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Possible Association Between Thyroid Nodule Formation and Developmental Alterations in the Pituitary–Thyroid Hormone Axis in Children and Adolescents: The Fukushima Health Management Survey

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Background: We previously found low thyrotropin (TSH) levels in children and adolescents with thyroid nodules, including papillary thyroid cancer, although it is generally accepted that high TSH levels are a risk factor for formation and growth of thyroid nodules in adults. To clarify the reasons for the discrepancy, we precisely analyzed the features of pituitary–thyroid hormone (TH) actions in children and adolescents with or without nodules at different ages.

Methods: Among the 4955 participants who participated in a second screening by thyroid ultrasound examination in the Fukushima Health Management Survey, 721 and 2849 euthyroid participants aged 6–20 years without or with nodules, including thyroid cancer, were selected for evaluation of TH regulation. The responsivity of TSH to THs was assessed by two thyroid feedback quantile-based indices (T4FQI and T3FQI). Logistic regression analyses were conducted to calculate the odds ratios (ORs) of serum concentrations related to thyroid functions for positive thyroid nodules compared with negative nodules.

Results: The feedback indices declined in a sex-specific manner with aging. In particular, T3FQI, the index for TSH response to free triiodothyronine (fT3), started to decline after $\sim$10 and 15 years of age in female and male participants, respectively. Compared with the absence of nodules, the age- and sex-adjusted ORs (confidence intervals) for logTSH, free thyroxine (fT4), fT3, T4FQI, T3FQI, and thyroglobulin levels were 0.586 (0.501–0.685), 1.036 (0.595–1.805), 1.059 (0.842–1.332), 0.569 (0.454–0.715), 0.564 (0.443–0.719), and 1.01 (1.005–1.014), respectively. Associations between the presence of nodules and either low logTSH or low feedback indices were observed in participants aged between 12 and 17 years among the total cohort.

Conclusions: The relationships between the levels of TSH and THs changed in a sex-dependent manner in children and adolescents. The age-dependent shift in the pituitary–TH set point may be associated with age-dependent nodule formation during restricted periods of growth and maturation in both young female and male participants.

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Introduction

Negative feedback mechanisms for thyrotropin (TSH) and thyroid hormones (THs) contribute to the homeostasis of TH regulation.[1] There are apparent negative relationships between the levels of TSH and free triiodothyronine (fT3) and the levels of TSH and free thyroxine (fT4) in clinical and pathological findings.[1] Physiologically, the set points of fT3 and fT4 to TSH are determined individually, suggesting that each individual has a unique thyroid function.[2] There is no doubt that THs are essential and play pivotal roles in growth and development during childhood.[3] Numerous studies have provided reference ranges for serum fT3, fT4, and TSH in children.[4] Recent epidemiological findings have produced evidence that the levels also differ between boys and girls, probably because of puberty.[5–10] Overall, the majority of previous studies support the notion that the levels of TSH, fT3, and fT4 change according to age and sex during growth in childhood.

Several indices have been proposed for assessment of TH negative feedback mechanisms using the relationship between serum concentrations of THs and TSH.[11–13] The thyroid feedback quantile-based index (TFQI) was demonstrated to act as a marker for thyroid responsivity and shown to be correlated with insulin resistance in diabetes patients, all-cause mortality in the general population, and metabolic abnormalities in participants with subclinical hypothyroidism.[14–16] It has been proposed that the feedback systems for the pituitary–thyroid axis may develop during growth from infancy to adulthood, and show chronological and sequential changes. Nevertheless, this hypothesis has not been assessed during the periods for childhood and adolescence.

The Fukushima Health Management Survey was started after the Fukushima Daiichi Nuclear power plant accident. One of the main projects in the survey, the thyroid ultrasound examination (TUE) program, was started in October 2011 and was planned to be repeated every two or five years.[17] Currently, the fifth-round examination is underway. Thyroid nodules of ≥5.1 mm were mainly screened in the first screening. In the second screening, serum thyroid function tests and confirmatory ultrasound examination were performed. Previously, we found a relationship between TH function and ultrasonographic findings in second-screening participants with TUE in the first-round survey, set as the preliminary baseline survey.[18] The study revealed that the levels of TSH were suppressed in patients with nodules, although it is generally accepted that high TSH levels are a risk factor for the growth of thyroid nodules and cancer in adults.[19]

In the present study, we initially focused on the physiological and sequential changes in the response of TSH to THs using the provided sensitivity indices in euthyroid children and adolescents without thyroid nodules from the perspective of sex differences. We next precisely analyzed the features of pituitary-TH actions in children and adolescents with or without nodules at different ages to clarify the reasons for the discrepancy between the low TSH levels in participants with nodules in our previous study and the risk factor of TSH for thyroid nodules reported generally.

Participants and Methods

Study participants

The participants were the ~360,000 children who lived or were staying in the Fukushima Prefecture at the time of the accident and were aged 18 years or younger on March 11, 2011.[20] A flowchart for the selection of study participants is shown in Figure 1. Data were obtained for participants who received the second confirmatory examinations in the first-, second-, and third-round survey of TUEs. Among the total 6025 subjects recommended for a second confirmatory screening, 5035 individuals were fully examined to reach a final diagnosis based on thyroid ultrasonography findings and blood test results. We noted that 825 (16.4%) participants underwent the examinations twice and 123 (2.4%) participants underwent the examinations three times because of repeated recommendations for a second screening. From the above participants, 734 subjects were excluded because of positive antithyroglobulin autoantibodies (TgAb: ≤28.0 IU/mL) and/or positive anti-thyroperoxidase (TPO) antibodies (TPOAb: ≤16.0 IU/mL).

