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Diagnostic Evaluation Update

BIOCHEMICAL TESTING OF THYROID FUNCTION

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Over the past decade it has been generally accepted that the serum thyrotropin (TSH) represents the best biochemical marker of thyroid function when measured using an adequately sensitive assay. Considerable debate centers on the role of other thyroid function tests in supplementing TSH and on the recommendations as to which patients should be tested. In the current cost-conscious era, significant issues focus on cost-effectiveness and medical outcomes. Routine laboratory testing, which has been a mainstay of medicine in the United States for many years, is now being closely scrutinized by both health insurance companies and managed care organizations. Algorithms and guidelines for thyroid function testing have been published by Klee and Hay [20] [21] and others, [3] [5] [8] [13] [23] including various medical societies. [2] [10] [19] [25] [28] [30] [31] These guidelines generally are based on pathophysiologic principles and practice consensus; few have been derived from actual practice outcomes data. Recently, some outcomes studies have been conducted, the results of which support some parts of the guidelines and question others. These issues are reviewed in this article.

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RATIONALE FOR USING TSH AS THE PRIMARY THYROID FUNCTION TEST

Thyroid hormone production by the thyroid gland is stimulated by TSH, which is synthesized and secreted from the anterior pituitary. In patients with an intact hypothalamic-pituitary-thyroid (HPT) axis, a negative feedback regulatory mechanism controls thyroid gland metabolism. The pituitary serves as a biosensor of thyroid hormone levels and regulates TSH levels according to the feedback of free thyroxine (FT_4) and free triiodothyronine (FT_3) levels. Decreases in thyroid hormone production stimulate more TSH, and overproduction of thyroid hormone suppresses TSH secretion. The control system may have a relatively slow response time. Generally, a period of 4 to 6 weeks is required for TSH levels to return to normal after a hypothyroid patient is treated with thyroxine replacement. Similarly, several months may be required for serum TSH levels to return to normal after therapeutic treatment of hyperthyroidism. During these periods of nonequilibrium, discordance may occur between the plasma thyroid hormone concentrations and the levels of TSH.

When the HPT axis is intact and the system is in equilibrium, there is an inverse log-linear relationship between the concentration of TSH and FT_4 (Fig. 1) (Figure Not Available) . [29] In such a system, small linear decreases in FT_4 concentrations are associated with exponential increases in TSH concentrations, whereas small linear increases in FT_4 concentrations are associated with exponential decreases in TSH concentrations. Almost all cases of hypothyroidism and hyperthyroidism encountered in general medical practice are caused by primary disease of the thyroid gland. In these cases, TSH concentration changes are a reactive response of the pituitary to compensate for thyroid hormone underproduction or overproduction. In rare instances, malfunction of the pituitary, hypothalamus, or both can alter TSH production, which, in turn, causes the thyroid gland to underproduce or overproduce thyroid hormone. A basic premise of assaying TSH-first as a test of thyroid function is that central hypothalamic-pituitary gland disorders are very rare, and that when they occur, they will be detected by the combination of signs and systems produced by their effects on multiple pituitary-target organ systems.

With the inverse log-linear relationship between TSH concentrations and free thyroid hormone concentrations, it is not surprising that TSH concentration measurements are more sensitive than free thyroid hormone measurements for the detection of early thyroid dysfunction. Early detection leads to biochemical changes that clinically are not

associated with obvious symptoms. *Subclinical hypothyroidism* is the term used to describe patients with elevated TSH concentration, normal FT_4 , and no clinical symptoms. By contrast, *subclinical hyperthyroidism* refers to patients with low TSH, normal FT_4 , normal FT_3 , and no clinical symptoms.

Figure 1. (Figure Not Available) Relationship between FT_4 index and TSH in 505 patients with stable thyroid status, showing the log TSH versus linear FT_4 relationship. Open symbols represent undetectable (< 0.005 mIU/L) TSH values. Solid lines represent the 95% confidence limits of the relationship (log TSH = 2.56-0.22 FT_4 Index; rho = 0.84) *(From Spencer CA, LoPresti JS, Patel A, et al: Applications of a new chemiluminometric thyrotropin assay to subnormal measurement. J Clin Endocrinol Metab 70:456, 1990; ©The Endocrine Society; with permission.)*

