Clinical Analysis Thyroid Function Testing: Dealing with Interpretation Difficulties

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Introduction

Thyroid function tests have always presented the clinician with difficulties in their interpretation. Clinical laboratory testing will often not reflect the diagnostic picture the physician is developing for the patient based on their history, signs and symptoms. This often leads to further diagnostic work-ups or a missed diagnosis. Laboratory data is often misleading due to the complexity and inherent shortcomings of the tests themselves, the differences in methodologies and time the specimens were obtained. Further, many physicians, not having an adequate understanding of what the test results mean, will often make incorrect assumptions based on them or interpret them too strictly. A narrow interpretation of thyroid function testing leads to many people not being treated for subclinical hypothyroidism. This article will review the interpretation of the most commonly ordered laboratory tests for assessment of thyroid function as well as discuss their merits in relation to basal body temperature.

Beginning with the protein bound iodine (PBI), physicians attempted to determine what was occurring with the thyroid gland by use of an easily obtainable medium, the blood. Being a nonspecific test for the assessment of the patient's thyroid function based on the amounts of iodine present, the PBI proved to be inadequate for this task, often showing normal results with clinically abnormal patients. The test was nonspecific for iodine bound to thyroid binding globulin (TBG) and was altered by various medications, such as lithium carbonate and Dilantin, and the effects of estrogen on TBG. Introduction of radioimmunoassay studies for T3 and T4 have proved only slightly better in thyroid hormone evaluation. The radioimmunoassay method is more sensitive in detecting hyper than hypothyroidism, a problem also encountered with the PBI. In addition, these tests are influenced by factors similar to the PBI which also make their interpretation difficult. This leaves the physician to fill in the gaps testing with other methods, which can prove difficult if there are a multiplicity of presenting symptoms.

Evidence that the basal body temperature (BBT) was more accurate in unmasking the hypothyroid state than the standard laboratory tests was provided by the late Broda Barnes, M.D. Studies comparing the basal metabolic rate (BMR) and the BBT showed good correspondence, especially if signs and symptoms of hypothyroidism were present. Barnes diagnosed and treated a large number of patients by this method, consistently obtaining good results. He also advocated the use of desiccated thyroid in its treatment, sparking an ongoing debate that continues to this day. Since then many other physicians have also evaluated patients using the BBT with both similar and conflicting results.

There are problems with the BBT, however, which affect its sensitivity and thus need to be considered by the clinician. In particular are those patients who sleep under electric blankets or on heated water beds. These will falsely elevate the body temperature while acting to decrease thyroid function in the process. Secondly, a thermometer with greater gradation must be used to obtain the more accurate readings needed. Thirdly, some clinicians claim that treatment with desiccated thyroid, while making the patient feel better, does not always raise the BBT to within

the acceptable range. Lastly, patient compliance may be difficult to obtain or is often inconsistent. It is easier for both the patient and the physician to obtain a blood sample for evaluation, thus widespread use of the BBT does not occur.

Since standard blood tests are most often used for the evaluation of thyroid function, a review of the current test procedures and their interpretation will help to clear some of the confusion and make interpretation easier. Even with unsupporting laboratory data, an understanding of what occurs with testing along with information obtained clinically can help the physician to clear through the diagnostic fog.

Physiology of the Thyroid Gland

A review of the function of the thyroid gland will help in understanding the basis and rationale behind the current laboratory tests available.

The thyroid is a butterfly-shaped gland which wraps itself part way around the trachea just superior to the sternal notch and just inferior to the thyroid cartilage. As the spine begins to curve and the gland atrophies with aging, the thyroid may slip down behind the sternum making it difficult to palpate in the elderly. In some patients the gland may be barely palpable due to the thickness of overlying tissue or skin.

