# Should the TSH Test be Utilized in the Diagnostic Confirmation of Suspected Hypothyroidism?

Rand Wheatland *

Hypothyroidism is an insidious disease that manifests a great number of non-specific symptoms. The prompt, accurate diagnosis of hypothyroidism will improve the quality of life for patients while controlling healthcare costs. Therefore, it is crucial that the protocol for diagnosing hypothyroidism has been properly evaluated. Its methods must be the best available to ensure that the resulting diagnoses will be as reliable as possible. When a patient presents with signs and symptoms of hypothyroidism and a medical history indicating hypothyroidism, a TSH test result is frequently utilized to assist in the diagnostic confirmation of hypothyroidism. In these circumstances, not only is performing the TSH test a waste of resources, utilizing the result will lead to a decrease in diagnostic certainty. The TSH test should not be utilized in the diagnostic confirmation of hypothyroidism because the diagnostic accuracy of the TSH test in confirming hypothyroidism is unknown, several aspects of the TSH test indicate its poor diagnostic utility and thyroid hormone trial therapy is the best method for achieving diagnostic certainty. Diagnostic confirmation of suspected hypothyroidism should be accomplished by evaluating the patient's response to a trial administration of thyroid hormone supplements. If the patient's chronic symptoms are relieved soon after beginning thyroid hormone supplements, it is very likely that the treatment is compensating for hypothyroidism. (*Med Hypotheses* 2010;75(5):458-63)

## Introduction

Hypothyroidism is an insidious disease that manifests a great number of non-specific symptoms [1]. It affects many sufferers by limiting every aspect of their lives. Fortunately, there is a simple, effective treatment. Daily thyroid hormone supplements hold the potential for total relief of all hypothyroid symptoms. But it is important that individuals with symptoms due to hypothyroidism are promptly and properly diagnosed. Early diagnosis and treatment of hypothyroidism will minimize the patient's suffering and halt the disease's transformation of their tissues and organs before it becomes irreversible. For example, a child's development can be permanently stunted if their hypothyroidism is not treated in time.

Since the term hypothyroidism has many interpretations, for this discussion hypothyroidism will refer to the disease syndrome resulting from insufficient action of thyroid hormone in the tissues and organs, due to thyroid hormone deficiency or resistance. Currently, the serum concentration of TSH (thyrotropin) is commonly used as a diagnostic test for hypothyroidism in three situations: the diagnostic confirmation of hypothyroidism in patients suspected of being hypothyroid, to identify an increased likelihood of hypothyroidism in patients not suspected of being hypothyroid (case finding) and in screening for hypothyroidism.

When a patient presents with signs and symptoms of hypothyroidism and a medical history indicating hypothyroidism, a TSH test result is frequently utilized to assist in the diagnostic confirmation of hypothyroidism. In these circumstances, not only is performing the TSH test a waste of resources, utilizing the result will lead to a decrease in diagnostic certainty. The TSH test should not be utilized in the diagnostic confirmation of hypothyroidism because the diagnostic accuracy of the TSH test in confirming hypothyroidism is unknown, several aspects of the TSH test demonstrate its poor diagnostic utility and thyroid hormone trial therapy is the best method for achieving diagnostic certainty.

## Unknown Diagnostic Accuracy

Before a diagnostic test is utilized to assist in making important medical decisions, it is crucial that the test's diagnostic accuracy be determined. Without this information, the diagnostician cannot know under which circumstances the test's indication can be relied on. For example, a test that is a good indicator for patients with obvious disease may be a poor indicator for patients with moderate disease severity, which would mean that the test is only reliable in situations where it is not needed.

Diagnostic accuracy is determined by comparing a test's diagnostic indication with the diagnosis determined by an established definitive diagnostic method in an appropriate spectrum of subjects [2-4]. For the results to be meaningful, these controlled diagnostic studies must conform to specific methodological requirements. Table 1 describes three methodological requirements that are frequently not satisfied in studies that attempt to estimate the accuracy of diagnostic tests.

Diagnostic accuracy can be measured by computing the sensitivity (true-positive rate) and the specificity (true-negative rate) for a test for a specific application. A particular test's sensitivity and specificity can then be compared to these measures from other tests as long as all the studies were conducted on similar populations and the tests were used for similar purposes [3]. By determining explicit values for the diagnostic accuracy of a test, claims of the superiority of a test can be removed from the realm of opinion.

