Age- and sex-related differences of serum thyroxine binding globulin (TBG) in healthy subjects

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Abstract. Serum concentrations of thyroxine binding globulin (TBG) were measured in healthy adult subjects aged 20–79 years (152 males and 148 females) by radioimmunoassay. In contrast to previous reports, there were no significant age-related differences in either sex. Significant sex-related differences were observed only in the fourth decade, being higher in females than males (P < 0.01).

Thyroid hormones circulate in the blood as bound forms with serum proteins. 99.96% of thyroxine (T4) and 99.6% of triiodothyronine (T3) are bound to their carrier proteins. Of the binding proteins for thyroid hormones in healthy subjects, thyroxine binding globulin (TBG), which is an α-globulin, binds 3/4 of circulating T4 by virtue of its exceptionally high affinity for the hormone (Robbins 1971). The concentration of TBG is very low, being 22–36 µg/ml in healthy subjects (Levy et al. 1971; Chopra et al. 1972; Cavalieri et al. 1975). It has been reported by many investigators that in several disorders its concentration varies. Thus the serum concentration is normal or slightly low in hypothyroidism, and normal or slightly high in hyperthyroidism. However, serum TBG levels are clearly increased during pregnancy, during oestrogen administration, in liver diseases such as chronic hepatitis, hepatoma, and in an X-linked dominant inherited disorder of TBG synthesis (Chopra 1981). Serum TBG concentration is decreased during androgen administration, in some cases with hepatic cirrhosis, and in a genetic disorder of TBG synthesis (Levy et al. 1971; Chopra et al. 1972).

Because changes in TBG concentrations directly affect the total T4 and T3 values measured by radioimmunoassay (RIA) (Larsen 1978), it is clinically relevant to measure its concentration in order to analyze the values of thyroid hormones. In earlier studies the concentration of TBG was estimated by measuring its binding capacity for thyroxine (Robbins 1956; Blumberg & Robbins 1960; Refetoff et al. 1972). However, these values did not necessarily correlate with its serum concentrations. Radioimmunoassay for the measurement of TBG concentration was described by Levy et al. (1971) and Hesch et al. (1976). Several radioimmunoassay kits for the measurement of TBG are now available and were used to provide us with additional information on patients’ thyroid function. Only two reports have been published from Europe (Hesch et al. 1976; Bigazzi et al. 1980) concerning the serum concentration of TBG of healthy subjects in relation to age and sex. In our present investigation, serum TBG concentration was measured in healthy adult subjects aged 20–79 years who were carefully selected on the basis of their medical histories and by blood chemistry including a 50 g oral glucose tolerance test. Our results indicate that in both males and females there were no age-related changes in TBG concentration. Comparisons between males and females at each decade showed that between the third and fifth decade, TBG concentration in females tended to be higher than in males of the same decade but statistical significance was attained only in the fourth decade.
(P < 0.01). Between the sixth and eighth decade, no significant differences between males and females were observed.

Materials and Methods

Studies were performed using sera obtained from 152 male and 148 female subjects between 20 and 79 years of age who were carefully selected from approximately 10,000 healthy subjects who visited Gifu Health Care Centre for regular check-up. Blood obtained 1 h after a 50 g oral glucose load was quickly separated and used for screening of blood chemistry (transaminase (GOT, GPT), lactic dehydrogenase, alkaline phosphatase, γ-glutamyltranspeptidase, total proteins, albumin, choline esterase, zinc sulphate turbidity test, total bilirubin, blood urea nitrogen, creatinine, uric acid, cholesterol, Ca, P, glucose) and for serum TBG measurement. Healthy subjects, who showed normal blood chemistry were further selected by enquiry about medical history, by physical examination and by measurement of serum triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH). None of the 300 healthy subjects thus selected had a history of thyroid disease, goitre or medications known to alter thyroid function.

