Relationship between the Thyroid Function and Cognitive Impairment in the Elderly in Japan

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Abstract:
Objective  The reference ranges of serum thyroid hormone levels are determined by the values of normal subjects aged 15 or 20 to 60 years old in Japan and may differ from the values in elderly patients. In addition, the relationship between the thyroid function and cognitive function remains controversial. We assessed the thyroid function of elderly subjects ≥60 years old and its impact on the cognitive function in Japanese adults.

Methods  We compared the thyroid function by age group and gender and investigated the effects of cognitive impairment on the thyroid function. This study was a cross-sectional, multi-institutional joint study.

Patients  The serum concentrations of thyroid hormones in 1,136 patients were measured; however, those taking thyroid hormones, anti-thyroid drugs, and steroid hormones were excluded. Among them, 1,016 cases in which the cognitive function was evaluated were divided into five groups according to their free thyroxine (FT4) levels.

Results  Excluding overt thyroid dysfunction (5.8%), the average age of the 1,070 remaining patients was 77.5 years old. The rate of cognitive impairment was lowest at FT4 levels of 1.1-1.2 ng/dL and highest at FT4 levels <0.9 ng/dL for both genders. Thyroid-stimulating hormone (TSH) levels in the elderly varied widely by age group and gender. The upper limit of the reference range of TSH for those ≥60 years old may be higher (7.7-9.2 mIU/L for men; 8.2-8.6 mIU/L for women) than the current range for those <60 years old (4.23 mIU/L).

Conclusion  The thyroid function seemed to be slightly higher (lower TSH and higher FT4) in the population without cognitive impairment than in those with cognitive impairment, except for men in their 90s.

Key words: thyroid hormone, cognitive impairment, elderly subjects, gender, age groups

(Intern Med 61: 3029-3036, 2022)
(DOI: 10.2169/internalmedicine.9034-21)

Introduction

The thyroid hormone plays an important role in the body’s metabolism and affects overall homeostasis, including the balance of energy, lipid metabolism, temperature regulation, and the cognitive function. The current reference values available for thyroid hormone are set using subjects 15 or 20 to 60 years old, and the standard values for those ≥60 years old remain unclear. However, it is difficult to set a reference value for the thyroid function in elderly individuals due to the influence of underlying diseases and the cor-

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Received: November 21, 2021; Accepted: January 30, 2022; Advance Publication by J-STAGE: March 19, 2022
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responding therapeutic agents.

We therefore conducted a multicenter cross-sectional study to clarify the actual state of the thyroid function in elderly patients ≥60 years old in Japan. The thyroid function was also assessed according to the environment, including the accompanying backgrounds of the patients who visited our clinic. In addition, we studied the relationship between the thyroid function and cognitive function in elderly Japanese adults ≥60 years old, as the association between hypothyroidism and cognitive impairment is still unclear (1–7).

Materials and Methods

The study was conducted in accordance with the Ethical Guidelines of the Japanese Ministry of Health and Labor for clinical studies. The study was approved by the ethics committee of the National Hospital Organization Kyoto Medical Center as well as that of each individual institution.

Patients

The subjects of the survey were those ≥60 years old who visited the participating research facilities from January 2000 to June 2020. Patients who had been treated with thyroxine, anti-thyroid drugs, or steroid hormones were excluded. As a result, a total of 1,136 patients, including 540 men and 596 women, were recruited. The oldest woman was 102 years old, and the oldest man was 97 years old.

Laboratory evaluations

Serum concentrations of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) were measured using an electro-chemiluminescence immunoassay (ECLIA; ECLusys FT3 II, FT4 II, and TSH, Roche Diagnostics, Mannheim, Germany) or chemiluminescence assay (CLIA; ARCHITECT FT3, FT4 and TSH, Abbott Japan, Tokyo, Japan). The values for FT3 and FT4 measured by the CLIA were converted into values for the ECLIA using the linear regression equations obtained from the relevant company as follows: FT3 [(CLIA)=0.78×(ECLIA)+0.87, R=0.989] and, FT4 [CLIA=0.56×(ECLIA)+0.49, R=0.983]. The values for TSH were harmonized based on the decision by the Standardization Committee of Japanese Society of Clinical Laboratory Medicine (8).

