serum Tg level of a sample with iodine poor Tg may be
underestimated (Schneider and Ikekubo, 1979).

The presence of endogenous anti-Tg antibodies interferes with the determination of Tg in serum. Although a passive hemagglutination test has been widely used in detecting anti-Tg antibodies, questions concerning its sensitivity have been reported (Izumi and Larsen, 1978; Wilkin et al., 1979). Izumi and Larsen (1978) reported that some sera which had negative anti-Tg antibodies as measured by the hemagglutination method bound significant amounts of $^{125}$I-Tg. In our study, the sera which had anti-Tg antibodies when measured by either the hemagglutination method (titer 1:100 or more) or RIA using $^{125}$I-Tg (bound $^{125}$I-Tg to $\gamma$-globulin $>10\%$) were excluded from the study. Therefore, the interference of endogenous

Fig. 1. Frequency distribution of serum thyroglobulin concentrations obtained from 110 normal subjects. The distributions of native values (A) and of the logarithms (B) of thyroglobulin concentrations are shown. The assumption that the dispersion of the logarithms of thyroglobulin values shows a normal distribution is not neglected when the $\chi^2$ test is used to check the fit.
anti-Tg antibodies in the measurement of serum Tg levels should be very small in our study.

As to the sex- and age-related changes in Tg levels, statistical analysis is also important, since the concentrations of serum Tg in healthy subjects don't show Gaussian distribution (Bodlaender et al., 1978) as shown in Figure 1. Van Herle et al. (1976) reported that the logarithms of serum Tg concentrations showed a normal distribution. In our study, because we obtained similar results we analyzed the data using Student's t-test after the logarithmic transformation. We also analyzed the data using the Mann and Whitney U test that does not require any assumption about the values' distribution.

Concerning the sex differences in serum Tg values, some workers (Van Herle et al., 1973; Pezzino et al., 1977; Pacini et al., 1980) reported significantly higher values in healthy females than in healthy males. Other workers, however, did not find significant difference (Roitt and Torrigiani, 1967; Torrigiani et al., 1969; Ochi et al., 1975; Gardner et al., 1979). In our present study, there was no significant difference in Tg levels between males and females. It is well known that females are more frequently affected by thyroid diseases than males. Melmed and Hershman (1982) reported a higher incidence of subclinical Hashimoto's thyroiditis in females than in males. Therefore, on the selection of healthy subjects, their thyroid function must be carefully examined. In contrast to our present study, most of the authors mentioned above have not paid such attention to this. Thus, patients with subclinical thyroid disorders might be included in their studies, especially females. Concerning this aspect, Pezzino et al. (1977) reported that sex-related differences in serum Tg levels might be related to the higher TSH levels often observed in females. In our study, subjects with subclinical thyroid

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>n (subjects)</th>
<th>log Tg [ng/ml] mean ± SD</th>
<th>Tg* (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>20 - 29</td>
<td>9</td>
<td>0.658 ± 0.392</td>
<td>4.5 (0.7 - 27.7)</td>
</tr>
<tr>
<td></td>
<td>30 - 39</td>
<td>11</td>
<td>0.616 ± 0.426</td>
<td>4.1 (0.6 - 29.4)</td>
</tr>
<tr>
<td></td>
<td>40 - 49</td>
<td>9</td>
<td>0.680 ± 0.281</td>
<td>4.8 (1.3 - 17.5)</td>
</tr>
<tr>
<td></td>
<td>50 - 59</td>
<td>9</td>
<td>0.760 ± 0.379</td>
<td>5.8 (1.0 - 33.0)</td>
</tr>
<tr>
<td></td>
<td>60 - 69</td>
<td>10</td>
<td>0.816 ± 0.311</td>
<td>6.5 (1.6 - 27.4)</td>
</tr>
<tr>
<td></td>
<td>70 - 79</td>
<td>5</td>
<td>0.646 ± 0.407</td>
<td>4.4 (0.7 - 28.8)</td>
</tr>
<tr>
<td></td>
<td>20 - 79</td>
<td>53</td>
<td>0.700 ± 0.357</td>
<td>5.0 (1.0 - 25.9)</td>
</tr>
<tr>
<td>Females</td>
<td>20 - 29</td>
<td>10</td>
<td>0.611 ± 0.376</td>
<td>4.1 (0.7 - 23.1)</td>
</tr>
<tr>
<td></td>
<td>30 - 39</td>
<td>10</td>
<td>0.844 ± 0.320</td>
<td>7.0 (1.6 - 30.5)</td>
</tr>
<tr>
<td></td>
<td>40 - 49</td>
<td>10</td>
<td>0.646 ± 0.254</td>
<td>4.4 (1.4 - 14.3)</td>
</tr>
<tr>
<td></td>
<td>50 - 59</td>
<td>10</td>
<td>0.852 ± 0.308</td>
<td>7.1 (1.7 - 29.4)</td>
</tr>
<tr>
<td></td>
<td>60 - 69</td>
<td>9</td>
<td>0.786 ± 0.349</td>
<td>6.1 (1.2 - 30.5)</td>
</tr>
<tr>
<td></td>
<td>70 - 79</td>
<td>8</td>
<td>0.511 ± 0.525</td>
<td>3.2 (0.3 - 36.4)</td>
</tr>
<tr>
<td></td>
<td>20 - 79</td>
<td>57</td>
<td>0.714 ± 0.364</td>
<td>5.2 (1.0 - 27.7)</td>
</tr>
<tr>
<td>Males &amp; Females</td>
<td>20 - 79</td>
<td>110</td>
<td>0.707 ± 0.359</td>
<td>5.1 (1.0 - 26.6)</td>
</tr>
</tbody>
</table>

Tg*: calculated from log Tg mean value (range: ± 2 SD)
disorders or higher TSH levels (>8 μU/ml) were carefully excluded. This may explain why we did not find higher levels of serum Tg in females.

As to the age-related changes in serum Tg levels, Feldt-Rasmussen et al. (1979) reported a rise in serum Tg levels with age among women but not men. However, consistent with the results of Torrigiani et al. (1969), Van Herle et al. (1973), Pezzino et al. (1977), and Pacini et al. (1980), we failed to find any age-related changes in serum Tg levels in either sex. At present, the differences between our results and those of Feldt-Rasmussen et al. (1979) are difficult to explain, since subjects in their study were reported to have normal levels of T3, T4, and TSH. Recently, Hegedüs et al. (1983) reported a high serum Tg level in patients with alcoholic liver cirrhosis. Without an effort of careful selection of healthy subjects, the presence of such nonthyroidal illness in healthy subjects may lead to a misleading conclusion. We would like to stress that the healthy subjects were carefully selected in our study in order to exclude the interference of any thyroidal and nonthyroidal diseases which could affect the results.

In conclusion, in our carefully selected healthy subjects neither sex- nor age-related change in the level of Tg was observed.

Acknowledgements

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References


