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Original Article

Adiposity rebound and body mass index in Japanese patients with congenital hypothyroidism

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Highlights

- Adiposity rebound in Japanese patients with CH did not occur early.
- The BMI of adolescents with CH was similar to that of the general population.
- Pre-treatment thyroid functions do not affect adiposity rebound.

Abstract. The long-term prognosis of congenital hypothyroidism (CH) has become apparent since the introduction of newborn screening programs; however, the risk of obesity in patients with CH remains unclear. Early adiposity rebound (AR) is one of the predictors of obesity in adults. This study evaluated AR and the adolescent body mass index (BMI) in Japanese patients with CH. We longitudinally collected anthropometric measurements from 288 patients aged 1–10 yr and plotted their BMI curves to determine the age at onset of AR. We also evaluated the effects of thyroid function, presence of distal femoral epiphysis (DFE) ossification, and disease type on AR age and adolescent BMI. The mean AR ages were determined to be 5.5 ± 1.4 yr in boys and 5.9 ± 1.5 yr in girls. There were no significant differences in AR age or adolescent BMI according to thyroid-stimulating hormone or free T4 levels before treatment initiation or according to disease type. However, at the last visit, more than half of the boys without DFE ossification had higher BMI SD scores than those with DFE ossification. These findings raise the possibility that severe prolonged fetal hypothyroidism may have a lasting influence after birth despite early treatment initiation.

Key words: congenital hypothyroidism, adiposity rebound, obesity, newborn screening, distal femoral epiphysis

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Introduction

Newborn screening (NBS) for congenital hypothyroidism (CH) was introduced in Japan in 1979 aimed at preventing neurodevelopmental delays and growth retardation in patients with CH through early diagnosis and treatment. With the introduction of NBS, intellectual and height prognoses were reported to have significantly improved and become comparable to those of the general population (1–4). However, the effects of CH on adult weight remain unclear. Previous studies have reported that the prevalence of obesity and overweight in adults with CH, detected by NBS, is comparable to that in the general population (3, 4), whereas others have reported a higher frequency of obesity in patients with CH (5, 6).

Adiposity rebound (AR) is a phenomenon characterized by a decrease in body mass index (BMI) after the age of 1 yr, followed by a subsequent increase from approximately 5–6 yr of age (7). Early AR is associated with obesity, glucose intolerance, lipid abnormalities, and cardiovascular risk in adulthood (8–14). By examining AR, it may be possible to predict adult obesity without long-term follow-up. Some studies have reported an earlier AR age in patients with CH than in the general population in Taiwan and the UK (15, 16). The mean AR age in Japanese patients with CH remains unknown, and no previous reports have examined the effects of CH severity and disease type on AR age and adolescent obesity in patients with CH in detail. We hypothesized that even with NBS, AR occurs earlier in Japanese patients with CH than in the general population, and that AR occurs earlier in those with more severe hypothyroidism.

In this study, we aimed to calculate the AR age and adolescent BMI in Japanese patients with CH detected by NBS and to examine the effects of thyroid function before the initiation of treatment, disease type, and presence of distal femoral epiphysis (DFE) ossification at the first visit, on AR age and adolescent BMI.

Materials and Methods

Patients

We recruited Japanese patients with primary hypothyroidism detected by NBS, aged >10 yr as of September 2022, who were treated with levothyroxine sodium (LT4) at one of the four hospitals (Hokkaido University Hospital, Sapporo Medical University Hospital, Niigata University Medical & Dental Hospital, and Tokyo Metropolitan Children's Medical Center). Pediatric endocrinologists at each facility adjusted the LT4 dose to maintain thyroid-stimulating hormone (TSH) levels within age-specific reference ranges. We excluded patients (i) with birth weight < 2,000 g, (ii) with malformation syndromes, (iii) with other diseases affecting growth, (iv) taking other hormone replacement therapies, (v) with central hypothyroidism, (vi) with incomplete data, (vii) with AR unconfirmed by 10 yr of age, and (viii) those judged inappropriate for participation in the study. Patients with AR unconfirmed by 10 yr of age were defined as those whose BMI had plateaued without a clear increase, those whose BMI increased continuously after 1 yr of age, and those whose BMI continued to decrease until 10 yr of age.

Evaluation of adiposity rebound (AR)

We retrospectively collected anthropometric measurements from the medical records of the patients between 1 yr 0 mo and 10 yr 11 mo of age at each visit, at least once per year. The median number of data collection encounters per participant was 23 (interquartile range: 18–34). BMI was calculated from the obtained data as weight in kilograms divided by height in meters squared (kg/m^2). The BMI curve was plotted by Kernel smoothing using JMP® version 16.0.0. (SAS Institute Inc., Cary, NC, USA). AR was defined as the lowest point on the curve.

