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Laboratory Tests Necessary at the First Examination of Patients with Suspected Thyroid Disorders

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Abstract. In order to determine what and how many test items are necessary for the initial tests when examining patients with thyroid disorders, a questionnaire was sent to the council members of the Japan Thyroid Association. Thyroid disorders were divided into 4 categories; hyperthyroidism, hypothyroidism, diffuse goiter, and nodular goiter. The questionnaire was designed to assess: 1) tests routinely ordered at the initial examination; 2) minimum test battery necessary; 3) the 5 most important tests in order; and 4) selection of only 2 tests at most. The data on 112 completed questionnaires were collected and analyzed. When the choice was limited to only 2 tests, TSH and fT_4 were commonly selected for hyperthyroidism, hypothyroidism and diffuse goiter, but these 2 tests would be insufficient for the differentiation of disorders. In the case of nodular goiter, ultrasonogram and fine needle aspiration biopsy (FNA) were selected. The mean number of routinely ordered tests was 6.62 ± 2.00 (S.D.) for hypothyroidism and 8.06 ± 2.48 for nodular goiter, but many fewer tests were cited as absolutely necessary. In hyperthyroidism, 4.56 ± 1.92 tests were required, in hypothyroidism 4.39 ± 1.92, in diffuse goiter 4.93 ± 1.75, and in nodular goiter 5.15 ± 2.13. Most of the function-related tests, ultrasonogram and autoantibodies were commonly selected, while TBII and thyroid ^{123}I or $^{99m}TcO_4^-$ uptake in hyperthyroidism, and FNA, Tg and scintigram in nodular goiter were considered to be for specific purposes. Summarizing all these, the authors propose 5 or 6 tests to be necessary as the initial tests when examining patients with 4 individual thyroid disorders.

Key words: Thyroid primary care, Laboratory tests, Graves' disease, Hypothyroidism, Diffuse goiter, Nodular goiter

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RECENT progress in hormone assays, immunological tests, cytology, and various tissue imaging devices and techniques has enabled the diagnosis of various thyroid disorders without any considerable difficulties. But, nowadays there may be too many tests available, and physicians may feel overwhelmed when attempting to order appropriate tests. Ordering too many tests should be avoided for reasons of cost effectiveness, while ordering too few is not advisable either. To our knowledge, there are no good guidelines as to what tests are actually necessary in the initial examination of patients with thyroid disorders.

The purpose of the present study was to obtain a consensus among Japanese thyroidologists as to the minimum test battery for the diagnosis of patients encountered in general practice. Toward this objective, a questionnaire regarding 4 types of thyroid disorders was sent to numerous thyroidologists, and the responses were reviewed to obtain a consensus regarding the minimum initial test battery.

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Materials and Methods

The survey pertained to 4 types of thyroid dis-

orders which were thought to include almost all of the initial diagnoses of patients encountered in general practice settings. These are: hyperthyroidism, hypothyroidism, diffuse (non-toxic) goiter, and nodular goiter.

A questionnaire was sent to 192 council members of the Japan Thyroid Association. The questionnaire was designed to assess: 1) tests routinely ordered at the initial examination; 2) the tests among them considered to be essential; 3) the 5 most important tests, in order of importance; and 4) the 2 tests most helpful in examining patients with symptoms of each of the 4 types of thyroid disorder. The 25 test options given in the questionnaire were T_4, T_3, free T_4 (fT_4), free T_3 (fT_3), thyroid stimulating hormone (TSH), thyroxine-binding globulin (TBG), thyroglobulin (Tg), anti-thyroglobulin antibody (anti-Tg or αTg), anti-thyroid microsomal antibody (anti-M or αM), anti-thyroid peroxidase antibody (anti-TPO, conventionally included in αM in this study), thyrotropin binding inhibitor immunoglobulin (TBII), thyroid stimulating antibody (TSAb), thyroid stimulation blocking antibody (TSBAb), thyroid ^{123}I or $^{99m}TcO_4^-$ uptake (uptake), thyroid ultrasonography (echo), X-ray computed tomography (CT), magnetic resonance imaging (MRI), soft X-ray photo, ^{123}I or $^{99m}TcO_4^-$ scintigram, ^{201}Tl-thallium chloride scintigram, fine needle aspiration biopsy (FNA), calcitonin, carcinoembryonic antigen (CEA), orbital CT, and orbital MRI. Regarding the tests routinely ordered for the initial examination, the physicians were allowed to mark as many items as they considered appropriate. In this study, the test items included were restricted to those considered to be specific to the thyroid disorders.