Thyroid releasing hormone (TRH) from the hypothalmus is released in response to a variety of factors, and causes thyroid stimulating hormone (TSH) to be released by the anterior pituitary. Under normal conditions TSH shows diurnal variation with 2 to 3X the baseline value being present from 10-11 PM and decreasing about 10-11 AM. This hormone in turn affects the thyroid gland to produce and release thyroid hormone in the form of tetriiodotyrosine (T4) and triiodotyrosine (T3). While in the thyroid gland, T3 and T4 are bound to thyroglobulin.

T4 is produced in greater amounts and is found in greater plasma concentrations than T3. In addition, it has a longer half life than T3. Most of the T4 is bound to TBG (85%) and thyroid binding prealbumin (10-15%). Albumin carries approximately 5%, with less than 1% being in the free, unbound form. T3 is primarily attached to TBG (70%) and the remainder to albumin. Both hormones are inactive in this state but are a measure of thyroid gland production of hormone.

Upon its entrance into the cell, T4 is deionated to its more biologically active form, T3 which has a higher affinity for the receptor site on the nucleus. When the metabolic rate has been increased sufficiently, feedback on the hypothalmus and pituitary causes a cessation of hormone production and release. The homeostatic mechanism allows for production of heat in response to cold or illness and possesses a diurnal variation (of up to 12%) with levels being greater in the early morning and lower in the evening. In addition, a significant day-to-day variation can occur which appears to be cyclic in nature.

Laboratory Tests

The key to understanding thyroid function tests lies with understanding what the tests measure, their capabilities and what other factors may influence them.

Most all thyroid function panels include the following: Total T4, T3 Uptake and Free Thyroxine Index (FTI). Individually these tests will not give much information but collectively they are a good screening panel to assess thyroid function. By itself, Total T4 does not provide much information and must be viewed along with other parameters. The exception to this would be in following a patient who is on exogenous thyroid therapy such as Synthroid or desiccated thyroid.

Total T4

This test is a direct measure of the circulating thyroxine released by the thyroid gland. The greater majority of T4 will be bound to TBG, TBPA and albumin, with very little (<0.05%) in the free form. For all practical purposes, the free T4 amount is considered negligible for this test. Assayed most often by RIA methodology (Competitive Protein Binding is also available), this value helps assess the amount of bound, circulating thyroid hormone. What must be taken into consideration is that the Total T4 is merely a reflection of the blood levels of the hormone released from the thyroid, not what is actually getting into the cell, a parameter better measured by the BMR. Further, the level is also influenced by alterations in thyroid binding proteins and albumin levels. Thyroid binding proteins in turn are influenced by birth control pill use, pregnancy, exogenous estrogens, certain drugs, severe non-thyroid illness, and in rare instances, congenital factors. These will alter thyroid binding proteins such that it will appear that the patient is hyperthyroid when in fact they are not. Further, this test is not considered to be as accurate for the evaluation of hypothyroidism (85-90% sensitivity) as it is for hyperthyroid states (90-95% sensitivity). This decrease in sensitivity is due in part to lower amounts of circulating hormone and the fact that patients with nonthyroidal illness may be included in the reference range. The test is not affected by increased iodine levels, while a severe iodine deficiency may decrease T4 levels.

