The clinical impact of subclinical hypothyroidism in Korean

Myung Won Lee

Department of Medicine

The Graduate School, Yonsei University

The clinical impact of subclinical hypothyroidism in Korean

Directed by Professor Eun Jig Lee

The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of Master
of Medical Science

Myung Won Lee

December 2013

This certifies that the Master's Thesis
of Myung Won Lee is approved.

Thesis Supervisor : Eun Jig Lee

Thesis Committee : Yumie Rhee

Thesis Committee : Jong Rak Choi

The Graduate School
Yonsei University

December 2013

ACKNOWLEDGEMENTS

I deeply thank my principal supervisor, Prof. Eun Jig Lee for the constant concern, infinite encouragement and worthy guidance during my whole master's course. This thesis would not have been completed without his educational support and patience. Prof. Yumie Rhee and Jong Rak Choi deserve a special thanks as my thesis committee members and advisors. I truly appreciate their theoretical and practical advice for this study. I also thank my colleagues for academic and emotional support. Lastly, I would sincerely like to dedicate this thesis to my beloved families who have supported and trusted me every step of my way.

<TABLE OF CONTENTS>

LIST OF TABLES

<ABSTRACT>

The clnical impact of subclinical hypothyroidism in Korean

Myung Won Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Eun Jig Lee)

Patients with subclinical hypothyroidism (SHT) are common in clinical practice. However, clinical significance of SHT, including prognosis, has not been clarified. Based on it, management plan and treatment guideline of SHT could have been established. The aim of this study was to investigate the prognostic factors of SHT. We reviewed the medical records of Korean patients who visited the endocrinology outpatient clinic of Severance Hospital from January 2008 to September 2012. Among them, newly-diagnosed patients with SHT were selected and reviewed retrospectively. We compared two groups; SHT maintenance group and Spontaneously improved group. Between SHT maintenance group and Spontaneously improved group, initial thyroid-stimulating hormone (TSH) level was significantly different (*p*-value=0.030). In sub-analysis for subjects with TSH between 5-10 μIU/mL, Spontaneously improved group showed significantly lower anti-thyroid peroxidase antibody (TPO-Ab) titer than SHT maintenance group (*p* -value=0.038). In the aspects of lipid profiles, only triglyceride level, other than total cholesterol and low density lipoprotein cholesterol (LDL-C), was related with TSH level, that is, the severity of SHT. Diffuse thyroiditis (DT) on ultrasonography (US) only contributed to the severity of SHT, not to the prognosis. High-sensitivity C-reactive protein (hsCRP) and urine iodine

excretion, generally regarded as possible prognostic factors, did not show any significant relation with the prognosis and severity of SHT. In conlusion, only initial TSH level was a definite prognostic factor of SHT. TPO-Ab titer was also a helpful prognostic factor for SHT with mildly elevated TSH. We could expect SHT patients with lower TSH level and lower TPO-Ab titer to be improved spontaneously to euthyroid state. Except TSH and TPO-Ab, we could not validate other biochemical prognostic factors in this retrospective study for Korean SHT patients. According to our experience, in clinical practice, we could explain to newly-diagnosed SHT patients that they have 50 percent chance to be improved to euthyroid after 10 months in its natural course. Considering this with other probable prognostic factors and clinical circumstances of the patient, we could also able to determine the management plan of the SHT patient.

Key words: subclinical hypothyroidism; thyroid stimulating hormone; thyroid peroxidase antibody; lipids; C-reactive protein; iodine

The clinical impact of subclinical hypothyroidism in Korean

Myung Won Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Eun Jig Lee)

I. INTRODUCTION

Patients with serum thyroid-stimulating hormone (TSH) levels above the reference range and free thyroxine (fT4) levels within the reference range are commonly found in clinical practice.[1] Such 'subclinical hypothyroidism (SHT)' is known to occur in 3-8% of total population, although each study reported various results according to their definition of normal TSH level and geographic/ethnic differences of their subjects.[2-6] Unlike overt hypothyroidism (OHT) with elevated TSH levels and decreased fT4 levels, SHT is generally asymptomatic, with the diagnosis made solely from laboratory results. Diagnosis of SHT has been recently growing due to popularized screening test for thyroid function and advanced sensitivity of TSH measurement. As a result, concerns about the natural course and prognosis of SHT and long-term consequences of persistent subclinical hypothyroid state are on the rise. However, clinical significance of SHT has not been clarified. Based on these clinical significance of SHT, management plan and treatment guideline of SHT could have been established.

In this study, we report our experience with 298 patients of SHT and aim to define the prognostic factors of SHT.

II. METHODS

Subjects

We reviewed the medical records of Korean patients who visited the endocrinology outpatient clinic of Severance Hospital from January 2008 to September 2012. Among them, patients who showed subclinical hypothyroid state, defined in this study as TSH > 5 μIU/mL and fT4 between 0.73 and 1.95 ng/dL, were selected for this study. A retrospective study was conducted and data was gathered on age, sex, fT4, TSH, anti-thyroid peroxidase antibody (TPO-Ab), lipid profile, high-sensitivity C-reactive protein (hsCRP), urinary iodine, as well as ultrasonographic(US) finding at diagnosis. According to independent and subjective decision making of five endocrinologists, based on the following situations, for example, subject's clinical presentation, pregnancy trial in woman in childbearing age, initial laboratory findings, subjects were observed without medication or under lovothyroxine supplement. In retrospective analysis, female subjects with lower fT4, higher TSH, higher anti-TPO, lower urinary iodine were more frequently prescribed with levothyroxine (except for TSH, all others were significantly different between two groups statistically).

