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Original Article

Aging-related Characteristics of Subclinical Hypothyroidism Detected in General Practice

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Subclinical hypothyroidism (SCH) is diagnosed when serum thyrotropin (TSH) is elevated despite a normal thyroxine level and is known to increase the risk of metabolic disorders. This study was conducted to identify potential laboratory markers suspicious for latent SCH. We retrospectively reviewed 958 outpatients in whom thyroid functions had been examined. Eighty-five (9.1%) of the 939 analyzed subjects had SCH (73% females). In the SCH group, median serum TSH and FT4 levels were 5.04 μU/ml and 1.19 ng/dl, respectively, and auto-thyroid antibodies were detected in 53.8% of patients. SCH group patients were significantly older than patients in the euthyroid group, while there was no intergroup difference in BMI. However, 56.5% of the SCH patients were asymptomatic. In the SCH group, serum aspartate aminotransferase and low-density lipoprotein cholesterol (LDL-C) levels were significantly higher, and the estimated glomerular filtration rate (eGFR) was significantly lower than in the euthyroid group. Among patients less than 65 years of age, SCH patients tended to have lower eGFR and higher LDL-C than euthyroid patients. Age-dependent reductions of red blood cells and serum albumin were more prominent in the SCH than the euthyroid group. Biochemical changes with aging are useful as potential clues for suspecting latent SCH.

Key words: aging, renal function, cholesterol, subclinical hypothyroidism, thyroid function

Subclinical hypothyroidism (SCH) is a state defined as an elevated serum level of thyrotropin (TSH) with a normal free thyroxine (FT4) level, and it is diagnosed solely by a biochemical examination. However, thyroid hormone levels are typically measured in response to reported symptoms; their routine measurement, for instance at annual wellness exams, is not recommended, and many SCH patients are asymptomatic. It has been reported that SCH is associated with increased risks of heart failure, coronary heart disease, and cardiovascular mortality [1-3]. As with clinical hypothyroidism [4], patients with SCH may be prone to various clinical conditions including mild derangements in lipid metabolism [5], liver function [6], and renal function [7,8], cognitive impairment [9,10], and frailty [11]; however, details of these relationships remain uncertain.

The connection of thyroid disease to specific clinical symptoms encountered in general practice has been previously studied. For instance, our colleagues Omura *et al.* [12] conducted a retrospective analysis using clinical data for 843 patients visiting a general medicine department for the first time. Interestingly, they found that serum FT4 levels in the patient group with complaints of dizziness were lower and were inversely cor-

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related with age, suggesting that the age-dependent decline of thyroid hormones is related to the occurrence of dizziness. Oka *et al*. [13] also analyzed 148 febrile patients who visited a general medicine department. In their retrospective study, body temperature was found to be positively correlated with heart rate and negatively correlated with serum TSH level and TSH/FT4 ratio, especially in the group of patients with viral infection, suggesting that occult thyrotoxicosis caused by viral infection can lead to febrile tachycardia.

In a general population, the prevalence of SCH was estimated to be 4-15% while the prevalence of clinical hypothyroidism, which increases with aging, was estimated to be 0.2-5.3% [14]. SCH is often caused by the autoimmune disorder, Hashimoto's thyroiditis. Patients who are positive for thyroid peroxidase antibodies (TPOAb) have a greater risk for progression of subclinical to clinical hypothyroidism, and positivity for TPOAb is more prevalent in older patients than in younger patients [3]. In a clinical setting, treatment with levothyroxine for subclinical hypothyroidism may be indicated for young or middle-aged (<65 years) patients with serum thyrotropin levels over 10 mU/l [1]. However, since the diagnosis of SCH can be solely based on laboratory data for thyroidal functions, clinical and biochemical characteristics indicating the possibility of SCH have been uncertain.

In the present study, we retrospectively investigated the clinical features of SCH with a focus on biochemical characteristics and changes with aging. The aim was to identify useful markers suspicious for SCH in the setting of a general practice.