Thyroid function and CH disease type

We collected thyroid function data from medical records during NBS and at the first visit. We categorized our cases by TSH (< 15 μIU/mL, 15–30 μIU/mL, and ≥ 30 μIU/mL), free thyroxine (FT4) (< 0.8 ng/mL, 0.8–1.2 ng/mL, and ≥ 1.2 ng/mL), and a visible or invisible ossification of DFE assessed by X-ray radiography at the first visit. BMI standard deviation scores (SDSs) were calculated as described by Kato *et al.* (17). We compared the BMIs of patients with available data between 15 and 18 yr of age with those of the general population from the 2019 National Health and Nutrition Survey (18). Patients were classified according to their disease type: dysgenesis, dyshormonogenesis, undiagnosed, or transient. Patients diagnosed with hypogenesis, agenesis, hemiagenesis, or ectopic thyroid gland using ultrasonography or thyroid scintigraphy were classified as having dysgenesis. Radioactive iodine uptake and perchlorate discharge tests were performed on patients without dysgenesis. Those with abnormal iodide uptake, positive perchlorate discharge test results, goiter, or abnormal serum thyroglobulin levels were categorized as having dyshormonogenesis. Finally, we classified patients without apparent abnormalities in their disease type diagnoses or those who had not been evaluated as undiagnosed. Patients who discontinued LT4 treatment before the final evaluation were categorized as transient.

Statistical analysis

Regression analysis was performed to examine the correlation between age at AR onset and BMI between 15 and 18 yr. Confidence intervals (CIs) were calculated based on Student's *t*-test distributions to compare the BMIs of patients aged 15–18 yr with those of the general population aged 15–19 yr (18). We also compared the

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95% CIs related to age at AR and BMI between 15 and 18 yr according to CH severity or disease type. The statistical analysis was performed using JMP® Ver.16 (SAS Institute, Cary, NC). All confidence coefficients were set at 0.95, and the multiplicity was not adjusted because this study intended to generate a hypothesis.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Hokkaido University Hospital (approval no. 020-0289; approval date 2021/01/18). We did not use patient tissue samples in this study and some patients had already completed their medical visits. Therefore, we adopted an opt-out consent approach. Detailed information concerning this study was announced on the Hokkaido University Hospital website, offering patients or their guardians the opportunity to opt out. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry (date, 2022/09/20; ID: UMIN000048971).

Results

Of the 354 patients with CH, we excluded one due to birth weight < 2,000 g, four due to malformation syndrome, one due to scoliosis, forty-five due to insufficient data (including thirteen patients without weight data during the neonatal period), and fifteen due to the absence of apparent AR by the age of 10 yr (including eight patients with plateaued BMI without significant increases, one patient with continuous BMI increase after 1 yr of age, and six patients with continuous BMI decrease until 10 yr of age). Consequently, 288 patients were included in this study (Supplementary Fig. 1). **Table 1** summarizes their characteristics. Of the 288 patients, 152 were boys. Based on TSH levels at the first visit (Median 21.8 [IQR 12.4, 60.2] μIU/mL), 92/268 patients (34.3%) had levels below 15 μIU/mL, 68/268 patients (25.4%) had levels between 15 and 30 μIU/mL, and 108/268 patients (40.3%) had levels 30 μIU/mL or higher. In addition, regarding FT4 levels, 13/263 patients (4.9%) had levels below 0.4 ng/mL, 32/263 patients (12.2%) had levels between 0.4 and 0.8 ng/mL, 68/263 (25.8%) had levels between 0.8 and 1.2 ng/mL, and 150/263 patients (57.0%) had levels 1.2 ng/mL or higher (**Fig. 1**). Of the 215 patients evaluated for DFE ossification at the first visit, 12 (5.6%) did not display ossification (8 boys and 4 girls). In terms of disease type, 56 (19.4%), 38 (13.2%), 115 (39.9%), and 79 (27.4%) patients were classified into the dysgenesis, dyshormonogenesis, transient, and undiagnosed groups, respectively. Among the 79 patients classified as transient, 10 were initially diagnosed with mild dysgenesis and 9 with dishormonogenesis. However, they eventually discontinued LT4 treatment and were classified as transient.

The mean AR ages were 5.5 ± 1.4 for boys and 5.9 ± 1.5 yr for girls. The mean BMI-SDS trends between 1 and 10 yr of age are shown in **Fig. 2**. The mean BMI-SDS of all ages for both sexes remained within ±1 SD. We evaluated 151 patients (80 boys and 71 girls) with BMIs between 15 and 18 yr. Among these patients with calculable height SDS, the average values were 0.01 ± 0.95 for boys (n = 45) and –0.15 ± 1.05 for girls (n = 42). There were no patients whose height SDS was greater than 2.5 SD or less than –2.5 SD. The mean BMIs were 21.1 ± 3.2 kg/m^2 (95% CI: 20.4, 21.8) for boys and 20.5 ± 2.5 kg/m^2 (95% CI: 19.9, 21.1) for girls, which was not significantly different from those of the general population (boys: 21.1 ± 3.6 kg/m^2; girls: 20.2 ± 2.2 kg/m^2; mean difference [95% CI], boys: 0.0 [–0.7, 0.7]; girls: 0.3 [–0.3, 0.9]) (18). Age at AR inversely correlated with BMI between 15 and 18 yr (r = –0.4630, p < 0.0001; Supplementary Fig. 2).