Diagnostic test studies that do not employ a criterion standard or select test subjects based on their established disease status cannot compute an unbiased result for the diagnostic accuracy of a test. These uncontrolled studies are only useful for initial assessment of a test to determine if the test satisfies minimal requirements for a diagnostic test. If the test demonstrates reasonable results in these uncontrolled studies, the test may be considered worthwhile to be subjected to controlled diagnostic studies to determine its clinical utility.

Since the TSH test is utilized as a diagnostic indicator of hypothyroidism for three distinct purposes, its diagnostic accuracy should have been determined for each of its applications: diagnostic confirmation, case finding and screening. The diagnostic accuracy for each purpose is not applicable to another purpose because the disease severity and incidence in each of the subject populations are very different.

An extensive literature search was unable to locate any controlled study that determined the diagnostic accuracy of the TSH test in confirming the suspicion of hypothyroidism. Therefore, the diagnostic accuracy of the TSH test in confirming hypothyroidism is currently unknown.

Even though the results from case finding and screening diagnostic studies are not pertinent to the TSH test's application in the diagnostic confirmation of hypothyroidism, these studies will be considered here because they are frequently cited as evidence of the general diagnostic accuracy of the TSH test. Only a few published studies employing a criterion standard and subjects with little or no selection based on their established thyroid disease status have attempted to determine the diagnostic accuracy of the TSH test for indicating hypothyroidism in case finding and screening situations (see Table 2). But the results of these studies are not valid because these studies did not conform to other

* The Endocrine Research Project
574 Sims Rd., Santa Cruz, CA 95060
E-mail: rwheatla@query.com

Originally published in *Medical Hypotheses* 2010;75(5):458-63

## Table 1. Important Methodological Requirements for Controlled Diagnostic Studies

(A) **Criterion Standard**. The definitive diagnostic status of all the subjects must be established by an independent, well-defined criterion standard [3].

- The diagnosis must be definitive (as accurate as possible). If the criterion is not accurate, the estimate of the accuracy of the test being compared will be unreliable. If the method is not well-defined, there is no way for a reader of the study's report to decide if the criterion standard was adequate.
- All subjects should be evaluated by the same criterion standard to avoid verification or work-up bias [5].
- The criterion must be independent of the test being compared to avoid incorporation bias [3,6]. If the criterion requires interpretation, the interpreters must be blinded to the results of the test being evaluated [4].

(B) **Determination of the reference interval/decision level**. The test's reference interval or decision level must be defined independently of the results from the diagnostic study's test subjects. If a test's decision level is set using the results from the subjects diagnosed as non-diseased, the specificity will merely reflect the method for computing the reference interval. When comparing two or more different tests, it is acceptable to adjust the decision levels so that, for example, all the tests' specificities are the same and the relative sensitivities are apparent [3].

(C) **Target Population**. The test must be evaluated in a population that is representative of the one for which the test is intended [3,4,7]. Generally, the acceptable false-negative and false-positive rates depend on the intended situation and the potential harm of the next step in the protocol, such as treatment or surgical exploration.

- If the test is intended for screening (testing of apparently healthy individuals not seeking medical care), the proper target population would be subjects similar to those who would ultimately be involved in the screening program.
- If the test is intended to be used for case finding (testing individuals seeking medical care without regard to signs or symptoms associated with the disease the test is intended to indicate), a proper target population would be consecutive patients attending a clinic who are not suspected of having the disease under investigation.
- If the test is intended for diagnostic confirmation, the target population would be consecutive patients with signs and symptoms of the particular disease the test is intended to indicate.
- The study should include subjects appropriate to the test's intended application [3,4]. For instance, the results would be inaccurate if only subjects with overt disease were selected for the study. Similarly, including subjects with established status of the disease under investigation will bias the results.

necessary methodological requirements for a controlled diagnostic evaluation.