During follow-up, patients who were kept under the observation progressed to euthyroid, subclinical hypothyroid, or overt hypothyroid state, respectively. The rest subjects were given levothyroxine supplements immediately after the diagnosis and they all became euthyroid state during the follow-up. Regular check-up on fT4, TSH, TPO-Ab, lipid profile, hsCRP status were conducted (not included urine iodine and US evaluation). To determine the prognostic factors of SHT, we compared two groups to each other; one group maintained subclinical hypothyroid state (SHT maintenance group) and another group improved to euthyroid state spontaneously (Spontaneously improved group). To evaluate the benefit of treatment in SHT, we analyzed the data of Levothyroxine supplement group. Patients with anti-thyroid drug, thyroid hormone replacement, previous thyroid disease history, other

comorbidities which could have affected lipid profile and hsCRP, such as diagnosed diabetes mellitus or hyperlipidemia, or pregnancy were excluded.

Thyroid function test and thyroid autoantibodies

Serum FT4 levels were measured by radioimmunoassay (Trinity Biotech plc, Ireland), as was serum TSH (SORIN Biomedica, Italy), serum TPO-Ab (B.R.A.H.M.S. AG, Germany), and Tg-Ab (B.R.A.H.M.S. AG, Germany). The reference ranges were 0.73-1.95 ng/dL for fT4 and 0.4-5.0 μIU/mL for TSH. The upper normal limit of both serum TPO-Ab and TG-Ab was 60 U/mL.

Biochemistry

Serum total cholesterol, triglyceride and high density lipoprotein cholesterol (HDL-C) were measured with Hitachi modular 7600(Hitachi, Japan) automated clinical chemistry analyser. The reference values used were 100-220 mg/dL for total cholesterol, 44-150 mg/dL for triglyceride, and 40-400 mg/dL for HDL-C. Serum LDL-C was calculated using the formula LDL-C =total cholesterol – HDL-C – (triglyceride/5.0). Serum hsCRP was analysed using the same automated chemistry analyser, and the reference values applied were 0-3.0 mg/L.

Determination of urinary iodine excretion

Fasting spot urine samples were collected from subjects and analyzed by potentiometric method using Metrohm pH/ion meter Model 692. The urinary iodine excretion was expressed as μmol iodine/g creatinine. The normal urinary iodine excretion range given was 8.6-41.3μmol/g of creatinine.

US evaluation of the thyroid gland

US evaluation of the thyroid gland was performed with an HDI 3000 or HDI 5000 system (Philips Medical Systems, Bothell, WA, USA) or an Acuson Sequoia 512 system (Siemens Medical Solutions, Mountain View, CA, USA). One of three radiologists with four, six, and ten years of experience in thyroid imaging performed a real-time US exam and interpreted the results. US features of diffuse thyroiditis (DT) were defined using the generally accepted standards of diffuse parenchymal hypoechogenicity or a heterogeneous echogenic pattern of the thyroid gland. If focal lesions were accompanied with DT - for example, suggestive of focal thyroiditis or benign nodule, we conducted a fine needle aspiration and ruled out other than focal thyroiditis showing lymphocytic infiltration.

Statistical analysis

Results are expressed as the mean value with standard deviation, the number of subjects with the percentage (%) or median (minimum-maximum). All data was analyzed using IBM SPSS version 21.0 for Windows. Between two groups (SHT maintenance and Spontaneously improved group, Observation and Levothyroxine supplement group or DT(+) and (-) group), mean values were compared by using t-test and sex ratio by using Pearson's chi-square test. Between initial and follow-up parameters in each three groups, mean values were compared by using paired t-test.

III. RESULTS

Baseline characteristics of SCH maintenance, Spontaneously improved and Levothyroxine supplement group

Table 1 shows the baseline clinical and biochemical characteristics of three groups. The data from 64 patients of SHT maintenance group (maintained subclinical hypothyroid state without medication), 66 of Spontaneously improved group (progressed to euthyroid state without medication) and 168 of Levothyroxine supplement group (attained to euthyroid state with medication) were analyzed. The mean follow-up period was 10.1 months for SHT maintenance group, 9.6 months for Spontaneously improved group, and 13.1 months for Levothyroxine supplement group.

Between SHT maintenance group and Spontaneously improved group, women showed better prognosis than men (*p*-value=0.039). And, initial TSH level was significantly different (8.51±4.91 μIU/mL in SHT maintenance group and 6.98±2.54 μIU/mL in spontaneously improved group; *p*-value=0.030). Except TSH level and sex ratio, there were no statistic differences in age, fT4, TPO-Ab, TG-Ab, lipid profile, hsCRP and urine iodine. We constructed ROC curves for TSH cut-off level associated with SHT prognosis (data not shown here). This ROC curve had 0.542 as area under the curve. We can assume that SHT patients with TSH above 5.895 μIU/mL have more probability to maintain SHT with sensitivity 70.3% and specificity 31.2%. We performed further analysis on the sub-population, according to TSH levels (Table 2). For subjects with TSH between 5-10 μIU/mL, those in Spontaneously improved group showed significantly lower TPO-Ab titer than SHT maintenance group (*p* -value=0.038).