Age at AR and BMI between 15 and 18 yr are shown in **Figs. 3 and 4** according to TSH and FT4 levels at NBS and at the first visit, disease type, and DFE ossification

Table 1. Participant characteristics

Sex	Boys : Girls	152 : 136	(n = 288)
NBS	TSH (μIU/mL blood)	Median 17.5 [11.9, 34.3]	(n = 272)
	FT4 (ng/dL)	1.6 ± 0.6	(n = 134)
The first visit	Age (d)	23.2 ± 10.2	(n = 266)
	TSH (μIU/mL)	Median 21.8 [12.4, 60.2]	(n = 268)
	FT4 (ng/dL)	1.2 ± 0.4	(n = 261)
Absence of DFE ossification at the first visit		12 / 215	(5.6%)
Disease type diagnosis	Dysgenesis	56 / 288	(19.4%)
	Dyshormonogenesis	38 / 288	(13.2%)
	Transient	115 / 288	(39.9%)
	Undiagnosed	79 / 288	(27.4%)

Data for Age and FT4 presented as means ± SD. Data for TSH presented as median [IQR]. Values outside the measurable sensitivity range were excluded from the mean value calculations. Data following the "absence of DFE ossification at the first visit" were expressed as the number of applicable persons. FT4, free thyroxine; TSH, thyroid-stimulating hormone; NBS, newborn screening; DFE, distal femoral epiphysis; SD, standard deviation.

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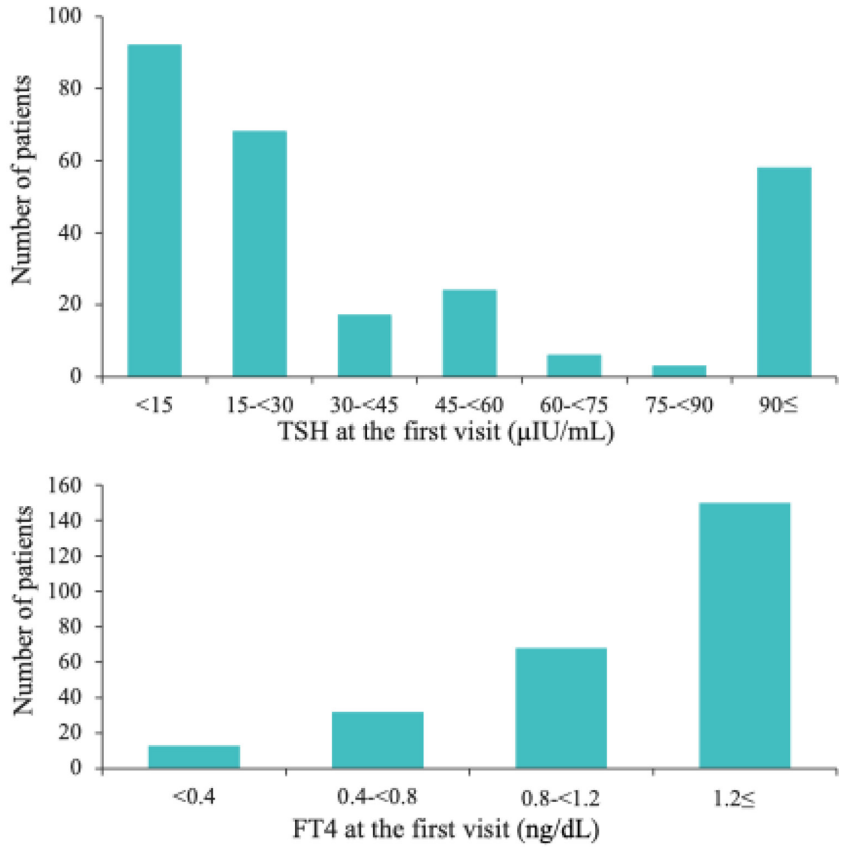

Fig. 1. Distribution of TSH and FT4 at the first visit. TSH, thyroid-stimulating hormone; FT4, free thyroxine.