Most importantly, none of the criterion standards utilized in these studies were well-defined or would establish a definitive diagnosis. Without establishing a definitive diagnosis of the patients in a study, it is not possible to determine the accuracy of the test being studied. Space constraints preclude inclusion in Table 2 of the criterion standards. As an example, this is the criterion standard from Spencer et al. [11]:

> We also measured retrospectively T4 in the remaining 1251 patients not evaluated as part of the 329-patient subgroup. We then measured T3UR and calculated FT4I for the 12.4% of the patients' sera that had abnormal T4 values (<45 or >120 μg/L). In 7.8% of these patients, FT4I values were also abnormal (<45 or >120). When possible, these patients were evaluated by recall, or otherwise by chart review, to exclude the presence of thyroid disease, and these data were used in calculating test specificity and sensitivity. [abbreviations defined as T4: total thyroxin; T3UR: total triiodothyronine uptake ratio; FT4I: free thyroxin index (total T4 X T3UR)]

Like the other studies in Table 2, this is not a well-defined criterion standard and will not produce a definitive diagnosis for thyroid disease. It is also likely that during chart review the reviewer was biased by knowledge of any TSH results in the charts.

Regarding bias, not only did these studies not state that use of the criterion standard diagnostic evaluation was blinded to the TSH result, three of the studies used a TSH result as part of their criterion standard. Furthermore, at least three of the studies used the TSH results from the study subjects to determine the TSH decision level for hypothyroidism, which was then used for determining the diagnostic accuracy of the TSH test in these same subjects.

The number of untreated hypothyroid patients encountered, in all but one study with 23, ranged from only 7 to 14. This is very few patients for judging the diagnostic sensitivity of any test. Some of these patients had iatrogenic hypothyroidism resulting from treatment for hyperthyroidism by subtotal thyroidectomy or radioactive ablation of their thyroid. These patients have a much higher pre-test likelihood of hypothyroidism than most patients with no history of medical intervention to partially remove or ablate their thyroid. For the purpose of evaluating the diagnostic accuracy of the TSH test for indicating hypothyroidism, these two patient groups are separate target populations that should be evaluated separately, as in two of the studies listed in Table 2 (Lawson et al. [10] and de los Santos et al. [13]).

The studies listed in Table 2 are the best available reports of the diagnostic accuracy of the TSH test for indicating hypothyroidism. But these studies were poorly designed and the results are biased, even erroneous in several instances. Therefore, their results are not valid evidence of the diagnostic accuracy of the TSH test for indicating hypothyroidism.

In 2001 Wikland et al. [15] reported that they had encountered a high false-negative rate for the thyrotropin concentration as a diagnostic indicator of "chronic lymphocytic (autoimmune) thyroiditis." In a series of 219 patients with chronic fatigue of more than a year's duration, 87 "were diagnosed with definite cytological lymphocytic thyroiditis." These patients also responded favorably to treatment with thyroxine. Of these 87 patients, the TSH result was within the reference range for 50, a 57% false-negative rate (confirmed in E-mail correspondence with author B. Wikland).

It is claimed that the TSH test is a reliable indicator of primary hypothyroidism. Since lymphocytic thyroiditis is a major type of primary hypothyroidism, the TSH test's demonstrated diagnostic failure in these definitively diagnosed patients is evidence that the claim is unfounded.

## Poor Diagnostic Utility

Four aspects of the TSH test establish that the test is not a useful indicator for the confirmation of hypothyroidism.

### *Only Diagnostic of One Type of Hypothyroidism*

TSH secreted by the pituitary gland induces the production and secretion of thyroid hormone. The value of the serum concentration of TSH as a diagnostic indicator of hypothyroidism is based upon the belief that the pituitary-thyroid axis operates as a simple negative feedback loop [16]. This simple model predicts that serum TSH concentrations will rise when thyroid hormone levels are deficient due to thyroid gland failure (primary hypothyroidism). This model makes no consistent prediction for the levels of serum TSH in other types of hypothyroidism, such as central hypothyroidism [17] or hypothyroidism due to thyroid hormone autoantibody interference [18]. Originally, this model predicted that TSH levels would be low in patients with central hypothyroidism [19], but it was found that patients with central hypothyroidism can have low, normal or elevated TSH levels [17]. Therefore, a TSH