Baseline characteristics of Levothyroxine supplement group were compared with those of the observed population (SHT maintenance and spontaneously improved group) (Table 1). SHT patients with lower fT4, higher TPO-Ab, lower urine iodine were more actively considered for

supplement therapy by doctor. Additionally, they showed the higher proportion of women than observation group.

Table 1. Baseline Characteristics of the SHT maintenance, Spontaneously improved and Levothyroxine supplement group

	Observation				Levothyroxine supplement group	
	SHT maintenance group (*n*=64)	Spontaneously improved group (*n*=66)	Total(*n*=130)	*P*-value[a]	(*n*=168)	*P*-value[c]
Age, yr	52.3±16.6	50.4±13.0	51.4±14.9	0.476	52.5±14.2	0.493
Women, *n*(%)	41(64.1)	53(80.3)	94(72.3)	0.039[b]	141(83.9)	0.015[d]
free T4, ng/dL	1.08±0.22	1.06±0.22	1.07±0.22	0.732	1.01±0.20	0.008
TSH, μIU/mL	8.51±4.91	6.98±2.54	7.73±3.95	0.030	8.69±7.80	0.203
TPO-Ab, U/mL	15.47(5.5-3000.0)	13.85(5.5-3000.0)	14.97(5.5-3000.0)	0.088	34.26(5.5-3000.0)	0.024
TG-Ab, U/mL	12.49(5.5-710.6)	13.0(5.5-3000.0)	12.68(5.5-3000.0)	0.243	26.25(5.5-3000.0)	0.485
Total cholesterol, mg/dL	204.6±140.0	191.8±41.4	198.0±101.3	0.512	191.2±34.6	0.473
Triglyceride, mg/dL	123.6±63.7	121.5±86.6	122.5±76.2	0.894	130.3±99.9	0.533
HDL-C, mg/dL	52.5±13.0	56.8±13.4	54.8±13.3	0.125	52.9±13.4	0.298
LDL-C, mg/dL	115.6±29.6	112.1±33.2	113.7±31.5	0.603	113.1±33.1	0.896
hsCRP, mg/L	1.00(0.18-35.99)	1.00(0.18-163.0)	1.00(0.18-163.0)	0.276	1.06(0.16-18.9)	0.233
urine Iodine, μmol iodine/g creatinine	76.75(7.3-450.8)	53.40(7.0-311.5)	59.1(7.0-450.8)	0.410	28.25(6.2-742.0)	0.021

Data are mean±standard deviation, number(%) or median(minimum-maximum).
SHT, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; TPO-Ab, anti-thyroid peroxidase antibody; TG-Ab, anti-thyroglobulin antibody; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.
[a]P-values for the comparison of the mean values between SHT maintenance and Spontaneously improved group by t-test.
[b]P-values for the comparison of the Sex ratio by Pearson's chi-square test.
[c]P-values for the comparison of the mean values between Observation and Levothyroxine supplement group by t-test.
[d]P-values for the comparison of the Sex ratio by Pearson's chi-square test.

Table 2. Baseline Characteristics of SHT maintenance and Spontaneously improved group in the Subjects with TSH between 5-10μIU/mL

	Observation		
	SHT maintenance group (n=50)	Spontaneously improved group (n=61)	P-value[a]
free T4, ng/dL	1.09±0.21	1.07±0.22	0.616
TSH, μIU/mL	6.68±1.27	6.42±1.20	0.267
TPO-Ab, U/mL	15.60(5.5-3000.0)	11.82(5.5-3000.0)	0.038
TG-Ab, U/mL	12.49(5.5-710.6)	13.0(5.5-3000.0)	0.262
Total cholesterol, mg/dL	209.3±159.8	192.3±42.8	0.461
Triglyceride, mg/dL	124.2±63.3	120.8±89.8	0.852
HDL-C, mg/dL	52.5±13.3	58.0±13.3	0.076
LDL-C, mg/dL	112.9±28.8	111.8±34.6	0.875
hsCRP, mg/L	1.00(0.18-19.63)	1.00(0.18-163.0)	0.237
urine Iodine, μmol iodine/g creatinine	58.15(7.3-450.8)	49.50(7.0-311.5)	0.471

Data are mean±standard deviation or median(minimum-maximum).
SHT, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; TPO-Ab, anti-thyroid peroxidase antibody; TG-Ab, anti-thyroglobulin antibody; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.
[a]P-values for the comparison of the mean values by using t-test.

Comparison between initial and follow-up parameters in SHT maintenance and Spontaneously improved group

Table 3 shows the changes in parameters during follow-up (about 10 months) in SHT maintenance and Spontaneously improved group. As expected, none of the measured parameters showed any changes during follow-up in SHT maintenance group (also no aggravation). In Spontaneously improved group, those who showed normalized TSH, there were no significant improvements in TPO-Ab and hsCRP. TPO-Ab titer showed only decreasing trend. Analysis of lipid profiles showed triglyceride level decreasing significantly during follow-up (125.7±90.0 mg/dL vs. 97.9±58.8 mg/dL; *p*-value =0.007).