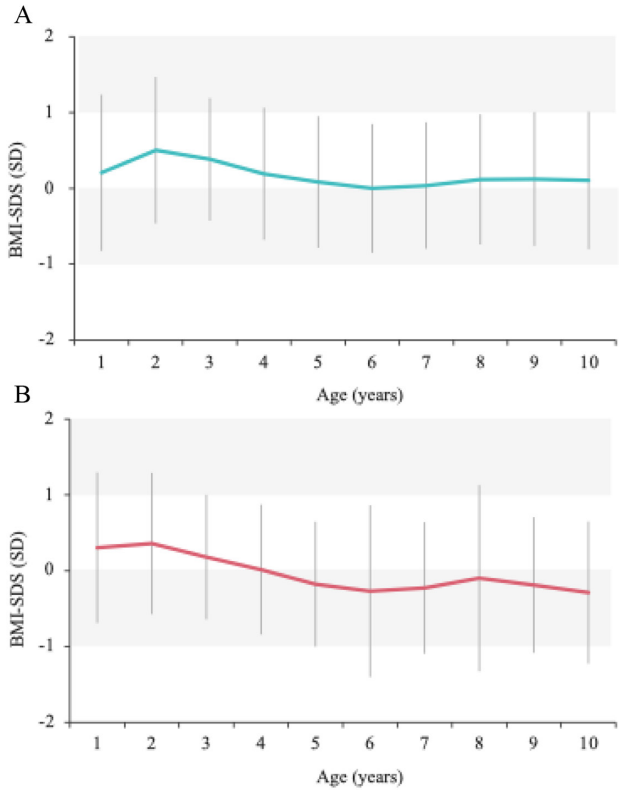

Fig. 2. Longitudinal BMI-SDS in (A) boys and (B) girls with CH. Error bars show ± 1SD. BMI, body mass index; CH, congenital hypothyroidism; SDS, standard deviation score.

at the first visit. There were no significant differences in age at AR or BMI between 15 and 18 yr according to TSH and FT4 levels at NBS and at the first visit, or disease type (**Figs. 3A–E**, **Figs. 4A–E**). Age at AR in patients without DFE ossification tended to be lower than that in patients with DFE ossification; however, this difference was not statistically significant (**Fig. 3F**). On the other hand, the BMI between 15 and 18 yr tended to be higher in the group without DFE ossification compared to the group with DFE ossification (**Fig. 4F**).

Individual BMI curves for CH without DFE ossification revealed that 5/8 boys had BMIs > 1 SD over the mean BMI for boys with DFE ossification at their last visit (**Fig. 5A**). However, these findings were absent in girls without DFE ossification, except for one patient (**Fig. 5B**).

Discussion

The long-term prognosis of adult obesity in patients with CH remains unclear. AR is considered one of the valuable predictors of obesity in adults. To the best of our knowledge, this is the first study to report the age at AR in Japanese patients with CH in Japan. Previous studies have indicated that prenatal and postnatal factors such as parental obesity, birth weight, gestational age, nutrition, and breastfeeding duration may all influence the timing of AR (19–23). In this study, we evaluated the effects of prenatal and neonatal thyroid function on age

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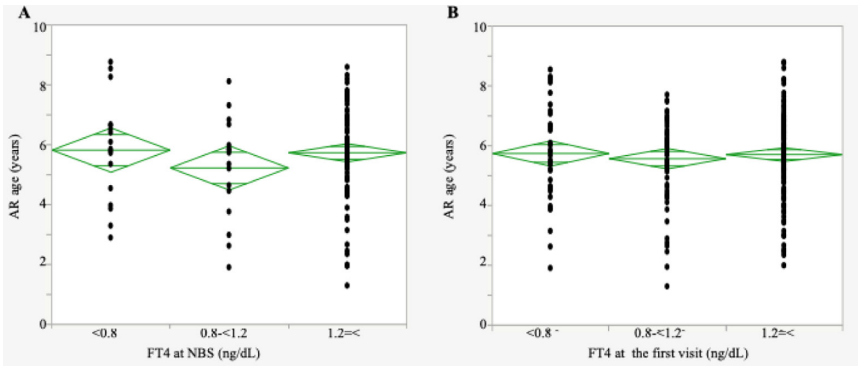
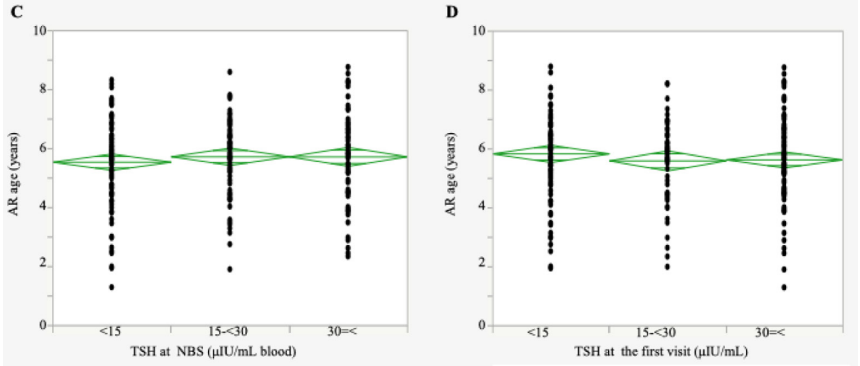


	n	Mean	SE	95% CI
<0.8	17	5.8	0.4	5.1, 6.6
0.8-<1.2	17	5.2	0.4	4.5, 6.0
1.2≦	101	5.7	0.2	5.4, 6.0

