
Clinical Evaluation of a Thyroxine Binding Globulin Assay in Calculating a Free Thyroxine Index in Normal, Thyroid Disease, and Sick Euthyroid Patients

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As assay for thyroxine binding globulin (TBG) that measures the thyroxine binding capacity of TBG and other proteins was used to calculate a free thyroxine index (FTI) in 108 consecutive thyroid patients, 2,559 normal patients, and 152 sick euthyroid patients. The TBG assay compared favorably with the triiodothyronine (T3) uptake test in producing a FTI for the clinical evaluation of thyroid patients. In addition, it did not suffer the disadvantages inherent in assays specific for only TBG. In the sick euthyroid population, the TBG assay produced an FTI that was more consistent with the clinical evaluation than did the T3 uptake test.

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There are several disadvantages in using a triiodothyronine (T3) uptake test to calculate a free thyroxine index (FTI-T3U). These include the use of T3 instead of thyroxine (T4) to measure the saturated binding capacity of T4-binding proteins, the absence of a defined standard curve for a more quantitative measurement, and the loss of sensitivity when very high or low amounts of T4-binding proteins are present.

These difficulties can be largely overcome by using a thyroxine binding globulin (TBG) assay to calculate the free thyroxine index (FTI-TBG). In addition, the TBG assay has been reported to be more useful than the T3U test in diagnosing the sick euthyroid hospital patient (1). However, we previously demonstrated that problems may occur if a radioimmunoassay specific for TBG is used (2). Falsely elevated FTI-TBG values are obtained in clinically euthyroid patients who have significant amounts of T4-binding proteins other than TBG. In these cases, a less specific TBG assay would be more advantageous in calculating a meaningful FTI-TBG, since TBG as well as other T4 binding proteins would be detected.

Consequently, we examined an assay for TBG* which measures the T4-binding capacity of proteins including TBG in a relatively large group of thyroid patients, both inpatient and outpatient. In addition, we examined the usefulness of this test in a subgroup of sick euthyroid patients.

MATERIALS AND METHODS

TBG Assay

The manufacturer states that the SPINSEP TBG is a modified protein binding analysis which measures the effect of T4-binding proteins in serum. A large excess of T4 in the reagent saturates the binding sites of any available T4-binding proteins with labeled T4. Resin tablets which bind any remaining free (nonprotein bound) T4 are subsequently added. Thus the protein bound T4 remains in solution. The standard curve is a plot of TBG concentration (in $\mu\text{g}/\text{dl}$ T4 binding capacity) versus the radioactivity of the centrifuged resin pellet which contains the free (labeled and unlabeled) T4.

FTI Calculation

The FTI-T3U is calculated from a total T4 assay and a T3 uptake determination ($T4 \times T3U$), while the FTI-TBG uses a TBG assay instead of the T3 uptake ($T4/\text{TBG} \times 10$). The calculated ratio ($T4/\text{TBG}$) is arbitrarily multiplied by 10 in order to obtain a whole number for the index. The TBG and T3 uptake tests used throughout this study were made by the same manufacturer.

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Population One

One hundred and eight consecutive thyroid outpatients were seen by one of us (SSS) and had or were suspected of having thyroid disease. Of these patients, 81 were determined to be clinically euthyroid, 16 were hypothyroid and 11 hyperthyroid. The average age (mean \pm s.d.) was 44.5 ± 15.8 yr.

Population Two

These patients were 4,675 consecutive patients on whom thyroid studies were performed (St. John Hospital). Subgroup A consisted of 2,559 patients with normal T4, TBG, T3 and TSH levels (mean age 49 ± 21 yr). Of this normal group, 397 (15.5%) were inpatients. Subgroup B consisted of 152 sick euthyroid patients who had a normal serum TSH and depressed T3 and TBG levels (3-7). The mean age was 66.6 ± 20.5 yr. There were 139 (91.4%) inpatients.

