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TFT's for Y2K

While laboratory thyroid function tests (TFT's) have evolved considerably over the years, physician ordering practices have not always mirrored these changes. Interpretation of thyroid function tests, particularly in hospitalized patients, can be challenging and lead to further diagnostic studies. This brief review is intended to increase the efficiency of thyroid function testing and reduce the number of superfluous tests.

*Things you should have learned in **medical** school (had you been paying attention)*

Thyrotropin (a.k.a. thyroid stimulating hormone or TSH) is secreted by the pituitary gland and provokes the thyroid gland to synthesize and release thyroxine (T4) and triiodothyronine (T3) into the blood. Both hormones circulate in the blood predominantly bound to one of three transport proteins - thyroid binding globulin (70%), transthyretin (20%), and albumin (10%). Minute amounts of the hormones (0.03% of T4 and 0.3% of T3) circulate in the physiologically active "free" form.[1] While T4 concentration is at least tenfold higher than T3 concentration, T3 is four times more potent.[2] In peripheral tissues (particularly the liver), up to one third of T4 is converted to T3. TSH secretion is regulated by thyrotropin releasing hormone (TRH) produced by the hypothalamus. A negative feedback loop maintains homeostasis where increased levels of free T3/T4 (FT3/FT4) inhibit synthesis and release of TRH and TSH while decreased FT3/FT4 promote TRH/TSH secretion. A log linear relationship exists between TSH and FT4 such that a twofold change in FT4 will ultimately result in a 50 to 100-fold inverse change in TSH. The circulating half-lives of TSH, T3, and T4 are roughly 1 hour, 1 day, and 1 week respectively.[3,4]

A variety of physiologic, pathologic and pharmacologic events affect the levels of circulating TSH, T4, T3, FT4 and FT3. Causes include inhibition of the pituitary-thyroid axis, alterations in binding protein concentrations, changes in peripheral metabolism of thyroid hormones, and a variety of medication effects. In pregnancy, human chorionic gonadotropin has a "TSH-like" effect which may lower TSH levels while increasing T4 and T3. Nonthyroidal illness (NTI) may produce a variety of abnormalities in TFT's, while the patient remains clinically and functionally euthyroid ("euthyroid sick syndrome"). In acutely ill patients, the overwhelming majority of "abnormal" TFT's are attributable to this phenomenon. A more detailed description of the effects of drugs and illness on TFT's can be found elsewhere.[1,2,6]

TFT's - The Classics

- **T4** Immunoassay. The most concentrated (and hence easiest to measure). Enjoyed immense popularity on "executive metabolic panels" when this type of laboratory testing was in vogue. Of limited value as a stand alone thyroid function test, because its concentration can be influenced by a variety of factors as discussed above. (Cost $8.00)
- **T3 Resin Uptake (T3U)** Immunoassay. Also referred to as "resin uptake ratio". Used to correct for changes in binding protein concentrations. Inversely proportional to unsaturated thyroid hormone binding sites. Decreased T3U suggests either increased protein binding sites or decreased thyroid hormone (e.g. hypothyroidism) while increased T3U indicates decreased protein binding sites or increased thyroid hormone (e.g. hyperthyroidism). Worthless as a stand-alone test, but useful in conjunction with T4 to calculate the FTI. ($9.00)

- **Free Thyroxine Index (FTI)** Referred to by some as "T7". A calculated value (FTI = T4 x T3U) which correlates reasonably well with FT4. Indeed the FTI was probably a more accurate representation of FT4 than some of the early methods that measured FT4 directly, but it may yield abnormal results in the setting of NTI. (Free - with purchase of T4 & T3U)
- **T3RIA** Earliest method used to measure total T3. Has been largely replaced by an immunochemiluminometric assay (ICMA). See next section. (Nichols Laboratory $67.00)
- **TSH** See next section
- **Reverse T3 (rT3)** Radioimmunoassay. Biologically inactive. Elevated in NTI or starvation (e.g. anorexia nervosa). Few, if any, indications for current use. (Mayo Medical Laboratories $134.90)

T4, T3U and FTI are still available at Rex, although they are not recommended for first or even second line testing. In time, they will probably be discontinued. Requests for T3RIA will be forwarded to Mayo Medical Laboratory for T3 by ICMA.