CRITERIA FOR DIAGNOSIS AND TREATMENT OF HYPOTHYROIDISM AND HYPERTHYROIDISM

The American Thyroid Association (ATA) recommends that "a decrease in serum FT_4 estimate and a raised level of serum TSH confirm the diagnosis of hypothyroidism caused by thyroid gland failure ... an increase in FT_4 estimate combined with a serum sensitive TSH level suppressed to less than 0.1 mIU/L establishes the diagnosis of thyrotoxicosis." [30] Although these criteria appear to be sufficient, they are not necessary for these diagnoses because the ATA [2] also has stated that, "in patients with mild hyperthyroidism or mild hypothyroidism of thyroid origin, the FT_4 measurement by any method is usually less sensitive than the TSH." The ATA recommends the additional measurement of total T_3 when hyperthyroidism is suspected and the FT_4 value is normal. [2] The ATA defines subclinical hypothyroidism as the condition in patients with normal free T_4 measurement or estimate and an elevated TSH concentration but few, if any, hypothyroid symptoms. Therapy is advocated for these patients, especially if thyroid autoantibodies are positive. [28] If these patients are not treated, yearly follow-up evaluations are recommended.

The practice guidelines published by the American Association of

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Clinical Endocrinologists (AACE) [10] endorse sensitive TSH measurements as "the single best screening test for hyperthyroidism." [8] Subclinical hyperthyroidism is defined by "a TSH value below normal (suppressed) with normal serum T_4 and T_3 RIA levels." Treatment is recommended when these findings are associated with "toxic goiter, toxic adenoma, or toxic multinodular goiter." Subclinical hypothyroidism is defined by "an elevated TSH with normal T_4 , FT_4 , and T_3 levels." The AACE recommends that, "most patients with subclinical hypothyroidism should be treated with levothyroxine replacement therapy, especially with positive thyroid autoantibodies." However, it is cautioned that treatment "might best be withheld" in elderly or cardiac patients "with only a slight TSH elevation."

The National Academy of Clinical Biochemistry recommends that measurement of serum TSH using an assay with a functional sensitivity of 0.1 mIU/L or less be the initial test for clinically suspected hyperthyroidism, and that T_4 be measured only in patients with TSH concentration of 0.1 mIU/L or less. [19] Serum T_3 measurement is recommended only when the TSH is low and T_4 levels are normal in patients with apparent clinical hyperthyroidism. For primary hypothyroidism, serum TSH measurement is recommended using a precise and sensitive method as "the initial step in the diagnosis." Measurement of T_4 , FT_4 , or FT_3 should not be used as the initial step. Routine measurement of thyroid antibodies in primary hypothyroidism is not recommended unless there is a "specific clinical reason."

The Royal College of Physicians of London has recently recommended that, "to confirm the diagnosis of hypothyroidism or hyperthyroidism, concentrations of serum thyroid stimulating hormone and total or free thyroxine (direct or indirect) must be measured." [31] They use the term subclinical hypothyroidism to describe patients with normal serum thyroxine and raised TSH concentrations who do not have symptoms. Treatment with thyroxine is recommended for these patients when microsomal (thyroid peroxidase) antibodies are present, but it is acceptable to defer treatment if the TSH level is less than 10 mU/L in patients without thyroid autoantibodies, provided that secure follow-up can be achieved.

The Health Insurance Commission in cooperation with the Australian Medicare program implemented a policy in 1994 that denies payment for thyroid function tests other than an assay for TSH except in limited cases. The exceptions to the use of TSH as the single first-line test of thyroid function include the monitoring of thyroid disease, the investigation of thyroid dysfunction in inpatients, the investigation of dementia or psychiatric disease, the investigation of amenorrhea or infertility, the investigation of suspected pituitary dysfunction, and the evaluation of drugs that interfere with thyroid hormone metabolism or function. [23] Following the implementation of this policy, there was more than a 20-fold increase in TSH tests and a 42% decrease in the total number of thyroid function tests. It was estimated that the policy might

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reduce expenditures for thyroid function testing by $3.4 million annually (8.3% reduction).

MONITORING THYROID HORMONE REPLACEMENT THERAPY

The general consensus is that sensitive TSH assays represent the "gold standard for evaluating thyroid hormone replacement levels in patients with an intact HPT axis." [10] [15] [19] [23] The replacement dose should be adjusted to keep the TSH in the normal range--neither suppressed nor elevated. [4] [26]

The role of other thyroid hormone measurements to supplement an assay for TSH in monitoring replacement is controversial. In a study of 127 hypothyroid patients on replacement therapy, Ross and co-workers [27] found 60% concordance between FT_4 and TSH; 14% of patients had subnormal TSH with normal FT_4 , 18% had high TSH with

normal FT_4 , and 4% had normal TSH with high FT_4 . [27] Knowledge of the FT_4 level was important in approximately 4% of the patients, particularly in patients with TSH levels below 0.05 mU/L (to assess the degree of hyperthyroidism) and in patients with pituitary/hypothalamic disease.