Cases in which both the TSH and FT4 values - namely, the reference values of the ECLIA method determined from the 95th percentile for the those <60 years old - fell outside the range according to the manufacturer’s instructions (those satisfying the following values) were defined as having overt thyroid dysfunction:

- Overt hypothyroidism: TSH >5.0 mIU/L and FT4 <0.9 ng/dL.
- Overt hyperthyroidism: TSH <0.5 mIU/L and FT4 >1.7 ng/dL.

Cognitive evaluations

The presence or absence of cognitive impairment was evaluated based on the guidelines of the Japan Geriatrics Society and the Japanese Society of Neurology (Clinical Practice Guideline for Dementia 2017, Japanese version).

Cognitive impairment was assessed by the patient’s history and the scores on the following cognitive tests: Mini-Mental State Examination [MMSE (9)], Hasegawa Dementia Scale revised [HSD-R (10, 11)], Dementia Behavior Disturbance Scale [DBD (12, 13)], Dementia Assessment Sheet for Community-based Integrated Care System 8-items [Dasc-8 (14)], and Dementia Assessment Sheet for Community-based Integrated Care System 21-items [Dasc-21 (14)].

Patients receiving drugs for dementia were regarded as having cognitive impairment.

Statistical analyses

Data are expressed as the mean±standard deviation. Data between two groups were compared using Student’s t-test for age and the body mass index (BMI) and the Mann-Whitney rank test for TSH, FT4 and FT3. For the trend test, a linear contrast analysis with a general linear model for FT4 or FT3 and the Jonckheere-Terpstra trend test for TSH were used. The chi-square statistic was used to test relationships among categorical variables. A p value of <0.05 was considered statistically significant.

Results

Out of the 1,136 patients surveyed, 66 (5.8%) had overt thyroid dysfunction (56.1% of whom were men). Overt hypothyroidism was found in 45 patients (4.0%; 68.9% of whom were men), and overt hyperthyroidism was found in 21 patients (1.8%; 28.6% of whom were men) (Table 1). Overt hypothyroidism was seen in 5.7% of men and 2.3% of women, and overt hyperthyroidism was seen in 1.1% of men and 2.5% of women. The age distribution by the thyroid function between men and women was similar, with some exceptions. Regarding the 1,070 (503 men and 567 women) patients, excluding those with overt thyroid dysfunction, the average age was 77.5 years old, with that of men (75.6 years old) being significantly lower than that of women (79.1 years old). There was no significant difference in the BMI, TSH, or FT4 values between genders, but FT3 levels were significantly higher in men than that in women (Table 2). Diabetes mellitus was seen in 67% of subjects, with no clear effect of diabetes mellitus on TSH detected.

The cognitive function was evaluated in 1,075 (94.6%) out of all 1,136 cases (Table 3). Cognitive impairment was observed in 32 (55.0%) out of 60 cases with overt thyroid dysfunction, and 66.7% of men and 75.0% of women with overt hypothyroidism and 16.7% of men and 33.3% of women with overt hyperthyroidism had cognitive impairment. The cognitive function in 1,015 (474 men and 541 women) patients, excluding those with overt thyroid dysfunction, was evaluated, and the relationship between cognitive impairment and the thyroid function was explored. By
Table 1. Frequency by Thyroid Function.

| Thyroid function | TSH (mIU/L) | Male | Female | Total |
|------------------|-------------|------|--------|-------|
|                  | n (%) | Age (mean±SD) | n (%) | Age (mean±SD) | n (%) | Age (mean±SD) |
| Overt hypothyroida | 31 (5.8) | 76.9±7.7 | 14 (2.3) | 81.6±8.6 | 45 (4.0) | 78.6±8.1 |
| Subclinical hypothyroid | >10 | 10 (1.9) | 81.8±7.5 | 10 (1.7) | 81.8±8.2 | 20 (1.8) | 81.8±7.6 |
|                  | 5.0-10 | 60 (11.1) | 77.0±7.3 | 58 (9.7) | 81.9±10.0 | 118 (10.4) | 79.4±9.1 |
| Euthyroid | 0.5-5.0 | 420 (77.9) | 75.3±8.2 | 483 (81.0) | 78.8±9.2 | 903 (79.5) | 77.5±9.0 |
| Subclinical hyperthyroid | <0.5 | 12 (2.2) | 74.2±9.3 | 16 (2.7) | 76.1±9.7 | 28 (2.5) | 75.3±9.4 |
| Overt hyperthyroidb | 6 (1.1) | 76.5±8.3 | 15 (2.5) | 76.0±10.0 | 21 (1.8) | 76.1±9.4 |
| Total | 540d (100) | 75.7±8.1 | 596 (100) | 79.1±9.4 | 1,136 (100) | 77.5±9.0 |