**Table 2. Studies that employed a criterion standard to evaluate the diagnostic accuracy of the TSH test in subjects that were selected with little or no regard to their established thyroid disease status**

| Study (Year) TSH test method(s) | Study Subjects (number) | Number of patients with untreated hypothyroidism (%) | Criterion Standard was independent of all TSH results [a] | TSH reference interval/decision level defined independently of all subjects' TSH results [b] |
|---|---|---|---|---|
| Toft et al. [8] (1973) Radioimmunoassay, double antibody | Consecutive new patients referred to the Endocrine Clinic with suspected thyroid disorders. (100) | 12 (12%) | Yes | No |
| Caldwell et al. [9] (1985) Immunoradiometric | Consecutive new patients referred to the endocrine unit, either with suspected thyroid disease or for therapy with iodine-131. (285) | 9 (3.2%) | No | No |
| Lawson et al. [10] (1986) [c] Two-site Fluoroimmunoassay | Patients who were being routinely assessed for thyroid function. (144) | 14 (9.7%) | Yes | NR |
| Spencer et al. [11] (1987) [d] Sensitive Immunoenzymometric | Hospitalized patients with sufficient sera remaining after their morning admission panel tests. (1,580) | NR [But not more than 14 (0.9%)] | Yes | Yes |
| Nuutila et al. [12] (1988) Immunoradiometric | Consecutive patients with suspected thyroid disease. 130 from the Department of Medicine, 224 from the municipal health centre. Patients undergoing thyroxine replacement therapy were excluded. (354) | 7 (2%) | No | NR |
| de los Santos et al. [13] (1989) [e] 1 conventional, 2 sensitive Immunoradiometric assays | Patients from an Internal Medicine Clinic and a gynecologist's office, subjects recruited from various sources, including faculty, staff and students, and elderly subjects from a Senior Citizen's Center. (597) | 23 (3.9%) | Yes | No |
| Roden et al. [14] (1993) 1 Chemiluminescent, 1 Immunoradiometric | Consecutive patients of a thyroid outpatient clinic. (115) | 9 (7.8%) | No | NR |

a – "Yes" signifies that the study satisfied this methodological requirement of a controlled diagnostic study, explained in Table 1A. NR, Not Reported.
b – Same as above but for the requirement explained in Table 1B.
c – The reported specificity of the TSH test for hypothyroidism and hyperthyroidism is erroneous, confirmed in E-mail correspondence with one of the study's authors (N. Lawson).
d – The reported specificity of the TSH test for hypothyroidism and hyperthyroidism of 90.6% is erroneous, confirmed in E-mail correspondence with one of the study's authors (C. Spencer). Specificity = (nondiseased subjects negative to the test / all nondiseased subjects tested). The correct specificity from their published data is the ratio 1305 / 1551 = 84.1%. The erroneous reported specificity of 90.6% represents a ratio of 1405 / 1551.
e – The reported sensitivities for hypothyroidism for the two sensitive TSH tests are erroneous, confirmed in E-mail correspondence with one of the study's authors (E.L. Mazzaferri).

result below the upper limit of the reference interval does nothing to discount a diagnosis of hypothyroidism. Even a TSH result above the upper limit does not confirm a diagnosis of primary hypothyroidism since there are other reasons why the serum TSH concentration may be elevated.

One argument for using the TSH test in confirming hypothyroidism, in general, in patients with signs or symptoms of hypothyroidism, even though the patient may have a form of hypothyroidism that the test cannot indicate, is that these other types of hypothyroidism are rare [20]. So, overall, if the patients with non-primary hypothyroidism are misdiagnosed, the diagnostic failure rate will be low. Unfortunately, for those patients with non-primary hypothyroidism for whom a diagnosis of hypothyroidism is missed because a test for a single type of hypothyroidism is used to indicate all types of hypothyroidism, their personal estimate of diagnostic failure will be 100%. Besides, it may be untrue that other types of hypothyroidism are rare [21]. The belief in the preponderance of primary hypothyroidism may have arisen because most hypothyroidism prevalence studies used the TSH test as part of their criterion standard, which would tend to significantly underdiagnose subjects with non-primary hypothyroidism.

Consequently, a TSH result above the reference interval from a patient with signs or symptoms of hypothyroidism is consistent with a diagnosis of primary hypothyroidism, but is not definitive. If the TSH level is below the upper limit of the reference interval, the result indicates nothing about hypothyroidism or euthyroidism.