Patients and Methods

Study design. We retrospectively screened the medical records of 958 outpatients whose serum levels of thyroid hormones were examined during the period from January to December in 2017 at the Department of General Medicine, Okayama University Hospital. Of those patients, 17 patients without simultaneous measurements of serum TSH and FT4 levels and 2 patients with severe renal or liver dysfunction were excluded. As a result, 939 patients were included in the present analysis. Examination of serum thyroid function was decided by each physician when thyroid dysfunction was clinically suspected on the basis of the patient's symptoms, laboratory data, and past medical history. In cases with multiple tests of thyroid function, data from the first test were used for analysis. Data for other biochemical markers were obtained within 1 day of measurement of thyroid function. Blood tests were performed patients with adequate insurance coverage. Information regarding the present study was provided on our hospital wall and on the website of our hospital, and patients who wished to opt out were offered that opportunity. This study was approved by the Ethical Committee of Okayama University Hospital (KEN-1801-030) and adhered to the Declaration of Helsinki.

Analysis of clinical parameters. Information on the patients' chief complaints was obtained from hospital medical records. For patients who had multiple chief complaints, we obtained information on up to three of them in each case. Data on age, gender, body mass index (BMI), self-rated depression scale (SDS), and frequency scale for symptoms of gastroesophageal reflux disease (FSSG) were also obtained [15].

Values for the following blood biochemical parameters were obtained from records, when available: white blood cells, red blood cells, hemoglobin, hematocrit, and platelets for blood cell counts; total bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyl transpeptidase (γGTP), creatine kinase (CK), C-reactive protein (CRP), creatinine (Cr), urea nitrogen (UN), estimated glomerular filtration rate (eGFR), sodium, potassium, chloride, calcium, corrected calcium, inorganic phosphate (iP), and magnesium for liver and renal functions; hemoglobin A1c (HbA1c), fasting blood glucose (FBG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides as metabolic markers; and thyrotropin (TSH), free thyroxine (FT4), free triiodothyronine (FT3), the ratio of TSH/FT4, thyroglobulin, TPOAb, anti-thyroglobulin antibody (TgAb), TSH receptor antibody (TRAb), and thyroid-stimulating antibody (TSAb) as thyroid function markers. eGFR was calculated by using the following formulas: male, $194 \times \mathrm{Age}^{-0.287} \times \mathrm{Cr}^{-1.094}$; female, $194 \times \mathrm{Age}^{-0.287} \times \mathrm{Cr}^{-1.094} \times 0.739$. The TSAb level was determined by a bioassay and enzyme immunoassay at BML, Inc. (Tokyo). All other levels were determined using an auto-analyzer system at the Central Laboratory of Okayama University Hospital.

Patient categories according to thyroid functions.

The patients analyzed in the present study were divided into the following groups depending on their serum levels of TSH (normal range: 0.33-4.05 μU/ml) and FT4 (0.97-1.69 ng/dl): a euthyroid (EU) group, subclinical hypothyroidism (SCH) group, hypothyroidism group, syndrome of inappropriate secretion of TSH group, subclinical hyperthyroidism group, hyperthyroidism group, and "others" group.

Statistical analysis. EZR, version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), was used in all statistical analyses [16]. It is modified from R commander, which is designed to add frequently used functions in biostatistics. The Mann-Whitney *U* test or Spearman's rank correlation coefficient were used to statistically analyze continuous measurements. All tests were performed as two-sided, and $P < 0.05$ was regarded as statistically significant.

Results

Characteristics of subclinical hypothyroidism in the patients. The age distribution of the 939 patients (male/female(M/F) = 290/649) analyzed in this study is shown in Fig. 1A. The numbers of patients in the different age groups were as follows: 20s, 78/939 (8.3%); 30s, 123/939 (13.1%); 40s, 185/939 (19.7%); 50s, 178/939 (19.0%); 60s, 228/939 (24.3%); and 70s, 147/939 (15.7%). As shown in Fig. 1B, the patients were categorized into the following groups depending on thyroid function: an EU group that included 73.3% of the patients ($n = 688$: M/F = 215/473), an SCH group that included 9.1% of the patients ($n = 85$: M/F = 23/62), a hypothyroidism group that included 1.5% of the patients ($n = 14$: M/F = 5/9), a syndrome of inappropriate secretion of TSH group that included 0.11% of the patients ($n = 1$: M/F = 0/1), a subclinical hyperthyroidism group that included 5.5% of the patients ($n = 52$: M/F = 16/36), a hyperthyroidism group that included 3.3% of the patients ($n = 31$: M/F = 8/23), and others group that included 7.2% of the patients ($n = 68$: M/F = 23/45) (Fig. 1C).