a TSH >5.0 mU/L and FT4 <0.9 ng/dL
b TSH <0.5 mU/L and FT4 >1.7 ng/dL
c p<0.05 vs. female
d TSH was not examined in one case.

Table 2. Sex Differences in Age, BMI and Thyroid Function (Excluding Overt Thyroid Dysfunctions).

|                | Total | Male | Female |
|----------------|-------|------|--------|
| n              | 1,070 | 503  | 567    |
| Age (years old) | 77.5±9.0 | 75.6±8.2b | 79.1±9.4 |
| BMI (kg/m²)    | 22.3±4.3 | 22.6±3.9 | 22.1±4.6 |
| TSH (mIU/L)a   | 2.9±2.4 | 3.0±2.5 | 2.8±2.3 |
| FT4 (ng/dL)    | 1.2±0.3 | 1.2±0.2 | 1.2±0.3 |
| FT3 (pg/mL)    | 2.4±0.6 | 2.5±0.6 | 2.3±0.6 |

a International Federation of Clinical Chemistry (IFCC) and Laboratory Medicine Committee for Standardization of Thyroid Function Tests (C-STFT)
b p<0.05 vs. female

gender, 38.6% of men and 46.8% of women had cognitive impairment. By age group, the rate of cognitive impairment increased with age for both men and women. Men more frequently had cognitive impairment than women in their 60s, while women had it slightly more frequently than men in their 70s and 80s, and women had it significantly more frequently than men at ≥90 years old (Fig. 1).

The analysis for age trends per 10 years revealed that TSH values in men without cognitive impairment increased with age (p=0.003), FT4 values in women with cognitive impairment increased with age (p=0.010), and FT3 values in both genders with and without cognitive impairment decreased with age (p<0.0001).

The thyroid function findings by age group and presence of cognitive impairment in men and women are shown in Fig. 2. The average TSH values were higher in men than in women in all the age groups, with or without cognitive impairment, except for the group ≥90 years old with cognitive impairment. The average TSH values among subjects in their 60s were significantly higher for men with cognitive impairment (3.94 mIU/L) than for men without cognitive impairment (2.40 mIU/L, p=0.005), and for women with cognitive impairment (2.44 mIU/L, p=0.039) and without cognitive impairment (2.40 mIU/L, p=0.0005). In contrast, the average TSH values among subjects ≥90 years old were particularly high for men without cognitive impairment (4.55 mIU/L), while those for women without cognitive impairment (2.14 mIU/L) were significantly lower than for others (p<0.05). The average FT4 values for men were constant among all the age groups, with or without cognitive impairment, with some differences among subjects in their 70s. The average FT4 values for women were lower in those with cognitive impairment in their 60s (1.15 ng/dL) than in other groups but increased with age. The average FT4 values for women ≥80 years old with (1.21 ng/dL) or without (1.23 ng/dL) cognitive impairment and for women ≥90 years old with (1.30 ng/dL) or without (1.35 ng/dL) were slightly higher than those for men of similar age groups (1.18, 1.20, 1.20, and 1.23, respectively). The average FT3 values for men and women showed a decline with age, regardless of cognitive impairment. The average FT3 values both for men (2.62 pg/mL in their 70s and 2.37 pg/mL in their 80s) and women with cognitive impairment (2.54 pg/mL in their 70s and 2.32 pg/mL in their 80s) were slightly higher than those for men and women with cognitive impairment in their 70s and 80s (2.51, 2.12, 2.31, and 2.13, respectively).