A further 83 participants were excluded because of apparent thyroid function abnormalities, such as TSH, fT3, or fT4 levels beyond the mean ± 3SD (logTSH <–1.94 [TSH: 0.144 mU/L] and logTSH >2.16 [TSH: 8.547 mU/L]; fT3 < 1.52 and >5.59; fT4 < 0.53 and >1.94 ng/dL). Thus, totally 817 participants were excluded because of abnormal thyroid function tests. Among the participants who underwent the confirmatory screening, 648 participants aged <6 or >20 years were excluded. After the confirmatory ultrasound examination, the ultrasonography findings were reassessed and recategorized. Retrospectively, participants with intrathyroidal thymus, lymph nodes, ultrasound artifacts, and aberrant vessels were prone to misdiagnosis at the time of the first screening. Fine needle aspiration cytology was performed in the participants with nodules based on the defined criteria.[21]

In our previous study, we categorized the subjects into four groups as follows: group 1, participants without cysts and nodules; group 2, participants with cysts; group 3, participants with nodules; and group 4, participants with papillary thyroid cancer.[18] The characteristics of the participants in the four groups are shown in Supplementary Table S1. The logTSH values were lower in the participants with nodules including thyroid cancer (groups 3 and 4) than in the participants without nodules (groups 1 and 2) in our previous study as well as in the present study.

We combined groups 1 and 2 as category 1 and groups 3 and 4 as category 2 in the present study. In total, 721 and 2849 participants were eventually diagnosed as euthyroid without nodules in category 1 and with nodules in category 2, respectively. The sex-specific features of the thyroid functions in the participants with and without nodules and their numbers at different ages are shown in Table 1 and Supplementary Table S2, respectively.

Measurements of serum THs, TSH, and Tg

fT3, fT4, and TSH levels were measured by electrochemiluminescence immunoassay using ECLusys fT3 (reference range:

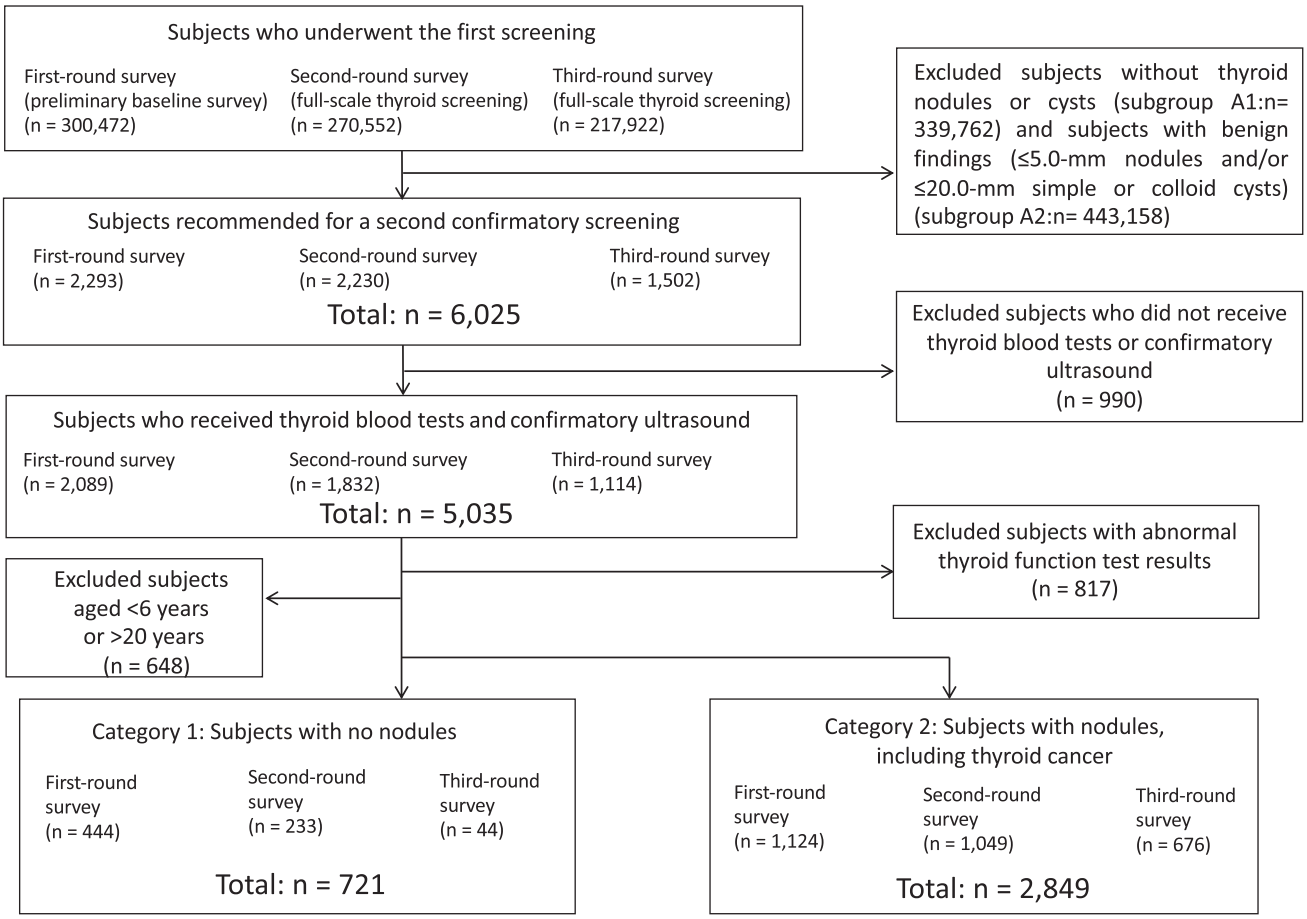

FIG. 1. Flowchart of subject selection. A total of 6025 subjects were tentative cases with nodules >5.0 mm and/or cysts >20.0 mm after the first screening in the first-, second-, and third-round surveys. Of these, 5035 subjects received either thyroid blood tests or confirmatory thyroid ultrasound examination. A total of 817 subjects were excluded for apparent thyroid function abnormalities, such as positive anti-TgAbs (TgAb: ≤28.0 IU/mL) and/or positive anti-TPO antibodies (TPOAb: ≤16.0 IU/mL) in addition to TSH, fT3, or fT4 levels beyond the mean ± 3SD (logTSH <−1.94 [TSH: 0.144 mU/L] and logTSH >2.16 [TSH: 8.547 mU/L]; fT3: <1.52 and >5.59 pg/mL; fT4: <0.53 and >1.94 ng/dL). After exclusion of 648 subjects aged younger than 6 years or older than 20 years, we selected a total of 721 subjects without nodules for category 1 and 2849 subjects with nodules for category 2. fT3, free triiodothyronine; fT4, free thyroxine; TgAb, thyroglobulin autoantibodies; TPO, thyroperoxidase; TSH, thyrotropin.

