Henry Ford Hospital Medical Journal

Volume 39
Number 1 *Festschrift: In Honor of Raymond C. Mellinger*

Article 7

3-1991

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A Thyroid Testing Algorithm: Results of a Pilot Study

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We conducted a pilot study to evaluate an algorithm for thyroid function testing consisting of initial serum thyrotropin values, measured by a sensitive immunoradiometric assay (TSH-IRMA), followed by a computer-directed decision to order further studies. We divided 216 outpatients according to their serum TSH-IRMA values as follows: suppressed (< 0.1 mU/L, group I); low (0.1 to 0.4 mU/L, group II); normal (0.5 to 5.0 mU/L, group III); and high (> 5.0 mU/L, group IV). Thyroxine (T_4), resin uptake (RU), and free thyroxine index (FTI) tests on groups I, II, and IV revealed that T_4 and RU were normal for most patients in all groups and FTI was normal in 80% of group I, 93.4% of group II, and 93.3% of group IV. All patients in group I were designated hyperthyroid from either an exogenous or endogenous source. All patients in group II were clinically euthyroid except one; 50% were taking either L-thyroxine or propylthiouracil and 50% had no identifiable thyroid disease. Patients in group IV were hypothyroid. Overall, TSH was more effective in detecting both hypothyroidism and hyperthyroidism than either serum T_4, RU ratio, or both combined in FTI since results of these measures fell in the normal range for most patients in all groups. We conclude that a computer-directed algorithm with TSH-IRMA as the initial step is useful in the evaluation of suspected thyroid dysfunction, that T_4 and RU may be helpful when TSH is abnormal or borderline, and that suppressed TSH-IRMA values (< 0.1 mU/L) but not low values (0.1 to 0.4 mU/L) are consistently associated with hyperthyroidism. Results obtained by use of the algorithm may be misleading in patients with hypothalamic pituitary dysfunction, but its use should reduce the number of redundant and unnecessary T_4 and RU tests. (Henry Ford Hosp Med J 1991;39:30-4)

The use of thyroid-stimulating hormone-immunoradiometric assay (TSH-IRMA) has improved the sensitivity and specificity of the TSH assay (1-3). Specificity is enhanced by use of monoclonal antibodies (4). The least detectable dose of TSH-IRMA, unlike that of conventional radioimmunoassay, is well below the lower limit of the normal range so that low values can be distinguished from normal (5). Patients with hyperthyroidism have values below the detection limit in even the most sensitive assays (6). This ability to distinguish euthyroid subjects from patients with hyperthyroidism has prompted the suggestion that TSH-IRMA can accurately predict normalcy and uncover early enhanced or suppressed TSH secretion (7). Conditions with increased TSH secretion include the entire spectrum of primary thyroid gland failure as well as the rare instance of pituitary hyperthyroidism. In contrast, suppressed TSH secretion could be secondary to a variety of conditions including hyperthyroidism, autonomous thyroid nodule, thyroid hormone therapy, use of medications such as dopamine or glucocorticoids, pregnancy, nonthyroidal illness, and pituitary hypothyroidism (8). Though the relationship of TSH and free thyroxine (T_4) is log-linear in ambulatory patients with normal pituitary function, there is significant scatter at low TSH levels and no correlation between these parameters in hospitalized patients (9). Nonetheless, the diagnostic efficiency of TSH-IRMA is better than that of either free or total T_4 measurements (10). With that in mind, we and others have recommended measurement of TSH-IRMA as the initial test of thyroid function in patients with suspected thyroid disease (6-12). We designed a diagnostic algorithm, termed directed TSH (DRTSH), in which TSH-IRMA values direct further evaluation by other thyroid function tests (11).

The concept of DRTSH is that because a normal TSH-IRMA level is consistent with normal thyroid function, except in relatively rare cases, no additional tests of thyroid function are required. On the other hand, low or high TSH-IRMA *may* reflect a thyroid abnormality and additional tests are indicated to clarify the clinical situation in terms of initial diagnosis or appropriate therapy. DRTSH automatically orders T_4, resin uptake (RU), and free thyroxine index (FTI) tests.