The distribution of the thyroid function by gender is shown in Table 4. Cases of overt thyroid dysfunction were excluded from this Table. TSH is expressed as values determined by the International Federation of Clinical Chemistry (IFCC) and Laboratory Medicine Committee for Standardization of Thyroid Function Tests (C-STFT) (1). The reference ranges in subjects ≥60s years old derived from this study were as follows: TSH (mIU/L) 0.5-9.2 for men and 0.5-8.6 for women; FT4 (ng/dL) 0.8-1.6 for men and 0.7-1.8 for women; FT3 (pg/mL) 1.2-3.3 for men and 1.0-3.3 for women in total subjects, except for those with overt thyroid dysfunction.

In contrast, the upper limit of the reference range of TSH
Table 3. Cognitive Impairment by Thyroid Function.

| Thyroid function     | Male                        | Female                       | Total                        |
|----------------------|-----------------------------|------------------------------|------------------------------|
|                      | n (%) | Age (mean±SD) | n (%) | Age (mean±SD) | n (%) | Age (mean±SD) |
| Overt hypothyroida   | 18/27 (66.7) | 80.6±5.9        | 9/12 (75.0) | 83.0±7.8      | 27/39 (69.2) | 81.4±6.6      |
| Overt hyperthyroidb  | 1/6 (16.7)  | 74              | 5/15 (33.3) | 82.2±13.5     | 6/21 (28.6)  | 80.8±12.5     |
| Subtotal             | 19/33 (57.6) | 80.3±6.0        | 14/27 (51.9) | 82.7±9.7      | 33/60 (55.0) | 81.3±7.7      |
| TSH (mIU/L)          |        |                |        |                |        |                |
| Subclinical          |        |                |        |                |        |                |
| hypothyroid          | >10   | 5/8 (62.5) | 81.6±3.2       | 6/10 (60.0) | 85.8±6.9      | 11/18 (61.1) | 83.9±5.7      |
| Euthyroid            | 5.0-10 | 27/60 (45.0) | 78.2±8.4c | 37/58 (63.8) | 85.7±8.3      | 64/118 (54.2) | 82.5±9.1      |
| Subclinical          | 0.5-5.0 | 148/396 (37.3) | 79.2±8.1c | 207/458 (45.2) | 83.5±7.9      | 355/854 (41.6) | 81.7±8.3      |
| hyperthyroid         | <0.5  | 3/10 (30.0) | 80.7±2.9       | 3/15 (20.0) | 85.7±4.2      | 6/25 (24.0)  | 83.2±4.2      |
| Subtotal             | 183/474 (38.6) | 79.1±8.0c | 253/541 (46.8) | 83.9±7.9      | 436/1,015 (43.0) | 81.9±8.3      |

a TSH >5.0 mIU/L and FT4 <0.9 ng/dL
b TSH <0.5 mIU/L and FT4 >1.7 ng/dL
c p<0.05 vs. female
TSH: thyroid-stimulating hormone

Figure 1. Prevalence of cognitive dysfunction in different age groups by gender, including subclinical and overt thyroid dysfunction. The percentage of cases with cognitive dysfunction is shown in the parentheses below each bar. ■, with cognitive dysfunction; □, without cognitive dysfunction

(IFCC) in the elderly (≥60s) may be 7.7 mIU/L for men and 8.2 mIU/L for women when restricted to subjects without cognitive impairment. Regarding the lower limit, the difference was not very large between subjects with and without cognitive impairment.

To investigate the relationship between thyroid hormone and cognitive impairment further, FT4 was divided into five fractions. Although there was a difference in the distribution range between genders, the quartile values were the same: Q1 1.1 ng/dL, Q2 1.2 ng/dL, Q3 1.4 ng/dL. Given that the lower limit of the threshold in the ECLIA was 0.9 ng/dL, a total of 5 fractions [I, <0.9, II, 0.9 to <1.1, III, 1.1 to 1.2, IV, >1.2 to 1.4, V, >1.4 of FT4 (ng/dL)] were chosen to compare the incidence of cognitive impairment. Fig. 3 shows the prevalence of cognitive impairment in each age group of each fraction when FT4 was divided into the above five fractions. Overall, the rate of cognitive impairment, for both men and women, was the lowest at FT4 levels of 1.1 to 1.2 ng/dL. In contrast, the rate of cognitive impairment was the highest at FT4 levels of <0.9 ng/dL for both men and women. No constant trend was noted in the relationship between the presence or absence of cognitive impairment and TSH values (data not shown).