2.13–4.07 pg/mL), fT4 (reference range: 0.95–1.74 ng/dL), TSH (reference range: 0.340–3.880 mIU/mL), and Tg (reference range: <27.8 ng/mL) (Roche Diagnostics GmbH, Mannheim, Germany). The interassay coefficients of variation for the fT3, fT4, TSH, and Tg assays were 4.0%, 6.0%, 4.0%, and 4.5%, respectively.

Organization of resistance to TH indices

The TFQI was first provided by Laclaustra et al.[14] Briefly, the order positions of THs and TSH within a population are individually converted to a quantile between 0 and 1, taking sampling weights into account. The conversion is achieved by applying the population empirical cumulative distribution function (cdf) to the hormone concentrations. We conventionally denoted cdfTH and cdfTSH. We then expressed the conventional feedback index (Fconv) as: Fconv = cdfTH + cdfTSH

This index ranged from 0 to 2 as previously described for the resistance index to THs.[13] Lower values indicate lower TSH (higher inhibition by TH) than expected for the actual TH (meaning higher sensitivity to TH), while higher values indicate higher TSH (lower inhibition by TH) than expected for the actual TH (meaning lower sensitivity to TH). The mean ± SD values for each hormone were fT3: 3.5268 ± 0.48541, fT4: 1.2285 ± 0.16158, and logTSH: 0.13121681 ± 0.593685. We applied into the standard normal cdf and established indices for not only fT4 to TSH (T4FQI) but also fT3 to TSH (T3FQI) as shown below:

$T3FQI = cdffT3 + cdfTSH = \Phi((fT3 - \mu_{fT3})/\sigma_{fT3}) + \Phi((\log TSH - \mu_{logTSH})/\sigma_{logTSH})$, and

$T4FQI = cdffT4 + cdfTSH = \Phi((fT4 - \mu_{fT4})/\sigma_{fT4}) + \Phi((\log TSH - \mu_{logTSH})/\sigma_{logTSH})$,

where $\mu_{fT3} = 3.5268$, $\sigma_{fT3} = 0.48541$, $\mu_{fT4} = 1.2285$, $\sigma_{fT4} = 0.16158$, $\mu_{logTSH} = 0.13121681$, and $\sigma_{logTSH} = 0.593685$ for the study population. Scatter plots between logTSH and fT4 and between logTSH and fT3 are shown in Supplementary Figure S1.

Statistical analysis

The nonparametric Spearman's correlation matrix coefficient was estimated between the series of thyroid function

Table 1. Comparison of Various Thyroid-Associated Serum Parameters and Spearman's Coefficient Between Each Parameter and Age in the Participants Without and With Nodules of Each Sex

	Female						*Male*					
	Nodule(−)			*Nodule(+)*			*Nodule(-)*			*Nodule(+)*		
n	412			1838			309			1011		
Age (years old)	14.8 ± 3.7[a]			16.1 ± 2.8			14.6 ± 3.7			16.1 ± 3.0		
BMI (kg/m^2)[b]	20.2 ± 3.7			20.6 ± 3.2			20.7 ± 4.4			21.0 ± 3.6		
	Mean ± SD	r[c]	p[d]	*Mean ± SD*	r	p	*Mean ± SD*	r	p	*Mean ± SD*	r	p
logTSH[e]	0.21 ± 0.57	−0.246	<0.001	0.01 ± 0.57	−0.073	0.002	0.39 ± 0.53	−0.421	<0.001	0.18 ± 0.54	−0.139	<0.001
fT3 (pg/mL)	3.46 ± 0.47	−0.664	<0.001	3.37 ± 0.41	−0.468	<0.001	3.99 ± 0.41	−0.550	<0.001	3.88 ± 0.41	−0.426	<0.001
fT4 (ng/dL)	1.21 ± 0.13	−0.176	<0.001	1.19 ± 0.14	−0.067	0.004	1.27 ± 0.15	0.164	0.004	1.30 ± 0.17	0.142	<0.001
Tg (ng/mL)	19.9 ± 26.3	−0.151	0.002	31.0 ± 77.9	0.003	0.892	18.6 ± 13.2	−0.233	<0.001	29.7 ± 80.1	−0.111	<0.001
T3FQI	0.97 ± 0.43	−0.580	<0.001	0.83 ± 0.39	−0.344	<0.001	1.39 ± 0.37	−0.579	<0.001	1.24 ± 0.36	−0.361	<0.001
T4FQI	1.00 ± 0.36	−0.308	<0.001	0.87 ± 0.37	−0.098	<0.001	1.19 ± 0.36	−0.186	<0.001	1.14 ± 0.38	0.001	0.980

[a]Mean ± SD.

[b]BMI data were missing in 19 cases. Three, six, three, and seven BMIs were excluded from the calculations of mean ± SD values in female nodule(−), female nodule(+), male nodule(−), and male nodule(+), respectively.

[c]Spearman's coefficient between age and indicated thyroid function levels.

[d]*p*-Value for Spearman's coefficient.

[e]Natural logarithm.

BMI, body mass index; fT3, free triiodothyronine; fT4, free thyroxine; SD, standard deviation; TSH, thyrotropin; Tg, thyroglobulin; T3FQI, T3 feedback quantile-based index; T4FQI, T4 feedback quantile-based index.

tests and age. The levels of logTSH, fT3, and fT4 at different ages were compared between male and female participants using Student's *t*-test. All probability values for statistical tests were two-tailed, and *p*-values <0.05 were considered statistically significant. Odds ratios (ORs) and confidence intervals [CIs] of positive thyroid nodules for sex, age, and markers of thyroid function were calculated using logistic regression models. Body mass index (BMI) data were missing in 19 cases. Consequently, three, six, three, and seven BMIs were excluded from the calculations of mean ± SD values in female participants without nodules, female participants with nodules, male participants without nodules, and male participants with nodules, respectively. The same BMIs were also excluded in the logistic analyses. SPSS version 28 (SPSS, Inc., Chicago, IL) was used for statistical analyses.

