

## *Thyroid Physiology and Thyroid Function Tests*

### **A. Thyroid Hormone**

\*Broadly speaking, thyroid hormones effect metabolic processes in several tissues by increasing metabolic rate, oxygen consumption, and heat production. Affected tissues include: the heart (increased rate and contractility)  
the gut (increased motility)  
skeletal effects (increased bone turnover)  
the lungs (maintenance of normal hypoxic and hypercapnic drive)  
the muscles (increased contraction/relaxation speed)  
metabolism of lipids and carbohydrates (increased gluconeogenesis, glycogenolysis, intestinal glucose absorption, cholesterol synthesis)  
sympathetic nervous system (increased beta receptors in the heart, muscles, lymphocytes, adipose cells, increased catecholamine sensitivity)  
hematopoietic system (increased 2,3-DPG to facilitate oxygen dissociation from hemoglobin and increase tissue availability)

\*The thyroid secretes both T4 (aka thyroxine, or 3,5,3',5'-tetraiodothyronine) and T3 (aka 3,5,3'-triiodothyronine). Dietary iodine is essential for both, around 150 mcg/day. T4 and T3 work by binding nuclear receptors and affecting gene transcription in the tissues mentioned. Secretion of T4 and T3 depend on TSH being taken up by the thyroid from the anterior pituitary.

\*T3 is three to eight times more potent than T4. The normal thyroid gland secretes 100 nmol T4, 5 nmol T3, and less than 5 nmol reverse T3, an inactive form of T3. Most circulating T3 is derived from deiodination of circulating T4 in the peripheral tissues. T4 is considered to be a pre-hormone for T3.

\*T4 and T3 are bound to thyroid binding globulin (TBG), thyroxine-binding prealbumin, and albumin. Around 70% of T4 is bound to TBG, 20% to TBPA, and 10% to albumin. All bound T3 is bound to TBG. Only 0.04% of T4 and 0.4% of T3 is unbound. The free hormone is taken up by the tissues, explaining how T3 is more active than T4. Alterations on TBG do not affect free circulating levels.

### **B. The Tests**

\*TSH (serum thyrotropin)—This can be measured very accurately through immunometric assays. At UNC the normal range is 0.46-4.68  $\mu$ IU/mL. Small changes in T3 and T4 feedback into large changes in TSH, so TSH is used as a sensitive marker of thyroid function. Values less than 0.1 in the setting of normal T3 and T4 concentrations reflect subclinical hyperthyroidism. In primary hypothyroidism (thyroid failure), TSH is

elevated, and in secondary (pituitary) and tertiary (hypothalamic) hypothyroidism, TSH is low.

\*Total T4/T3—This measures the bound and unbound T4/T3 levels in the blood. At UNC, normal ranges are 5.5-11 mcg/dL (T4) and 1.0-1.7 mcg/dL (T3). The utility of total T4 and T3 are affected by levels of TBG, TBPA, and albumin, however. Pregnancy and exogenous estrogen can raise protein concentrations, and cirrhosis, nephrotic syndrome, and glucocorticoids can lower binding protein concentrations. This can lead to incorrectly high or low T4/T3 levels.

\*Free T4—At UNC, this is a sent out test to Mayo clinic and is measured by equilibrium dialysis. Normal values range between 1.0 and 2.0 ng/dL.

\*Free T4 index—Hold on for this explanation... The free T4 (or thyroxine) index is defined as  $(\text{total T4}) \times (\text{thyroid hormone binding index})$  where the total T4 is measured directly and the THBI is the patient's T3 resin uptake divided by normal pool T3 resin uptake. Resin uptake is performed by incubating the patient's serum with radiolabeled T3 tracer, and subsequently adding an insoluble resin that traps the remaining unbound radiolabeled T3. Dextran-coated charcoal is often used as the resin. The value reported is the percent tracer bound to the resin, which varies inversely with the number of available free binding sites for T3. The number of free binding sites is determined by both binding protein levels and endogenous hormone production. The T3-resin uptake was designed to distinguish TBG excess and deficiency from hyperthyroidism and hypothyroidism. Examples of the use of T4 index are below:

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Hyperthyroidism — high serum total T4, high T3-resin uptake or THBI, high free T4 index

TBG excess — high serum total T4, low T3-resin uptake or THBI, normal free T4 index

Hypothyroidism — low serum total T4, low T3-resin uptake or THBI, low free T4 index

TBG deficiency — low serum total T4, high T3-resin uptake or THBI, normal free T4 index

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Free T4 index is used more commonly to assess free thyroxine, as dialysis-measured free T4 is not offered at most labs. At UNC, the normal value of T3 uptake is 23-41%, and the normal value of the free thyroxine (T4) index is 1.2-4.5.

\*Antibodies against thyroid antigens have been described in chronic autoimmune thyroiditis. These include: thyroglobulin (Tg), thyroid peroxidase (TPO, formerly known as the microsomal antigen), and the TSH receptor.

### **C. A Strategy For Clinical Use**

1. Screening for hyperthyroidism and hypothyroidism
  - Serum TSH normal — no further testing performed
  - Serum TSH high — free T4 added to determine the degree of hypothyroidism
  - Serum TSH low — free T4 and T3 added to determine the degree of hyperthyroidism
  - If hyperthyroidism or hypothyroidism are suspected clinically, test free T4 initially along with TSH
2. Monitoring thyroid replacement
  - TSH alone needs to be checked, with dose changes reflected 2-3 weeks later
3. Monitoring treatment of hyperthyroidism
  - Free T3 and T4 levels need to be monitored since TSH will remain below normal for weeks to months after the patient has become euthyroid

### **References**

1. Guyton, AC and JE Hall. Textbook of Medical Physiology. 1998.
2. Andreoli, TE, JC Bennett, et. al. Cecil Essentials of Medicine. 1997.
3. UpToDate, "Laboratory Assessment of Thyroid Function," 2004