Franklyn and co-workers [9] studied 153 patients receiving long-term thyroxine therapy, 82 of whom were found to have subnormal TSH concentrations. Twenty-seven of these patients had elevated FT_4 concentrations; only ten had elevated FT_3 concentrations. Fifty-five of the patients with subnormal TSH had TSH levels below 0.03 mU/L. It is unclear from this study how the additional information about FT_4 and FT_3 was utilized in the management of patients.

MONITORING THERAPY FOR HYPERTHYROIDISM

The treatment for hyperthyroidism generally is pharmacologic blockage of thyroid hormone production or destruction of thyroid tissue by surgery with or without radioablation. [24] [28] Ross and co-workers [27] studied 43 patients and found that, after therapy, 50% had discordant TSH and FT_4 concentrations. Fourteen had subnormal TSH and normal FT_4 , seven had subnormal TSH and low FT_4 , and two had normal TSH but low FT_4 . It was assumed that the TSH levels were inappropriately low as a result of the delayed recovery of the pituitary-thyroid axis following therapy for hyperthyroidism. After several months, the negative feedback function of the pituitary generally returns, and TSH concentrations again become a reliable monitor of thyroid function.

THYROID FUNCTION TESTS IN PATIENTS WITH DEPRESSION

Numerous studies have noted an interaction between disorders of mood and thyroid function, including hyperthyroidism, hypothyroidism,

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and subclinical hypothyroidism. [18] These alterations in thyroid function tests are complex and may be inconsistent with the usual negative feedback control of the thyroid-pituitary axis. Decreases in both T_3 and TSH may be encountered. Use of the thyrotropin-releasing hormone (TRH) stimulation test for the evaluation of hyperthyroidism or hypothyroidism was essentially abandoned following the introduction of sensitive TSH assays; however, TRH stimulation tests still are used in some neuropsychiatric evaluations.

Approximately 25% of patients with depression have a blunted TSH response to TRH stimulation, whereas 15% have an exaggerated response. [14] The mechanisms of these altered responses to TRH are not fully known, but it is suspected that elevated glucocorticoids may inhibit the TSH response. The blunted TSH response can be associated with a decreased T_3 concentration in comparison with the elevated T_3 typically found in thyrotoxicosis. Most of the patients with an exaggerated TSH response have positive thyroid autoantibodies, which may indicate latent hypothyroidism due to destructive autoimmune thyroiditis.

Several studies have shown that treatment with T_3 improves the antidepressant response. [16] [17] [18] However, there is no consensus on the value of thyroid function testing, including

TRH stimulation tests, for predicting which patients will be refractory to therapy. [7] [16] [18] There is support for the measurement of TSH in the routine assessment of depression (especially in patients with eating disorders) to rule out overt hypothyroidism, subclinical hypothyroidism, or both. [11] [12] There also is some support for measuring microsomal antibodies, particularly in women aged more than 45 years. [11] Davey and co-workers [5] from Australia reported that a TSH first testing strategy, without concurrent FT_4 measurements, worked as well in patients with psychiatric disorders as it did in other patients.

MAYO CLINIC EXPERIENCE

In 1986 the authors implemented a highly sensitive TSH assay and advocated TSH-first testing as depicted by the algorithm shown in Figure 2. [20] Testing patterns gradually switched from a predominantly T_4 -first strategy to TSH-first strategy over the next 8 years. Table 1 demonstrates an 87% reduction in T_4 tests and a 469% increase in TSH assays from 1988 to 1994. During that time, annual patient registrations increased by 14%. There also were significant increases in the number of FT_4 and microsomal antibody assays.

