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# 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  $\text{ng/dL}$  (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  $\text{ng/dL}$  (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.<sup>1</sup> 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
<b>Genetic</b>	Inherited TBG excess	Inherited TBG deficiency (complete and partial)
<b>Hormonal</b>	Hyperestrogenic states Choriocarcinoma Estrogen-producing tumors Estrogen therapy Newborn state Pregnancy (especially molar)	Androgen and anabolic steroid use
<b>Drug use</b>	Clofibrate 5-Fluorouracil Heroin Methadone Nicotinic acid Perphenazine Tamoxifen	Glucocorticoids L-Asparaginase
<b>Diseases</b>	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).<sup>1,2</sup>





Hereditary TBG excess was first described in 1959.<sup>3</sup> 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.<sup>4</sup> Numerous analyses have indicated that all inherited TBG abnormalities are X-chromosome linked.<sup>5-9</sup> Gene amplification has recently been reported to be the cause of hereditary TBG excess in two families.<sup>10</sup> However, other causes remain possible.<sup>1,11</sup> The prevalence of euthyroid hyperthyroxinemia caused by hereditary excess of TBG in the general population is 1 in 25,000 live births.<sup>12</sup>

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.<sup>11</sup>

#### ■ T<sub>4</sub> AND T<sub>3</sub> UPTAKE TESTING IN HEREDITARY TBG EXCESS

Although many causes of euthyroid hyperthyroxinemia have been described (TABLE 2),<sup>12</sup> 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<sub>4</sub> uptake (T<sub>4</sub>U)** is the amount of fluorescein-labeled T<sub>4</sub> 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<sub>4</sub> level divided by the T<sub>4</sub>U. Thus, an elevated total T<sub>4</sub> level caused by TBG excess would be adjusted downwards by the concomitant elevation in the T<sub>4</sub>U, yielding a normal FTI value (ie, 6.4 to 10.7 µg/dL).

**T<sub>3</sub> resin uptake (T<sub>3</sub>RU)**, in contrast to T<sub>4</sub>U, makes use of a different ligand (radiola-

TABLE 2

### Causes of euthyroid hyperthyroxinemia

#### Altered T<sub>4</sub> 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<sub>4</sub> alone)

Hereditary or acquired

Thyroid hormone binding autoantibodies

#### Thyroxine resistance

Generalized

Selective resistance to intracellular transport of T<sub>4</sub>

#### 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 T<sub>3</sub> instead of fluorescein-labeled T<sub>4</sub>) 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<sub>7</sub>, is derived: T<sub>3</sub>RU





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$\times$  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.

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