Our TSH normal range is 0.4 to 5.0 mU/L with a detection limit of 0.1 mU/L. The DRTSH limits set for follow-up testing were based on these assumptions: 1) in the absence of pituitary or hypothalamic disease or other factors affecting TSH secretion, low TSH values (< 0.5 mU/L) represent either hyperthyroidism when TSH is < 0.1 mU/L or a variety of other conditions when TSH is < 0.1 to 0.4 mU/L; 2) normal values of TSH (0.5 to 5.0 mU/L) are likely to represent euthyroidism; 3) TSH values

Submitted for publication: May 31, 1990.
Accepted for publication: September 28, 1990.
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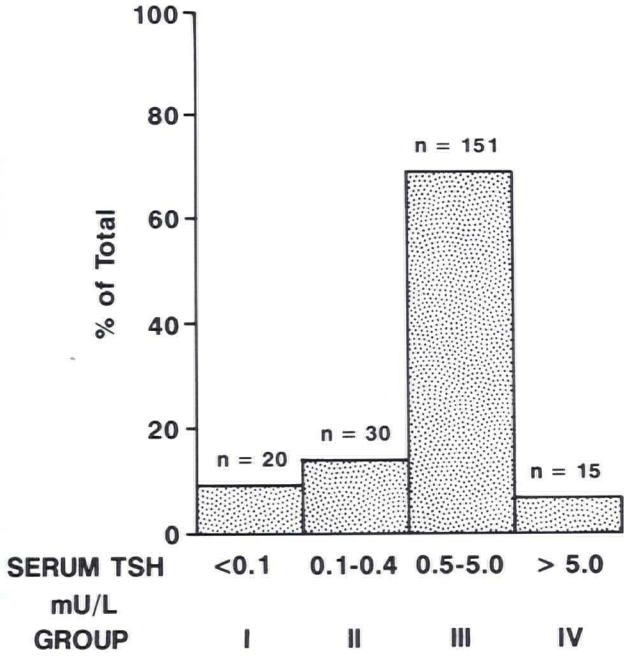

Fig 1—Distribution (%) of concentrations of TSH-IRMA among 216 patients evaluated for thyroidal illness.

of 5.0 to 10.0 mU/L are likely to represent primary hypothyroidism; and 4) TSH values > 10.0 mU/L represent primary hypothyroidism in absence of rare secondary hyperthyroidism. It was projected that this program would be efficient and cost-saving. The complexities of interpreting borderline TSH-IRMA or apparent discrepancies are described in abundance (6-12).

The purpose of this report is to describe the function of the algorithm and to examine whether the T_4, RU, and FTI tests directed by the algorithm were consistent with the patients' clinical conditions. Furthermore, we wished to establish whether the T_4, RU, and FTI follow-up tests directed by the algorithm were *useful*, i.e., provided new information or confirmed the diagnosis suggested by TSH-IRMA.

Study Design

Our computer was programmed to order T_4 and RU and to calculate FTI if the TSH value was < 0.5 mU/L or > 5.0 to 10.0 mU/L. In addition, for the purpose of the study, T_4, RU, and FTI were measured on 30 consecutive patients with normal TSH (0.5 to 5.0 mU/L) and on 10 consecutive patients with high TSH (> 10.0 mU/L). A total of 216 samples were tested for TSH-IRMA over a six-week period, and the results were categorized into five groups according to TSH values.

We reviewed the medical records for all patients identified by the algorithm with TSH value < 0.5 or > 5.0 mU/L to confirm the presence or absence of primary hypothyroidism or primary hyperthyroidism, to exclude the presence of pituitary and hypothalamic disorders, and to identify drugs or diseases known to affect thyroid function tests, including L-thyroxine and antithyroid medications. Patients were considered 1) hypothyroid if TSH was > 5.0 mU/L, 2) hyperthyroid (endogenous or exogenous) if TSH was < 0.1 mU/L, or 3) euthyroid if TSH was 0.5 to 5.0 mU/L or if TSH was 0.1 to 0.4 mU/L in absence of drugs or diseases known to interfere with thyroid function tests.

Table 1
Clinical Data

Group (TSH)	Primary Hyperthyroidism	Thyroxine Therapy	Normal Euthyroid	Primary Hypothyroidism	Others
I	9	11	—	—	—
II	1*	12†	14‡	—	3§
IV	—	10	—	5	—

*T_4 was 17.0, repeat TSH in 2 weeks was < 0.1.
†One patient was receiving both estrogen and thyroxine.
‡One patient was pregnant.
§All had Graves' disease and were receiving propylthiouracil.

Assays

Serum TSH was determined by a sensitive immunoradiometric assay (TSH-IRMA) using Magic mab TSH kit (Ciba-Corning Diagnostic Corp., Medfield, MA) (normal range 0.4 to 5.0 mU/L), T_4 by Gammacoat (^{125}I) Total T_4 Radioimmunoassay kit (Baxter Health Care Corp., Dade Division, Cambridge, MA) (normal range 5.0 to 11.0 µg/dL), and RU ratio by Magic T_3 Uptake (^{125}I) Radioassay kit (Ciba-Corning Diagnostic Corp.) (normal range 0.84 to 1.17). FTI was calculated as the product of T_4 and RU (normal range 4.5 to 11.0 µg/dL).