In the summer of 1994 the authors introduced a thyroid function cascade for ordering thyroid tests. [21] This cascade provides for clinician-initiated follow-up tests based on the results of the initial TSH assay. When the TSH concentration is elevated, FT_4 and microsomal antibody tests are performed. When TSH is suppressed, FT_4 is measured. If the FT_4 concentration is normal, a total T_3 concentration is measured. If the TSH concentration is suppressed below the detection limit of the routine

Figure 2. (Figure Not Available) TSH-based strategy for laboratory investigation of thyroid function proposed at Mayo Clinic in 1986. *(From Klee GG, Hay I: Assessment of sensitive thyrotropin assays for an expanded role in thyroid function testing: Proposed criteria for analytic performance and clinical utility. J Clin Endocrinol Metab 64:469, 1987; ©The Endocrine Society; with permission.)*

assay, a highly sensitive assay is performed which can quantitate TSH to a level of 0.002 mIU/L. [22] As illustrated in Figure 3 , this new ordering format was added to our medical service record while retaining all of the individual request formats. The major objective in introducing the thyroid cascade was to provide a faster turnaround time for follow-up tests while reducing the need for concurrent test orders. The change in test ordering patterns after the introduction of the cascade is shown in Table 2 . Of particular note is the marked increase in the TSH, FT_4 , and microsomal antibody grouping; the increase in TSH, FT_4 , and T_3 testing patterns and the decline in T_4 -only ordering.

Serum TSH is measured using a modification of the ACS:180® (Chiron Diagnostics Corporation, East Walpole, MA) procedure. Extra sheep immunoglobulin is added to the reagents to minimize assay

TABLE 1 -- TRENDS IN TEST ORDERING AT THE MAYO CLINIC

Year	Registrations *	T_4	TSH	FT_4	T_3	TMAb
1988	205,232	91,839	16,392	770	2432	2169
1990	210,489	67,160	81,122	1854	2571	2283
1992	223,495	52,116	87,010	2897	2603	2771
1994	234,360	12,166	93,270	4477	2039	4322
1996	242,706	13,468	96,245	9585	3048	7027
1996--individual	--	13,468	55,621	2801	1350	2085
1996--cascade	--	--	40,624	6784	1698	4942

T_4 = thyroxine; TSH = serum thyrotropin; FT_4 = free thyroxine; T_3 = triot iodothyronine; TMAb = thyroid microsomal antibody.

*Based on one registration per year rather than the number of medical encounters per years.

Figure 3. Thyroid test request form providing for direct clinical ordering of thyroid function cascade while retaining ability for clinicians to order tests individually.

interference caused by heterophile antibodies. [22] The high-sensitivity TSH assay is a locally developed test which employs a preincubation step and special low-concentration standards prior to quantitation on the ACS:180. [22] Serum thyroxine is measured on the ACS:180; serum FT_4 and T_3 are measured on the Abbott® analyzer (Abbott Laboratories, Abbott Park, IL). Microsomal antibodies are measured with the Serodia-AMC (Fujirebio, Tokyo) agglutination assay (formerly, Ames Sera-TeK assay). The treatment setting at the Mayo Clinic in Rochester, Minnesota, is predominantly a large multispecialty outpatient clinic combined with two acute care hospitals with a total of 1595 beds.

During 1996 approximately 42% of the requests for TSH measurement at the Mayo Clinic (excluding Mayo Medical Laboratory referral specimens) were ordered using the thyroid cascade. The test results from 39,728 test orders received during the first 5 months of 1996 were retrieved from the laboratory information system and analyzed using Statistical Analysis Systems software (SAS, Institute, Cary, NC). Approximately

TABLE 2 -- PATTERNS OF TEST ORDERING

TSH	T_4	FT_4	T_3	TMAb	1994 *(%)	1996 (%)
X	-	-	-	-	82.97	76.84

TABLE 2 -- PATTERNS OF TEST ORDERING

TSH	T_4	FT_4	T_3	TMAb	1994* (%)	1996 (%)
-	X	-	-	-	12.44	2.91
X	-	-	X	-	0.93	0
-	-	X	X	-	0.07	0.07
X	-	X	-	-	1.89	1.40
-	-	X	-	-	0.61	0.45
X	-	X	X	-	0.54	1.35
X	-	X	-	X	0.31	4.84
-	-	-	X	-	0.20	0.04
X	-	X	X	-	0.01	1.35
X	X	-	-	-	0	8.70
X	X	-	X	-	0	0.51
X	X	X	X	-	0	0.33
X	X	X	-	-	0	0.42

X = test ordered; - = test not ordered; TSH = serum thyrotropin; T_4 = thyroxine; FT_4 = free thyroxine; T_3 = triiodthyronine; TMAb = thyroid microsomal antibody.

*Prior to implementation of thyroid test cascade.