*Invalid Assumption of Normal Pituitary Function*

To use the TSH test for indicating primary hypothyroidism, it must be assumed that the patient's pituitary gland is functioning normally. Even after a thorough evaluation of pituitary function, this assumption cannot be justified. Furthermore, the fact that hypothyroidism can pathologically affect the pituitary gland makes this assumption impossible.

In rats, thyroidectomy is followed by profound changes in the pituitary gland, including hyperplasia of thyrotrophic cells [22,23]. Pituitary enlargement and cellular changes are also noted in hypothyroid humans [24,25]. The pituitary enlargement seems to be due primarily to hyperplasia of thyrotrophic cells that are under increased stimulation to produce and secrete high levels of thyrotropin. Is it possible that after an extended period of untreated hypothyroidism, these cells become exhausted and are not able to sustain high levels of TSH secretion? This could explain why the serum TSH concentration is not high in some patients with long-standing hypothyroidism.

In any event, the normal function of the pituitary gland cannot be assumed because unidentified coexisting dysfunctions may alter the pituitary gland's expected responses.

*Diagnostic Utility is Based on an Inadequate Model of Thyroid Hormone Regulation*

The following are several significant mechanisms of thyroid hormone regulation that are not taken into account in the simple model of pituitary-thyroid negative feedback. Without including these factors, this model is inadequate to represent the true complexity of the thyroid regulatory system.

(A) There is innervation of the thyroid gland by the sympathetic nervous system [26]. Animal studies suggest that sympathetic stimulation induces release of thyroid hormone [27].
(B) The pituitary gland secretes various isoforms of thyrotropin that possess different levels of biological activity [28]. Current TSH

immunoassays measure the concentration of TSH without regard to the relative bioactivity of the isoforms [29].
(C) Availability of $T_3$ (triiodothyronine), the active form of thyroid hormone, is significantly dependent on regulation of the peripheral deiodination of $T_4$ (thyroxine) [30]. Little is known about this regulatory process.
(D) The hypothalamus has a significant influence on the pituitary's secretion of TSH, including pulsatile and circadian secretions that are predominantly controlled by thyrotropin-releasing hormone [31].
(E) Other hormones, such as cortisol [32,33], can have a profound effect on serum TSH levels.

Since there are many factors affecting thyroid gland secretion and thyroid hormone levels, directly and indirectly, it is not possible to infer euthyroid or hypothyroid status by examining just one component, the serum TSH concentration.

*Very Poor Indicator of Hypothyroidism in Ill Patients*

The TSH test's poor reliability for indicating hypothyroidism has been repeatedly reported for patients with a variety of illnesses and conditions since TSH and other hormone levels are affected by the disease process [34]. These apparently non-hypothyroid patients are said to have non-thyroidal illness (NTI). Since the mechanism for the changes in TSH levels in NTI patients has not been identified, there is no good definition of a probable NTI patient, and this confounding factor may be present in any ill patient.

When attempting a diagnosis of an ill patient, the diagnostician cannot know whether the patient is a good candidate for evaluation with the TSH test or if the TSH result would be meaningless because of NTI. Is a high TSH result due to NTI or does it indicate primary hypothyroidism? Does a TSH result that is within the reference interval indicate that the patient does not have primary hypothyroidism or does this TSH level reflect concurrent hypothyroidism and NTI? How can a test be utilized for diagnostic confirmation in symptomatic (ill) patients that demonstrates such uncertainty in ill patients?

## Trial Therapy is the Best Method for Diagnostic Confirmation of Hypothyroidism

The principal purpose in attempting to make a diagnosis of hypothyroidism is to identify patients that will benefit from the treatment for hypothyroidism, thyroid hormone supplements. If a patient is suspected of suffering from hypothyroidism and does not benefit from thyroid hormone supplements, they probably do not have hypothyroidism. If a patient with suspected hypothyroidism benefits from thyroid hormone supplements, it is very likely that they have hypothyroidism.

Since the adverse effects of low subphysiological doses of thyroid hormone administration are minimal, the best method for confirming a diagnosis of hypothyroidism is to monitor for symptom relief from a trial therapy of thyroid hormone. Hypothyroid patients will benefit from even low doses of thyroid supplements, whereas patients without hypothyroidism will see no positive effect because their systems will reduce their endogenous thyroid hormone production in response to low doses of exogenous hormone. To avoid abrupt increases in metabolic demands, patients can be started on very low doses of thyroid hormone supplements and increased by small increments, such as 25 μg of thyroxine or .25 grain of natural thyroid.

