

IN VITRO NUCLEAR MEDICINE

Clinical Evaluation of a Thyroxine-Binding Globulin Assay in Calculating a Free-Thyroxine Index

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**A free-thyroxine index (FTI) using the thyroxine-binding globulin (TBG) assay of Corning Medical (FTI-TBG) was compared with a FTI using a tri-iodothyronine (T<sub>3</sub>) uptake (FTI-T<sub>3</sub>U) in 173 patients. Markedly elevated FTI-TBG values were obtained in clinically euthyroid patients with a relatively low T<sub>3</sub> uptake and an elevated thyroxine level. In contrast, the FTI-T<sub>3</sub>U values for these same patients agreed with the clinical evaluation. Under these circumstances, the T<sub>3</sub> uptake is clearly superior to the TBG assay in calculating a free-thyroxine index.**

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One of the most commonly used tests for thyroid evaluation is a free-thyroxine index (FTI-T<sub>3</sub>U) that is calculated from a total thyroxine (T<sub>4</sub>) assay and a tri-iodothyronine (T<sub>3</sub>) uptake determination (T<sub>4</sub> × T<sub>3</sub> uptake). Previously we have shown that the FTI-T<sub>3</sub>U is superior to several free-T<sub>4</sub> assays in accurately assessing the thyroid status of clinically euthyroid patients with a relatively high or low T<sub>3</sub> uptake (1). Recently several investigators have suggested that a free-thyroxine index (FTI-TBG) that uses a thyroxine-binding globulin (TBG) assay instead of the T<sub>3</sub> uptake (T<sub>4</sub>/TBG) is superior in some respects to the FTI-T<sub>3</sub>U (2-4).

We examined a TBG radioimmunoassay\* and compared the FTI-TBG obtained with it against our current FTI-T<sub>3</sub>U in 49 consecutive clinically euthyroid patients, along with 49 hypothyroids and 48 hyperthyroids. We also determined the FTI-TBG in 27 consecutive clinically euthyroid patients who had a normal FTI-T<sub>3</sub>U with an elevated T<sub>4</sub> and a relatively low T<sub>3</sub> uptake.

METHODS

The TBG assay was run according to the manufacturer's protocol. Commercial antibody† and I-125 T<sub>4</sub>‡

were used in the T<sub>4</sub> test, and the TSH was assayed by a commercial method.¶ The FTI-T<sub>3</sub>U was calculated from a commercial T<sub>3</sub> uptake test.§

All patients underwent a physical examination and had appropriate thyroid function studies. Three discordant FTI-TBG values in Table 1 (Patients A, B, and C) were obtained from an initial group of patients (N = 35), of whom 24 were clinically euthyroid, 6 were hyperthyroid, and 5 were hypothyroid with either a relatively high (33-47%) or low (19-26%) T<sub>3</sub> uptake.

In order to establish a FTI-TBG normal range that incorporated our current T<sub>4</sub> assay, the FTI-T<sub>3</sub>U and FTI-TBG were determined in 49 consecutive clinically euthyroid, 49 hypothyroid, and 48 hyperthyroid patients

TABLE 1. INITIAL FOUR PATIENTS WITH DISCORDANT FTI-TBG VALUES\*

Patient	FTI-T <sub>3</sub> U	FTI-TBG	T <sub>4</sub>	T <sub>3</sub> U	TBG	TSH
A	2.6	10.9	13.9	19	12.7	4.2
B	2.5	9.7	13.4	19	13.8	2.3
C	2.4	6.9	12.0	20	17.5	2.9
D	2.6	9.0	12.2	21	13.6	3.7

\* Normal ranges: FTI-T<sub>3</sub>U 1.4-4.0; Corning FTI-TBG 2.5-6.0; T<sub>4</sub> 5.5-11.5 µg/dl; T<sub>3</sub> uptake 25-35%; Corning TBG 12.0-30.0 µg/ml; Pantex TSH <8 µIU/ml.