Ethics

The survey was approved by the Ethics Review Committee of Fukushima Medical University (No. 1318). Written informed consent was obtained from the participants or the parents of the surveyed participants. The raw data used to create the tables and figures in the present study are unavailable due to a restriction outlined in the informed consent agreement.

Results

Characterization of mean ± SE values for logTSH, fT4, fT3, T4FQI, T3FQI, and Tg in female and male participants at different ages in category 1

Although the mean values did not change linearly, a negative relationship between age and logTSH was observed in both female and male participants (Fig. 2a). In particular, at ages above 14 and 16 years, prominent decreases were observed in female and male participants, respectively. The mean level of logTSH was significantly higher in male participants than in female participants at 10, 11, 15, and 16 years of age. Regarding the relationship between age and fT4, there were no apparent changes except for a slight increase in male participants aged older than 16 years (Fig. 2b). In contrast to the fluctuating changes in logTSH and fT4, prominent smooth suppression of fT3 was observed in both sexes at ages between 10 and 20 years (Fig. 2c). Apparently higher levels of fT3 were observed in male participants during the same period.

A negative relationship was observed between the levels of T4FQI and age in both female and male participants, but clear sex differences were not observed except at 9 and 10 years of age and from 15 to 18 years of age (Fig. 2d). As shown in

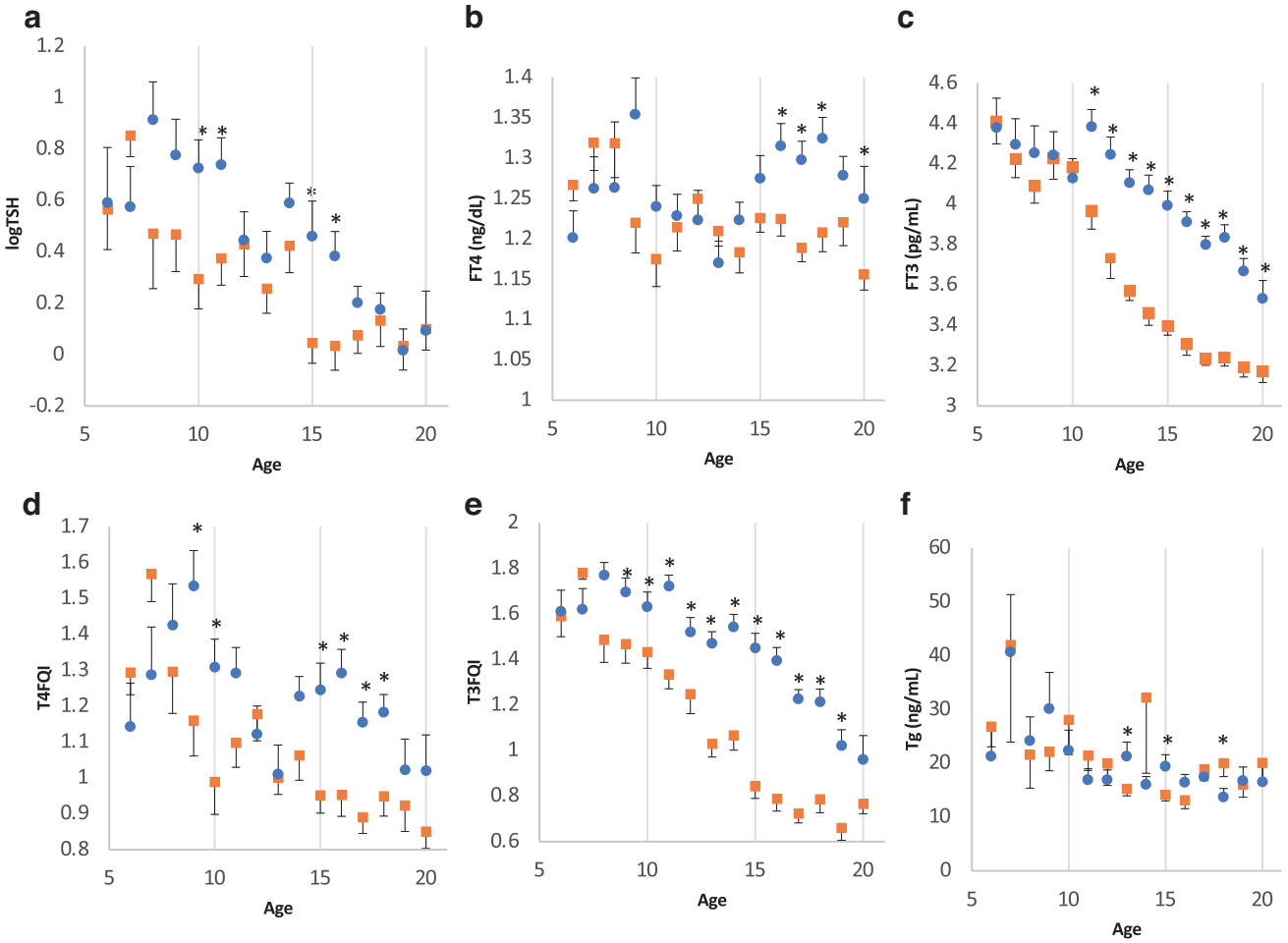

FIG. 2. Relationships between age and logTSH (**a**), fT4 (**b**), fT3 (**c**), T4FQI (**d**), T3FQI (**e**), and Tg (**f**) in male and female subjects. Squares and circles represent female and male subjects, respectively. Data are shown as mean ± SE. Asterisks denote significant differences between subjects at the same age. T4FQI, T4 feedback quantile-based index.

Figure 2e, there was a prominent feature of an age-dependent decline in the levels of T3FQI in both female and male participants. In female participants, the levels sharply decreased until 17 years of age, following a gradual decrease below 10 years of age. After 17 years of age, the levels plateaued. In male participants, a gradual decrease in the levels was observed below 14 years of age. The levels then rapidly decreased until 20 years of age. The levels of T3FQI in male participants were significantly higher than those in female participants between 11 and 19 years of age.