All subjects showed normal blood chemistry except for the glucose tolerance test. The serum glucose level 1 h after load was less than 8.9 mM (160 mg/dl) in all subjects, except for males of the eight decade and females of the seventh and eighth decades. Of 25 males of 70–79 years of age: 13 showed serum glucose levels less than 8.9 mM, 6 showed between 9.0–11.1 mM (161–200 mg/dl) and 6 showed values between 11.2–16.1 mM (201–290 mg/dl). Of 25 females of 60–69 years of age: 8 showed below 8.9 mM, 8 showed between 9.0–11.0 mM and 9 showed between 11.2–15.2 mM. Of 13 females in the eight decade, 4 showed values below 8.9 mM, 6 showed values between 9.0–11.1 mM and 3 showed values between 11.2–12.0 mM. Because the sera obtained 1 h after the glucose load were used for the measurement of TBG, the effect of a 100 g oral glucose load on the serum TBG concentration was investigated separately using 5 healthy male volunteers. All were medical students aged 20–22 years.

Serum TBG was measured using a radioimmunoassay kit (RIA-gnost TBG) which was kindly supplied by Hoechst Japan Co. Briefly, 20 µl of serum was incubated together with anti-TBG antiserum and [125I]TBG for 3 h at 20°C followed by precipitation of the bound [125I]TBG to γ-globulin fraction with 16.9% polyethyleneglycol (MW: 6000) and radioactivity of the bound [125I]TBG was counted. Statistical analysis was conducted according to Student's t-test.

Results

1. Changes in TBG concentration after a 100 g oral glucose tolerance test (Table 1)

The effects of acute changes of serum glucose and insulin on serum TBG concentration were investigated and are summarized in Table 1. Serum glucose levels before and after an oral glucose load were 4.5 ± 0.3 mM (80.3 ± 5.3 mg/dl) (before glucose load, mean ± SD) 4.0 ± 1.0 mM (72.6 ± 18.6 mg/dl) (1 h) and 4.1 ± 0.6 mM (73.0 ± 10.8 mg/dl) (2 h), and thus there were no significant changes in serum glucose levels before and after glucose load.

On the other hand, the concentrations of immunoreactive insulin before and after glucose load were 8.2 ± 2.2 µU/ml (before), 44.8 ± 20.8 µU/ml (1 h) and 32.2 ± 14.7 µU/ml (2 h). Thus the concentrations of immunoreactive insulin increased steeply 1 h after glucose load.

Serum TBG concentration before glucose load was 17.4 ± 3.0 µg/ml and did not change after a 100 g glucose load.

2. Differences of serum TBG concentration by age (Fig. 1)

In males, serum TBG concentration in the third decade was 20.5 ± 3.6 µg/ml (mean ± SD) and the value was not significantly different up to the eighth decade. In females, the TBG concentration in the third decade was 22.0 ± 3.0 µg/ml and no significant differences were observed up to the eighth decade. In females of the eighth decade, the TBG concentration was 19.8 ± 3.3 µg/ml, but this decline is not statistically significant. Since 12 out of 25 males of the eighth decade, 9 out of 13 females of the eighth decade, and 17 out of 25 females of the seventh decade showed glucose intolerance according to the criteria supplied by WHO, the relationship between the degree of glucose intolerance and TBG concentration was also examined.

As shown in Table 2, there were no consistent
changes in the level of TBG concentration according to the degree of glucose intolerance.

3. **Differences of serum TBG concentration according to sex** (Fig. 1)

Sex-related differences in TBG concentration were studied in each corresponding age group. As shown in Fig. 1, a statistically significant sex-related difference was seen only in the fourth decade, with females higher than males: 22.3 ± 3.4 µg/ml and 19.5 ± 3.2 µg/ml, respectively. The mean concentration of TBG of 148 females aged 20–79 years was 21.5 µg/ml (SD = 3.5), which was significantly higher ($P < 0.01$) than that of 152 males aged 20–79 years (mean = 20.3 µg/ml, SD = 3.3).