		Difference	SE	95%CI
<0.8	**0.8-<1.2**	0.6	0.5	-0.4, 1.6
1.2=<	**0.8-<1.2**	0.5	0.4	-0.3, 1.3
<0.8	**1.2=<**	0.1	0.4	-0.7, 0.9

	n	Mean	SE	95% CI
<0.8	45	5.7	0.2	5.3, 6.2
0.8-<1.2	68	5.6	0.2	5.2, 5.9
1.2=<	150	5.7	0.1	5.5, 5.9

		Difference	SE	95%CI
<0.8	**0.8-<1.2**	0.2	0.3	-0.4, 0.7
1.2=<	**0.8-<1.2**	0.1	0.2	-0.3, 0.6
<0.8	**1.2=<**	0.0	0.2	-0.4, 0.5

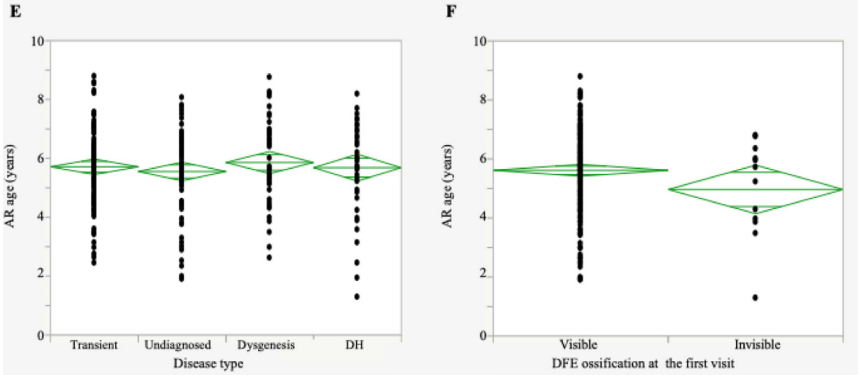


	n	Mean	SE	95% CI
<15	103	5.5	0.1	5.3, 5.8
15-<30	92	5.7	0.2	5.4, 6.0
30=<	77	5.7	0.2	5.4, 6.0

		Difference	SE	95%CI
15-<30	**<15**	0.2	0.2	-0.2, 0.6
30=<	**<15**	0.2	0.2	-0.2, 0.6
15-<30	**30=<**	0.0	0.2	-0.4, 0.4

	n	Mean	SE	95% CI
<15	92	5.8	0.2	5.5, 6.1
15-<30	68	5.6	0.2	5.3, 5.9
30=<	108	5.6	0.1	5.4, 5.9

		Difference	SE	95%CI
<15	**15-<30**	0.2	0.2	-0.2, 0.7
<15	**30=<**	0.2	0.2	-0.2, 0.6
30=<	**15-<30**	0.0	0.2	-0.4, 0.5



	n	Mean	SE	95% CI
Transient	115	5.7	0.1	5.5, 6.0
Undiagnosed	79	5.6	0.3	5.2, 5.9
Dysgenesis	56	5.9	0.2	5.5, 6.2
DH	38	5.7	0.2	5.2, 6.1

		Difference	SE	95%CI
Dysgenesis	**Undiagnosed**	0.3	0.3	-0.2, 0.8
Dysgenesis	**DH**	0.2	0.3	-0.4, 0.8
Transient	**Undiagnosed**	0.2	0.2	-0.3, 0.6
Dysgenesis	**Transient**	0.2	0.2	-0.3, 0.6
DH	**Undiagnosed**	0.1	0.3	-0.4, 0.7
Transient	**DH**	0.0	0.3	-0.5, 0.6

	n	Mean	SE	95% CI
Visible	203	5.6	0.1	5.4, 5.8
Invisible	12	5.0	0.4	4.1, 5.8

		Difference	SE	95%CI
Visible	**Invisible**	0.7	0.4	-0.2, 1.5

Fig. 3.

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Fig. 3. The age at AR by (A) FT4 at NBS, (B) FT4 at the first visit, (C) TSH at NBS, (D) TSH at the first visit, (E) Disease type, and (F) DFE ossification at the first visit. Green diamonds represent means and 95% CI; AR, adiposity rebound; NBS, newborn screening; FT4, free thyroxine; TSH, thyroid-stimulating hormone; DFE, distal femoral epiphysis; DH, dyshormonogenesis; CI, confidence interval; SE, standard error.

at AR. Because several patients exhibited outlier values or values exceeding the measurement sensitivity, we stratified them according to disease severity.

