Diagnostic Significance of Subclinical Hypothyroidism in Health Check-ups

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ABSTRACT

Subclinical hypothyroidism (SHT) is defined as an asymptomatic state associated with normal serum FT4 and a slightly elevated serum TSH concentration. Patients with SHT have a high rate of progression to clinically overt hypothyroidism (OHT), and in addition, SHT is thought to be a risk factor for atherosclerosis and coronary heart disease. The aim of this study was to identify SHT patients and refer them to a thyroid specialist for treatment and management. We retrospectively studied 1168 subjects (324 males and 844 females) who received health check-ups including thyroid function tests in our Health Service Association Clinic over a period of three years and eleven months. Sixty subjects (5.1%) were diagnosed as SHT. The TSH/FT4 ratio (SHT index) was found to be helpful for diagnosing SHT. The main causes of SHT were Hashimoto's thyroiditis, excess dietary iodine intake. L-thyroxine replacement therapy was recommended for patients with a TSH greater than 10 μ U/mL. For patients with very mild SHT who are pregnant or anticipate becoming pregnant, L-thyroxine therapy should be started. We devised a flowchart for the diagnosis and management of SHT.

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Key words Subclinical Hypothyroidism, TSH, Health Check-up, Excess Iodine Intake, Hashimoto's Thyroiditis

INTRODUCTION

Subclinical hypothyroidism (SHT) has no apparent clinical symptoms diagnosed by using biochemical methods (elevated serum TSH and normal FT4 concentration)^{1,2)}. Concerns about SHT have been increasing in recent years^{3,4)}. The thyroid state of SHT is very frequently encountered in clinical practice due to such reasons as previous therapy for hyperthyroidism with anti-thyroid drugs, radioiodine therapy or surgery, post-destructive thyroiditis, patients on L-T4 replacement therapy for hypothyroidism, postpartum autoimmune thyroid syndrome⁵⁾, painless thyroiditis, recovery from nonthyroidal illness, central hypothyroidism, thyroid hormone-resistant syndrome, polycystic thyroid disease⁶⁾ and adrenal insufficiency.

The purpose of this study was to correctly diagnose SHT in healthy people who visited us for a medical check-up to prevent progression to overt hypothyroidism (OHT)^{7,8)} and the risk of coronary heart disease^{9,10)}, and to introduce them to a suitable hospital for treatment and management of the disease.

Subjects and Methods

1) Subjects

We retrospectively studied 1168 subjects (324 males and 844 females) who received health check-ups including thyroid function tests in our Health Service Association Clinic over a period

of three years and eleven months from April 2007 to February 2011. The mean age was 53.2 (26–80) for males and 50.8 (21–80) for females. Known thyroid patients were excluded from the present study.

The thyroid function test (serum FT4 and TSH concentrations) was performed in all 1168 subjects. Of the 1168 subjects, 959 (247 males and 712 females) had the thyroid function test only once and the remaining 209 underwent repeated examinations of thyroid function during the study.

2) Methods

a) Measurement of serum TSH and FT4 concentrations and antithyroid antibodies

Serum concentrations of TSH and FT4 were measured with a CLEIA (ARCHITECT TSH, Chemilumi E-FT4; Mitsubishi Chemical Medience, Tokyo, Japan). The reference ranges (mean $\pm$ 2SD) were: FT4 1.0–1.7 ng/dL and TSH 0.44–3.78 μ U/mL. The reference range (mean $\pm$ 3SD) for TSH was 0.25–6.48 μ U/mL.

Antithyroid antibodies (TgAb, TPOAb) were determined by ECLIA (ECLusys Anti Tg, Anti TPO).

b) Diagnosis of SHT

The diagnostic method was divided into four groups from the number of times of measurement of TSH concentrations and normal FT4 concentration as follows (A–D).

Groups A and C had a thyroid function test only once and groups B and D underwent repeated measurements of FT4 and TSH during the study.

A: SHT was diagnosed on the basis of a serum TSH concentration of 3.78–6.48 μ U/mL.

B: Subjects with a majority of serum TSH concentrations of 3.78–6.48 μ U/mL.

C: Subjects with a serum TSH concentration of above 6.48

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μU/mL.

D: Subjects with a majority of serum TSH concentrations above 3.78 μU/mL, including serum TSH greater than 6.48 μU/mL.

c) Relationship between age and serum TSH concentration in control subjects and SHT patients

To examine the influence of age on serum TSH concentration, we investigated the distribution of serum TSH concentration in each age group of 793 healthy adults among the 1168 subjects who received health check-ups including thyroid function tests and 60 SHT patients.