There were also significant differences in the Tg levels at 13, 15, and 18 years of age in female and male participants. As shown by the Spearman coefficients in Table 1, negative relationships between age and thyroid function levels such as logTSH, fT4, fT3, T4FQI, T3FQI, and Tg were observed in both female and male participants, except for a positive relationship between age and fT4 in male participants ($r = 0.164$, $p = 0.004$), as shown in Table 1.

Characterization of mean ± SE values of logTSH, fT4, fT3, T4FQI, T3FQI, and Tg in female and male participants at different ages in categories 1 and 2

In female participants, there were similar trends that logTSH was suppressed among participants with or without nodules and fT3 and fT4 were unchanged in both groups, in addition to T4FQI and T3FQI being suppressed from ~12 to 16 years of age (Fig. 3a–e). In male participants with nodules, the logTSH levels were suppressed at 8, 11, 14, and 15 years of age compared with those in participants without nodules, while the fT4 and fT3 levels remained unchanged except for the fT3 level at 7 years of age (Fig. 4a–c). T4FQI and T3FQI showed a tendency to be suppressed in the presence of nodules in participants younger than 17 years (Fig. 4d, e).

Although the Tg levels in the presence of nodules were high in both female and male participants older than 9 years except for female participants at 14 years of age, there were no significant differences in the levels between participants with and without nodules for both sexes (Figs. 3f and 4f).

To clarify whether the thyroid markers significantly affected the presence of nodules, we conducted logistic regression analyses to calculate ORs and CIs of positive thyroid nodules for sex, age, BMI, and markers of thyroid function (Table 2). Lower logTSH, T4FQI, and T3FQI and higher Tg independently increased the prevalence of nodules after correction by age, sex, and BMI. For more precise analyses, logistic analyses were performed in different age groups. There were no significant correlations with individual thyroid markers in the age groups of 6–8 and 9–11 years. In the age groups of 12–14 and 15–17 years, increases in logTSH,

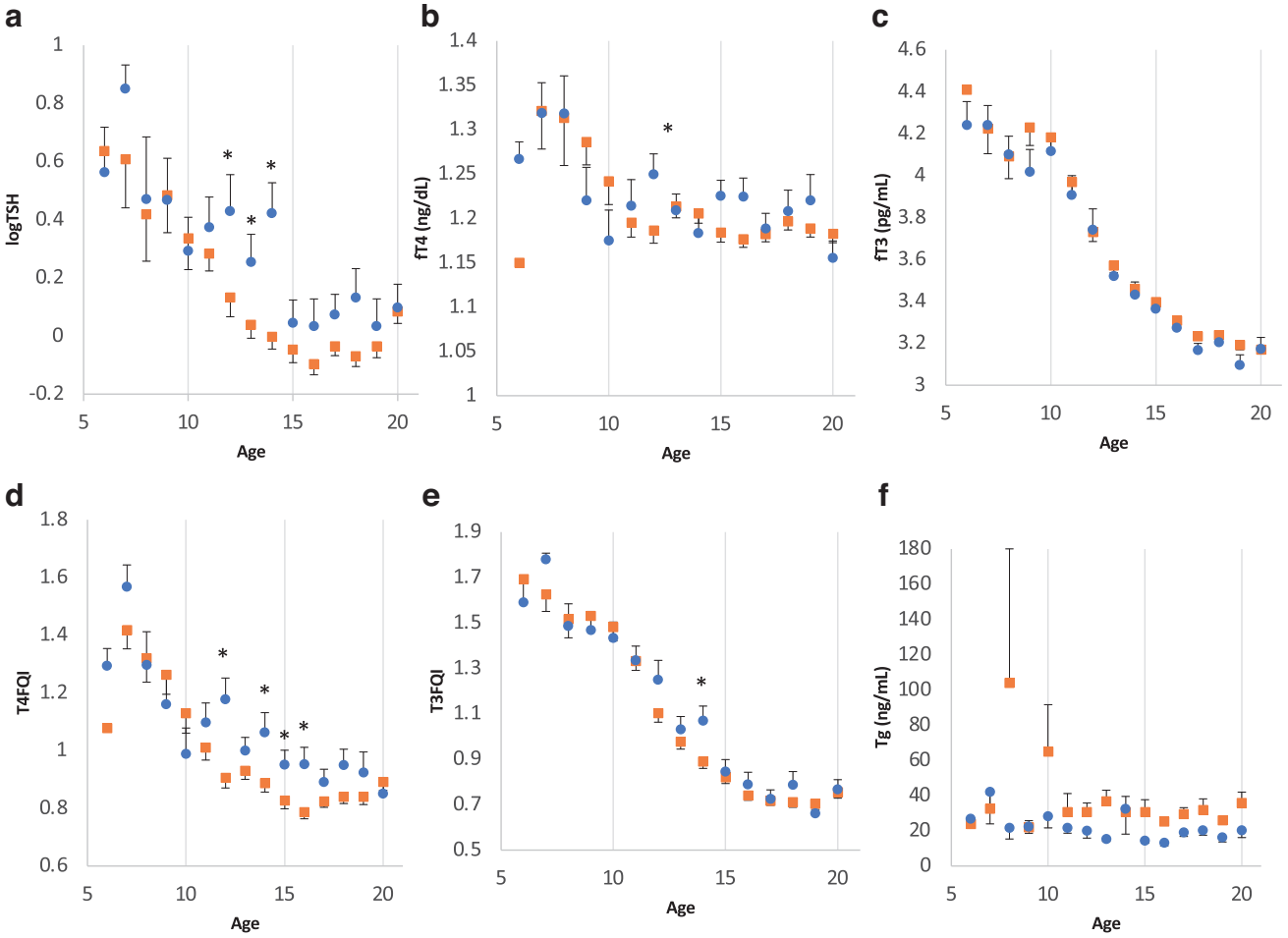

FIG. 3. Relationships between age and logTSH (**a**), fT4 (**b**), fT3 (**c**), T4FQI (**d**), T3FQI (**e**), and Tg (**f**) in female subjects. Squares and circles represent the subjects with and without nodules, respectively. Data are shown as mean ± SE. Asterisks denote significant differences between subjects at the same age.