### Table 2.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Serum glucose mm</th>
<th>No. of subjects</th>
<th>Serum TBG µg/ml</th>
</tr>
</thead>
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<tr>
<td>60–69</td>
<td>F</td>
<td>&lt; 8.9</td>
<td>8</td>
<td>21.2 ± 2.7</td>
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<tr>
<td></td>
<td></td>
<td>9.0–11.1</td>
<td>8</td>
<td>21.7 ± 3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.2–15.2</td>
<td>9</td>
<td>22.9 ± 4.6</td>
</tr>
<tr>
<td>70–79</td>
<td>F</td>
<td>&lt; 8.9</td>
<td>4</td>
<td>21.5 ± 2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.0–11.1</td>
<td>6</td>
<td>19.1 ± 3.8</td>
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<td>3</td>
<td>19.7 ± 4.3</td>
</tr>
<tr>
<td>70–79</td>
<td>M</td>
<td>&lt; 8.9</td>
<td>13</td>
<td>19.6 ± 3.4</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td></td>
<td>11.2–16.1</td>
<td>6</td>
<td>19.8 ± 5.7</td>
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</table>

Because 17 of 25 females in the seventh decade, 9 of 13 females of the eighth decade and 12 of 25 males of the eighth decade in this study showed glucose intolerance as judged by serum glucose levels 1 h after a 50 g oral glucose load, the relationships between the degree of glucose intolerance and serum TBG concentrations were investigated. No significant relationships between serum glucose levels and serum TBG concentrations were observed.

### Discussion

Despite the fact that radioimmunoassay has become available for the measurement of TBG concentration, there is still little data concerning normal values in relation to age and sex. Hesch et al. (1976) studied 96 healthy subjects and reported that serum TBG levels were significantly elevated in pre-pubescent and elderly subjects as compared to other age groups between 19–45 years; no distinction was made between the two sexes. Bigazzi et al. (1980) extended the study and demonstrated that the TBG concentration in the 21–50 year age group was slightly higher in females than in males. They also reported that TBG declined in the third and fourth decades in healthy males, and increased after the fifth decade. Braverman et al. (1966) reported similar age-related changes of serum TBG in healthy males, while an inverse pattern was observed in the serum thyroxine binding pre-albumin level.

In our present communication, in order to exclude non-thyroidal illnesses affecting thyroid functions, normal subjects were carefully screened.
by means of medical history and blood tests. After confirming by separate studies that an 100 g oral glucose load did not affect the TBG concentration, the concentration of TBG was measured in sera obtained 1 h after an 50 g oral glucose load. In contrast to previous findings, the serum concentration of TBG was quite constant in both healthy males and females aged 20—79 years.

Because 12 out of 25 males in the eighth decade, 17 out of 25 females in the seventh decade, and 9 out of 13 females in the eighth decade showed serum glucose levels higher than 8.9 mM 1 h after a 50 g oral glucose load, the relationship between TBG levels and the degree of glucose intolerance in these elderly subjects was investigated. The results shown in Table 2 clearly indicate that hyperglycaemia per se does not affect serum TBG levels. Thus it is apparent that in healthy subjects acute increments of both insulin and serum glucose do not affect the serum concentration of TBG.

Sex-related differences in TBG concentration in each decade were studied. Statistically significant sex differences were observed only in the fourth decade, the concentration being higher in females. Although it was not statistically significant, the TBG concentrations of females in the third and fifth decades tended to be higher than in males in the same decade. This difference could be attributed to the increased oestrogen output in females in that age group. According to the report of Pincus et al. (1954), oestrogen output in females was highest in the fourth decade, maintained at rather high levels in the third and fifth decades and declined after the menopause. It is conceivable that this difference in serum oestrogen levels is responsible for the difference in TBG levels between males and females. The concentrations of serum TBG obtained from 152 healthy males (20—79 years) and 148 females (20—79 years) were 20.3 ± 3.3 μg/ml and 21.5 ± 3.5 μg/ml, respectively. The difference between the two concentrations is statistically significant. The higher mean TBG concentration in the females is probably due to the tendency towards higher TBG concentration (significantly higher in the fourth decade) between the third and fifth decades.

The differences between our results and the results obtained by Hesch et al. (1976) and Bigazzi et al. (1980) are difficult to explain. They might be caused by ethnic differences, or differences in environmental factors (food, etc.). They might be caused by differences in the selection of healthy subjects for study. We would like to stress that in our study, selection was done carefully enough to avoid interference from any thyroidal or non-thyroidal disease which could affect the results.

References


Received on January 5th, 1983.