TFT's - The Next Generation

- **TSH** Two Site Chemiluminometric assay. The most significant advancement in TFT's is the remarkable improvement in sensitivity of TSH assays. Each "generation" of TSH assays represents a 10-fold improvement in sensitivity. The original assays had a functional sensitivity of 1 mIU/L. The 2nd generation assay ("sensitive TSH") improved to 0.1 mIU/L, while the 3rd generation ("supersensitive") detects 0.01 mIU/L, and the 4th generation ("highly sensitive") detects 0.001 mIU/L. The improved sensitivity of 3rd and 4th generation assays allows reasonably efficient separation of hyperthyroid patients from NTI. **Almost all hyperthyroid patients will have values < 0.01 mIU/L, while over 90% of those with values between 0.01 - 0.1 mIU/L have NTI or drug effect (most commonly glucocorticoid therapy).** [5] **The likelihood of hyperthyroidism in patients with a TSH between 0.1 - 0.4 mIU/L is essentially <u>zero</u>!** [7] A testing strategy recognizing the power of the newer TSH assays can eliminate the need for many TFT's and reduce a lot of the confusion regarding the interpretation of "abnormal" results. (See enclosed TSH Algorithm.) The sensitive assays have all but eliminated the need for the TRH stimulation test unless one suspects either TSH-producing pituitary tumor, pituitary thyroid resistance or central (pituitary/hypothalamic) hypothyroidism. The Rex Laboratory uses a 3rd generation assay. ($23.00)
- **FT4** Two Site Chemiluminometric assay. Equilibrium dialysis is the "reference method", but most laboratories use immunoassays as they are less expensive and more rapid. While early immunoassays were sensitive to the level of binding proteins in the specimen, the current generation of ("two step") FT4 immunoassays are minimally affected by this or the presence of thyroid antibodies. FT4 levels by any method can be affected by NTI, drugs, pregnancy, etc. as discussed above. FT4 is less sensitive to the effects of NTI than the FTI and thus represents a superior test. For optimum diagnostic efficiency, FT4 should be interpreted in conjunction with TSH. ($13.00)
- **T3** Method - immunochemiluminometric assay (ICMA). Useful as a **third-order** test in patients with **undetectable or suppressed (≤ 0.01 mIU/L)** TSH and normal FT4 to exclude the possibility of T3 hyperthyroidism ("T3 thyrotoxicosis"), but subject to overutilization (see "*T3 or not T3"*). Not necessary in cases with suppressed TSH and elevated FT4 or in the evaluation of hypothyroidism. Frequently low in NTI. (Mayo $17.00)
- **FT3** Immunoassay. Generally provides similar information as T3, but more expensive. May be helpful in evaluating patients with suspected abnormal binding proteins. (Mayo $142.20)

TFT's in acutely hospitalized patients (You better think twice)

As discussed above, nonthyroidal illness (NTI) can produce a wide variety of abnormalities in TFT's, even the newer ones. This is a reflection of various physiologic, pathologic, and pharmacologic effects on the levels of circulating hormones, rather than "lab error". The net result is loss of specificity and poor positive predictive value for thyroid disease. The prevalence of hyperthyroidism in those with "abnormally low" TSH values is discussed above (*TFT's - The Next Generation* **TSH**). A similar phenomenon exists for patients with "abnormally high" TSH. In one study of hospitalized patients, 86% of patients with TSH greater than the reference range but less than 20 mIU/L had either NTI or medication effect, while 14% had hypothyroidism. If the threshold was raised to those having TSH > 20 mIU/L, the prevalence of hypothyroidism increased only to 50%, with the remainder representing NTI or medication effect. [7] Accordingly, evaluation of TFT's in acutely ill patients is not recommended unless there is a strong suspicion that thyroid dysfunction is contributing to the current illness. If TSH is evaluated in an acutely ill patient, the threshold for considering hyperthyroidism should be lowered to 0.1 or even 0.01 mIU/L, while that for hypothyroidism should be increased to 20 mIU/L. [5,7] Discordant TSH and FT4 results increase the likelihood of NTI/drug effect. Follow-up testing, preferably after the acute illness resolves, is recommended to confirm thyroid dysfunction prior to beginning therapy. [5]