Discussion

The Thyroid function of elderly subjects

In 2009, Takeda et al. (15) reported the distribution of anti-thyroid antibody and TSH, FT4 by gender in Japanese
**Figure 2.** Mean levels of thyroid hormones according to the cognitive function in different age groups by gender, excluding overt thyroid dysfunction. The solid and dotted lines (wire, men; thick, women) indicate the presence and absence of cognitive dysfunction, respectively. *Men, **women; p<0.05 between the groups with and without cognitive dysfunction in the indicated age group. TSH: thyroid-stimulating hormone, FT4: free thyroxine, FT3: free triiodothyronine

**Table 4.** Distribution of Thyroid Function by Sex.

| CI (-) | Total | Male (n) | Female (n) | Min 2.5 50 95 97.5 Max | Min 2.5 50 95 97.5 Max |
|--------|-------|----------|------------|--------------------------|--------------------------|
| CI (-) | TSH  | 502      | 131 198 149 24  | 0.2 0.5 0.7 2.3 7.5 9.2 23.5 | 0.1 0.5 0.7 2.2 6.8 8.6 24.0 |
|       | 60s  | 131      | 0.2 0.4 0.6 2.1 5.8 8.3 23.5 | 0.1 0.4 0.5 1.9 6.0 7.3 9.7 |
|       | 70s  | 198      | 0.2 0.5 0.6 2.2 7.3 7.8 15.0 | 0.3 0.6 0.7 2.0 6.3 8.0 14.2 |
|       | 80s  | 149      | 0.4 0.7 1.0 2.6 9.2 11.8 | 0.2 0.4 0.7 2.3 8.0 9.3 24.0 |
|       | ≥90s | 24       | 0.3 0.5 0.7 3.3 9.3 11.1 | 0.3 0.6 0.7 2.5 5.8 6.3 12.9 |
|       | FT4  | 501      | 130 198 149 24  | 0.4 0.8 0.9 1.2 1.6 1.6 2.9 | 0.3 0.7 0.8 1.2 1.6 1.8 2.5 |
|       | 60s  | 130      | 0.4 0.7 0.9 1.2 1.6 | 0.3 0.6 0.9 1.2 1.7 1.7 2.3 |
|       | 70s  | 198      | 0.5 0.9 0.9 1.2 1.6 | 0.5 0.8 0.8 1.2 1.6 1.7 2.0 |
|       | 80s  | 149      | 0.5 0.7 0.8 1.2 | 0.4 0.7 0.8 1.2 1.7 | 1.2 2.0 2.5 |
|       | ≥90s | 24       | 0.9 0.9 0.9 1.2 | 1.5 1.6 1.6 8.1 0.9 0.9 1.0 | 1.3 1.8 1.9 2.0 |
|       | FT3  | 433      | 117 171 123 8  | 0.8 1.2 1.4 2.5 3.2 3.3 3.8 470 | 0.6 1.0 1.2 2.4 3.1 3.3 5.7 |
|       | 60s  | 117      | 0.8 1.6 1.7 | 3.3 3.6 | 82 0.9 1.1 1.7 2.7 | 3.2 3.5 4.2 |
|       | 70s  | 171      | 0.9 1.5 1.7 | 2.6 3.3 3.5 3.8 144 | 0.8 1.2 1.4 2.6 3.1 3.3 4.2 |
|       | 80s  | 123      | 0.9 1.1 1.2 | 2.3 2.9 | 3.1 173 0.6 1.0 1.1 2.3 | 3.0 3.3 5.7 |
|       | ≥90s | 22       | 0.9 0.9 0.9 | 1.8 2.7 2.8 | 2.9 71 0.8 1.0 1.1 2.0 | 2.7 2.8 2.8 |
| CI (-) | TSH  | 291      | 94 134 55 8  | 0.3 0.7 0.9 1.2 1.6 1.6 1.9 286 | 0.3 0.8 0.9 1.2 1.6 1.9 2.3 |
|       | 60s  | 94       | 0.3 0.4 0.6 | 2.0 4.9 5.3 | 23.5 79 0.9 0.4 0.4 | 1.9 6.0 7.6 9.7 |
|       | 70s  | 134      | 0.3 0.5 0.6 | 2.1 7.1 | 7.7 9.2 117 0.3 0.6 0.8 | 2.1 5.7 8.5 14.2 |
|       | 80s  | 55       | 0.4 0.7 0.7 | 2.7 6.3 | 6.5 12.4 73 0.4 0.5 0.6 | 2.5 6.3 8.5 10.8 |
|       | ≥90s | 8        | 0.3 0.4 | 0.5 12.0 | 12.6 13.3 19 0.3 0.4 0.6 | 1.3 4.8 4.9 5.1 |
|       | FT4  | 290      | 93 134 55 8  | 0.5 0.9 | 0.9 1.2 1.6 1.6 | 1.9 286 0.3 0.8 0.9 1.2 1.6 1.9 2.3 |
|       | 60s  | 93       | 0.7 0.9 | 0.9 1.2 | 1.6 1.6 | 1.9 79 0.3 0.8 0.9 | 1.2 1.6 1.6 2.3 |
|       | 70s  | 134      | 0.9 0.9 | 0.9 1.2 | 1.6 1.7 | 1.8 115 0.7 0.8 0.9 | 1.2 1.6 1.8 2.0 |
|       | 80s  | 55       | 0.8 0.8 | 0.9 1.5 | 1.6 1.6 | 1.6 73 0.7 0.7 0.7 | 1.3 1.6 1.7 2.1 |
|       | ≥90s | 8        | 1.0 1.0 | 1.0 1.2 | 1.5 1.5 | 1.6 19 1.1 1.1 1.1 | 1.3 1.9 1.9 2.0 |
|       | FT3  | 266      | 87 125 47 7  | 0.8 1.4 | 1.7 2.7 | 3.2 3.3 | 3.8 250 0.9 1.1 1.4 2.6 3.2 3.4 4.2 |
|       | 60s  | 87       | 0.8 1.7 | 1.7 2.8 | 3.3 3.6 | 73 0.9 1.1 1.7 | 2.7 3.2 3.5 4.2 |
|       | 70s  | 125      | 0.9 1.7 | 1.9 2.6 | 3.1 3.2 | 3.8 95 1.0 1.4 1.7 | 2.6 3.2 3.4 4.2 |
|       | 80s  | 47       | 1.0 1.2 | 1.3 2.5 | 3.1 3.1 | 3.1 65 1.0 1.1 1.4 | 2.4 3.2 3.3 3.4 |
|       | ≥90s | 7        | 1.4 1.5 | 1.5 1.8 | 2.3 2.3 | 2.3 17 1.2 1.2 1.2 | 1.9 2.5 2.7 2.8 |