Clearly, a trial of thyroid hormone supplements can identify all symptomatic patients that can benefit from the treatment. Using trial therapy for the diagnostic confirmation of hypothyroidism will minimize the expected cost of making diagnostic mistakes. It is very difficult for the patient that must continue suffering the symptoms of hypothyroidism due to a missed diagnosis, much more trouble than the few, if any, adverse effects the trial therapy will produce in the patients who are ultimately demonstrated to be euthyroid.

## Discussion

It is widely recommended that the TSH test be utilized in the diagnostic confirmation of hypothyroidism, but these recommendations are not supported by unbiased clinical evidence. For example, guidelines have recommended that determinations of the serum free $T_4$ and serum TSH concentrations be used to confirm the diagnosis of hypothyroidism [16]. No reference is made to any controlled diagnostic study that demonstrated the utility of this diagnostic method. As with the TSH test, there is inadequate evidence for the diagnostic accuracy of the free $T_4$ test as an indicator of hypothyroidism. Furthermore, if both tests are required for confirmation of hypothyroidism, these tests must be evaluated together in a controlled diagnostic study to determine their combined diagnostic accuracy.

Does the application of the TSH test in the diagnostic confirmation of hypothyroidism improve the health of patients? If some hypothyroid patients that would benefit from thyroid hormone supplements are denied treatment because a diagnosis of hypothyroidism is ruled out on the basis of the TSH result, the answer is no. It is not clear how a patient's health is improved by use of the TSH test in lieu of or in addition to the traditional method for a definitive diagnosis of hypothyroidism: clinical suspicion by a knowledgeable diagnostician confirmed by a positive response to a trial of thyroid hormone supplements.

Should a diagnosis of hypothyroidism rely on the TSH result from a patient with signs, symptoms and a medical history consistent with hypothyroidism? When a patient has a high pre-test probability of having hypothyroidism, any TSH result that indicates otherwise would have little effect on the high pre-test likelihood. Consequently, trial thyroid hormone supplements should be given to any patient with a high pre-test probability of being hypothyroid, regardless of their TSH result.

If a diagnostician believes that hypothyroidism is the most likely diagnosis, what is wrong with beginning a trial of thyroid hormone replacement therapy? What is the value of ordering a TSH test at this time? Will a high TSH result indicate that the patient has primary hypothyroidism or will it indicate that the patient has NTI due to some other disease? Will a TSH result within the reference interval indicate that the patient's symptoms are caused by some other disease or that the patient's hypothyroidism is probably a non-primary type?

It has never been objectively demonstrated that the diagnostic indication of a serum TSH level outweighs the clinical suspicion of hypothyroidism. Furthermore, since a TSH result may be inaccurate due to assay interference [35], the TSH result cannot be utilized to support a diagnosis of euthyroidism if the clinical suspicion supports a diagnosis of hypothyroidism. Therefore, when the clinical suspicion of hypothyroidism precedes testing the patient's TSH level, performing the test is of no diagnostic value.

The first step in reaching an appropriate diagnosis of hypothyroidism is to consider hypothyroidism as a possible diagnosis. If hypothyroidism is not considered, its signs, symptoms and history are less likely to be explored. To diagnose hypothyroidism, the clinician must maintain a high index of suspicion in all patients with non-specific symptoms. The clinician may need to probe for additional hypothyroid symptoms since a patient's hypothyroid symptoms usually have gradually worsened and the patient can be unaware that their condition is abnormal.

If, after a thorough medical examination and history is taken, hypothyroidism is considered the most probable diagnosis, the patient should be started on a low dose of thyroid hormone. If the patient benefits from the trial therapy, the thyroid hormone dosage should then be increased step-wise until the optimal therapeutic effect is attained. When the trial dosage is considered to be an effective dose and seems to have no beneficial effect, another diagnosis should be explored.

