Case Report

A Case of Total Thyroxine-Binding Globulin Deficiency with Graves' Disease: Fluctuations of Plasma Triiodothyronine/Thyroxine Ratio

Keita Kamikubo, Noriko Kojima, Noriyoshi Yamakita and Kiyoshi Miura

A 37-year-old male with total thyroxine-binding globulin (TBG) deficiency associated with Graves' disease is described. Both TBG immunoreactivity and TBG capacity were not detectable in his serum. Serum concentrations of thyroxine-binding prealbumin and albumin were normal. He was initially hyperthyroid. During methimazole-treatment he was maintained in an euthyroid state except for two short hypothyroid periods. His plasma triiodothyronine/thyroxine (T3/T4) ratios during both the untreated hyperthyroid and the methimazole-induced hypothyroid states were higher than those during his methimazole-induced euthyroid state. These findings on changes in his T3/T4 ratio accompanying thyroidal dysfunction were qualitatively comparable with those in patients with Graves' disease with normal TBG levels: that both untreated hyperthyroid and methimazole-induced hypothyroid patients showed higher T3/T4 ratios than methimazole-induced euthyroid patients. These results may provide indirect evidence that changes in hormonal secretion and conversion that raise T3/T4 ratio can occur in thyroidal dysfunctions even in the complete absence of TBG.

Key Words: TBG deficiency, Graves' disease, Hyperthyroidism, Hypothyroidism, Hormonal kinetics, Hormonal metabolism, Hormonal conversion, Thyroid hormone, Triiodothyronine.

In patients without any genetic abnormalities in plasma concentrations of thyroid hormone-binding proteins, the ratio of plasma concentration of triiodothyronine (T3) to that of thyroxine (T4) (T3/T4 ratio) increases in both primary hyperthyroidism and primary hypothyroidism. It has been shown that differential changes in metabolisms of T3 and T4 — an increase in peripheral conversion of T4 to T3 and an increase in thyroidal secretion of T3 — are responsible for the elevated T3/T4 ratios in these thyroidal dysfunctions. Mechanisms underlying these alterations in hormonal conversion and secretion are not known. In addition, it has been obscure whether thyroid hormone-binding proteins play any essential role in the occurrence of these alterations of hormonal metabolism.

In this paper we describe a patient with total thyroxine-binding globulin (TBG) deficiency associated with Graves' disease. He was initially hyperthyroid. During methimazole (MMI)-treatment he was maintained in an euthyroid state except for two short hypothyroid periods. His plasma T3/T4 ratios during the hyperthyroid, the hypothyroid and the euthyroid states were compared with each other to study whether the changes in the hormonal ratio accompanying thyroidal dysfunctions can occur in the complete absence of TBG. For comparison, T3/T4 ratios were also studied in untreated hyperthyroid, MMI-induced euthyroid and MMI-induced hypothyroid patients with Graves' disease with normal TBG levels.
SUBJECTS AND METHODS

In addition to plasma T3/T4 ratio of the patient with total TBG deficiency, plasma T3/T4 ratios of the following subjects were studied: 25 normal subjects (13 males and 12 females, 30–39-year-old), 17 patients with untreated Graves’ disease (5 males and 12 females, 11–49-year-old), 6 patients with Graves’ disease maintained in an euthyroid state with MMI (1 male and 5 females, 17–70-year-old) and 6 patients with Graves’ disease in a MMI-induced hypothyroid state (1 male and 5 females, 21–75-year-old). Serum concentrations of TBG in these subjects, ranging 14.0 to 25.9 μg/ml, were all within normal range.

Concentrations of plasma T3, T4, free T4 (Eiken T3 RIA Kit, Eiken T4 RIA kit; Eiken Immunochemical; Amerlex Free T4 RIA kit; Amersham Japan), thyrotropin (TSH) (TSH RIA Kit Daiichi; Daiichi Radioisotope) and serum TBG (RIAgnost TBG; Hoechst) were assayed by radioimmunoassays. The serum TBG capacity was determined by the electrophoretic method. The serum thyroxine-binding prealbumin (TBPA) concentration was assayed by the single radial immunodiffusion method (Partigen-TBPA; Hoechst). The titers of microsomal hemagglutination antibody (MCHA) and thyroglobulin hemagglutination antibody (TGHA) were determined by the tanned-red-blood-cell hemagglutination methods (Microsome Test, Thyroid Test; Fujizoki Pharmaceutical Co.).

CASE REPORT AND RESULTS

A 37-year-old Japanese male without any past medical record presented in November 1980 with exophthalmos, palpitation, finger tremor and body weight loss. There was neither consanguineous marriage nor known history of thyroidal disease in his family. On physical examination, his height was 165.5 cm and his weight was 65 kg. The pulse was 96 beats/min and the skin was moist. The thyroid gland was diffusely enlarged and soft. The remainder of his physical examination was normal. The urine was normal. The electrocardiogram showed a sinus tachycardia.

