CHANGES IN THYROXINE-BINDING GLOBULIN LEVELS IN THYROTOXICOSIS AND IN HEALTHY SUBJECTS AFTER TRIIODOTHYRONINE ADMINISTRATION

By

R. F. Harvey, E. S. Williams, S. Ellis
and R. P. Ekins

ABSTRACT

Thyroxine-binding globulin (TBG) levels were found to be significantly lower in 40 thyrotoxic patients than in 70 healthy subjects. A similar mean fall in TBG of 18% was produced by administration of 'physiological' doses of triiodothyronine to healthy volunteers. However, intramuscular injection of thyroid-stimulating hormone (TSH) had no consistent effect on the level of TBG as measured up to 4 days after injection. These findings are believed to explain the anomalous results described by earlier workers. It is suggested that TBG concentration is regulated by unknown mechanisms subject to the influence of many hormones, including triiodothyronine.

Thyroxine-binding globulin (TBG) is the major thyroxine-binding protein in plasma, carrying about 75% of the total serum thyroxine in normal subjects (Woeb et al. 1968). It plays an important role in the transport and distribution of thyroxine to the tissues (Robbins & Rall 1967; Oppenheimer 1968). Little is known about factors that control its formation or metabolism, and because only very small concentrations are present in the blood, it has only recently been possible to isolate TBG in a near-pure state (Sterling et al. 1968). Changes in TBG levels have been described in patients with thyroid disease, there being an increase in TBG concentration in myxoedema and a decrease in thyrotoxicosis (Albright et al. 1955; Inada & Sterling 1967). A preliminary report (Harvey et al. 1968) indicated that a fall in TBG could be produced by administration of triiodothyronine (T₃) to normal subjects. This
work has been extended to confirm and to investigate further these preliminary findings.

METHODS

Triiodothyronine (T₃), 60 to 120 µg daily in divided doses was administered to 10 normal subjects for 7-10 days. Serum was obtained at intervals for estimation of thyroxine and TBG levels, and kept frozen at -25°C until assayed. Serum thyroxine was measured in duplicate by the method of Ekins et al. (1969). TBG was measured as maximum thyroxine-binding capacity by the method of Robbins (1956) modified by Tanaka & Starr (1959), using reverse flow paper electrophoresis in barbitone buffer. This technique gives somewhat lower values for TBG capacity than methods using other buffer systems.

Measurements of serum thyroxine and TBG were also made in 70 euthyroid subjects, either staff of the hospital or medical school, and in 40 patients with thyrotoxicosis, the diagnosis being made on clinical findings and substantiated in every case by radioactive iodine studies. TBG levels were measured in 8 healthy volunteers at intervals for four days after intramuscular injection of 10 IU of bovine thyrotrophin (TSH), and before and 24 hours after a similar injection in 22 patients.

RESULTS

The level of TBG in 40 patients with thyrotoxicosis was significantly lower than in the 70 euthyroid subjects, the mean concentration (112.4 ng/ml) being 82.2% of that in the normal group (137.0 ng/ml), as shown in Table 1. In 9 patients with thyrotoxicosis (22.5%) the serum thyroxine was less than 115

<table>
<thead>
<tr>
<th>No.</th>
<th>Mean</th>
<th>Range</th>
<th>Mean</th>
<th>± sd</th>
<th>Range</th>
<th>Standard error of mean</th>
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<td>Normal subjects</td>
<td>70</td>
<td>74.6</td>
<td>45-115</td>
<td>137.0</td>
<td>± 28.2</td>
<td>82-197</td>
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<td>Patients with thyrotoxicosis</td>
<td>40</td>
<td>177.5</td>
<td>86-366</td>
<td>112.4</td>
<td>± 26.3</td>
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Table 1.
Serum thyroxine and TBG levels in euthyroid subjects and patients with thyroid disease. There is a significant difference between the mean TBG level in each group. (Standard error of difference between the two means = 5.36. Actual difference = 14.6, P < 0.05).
ng/ml (i.e. within the normal range). However, because of the low TBG levels, the concentration of free T₄ and/or of free T₃ should be in the thyrotoxic range in all these patients.

The changes in TBG capacity and total serum thyroxine after triiodothyronine are shown in Table 2. A consistent fall was observed in all subjects, which was highly significant \((P < 0.001\) by paired Student’s \(t\) test). The mean fall of 18.0 \% was similar to the difference noted between normal subjects and patients with thyrotoxicosis. However, as shown in Fig. 1, TBG levels appeared still to be falling in most subjects when the experiment was terminated, so it is probable that a further fall would have occurred.