Originally published in *Medical Hypotheses* 2010;75(5):458-63

## Summary

The accuracy of the TSH test in confirming a suspected diagnosis of hypothyroidism has not been adequately measured. The TSH test's accuracy has not been adequately measured for case finding and screening situations, either. Even though no one can honestly say what the sensitivity and specificity of the TSH test is for indicating hypothyroidism, this test is routinely used in the diagnosis of hypothyroidism as though the test was highly reliable.

If diagnostic certainty of hypothyroidism is desired, the TSH test should not be utilized in the diagnostic confirmation of suspected hypothyroidism. Instead, diagnostic confirmation of suspected hypothyroidism should be accomplished by evaluating the patient's response to a trial administration of thyroid hormone supplements. If the patient's chronic symptoms are relieved soon after beginning thyroid hormone supplements, it is very likely that the treatment is compensating for hypothyroidism.


## Conflicts of interest statement

None declared.

## References


1. Watanakunakorn C, Hodges RE, Evans TC. Myxedema. A study of 400 cases. *Arch Intern Med* 1965;116:183-90. [Citation]
2. Bruns DE, Huth EJ, Magid E, Young DS. Toward a checklist for reporting of studies of diagnostic accuracy of medical tests. *Clin Chem* 2000;46(7):893-5. [Abstract] [Free Full Text]
3. Zweig MH, Robertson EA. Why we need better test evaluations. *Clin Chem* 1982;28(6):1272-6. [Abstract] [Free Full Text]
4. Köbberling J, Trampisch HJ, Windeler J. Memorandum for the evaluation of diagnostic measures. *J Clin Chem Clin Biochem* 1990;28(12):873-9. [Abstract]
5. Begg CB. Biases in the assessment of diagnostic tests. Stat Med 1987;6(4):411-23. [Abstract]
6. Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. *N Engl J Med* 1978;299(17):926-30. [Abstract]
7. Holland WW, Whitehead TP. Value of new laboratory tests in diagnosis and treatment. *Lancet* 1974;2(7877):391-4. [Citation]
8. Toft AD, Seth J, Kirkham KE, Marshall A, Irvine WJ. Assessment of *in vitro* thyroid function tests in 100 consecutive patients referred to a thyroid clinic. *Clin Endocrinol (Oxf)* 1973;2(2):127-34. [Citation]
9. Caldwell G, Kellett HA, Gow SM, Beckett GJ, Sweeting VM, Seth J, Toft, AD. A new strategy for thyroid function testing. *Lancet* 1985;1(8438):1117-9. [Abstract]
10. Lawson N, Mike N, Wilson R, Pandov H. Assessment of a time-resolved fluoroimmunoassay for thyrotropin in routine clinical practice. *Clin Chem* 1986;32(4):684-6. [Abstract] [Free Full Text]
11. Spencer C, Eigen A, Shen D, Duda M, Qualls S, Weiss S, Nicoloff, J. Specificity of sensitive assays of thyrotropin (TSH) used to screen for thyroid disease in hospitalized patients. *Clin Chem* 1987;33(8):1391-6. [Abstract] [Free Full Text]
12. Nuutila P, Irjala K, Viikari J, Prinssi VP, Kaihola HL. Comparative evaluation of serum thyroxine, free thyroxine and thyrotropin determinations in screening of thyroid function. *Ann Clin Res* 1988;20(3):158-63. [Abstract]
13. de los Santos ET, Starich GH, Mazzaferri EL. Sensitivity, specificity, and cost-effectiveness of the sensitive thyrotropin assay in the diagnosis of thyroid disease in ambulatory patients. *Arch Intern Med* 1989;149(3):526-32. [Abstract]
14. Roden M, Nowotny P, Hollenstein U, Schneider B, Vierhapper H, Waldhäusl W. Equivalent discrimination among states of thyroid function by immunochemiluminimetric and immunoradiometric determination of thyrotropin. *Clin Chem* 1993;39(3):544-7. [Abstract] [Free Full Text]
15. Wikland B, Löwhagen T, Sandberg PO. Fine-needle aspiration cytology of the thyroid in chronic fatigue. *Lancet* 2001;357(9260):956-7. [Citation]