The mean AR ages were 5.5 ± 1.4 yr for boys and 5.9 ± 1.5 yr for girls. The data in this study were collected from three prefectures (Tokyo, Niigata, and Hokkaido) and no regional differences in age at AR were observed. Koyama *et al.* reported that the age at AR in Japanese children was 4.8 ± 1.4 yr for boys and 4.7 ± 1.5 yr for girls, respectively (11). Thus, we did not observe a significantly earlier AR in Japanese patients with CH than in the general population.

In contrast, several studies have reported that AR occurs earlier in patients with CH than in the general population (15, 16), suggesting that hypothyroidism is a risk factor for adult obesity. In those reports, patients with CH had higher mean pre-treatment TSH levels (Chen *et al.*: mean 259.8 μU/mL; Wong *et al.*: mean 162 μU/mL) than our patients (mean 79.4 μU/mL). We suspected that this difference is due to the predominance of mild hypothyroidism in our patient population. However, we found no significant differences in age at AR or adolescent BMI between 15 and 18 yr of age according to TSH and FT4 levels. Since TSH and FT4 levels at NBS and first visits do not necessarily reflect persistent hypothyroidism over prolonged fetal periods, this may explain why age at AR did not differ according to thyroid function levels. There were also no significant differences in age at AR based on disease type, possibly because the severity of hypothyroidism can vary widely even among patients with the same disease type.

In contrast, the BMI between 15 and 18 yr of age may be higher in patients without DFE ossification than in those with DFE ossification. In particular, when comparing individual BMI trends, boys without DFE ossification tended to have higher BMIs than those with DFE ossification. DFE typically ossifies by 35 wk of gestation, and delayed ossification is associated with severe persistent fetal hypothyroidism (24, 25). Some studies suggest that despite early initiation of LT4 treatment, motor and cognitive decline remain significant problems, especially in patients with severe CH and delayed bone maturation (26–30). These findings suggest that the postnatal consequences of severely prolonged prenatal hypothyroidism cannot be entirely avoided. In humans, there is limited evidence regarding the impact of persistent fetal hypothyroidism on adipose tissue and obesity after birth.

Harris *et al.* reported that sheep models undergoing in utero thyroidectomy had increased white adipose tissue and reduced expression of uncoupling protein 1, which is associated with thermogenesis in brown adipose tissues at birth (31, 32). It is unclear whether these effects persist after birth; however, an unfavorable intrauterine environment, such as maternal starvation or overnutrition, is known to cause childhood obesity (33–35). Thus, the effects of fetal hypothyroidism on adipose tissue may persist after birth. Further investigations are needed to provide evidence that severe fetal hypothyroidism affects adult obesity.

A higher BMI tendency was observed in patients without DFE than in those with DFE, particularly among boys relative to girls. Although the mechanism underlying this sex difference remains unclear, previous reports suggest that maternal thyroid dysfunction has a more substantial impact on birth weight in male newborns (36). This raises the possibility that fetal thyroid hormone deficiency may have a more pronounced effect in boys. However, further investigations are required because of the limited number of eligible patients in this study.

This study has several limitations that must be considered. First, the timing of AR can be influenced by multiple factors, including parental obesity, birth weight inconsistent with gestational age, and nutrition, which were not considered sufficiently in this study. Considering low birth weight for gestational age, among 274 patients whose birth weight SDS could be examined, only four patients (two boys and two girls) had birth weights below –2SD. Therefore, we believe that birth weight had little effect on the AR age in this study. Second, due to the absence of longitudinal thyroid function data after the initiation of LT4 treatment, we could not definitively confirm whether thyroid function was strictly controlled. However, given that the treatment was managed by pediatric endocrinologists, we assume that all patients in this study received optimal thyroid hormone replacement. Third, we did not evaluate age at AR in the general population using a similar method. Therefore, it was not possible to directly compare the age at AR in the general population with that in patients with CH in our study. However, both boys and girls aged 1–10 yr had a BMI within ± 1 SD, and there was no obvious tendency toward obesity. Consequently, it is reasonable to conclude that there is no significant difference in age at AR onset compared with that in the general population. Finally, assessing the statistical significance of the difference in adolescent BMI between patients with CH with and without DFE ossification was challenging because of the small number of patients without DFE ossification (three boys and one girl) included in this study (**Fig. 4F**).

