



GREGG H. FAIMAN, MD
Department of Endocrinology,
Cleveland Clinic.

CHARLES FAIMAN, MD
Chairman, Department of
Endocrinology, Cleveland Clinic.

A 29-year-old man with abnormal thyroid function tests

A 29-YEAR-OLD CAUCASIAN MAN is referred to a tertiary care outpatient clinic for evaluation of hyperthyroidism. Earlier, during an investigation of diarrhea, he had been found to have a total serum thyroxine (T_4) value of 20.9 $\mu\text{g/dL}$ (normal: 4.5–12.0), and a total triiodothyronine (T_3) value of 299 ng/dL (normal: 60–181). His primary care physician had prescribed propylthiouracil, which the patient had not taken.

The patient denies symptoms of temperature intolerance, tremor, edema, visual abnormalities, or weight change. He takes cispripide for gastrointestinal reflux, but no other medications. He does not know of any family members with thyroid abnormalities.

Physical examination reveals a euthyroid man, 178 cm in height and 106.4 kg in weight. His blood pressure is 124/80 mm Hg sitting, and his resting heart rate is 66 beats per minute. His thyroid gland is nontender and normal in size, shape, and texture. There is no evidence of exophthalmos, tremor, or hyperreflexia.

■ WHEN IS HYPERTHYROXINEMIA NOT HYPERTHYROIDISM?

1 What single test would be most helpful in delineating the patient's thyroid status?

- ☐ TSH (thyroid-stimulating hormone)
- ☐ Thyroid receptor antibodies
- ☐ Radioactive iodine uptake and scan
- ☐ T_3 resin uptake ($T_3\text{RU}$)
- ☐ None of the above

An ultrasensitive TSH assay is the single best indicator of thyroid function and should be used as the initial screening test in patients suspected of having either hypo- or hyperthy-

roidism. The patient's laboratory report came back the next day showing a TSH level of 0.6 $\mu\text{U/mL}$ (normal: 0.4–5.5). In addition, his free T_4 value was 1.4 ng/dL (normal: 0.8–1.8).

■ WHAT IS THE NEXT STEP?

2 You should now do which of the following?

- ☐ Order a radioactive iodine uptake and scan
- ☐ Order thyroid receptor antibodies
- ☐ Observe and reassure the patient
- ☐ Start propylthiouracil
- ☐ Consult an endocrinologist

The correct approach is observation and reassurance. This patient has no symptoms or clinical signs of hyperthyroidism, and his TSH and free T_4 levels are normal. The most likely explanation for the elevations in total T_4 and T_3 is an elevation in a thyroid-binding protein.

■ T_4 and T_3 , BOUND AND FREE

Of the T_4 and T_3 in the circulation, more than 99% is bound to proteins, primarily thyroxine-binding globulin (TBG) and transthyretin (also called thyroxine-binding prealbumin). Normally, 75% to 80% of T_4 binds to TBG, with nearly all of the remainder binding to transthyretin and albumin.¹ Only free T_4 and T_3 are biologically active; the bound T_4 and T_3 serve as reservoirs for the free hormones. The serum T_4 value is a measure of both free T_4 and the T_4 that is bound to protein.

Because TBG binds both T_4 and T_3 , whereas transthyretin binds T_4 alone, the biochemical findings in this patient support the

Serum T_4 measures both free T_4 and protein-bound T_4

TABLE 1

Conditions associated with alterations in thyroxine-binding globulin (TBG) concentration

CONDITION	INCREASED TBG	DECREASED TBG
Genetic	Inherited TBG excess	Inherited TBG deficiency (complete and partial)
Hormonal	Hyperestrogenic states Choriocarcinoma Estrogen-producing tumors Estrogen therapy Newborn state Pregnancy (especially molar)	Androgen and anabolic steroid use
Drug use	Clofibrate 5-Fluorouracil Heroin Methadone Nicotinic acid Perphenazine Tamoxifen	Glucocorticoids L-Asparaginase
Diseases	Acute intermittent porphyria Acute viral hepatitis Chronic active hepatitis Collagen diseases Hepatocellular carcinoma HIV infection Hypogammaglobulinemia Hypothyroidism Myeloma Primary biliary cirrhosis	Acromegaly (active) Carbohydrate deficient glycoprotein syndrome Cirrhosis of liver Galactosemia Hyperthyroidism Major illness Nephrotic syndrome Protein-calorie malnutrition Protein-losing enteropathy