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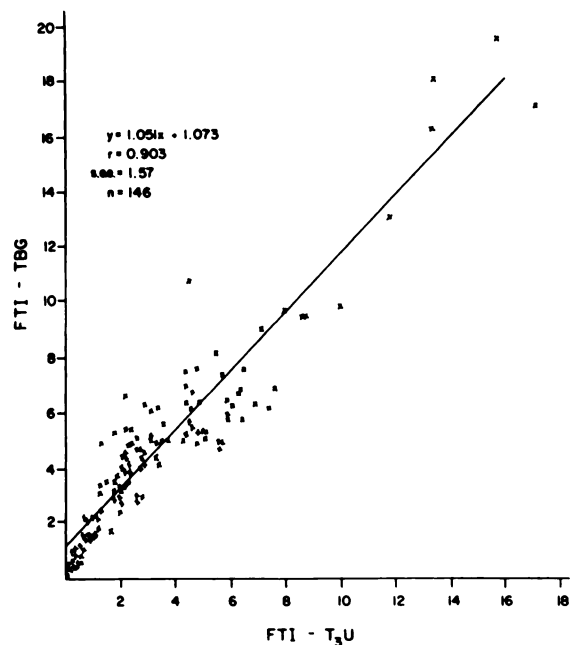


FIG. 1. Linear regression curve for FTI-TBG against FTI-T<sub>3</sub>U.

(N = 146). The plot obtained (Fig. 1) is a first-order linear regression by least squares. One discordant FTI-TBG value (Table 1, Patient D) was noted in the clinically euthyroid group of this population and was omitted from the linear regression curve. By letting X equal the FTI-T<sub>3</sub>U results, corresponding values for Y (FTI-TBG) were obtained from this regression curve. The calculated FTI-TBG normal range is 2.6–5.3, while the suggested normal range using Corning's T<sub>4</sub> assay is 2.5–6.0.

In addition we selected 27 consecutive clinically euthyroid patients with a relatively low T<sub>3</sub> uptake and high T<sub>4</sub> (Table 2). Five of these patients had no disease, 18 were on maintenance doses of thyroxine, and four were not on thyroxine but had goiters with no other abnormal clinical signs or symptoms.

#### RESULTS AND DISCUSSION

Since a high T<sub>3</sub> uptake is usually thought to indicate a low TBG concentration, and vice versa, the initial group we examined consisted of 35 patients with either a relatively high or low T<sub>3</sub> uptake. Three of the clinically euthyroid patients had a normal FTI-T<sub>3</sub>U, but a markedly elevated FTI-TBG (Table 1, Patients A, B, and C).

In order to standardize the FTI-TBG against the FTI-T<sub>3</sub>U, a linear regression curve was obtained from 146 consecutive clinically euthyroid, hypothyroid, and hyperthyroid patients (Fig. 1). Good correlation was obtained between the FTI-T<sub>3</sub>U and FTI-TBG ( $r = 0.903$ ), but once again a markedly elevated FTI-TBG value was obtained for a clinically euthyroid patient (Table 1, Patient D).

The common factors among the patients with the discordant FTI-TBG values were: (a) a clinically euthyroid status, (b) a normal FTI-T<sub>3</sub>U, (c) an elevated T<sub>4</sub>, and (d) a relatively low, but not necessarily abnormal, T<sub>3</sub> uptake. Consequently, we examined 27 clinically euthyroid patients with a normal FTI-T<sub>3</sub>U, a T<sub>3</sub> uptake <30%, and a T<sub>4</sub> >11.5 μg/dl (Table 2). All 27 had an FTI-TBG >5.3; therefore, all would be in the hyperthyroid range if the TBG assay was used instead of the T<sub>3</sub> uptake. The standard error of estimate (s.e.e.) in the linear regression was 1.56. This value is a general indicator with which the fitted regression function predicts the dependence of Y (FTI-TBG) on X (FTI-T<sub>3</sub>U). When the s.e.e. is added to 5.3, the upper limit of the calculated FTI-TBG, the normal range is extended to 6.9. Even with this expanded normal range, a sizable percentage of discordant FTI-TBG values was obtained. Seventeen patients (63.0%) had an FTI-TBG >7.0 and in 10 (37.0%) it was above 9.0, yet these patients are clinically euthyroid, with a normal FTI-T<sub>3</sub>U.

