A SELF-TEST OF CLINICAL RECOGNITION

CME CREDIT

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 µg/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 cisapride 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_3RU)
- ❑ 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 hyperthyroidism. The patient's laboratory report came back the next day showing a TSH level of 0.6 µU/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.

Serum T_4 measures both free T_4 and protein-bound T_4

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

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

SOURCE: MODIFIED FROM REFETOFF 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 µg/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]

T_4 AND T_3 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.

T_4 uptake (T_4U) is the amount of fluorescein-labeled T_4 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 T_4 level divided by the T_4U. Thus, an elevated total T_4 level caused by TBG excess would be adjusted downwards by the concomitant elevation in the T_4U, yielding a normal FTI value (ie, 6.4 to 10.7 µg/dL).

T_3 resin uptake (T_3RU), in contrast to T_4U, makes use of a different ligand (radiolabeled T_3 instead of fluorescein-labeled T_4) 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 T_7, is derived: T_3RU

TABLE 2

Causes of euthyroid hyperthyroxinemia

- **Altered T_4 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 T_4 alone)
    - Hereditary or acquired
  - Thyroid hormone binding autoantibodies
- **Thyroxine resistance**
  - Generalized
  - Selective resistance to intracellular transport of T_4
- **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

× 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 = total $T_4 \times T_3RU$ 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.*