TABLE 3 -- FT_4 AND TMAb ABNORMALITIES ASSOCIATED WITH ELEVATED TSH FROM TSH CASCADE

TSH (mIU/L)	Number	FT_4 $\leq$ 0.6 ng/dL	TMAb $\geq$ 1:400
		Number (%)	Number (%)
5.1-7.4	1202	2 (0.2)	342 (28.5)
7.5-9.9	366	3 (0.8)	145 (39.6)
10.0-14.9	253	2 (0.8)	140 (55.3)
15.0-19.9	64	4 (6.3)	37 (57.8)
$\geq$20	108	25 (23.1)	68 (63.0)

TABLE 3 -- FT_4 AND TMAb ABNORMALITIES ASSOCIATED WITH ELEVATED TSH FROM TSH CASCADE

TSH (mIU/L)	Number	FT_4 ≤0.6 ng/dL	TMAb ≥1:400
		Number (%)	Number (%)
Total	1993	36 (1.8)	732 (36.7)

TSH = serum thyrotropin; FT_4 = free thyroxine; TMAb = thyroid microsomal antibody.

58% of the TSH requests were ordered for female patients with a median age of 59 years. The median age for men was 63 years. Overall, 12.7% of the TSH test results were elevated above 5 mIU/L, and 4.4% were suppressed below 0.3 mIU/L. The distribution of the test values ordered using the cascade was similar to the distribution for the tests ordered as TSH requests, with the exception that only 4.0% of the cascade orders had decreased TSH concentrations compared with 4.8% in the TSH tests ordered alone.

The results of the follow-up FT_4 and microsomal antibody measurements performed as part of the cascade are shown in Table 3 . For the 12.7% of the cascade requests with elevated TSH, the yield of abnormalities from FT_4 testing was less than 1% until the TSH concentration exceeded 15 mIU/L. On the other hand, a considerable percentage (28% to 55%) of patients with TSH concentrations between 5.0 and 15.0 mIU/L had positive thyroid microsomal antibody tests with titers of 1:400 or greater.

The yield of abnormalities found in follow-up FT_4 and T_3 tests in patients with suppressed TSH is shown in Table 4 . A higher percentage

TABLE 4 -- FT_4 AND T_3 ABNORMALITIES ASSOCIATED WITH SUPPRESSED SERUM TSH LEVELS MEASURED IN TSH CASCADES

TSH	Number	FT_4 >2.0 ng/dL	T_3 >180 ng/dL and FT_4 <2 ng/dL
		Number (%)	Number (%)
0.20-0.29	127	0 (0)	0 (0)
0.10-0.19	147	8 (5.4)	2 (1.4)
0.05-0.09	85	12 (14.1)	5 (5.0)
0.02-0.049	77	13 (16.9)	9 (11.7)
0.02-0.049	77	13 (16.9)	9 (11.7)
0.010-0.019	49	15 (30.6)	3 (6.1)
0.009-0.005	57	18 (31.6)	1 (1.8)
<0.005	83	37 (44.6)	5 (13.1)
Total	625	103 (16.5)	25 (4.0)

FT_4 = free thyroxine; T_3 = triiodothyronine; TSH = serum thyrotropin.

Figure 4. Comparison of TSH and FT_4 test values from 5 months of assays performed at the Mayo Clinic in Rochester, Minnesota. Bold solid line in the middle of each box represents the average FT_4 for patients with that range of TSH values. Lower and upper thin lines on each box represent the group's 10th and 90th percentiles of FT_4 values. Dashed horizontal lines at 0.7 and 2.0 ng/dL represent the normal values for the FT_4 assay.

of suppressed TSH levels was found in women than in the overall group (77% versus 58%). Median ages for the males and females in this subgroup were the same as in the whole population tested. No patient with a TSH level between 0.20 and 0.29 mIU/L had abnormal FT_4 or T_3 tests. The yield of abnormal FT_4 and T_3 tests was relatively low until the TSH concentration was suppressed below 0.1 mIU/L.

Figure 4 shows the relationship between TSH and FT_4 concentrations in subgroups according to TSH concentration. The horizontal lines across the boxes represent the mean values for each group. The lower and upper boundaries of each box represent the tenth and ninetieth percentiles of the FT_4 distributions. These distributions do not exceed the normal FT_4 range (0.70 to 2.0 ng/dL) until the TSH level is greater than 20 mIU/L or below 0.10 mIU/L. The mean FT_4 concentrations for these groups never fall outside of the normal range except when TSH exceeds 100 mIU/L.