Table 3. Comparison between the Parameters at Initial presentation and Follow-up of the SHT maintenance and Spontaneously improved group

	Observation					
	SHT maintenance group (*n*=64)			Spontaneously improved group (*n*=66)		
	Initial	Follow-up	*P*-value[a]	Initial	Follow-up	*P*-value[a]
free T4, ng/dL	1.08±0.22	1.05±0.20	0.374	1.06±0.22	1.11±0.25	0.176
TSH, μIU/mL	8.51±4.91	9.12±9.52	0.447	6.98±2.54	3.26±0.89	<0.001
TPO-Ab, U/mL	15.47(5.5-3000.0)	10.7(5.5-3000.0)	0.784	13.85(5.5-3000.0)	10.60(5.5-3000.0)	0.261
TG-Ab, U/mL	12.49(5.5-710.6)	14.53(5.5-853.0)	0.265	13.0(5.5-3000.0)	10.73(5.5-3000.0)	0.438
Total cholesterol, mg/dL	186.4±37.0	184.0±37.2	0.589	191.6±40.9	185.2±36.3	0.151
Triglyceride, mg/dL	126.2±63.9	145.1±132.1	0.252	125.7±90.0	97.9±58.8	0.007
HDL-C, mg/dL	52.3±13.3	51.8±13.6	0.653	57.5±13.2	56.6±11.7	0.546
LDL-C, mg/dL	115.3±29.6	104.2±34.0	0.111	112.7±34.3	107.4±31.5	0.236
hsCRP, mg/L	1.00(0.18-35.99)	0.71(0.30-16.70)	0.679	1.00(0.18-163.0)	0.47(0.30-8.00)	0.515

Data are mean±standard deviation or median(minimum-maximum).
SHT, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; TPO-Ab, anti-thyroid peroxidase antibody; TG-Ab, anti-thyroglobulin antibody; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.
[a]P-values for the comparison of the mean values between initial and follow-up parameters by paired t-test.

Comparison between initial and follow-up parameters in Levothyroxine supplement group

Table 4 shows the changes in parameters during follow-up in Levothyroxine supplement group. About 13.1 months later, their thyroid functions improved to euthyroid state. TPO-Ab titer and triglyceride level significantly decreased during follow-up (for TPO-Ab, median value, 34.26 U/mL vs. 20.91 U/mL; *p*-value = 0.011, for triglyceride, mean value, 131.4±101.8 μIU/dL vs. 107.7±54.3 μIU/dL; *p*-value = 0.004, respectively). hsCRP titer did not show significant changes.

Table 4. Comparison between the Parameters at Initial presentation and Follow-up of Levothyroxine supplement group

	Levothyroxine supplement group (*n*=168)		
	Initial	Follow-up	*P*-value[a]
free T4, ng/dL	1.01±0.20	1.28±0.25	<0.001
TSH, μIU/mL	8.69±7.80	2.44±1.13	<0.001
TPO-Ab, U/mL	34.26(5.5-3000.0)	20.91(5.5-3000.0)	0.011
TG-Ab, U/mL	26.25(5.5-3000.0)	24.38(5.5-3000.0)	0.817
Total cholesterol, mg/dL	191.3±34.4	187.4±33.9	0.207
Triglyceride, mg/dL	131.4±101.8	107.7±54.3	0.004
HDL-C, mg/dL	52.9±13.6	53.0±11.5	0.946
LDL-C, mg/dL	113.1±33.1	112.3±30.3	0.806
hsCRP, mg/L	1.06(0.16-18.90)	0.83(0.30-12.30)	0.442

Data are mean±standard deviation or median(minimum-maximum).
SHT, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; TPO-Ab, anti-thyroid peroxidase antibody; TG-Ab, anti-thyroglobulin antibody; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.
[a]P-values for the comparison of the mean values between initial and follow-up parameters by paired t-test.

US finding in SHT

The existence of DT on US at diagnosis was not significantly different between SHT maintenance group and Spontaneously improved group (53.6% of SHT maintenance group and 42.1% of Spontaneously improved group; *p*-value =0.222). But, when we looked into the clinical and laboratory characteristics at diagnosis by according to US finding (Table 5), the existence of DT was associated with higher TSH, TPO-Ab and triglyceride (*p*-value =0.040, <0.001 and 0.017, respectively) at that time.

Table 5. The Presentation of SHT according to US finding

	US finding		
	Diffuse thyroiditis (+)	Diffuse thyroiditis (-)	
	(*n*=130)	(*n*=135)	*P*-value[a]
Age, yr	50.8±13.0	53.4±15.1	0.131
Women, *n*(%)	105(80.8)	107(79.3)	0.759[b]
free T4, ng/dL	1.03±0.21	1.04±0.21	0.589
TSH, μIU/mL	8.55±6.22	7.34±2.72	0.040
TPO-Ab, U/mL	269.1(5.5-3000.0)	11.78(5.5-3000.0)	<0.001
TG-Ab, U/mL	39.55(5.5-3000.0)	9.48(5.5-2000.0)	0.083
Total cholesterol, mg/dL	202.3±97.8	186.0±35.8	0.118
Triglyceride, mg/dL	139.8±103.0	109.0±72.0	0.017
HDL-C, mg/dL	53.1±12.8	54.5±14.2	0.479
LDL-C, mg/dL	115.2±30.2	110.4±33.0	0.294
hsCRP, mg/L	1.00(0.18-22.70)	1.00(0.16-163.00)	0.112
urine Iodine, μmol iodine/g creatinine	33.80(6.4-742.0)	38.70(6.4-311.5)	0.831

Data are mean±standard deviation, number(%) or median(minimum-maximum).
SHT, subclinical hypothyroidism; US, ultrasonographic; TSH, thyroid-stimulating hormone; TPO-Ab, anti-thyroid peroxidase antibody; TG-Ab, anti-thyroglobulin antibody; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein.
[a]P-values for the comparison of the mean values of two groups by t-test.
[b]P-values for the comparison of the Sex ratio of two groups by Pearson's chi-square test.