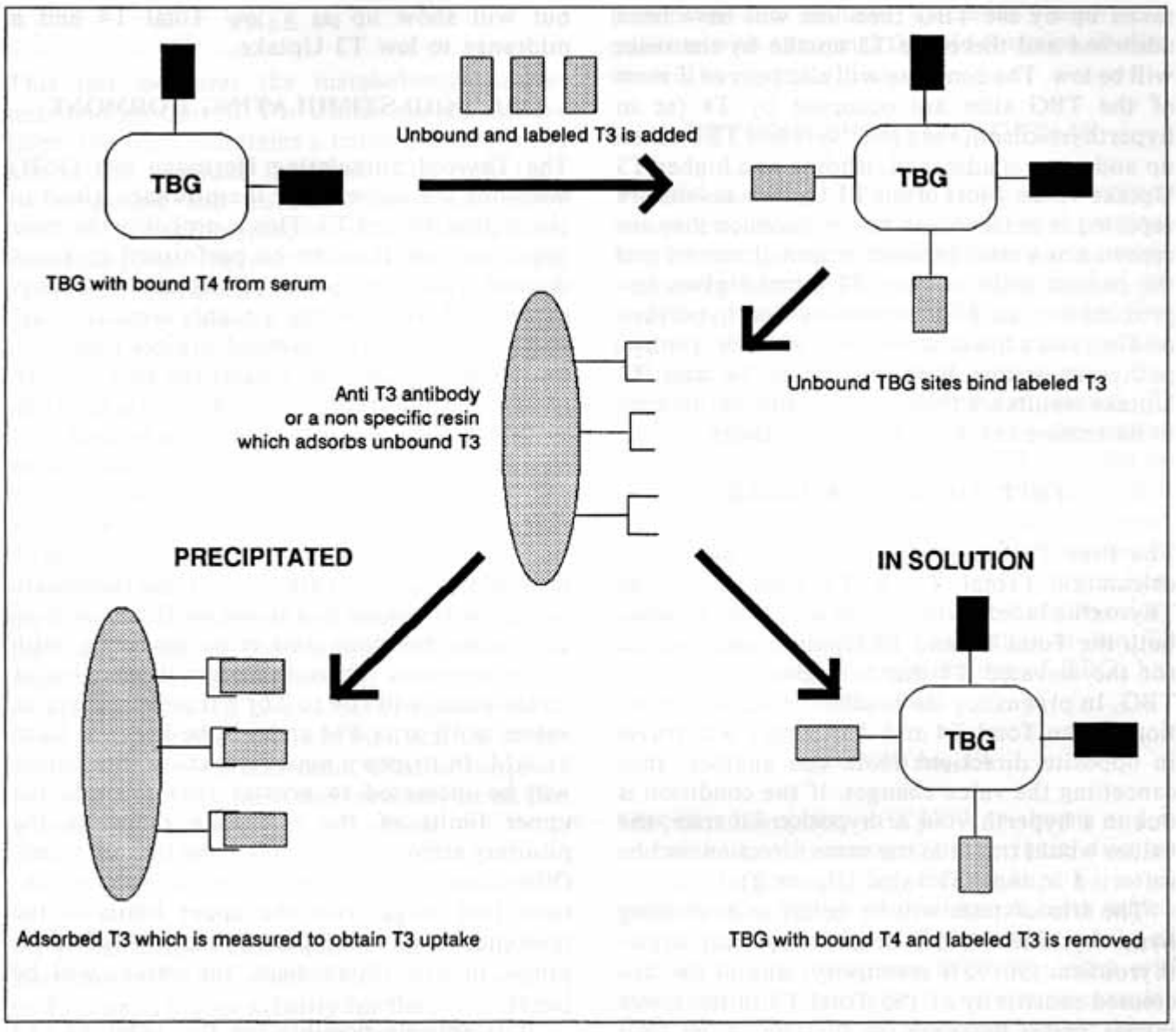

Figure 1: Methodology of the T3 Uptake Test

T3 Uptake

The T3 Uptake does not measure T3 but is an estimate of the amount of TBG sites unsaturated by T4. Radioactive T3 is used in the procedure (thus the name) which is taken up by the unsaturated TBG (TBG here is meant to include TBG, TBPA and albumin). TBG, however, has a greater affinity for T4 than T3 and will bind to any T4 that is released from the thyroid.