The main symptoms in patients in the SCH group were weight gain (4.7%: 4/85), dizziness (4.7%: 4/85), general fatigue (3.5%: 3/85), palpitations (3.5%: 3/85), headache (3.5%: 3/85), and others (34.1%: 29/85), while 56.5% (48/85) of the SCH patients had no symptoms. Patients in the EU group had main complaints of general fatigue (8.4%: 58/688), fever (6.1%: 42/688),

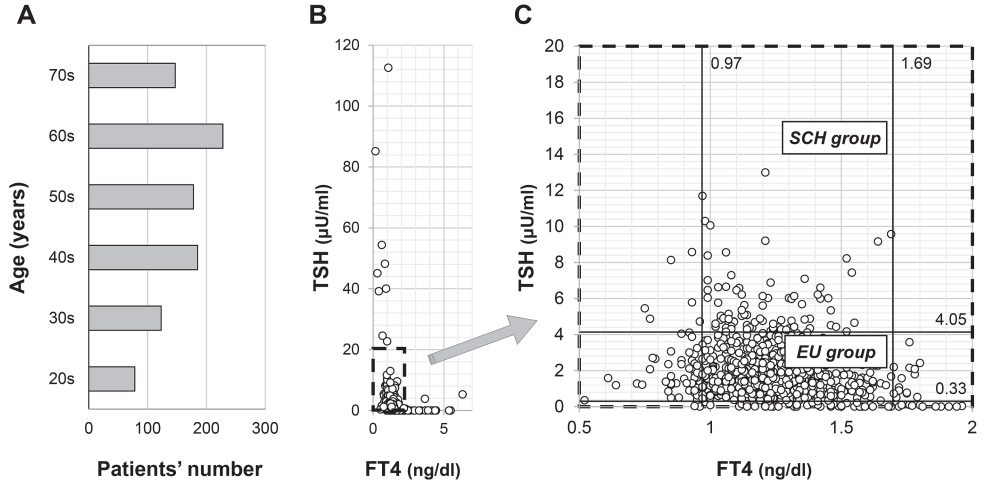

Fig. 1 Distribution of patients according to serum levels of TSH and FT4. A) Ages of the 939 patients are shown in a bar chart; B) Out of 958 patients in whom TSH and FT4 were measured, 939 patients were included in the present analysis. The dotted line in the graph corresponds to the outline of panel C); C) The patients were categorized by normal ranges of free thyroxine (FT4; 0.97–1.69 ng/dl) and thyrotropin (TSH; 0.33–4.05 μU/ml) into a euthyroid (EU) group that included 73.3% of the patients ($n = 688$: M/F = 215/473), a subclinical hypothyroidism (SCH) group that included 9.1% of the patients ($n = 85$: M/F = 23/62), a hypothyroidism group that included 1.5% of the patients ($n = 14$: M/F = 5/9), a syndrome of inappropriate secretion of TSH group that included 0.11% of the patients ($n = 1$: M/F = 0/1), a subclinical hyperthyroidism group that included 5.5% of the patients ($n = 52$: M/F = 16/36), a hyperthyroidism group that included 3.3% of the patients ($n = 31$: M/F = 8/23), and an "others" group that included 7.2% of the patients ($n = 68$: M/F = 23/45).

headache (6.0%: 41/688), chest pain (4.7%: 32/688), dizziness (4.2%: 29/688), and others (4.6%: 319/688), while 44.5% (306/688) of the EU patients had no symptoms. Positive rates of serum TPOAb and TgAb in the SCH group were 38.5% (20/52) and 53.8% (28/52), respectively.