Results

Serum TSH

Fig 1 shows the distribution of TSH-IRMA values in 216 consecutive samples: 20 (9.3%) had TSH-IRMA < 0.1 mU/L (group I), 30 (13.9%) had TSH-IRMA 0.1 to 0.4 mU/L (group II), 151 (69.9%) had TSH-IRMA 0.5 to 5.0 mU/L (group III), 6 (2.8%) had TSH-IRMA 5.0 to 10.0 mU/L, and 9 (4.2%) had TSH-IRMA > 10.0 mU/L (group IV).

Table 1 shows a summary of the clinical data for groups I, II, and IV. The cases of hyperthyroidism are divided between primary hyperthyroidism and excessive replacement of thyroxine. The medical records revealed that in many cases after TSH-IRMA measurement the physician adjusted the thyroxine dose in absence of noted clinical symptoms or signs of hyperthyroidism or hypothyroidism. In the nine hyperthyroid patients and in the five hypothyroid patients, serum TSH-IRMA correctly predicted the diagnosis. All patients in group II except one were euthyroid clinically. Group II was the most diverse group consisting of patients who were either normally euthyroid, euthyroid on propylthiouracil or thyroxine, euthyroid pregnant, or developing hyperthyroidism. Among all patients receiving thyroxine, approximately one-third were hypothyroid, one-third

Table 2
Results of T_4 and RU According to Groups Based on TSH Results

		Group I (n = 20)	Group II (n = 30)	Group III (n = 30)*	Group IV (n = 15)
T_4	N	10 (50%)	23 (76.6%)	29 (96.7%)	14 (93.3%)
	H	10 (50%)	5 (16.7%)	1 (3.3%)	0 (0%)
	L	0 (0%)	2 (6.7%)	0 (0%)	1 (6.7%)
RU	N	16 (80%)	17 (56.7%)	26 (86.7%)	6 (40%)
	H	2 (10%)	2 (6.7%)	0 (0%)	0 (0%)
	L	2 (10%)	11 (36.7%)	4 (13.3%)	9 (60%)
FTI	N	16 (80%)	28 (93.4%)	30 (100%)	14 (93.3%)
	H	4 (20%)	1 (3.3%)	0 (0%)	0 (0%)
	L	0 (0%)	1 (3.3%)	0 (0%)	1 (6.7%)

*Detailed information of T_4, RU, and FTI was obtained on only 30 patients in group III.
T_4 = total thyroxine, RU = triiodothyronine resin uptake ratio, FTI = free thyroxine index, N = normal, H = high, L = low.

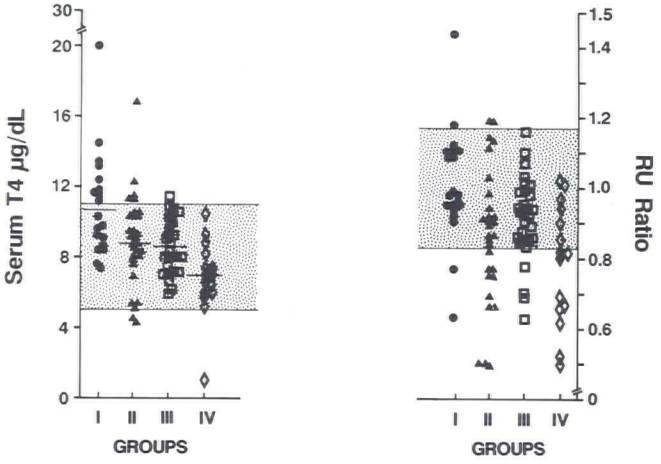

Fig 2—Distribution of T_4 (left) and RU (right) in four different groups. Groups are the same as in Fig 1. Circles represent group I, triangles group II, squares group III, and diamonds group IV. Shaded areas represent the reference range. Horizontal lines represent the means.

were euthyroid, and one-third were hyperthyroid (10, 12, and 11 patients, respectively).