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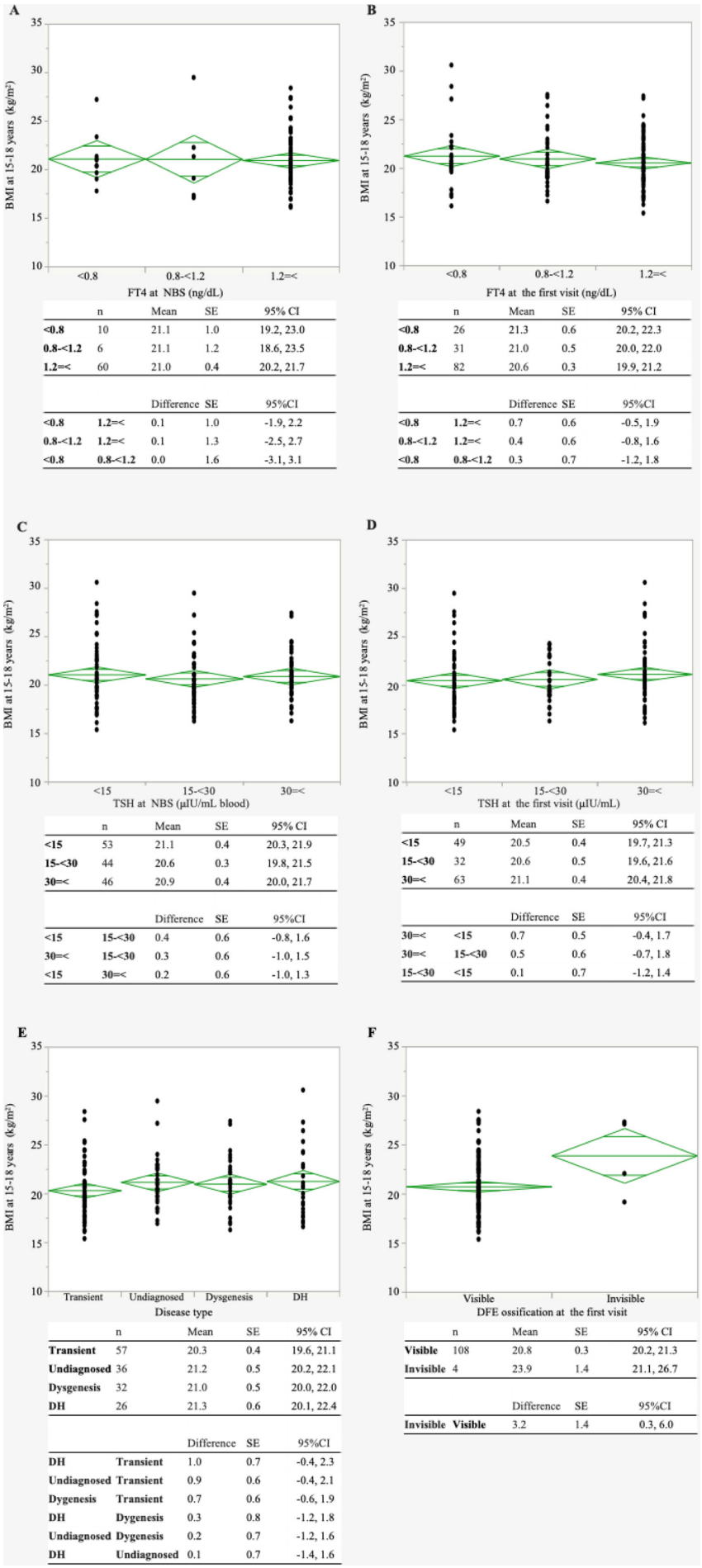

	n	Mean	SE	95% CI
<0.8	10	21.1	1.0	19.2, 23.0
0.8-<1.2	6	21.1	1.2	18.6, 23.5
1.2=<	60	21.0	0.4	20.2, 21.7

		Difference	SE	95%CI
<0.8	**1.2=<**	0.1	1.0	-1.9, 2.2
0.8-<1.2	**1.2=<**	0.1	1.3	-2.5, 2.7
<0.8	**0.8-<1.2**	0.0	1.6	-3.1, 3.1

	n	Mean	SE	95% CI
<0.8	26	21.3	0.6	20.2, 22.3
0.8-<1.2	31	21.0	0.5	20.0, 22.0
1.2=<	82	20.6	0.3	19.9, 21.2

		Difference	SE	95%CI
<0.8	**1.2=<**	0.7	0.6	-0.5, 1.9
0.8-<1.2	**1.2=<**	0.4	0.6	-0.8, 1.6
<0.8	**0.8-<1.2**	0.3	0.7	-1.2, 1.8

	n	Mean	SE	95% CI
<15	53	21.1	0.4	20.3, 21.9
15-<30	44	20.6	0.3	19.8, 21.5
30=<	46	20.9	0.4	20.0, 21.7

		Difference	SE	95%CI
<15	**15-<30**	0.4	0.6	-0.8, 1.6
30=<	**15-<30**	0.3	0.6	-1.0, 1.5
<15	**30=<**	0.2	0.6	-1.0, 1.3

	n	Mean	SE	95% CI
<15	49	20.5	0.4	19.7, 21.3
15-<30	32	20.6	0.5	19.6, 21.6
30=<	63	21.1	0.4	20.4, 21.8