CI: cognitive impairment, TSH: thyroid-stimulating hormone, FT4: free thyroxine, FT3: free triiodothyronine
subjects in their 20s, 30s, 40s, 50s, 60s, and ≥70s. Using Smirnov-Grubbs’ outlier test (p<0.01), after values exceeding 3 standard deviations from the mean were excluded and the percentiles of FT4 and TSH were determined, the 2.5th, 50th, 97.5th, and mean values of FT4 for men were 1.07, 1.29, 1.63, and 1.31 for those in their 60s and 1.00, 1.29, 1.53, and 1.27 for those ≥70 years old, respectively, while those for women were 1.01, 1.22, 1.65, and 1.26 for those in their 60s and 1.05, 1.24, 1.46, and 1.24 for those ≥70 years old, respectively, and these values of TSH for both men and women were 0.57, 2.01, 4.75, and 2.25 for those in their 60s and 0.75, 2.17, 5.37, and 2.38 for those ≥70 years old, respectively. The ranges of both FT4 and TSH were narrower than our results for subjects in their 60s and 70s, possibly due to the varying target population as these were the subjects to get ‘Comprehensive Health Checkup System’. Although anti-thyroid antibody was positive in 12.8% of their subjects, they concluded that there was no marked influence on determining the cut-off values between the presence and absence of the anti-thyroid antibody.