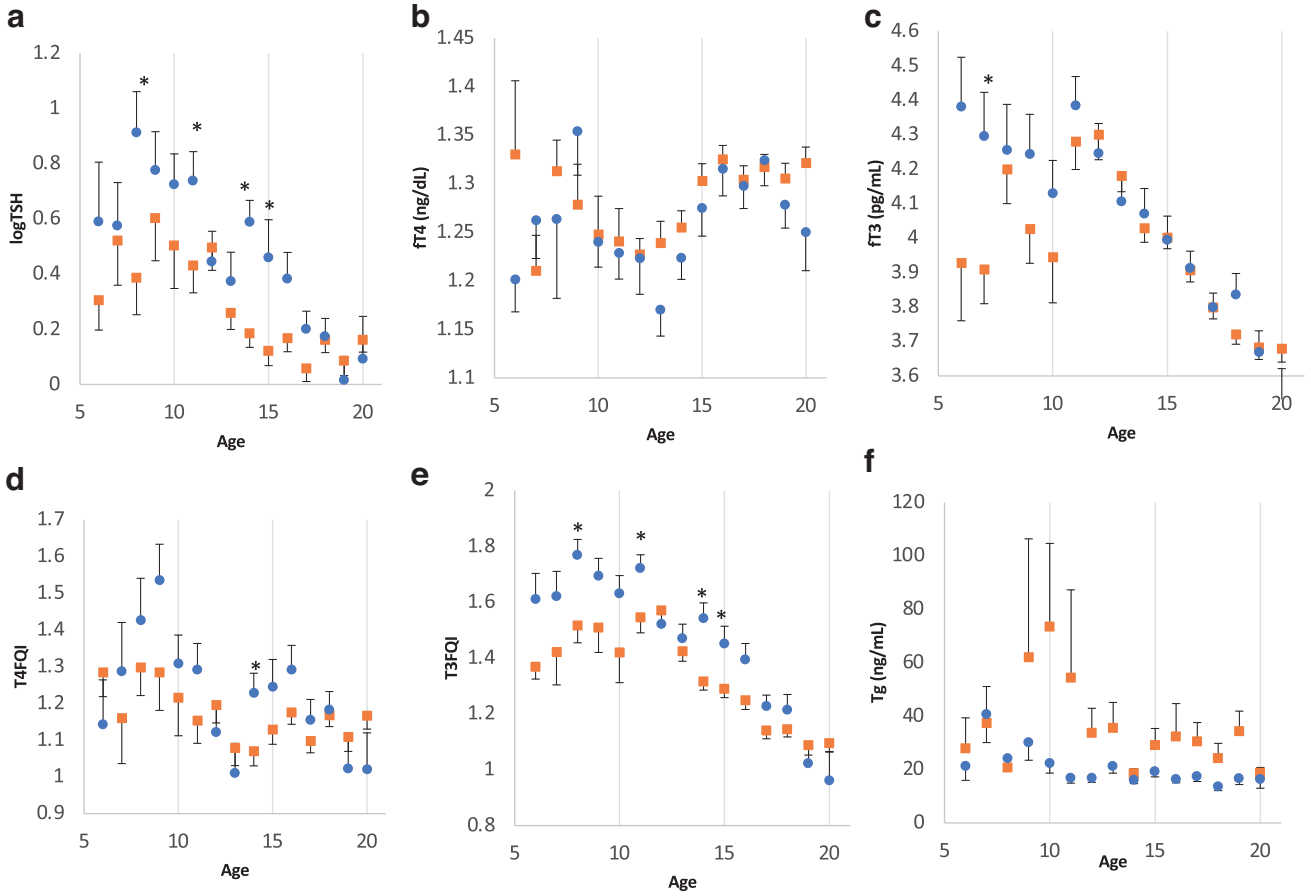

FIG. 4. Relationships between age and logTSH (**a**), fT4 (**b**), fT3 (**c**), T4FQI (**d**), T3FQI (**e**), and Tg (**f**) in male subjects. Squares and circles represent the subjects with and without nodules, respectively. Data are shown as mean ± SE. Asterisks denote significant differences between subjects at the same age.

T4FQI, and T3FQI had lower ORs for the presence of nodules. These trends were not observed in the age group of 18–20 years. An increase in Tg had a higher OR for the presence of nodules in the age groups of 15–17 and 18–20 years.

Discussion

The initial purpose of the present study was to determine the chronological features of pituitary-TH regulation in children and adolescents from the perspective of sex. Among the previous studies on reference ranges for fT3, fT4, and TSH in the period including puberty, fewer than 20 studies had >700 participants.[6,7,8,22–35] Of these, approximately two-thirds of the recent articles demonstrated evidence for sex differences in fT3, fT4, and TSH levels during adolescence.[4,7,8,19,24,29,33–36] In general, TSH and fT3 levels in male participants were higher than those in female participants, while the differences in fT4 levels were small or controversial during childhood and adolescence.[4,5,7,24,32,33,35]

In the present study, the level of logTSH decreased and plateaued at 16 years of age in female participants and 19 years of age in male participants. The level of fT4 fluctuated and was not associated with age in male participants, while gradual suppression was observed in female participants. The overall dispersion in the levels of fT3 was small compared with that in the levels of TSH and fT4. The fT3 levels fluctuated until 10 years of age and then decreased. The levels in female participants rapidly decreased and reached a plateau at ∼17 years of age, while the levels in male participants were gradually suppressed until 20 years of age.

Taken together, and similar to previous reports, TSH and fT3 levels were dominantly higher in male participants and decreased in an age-dependent manner. The degree of the sex difference in fT4 levels at the same age was not prominent compared with that in TSH and fT3 levels.

Several confounding factors for the levels of TSH, fT4, and fT3 were demonstrated in previous studies, including age, sex, ethnicity, puberty, BMI, circadian rhythm, and season.[4,36] TSH and THs such as fT3 and fT4 also affect one another as confounding factors, given the apparent negative relationships between the levels of TSH and fT3 and the levels of TSH and fT4 in clinical and pathological findings.[1] To assess the responsivity of TSH to THs, several sensitivity (resistance) indices have been proposed.[11–16] Among them, the TFQI was uniquely created for population-based statistical analysis applied with cdf. The original TFQI was calculated with TSH and fT4 because of the negative relationship between these two hormones. An additional index involving fT3 and TSH, namely T3FQI, was provided in the present study.