Results

Is selection of only 2 tests sufficient?

The questionnaire response rate was 58% (112 of 192 members). As shown in Table 1, when the physicians were limited to only 2 tests for the initial examination of patients with symptoms of thyroid disorders, TSH was the 1st test selected for the 3 types of disorder of hyperthyroidism, hypothyroidism and diffuse goiter, and more than 79% of the respondents chose this test. Further, fT_4 was consistently the next most frequently ordered test, even though the frequency of selection in diffuse goiter was less than 50%. Therefore, among these 3 disorders, the one the thyroidologists wanted to know the results of at first was thyroid function state, and most of them apparently felt that they did not enjoy the luxury of attempting the differentation of individual disorders if forced to only 2 items. On the other hand, in the case of nodular goiter, they selected ultrasonography (echo) very frequently and also FNA. These 2 tests may not always be available, and these results can therefore be interpreted as indicating that a patient with suspected nodular goiter should be sent directly to a thyroidologist and that no tests are necessary in the general practice set-

Table 1. The best 5 items selected when only 2 tests were allowed at the initial examination of patients with 4 types of thyroid disorders

	1	2	3	4	5
Hyperthyroidism	TSH 88* (79)	fT_4 72 (64)	TBII 23 (21)	T_4 16 (14)	fT_3 13 (12)
Hypothyroidism	TSH 106 (95)	fT_4 82 (73)	T_4 18 (16)	αM# 9 (8)	fT_3/αTg▼ 3 (3)
Diffuse goiter	TSH 89 (79)	fT_4 49 (44)	αM 34 (30)	ultrasonography 14 (13)	T_4/αTg 13 (12)
Nodular goiter	ultrasonography 83 (74)	FNA 55 (49)	TSH 29 (26)	fT_4 18 (16)	T_4 10 (9)

Numbers in parenthesis show percent selected. *: Numbers under the item indicate selected frequencies in 112 answers. #: αM and αTg stand for anti-thyroid microsomal antibody and anti-thyroglobulin antibody, respectively, and αM includes anti-TPO (thyroid peroxidase) antibody also. ▼: Tests devided by / are those showing the same frequency of selection.

ting.

In brief, the selection of only 2 items was concluded to be quite insufficient.

Number of tests routinely ordered

The number of tests routinely ordered for hyperthyroidism ranged from 3 to 14 (mean ± SD, 7.69 ± 2.04). The mean number in hypothyroidism, diffuse goiter, and nodular goiter was 6.62 ± 2.00, 6.83 ± 2.08, and 8.06 ± 2.48, respectively. Thus, more test items are chosen in the examination of nodular goiter patients than in the examination of patients with other types of disorders. Among the 25 tests listed, 6 tests (TSH, αM, fT_4, αTg, fT_3 and echo) were found to be chosen commonly in examining patients with all 4 types of thyroid disorders.

Minimum initial test battery

Table 2 demonstrates the 10 tests most often selected when the respondent was asked for a listing of the minimum test battery in examining patients with all 4 types of thyroid disorders. The mean number of tests chosen was fewer than that of routinely ordered items, (4.56 ± 1.92 tests for hyperthyroidism, 4.39 ± 1.92 for hypothyroidism, 4.93 ± 1.75 for diffuse goiter and 5.15 ± 2.13 for nodular goiter). Comparisons of the tests selected for the 4 types of disorders showed that the same 6 tests (TSH, fT_4, αM, echo, fT_3 and αTg) were included among the most frequently selected tests for each. For hyperthyroidism, 74% of the respondents chose TBII and 29% chose uptake. For hypothyroidism and diffuse goiter, no special tests other than the above 6 tests were chosen at a frequency exceeding 30%, but for nodular goiter the most frequently chosen tests were echo and FNA; Tg and scintigram were also frequently selected. The necessity for these specific tests for the diagnosis of nodular goiter may be related to this disorder showing the highest number of tests required. In the case of diffuse goiter, the immunological background should be considered and this may be a reason for the large number of tests required.