In a nationwide US survey, the Third National Health and Nutrition Examination Survey (NHANES III) (16), the serum TSH level was evaluated after excluding those with thyroid disease or taking levothyroxine or anti-thyroid drugs. The survey was conducted among the elderly subjects in their 60s, 70s, and ≥80s. In the four categories analyzed, (non-Hispanic Caucasians, African-Americans, Mexican-Americans, and other races), TSH levels were higher in women than in men and increased with age. The TSH levels in non-Hispanic Caucasians, and Mexican-Americans were higher than those in African-Americans. Not only races but also environmental and dietary differences were considered to influence the level of TSH. A cohort in Scotland (17) included subjects ≥90 years old. The TSH level increased with age, especially for those ≥70 years old. In those ≥90 years old, the 2.5th, 50th, and 97.5th percentiles of TSH were 0.31, 1.86, and 5.94 mIU/L, respectively. The distribution of TSH in those ≥90 years old was wide, with lower values for the 2.5th percentile and higher values for the 97.5th percentile than in the other age groups.

Relationship between thyroid and cognitive impairment

The association between subclinical hypothyroidism and cognitive impairment remains unclear (1-7). A recent meta-analysis reported no association between subclinical hypothyroidism and the cognitive function, or dementia (18). This meta-analysis of observation studies yielded inconsistent results on associations of subclinical and overt thyroid dysfunction with cognitive impairment and risk of dementia (18). The authors remarked that while prior study-level meta-analyses also reported no association between subclinical hypothyroidism and the cognitive function, cognitive decline, or dementia, these were limited by heterogeneity in the definitions of thyroid dysfunction and choices of covariates in the statistical methods. Dementia is clinically difficult to diagnose, and some misclassification may have occurred, which may have led to an underestimation of the association. The heterogeneity between studies may have been increased using different cognitive function tests, differences in the age and sex distribution, and different inclusion criteria (18). Furthermore, few previously published reports have...
excluded the subjects taking thyroid hormones or antithyroid drugs. In the present study, we excluded these cases. Van Vliet et al. (18) did not support screening for the thyroid function in elderly patients with a cognitive decline. They did not find any association between the thyroid function and the cognitive function in elderly subjects when examined as a whole population. In other words, the subdivision of the population by gender, age, or background may make it possible to reveal such associations in some subgroup(s), as we were able to do to some degree in this study.

In our study, the thyroid function of the population without out cognitive impairment seemed to be slightly higher (lower TSH and higher FT4) than that with cognitive impairment, except for men in their 90s. Pasqualetti et al. (19) reported that a relationship between hypothyroidism and cognitive impairment only in individuals <75 years old and those with elevated TSH concentrations. No correlation was found on considering the study as a whole. The authors mentioned that the lack of utilization of age-related serum TSH reference ranges and the consequent potential misdiagnosis of subclinical hypothyroidism in older people may account for this finding. Similarly, the TSH level was also higher in subjects of both genders under 75 years old with cognitive impairment than in those without cognitive impairment according to our results (Fig. 2). Both results support the notion that it might be better to distinguish the super-aged group from the moderately-aged group. According to our results, cognitive impairment was more frequently observed in the subjects with FT4<0.9 ng/dL than in the other subjects. However, this does not necessarily mean that compensation needs to be initiated. Such cases must be managed carefully to avoid various risks including atrial fibrillation.

**Limitations**

Several limitations associated with the present study warrant mention. Because many of the subjects were patients visiting the geriatric hospital or the Department of Neurology, detailed examinations, such as anti-thyroid antibodies and thyroid echo, were not performed in all subjects. Furthermore, the subjects had varied and diverse backgrounds, including hypertension, hyperlipidemia, and chronic kidney disease.

**Conclusions**

Based on the current study, the upper limit of the reference range of TSH (IFCC) in the elderly (≥60s) may be higher (9.2 mIU/L for men; 8.6 mIU/L for women) than the current range for those under 60 years old (4.23 mIU/L). The upper limit of the reference range of TSH (IFCC) in the elderly (≥60s) may be 7.7 mIU/L for men and 8.2 mIU/L for women.

The authors state that they have no Conflict of Interest (COI).

**Financial Support**

This research was supported by Metabolic and Obese Research Fund.

**Acknowledgements**

We would like to show our appreciation to Prof. Masatomo Mori, Director of Metabolic and Obese Research Institute (Mae-bashi, Japan) for his support. We would like to thank Dr. Kana Yamamoto for recruiting the clinical patients.

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