Table 2. Odds Ratio and Confidence Intervals of Nodules for Age, Sex, Body Mass Index, and the Indicated Thyroid Marker

logTSH	*Odds ratio*	*[CI]*	p	*fT4*	*Odds ratio*	*[CI]*	p	*fT3*	*Odds ratio*	*[CI]*	p
Total				Total				Total			
Sex (male)	0.820	[0.690–0.975]	0.025	Sex (male)	0.745	[0.625–0.889]	0.001	Sex (male)	0.728	[0.594–0.893]	0.002
Age, 1 year	1.125	[1.094–1.158]	<0.001	Age, 1 year	1.150	[1.118–1.182]	<0.001	Age, 1 year	1.155	[1.117–1.193]	<0.001
BMI (kg/m^2)	0.985	[0.961–1.010]	0.228	BMI (kg/m^2)	0.982	[0.958–1.007]	0.163	BMI (kg/m^2)	0.982	[0.958–1.007]	0.161
logTSH	0.589	[0.503–0.689]	<0.001	fT4 (1 ng/dL)	1.060	[0.607–1.850]	0.837	fT3 (1 pg/mL)	1.058	[0.841–1.332]	0.630
Total				Total				Total			
Sex (male)	0.816	[0.687–0.970]	0.021	Sex (male)	0.742	[0.622–0.884]	<0.001	Sex (male)	0.723	[0.590–0.886]]	0.002
Age, 1 year	1.120	[1.091–1.150]	<0.001	Age, 1 year	1.143	[1.115–1.173]	<0.001	Age, 1 year	1.148	[1.114–1.184]	<0.001
logTSH	0.586	[0.501–0.685]	<0.001	fT4 (1 ng/dL)	1.036	[0.595–1.805]	0.900	fT3 (1 pg/mL)	1.059	[0.842–1.332]	0.624
6–8 years				6–8 years				6–8 years			
Sex (male)	1.946	[0.844–4.488]	0.118	Sex (male)	1.981	[0.856–4.587]	0.111	Sex (male)	1.932	[0.832–4.488]	0.126
Age, 1 year	1.829	[1.063–3.147]	0.029	Age, 1 year	1.819	[1.054–3.141]	0.032	Age, 1 year	1.775	[1.025–3.073]	0.041
logTSH	0.525	[0.224–1.230]	0.138	fT4 (1 ng/dL)	1.308	[0.047–36.147]	0.874	fT3 (1 pg/mL)	0.277	[0.077–1.002]	0.050
9–11 years				9–11 years				9–11 years			
Sex (male)	0.546	[0.314–0.948]	0.032	Sex (male)	0.472	[0.275–0.811]	0.007	Sex (male)	0.492	[0.286–0.845]	0.010
Age, 1 year	1.106	[0.794–1.540]	0.530	Age, 1 year	1.168	[0.836–1.632]	0.364	Age, 1 year	1.139	[0.820–1.580]	0.438
logTSH	0.616	[0.358–1.062]	0.081	fT4 (1 ng/dL)	2.076	[0.275–15.683]	0.479	fT3 (1 pg/mL)	0.898	[0.468–1.721]	0.745
12–14 years				12–14 years				12–14 years			
Sex (male)	0.742	[0.515–1.070]	0.110	Sex (male)	0.614	[0.430–0.877]	0.007	Sex (male)	0.564	[0.361–0.880]	0.012
Age, 1 year	1.158	[0.925–1.451]	0.201	Age, 1 year	1.233	[0.989–1.537]	0.063	Age, 1 year	1.264	[1.006–1.588]	0.045
logTSH	0.402	[0.286–0.565]	<0.001	fT4 (1 ng/dL)	1.632	[0.488–5.462]	0.427	fT3 (1 pg/mL)	1.186	[0.747–1.883]	0.469
15–17 years				15–17 years				15–17 years			
Sex (male)	0.906	[0.669–1.226]	0.521	Sex (male)	0.886	[0.644–1.221]	0.461	Sex (male)	0.691	[0.462–1.034]]	0.073
Age, 1 year	0.985	[0.823–1.179]	0.871	Age, 1 year	0.992	[0.830–1.187]	0.933	Age, 1 year	1.021	[0.850–1.227]	0.824
logTSH	0.608	[0.465–0.794]	<0.001	fT4 (1 ng/dL)	0.561	[0.216–1.457]	0.235	fT3 (1 pg/mL)	1.349	[0.850–2.140]	0.204
18–20 years				18–20 years				18–20 years			
Sex (male)	0.802	[0.583–1.103]	0.175	Sex (male)	0.751	[0.535–1.055]	0.099	Sex (male)	0.738	[0.498–1.093]	0.129
Age, 1 year	1.049	[0.869–1.268]	0.617	Age, 1 year	1.047	[0.866–1.265]	0.637	Age, 1 year	1.049	[0.867–1.268]	0.625
logTSH	0.837	[0.627–1.117]	0.227	fT4 (1 ng/dL)	1.425	[0.510–3.978]	0.499	fT3 (1 pg/mL)	1.129	[0.707–1.804]	0.611

T4FQI	*Odds ratio*	*[CI]*	p	*T3FQI*	*Odds ratio*	*[CI]*	p	*Tg*	*Odds ratio*	*[CI]*	p
Total				Total				Total			
Sex (male)	0.853	[0.714–1.021]	0.083	Sex (male)	0.934	[0.769–1.134]	0.490	Sex (male)	0.757	[0.638–0.898]	0.001
Age, 1 year	1.136	[1.104–1.168]	<0.001	Age, 1 year	1.110	[1.076–1.145]	<0.001	Age, 1 year	1.156	[1.124–1.189]	<0.001
BMI (kg/m^2)	0.986	[0.962–1.011]	0.259	BMI (kg/m^2)	0.985	[0.961–1.009]	0.215	BMI (kg/m^2)	0.985	[0.960–1.010]	0.227
T4FQI	0.576	[0.458–0.724]	<0.001	T3FQI	0.567	[0.444–0.723]	<0.001	Tg (1 ng/mL)	1.010	[1.005–1.014]	<0.001
Total				Total				Total			
Sex (male)	0.851	[0.713–1.017]	0.077	Sex (male)	0.930	[0.766–1.128]	0.460	Sex (male)	0.753	[0.635–0.892]	0.001
Age, 1 year	1.131	[1.102–1.160]	<0.001	Age, 1 year	1.104	[1.073–1.137]	<0.001	Age, 1 year	1.151	[1.122–1.181]	<0.001
T4FQI	0.569	[0.454–0.715]	<0.001	T3FQI	0.564	[0.443–0.719]	<0.001	Tg (1 ng/mL)	1.010	[1.005–1.014]	<0.001