To investigate the clinical characteristics of patients with SCH status, we focused on a comparison of the SCH group with the EU group. Patients with SCH included those who had thyroid disease (48.2%, 41/85): chronic thyroiditis (24.7%, 21/85), thyroid tumor (11.8%, 10/85), subacute thyroiditis (1.8%, 1/85), and undiagnosed thyroid disorder (10.6%, 9/85). Drugs associated with thyroid function were used in 20% (17/85) of the patients with SCH. The drugs included an antithyroid drug (4.7%, 4/85) and levothyroxine (15.3%, 13/85). The median serum levels of TSH were 1.54 μU/ml (interquartile range (IQR), 1.04-2.33) in the EU group and 5.04 μU/ml (4.45-6.47) in the SCH group (Fig. 2A), compatible with the definitions of euthyroidism and subclinical hypothyroidism. The serum level of FT4 was significantly lower in the SCH group (median, 1.19 ng/dl; IQR, 1.07-1.32) than in the EU group (1.24 ng/dl; 1.14-1.35) (Fig. 2B). Notably, the median age in the SCH group (61 years) was significantly older (IQR, 48-69) than that in the EU group (53 years; 41-67) (Fig. 2C), while the median BMI of the two groups did not differ (EU: 22.7 kg/m^2; 20.3-25.4 and SCH: 22.5 kg/m^2; 19.3-25.5) (Fig. 2D).

Regarding blood biochemical parameters, the serum AST level was significantly higher in the SCH group (median, 22 U/l; IQR, 18-26) than in the EU group (19 U/l; 19-23) (Fig. 3A), but the serum CK level was not significantly different between the EU (82 U/l; 62-119) and SCH groups (86.5 U/l; 63.8-122.5). Interestingly, eGFR was significantly lower in the SCH

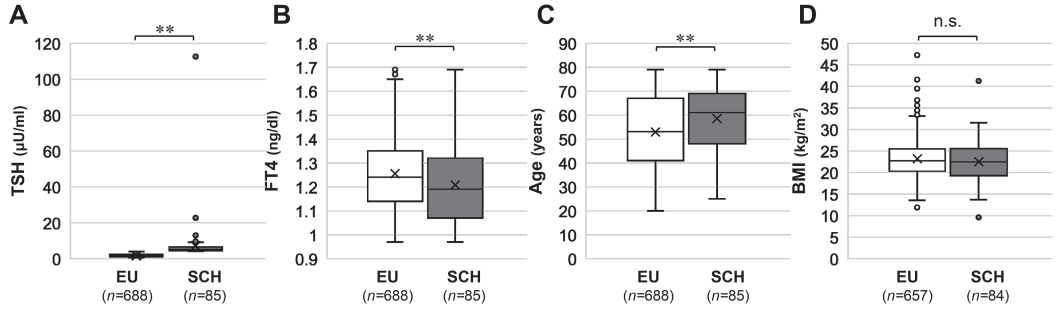

Fig. 2 Clinical features of patients with subclinical hypothyroidism. Thyroid functions (A, B), age (C) and BMI (D) were compared between the subclinical hypothyroid (SCH) group and euthyroid (EU) group. In each panel, the upper horizontal line of the box is the 75th percentile, the lower horizontal line of the box is the 25th percentile, the horizontal bar within the box is the median, the upper horizontal bar outside the box is the maximum value within 1.5 times the interquartile range, and the lower horizontal bar outside the box is the minimum value within 1.5 times the interquartile range. $^{**}p<0.01$ and $^{*}p<0.05$, statistically significant between the indicated groups. n.s.: not significant.

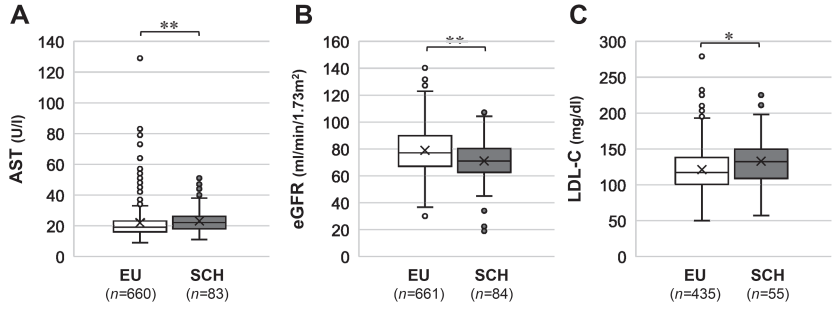

Fig. 3 Laboratory trends of patients with subclinical hypothyroidism. Biochemical data including aspartate aminotransferase (AST; A), estimated glomerular filtration rate (eGFR; B), and low-density lipoprotein cholesterol (LDL-C; C) were compared between the subclinical hypothyroid (SCH) group and euthyroid (EU) group. Bar graphs in each panel were made as described in the legend of Fig. 2. $^{**}p<0.01$ and $^{*}p<0.05$, statistically significant differences between the indicated groups. n.s.: not significant.