The laboratory tests showed the following results: serum total protein 7.0 g/dl; serum albumin 4.8 g/dl; serum total cholesterol 148 mg/dl; triglyceride 135 mg/dl; alkaline phosphatase 83 IU/l; SGOT 10 IU/l; SGPT 34 IU/l; LDH 118 IU/l. The thyroid function tests showed the following results: plasma T4 9.8 μg/dl (normal range 5.7–
12.9 μg/dl; plasma T3 259 ng/dl (normal range 84–201 ng/dl); plasma TSH 1.3 μU/ml (no response to 500 μg thyrotropin-releasing hormone); titer of MCHA 1:6400; titer of TGHA 1:100. The 131I scintigraphy also showed the diffuse enlargement of the thyroid gland. A diagnosis of Graves' disease was made by these findings.

His clinical course is shown in Fig 1. Results of thyroid function tests during his course are summarized in Table 1. Oral MMI rapidly reduced plasma T3 and T4. The signs and symptoms of hyperthyroidism also disappeared. In April to May and October to November 1981 he was hypothyroid and had extremely low levels of plasma T3 and T4, and elevated levels of plasma TSH. During the other periods of his clinical course he has been kept physically euthyroid with normal TSH levels despite consistently low or low-normal levels of plasma T3 and low levels of plasma T4. These discrepancies between physical status and plasma concentrations of thyroid hormones suggested reduced binding capacities for thyroid hormones in his serum. Serum concentrations of thyroid hormone-binding proteins were first measured in September 1982. The examination revealed the following: serum TBG concentration not detectable (normal range 13.7–26.9 μg/ml); serum TBG capacity not detectable (normal range 13.1–32.3 μg/ml); serum TBPA concentration 34 μg/ml (normal range 10–40 mg/ml); serum albumin 4.4 g/dl. Repeated radioimmunoassays in March, April and June 1983 also failed to detect TBG in his serum. Since January 1983 serum free T4 concentrations (ranging from 0.7 to 2.1 ng/dl) have also been measured and have been maintained within normal range (0.7–2.2 ng/dl).

Serum concentration of TBG in his wife (33-year-old) was normal (18 μg/ml). He had two children (both female; 4- and 6-year-old). In both his two daughters serum concentrations of TBG (both 15 μg/ml) were below age-matched normal range (17.6–35.2 μg/ml) determined using the same radioimmunoassay kit as we used5. All of them were euthyroid.

### Table 1. Comparison of thyroidal functions and T3/T4 ratio

<table>
<thead>
<tr>
<th>Subject</th>
<th>TBG (μg/ml)</th>
<th>TSH (μU/ml)</th>
<th>T3 (ng/dl)</th>
<th>T4 (μg/dl)</th>
<th>T3/T4 (ng/μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects (n=25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBG-deficient patient</td>
<td></td>
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<tr>
<td>euthyroid state (n=12)</td>
<td>n.d.</td>
<td>1.9±1.0</td>
<td>72±14</td>
<td>3.5±0.7</td>
<td>20.5±2.5a</td>
</tr>
<tr>
<td>hyperthyroid state (n=2)</td>
<td></td>
<td>1.1, 1.3</td>
<td>220, 259</td>
<td>8.8, 9.8</td>
<td>25.0, 26.4</td>
</tr>
<tr>
<td>hypothyroid state (n=4)</td>
<td></td>
<td>26.0±13.9</td>
<td>41±8</td>
<td>1.4±0.4</td>
<td>32.3±6.1b</td>
</tr>
<tr>
<td>Graves' disease with normal TBG level</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>euthyroid patients (n=6)</td>
<td>21.4±3.2</td>
<td>3.7±0.8</td>
<td>143±26</td>
<td>8.5±0.7</td>
<td>16.5±2.9</td>
</tr>
<tr>
<td>hyperthyroid patients (n=17)</td>
<td>18.1±2.3</td>
<td>1.0±0.3</td>
<td>513±160</td>
<td>20.0±4.9</td>
<td>26.0±7.0c</td>
</tr>
<tr>
<td>hypothyroid patients (n=6)</td>
<td>22.0±1.8</td>
<td>32.6±18.7</td>
<td>114±38</td>
<td>3.7±1.6</td>
<td>35.5±14.0c</td>
</tr>
</tbody>
</table>

Data shown are means±S.D. n, number of observations (TBG-deficient patient) or subjects (normal subjects & Graves' disease with normal TBG level), n.d., not detectable. -, not determined. Only statistical significance of difference in T3/T4 ratios is given. In the TBG-deficient patient, the ratios in the hyperthyroid and hypothyroid states were compared with that in the euthyroid state. In the patients with Graves' disease with normal TBG level, the ratios of hyperthyroid and hypothyroid patients were compared with that of euthyroid patients. The T3/T4 ratio in the euthyroid state of TBG-deficient patient was compared with those of normal subjects and euthyroid patients with Graves' disease with normal TBG level. No other comparison of T3/T4 ratios was made.

a p < 0.001 vs. normal subjects, p < 0.01 vs. euthyroid patients with Graves' disease with normal TBG level.

b p < 0.001 vs. euthyroid state of TBG-deficient patient.