SOURCE: MODIFIED FROM REFETTOFF AND NICOLOFF, REFERENCE 1

Only free T_3 and T_4 are biologically active

diagnosis of euthyroid hyperthyroxinemia due to TBG excess. This condition was confirmed by obtaining a TBG level, which was elevated at 70 $\mu\text{g/mL}$ (normal: 12.2–33.0). No further evaluation was required, and the patient was advised against taking the antithyroid medicine recommended by the referring doctor.

WHAT CAN CAUSE AN EXCESS OF THYROXINE-BINDING GLOBULIN?

The serum TBG concentration can increase or decrease with use of a variety of drugs, and in many diseases and hormonal conditions (TABLE 1).^{1,2}



Hereditary TBG excess was first described in 1959.³ TBG is a 54-kDa acidic glycoprotein encoded by a single gene copy, mapping to the q22.2 band region of the long arm of the human X chromosome.⁴ Numerous analyses have indicated that all inherited TBG abnormalities are X-chromosome linked.⁵⁻⁹ Gene amplification has recently been reported to be the cause of hereditary TBG excess in two families.¹⁰ However, other causes remain possible.^{1,11} The prevalence of euthyroid hyperthyroxinemia caused by hereditary excess of TBG in the general population is 1 in 25,000 live births.¹²

No direct relationship exists between defective types of TBG and other diseases. TBG defects have been reported in patients with mental retardation, Turner's syndrome and mosaic variants, goiter, ectopic thyroid, asthma, pernicious anemia, herpes infection, hyperlipoproteinemia, and hereditary anhydrotic ectodermal dysplasia, but the associations were thought to coincidental.¹¹

■ T₄ AND T₃ UPTAKE TESTING IN HEREDITARY TBG EXCESS

Although many causes of euthyroid hyperthyroxinemia have been described (TABLE 2),¹² a careful history and physical examination, coupled with the prudent use of laboratory evaluations, should yield the correct diagnosis. Physicians should consider the diagnosis of hereditary TBG excess to avoid unnecessary and potentially harmful treatment.

Because the results of thyroid uptake tests are frequently misinterpreted, we include a brief summary below.

T₄ uptake (T₄U) is the amount of fluorescein-labeled T₄ that binds to serum protein. The result is expressed as a binding ratio compared with a control serum pool. The normal range varies from laboratory to laboratory; at our hospital, it is 0.7 to 1.2.

The free thyroxine index (FTI) is the total T₄ level divided by the T₄U. Thus, an elevated total T₄ level caused by TBG excess would be adjusted downwards by the concomitant elevation in the T₄U, yielding a normal FTI value (ie, 6.4 to 10.7 µg/dL).

T₃ resin uptake (T₃RU), in contrast to T₄U, makes use of a different ligand (radiola-

TABLE 2

Causes of euthyroid hyperthyroxinemia

Altered T₄ binding

- Increased TBG level
 - Liver diseases
 - Acute intermittent porphyria
 - Hepatitis
 - Primary biliary cirrhosis
 - Drugs
 - Narcotics
 - 5-Fluorouracil
 - Clofibrate
 - Hyperestrogenism
 - Estrogen therapy
 - Estrogen-producing tumors
 - Pregnancy
 - Chorionic gonadotropin-producing tumors
 - Newborns
- Lymphosarcoma
- X-linked hereditary excess
- Familial dysalbuminemia
- Increased transthyretin (binds T₄ alone)
 - Hereditary or acquired
- Thyroid hormone binding autoantibodies

Thyroxine resistance

- Generalized
- Selective resistance to intracellular transport of T₄

Nonthyroidal illness

- Medical or surgical
- Psychiatric

Drugs

- Oral cholecystographic agents
- Amiodarone
- Amphetamines
- Heparin
- Propranolol (high doses)