group (median, 70.9 ml/min/1.73 m^2; IQR, 62.6-80.1) than in the EU group (77 ml/min/1.73 m^2; 67.1-89.7) (Fig. 3B), whereas there was no difference between the two groups in serum UN (EU: 13.4 mg/dl; 10.9-16.1 and SCH: 13.5 mg/dl; 11.3-16.9) or serum Cr (EU: 0.67 mg/dl; 0.59-0.8 and SCH: 0.71 mg/dl; 0.61-0.82). The serum LDL-C level was also significantly higher in the SCH group (median, 132 mg/dL; IQR, 109-149.5) than in the EU group (117 mg/dl; 100.5-138.0) (Fig. 3C), while total cholesterol (EU: 203.0 mg/dl; 176.0-225.0, and SCH: 204.5 mg/dl; 181-235.5), HDL-C (EU: 61 mg/dl; 50-75 and SCH: 55 mg/dl; 47-65), and triglycerides (EU: 104 mg/dl; 73.0-159 and SCH: 116 mg/dl; 91.8-158) were not significantly different between the two groups. Other clinical parameters including SDS, FSSG and biochemical markers showed no statistically significant differences between the EU and SCH groups.

Age-related biochemical features of subclinical hypothyroidism. Next, we divided the SCH and EU patients into two age groups at the cutoff of 65 years and compared biochemical markers in the two groups. Among patients <65 years of age, as shown in the upper panel of Fig. 4, eGFR was significantly lower in SCH patients (median, 74.3 ml/min/1.73 m^2; IQR, 66.3-82.1) than in EU patients (81.8 ml/min/1.73m^2; 71.4-93.8) (Fig. 4A, *middle*), and serum LDL-C was significantly higher in SCH patients (137 mg/dl 114.5-149.8) than in EU patients (118 mg/dl; 101.0-140.0) (Fig. 4A, *right*), while serum AST levels were not significantly different (EU: 18.0 U/l; 15.5-22.0 and SCH: 20.5 U/l; 16.3-23.8) (Fig. 4A, *left*). On the other hand, in patients ≥65 years of age, as shown in the lower panel of Fig. 4, serum AST was significantly higher in SCH patients (median, 21.0 U/l; IQR, 18.0-25.0) than in EU patients (24.0 U/l; 19.0-30.0) (Fig. 4B, *left*), whereas there was no significant difference in eGFR (Fig. 4B, *middle*) or serum LDL-C level (Fig. 4B, *right*) between EU patients (eGFR: 67.3 ml/min/1.73 m^2; 60.1-77.0 and LDL-C: 117 mg/dl; 99.0-134.0) and SCH patients (eGFR: 64.9 ml/min/1.73 m^2; 58.0-76.1 and LDL-C: 119 mg/dl; 104.5-146.5).

Age-related changes of biochemical parameters in the euthyroid and subclinical hypothyroidism groups. Correlations of various clinical parameters with age in the SCH group were investigated and are summarized in Table 1. The serum level of FT4 was not significantly correlated with age in either the SCH group ($R=-0.11$, $p=0.31$; Fig. 5B) or the EU group ($R=-0.071$, $p=0.06$; Fig. 5A). Red blood cell count (RBC) ($R=-0.39$, $^{**}p<0.01$; Fig. 5B) in the SCH group showed a relatively close inverse correlation with age compared to that in the EU group ($R=-0.16$, $^{**}p<0.01$; Fig. 5A). Also, the SCH group (Fig. 5B) had closer interrelationships of