Difference between ordered tests and minimum initial test battery

Table 3 shows the 10 tests most frequently cited as those routinely ordered and would be minimally necessary, and the 5 tests were considered to see which should be selected because of great importance in examining patients with hyper-

Table 2. The best 10 tests most frequently selected for inclusion in the minimum test battery in examining patients with 4 types of thyroid disorders

	1	2	3	4	5	6	7	8	9	10	No. of tests chosen
Hyper thyroidism	TSH	fT_4	TBII	fT_3	uptake◆/αM#▼		T_3	αTg	T_4	ultra-sonography	4.56 ± 1.92 (SD)
	102*	93	83	54	33		32	29	24	10	
	(91)	(83)	(74)	(48)	(29)		(29)	(26)	(21)	(9)	
Hypo thyroidism	TSH	fT_4	αM	αTg	fT_3	T_4	T_3	ultra-sonography	TBII	uptake	4.39 ± 1.92
	109	93	75	64	36	23	22	21	14	12	
	(97)	(83)	(67)	(57)	(32)	(21)	(20)	(19)	(13)	(11)	
Diffuse goiter	TSH	αM	fT_4	αTg	ultra-sonography	fT_3	T_4/T_3/uptake			TBII	4.93 ± 1.75
	108	86	83	67	41	38	22			21	
	(96)	(77)	(74)	(60)	(37)	(34)	(20)			(19)	
Nodular goiter	ultra-sonography	TSH	FNA	fT_4	Tg	αM	scintigram	αTg	fT_3	X-P	5.15 ± 2.13
	94	90	71	64	45	34	32	28	25	16	
	(84)	(80)	(63)	(57)	(40)	(30)	(29)	(25)	(22)	(14)	

Common items selected throughout 4 disorders: TSH, fT_4, αM, echo fT_3, αTg. *, #, ▼, numbers and those in parenthesis: same as Table 1. ◆: thyroid ^{123}I or $^{99m}TcO_4^-$ uptake.

thyroidism.

TSH was consistently the most frequent test, and TBII was the test next most frequently cited as "would be ordered", even though it ranked third as a test considered "required". Further, fT_4, fT_3, uptake and T_3 showed a shift to the left indicating preferential consideration of these tests as required. On the other hand, both αM and αTg showed a great shift to the right. Thus, the need for function tests appeared to be greater than that for immunological tests. Comparison of the tests considered necessary with the 5 most important tests revealed that the frequency of selection of T_4 as an essential test was rather low but that the physicians who did select it considered it to be of much value.

Table 4 shows the same data for hypothyroidism. Again, function tests were perceived as important and immunological tests as less so. Even though TBII and uptake are reported to be useful tests in the differentiation of hypothyroidism, these were both ranked at low frequency.

Characteristics of the respondents

Of the 96 respondents who identified themselves, 64 were employees of a medical college or university and 32 work at a hospital or private office. As for their specialties, 43 were in internal medicine, 21 were surgeons, 20 were employed in laboratory medicine or a radioisotope division, and 12 were in miscellaneous specialities including basic medical science, pediatrics, gynecology and so on. Various analyses of possible effects due to their relation with the situation or specialty were conducted. The reason is not clear, but the 16 respondents who did not identify themselves

Table 3. Comparison of tests the respondents would order and consider necessary, and 5 most important tests in examination of patients with hyperthyroidism

	1	2	3	4	5	6	7	8	9	10	No. of items
would order	TSH	TBII	αM	fT_4	αTg	fT_3	uptake◆	T_3	T_4/ultrasonography▼		7.69 ± 2.04 (SD)
	106	100	95	93	91	73	53	45	43		
consider required	TSH	fT_4	TBII	fT_3	uptake/αM		T_3	αTg	T_4	ultra-sonography	4.56 ± 1.92
	102	93	83	54	33		32	29	24	10	
5 most important	TSH	fT_4	TBII	fT_3	T_4	uptake	T_3	αM	αTg	TSAB	
	426	389	258	178	100	97	93	56	16	15	

Numbers below the item indicate individual frequencies selected. In the case of the 5 most important tests, numbers obtained from frequencies multiplied by ordered points (1st 5, 2nd 4, 3rd 3, 4th 2 and 5th 1) are shown. ▼ and ◆: same as Table 2.