Serum T_4 and FTI

Of the 20 patients in group I, 10 (50%) had normal T_4, 10 (50%) had high T_4, and none had low T_4 (Table 2). Of the 30 patients in group II, 23 (76.6%) had normal T_4, 5 (16.7%) had high T_4, and 2 (6.7%) had low T_4. Of the 30 subjects studied in group III, all but one had normal serum T_4. This subject with high serum T_4 had low serum RU and normal FTI, consistent with euthyroid status and increased thyroid-binding globulin. Also, all subjects in group IV, except one, had normal serum T_4. The exception was a patient with the highest TSH-IRMA (34.3 mU/L) in whom the serum T_4 was 1.1 µg/dL. Fig 2 shows the distribution of T_4 concentrations for subjects in each group. For T_4 the mean ± SD for groups I, II, III, and IV were 10.69 ± 3.1, 8.79 ± 2.61, 8.56 ± 1.42, and 6.95 ± 2.04 µg/dL, respectively. As expected, RU varies widely and did not discriminate between groups (Fig 2). The RU test reflects thyroxine binding capacity which is dependent on many other factors in addition to thyroid status.

As was the case with T_4, we were not able to differentiate between the four groups based on FTI because results fell within our reference range except for a few cases with severe hypothyroidism or hyperthyroidism (Table 2). For this evaluation of the FTI of different groups, we used a reference range which was previously established on 250 healthy volunteers during employment health examinations (4.5 to 11.0 µg/dL). When we used data from the 30 patients tested from group III with normal TSH-IRMA values as a reference range (5.4 to 10.1 µg/dL), more patients were categorized in the group consistent with the TSH value. In hypothyroid patients, FTI calculation frequently adjusted serum T_4 values within the normal range to slightly lower than normal values. In hyperthyroid patients, FTI failed to adjust serum T_4 to higher values in most of the patients (Fig 3). This finding is consistent with the fact that many patients in this group were receiving thyroxine or had nonthyroidal causes for the lowered TSH.

Discussion

This study shows that, consistent with other reports (6,7), the majority of patients tested for thyroid dysfunction had normal TSH-IRMA (69.9%). The majority of patients fell in group III, and all of those tested had normal FTI. Thus, our data support the conclusions of others that normal TSH virtually defines normal thyroid function and that there is no need to measure T_4 and RU or to calculate FTI when TSH-IRMA is within the normal range (6,7). Most of the subjects with low TSH-IRMA (0.1 to 0.4 mU/L) were either euthyroid taking thyroxine supplements or were normally euthyroid. As expected, TSH was elevated (> 5.0 mU/L) in all the newly diagnosed hypothyroid patients and suppressed (< 0.1 mU/L) in all but one of the hyperthyroid patients which was enough to make the correct diagnosis. T_4, RU, and FTI did not indicate the correct thyroid status of those patients. Surprisingly, 50% of group I and 93.3% of group IV had normal T_4. FTI was even less helpful in predicting the correct diagnosis of hypothyroidism and hyperthyroidism, being normal in 93.3% and 80%, respectively. Most group II patients, with low TSH-IRMA, had normal T_4, RU, and FTI. We are not confident that measurement of T_4 and RU and calculating FTI adds much understanding of the thyroid status of these patients (8). Our study shows that all but one were euthyroid clinically and most had normal T_4 and FTI. However, examining T_4, RU, and FTI confirmed euthyroidism and helped in understanding the thyroid status when other factors affected the thyroid function tests. Determining T_4, RU, and FTI would help uncover developing hyperthyroidism as well as pituitary or hypothalamic hypothyroidism. Although TSH-IRMA alone is sufficient to make the correct diagnosis in new cases of hypothyroidism and hyperthyroidism, results of T_4 and RU confirm the initial diagnosis and establish baseline values before starting therapy (6,7).

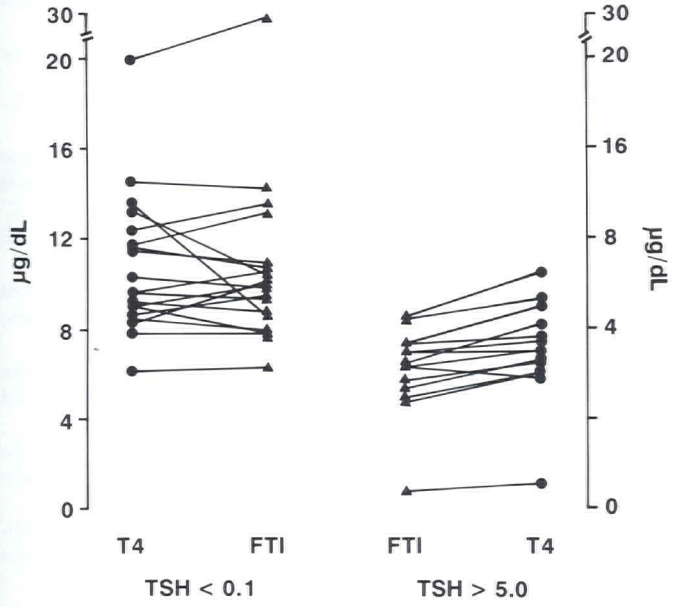

Fig 3—Relationship between total thyroxine (T_4) and free thyroxine index (FTI) in hyperthyroid patients (left) and hypothyroid patients (right).