(*continued*)

Table 2. (Continued)

T4FQI	*Odds ratio*	*[CI]*	p	*T3FQI*	*Odds ratio*	*[CI]*	p	*Tg*	*Odds ratio*	*[CI]*	p
6–8 years				6–8 years				6–8 years			
Sex (male)	1.858	[0.804–4.291]	0.147	Sex (male)	1.867	[0.803–4.340]	0.147	Sex (male)	2.027	[0.883–4.653]	0.096
Age, 1 year	1.875	[1.091–3.223]	0.023	Age, 1 year	1.830	[1.061–3.157]	0.03	Age, 1 year	1.801	[1.048–3.095]	0.033
T4FQI	0.584	[0.156–2.187]	0.425	T3FQI	0.206	[0.042–1.005]	0.051	Tg (1 ng/mL)	1.004	[0.995–1.013]	0.401
9–11 years				9–11 years				9–11 years			
Sex (male)	0.522	[0.300–0.906]	0.021	Sex (male)	0.554	[0.318–0.968]	0.038	Sex (male)	0.464	[0.270–0.797]	0.005
Age, 1 year	1.100	[0.787–1.538]	0.577	Age, 1 year	1.104	[0.793–1.538]	0.556	Age, 1 year	1.169	[0.840–1.628]	0.354
T4FQI	0.657	[0.293–1.472]	0.307	T3FQI	0.453	[0.179–1.142]	0.093	Tg (1 ng/mL)	1.008	[0.998–1.017]	0.119
12–14 years				12–14 years				12–14 years			
Sex (male)	0.710	[0.493–1.024]	0.067	Sex (male)	0.934	[0.616–1.415]	0.747	Sex (male)	0.63	[0.442–0.900]	0.011
Age, 1 year	1.219	[0.977–1.522]	0.080	Age, 1 year	1.128	[0.899–1.415]	0.298	Age, 1 year	1.26	[1.010–1.572]	0.040
T4FQI	0.448	[0.273–0.734]	0.001	T3FQI	0.383	[0.226–0.650]	<0.001	Tg (1 ng/mL)	1.007	[1.000–1.015]	0.060
15–17 years				15–17 years				15–17 years			
Sex (male)	1.054	[0.763–1.457]	0.749	Sex (male)	1.070	[0.745–1.538]	0.713	Sex (male)	0.832	[0.617–1.121]	0.226
Age, 1 year	0.983	[0.821–1.176]	0.848	Age, 1 year	0.960	[0.801–1.151]	0.659	Age, 1 year	0.996	[0.832–1.193]	0.967
T4FQI	0.461	[0.310–0.686]	<0.001	T3FQI	0.583	[0.380–0.897]	0.014	Tg (1 ng/mL)	1.016	[1.006–1.027]	0.002
18–20 years				18–20 years				18–20 years			
Sex (male)	0.797	[0.569–1.117]	0.188	Sex (male)	0.813	[0.566–1.167]	0.261	Sex (male)	0.826	[0.600–1.137]	0.241
Age, 1 year	1.044	[0.864–1.261]	0.657	Age, 1 year	1.043	[0.863–1.260]	0.664	Age, 1 year	1.034	[0.855–1.249]	0.732
T4FQI	0.940	[0.621–1.422]	0.769	T3FQI	0.910	[0.579–1.429]	0.682	Tg (1 ng/mL)	1.014	[1.004–1.025]	0.007

CI, confidence interval.

As shown in Figure 2d, the T4FQI exhibited gradual suppression in the age groups examined. The levels in male participants were sequentially higher than those in female participants between 9 and 10 years of age and between 15 and 18 years of age. Meanwhile, the levels of T3FQI changed in an age- and sex-dependent manner (Fig. 2e). The levels started to become suppressed after 7 years of age in female participants and 10 years of age in male participants. After 10 years of age, significant differences between male and female participants were observed until 20 years of age.

Recent findings showed that TSH levels gradually became suppressed with the progression of puberty.[5] The fT4 levels decreased and then increased with progression through the Tanner stages, while the fT3 levels in female and male participants started to decline in stages 3 and 4, respectively. Considering that female participants experience puberty earlier than male participants, two phases of male-dominant T4FQI are plausible and the sequential changes in T3FQI may also be associated with puberty phases.

As shown in Figures 3 and 4 and Table 2, logTSH, T4FQI, and T3FQI levels were suppressed in the participants with nodules, especially between 12 and 17 years of age. This suppression was not observed in participants aged younger than 12 years or older than 17 years. Taken together, the pituitary-TH axis may be developing in participants who develop thyroid nodules during specific periods such as puberty. The reverse scenario is also possible, namely that thyroid nodules develop in participants who are developing the pituitary-TH axis during specific periods in childhood and adolescence. Although TSH is well known to stimulate nodule formation and accelerate nodule growth in adults, TSH may not be the cause of nodule formation in children and adolescents.[19]

The present study has some limitations. First, the study had a cross-sectional design. Second, the participants were selected from the participants recommended for second screening of thyroid nodules, suggesting that some selection bias was present even though the participants did not have thyroid nodules.

In conclusion, the levels of fT3, fT4, and TSH changed in an age- and sex-dependent manner. The set point of TSH to fT3 may have changed, probably due to puberty or sexual development. Inappropriate suppression of TSH in participants with nodules was observed in limited periods for the development of the pituitary-TH axis such as puberty. The present results may lead to better understanding of the relationship between nodule formation and development of the pituitary-TH axis in children and adolescents.

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Disclaimer

The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the Fukushima Prefecture government.

Appendix

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Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Figure S1
Supplementary Table S1
Supplementary Table S2

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