Table 4. Comparison of tests the respondents would order and consider necessary, and 5 most important tests in examination of patients with hyperthyroidism

	1	2	3	4	5	6	7	8	9	10	No. of items
would order	TSH	αM	αTg	fT_4	fT_3	T_3	TBII	ultrasonography	T_4	uptake◆	6.62 ± 2.00 (SD)
	109	102	100	96	66	42	41	39	38	30	
consider required	TSH	fT_4	αM	αTg	fT_3	T_4	T_3	ultrasonography	TBII	uptake	4.39 ± 1.92
	109	93	75	64	36	23	22	21	14	12	
5 most important	TSH	fT_4	αM	αTg	fT_3	T_4	T_3	TBII	ultrasonography	uptake	
	491	396	205	155	121	93	61	30	27	25	

Numbers below the tests and lines are the same as Table 3. ◆: same as Table 2.

would have ordered many more tests (8.65 ± 2.10) compared to the other respondents. The university or college personnel, who could be regarded as perhaps more research-oriented, ordered a slightly greater number of tests than the other respondents (7.67 ± 1.98 *vs.* 7.42 ± 2.24; not significant statistically); the higher prevalence was for T_3, TBII, αM and αTg, while the other respondents were more likely to order fT_4 and fT_3. None of these tests showed any significant difference between these 2 respondent subgroups either. When grouped by their specialties, the internists (7.84 ± 1.98 tests) did not show any significant difference from the total number of respondents in the number of tests ordered and their prevalence. Surgeons (6.63 ± 0.99) preferred fT_3 and fT_4 but they did not order as many tests as the other respondents, and especially did not order uptake and T_3 as often. Personnel in laboratory medicine and radioisotopes (7.90 ± 2.24) showed a pattern opposite to that of surgeons, ordering TBII, uptake and T_3 quite frequently while ordering fT_3 much less frequently. None of these differences was significant.

Discussion

The present study was an attempt to evaluate the considerations of Japanese thyroidologists about the necessary tests when evaluating a patient with suspected thyroid disorder. Of course, diagnoses should be established based on history taking, physical examination and laboratory findings, but this study did not address the role of history taking and physical examinations but focused exclusively on the test items. At the initial diagnosis all patients with thyroid disorders show symptoms that may be roughly divided into the 4 categories of hyperthyroidism, hypothyroidism, diffuse (non-toxic) goiter, and nodular goiter. These 4 disorder types were the basis for the questionnaire we mailed to council members of the Japan Thyroid Association.

When the respondents were forced to choose only 2 tests, TSH and fT_4 were the test most frequently chosen for hyperthyroidism, hypothyroidism and diffuse goiter, while echo and FNA were most frequently chosen for nodular goiter. Except in the evaluation of nodular goiter, the major concerns of the respondents appear to be the thyroid function status, and 2 test items would not be sufficient to allow further differentiation among the disorders. Thus, TSH and fT_4 constitute minimal screening of these 3 disorders at the site of primary care. Since the development of highly sensitive TSH immunoassay, TSH seems to be the most reliable thyroid function test, even in the evaluation of hyperthyroidism [1–6]. There has been great debate as to the reliability of the measurement of fT_4 [6–9]. No available simple laboratory fT_4 assays measure actual fT_4 concentrations but are instead just conventional substitutes, and most previously developed assays were affected by various non-specific serum factors, but recent improvements, especially the application of monoclonal antibody, have made the assay much more reliable and specific [10].

As for nodular goiter, ultrasonography to confirm the presence of a nodule and to visualize its characteristics may be the only option at the site of primary care, since FNA testing requires specifically trained personnel and may not always be available [11–13].

With regard to the minimum number of tests necessary to diagnose patients with these 4 disorders, the respondents selected 4.39 to 5.15 tests, and TSH, fT_4, anti-M (anti-TPO), ultrasonography, fT_3 and anti-Tg were selected commonly for the evaluation of all 4 disorders. Differences among these disorders in the number of tests selected appear to relate closely to the necessity for additional specific tests in certain disorders. Hypothyroidism can be accurately diagnosed with only the common tests, but further differentiation of primary hypothyroidism, especially of hypothyroidism due to TSBAb [14, 15], transient hypothyroidism due to destructive thyroiditis [16, 17] or excessive iodide intake [18], is also considered to be necessary at the site of primary care. This is accomplished mainly by application of TBII and uptake tests, and this differentiation is quite useful for the initiation of treatment.

In hyperthyroidism, the usefulness of TSH receptor antibody assay is widely accepted, and the commercial availability of TBII assay has greatly improved the accuracy of diagnosis of Graves' disease [19–21]. TSAb assay may be a better index in this regard, but this test is not generally available [22–24]. Thyroid ^{123}I or ^{99m}Tc– pertechnetate uptake test is also very important in assessing whether thyrotoxicosis is the result of hyperthyroidism or of tissue destruction [17]. The rather low frequen-

cy of selection of uptake test is likely to be due to the special nature of this test, which may not be generally available at sites of primary care.