IV. DISCUSSION

Some patients of SHT make spontaneous recovery in thyroid function without specific treatment, but others maintain subclinical hypothyroid state without improvement, while some even progress to overt hypothyroid state, requiring thyroid hormone supplement. Therefore, general understanding of natural course of SHT, prognostic factors, clinical consequences of persistent subclinical hypothyroid state and effect of levothyroxine supplement is necessary in planning SHT management as clinician, including determination of the necessity and appropriate time of treatment.

So far, various studies have regarded TSH level and TPO-Ab titer as the most reliable clinical parameters in predicting the progression of SHT or euthyroidism to OHT. In a cohort study conducted for 20 years in the United Kingdom reported in 1995,[7] the odds ratios (with 95% confidence intervals) of developing hypothyroidism in euthyroid subjects with raised serum TSH alone (TSH > 2 μIU/mL) were 8(3-20) for women and 44(19-104) for men, while that with positive anti-thyroid antibodies alone were 8(5-15) for women and 25(10-63) for men 7. In subjects with elevated serum TSH and positive anti-thyroid antibodies simultaneously, the odds ratios became 38 (22-65) for women and 173 (81-370) for men. In another 4-year cohort study conducted in the United States,[8] one-third of subjects with SHT developed OHT within the course of the study. The initial TSH level of all subjects who became overtly hypothyroid was above 20 μIU/mL, and 80% of all of subjects, regardless of initial TSH level, also showed high-titer of TPO-Ab. Another prospective long-term study of 82 female patients with SHT also showed that higher initial TSH concentrations and positive TPO-Ab allowed initial risk stratification for the development of overt thyroid failure within ten years.[9] Other numerous

prospective studies conducted since 2000 also have proved that both elevated TSH level and presence of TPO-Ab are poor prognostic factors of SHT.

In this study, to determine the prognostic factors of SHT, we compared two groups to each other; SHT maintenance group and Spontaneously improved group. Comparison of numerous parameters including age, sex, fT4, TSH, TPO-Ab, TG-Ab, lipid profile, hsCRP, urine iodine and the presence of DT on US at initial presentation found that women had favorable prognosis than men and, among biochemical parameters considered for prognostic factors in many studies, only initial TSH level was significantly different. It is well-known that women have higher prevalence of both SHT and OHT than men. But sexual difference of disease prognosis has not been established. Subjects with higher TSH level seemed to maintain subclinical hypothyroid state, while subjects with lower TSH level showed a tendency to spontaneously improve. As shown in our ROC curves for TSH cut-off level associated with SHT prognosis, we may be able to expect that SHT patients with TSH under 5.895 μIU/mL will have a higher probability to be improved spontaneously to euthyroid state about 10 months later. In this study, among patients who was newly-diagnosed with SHT, about half of them improved to euthyroid in just 10 months. In clinical practice, we could explain to those patients that they have 50 percent chance to be improved to euthyroid after 10 months in its natural course of the disease. Considering this with other probable prognostic factors and clinical circumstances of the patient, we could able to determine the management plan of the SHT patient. Our result is consistent with a study of 107 elderly SHT patients in Spain, which reported that TSH concentration was the most powerful predictor for the outcome of SHT.[10] TPO-Ab, known as the other apparent major predictor of OHT and SHT in other several

studies, was not shown to be a significant predictor in our entire SHT patients. But, when we performed further sub-analysis for subjects with TSH between 5-10 μIU/mL, those in Spontaneously improved group showed significantly lower TPO-Ab titer than SHT maintenance group. So we can say that TPO-Ab titer is also a useful predictor for SHT. Although TSH level is the most powerful prognostic factor in all SHT population, TPO-Ab titer can predict the outcome in SHT with mildly elevated TSH (between 5-10 μIU/mL). This could be explained, at least partially, because TPO-Ab titer would contribute to prognosis earlier than TSH in pathogenesis of SHT. TPO-Ab titer can be regarded as earlier prognostic factor, especially helpful in mild SHT, and then TSH level take a place as most strong prognostic factor, regardless of TPO-Ab titer, in advanced SHT. On the other hand, TG-Ab, an anti-thyroid antibody, just like TPO-Ab, did not show any significance in SHT.