The key to understanding the T3 Uptake tests is comprehending what occurs during the procedure. TBG with bound T4 is already present in the serum that is being assayed. During pregnancy (beginning in the second to third month) where there is an increase in the amount of

protein and subsequently the TBG, the number of binding sites increases. The amount of T4 also increases, but not in proportion to the TBG binding sites. Thus, the patient appears to be hyperthyroid. When radioactive T3 is added, it attaches to the unbound or remaining sites on the TBG, saturating the molecule (figure 1). The remaining radioactive T3 is adsorbed by a resin which will be assayed to determine how much is left after saturation of TBG. If more T3 has been taken up by the TBG then less will have been adsorbed and therefore T3 uptake by the resin will be low. The converse will also be true if most of the TBG sites are occupied by T4 (as in hyperthyroidism), then relatively less T3 is taken up and more is adsorbed, leading to a higher T3 Uptake value. Most often T3 Uptake results are reported in percentages, but on occasion they are reported as a ratio between a normal control and the patient resin uptake. T3 Uptake gives approximately an 80% sensitivity for hyperthyroidism and a lower sensitivity (50-60%) for hypothyroid states. Both the Total T4 and T3 Uptake results are then compared to one another to determine the Free Thyroxine Index.

Free Thyroxine Index

The Free Thyroxine Index (FTI) is actually a calculation (Total T4 X T3 Uptake = Free Thyroxine Index) which takes into consideration both the Total T4 and T3 Uptake, and corrects for the elevated T4 due to higher amounts of TBG. In pregnancy (as in other conditions mentioned) the Total T4 and T3 Uptake will travel in opposite directions from one another, thus cancelling the value changes. If the condition is due to a hyperthyroid or hypothyroid state, the values would travel in the same direction and be reflected in the FTI value (figure 2).

The trio of tests will be better at evaluating hyperthyroidism (95% sensitivity) than hypothyroidism (90-95% sensitivity) due to the decreased sensitivity of the Total T4 in the lower ranges, and if there are fluctuations of the TBG due to nonthyroid-related illness. The value of the tests lie in the ability to show the clinician the directions in which the T4 and TBG are headed. Due, however, to the wide reference range provided, large variations must occur in order for the FTI to show any abnormalities. It has been the author's experience that the value is most often seen to be abnormal in patients taking synthetic thyroid, while an extreme hypothyroid condition often must be present before the FTI will be reflected as abnormal. Even in these severe cases of hypothyroidism, it is not unusual to find either the T3 Uptake or Total T4 to be within the "reference range". Subclinical hypothyroidism is usually not seen with the FTI but will show up as a low Total T4 and a midrange to low T3 Uptake.

Thyroid Stimulating Hormone

The Thyroid Stimulating Hormone test (TSH) measures the response of the pituitary gland to circulating T4 and T3. This is probably the most important test that can be performed to assess thyroid function. Some physicians will only request a TSH, now that a highly sensitive TSH test is available. This method utilizes monoclonal antibodies directed against the beta subunit of the molecule and is therefore specific for TSH.

TSH will be elevated with myxedema due to primary thyroid disease, iodine deficient goiter and Addison's disease. A severe non-thyroid illness will also cause an elevation, as will thyroiditis on occasion. Prior to the introduction of the highly sensitive TSH, the test was inaccurate in the

lower ranges due to the small amounts of circulating hormone and cross reactivity with other hormones. There is a diurnal variation of levels which will rise to 2 or 3 times the baseline values at 10 to 11 PM and will be lower at 10 to 11 AM. In primary hypothyroidism, the values will be increased to greater than 2 times the upper limits of the reference range as the pituitary attempts to stimulate the thyroid gland. Other cases of hypothyroidism will show elevations that range from the upper limits of the reference range to less than 2 times the reference range. In hyperthyroidism, the values will be lower.

It is entirely possible for the Total T4, T3 Uptake and FTI to be within the reference range and to also have an abnormal TSH. This is felt to be due to the inability of the thyroid gland to produce adequate hormone with minimal stimulation. The pituitary works at a higher rate in order to achieve the same levels of thyroid hormone release. This represents a hypothyroid state that is probably in the early stages. It may also indicate pituitary disease which can be further evaluated by the TSH Stimulation and Thyrotrophin-Releasing Hormone tests. The TSH, along with the Free T4 (reviewed later), is best used for evaluation of the hypothyroid patient where the Free T4 by itself is marginal.