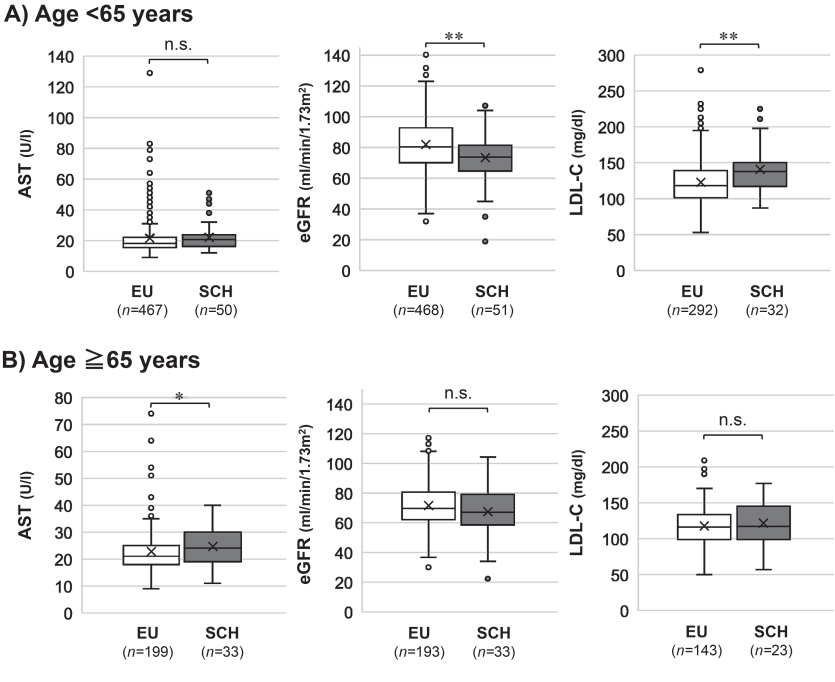

Fig. 4 Laboratory characteristics of younger and elderly patients with subclinical hypothyroidism. Biochemical data including aspartate aminotransferase (AST), estimated glomerular filtration rate (eGFR), and low-density lipoprotein cholesterol (LDL-C) were compared between the subclinical hypothyroid (SCH) group and euthyroid (EU) group according to age: **A**) age <65 years and **B**) age ≥65 years. Bar graphs in each panel were made as described in the legend of Fig. 2. $^{**}p<0.01$ and $^{*}p<0.05$, statistically significant between the indicated groups. n.s.: not significant.

Table 1 Correlations between age and clinical parameters in patients with subclinical hypothyroidism (SCH)

Comparison	with age		
	number	*R*	*P* values
Patients' profiles			
BMI	84	0.12	0.29
SDS	28	−0.13	0.51
FSSG	29	−0.15	0.45
Blood cell counts			
White blood cells	84	−0.13	0.25
Red blood cells	84	−0.39	**0.00026
Hemoglobin	84	−0.23	*0.034
Hematocrit	84	−0.27	*0.014
Platelets	84	−0.27	*0.014
Liver and renal functions			
Total bilirubin	76	0.015	0.90
Total protein	43	−0.082	0.60
Albumin	70	−0.44	**0.00013
AST	83	0.34	**0.0016
ALT	83	0.062	0.58
ALP	64	0.17	0.18
LDH	67	0.23	0.064
γ GTP	81	0.15	0.18
CK	52	0.061	0.67
CRP	57	0.24	0.068
UN	81	0.32	**0.0035
Creatinine	84	0.094	0.40
eGFR	84	−0.37	**0.00060
Sodium	77	0.17	0.14
Potassium	77	0.024	0.83
Chloride	77	0.10	0.38
Corrected calcium	62	−0.15	0.26
Inorganic phospate	46	−0.22	0.14
Magnesium	21	0.21	0.37
Endocrine and metabolic markers			
HbA1c	59	0.15	0.27
FBG	40	0.17	0.28
Total cholesterol	72	0.06	0.62
LDL-C	55	−0.17	0.21
HDL-C	29	−0.13	0.49
Triglyceride	44	0.15	0.34
TSH	85	−0.051	0.64
FT4	85	−0.11	0.31
FT3	42	−0.15	0.33
TSH/FT4	85	0.0033	0.98
Thyroglobulin	23	−0.021	0.92

$^{**}p<0.01$ and $^{*}p<0.05$, statistically significant between the indicated factors.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CK, creatine kinase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; FSSG, frequency scale for symptoms of gastroesophageal reflux disease; FT4, free thyroxine; FT3, free triiodothyronine; γGTP, γ-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; SDS, self-rating depression scale; TSH, thyroid-stimulating hormone; UN, urea nitrogen.