High altitude

SOURCE: FROM TUCKER, REFERENCE 12

A TSH assay is the best indicator of thyroid function

beled T₃ instead of fluorescein-labeled T₄) and measures the proportion of trace ligand *unbound* to serum protein and trapped by an added resin sponge. Results are usually expressed as a percentage bound to the resin, and a new value, termed T₇, is derived: T₃RU



THE CLEVELAND CLINIC FOUNDATION

10th Annual

INTENSIVE REVIEW OF INTERNAL MEDICINE

Featuring:

Board simulation sessions

Interactive computer system
for lectures and simulation sessions

June 7-12, 1998

Renaissance Cleveland Hotel
Cleveland, Ohio

For further information please write or call:

The Cleveland Clinic Educational Foundation
Continuing Education Department
9500 Euclid Avenue, TT-31
Cleveland, OH 44195

216-444-5695
800-762-8173
216-445-9406 (FAX)

FAIMAN AND FAIMAN



× total T_4). Similar to the T_4U test described above, values may also be expressed as a ratio to a control serum pool. In this case, however, the FTI is calculated in an obverse manner: $FTI = \text{total } T_4 \times T_3RU \text{ ratio}$.

Patients with hereditary TBG excess have elevations in T_4 , T_3 , and T_4U , and decreased T_3RU values. These abnormalities are often found incidentally. However, their values for TSH, FTI, free T_4 , and free T_3 are normal. Clinically, the patients are euthyroid and frequently have a family history of abnormal thyroid function tests.

REFERENCES

1. Refetoff S, Nicoloff JT. Thyroid hormone transport and metabolism. In: Degroot LJ, Besser M, Burger HG, et al, editors. *Endocrinology*, 3rd ed. Philadelphia: WB Saunders, 1995:560-582.
2. Sellmeyer DE, Grunfeld C. Endocrine and metabolic disturbances in human immunodeficiency infection and the acquired immune deficiency syndrome. *Endocrine Rev* 1996; 17:518-532.
3. Beierwaltes WH, Robbins J. Familial increase in the thyroxine-binding sites in serum α globulin. *J Clin Invest* 1959; 38:1683-1688.
4. Mori Y, Yoshitaka M, Oiso Y, Hisao S, Takazumi K. Precise localization of the human thyroxine-binding globulin gene to chromosome Xq22.2 by fluorescence in situ hybridization. *Hum Genet* 1995; 96:481-482.
5. Burr WA, Ramsden DB, Hoffenberg R. Hereditary abnormalities of thyroxine-binding globulin concentration. *Quart J Med* 1980; 195:295-313.
6. Refetoff S, Robin NI, Alper CA. Study of four new kindreds with inherited thyroxine-binding globulin abnormalities. *J Clin Invest* 1972; 51:848-867.
7. Penhaligon J, Welby ML. Elevated serum thyroxine-binding globulin by X-chromosome transmission. *Acta Endocrinol (Copenh)* 1982; 99:393-396.
8. Jones EJ, Seal US. X-chromosome linked inheritance of elevated thyroxine-binding globulin. *J Clin Endocrinol Metab* 1967; 27:1521-1528.
9. Thomson JA, Meredith FM, Baird SG, McAinsh WR, Hutchison JH. Raised free thyroxine values in patients with familial elevation of thyroxine binding globulin. *Quart J Med* 1972; 161:49-56.
10. Mori Y, Miura Y, Takeuchi H, et al. Gene amplification as a cause of inherited thyroxine-binding globulin excess in two Japanese families. *J Clin Endocrinol Metab* 1995; 80:3758-3762.
11. Refetoff S. Inherited thyroxine-binding globulin abnormalities in man. *Endocrine Rev* 1989; 10:275-293.
12. Tucker WS. Euthyroid hyperthyroxinemia due to familial excess of thyroxine-binding globulin. *South Med J* 1989; 82:368-371.

ADDRESS: Charles Faiman, MD, Department of Endocrinology, A30, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.