As previously mentioned, FNA appears to be highly esteemed in diagnosing nodular goiter [11–13]. Measurement of thyroglobulin concentrations is also useful in revealing the presence of a growing mass [25, 26]. Scintigraphy provides us with information as to the location of the tumor and its functional state as well. In the case of diffuse goiter, most of the respondents felt that numerous common tests, especially both anti-M and anti-Tg, were necessary. It may be for these reasons that wide variation was seen in the number of tests considered necessary.

At the time of the first examination, it appears that the respondents typically order many more tests (6.62 to 8.06) than they consider necessary. This difference may be related to the role of the present respondents as thyroid specialists, who may feel required to make a final diagnosis even as early as the initial examination. Comparisons of the tests the respondents would order, consider necessary and consider most important, indicated some additional interesting findings. In the examination of patients with suspected thyroid function disorders, whether hyper- or hypo-thyroidism, the need to know the exact thyroid function state seems to be of primary importance, prevailing over general immunological test results. In addition to the marked shifts in fT_4 and fT_3, T_4 also shifts in both dysfunction states. As mentioned above, there is some doubt as to the reliability of presently available free hormone assays [6–9]. Some respondents therefore chose T_4 instead of fT_4, or even both. Interestingly, surgeons tended to favor ordering fT_4 and fT_3, while laboratory medicine and radioisotope personnel prefer T_4. The difference between the attitudes of these 2 groups was also apparent in the frequency of ordering TBII, T_3 and uptake study, but none of these differences was statistically significant. Furthermore, the characteristics of the patient groups sent to physicians with these various specialties may differ. Surgeons, for instance, may more frequently encounter already diagnosed patients.

Except for TSH receptor antibodies, most of the anti-thyroid autoantibodies detectable in serum do not have any biological or causative significance at all, and these can be regarded merely as the results of an autoimmune process. Recent application of highly sensitive assays for the measurement of anti-TPO or anti-Tg has increased the detection rate considerably, and this may introduce some confusion because such a large percentage of the tested population show positive results, but not of all of them should be managed as diseased patients. It is quite desirable in this sense to establish immunological tests which are directly indicative of causes of the individual autoimmune (thyroid) disorders.

Summarizing all these data and some of our considerations, we would like to propose a tentative minimum test battery for each of the 4 thyroid disorders (Table 5). This may not be useful for physicians working in a small private office or hospital but is designed to be of assistance to primary care physicians working in well-equipped institutes. Considering this, tests for each of the 4 disorders are shown in 2 parts. The underlined 3 tests each should be the minimal initial tests, and an additional 2 to 3 tests each are desirable, if available. In hyperthyroidism, in addition to TSH, fT_4 (or T_4) and TBII, T_3, uptake and anti-M (or anti-TPO) should be tested. We consider that fT_3 is better replaced by T_3. In hypothyroidism, uptake and TBII studies should be added to TSH, fT_4 (or T_4) and anti-M (or anti-TPO). In diffuse goiter, 5 common tests, TSH, anti-M (or anti-TPO), fT_4 (or T_4), anti-Tg and ultrasonography (echo), should be sufficient. As for nodular goiter, echo, FNA and TSH may be adequate as screening at the site of primary care, but the addition of Tg, fT_4 (or T_4) and scintigram would also provide much information necessary to establish a final diagnosis.

Finally, we would like to emphasize that the purpose of this study was to identify the test items considered by thyroidologists to be most impor-

Table 5. Minimum initial test battery for each of the 4 thyroid disorders proposed by the authors

Hyperthyroidism	TSH, TBII, fT_4 (or T_4)	
	T_3, ^{123}I or $^{99m}TcO_4^-$ uptake, αM (or αTPO)	
Hypothyroidism	TSH, fT_4 (or T_4), αM (or αTPO)	
	^{123}I or $^{99m}TcO_4^-$ uptake, TBII	
Diffuse goiter	TSH, αM (or αTPO) fT_4 (or T_4)	
	αTg, ultrasonography	
Nodular goiter	ultrasonography, FNA, TSH	
	Tg, fT_4 (or T_4) scintigram	

tant in the initial screening of patients with suspected thyroid disorder, and various other tests would of course be necessary to establish the final diagnosis in individual patients.

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