T3 or not T3

To evaluate use of T3 testing at Rex, 69 consecutive requests for T3RIA analysis ($67.00) were reviewed. A number of these appear to have been ordered to evaluate for "T3 thyrotoxicosis" in the setting of decreased TSH and normal FT4/FTI. The majority appeared to have been ordered as part of general thyroid testing (e.g. TSH normal or elevated). In only one case (the first one listed below) did the T3 result add **useful** information. The cost of finding the one case of T3 thyrotoxicosis in this sample set of 69 cases (efficiency of 1.4%) was $4623. If the enclosed algorithm (i.e. reserving testing for those cases where TSH is suppressed and FT4 is not elevated) had been used, a total of 3 cases would have been tested for an efficiency of 33.3% and cost of $201.

TSH	FT4 (FTI)	T3RIA	No. Cases	Interpretation
↓↓	N	↑	1	T3 thyrotoxicosis
↓↓	↑	N	1	Hyperthyroidism
↓↓	↑	↑	1	Hyperthyroidism
↓	N	N	11	Normal, Nonthyroidal illness, Medication effect
↓	N, ↓	↓	8	Normal, Nonthyroidal illness, Medication effect
N	↓, N, ↑	N	27	Normal, Nonthyroidal illness, Medication effect
N	N	L	15	Normal, Nonthyroidal illness, Medication effect
↑	N	N,↓	4	Normal, Nonthyroidal illness, Medication effect
↑↑	↓	↓	1	Hypothyroidism

↓↓ = TSH ≤ 0.01 mIU/L (suppressed)
↓ = TSH, FT4, FTI or T3RIA below reference range
N = TSH, FT4, FTI or T3RIA within reference range
↑ = TSH, FT4, FTI or T3RIA above reference range
↑↑ = TSH > 20.0 mIU/L

Testing Recommendations
The following are compiled from the references below and include recommendations from the American College of Physicians, US Preventive Services Task Force, and College of American Pathologists' Laboratory Testing Strategy Task Force. [8-10] These recommendations do **not** apply to those suspected of having **pituitary** disease.

- Avoid TFT's on inpatients. If testing is necessary, start with TSH and expand "reference range" for ill patients from 0.1 (or even 0.01) - 20 mIU/L. Patients with TSH values between 0.01 and 20 mIU/L are unlikely to have thyroid dysfunction. Consider NTI or

drug effect before ordering additional tests.

- Screening for thyroid disease is recommended for neonates, those with newly diagnosed dyslipidemia, those on medication known to affect thyroid function (e.g. amiodarone, lithium), and women over 50 years old.
- Test others based on clinical signs and symptoms suggesting thyroid dysfunction.
- The preferred initial test for thyroid dysfunction is TSH.
- Patients with **suppressed or significantly elevated** (cf. abnormal) TSH should be followed up with FT4 test.
- T3 testing should be reserved for those with **suppressed** (cf. decreased) TSH and normal FT4.
- Monitor thyroid replacement therapy and thyroid suppression therapy with TSH. Wait 8 weeks after changing the dose to see effect.
- Monitor thyroid ablation for hyperthyroidism with FT4.
- The management of patients with subclinical thyroid disease is subject to debate. [11,12]

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