One purported disadvantage of the T<sub>3</sub> uptake test is that it does not specifically correspond to TBG concentrations. This is partly because the T<sub>3</sub> uptake measures not only the unsaturated binding capacity of TBG, but also includes that of any other available T<sub>4</sub>-binding

TABLE 2. FTI-TBG DEVIATIONS IN EUTHYROID GROUP WITH LOW T<sub>3</sub> UPTAKE AND HIGH T<sub>4</sub> VALUES\*

Patient	FTI-T <sub>3</sub> U	FTI-TBG	T <sub>4</sub>	T <sub>3</sub> U	TBG	TSH
1-T	3.4	9.5	14.8	23	15.5	3.3
2-T	3.7	9.6	15.4	24	16.0	2.3
3-G	2.9	10.6	13.3	22	12.6	2.3
4-T	3.6	9.4	14.5	25	15.5	1.9
5-T	3.5	9.9	14.6	24	14.8	2.9
6-T	2.8	6.3	11.7	24	18.7	3.9
7-T	3.8	12.3	17.4	22	14.2	3.0
8-T	3.6	9.4	14.5	25	15.5	2.7
9-N	2.8	8.7	12.9	22	14.8	2.9
10-N	2.9	8.4	12.4	23	14.8	2.5
11-G	3.0	5.7	11.6	26	20.2	3.0
12-T	2.7	7.6	12.1	22	15.9	3.8
13-N	3.2	12.2	15.0	21	12.3	3.4
14-T	3.9	7.2	13.4	29	18.7	2.3
15-T	3.0	6.5	11.7	26	17.9	4.0
16-T	3.7	6.8	12.6	29	18.4	2.8
17-T	3.7	6.6	12.9	29	19.6	2.8
18-N	2.9	7.1	11.9	24	16.7	3.0
19-T	2.9	11.4	13.2	22	11.6	3.4
20-G	3.0	11.7	14.4	21	12.3	2.9
21-T	3.5	6.3	12.4	28	19.8	2.5
22-T	3.6	6.9	12.7	28	18.4	2.1
23-N	2.7	7.5	11.7	23	15.5	2.7
24-T	3.5	6.3	12.4	28	19.6	2.4
25-T	3.7	8.2	14.3	26	17.4	2.6
26-T	3.7	5.9	12.7	29	21.7	2.7
27-G	3.4	6.6	12.1	28	18.2	3.6

\* Normal ranges are listed under Table 1. FTI-TBG calculated normal range is 2.6–5.3. T = on thyroxine; G = goiter, not on thyroxine; N = no disease.

protein. This lack of specificity is not a problem since TBG is the primary T<sub>4</sub>-binding protein. In our current T<sub>3</sub> uptake assay, thyroxine-binding prealbumin is not one of the available proteins, since such potential binding of T<sub>3</sub>, if present (5,6), is inhibited by a barbital buffer. In those cases in which binding proteins other than TBG play a prominent role, such nonspecificity could be an advantage, since a more meaningful FTI may be obtained. Unfortunately, when very high or low amounts of binding proteins are present, the T<sub>3</sub> uptake test does lose its sensitivity.

The TBG assay also has its sensitivity limitations. Since it is specific for TBG, an FTI-TBG for a person with a very low TBG concentration will usually produce an elevated result regardless of the clinical status involved. Perhaps in this situation binding proteins other than TBG assume increased importance and distort the FTI-TBG.

The clinically euthyroid population (n = 49) had a TBG concentration of  $22.6 \pm 3.4 \mu\text{g/ml}$  ( $\bar{x} \pm \text{s.d.}$ ), whereas the clinically euthyroid patients with the elevated FTI (n = 27) had a TBG concentration of  $16.5 \pm 2.7 \mu\text{g/ml}$  (P < 0.01). It is possible that T<sub>4</sub>-binding proteins other than TBG are more prominently involved in the latter group. The T<sub>3</sub> uptake reflects this increased involvement, but the more specific TBG assay does not. In such circumstances, the T<sub>3</sub> uptake is clearly superior

to the TBG assay in the calculation of a free-thyroxine index.

#### FOOTNOTES

- \* Corning Medical, Medfield, MA.
- † Antibodies Inc., Davis, CA.
- ‡ Amersham, Arlington Heights, IL.
- § Pantex, Santa Monica, CA.
- ¶ Diagnostic Corporation of America, Arlington, TX.

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