16. Surks MI, Chopra IJ, Mariash CN, Nicoloff JT, Solomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. *JAMA* 1990;263(11):1529-32. [Abstract]
17. Faglia G, Bitensky L, Pinchera A, Ferrari C, Paracchi A, Beck-Peccoz P, et al. Thyrotropin secretion in patients with central hypothyroidism: evidence for reduced biological activity of immunoreactive thyrotropin. *J Clin Endocrinol Metab* 1979;48(6):989-98. [Abstract]
18. Sakata S. Autoimmunity against thyroid hormones. *Crit Rev Immunol* 1994;14(2):157-91. [Abstract]
19. Utiger RD. Thyrotrophin radioimmunoassay: another test of thyroid function. *Ann Intern Med* 1971;74(4):627-9. [Citation]
20. Melmed S, Geola FL, Reed AW, Pekary AE, Park J, Hershman JM. A comparison of methods for assessing thyroid function in nonthyroidal illness. *J Clin Endocrinol Metab* 1982;54(2):300-6. [Abstract]
21. Wardle CA, Fraser WD, Squire CR. Pitfalls in the use of thyrotropin concentration as a first-line thyroid-function test. *Lancet* 2001;357(9261):1013-4. [Abstract]
22. Baker BL, Yu YY. Hypophyseal changes induced by thyroid deficiency and thyroxine administration as revealed by immunochemical staining. *Endocrinology* 1971;89(4):996-1004. [Citation]
23. Farquhar MG, Rinehart JF. Cytologic alterations in the anterior pituitary gland following thyroidectomy: An electron microscope study. *Endocrinology* 1954;55:857-76. [Citation]
24. Scheithauer BW, Kovacs K, Randall RV, Ryan N. Pituitary gland in hypothyroidism. Histologic and immunocytologic study. *Arch Pathol Lab Med* 1985;109(6):499-504. [Abstract]
25. Yamamoto K, Saito K, Takai T, Naito M, Yoshida S. Visual field defects and pituitary enlargement in primary hypothyroidism. *J Clin Endocrinol Metab* 1983;57(2):283-7. [Abstract]
26. Melander A, Ericson LE, Ljunggren JG, Norberg KA, Persson B, Sundler F, et al. Sympathetic innervation of the normal human thyroid. *J Clin Endocrinol Metab* 1974;39(4):713-8. [Citation]
27. Melander A, Nilsson E, Sundler F. Sympathetic activation of thyroid hormone secretion in mice. *Endocrinology* 1972;90(1):194-9. [Citation]
28. Sergi I, Papandreou MJ, Medri G, Canonne C, Verrier B, Ronin C. Immunoreactive and bioactive isoforms of human thyrotropin. *Endocrinology* 1991;128(6):3259-68. [Abstract]
29. Beck-Peccoz P, Persani L. Variable biological activity of thyroid-stimulating hormone. *Eur J Endocrinol* 1994;131(4):331-40. [Abstract]
30. Nicoloff JT, Lum SM, Spencer CA, Morris R. Peripheral autoregulation of thyroxine to triiodothyronine conversion in man. *Horm Metab Res Suppl* 1984;14:74-9. [Abstract]
31. Brabant G, Prank K, Hoang-Vu C, Hesch RD, von zur Mühlen A. Hypothalamic regulation of pulsatile thyrotopin secretion. *J Clin Endocrinol Metab* 1991;72(1):145-50. [Abstract]
32. Hangaard J, Andersen M, Grodum E, Koldkjær O, Hagen C. Pulsatile thyrotropin secretion in patients with Addison's disease during variable glucocorticoid therapy. *J Clin Endocrinol Metab* 1996;81(7):2502-7. [Abstract]
33. Samuels MH. Effects of variations in physiological cortisol levels on thyrotropin secretion in subjects with adrenal insufficiency: a clinical research center study. *J Clin Endocrinol Metab* 2000;85(4):1388-93. [Abstract] [Free Full Text]
34. Maturlo SJ, Rosenbaum RL, Pan C, Surks MI. Variable thyrotropin response to thyrotropin-releasing hormone after small decreases in plasma free thyroid hormone concentrations in patients with nonthyroidal diseases. *J Clin Invest* 1980;66(3):451-6. [Abstract] [Free Full Text]
35. Després N, Grant AM. Antibody interference in thyroid assays: a potential for clinical misinformation. *Clin Chem* 1998;44(3):440-54. [Abstract] [Free Full Text]


Originally published in *Medical Hypotheses* 2010;75(5):458-63