c p < 0.01 vs. euthyroid patients with Graves' disease with normal TBG level.
As shown in Fig 1, plasma T3/T4 ratios of this patient fluctuated during his course. In order to ascertain relationships between the hormonal ratio and his thyroidal function, T3/T4 ratios during the untreated hyperthyroid state and the MMI-induced hypothyroid state were compared with those during his MMI-induced euthyroid state (Table 1). The T3/T4 ratios during his hypothyroid state were significantly higher than those during his euthyroid state. In addition, while a statistical significance was not proved, the T3/T4 ratios during his hyperthyroid state were also higher than those during his euthyroid state. In the patients with Graves' disease without abnormalities in serum TBG concentration, T3/T4 ratios of both groups of the untreated hyperthyroid patients and the MMI-induced hypothyroid patients were higher than those of the group of the MMI-induced euthyroid patients.

When the T3/T4 ratio during the euthyroid state of the totally TBG-deficient patient was compared with those of other euthyroid subjects, the ratio during the euthyroid state of this patient was significantly higher than those of both normal subjects and the MMI-induced euthyroid patients.

DISCUSSION

TBG deficiency first described in 1959 is not regarded as so rare a trait at present. However, TBG deficiency associated with hyperthyroidism is a rare condition. Moreover, only two cases have been reported as total TBG deficiency with hyperthyroidism.

The discrepancy between physical status and plasma concentrations of thyroid hormones in the present patient suggested reduced binding capacities for thyroid hormones in his serum. The measurements of his serum TBG immunoreactivity and TBG capacity revealed total TBG deficiency. The examination of his family members suggested partial TBG deficiency in both of his two daughters. These findings are compatible with an X-linked codominant mode of transmission of familial TBG deficiency. The causes lowering TBG level such as protein-caloric malnutrition, nephrotic syndrome, liver cirrhosis, and androgen or glucocorticoid excess were not found in this patient. All these findings suggest inherited total TBG deficiency in the patient.

Plasma T3/T4 ratios during the MMI-induced euthyroid state of this TBG-deficient patient were higher than those of normal subjects and of MMI-induced euthyroid patients with Graves' disease with normal serum TBG concentrations. High T3/T4 ratios in euthyroid subjects with TBG deficiency have also been noted by other workers. The plasma concentration of T4, compared with that of T3, much largely depends on plasma TBG level. A decrease in TBG concentration, therefore, more significantly reduces a plasma concentration of T4 than that of T3 and results in an increase in T3/T4 ratio. This could be true for the present patient.

Regarding the changes in T3/T4 ratio following alterations of thyroidal function, his T3/T4 ratio further increased in both the untreated hyperthyroid and the MMI-induced hypothyroid states. These findings on changes in his T3/T4 ratio accompanying thyroidal dysfunctions were comparable with those in the patients with Graves' disease with normal TBG levels: that both the untreated hyperthyroid and the MMI-induced hypothyroid patients showed higher T3/T4 ratios than the MMI-induced euthyroid patients (Table 1). The latter findings are compatible with those by other workers that patients with primary hyperthyroidism and patients with primary hypothyroidism show high T3/T4 ratios. In these primary thyroidal dysfunctions it has been shown that an increased peripheral conversion of T4 to T3 and an increased thyroidal secretion of T3 are responsible for the elevated T3/T4 ratios. Mechanism underlying these alterations in hormonal conversion and secretion are not yet known at present.

Although TBG carries the majority of circulating thyroid hormones to tissues in which enzymic conversion and degradation of the hormone occur, it has been shown that net production and net degradation rates of T3 and T4, and plasma concentrations of their free forms are normal in euthyroid TBG deficiency. From these findings, it has been widely accepted that TBG has little significance in maintaining normal metabolism of thyroid hormones. However, contradictions
have been recently raised that TBG plays regulatory roles in peripheral metabolism of thyroid hormones\(^{15-18}\). In addition, it has been obscure whether TBG is implicated in the alterations of thyroid hormone metabolism in primary thyroidal dysfunctions.

Since the association of TBG deficiency with a functional thyroidal disorder is rare, it might be not easy to study secretion and metabolism of thyroid hormones in patients with TBG deficiency with thyroidal dysfunction. By virtue of incidental fluctuations of thyroidal function, we could observe the alterations of T3/T4 ratio in the patient with total TBG deficiency. The alterations of hormonal ratio accompanying thyroidal dysfunctions in the TBG-deficient patient were qualitatively similar to those in patients with normal TBG levels. These results suggest that apart from the extent of the changes, the changes in hormonal conversion and secretion that raise T3/T4 ratio can occur in thyroidal dysfunctions even in the complete absence of TBG. Therefore, it seems unlikely that TBG is essential to these alterations of thyroid hormone metabolism in thyroidal dysfunctions. However, further studies on other TBG-deficient patients and more quantitative evaluation such as direct measurements of hormonal production and degradation are necessary to clarify whether TBG plays any subtle roles in these changes in hormonal metabolism in thyroidal dysfunctions or not.

REFERENCES