Free T4

This test measures the metabolically active, unbound portion of T4. Under normal conditions, the body maintains a balance between the bound and unbound fractions. This ratio (between bound and unbound) most accurately reflects the thyrometabolic state, showing good discrimination between hyperthyroid and euthyroid conditions (95% sensitivity). There is some overlap between the euthyroid and hypothyroid conditions, however, due again to a decreased sensitivity when lower amounts of hormone are present.

Whereas the Total T4 correlates well with thyrometabolic states, provided the TBG is not affected, the Free T4 gives a better correlation of the thyrometabolic state if TBG is affected. It has been found that Free T4 levels are somewhat lower in adolescents than adults and are affected by severe illness such as cirrhosis of the liver. However, there is some indication that with other non-thyroid illnesses which are not as severe, the Free T4 gives a better assessment of the thyrometabolic state than the Total T4, which will more often be decreased. Used in conjunction with the TSH, these two tests may be all that is needed to assess thyroid function.

Total T3

T3 is the metabolically active form of thyroid hormone or T4. By itself T4 can be active, but as T3 it has a higher affinity for the cell nucleus, this form predominates intracellularly. In hyperthyroidism the T3 is always increased along with the T4. The ratio of T4 to T3 (T4/T3), will decrease as the amount of T3 increases somewhat greater than does T4 in this condition. This may be due to excess T3 secretion or increased T4 conversion. Therefore, it seems to be a more sensitive indicator of the hyperthyroid state than either test by itself.

The main value for the clinician lies in the evaluation of patients who appear euthyroid by lab testing but hyperthyroid clinically. A rare condition termed T3 toxicosis, in which the thyroid secretes increased amounts of T3, or there is excessive conversion of T4 to T3, may occur.

Reverse T3 (rT3) is an isomer of T3 and is metabolically inactive. A measurement of this parameter can be used to identify euthyroid patients with abnormal thyroid function studies caused by severe illness.

Thyroid Binding Globulin

Thyroid Binding Globulin (TBG) is simply a measurement of the protein carrier of thyroxine. In pregnancy, and with other conditions previously mentioned, TBG will change as part of the body's normal mechanism of homeostasis. The primary value of this test is in the evaluation of eumetabolic thyroid patients who show a decreased T4 and an increased or normal T3 Uptake. In this case the TBG may be altered due to hereditary conditions. The TBG can also be elevated with primary thyroid carcinoma, but is not diagnostic for this condition. It can, however, be used to follow the course of the disease. In addition, it will be elevated in hyperthyroidism and may also be elevated with subacute thyroiditis or benign adenoma. Evaluation of the T3 Uptake, an indirect measurement of TBG, has largely supplanted this test.

Neonatal T4

Low thyroid occurs in 1:4000 newborns and is one of the most common of the perinatal diseases that can be screened for. Infants have T4 levels considerably higher than adults at birth which will begin decreasing during the first weeks of life. Failure to recognize hypothyroidism will lead to neurological deficits and mental retardation. This test can be done on whole blood obtained from a heel stick after birth and a few months later if the condition is suspected.

Basal Body Temperature

Advocated and extensively researched by Broda Barnes, M.D., this technique has been shown to be a more sensitive indicator of hypothyroidism than blood testing. The basal body temperature (BBT) has continued to be a controversial technique, as has the form of therapy, desiccated thyroid, advocated by Barnes and others. The tests are done for a five day period with first waking in the morning. In women, this should be done 3-4 days after the menstrual period has begun. At this time thyroid hormone is reaching its highest point and cellular metabolism is optimal. Therefore, under ideal conditions, the basal body temperature gives an indication of what is occurring during optimal thyroid output rather than from a random blood draw, even if done at the same time. Further, it gives a better indication of what is occurring at the cellular level by measuring the body's metabolic response.

According to Barnes, a temperature of greater than 98.0 degrees F denotes a normally functioning thyroid. Temperatures from 97.6 to 98.0 degrees F are marginal while temperatures less than 97.6 degrees F indicate hypothyroidism. Some practitioners consider any temperature under 98 degrees F to be hypothyroid under these conditions. As previously mentioned, the test must be conducted under optimal conditions in order to be an effective indicator of the thyroid state.