		Difference	SE	95%CI
30=<	**<15**	0.7	0.5	-0.4, 1.7
30=<	**15-<30**	0.5	0.6	-0.7, 1.8
15-<30	**<15**	0.1	0.7	-1.2, 1.4

	n	Mean	SE	95% CI
Transient	57	20.3	0.4	19.6, 21.1
Undiagnosed	36	21.2	0.5	20.2, 22.1
Dysgenesis	32	21.0	0.5	20.0, 22.0
DH	26	21.3	0.6	20.1, 22.4

		Difference	SE	95%CI
DH	**Transient**	1.0	0.7	-0.4, 2.3
Undiagnosed	**Transient**	0.9	0.6	-0.4, 2.1
Dygenesis	**Transient**	0.7	0.6	-0.6, 1.9
DH	**Dygenesis**	0.3	0.8	-1.2, 1.8
Undiagnosed	**Dygenesis**	0.2	0.7	-1.2, 1.6
DH	**Undiagnosed**	0.1	0.7	-1.4, 1.6

	n	Mean	SE	95% CI
Visible	108	20.8	0.3	20.2, 21.3
Invisible	4	23.9	1.4	21.1, 26.7

		Difference	SE	95%CI
Invisible	**Visible**	3.2	1.4	0.3, 6.0

Fig. 4.

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Fig. 4. BMI at 15–18 yr by (A) FT4 at NBS, (B) FT4 at the first visit, (C) TSH at NBS, (D) TSH at the first visit, (E) Disease type, and (F) DFE ossification at the first visit. Green diamonds represent means and 95% CI; BMI, body mass index; NBS, newborn screening; FT4, free thyroxine; TSH, thyroid-stimulating hormone; DFE, distal femoral epiphysis; DH, dyshormonogenesis; CI, confidence interval; SE, standard error.

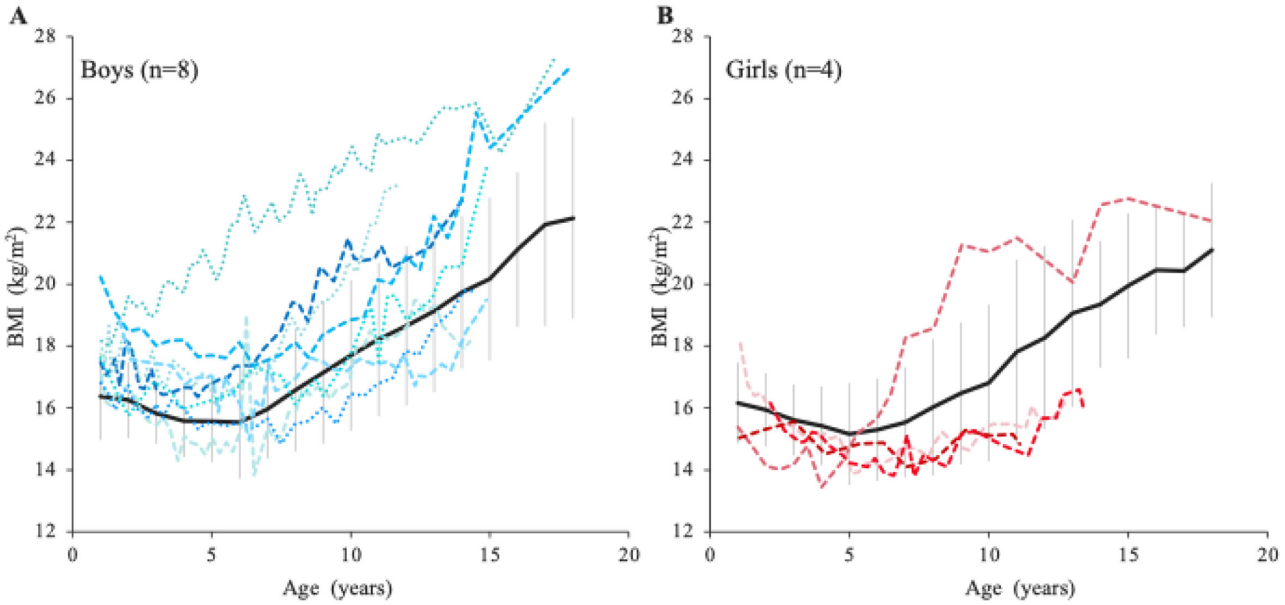

Fig. 5. BMI curves for (A) boys and (B) girls with CH. Error bars show ± 1SD. Dotted lines depict BMI of patients without DFE at the first visit. Solid line depict the mean BMI of patients with DFE at the first visit. BMI, body mass index; CH, congenital hypothyroidism; SD, standard deviation; DFE, distal femoral epiphysis.

Conclusion

AR in Japanese patients with CH does not occur early, and the adolescent BMI in this patient group is comparable to that of the general population.

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