The control subjects were 213 males and 580 females. The mean age was 52.7 (range: 26–80 yrs) for males and 50.7 (range: 21–80 yrs) for females. Of the 60 SHT patients, there were 20 males and 40 females. The mean age was 52.5 (range: 31–76) for males and 52.2 (range: 32–73) for females.

d) Analysis of causes in subjects with SHT

The causes of SHT were investigated by physical findings, ultrasonogram of the thyroid, clinical laboratory data and medical questionnaire concerning personal and family history and eating habits concerning seaweed and iodine-containing medications, etc.

e) TSH/FT4 ratio (SHT index)

Each serum FT4 concentration mostly contributed to the negative correlation with its individual TSH concentration. Therefore, the TSH/FT4 ratio was calculated in control and all subjects with SHT and we evaluated the usefulness of the SHT index for the diagnosis of SHT.

f) Analysis of biochemical data and electrocardiogram (ECG)

The concentrations of TC, HDL-C, LDL-C, and TG were compared between the control subjects and SHT patients. The ECG patterns of control and SHT patients were investigated.

g) Presentation of the cases whom we had referred to the thy-

roid special hospital during the study

3) Statistical analysis

All data were analyzed for statistical significance by Student’s t-test and χ^2 test, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

1) The data on the number of all subjects by sex and age are presented in **Fig. 1**.

The largest number of subjects was those in their 50s, in both males and females.

2) There was no significant correlation between age and TSH concentration in either the 793 control subjects ($r = 0.115$, $p = ns$) or 60 SHT patients ($r = 0.284$, $p = ns$) (**Fig. 2, 3**).

3) Results of SHT

Of the 959 subjects who had a thyroid function test only once, 45 (4.7%) were group A and eight (0.8%) were group C. Of the 209 subjects who underwent repeated thyroid function tests, five (2.4%) were group B and two (1.0%) were group D (**Table 1**).

Fig. 4 shows the distribution of age and sex in the 60 patients with SHT. Combining the numbers of male and female patients, there were 6, 2, 4 and 3 SHT (B+C+D) patients in their 30s, 40s, 50s and 60s, respectively.

4) Analysis of causes of SHT

Clinical data of the 60 SHT patients are shown in **Table 2**.

a) Of the 60 SHT patients, 44 were examined by palpation and/or ultrasonography of the thyroid and 13 (29.5%) had goiter.

b) Seven of 12 patients (58.3%) who underwent antithyroid antibody tests had positive antibodies and two of them had a serum TSH concentration of greater than 10 μU/mL.

c) Eleven SHT patients (18.3%) were ingesting excessive amounts of seaweed.

Fig. 1 Distribution of age and sex in the 1168 subjects who underwent health check-ups

Fig. 2 Distribution of serum TSH concentration in each age group of 793 control subjects

Fig. 3 Relation between serum TSH concentration and age in 60 patients with SHT

Serum TSH concentration was measured multiple times in each subject of groups B and D during the study and the highest serum TSH concentrations are plotted.

Table 1 Number (%) of patients in each group of SHT
The denominator shows the number of subjects who underwent health check-ups and thyroid function tests. Percentage values are in parentheses.

Group	Male (%)	Female (%)	Total (%)
A	15/247 (6.1)	30/712 (4.2)	45/959 (4.7)
B	1/77 (1.3)	4/132 (3.0)	5/209 (2.4)
C	3/247 (1.2)	5/712 (0.7)	8/959 (0.8)
D	1/77 (1.3)	1/132 (0.8)	2/209 (1.0)

Fig. 4 Distribution of age and sex in 60 patients with SHT

Table 2 Clinical data of the patients in each group of the 60 SHT patients

	A (n=45)	B (n=5)	C (n=8)	D (n=2)	Total (n=60)
^a Goiter (+)	8	1	3	1	13
Goiter (–)	23	4	4	0	31
^b ND	14	0	1	1	16
^c Ab (+)	4	0	3	0	7
Ab (–)	4	1	0	0	5
ND	37	4	5	2	48
Excess iodine intake (+)	7	2	1	1	11
Excess iodine intake (–)	38	3	7	1	49
Thyroid history					
personal (+)	2	0	0	0	2
personal (–)	43	5	8	2	58
family (+)	4	1	0	0	5
family (–)	41	4	8	2	55

^a by palpation and/or US
^b not done
^c antithyroid antibodies

d) Two SHT patients had undergone a thyroidectomy for tumor or Graves’ disease, and five (11.4%) had a family history of thyroid disease.