Interpretation of Thyroid Function Testing

At best, interpretation of thyroid function tests can be difficult and frustrating. The assumption is made with blood tests that they reflect the inner state of the individual and are a measure of what is occurring at the cellular level. Inconsistencies between test results and the clinical presentation of the patient, coupled with the patient response to clinical trials of thyroid medication, suggest that this does not occur. Thyroid hormone available in the blood stream may not reach proper equilibrium with the extra cellular fluid and cells. For unexplained reasons, the body will attempt to maintain the blood levels within certain ranges no matter what is occurring at the cellular level.

Laboratory testing itself is subject to a wide range of variables which may alter the test results. Among them is exact time of draw. In order to be consistent, thyroid tests should be drawn at approximately the same times as their increases, or in the case of TSH, at the lowest point. Therefore, an early morning blood draw is desirable. The physician needs to keep in mind these variables if the sample is procured at other times. Laboratory error and differences in testing methods add further to variations in test results. Developing a working relationship with the clinical pathologist whose laboratory you are working with will help in determining if there are problems with the results.

The reference ranges provided are determined from a wide population base and do not reflect individual groups. Further, they are wide enough so that if the patient falls outside of them, the certainty that they may have the disease becomes greater. The flip side of this involves patients who are marginally ill who are included within the reference range and therefore missed. As mentioned previously, persons with non-thyroid illness are often included in the reference population and will influence its distribution. A strict interpretation of laboratory tests will mean that those patients that are marginal will be missed strictly on the basis of a lab tests without taking into consideration the presenting signs and symptoms of the patient. Lab tests should never be used to make a diagnosis, but rather to substantiate clinical signs and symptoms.

Laboratory testing, however, can be useful if interpreted with a modicum of caution. Therefore, this writer advocates the interpretation of lab tests within a narrower range with emphasis on the patient’s symptomatology as the main guide. Further, evaluation of the direction the studies are headed or their relationship to one another will also be helpful. Drawing follow-up studies after therapy has been initiated will also help to find the patient's optimal range, rather than references based on population studies.

As a general rule, the author narrows reference ranges by about 25% from both ends when interpreting lab results. Therefore, a reference range for T4 of 5.0 to 12.0 ug/dL becomes 6.75 to 10.25 ug/dL. Any patient approaching these limits that have the signs of hypo- or hyper thyroidism is treated. We can perhaps be a bit more tolerant of higher values due to the better sensitivity of the tests in those ranges. It is also important to realize that some patients on synthetic thyroid will buildup tolerance and may be taking large amounts to compensate for their fatigue and lethargy. Displacement by other medications must also be kept in mind and may account for some of the difficulty select patients may have in regulating thyroid supplementation.

T3 Uptake +	Total T4 =	Free Thyroxine Index	Found in
D	I	N	Pregnancy, BCP estrogen use
I	D	N	Chronic liver disease androgen use
N/I	I	I	Hyperthyroidism
N/D	D	D	Hypothyroidism

Figure 2. T3 Uptake, Total T4 and Free Thyroxine Index values in selected thyroid states. D = decreased, I = increased, N = normal

Replacement of synthetic thyroid medications by desiccated or extract forms of thyroid should also be monitored. For these purposes the writer will periodically run Total T4, T3 Uptake and FTI (or T7) , comparing the results with previous levels. Patient's symptoms also play a role in deciding how to proceed with the therapy and need to be monitored throughout the process. It takes upwards of a month for the thyroid/pituitary axis to reach equilibrium once the medication has been adjusted; therefore it is best to wait at least this length of time before retesting.

Each method of lab testing has its strong and weak points, but laboratory tests can be of assistance in patient evaluation and monitoring therapeutics. Understanding what their limitations are and taking them into consideration along with what the patient is presenting, will make thyroid function evaluation less of a dilemma and more of an art.

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