We also investigated the changes in parameters during follow-up in each groups. As for TPO-Ab changes, in Levothyroxine treatment group, TPO-Ab titer was decreased significantly. In contrast, in Spontaneously improved group, those who showed normalized TSH at follow-up, there was no significant improvement of TPO-Ab titer, showing only decreasing trend. Given that most of the subjects in Spontaneously improved group were those who had relatively low TPO-Ab titer (only seven subjects of Spontaneously improved group had TPO-Ab titer > 60 U/mL) and that the subjects in Levothyroxine treatment group had higher TPO-Ab titer, we cannot generalize our result for entire SHT subjects. But, at least, the benefit of levothyroxine supplement in SHT may be supported by the purpose of decreasing TPO-Ab, thus decreasing autoimmunity and parenchymal pathologic process.

When it comes to lipid profiles, as of yet, there is no conclusive evidence regarding the effect

of SHT on lipid profile. In an observational cohort study in the United States, lipid levels including total cholesterol, LDL-C and triglyceride increased in a graded fashion as thyroid function declined.[11] On the other hand, in another randomized placebo-controlled study in SHT where patients were randomly assigned to Levothyroxine therapy or placebo and re-evaluated after 6 months of euthyroidism, triglyceride levels remained similar regardless of TSH levels, although total cholesterol and LDL-C levels were lowered by levothyroxine therapy and did correlate with baseline TSH levels.[12] The study concluded that only LDL-C levels are increased specifically and reversibly in association with SHT. Another study in Switzerland reported, SHT subjects showed a borderline elevated LDL-C and similar total cholesterol and triglyceride concentrations compared to controls, matched for age, sex and body mass index.[13] In our study, in both Spontaneously improved group and Levothyroxine treatment group, triglyceride level decreased significantly during follow-up. However, most of them did not have hypertriglyceridemia (triglyceride > 150 mg/dL) at diagnosis, so it should be interpreted as the decrease of mean triglyceride level, not the improvement of hypertriglyceridemia. Unlike most previous studies stating total cholesterol and LDL-C as lipid profiles correlating with changes in thyroid function, an apparent correlation between triglyceride level and subclinical hypothyroid state was shown in this study. Therefore, we suggest that triglyceride level should not be ignored in evaluating SHT at least in Korean patients.

There were several studies about the correlation between hsCRP, a low grade inflammatory marker, and OHT or SHT. In several small-sized overseas studies, some investigators reported that patients with SHT had significantly higher levels of serum hsCRP[14, 15] and others

observed no significant differences.[16] Recently, there was a report in more than nine hundred Korean elderly patients, stating CRP did not showed any differences between the subclinical hypothyroid and the euthyroid group.[17] As hsCRP started being considered as a potential marker for coronary heart disease, testifying hsCRP elevation in SHT will imply the cardiologic consequences in SHT, which is not yet confirmed. But, in this study, hsCRP did not show any significant differences at diagnosis between SHT maintenance group and Spontaneously improved group or significant change during follow-up in all three groups.

Recently, dietary iodine excess is considered to be associated with decreased thyroid function. Iodine is the most notable environmental factor in thyroid dysfunction and also determines the vulnerability to other possible harmful environmental factors.[18] However, in this study, higher iodine concentration in the body quantified by urinary iodine excretion was not associated with poor prognosis of SHT. A 1-year observational study of SHT in Denmark[19] have reported a significant positive correlation between TSH and urinary iodine excretion in monthly measurement. Furthermore, high urinary iodine excretion predicted high TSH and TPO-Ab titer on the following month. In another study of adults in iodine-rich area in Japan,[20] hypothyroidism was more prevalent in anti-thyroid antibodies-negative subjects with high urinary iodine excretion than with normal urinary iodine excretion. They reported significantly higher TSH and lower fT4 levels in SHT with high urinary iodine excretion and concluded that the prevalence of hypothyroidism in iodine sufficient areas may be associated with the amount of iodine ingested. Based on our study, however, the restriction of excessive iodine intake, which is possible prognostic factor, mostly only modifiable, is weakly supported for SHT management at present, at least in Korean subjects. As serial

measurements of urinary iodine excretion after initial laboratory test were not conducted, however, we cannot rule out the possibility that the altered iodine status during follow-up may influence to the clinical course of our subclinical hypothyroid subjects.

Decreased or irregular heterogeneous echogenicity on US is a characteristic finding in diffuse thyroid disease, including both OHT and SHT.[21-24] But, the value of DT on US as predicting factor of SHT has not been established until recently. In a 3-year follow-up study of 117 mild SHT in Brazil, the likelihood of a progression toward OHT and improvement to euthyroidism, respectively, were similar between patients with positive TPO-Ab and/or US alteration and patients with negative TPO-Ab but with positive US alteration, thus suggesting that US findings may be useful in determining the prognosis of mild SHT.[25] In a retrospective study of Korean SHT patients, which aimed to see the difference of response to levothyroxine replacement according to autoantibody status and US finding, patients who initially showed DT on US, regardless of thyroid autoantibody level, showed poor response after levothyroxine replacement.[26] They suggested the possibility that DT pattern on thyroid US can serve as a prognostic factor when combined with other known parameters. In our study, the existence of DT on US at diagnosis was not significantly different between SHT maintenance group and Spontaneously improved group. It seems that DT on US only reflect the severity of hypothyroid state at that time of US evaluation, marked by higher TSH and TPO-Ab. It could not predict the prognosis of SHT.