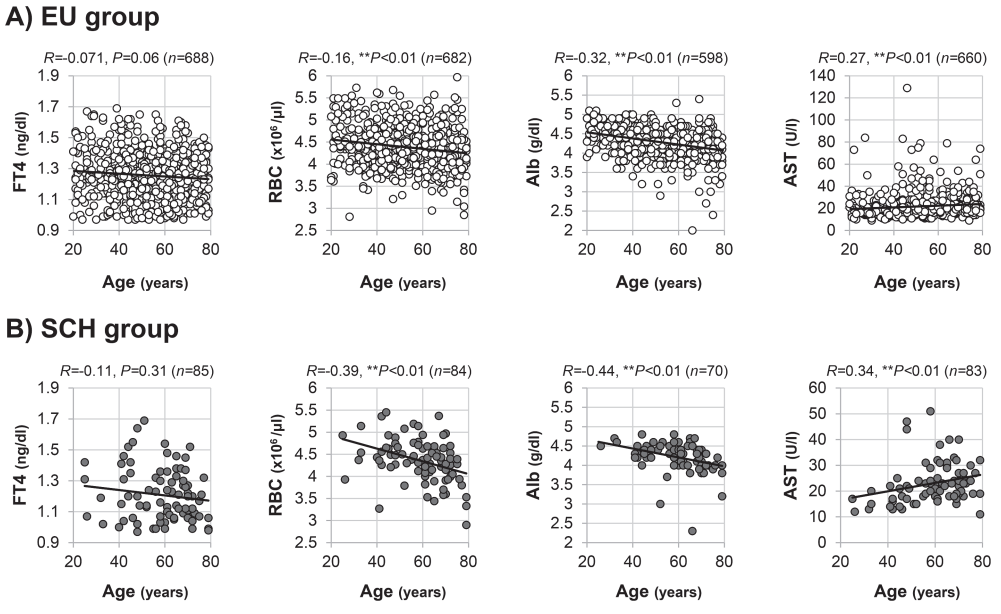

Fig. 5 Age-related changes in laboratory characteristics of patients with subclinical hypothyroidism. Both euthyroid (EU; A) patients and subclinical hypothyroidism (SCH; B) patients were further examined for interrelationships between their age and levels of biochemical markers including free thyroxine (FT4), red blood cell count (RBC), albumin (Alb), and aspartate aminotransferase (AST). $^{**}p<0.01$ and $^{*}p<0.05$, statistically significant between the indicated factors.

serum levels of albumin ($R=-0.44$, $^{**}p<0.01$) and AST ($R=0.34$, $^{**}p<0.01$) with age than those in the EU group (Fig. 5A): albumin ($R=-0.32$, $^{**}p<0.01$) and AST ($R=0.27$, $^{**}p<0.01$). Regarding lipid metabolism, the serum LDL-C level did not have a significant correlation with age ($R=-0.17$, $p=0.21$; Table 1).

Discussion

In the present study, we screened clinical and laboratory data of patients seen in general medicine for associations with latent SCH. The main etiology of SCH, which is the same as that of overt hypothyroidism, is chronic lymphocytic thyroiditis such as Hashimoto's thyroiditis and atrophic thyroiditis [3]. In the present study, auto-thyroid antibodies indicating Hashimoto's thyroiditis including TPOAb and TgAb were detected in 53.8% of the patients in the SCH group, similar to the results of a previous study in which approximately 60% of patients with a high serum TSH level had antithyroid antibodies [17]. Since the prevalence of TPOAb is higher in older patients and the presence of anti-thyroid antibodies such as TPOAb is a risk for progression of SCH to clinical hypothyroidism [3,14], aging could have a significant effect on the development of SCH. SCH is known to be associated with cardiovascular abnormalities [1] and liver diseases [6]. SCH is also linked to increasing cardiovascular risk [2,3,18,19] via hypercholesterolemia, hypertension, atherosclerosis [5,20] and insulin resistance [21]. Therefore, it is important to detect SCH as early as possible. Clinical and laboratory features of SCH and changes in the aging process can provide hints for suspecting SCH in general practice.