COMPARISON WITH OTHER TESTING PROGRAMS

Investigators at the Henry Ford Hospital recently reported their experience with a directed thyroid-testing algorithm based on a TSH assay followed by FT_4 indices (FTI). [8] Within 3 years of its implementation,

approximately 60% of tests were ordered using this algorithm. Approximately 92% of tests were ordered for outpatients. Overall, 31% of patients had a TSH level greater than 5.5 mU/L and 10% had TSH less than 0.4 mU/L. The percentage of patients with FTI greater than 10 mug/dL increased progressively with the suppression of TSH--12% of patients at 0.2 to 0.3, 53% at 0.04 to 0.1, 72% at 0.02 to 0.04, and 80% at 0.01 mIU/L of TSH. It was concluded that the algorithm resulted in a 19% reduction in the number of thyroid tests performed in comparison with the prealgorithm period, which resulted in a significant cost savings.

In a study of 364 consecutive specimens obtained from patients admitted to an acute general care teaching hospital at the University of Chicago, 12.1% had elevated TSH levels above 5 mIU/L, and 3.9% had TSH concentrations less than 0.3 mIU/L. [6] In contrast to the author's study, most of the patients who had abnormal FT_4 (measured as an index) had normal TSH and were younger than 49 years.

Several other studies of thyroid tests have been reported. Ross and co-workers [27] at the Massachusetts General Hospital measured TSH and FT_4 on 460 consecutive visits for endocrine evaluation. The TSH level alone provided enough information to assess thyroid function in 64% of the patients. Davey and colleagues [5] at Western Hospital in Melbourne tested TSH and FT_4 in 1000 consecutive cases. They found that 2.7% of abnormal FT_4 values were not associated with abnormal TSH concentrations. However, these values were very close to normal and were accepted as indicating a euthyroid state. In a study of 270 patients at Tel Aviv University, FT_4 was measured. If the result of this test was abnormal, TSH was also measured. [1] FT_4 was abnormal in 37% of patients. Only 11% of the patients, however, had true biochemical thyroid dysfunction. A study of 68 patients by Hamburger and Kaplan [13] showed that both the percentage of patients with abnormal FT_4 and the percentage with positive thyroid antibodies increased with the level of serum TSH. With a TSH range of 5.1 to 9.9 mIU/L, only 3% of patients had low FT_4 , whereas with a TSH level of 20 mIU/L or greater, 72% had low FT_4 . In contrast, most of the patients with TSH of 5.1 mIU/L or greater had positive antibody titers. Ninety-seven percent of 34 patients with a TSH level less than 0.1 mIU/L had high FT_4 levels.

RECOMMENDATIONS FOR THE FUTURE

The TSH first testing strategy has become widely used and seems to work well. The thyroid function ordering cascade, in terms of more rapid provision of test results without the necessity to order thyroid panels, is administratively appealing. The major concern with the cascade is the setting of limits for triggering additional tests. Based on the review of the authors' data and the experience of others, the major benefit of the FT_4 and T_3 assays is in patients with markedly abnormal TSH levels. For patients with subnormal TSH concentrations, most of the additional FT_4 and T_3 tests performed as part of the cascade are

normal unless the serum TSH level is below 0.1 mIU/L. That TSH level compares well with the ATA recommended limit for the diagnosis of hyperthyroidism. Therefore, it may not be necessary to measure FT_4 or T_3 unless the TSH concentration is below 0.1 mIU/L; however, the authors continue to recommend these measurements in patients with abnormally suppressed TSH concentrations because many clinicians find the reports useful for confirming the subclinical hyperthyroid status.

In patients with an elevated serum TSH level, measurement of thyroid microsomal antibodies detects a considerable number of positive cases even when TSH is only mildly elevated. Because this provides evidence for disordered thyroid immunity, the authors suggest that tests for antibodies be triggered as part of the cascade when TSH levels are 5.1 mIU/L or greater. On the other hand, the yield of FT_4 assays seems minimal at this level; however, the authors continue to recommend measurement of FT_4 levels in patients with elevated TSH concentrations to confirm the subclinical hypothyroid status of such patients.

CONCLUSION

Newer assays are becoming available for measurement of FT_3 and antithyroid peroxidase (anti-TPO) antibodies. When these assays are available in automated forms, the authors recommend that the FT_3 replace the T_3 assay and the anti-TPO replace the microsomal antibody assay in thyroid function cascades.

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