This study has several limitations. First, as a retrospective study, the impacts and powers of the results may be weakened. Second, the study population was not representative of the Korean population. They were patients of a single center of tertiary health care. Mostly SHT

patients may be recognized by physician of local, primary health care clinic and followed-up without appropriate concern. Therefore, the number of eligible participants was small, compared to relatively many OHT patients. Third, in line with that, follow-up period was not sufficiently long (less than 13.0 months). Without apparent progression to OHT, they tend to go back to local clinic follow-up. Fourth, as we didn't have additive data, such as body mass index and pre/post-menopause state, we could not interpret our data more specifically according to these epidemiologic factors, which might have affected to the prognosis of SHT. Lastly, as mentioned above, as urinary iodine excretion were not measured serially, altered iodine status during follow-up might have influenced to the clinical course of our SHT subjects.

V. CONCLUSION

In conclusion, only initial TSH level was a definite prognostic factor of SHT. TPO-Ab titer was also a helpful prognostic factor for SHT with mildly elevated TSH (between 5-10 μIU/mL). We could expect SHT patients with lower TSH level and lower TPO-Ab titer to be improved spontaneously to euthyroid state. In the aspects of lipid profiles, only triglyceride level, other than total cholesterol and LDL-cholesterol, was related with TSH level, that is, the severity of SHT. And finding of DT on US only contributed to the severity of SHT, not to the prognosis of it. hsCRP and urine iodine excretion, generally regarded as possible prognostic factors, did not show any significant relation with the prognosis and severity of SHT. Except TSH and TPO-Ab, we could not validate any other biochemical prognostic factors in this retrospective analysis. Among our patients who was newly-diagnosed with SHT, about half of them improved to euthyroid in 10 months. So, in clinical practice, we could explain to those patients that they have 50 percent chance to be improved to euthyroid after 10 months in its natural course of the disease. Considering this with other probable prognostic factors and clinical circumstances of the patient, we could also able to determine the management plan of the SHT patient. Later, a large-scaled, prospective trials are needed to determine the definite prognostic factors of SHT.

REFERENCES

1. Fowler PB, Swale J, Andrews H, Ikram H, Banim SO. Grades of hypothyroidism. Br Med J. 1973;2(5859):178.
2. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, *et al*. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87(2):489-99.
3. Riniker M, Tieche M, Lupi GA, Grob P, Studer H, Burgi H. Prevalence of various degrees of hypothyroidism among patients of a general medical department. Clin Endocrinol (Oxf). 1981;14(1):69-74.
4. Herrmann J. Prevalence of hypothyroidism in the elderly in Germany. A pilot study. J Endocrinol Invest. 1981;4(3):327-30.
5. Bilous RW, Tunbridge WM. The epidemiology of hypothyroidism--an update. Baillieres Clin Endocrinol Metab. 1988;2(3):531-40.
6. Kostoglou-Athanassiou I, Ntalles K. Hypothyroidism - new aspects of an old disease. Hippokratia. 2010 Apr;14(2):82-7.
7. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, *et al*. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf). 1995;43(1):55-68.
8. Rosenthal MJ, Hunt WC, Garry PJ, Goodwin JS. Thyroid failure in the elderly. Microsomal antibodies as discriminant for therapy. JAMA. 1987;258(2):209-13.
9. Huber G, Staub JJ, Meier C, Mitrache C, Guglielmetti M, Huber P, *et al*. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin,

thyroid reserve, and thyroid antibodies. J Clin Endocrinol Metab. 2002;87(7):3221-6.

10. Diez 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. 2004;89(10):4890-7.
11. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000;160(4):526-34.
12. Caraccio N, Ferrannini E, Monzani F. Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab. 2002;87(4):1533-8.
13. Althaus BU, Staub JJ, Ryff-De Leche A, Oberhansli A, Stahelin HB. LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease. Clin Endocrinol (Oxf). 1988;28(2):157-63.
14. Sharma R, Sharma TK, Kaushik GG, Sharma S, Vardey SK, Sinha M. Subclinical hypothyroidism and its association with cardiovascular risk factors. Clin Lab. 2011;57(9-10):719-24.
15. Tuzcu A, Bahceci M, Gokalp D, Tuzun Y, Gunes K. Subclinical hypothyroidism may be associated with elevated high-sensitive c-reactive protein (low grade inflammation) and fasting hyperinsulinemia. Endocr J. 2005;52(1):89-94.
16. Toruner F, Altinova AE, Karakoc A, Yetkin I, Ayvaz G, Cakir N, *et al*. Risk factors for cardiovascular disease in patients with subclinical hypothyroidism. Adv Ther. 2008;25(5):430-7.

17. Park YJ, Lee EJ, Lee YJ, Choi SH, Park JH, Lee SB, *et al*. Subclinical hypothyroidism (SCH) is not associated with metabolic derangement, cognitive impairment, depression or poor quality of life (QoL) in elderly subjects. Arch Gerontol Geriatr. 2010;50(3):e68-73.

18. Hyun-Kyung Chung. Environmental Factors and Thyroid Dysfunction. Endocrinol Metab 2012;27(3):191-3.

19. Karmisholt J, Laurberg P. Serum TSH and serum thyroid peroxidase antibody fluctuate in parallel and high urinary iodine excretion predicts subsequent thyroid failure in a 1-year study of patients with untreated subclinical hypothyroidism. Eur J Endocrinol. 2008;158(2):209-15.