Among the serum laboratory values examined in the present study, AST and LDL-C levels were significantly higher and eGFR was lower in the SCH group than in the euthyroid group. Of note, younger patients (<65 years) in the SCH group showed patterns of lower eGFR and higher LDL-C than those in the euthyroid group. In the SCH patients, red blood cell count and liver functions showed closer inverse interrelationships with aging than those in EU patients. Regarding blood cell counts, it is well known that the prevalence of anemia increases with aging. A prospective population-based cohort study showed that subclinical thyroid dysfunction had no direct association with anemia [22]. However, our results newly showed that age-dependent reduction of

red blood cell count was more pronounced in the SCH group than in the EU group; despite there being no significant difference in red blood cell counts between the SCH group (median, 4.38×10^6/μl; IQR, 4.10-4.65) and EU group (4.37×10^6/μl; 4.05-4.66). It is thus possible that the existence of SCH facilitates aging-related changes such as an anemic condition.

Biomarkers of liver functions including serum levels of AST and albumin were also found to be more greatly affected by aging in the SCH group than in the EU group in the present study. It is known that liver functions and thyroid hormones have a close interrelationship: hypothyroid status leads to impaired lipid metabolism, hepatic steatosis and myopathy; likewise, liver diseases such as chronic hepatitis C, liver cirrhosis, hepatocellular carcinoma and cholangiocarcinoma tend to be accompanied by abnormal thyroid function [6]. Hyperlipidemia and obesity induced by hypothyroidism are considered to play a main role in the promotion of steatosis and fibrosis in the liver [23]. Liver function also influences circulating levels of FT4: namely, 5-10% of plasma FT4 is extracted by a single passage, and the major thyroid hormone-transport proteins including thyroxine-binding globulin, transthyretin, and albumin are synthesized in the liver [6]. Such a thyroid-liver interrelationship might be involved in the increased AST level and decreased albumin level in elderly patients with SCH.

Among younger patients (< 65 years) in this study, impairment of renal function was remarkable in SCH patients compared to EU patients. The eGFR is used to detect chronic kidney disease and is affected by thyroid function: decreased cardiac output due to relatively low thyroid function causes reduced renal blood flow and a decline in the glomerular filtration rate [1]. Median eGFR values have been reported to be 64 ml/min/1.73m^2 in hypothyroid patients, 77 ml/min/1.73 m^2 in euthyroid patients and 107 ml/min/1.73 m^2 in hyperthyroid patients [24]. Clinical hypothyroidism is associated with low eGFR [25-27], and SCH patients have also been reported to have a higher serum Cr level and lower eGFR [7].

Despite the increased prevalence of hypothyroidism with aging, the vagueness and often absence of complaints has made recognition difficult, such that symptoms of hypothyroidism can go unnoticed in the elderly [28, 29]. Accordingly, the relationships between chief complaints and thyroid function were examined in a general medicine department in our previous study [12], and it was found that patients with a complaint of dizziness had a significantly lower serum FT4 level than symptom-free patients and that the serum FT4 level was inversely correlated with age in patients with dizziness but not in patients without dizziness. In the present study, the main complaints of SCH patients were weight gain, dizziness, and general fatigue, but 56.5% of the SCH patients did not show any specific symptoms. Therefore, it is important to suspect a latent SCH condition by considering commonly used laboratory data including blood cell count, lipids, and liver and renal functions.

There were several limitations in the present study. The present study was a retrospective single-center study in which the number of subjects was not large enough to make absolute conclusions based on the findings and in which samples for biochemical data were not all obtained in the same period. A multi-center database would be required to elucidate the aging-related thyroidal changes and other metabolic changes in general practice patients. In addition, from the recent viewpoint of laboratory data management, it is important to consider the standardization of FT4 and the harmonization of TSH measurements [30] in a future study. From a clinical viewpoint, the results of the present study seem to indicate real-world data in a general practice setting since the patients included those with wide-ranging disorders and various complaints and symptoms. However, a prospective study in age- and gender-matched cohorts would be ideal as a future study.

Collectively, the results of this study indicate that there is a relatively high percentage (9.1%) of SCH patients in our department. As for the clinical characteristics of SCH, serum levels of AST and LDL-C were significantly higher, but eGFR levels were significantly lower. This pattern for lower eGFR and higher LDL-C was more remarkable in SCH patients less than 65 years of age. Laboratory data for red blood cell count and liver functions showed closer negative interrelationships with aging in SCH patients than in EU patients, suggesting that these factors are potential cues for screening for latent SCH status in general practice.

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