

IN VITRO NUCLEAR MEDICINE

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

Walter E. Szpunar, Sheldon S. Stoffer, and Miroslava N. Bednarz

Associated Endocrinologists, Southfield, Michigan

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_3) uptake (FTI- T_3U) in 173 patients. Markedly elevated FTI-TBG values were obtained in clinically euthyroid patients with a relatively low T_3 uptake and an elevated thyroxine level. In contrast, the FTI- T_3U values for these same patients agreed with the clinical evaluation. Under these circumstances, the T_3 uptake is clearly superior to the TBG assay in calculating a free-thyroxine index.

J Nucl Med 22: 793-795, 1981

One of the most commonly used tests for thyroid evaluation is a free-thyroxine index (FTI- T_3U) that is calculated from a total thyroxine (T_4) assay and a tri-iodothyronine (T_3) uptake determination ($T_4 \times T_3$ uptake). Previously we have shown that the FTI- T_3U is superior to several free- T_4 assays in accurately assessing the thyroid status of clinically euthyroid patients with a relatively high or low T_3 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_3 uptake (T_4/TBG) is superior in some respects to the FTI- T_3U (2-4).

We examined a TBG radioimmunoassay* and compared the FTI-TBG obtained with it against our current FTI- T_3U 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_3U with an elevated T_4 and a relatively low T_3 uptake.

METHODS

The TBG assay was run according to the manufacturer's protocol. Commercial antibody† and I-125 T_4 ‡

were used in the T_4 test, and the TSH was assayed by a commercial method.|| The FTI- T_3U was calculated from a commercial T_3 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_3 uptake.

In order to establish a FTI-TBG normal range that incorporated our current T_4 assay, the FTI- T_3U 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_3U	FTI-TBG	T_4	T_3U	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_3U 1.4-4.0; Corning FTI-TBG 2.5-6.0; T_4 5.5-11.5 μ g/dl; T_3 uptake 25-35%; Corning TBG 12.0-30.0 μ g/ml; Pantex TSH <8 μ IU/ml.

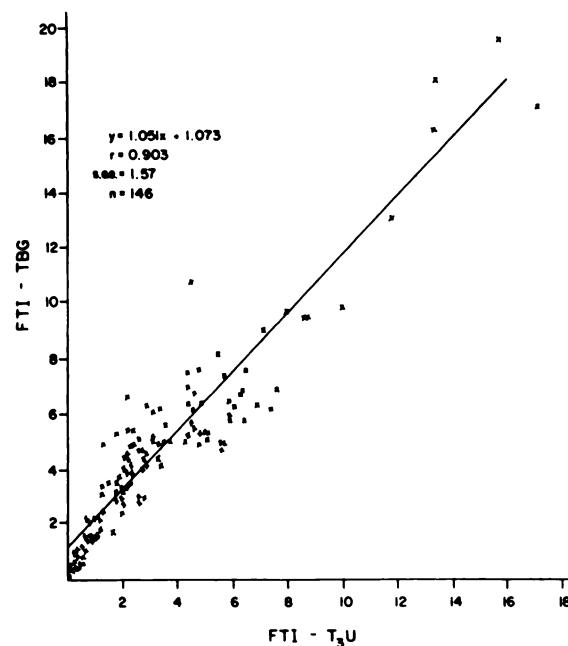


FIG. 1. Linear regression curve for FTI-TBG against FTI-T₃U.

(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-T₃U 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 T₄ assay is 2.5–6.0.

In addition we selected 27 consecutive clinically euthyroid patients with a relatively low T₃ uptake and high T₄ (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 T₃ 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 T₃ uptake. Three of the clinically euthyroid patients had a normal FTI-T₃U, but a markedly elevated FTI-TBG (Table 1, Patients A, B, and C).

In order to standardize the FTI-TBG against the FTI-T₃U, a linear regression curve was obtained from 146 consecutive clinically euthyroid, hypothyroid, and hyperthyroid patients (Fig. 1). Good correlation was obtained between the FTI-T₃U 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-T₃U, (c) an elevated T₄, and (d) a relatively low, but not necessarily abnormal, T₃ uptake. Consequently, we examined 27 clinically euthyroid patients with a normal FTI-T₃U, a T₃ uptake <30%, and a T₄ >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 T₃ 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-T₃U). 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-T₃U.

One purported disadvantage of the T₃ uptake test is that it does not specifically correspond to TBG concentrations. This is partly because the T₃ uptake measures not only the unsaturated binding capacity of TBG, but also includes that of any other available T₄-binding

TABLE 2. FTI-TBG DEVIATIONS IN EUTHYROID GROUP WITH LOW T₃ UPTAKE AND HIGH T₄ VALUES*

Patient	FTI-T ₃ U	FTI-TBG	T ₄	T ₃ 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 T₄-binding protein. In our current T₃ uptake assay, thyroxine-binding prealbumin is not one of the available proteins, since such potential binding of T₃, 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 T₃ 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 $22.6 \pm 3.4 \mu\text{g}/\text{ml}$ ($\bar{x} \pm \text{s.d.}$), whereas the clinically euthyroid patients with the elevated FTI (n = 27) had a TBG concentration of $16.5 \pm 2.7 \mu\text{g}/\text{ml}$ ($P < 0.01$). It is possible that T₄-binding proteins other than TBG are more prominently involved in the latter group. The T₃ uptake reflects this increased involvement, but the more specific TBG assay does not. In such circumstances, the T₃ 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.

REFERENCES

1. SZPUNAR WE, BLOCK M, BEDNARZ MN, et al: Clinical evaluation of three free-thyroxine assays. *J Nucl Med* 21: 576-578, 1980
2. BURR WA, EVANS SE, LEE J, et al: The ratio of thyroxine to thyroxine-binding globulin in the assessment of thyroid function. *Clin Endocrinol* 11:333-342, 1979
3. ALBERTSON DF: Which free thyroxine index is best? An *in vitro* study. *Clin Chem* 26:1067-1068, 1980 (abst)
4. CHAN DW, PERLSTEIN MT, STEM J, et al: Three approaches for measuring thyroxine-binding globulin. *Clin Chem* 26:1070, 1980 (abst)
5. INGBAR SH: Observations concerning the binding of thyroid hormones by human serum prealbumin. *J Clin Invest* 42: 143-160, 1963
6. LARSEN PR: Salicylate-induced increases in free triiodothyronine in human serum. Evidence of inhibition of triiodothyronine binding to thyroxine-binding globulin and thyroxine-binding prealbumin. *J Clin Invest* 51:1125-1134, 1972

27th ANNUAL MEETING SNM SOUTHWESTERN CHAPTER TECHNOLOGIST SECTION

March 26-28, 1982

North Park Inn

Dallas, Texas

Announcement and Call for Abstracts and Exhibits

The Scientific Program Committee invites for presentation abstracts of original papers to be given at the technologist session of the 27th Annual Meeting of the Southwestern Chapter of the Society of Nuclear Medicine.

Papers are to be seven to ten minutes in length; each abstract should be typed; contain a statement of purpose, methods used, results, as well as the conclusion; and should not exceed 250 words. The title of the paper and names of authors should be stated as they are to appear in the program.

Abstract and exhibit forms can be obtained from the address below.

Please send the original abstract form and four copies to:

Ann A. Thorne
Radiation Center
1425 E. Enderly Place
Fort Worth, TX 76104