RESULTS AND DISCUSSION

The FTI-TBG showed good correlation with the FTI-T3U ($r = 0.888$) in 108 consecutive patients (population one). Both methods correctly identified the clinical status and agreed with each other in all but five cases (Table 1). Interestingly, the FTI-T3U was slightly elevated in all five patients while the FTI-TBG was normal. Patients 2 and 5 had minimal nonspecific symptoms sometimes seen in hyperthyroidism which agreed with the FTI-T3U. Patients 1, 3, and 4 had no symptoms of hyperthyroidism and agreed better with the FTI-TBG. Thus no significant difference was observed between the two methods.

In population one there were 17 patients who met the criteria necessary for producing falsely elevated FTI-TBG levels (Table 2). All 17 patients were clinically euthyroid with a normal FTI-T3U, a T3 uptake less than average (not necessarily abnormal), and a T4 level greater than normal. Only one of these 17 patients was on estrogens. As we previously reported (2), an assay specific for TBG will produce markedly elevated FTI-TBG values in these types of patients. This assay for TBG produced FTI-TBG values which were normal and which agreed with the FTI-T3U and the clinical

TABLE 1
Population One—Patients with Discordant FTI-TBG/FTI-T3U Values*

Patient	FTI-T3U	FTI-TBG	T4	T3U	TBG	Symptoms
1	4.4	6.0	14.8	30	24.7	No
2	4.4	6.4	15.6	28	24.3	Yes
3	4.4	5.1	15.0	29	29.4	No
4	4.2	6.5	15.7	27	24.1	No
5	4.2	5.9	15.0	28	25.4	Yes

* Normal ranges: FTI-T3U: 1.4-4.0; FTI-TBG: 2.6-6.8; T4: 5.5-11.5 μ g/dl; T3U: 25-35%; TBG: 17-27 μ g/dl. Symptoms include sleeplessness, nervousness, tremor and palpitation. All five patients were on thyroxine.

TABLE 2
Population One—Euthyroid Group with Low T3 Uptake and High T4 Values*

Patient	FTI-T3U	FTI-TBG	T4	T3U	TBG
1-T	3.4	6.6	11.7	29	17.6
2-T	3.8	5.3	14.5	26	27.4
3-GT	3.0	5.8	12.5	24	21.4
4-GT	3.5	5.3	12.6	28	23.7
5-GT	3.5	5.4	12.1	29	22.4
6-T	3.4	6.5	12.5	27	19.1
7-T	3.9	6.7	13.5	29	20.2
8-GT	3.7	5.9	12.9	29	22.0
9-G	2.6	4.0	11.6	22	29.1
10-GT	3.3	4.8	12.1	27	25.2
11-GT	3.3	5.0	15.5	21	31.2
12-GT	3.2	4.9	12.6	25	25.9
13-T	3.7	6.6	12.8	29	19.5
14-T	3.6	5.7	16.5	22	28.9
15-T	3.1	5.2	12.1	26	23.2
16-T	3.5	6.0	13.3	26	22.3
17-GT	3.1	5.7	12.4	25	21.6

* Normal ranges are listed under Table 1. T = on thyroxine; G = goiter

evaluation in all 17 cases. Such results would not be expected with an assay specific for TBG.

In population two the FTI-TBG and FTI-T3U levels of 2,559 clinically euthyroid patients and 152 sick euthyroid patients were compared (Table 3). Of the 152 sick euthyroid patients, 123 (81%) had a normal FTI-TBG, while 15 (10%) had an elevated and 14 (9%) had a low FTI-TBG. In contrast only 79 (52%) patients of the sick euthyroid patients had a normal FTI-T3U, while 72 (47%) patients had a low and one patient (1%) had an elevated FTI-T3U.