5) TSH/FT4 ratio (SHT index)
The TSH/FT4 ratio (SHT index) is compared among the four groups in Fig. 5.
The SHT index in A and (B+C+D) was significantly higher ($p < 0.0001$ in A; $p < 0.0001$ in (B+C+D)) than in the control subjects.

The mean of the SHT index was 1.33 for the control subjects, 4.10 for A and 7.38 for (B+C+D).

6) Relation between FT4 and TSH
The relation between FT4 and TSH in the 60 patients with SHT is shown in Fig. 6.

There were five patients with a TSH concentration greater than or equal to 10 $\mu\text{U/mL}$, five patients with a TSH concentration of 6.48–10.0 $\mu\text{U/mL}$ and 50 patients with a TSH concentration of 3.78–6.48 $\mu\text{U/mL}$.

Fig. 5 TSH/FT4 ratio (SHT index) in control subjects, SHT patients (A) and (B+C+D). Vertical lines indicate mean±SD

Serum TSH was measured multiple times in each subject of groups B and D during the study and the highest serum TSH concentrations were used for calculating the TSH/FT4 ratio in groups B and D.

Fig. 6 Relation between serum FT4 and TSH concentration in 60 patients with SHT

Serum TSH was measured multiple times in each subject of groups B and D during the study and the highest serum TSH concentrations are plotted.

7) Examination of lipid profiles and electrocardiogram (ECG)

a) Evaluation of TC, HDL-C, LDL-C and TG (**Table 3**)

There was no significant difference in serum TC, HDL-C, LDL-C or TG between the control subjects and SHT patients.

b) There was no significant difference between SHT (A+B+C+D) and the control subjects in ECG findings. Heart diseases (old myocardial infarction and angina pectoris) were found in 5.0% of the 60 SHT patients and 2.8% of the 969 control

subjects.

8) A clinical summary of the patients with SHT who had been referred to a hospital is shown in **Table 4**. Of 10 SHT patients, four patients had Hashimoto's thyroiditis and two of them had started L-thyroxine treatment. One of them was pregnant.

As the four patients had excess iodine intake, they were followed up on an iodine-restricted diet.

Table 3 Concentrations of serum TC, HDL-C, LDL-C, and TG in control subjects and SHT patients

Variable	Thyroid function	N	Mean (mg/dL)	p value
TC	control	785	211.9	0.1047
	SHT (A)	45	220.9	
	SHT (B+C+D)	15	204.3	
				0.4164
HDL-C	control	793	67.4	0.6543
	SHT (A)	45	66.3	
	SHT (B+C+D)	15	65.5	
				0.6594
LDL-C	control	748	128.6	0.2693
	SHT (A)	41	134.5	
	SHT (B+C+D)	15	113.0	
				0.0729
TG	control	793	89.5	0.3698
	SHT (A)	45	96.6	
	SHT (B+C+D)	14	86.9	
				0.8510

Table 4 Clinical summary of 10 patients with SHT who had been referred to a thyroid special hospital

*^a according to the referral reply letter from the hospital to which we had referred patients
*^b early gestation
*^c not done

Patient	Age (yrs)	Sex	TSH (μU/mL)	Diagnosis* ^a	Iodine intake	Treatment* ^a	Antithyroid antibody
1* ^b	35	F	4.27	Hashimoto's thyroiditis	normal	L-thyroxine	+
2	36	F	14	Hashimoto's thyroiditis	normal	L-thyroxine	+
3	62	F	5.82	Hashimoto's thyroiditis	excess	iodine restricted diet	+
4	56	M	5.44	iodine-induced SHT	excess	iodine restricted diet	—
5	55	F	5.16	post hemithyroidectomy	excess	iodine restricted diet	—
6	54	F	11.9	Hashimoto's thyroiditis susp.	excess	iodine restricted diet	ND* ^c
7	62	F	6.27	normal	normal	iodine restricted diet	ND
8	60	M	5.09	nodular goiter	normal	follow up	—
9	60	F	4.38	SHT	normal	follow up	—
10	50	F	5.52	nodular goiter	normal	follow up	—

DISCUSSION

The diagnosis and management of SHT is an important role of the Health Examination Center. SHT is a mild thyroid failure and has no apparent clinical symptoms. Therefore, SHT is diagnosed only by a biochemical examination of FT4 and TSH. TSH measurement is the most sensitive, accurate and useful method for the diagnosis of SHT.