20. Konno N, Makita H, Yuri K, Iizuka N, Kawasaki K. Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. J Clin Endocrinol Metab. 1994;78(2):393-7.

21. Loy M, Cianchetti ME, Cardia F, Melis A, Boi F, Mariotti S. Correlation of computerized grayscale sonographic findings with thyroid function and thyroid autoimmune activity in patients with Hashimoto's thyroiditis. J Clin Ultrasound. 2004;32(3):136-40.

22. Rago T, Chiovato L, Grasso L, Pinchera A, Vitti P. Thyroid ultrasonography as a tool for detecting thyroid autoimmune diseases and predicting thyroid dysfunction in apparently healthy subjects. J Endocrinol Invest. 2001;24(10): 763-9.

23. Schiemann U, Avenhaus W, Konturek JW, Gellner R, Hengst K, Gross M. Relationship of clinical features and laboratory parameters to thyroid echogenicity measured by standardized grey scale ultrasonography in patients with Hashimoto's thyroiditis. Med Sci Monit. 2003;9(4): MT13-7.

24. Vejbjerg P, Knudsen N, Perrild H, Laurberg P, Pedersen IB, Rasmussen LB, *et al*. The association between hypoechogenicity or irregular echo pattern at thyroid ultrasonography and thyroid function in the general population. Eur J Endocrinol. 2006;155(4): 547-52.

25. Rosario PW, Bessa B, Valadao MM, Purisch S. Natural history of mild subclinical hypothyroidism: prognostic value of ultrasound. Thyroid. 2009;19(1):9-12.

26. Shin DY, Kim EK, Lee EJ. Role of ultrasonography in outcome prediction in subclinical hypothyroid patients treated with levothyroxine. Endocr J. 2010;57(1):15-22.

< ABSTRACT(IN KOREAN)

한국인에서의 불현성 갑상선기능저하증의 임상적 고찰

<지도교수 이은직>

연세대학교 대학원 의학과

이 명 원

임상적으로 흔하게 마주하게 되는 불현성 갑상선기능저하증은 아직 예후를 포함한 그 임상적 중요성이 명확히 밝혀지지 않았고 따라서 이에 기반한 치료 가이드라인 또한 정립되지 못한 상태이다. 이 연구는 한국인에서 나타나는 불현성 갑상선기능저하증의 예후 인자를 살펴보고자 하였다. 2008년 1월부터 2012년 9월까지 세브란스 병원 내분비내과 외래 내원 환자들 중 불현성 갑상선기능저하증을 처음 진단 받은 298명의 환자들을 대상으로 후향적 연구를 진행하였다. 이 중 추적관찰 기간 동안 불현성 갑상선기능저하 상태가 유지된 군과 자발적으로 정상갑상선기능으로 호전된 군 두 군을 비교하였다. 불현성 갑상선기능저하증 유지군과 자발적 호전군 간 통계적으로 유의한 예후 인자로 나타난 것은 진단 당시 갑상선자극호르몬 농도로 낮을수록 자연적인 갑상선기능 호전을 기대할 수 있었다 (p-value=0.030). 또한 갑상선자극호르몬이 비교적 경한 정도로 상승되어 있던 (5-10 μIU/mL) 이들에 있어서는 자발적 호전군이 유지군에 비해 더 낮은 갑상선 과산화효소 항체 농도를 보였다 (p-value=0.038). 지질 농도와 관련하여서는 총콜레스테롤, 저밀도지단백 콜레스테롤이 아닌 중성지방만이 갑상선자극호르몬 농도, 즉 불현성 갑상선기능저하증의 중증도와

관련을 보였다. 초음파 상 미만성 갑상선염 또한 질환의 중증도와 관련을 보였을 뿐 예후와는 관련이 없었다. 이외에 최근 가능성 있는 예후 인자로 거론되고 있는 C-반응성 단백과 요오드 섭취 정도는 질환의 예후 및 중증도 모두와 관련이 없었다. 결론적으로, 진단 당시의 갑상선자극호르몬 농도만이 전체 불현성 갑상선기능저하증 인구에서의 유일한 예후 인자로 나타났으며, 이중에서 비교적 경한 갑상선자극호르몬 상승을 가진 이들의 경우에서는 갑상선 과산화효소 항체가 예후 인자인 것으로 나타났다. 즉, 불현성 갑상선기능저하증 환자에서 갑상선지극호르몬 농도가 낮을수록, 갑상선 과산화효소 항체 농도가 낮을수록 정상 갑상선기능으로의 자연적인 호전을 기대할 수 있겠다. 갑상선자극호르몬과 갑상선 과산화효소 항체를 제외하고는 나머지 생화학적 예후 인자들은 입증할 수 없었다. 처음 불현성 갑상선기능저하증을 진단받은 환자에게, 임상적으로는 이 연구에서 관찰된 대로 10개월 경과 동안에 약 반 수에서 자발적으로 호전, 나머지 반 수에서는 호전없이 유지됨을 설명해 줄 수 있겠으며, 이와 함께 환자가 가진 여러 가능한 예후 인자들과 임상적 환경을 고려하여 환자에 있어 적절한 치료 계획을 세우는 도움이 될 수 있을 것이다.

핵심되는 말: 불현성 갑상선기능저하증; 갑상선자극호르몬; 갑상선 과산화효소 항체; 지질; C-반응성 단백질; 요오드