The average T4 of the sick euthyroid group (5.3 ± 1.5 μ g/dl) was much lower than the average T4 of the clinically euthyroid patients (8.7 ± 1.7). The data in Table 4 indicate that still lower T4 values (1.8 ± 0.7) will produce either a low FTI-T3U or FTI-TBG that is

TABLE 3
Population Two—Comparison of FTI-TBG and FTI-T3U in Normal Euthyroid and Sick Euthyroid Patients

	Normal patients Subgroup A (n = 2,559)	Sick euthyroid Subgroup B (n = 152)	Normal range*
FTI-TBG	3.8 (0.7 [†])	3.9 (0.9)	2.5-5.7
FTI-T3U	2.4 (0.5)	1.8 (0.5)	1.7-3.8
T4	8.7 (1.7)	5.3 (1.5)	5.0-12.5 μ g/dl
T3	125 (24)	28.0 (12)	80-200 ng/dl
T3U	28.0 (2.0)	34.3 (3.9)	26.0-34.0%
TBG	22.9 (2.3)	13.2 (2.6)	17.0-27.0 μ g/dl

* Normal ranges differ from those in Tables 1 and 2, since the assays represented in Table 3 were done in a different laboratory. Only the TBG and T3U tests were common to both laboratories.

[†] Standard deviation.

TABLE 4
Population Two (Subgroup B)—Comparison of
Discordant FTI-TBG Populations in Sick Euthyroid
Patients*

	Low FTI-TBG (n = 14)	Elevated FTI-TBG (n = 15)	Normal FTI-TBG (n = 123)	Total sick euthyroid (n = 152)
FTI-TBG	1.6 (0.5) [†]	6.4 (0.7)	3.9 (0.9)	3.9 (0.9)
FTI-T3U	0.7 (0.3)	2.8 (0.6)	1.8 (0.5)	1.8 (0.5)
T4	1.8 (0.7)	8.5 (1.7)	5.3 (1.5)	5.3 (1.5)
T3	21 (6)	42 (11)	27 (13)	28 (12)
T3 Uptake	41.5 (6.3)	32.7 (2.5)	33.7 (3.7)	34.3 (3.9)
TBG	11.0 (2.1)	13.2 (2.7)	13.5 (2.6)	13.2 (2.6)

* Normal ranges listed in Table 3.

[†] Standard deviation.

inconsistent with the "normal" thyroid diagnosis of the sick euthyroid. There is an interesting subpopulation of 15 sick euthyroid patients with an elevated FTI-TBG (Table 4). The T4 as well as the FTI-T3U were normal. At present we cannot offer an adequate explanation of why the FTI-T3U appears to correctly classify this small subpopulation. Overall, however, the FTI-TBG more consistently classified the sick euthyroid patients as euthyroid. The mean FTI-TBG of 3.9 agreed very well with the mean of 3.8 for the 2,559 clinically euthyroid patients (normal range 2.5–5.7), while the mean FTI-T3U of 1.8 was significantly lower than the normal group mean of 2.4 ($p < 0.001$).

The T3 uptake values, like those in the assay for TBG, reflect the presence of proteins other than TBG. However, in unusual situations such as the sick euthyroid, the use of labeled T4 instead of T3 is an apparent advantage (7). The fact that 81% of the sick euthyroid patients had normal FTI-TBG levels as opposed to only 52% for the FTI-T3U indicates a much better patients classification capability for the TBG assay ($p < 0.001$). The TBG assay's superiority over the T3U is further

demonstrated by the mean FTI in the sick euthyroid group (Subgroup B). The average sick euthyroid FTI-TBG was virtually identical to that of the normal population, while the average sick euthyroid FTI-T3U was significantly lower than in the normal group.

In conclusion, this TBG assay compares favorably with the T3 uptake in producing a FTI for the clinical evaluation of thyroid patients while suffering none of the disadvantages of a more specific TBG assay. In a sick euthyroid population, this TBG assay produced an FTI that was more consistent with the clinical evaluation than did the T3 uptake.

NOTE

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