For the determination of a normal reference range of TSH, it is important to know whether serum TSH concentration is related to age. There have been two different papers on the change of serum TSH concentration with age.

One recent report stated that TSH distribution progressively shifts toward higher concentrations with age⁽¹¹⁾. The other study reported the opposite result that TSH concentrations showed a significant inverse correlation with age⁽¹²⁾. In our study of a limited number of subjects, there was no apparent variation in TSH with age or sex in both the control subjects and SHT patients.

Since serum TSH has a log-linear relationship with FT4 concentration, a slight reduction of individual FT4 concentration will result in a significant elevation of serum TSH concentration by the feedback mechanism. Therefore, we devised a TSH/FT4 ratio (SHT index) for each subject. This indicator is considered particularly helpful for the diagnosis of SHT.

SHT occurs in 3–8% of the general population⁽¹³⁾. Although the diagnostic criteria for SHT are not well established, the present study found that 60/1168 (5.1%) could be diagnosed as SHT.

Since some of the SHT patients returned to normal⁽⁸⁾, it is difficult to make a diagnosis of SHT with only one measurement of TSH and FT4. Therefore, we followed up the subjects with repeated TSH measurements and proposed using a cut-off value of 6.48 μU/mL (mean + 3SD) for TSH to diagnose SHT. Some of the SHT patients with a serum concentration above 3.78 μU/mL (10/60; 17%) had been referred to hospital based on a physician's decision.

Levothyroxine (L-thyroxine) replacement therapy is generally

Ab: Antithyroid antibodies

Fig. 7 Proposed flowchart for the diagnosis and management of SHT

recommended for all SHT patients with a serum TSH concentration above 10 $\mu\text{U/mL}$ ^{7, 14}. However, the management of patients with a serum TSH concentration of less than 10 $\mu\text{U/mL}$ is controversial.

The most important implication of SHT is the high likelihood of progression to clinical hypothyroidism^{7, 8}) and cardiovascular risk^{9, 10}). There is some evidence that L-thyroxine replacement improves some parameters of lipid profiles and left ventricular function^{7, 14}). Other researchers reported that L-thyroxine treatment for SHT patients is not necessarily required^{14, 15}). In the present study, we did not find a significant relation between SHT and cardiovascular risk factor or lipid profiles. Further detailed studies are required to solve this problem.

Several patients of Hashimoto's thyroiditis and iodine-induced SHT were observed in this study. Although iodine is an essential element for thyroid hormone synthesis, excess iodine intake can induce thyroid dysfunction in both control subjects and in patients with an underlying thyroid disorder (Wolff-Chaikoff effect). Japanese people mainly ingest much iodine from seaweed; such patients should avoid excessive dietary intake of iodine.

We found an SHT patient during early pregnancy and immediately referred her to a thyroid clinic for treatment. The TSH screening test is very important for females who are pregnant, wish to bear children and who are undergoing tests for infertility.

Different normal TSH values are proposed for pregnancy by the clinical practice guideline^{16, 17}). The range of serum TSH concentration in early pregnancy is 0.03–2.3 $\mu\text{U/mL}$; the upper limit of normal is 3.5 $\mu\text{U/mL}$ in late pregnancy. If hypothyroidism has been diagnosed before pregnancy, it is recommended to adjust the intended T4 dose to be reached before pregnancy to a TSH concentration of not higher than 2.5 $\mu\text{U/mL}$.

Maternal hypothyroidism is known to have adverse effects on the fetus¹⁸). On the other hand, a paper reported that maternal T4 deficiency in early pregnancy does not necessarily affect neuro-development¹⁹).

All SHT patients who are pregnant or planning to become pregnant should be treated with L-thyroxine.

We devised the following flowchart as an indicator for the future diagnosis and management of SHT based on the above research findings (**Fig. 7**).

Euthyroid subjects with antithyroid antibodies (autoimmune thyroid diseases) should be followed up by both serum TSH and FT4 measurements at 1 year without eating too much seaweed.

The dietitian will provide advice and support on the dietary management of patients with SHT by iodine excess intake. Management of SHT differs depending on whether the serum TSH concentration is 3.78–6.48 $\mu\text{U/mL}$ or higher than 6.48 $\mu\text{U/mL}$. All patients with a serum TSH concentration above 6.48 $\mu\text{U/mL}$ should consult a thyroid specialist. We recommend follow-up with clinical and biochemical monitoring in patients with a serum TSH concentration of 3.78–6.48 $\mu\text{U/mL}$. SHT patients with a continuous serum TSH concentration of more than 3.78 $\mu\text{U/mL}$ by repeated TSH measurements should consult a thyroid specialist. Particularly, SHT patients who are pregnant or want to become pregnant should consult a thyroid specialist for treatment.