The rate of decrease in TBG concentration did not appear to be related either to the dose of triiodothyronine given (60–120 \(\mu\)g/day) or to the fall in serum thyroxine. When plotted on semilogarithmic paper (an exponential line being drawn by eye for each subject), the mean ‘halflife’ of thyroxine was 9.6 days, that of TBG being 33.7 days. ‘Halflife’ in this context is used to mean the time taken for the serum thyroxine or TBG concentration to reach half their initial values, assuming an exponential loss. Four women taking oral contraceptives were included among the 10 healthy subjects, but no difference

### Table 2.

Changes in serum TBG and total thyroxine after triiodothyronine administration. The fall in TBG is highly significant \((P < 0.001\) by paired Student’s \(t\) test) when the lowest value obtained is compared with the corresponding initial value. The times when serum samples were obtained during and after the course of triiodothyronine are shown in Fig. 1.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Initial TBG capacity (ng/ml)</th>
<th>TBG capacity after T₃ administration (ng/ml)</th>
<th>Decrease in TBG capacity (ng/ml)</th>
<th>Decrease in TBG as % of initial value</th>
<th>Decrease in serum thyroxine as % of initial value</th>
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<td>-34</td>
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<td>Mean</td>
<td>165.8</td>
<td>136.9</td>
<td>-28.9</td>
<td>18.0</td>
<td>42.3</td>
</tr>
</tbody>
</table>

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Actual changes in TBG levels (expressed as maximum thyroxine-binding capacity) in 10 healthy subjects given triiodothyronine. Two subjects took triiodothyronine for 10 days, the rest for 7 days, as indicated by the black bar.

in the response to triiodothyronine was noted, although the initial TBG levels were higher than in the other healthy subjects.

After intramuscular administration of TSH, no consistent changes in TBG concentration were noted in any of the 30 subjects studied. In 16 cases the change in TBG level was 5% or less, in 8 cases TBG concentration rose by more than 5%, and in 6 it fell by more than 5%.

**DISCUSSION**

Thyroxine-binding globulin (TBG) is believed to play an important role in thyroid physiology (*Robbins & Rall* 1967; *Oppenheimer* 1969; *Lancet* 1969). Many conditions have been described in which alterations in TBG are seen, and its level is influenced by many hormones, including corticosteroids (*Oppenheimer & Werner* 1966), oestrogens (*Dowling et al.* 1956), androgens (*Engbring & Engstrom* 1959) and growth hormone (*Oliner & Ballantine* 1968). Although low TBG levels in thyrotoxicosis have been recognised for many years (*Albright et al.* 1955; *Tanaka & Starr* 1959; *Inada & Sterling* 1967) it has been generally believed that such changes were due to non-specific effects.
of thyrotoxicosis on protein metabolism (Buchanan et al. 1962). A change in TBG concentration following physiological doses of triiodothyronine was described recently (Harvey et al. 1968).

No other direct studies of the effect of triiodothyronine on TBG have been reported. However, Alley et al. (1968) measured the T₃ resin uptake in euthyroid patients given triiodothyronine (100 µg daily for six weeks). After a slight fall in resin uptake in the second week, there was a significant rise at the fourth week. The authors offered no explanation for this unexpected finding. A previous study (Levy et al. 1964) had shown no change in T₃ resin sponge uptake after triiodothyronine (75 µg daily for 3 weeks) given to normal volunteers. This study was repeated more recently (Dussault et al. 1969), triiodothyronine (75 µg daily) being given for 10 days to 11 healthy volunteers. These workers found the same decrease in resin uptake as was found previously by Alley et al. (1968) in the second week of treatment. However, they did not continue for a further period after the initial ten days. In further studies, they gave small doses of triiodothyronine (30 to 75 µg daily) to 8 patients with hypothyroidism, and large doses (150–300 µg daily) to 14 women in the last few weeks of pregnancy, and in both groups there was a significant rise in T₃ resin uptake. These findings could not be explained by the authors.

As the T₃ resin uptake depends on a balance between the amount of thyroxine in serum and the available binding sites on TBG, changes in either one may alter the resin uptake, and a parallel change in both will have no resultant effect. In the present study, serum thyroxine initially fell faster than did TBG capacity. This would be expected to result in an increase in available binding sites on TBG, with a corresponding fall in resin uptake, as found by both Alley et al. (1968) and Dussault et al. (1969). Although we have not studied the effect of prolonged triiodothyronine administration on TBG levels, it seems likely that TBG may continue to fall until the net fall in TBG capacity is greater than the net fall in serum thyroxine, with a resultant increase in resin uptake, as described by Alley et al. (1968). The different resin uptake results described could be well accounted for by differences in the relative rates of fall of thyroxine and TBG.

The fact that low doses of triiodothyronine (60 µg daily) produced a change in TBG not appreciably different from that seen after larger doses (120 µg daily) indicates that the fall in TBG concentration is a physiological one rather than a non-specific response to thyrotoxic disease. The failure of administered TSH to produce a consistent change in serum TBG levels suggest that triiodothyronine does not lower TBG by inhibiting TSH release from the pituitary gland. It may be that triiodothyronine acts directly on the cells manufacturing TBG, or increases its catabolism in the tissues. Further work on the secretion and fate of TBG is needed, as this protein may well play a more active role in thyroid physiology than was previously supposed.
ACKNOWLEDGMENTS

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REFERENCES


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