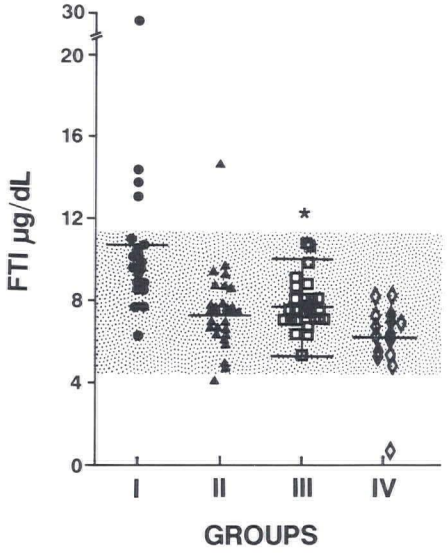

*Fig 4—Free thyroxine index in the four groups. Horizontal lines represent the means. Shaded areas represent the reference range. * = Mean ± 2 SD of 30 normal euthyroid patients. Circles represent group I, triangles group II, squares group III, and diamonds group IV.*

To measure T_4, much less RU, in addition to TSH-IRMA is probably not important when monitoring thyroxine therapy or following established thyroid disease. In contrast, T_4 and/or RU should be used in following patients with pituitary and hypothalamic hypothyroidism for which TSH-IRMA measurement is of limited diagnostic value.

The failure of FTI and T_4 to identify patients with hyperthyroidism probably reflects the mild nature of the newly diagnosed disorder. About half of these patients were hyperthyroid secondary to over-replacement with thyroxine. TSH is a more sensitive diagnostic test because the pituitary thyrotroph senses early elevation in serum thyroxine which results in suppression of TSH before other clinical and biochemical indices are affected. In severe cases of hyperthyroidism where serum T_4 is elevated, the binding proteins became more saturated so that the FTI exceeds the serum T_4 value. Selecting a more narrow reference range for FTI improves diagnostic usefulness (Fig 4).

A testing strategy for the evaluation of thyroid function and the use of computer technology based on TSH-IRMA results has a number of advantages: 1) the number of tests required to reach a diagnosis is minimized, diagnostic efficiency is enhanced, and costs reduced; 2) only a single blood specimen is required as the computer program ensures that appropriate orders for T_4 and RU appear on the laboratory worksheet of the original sample, further limiting cost and inconvenience to the patient; 3) a computer-generated calculation of FTI (the product of T_4 and RU) is readily available as part of the final report; and 4) this two-step approach (initial TSH-IRMA order and subsequent decision about further tests) offers the clinician a systematic means of identifying patients who require further evaluation. There are two limitations to the DRTSH algorithm. First, it may provide misleading data in patients with hypothalamic-pituitary disease. In these patients it is appropriate to order an FTI directly because the TSH can be within normal limits. Thyrotropin-releasing hormone stimulation test of TSH may yield additional information in this group (13). Second, clinical judgment must be used in the interpretation of low TSH values (0.1 to 0.5 mU/L), particularly in hospitalized patients with other illnesses.

Conclusion

The thyroid testing algorithm DRTSH effectively distinguishes euthyroid individuals from hypothyroid and hyperthyroid subjects, and measurement of T_4, RU, and FTI is not required unless central hypothyroidism or hyperthyroidism is suspected. Because results in a large proportion of evaluated individuals fall within the normal range, the number of tests is reduced. For patients with serum TSH-IRMA values < 0.1 mU/L or > 5.0 mU/L, serum T_4 and serum RU measured at the initial evaluation usually confirm the initial impression. Because most patients in all groups have a normal FTI, in stable and well-studied subjects, e.g., those receiving long-term thyroxine therapy, the follow-up tests T_4 and RU generated by the algorithm may not be useful. In these patients TSH-IRMA alone is an adequate monitor of the effectiveness of therapy. For patients not receiving thyroxine but in whom the serum TSH-IRMA value lies between 0.1 to 0.4 mU/L, additional information may be necessary to understand the thyroid status. Certainly, TSH-IRMA is more sensitive than FTI in distinguishing between euthyroid and noneuthyroid patients. Although cost data are not reported here,

DRTSH is both effective and cost-efficient in the evaluation of thyroid function (11).

Acknowledgments

We thank Earl Goad, BS, for assistance in collecting the data.

Financial support for this study was provided (to MJM) by the Robert and June Gurwin Research Fund.

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