CONCLUSIONS

In our study, 60/1168 (5.1%) were diagnosed with SHT. Ten SHT patients with serum TSH concentration above 3.78 $\mu\text{U/mL}$ were referred to a hospital and a mild SHT patient with serum concentration of 3.78–6.48 $\mu\text{U/mL}$ was followed up and recommended to undergo repeated thyroid function tests. L-thyroxine

therapy should be recommended for pregnant women and women who anticipate becoming pregnant. Iodine restriction is recommended for suspected iodine-induced SHT patients.

The cut-off value of 6.48 $\mu\text{U/mL}$ (mean + 3SD) for TSH and the SHT index are useful for the diagnosis of SHT.

The cause of SHT in some patients was considered to be Hashimoto's thyroiditis and/or excess iodine intake.

REFERENCES

- 1) Cooper DS: Subclinical hypothyroidism. *N Engl J Med*: 345: 260-265, 2001.
- 2) Gillet M: Subclinical Hypothyroidism: Subclinical Thyroid Disease: Scientific Review and Guidelines for Diagnosis and Management. *JAMA*: 291: 228-238, 2004.
- 3) Amino N, Ozawa Y, Abe Y, Kubota S, Ito M: Guidelines for the diagnosis and treatment of subclinical hypothyroidism. *Clinical Endocrinology*: 56: 705-724, 2008 (in Japanese).
- 4) Vahab F: Subclinical Hypothyroidism: An Update for Primary Care Physicians. *J Endocrinol Invest*: 22: 693-697, 1999.
- 5) Amino N, Tada H, Hidaka Y: Postpartum autoimmune thyroid syndrome: a model of aggravation of autoimmune disease. *Thyroid*: 9: 705-713, 1999.
- 6) Kubota S, Hirokawa M, Takamura Y, Ito Y, Tamai H, Kudo T, Nishihara E, Ito M, Amino N, Miyauchi A: Pathologic features of polycystic thyroid disease: Comparison with benign nodular goiter. *Endocrine Journal*: 58: 783-788, 2011.
- 7) McDermott MT, Ridgway EC: Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Metab*: 86: 4585-4590, 2001.
- 8) Díez JJ, Iglesias P: Spontaneous subclinical hypothyroidism in patients older than 55 years: an analysis of natural course and risk factors for the development of overt thyroid failure. *J Clin Endocrinol Metab*: 89: 4890-4897, 2004.
- 9) Rodondi N, Aujesky D, Vittinghoff E, Cornuz J, Bauer DC: Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. *Am J Med*: 119: 541-551, 2006.
- 10) Singh S, Duggal J, Molnar J, Maldonado F, Barsano CP, Arora R: Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis. *Int J Cardiol*: 125: 41-48, 2008.
- 11) Surks MI, Hollowell JG: Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab*: 92: 4575-4582, 2007.
- 12) Mariotti S, Franceschi C, Cossarizza A, Pinchera A: The aging thyroid. *Endocr Rev*: 16: 686-715, 1995.
- 13) Hollowell JG, Staehling NW, Flanders WD, et al: Serum TSH, T₄, and thyroid antibodies in the United States population (1988-1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*: 87: 489-499, 2002.
- 14) Chu JW, Crapo LM: The treatment of subclinical hypothyroidism is seldom necessary. *J Clin Endocrinol Metab*: 86: 4591-4599, 2001.
- 15) Villar HC, Saconato H, Valente O, Atallah AN: Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database Syst Rev*. 2007; (3): CD003419.
- 16) Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinioer D, Mandel SJ, Stagnaro-Green A: Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*: 92 (8 Suppl): S1-47, 2007.
- 17) De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, Eastman CJ, Lazarus JH, Luton D, Mandel SJ, Mestman J, Rovet J, Sullivan S: Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*: 2543-2565, 2012.
- 18) Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ: Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*: 341: 549-555, 1999.
- 19) Momotani N, Iwama S, Momotani K: Neurodevelopment in children born to hypothyroid mothers restored to normal thyroxine (T₄) concentration by late pregnancy in Japan: no apparent influence of maternal T₄ deficiency. *J Clin Endocrinol Metab*: 97: 1104-1108, 2012.