Early growth hormone treatment accelerates delayed onset of puberty in patients with growth hormone deficiency

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Abstract. We investigated whether growth hormone (GH) treatment could accelerate the onset of puberty in patients with isolated GH deficiency (GHD). Of the 135 boys and 89 girls who started GH treatment before the onset of puberty and were followed up at Tanaka Growth Clinic, 83 boys and 51 girls who started GH treatment sufficiently earlier than the average age at onset of puberty of GHD patients (<10 years vs. 11.7 years for boys; <9.5 years vs. 11.4 years for girls) were analyzed. Age at onset of puberty significantly positively correlated to age at the start of GH treatment (boys: \( r = 0.427, p < 0.0001 \); girls: \( r = 0.302, p < 0.05 \)). When the subjects were divided into two groups each: for boys, Groups A (n = 45) and B (n = 39), treatment was started at age <8 and 8 to <10 years, respectively; for girls, Groups A (n = 26) and B (n = 21), treatment was started at age <7 and 7 to <9.5 years, respectively, age at the onset of puberty was significantly lower in Groups A than in Groups B by the Mann-Whitney \( U \) test (boys: \( p < 0.01 \); girls: \( p < 0.05 \)) and Kaplan-Meier log-rank test (boys: \( p < 0.01 \); girls: \( p < 0.05 \)). These results indicate that GH treatment accelerates the delayed onset of puberty in patients with GHD. Heights at the onset of puberty in Groups A and B were not significantly different, suggesting that early treatment does not increase adult height.

Key words: Growth hormone (GH) treatment, Growth hormone deficiency (GHD), Puberty

THE GROWTH HORMONE (GH) treatment in growth hormone deficiency (GHD) aims to resolve psychosocial issues due to short stature by helping the patient achieve a normal stature at an early stage and adapt to social life by achieving a normal adult stature. When GH treatment is started early, a good response to GH helps patients catch up to a normal height at an early stage [1]. Since adult height reportedly shows a strong positive correlation with height at the onset of puberty [2], the earlier the start of treatment, the greater the height at the onset of puberty and the greater the adult height, if GH does not affect the onset of puberty or if puberty starts at an age at which starting GH treatment early versus late makes no difference. Therefore, early diagnosis and treatment of GHD is recommended.

However, according to reports published after 2001, no improvement in adult height was observed despite an earlier starting age of treatment [3-6]. One reason is that the therapeutic dose of GH treatment in Japan is smaller than that in other countries. However, it is possible that since GH treatment accelerates the onset of puberty, the height at the onset of puberty may not increase and, accordingly, the adult height may not increase.

Pubertal onset in GHD patients is reportedly delayed compared with that in healthy children [7-9]. Regarding whether GH treatment accelerates puberty in GHD, no conclusion has been reached, although the age at the start of GH treatment is reportedly positively correlated with the age at onset of puberty [8, 10].

According to the preliminary analysis of data from the Foundation for Growth Science (FGS) in GHD [11], the onset of puberty was early in the group of patients who started treatment early and late in the group of patients who started treatment late, suggesting that GH treatment accelerates puberty. Thus, regardless of early versus late
start of GH treatment, no differences were noted in height at the onset of puberty or adult height. This study aimed to prove the hypothesis that early treatment might not lead to an improvement in adult height since GH treatment accelerates the delayed onset of puberty in GHD.

**Subjects and Methods**

This study included 135 boys and 89 girls who were diagnosed with idiopathic GHD by at least two GH provocation tests at the Tanaka Growth Clinic between 2007 and 2017, started GH treatment before puberty, and were followed up until the onset of puberty. The patient background factors are shown in Table 1.

Clinical factors at the start of treatment are shown in Table 2. All patients had isolated GHD and received no other hormone replacement therapies. The mean ages at the start of treatment were 8.9 years for boys and 8.9 years for girls, while the mean height SD scores at the start were –2.42 SD for boys and –2.58 SD for girls. GH treatment was provided by injection 7 times a week. Heights and body weights were measured every 3 months. Bone age assessments, blood tests, and urine tests were performed every 3 months within the first 1 year and every 6 months thereafter.

When puberty was suspected after the age of 10 years in boys and 8 years in girls, they were examined every 3 months. The definition of puberty was testicular volume ≥4 mL for boys and Tanner stage 2 breast development for girls, and luteinizing hormone (LH) ≥0.3 mIU/mL and a single physician (TT) made the assessment. The clinical factors at the onset of puberty are shown in Table 3. The mean ages and heights at the onset of puberty were 11.7 years and 135.1 cm for boys and 11.4 years and 133.8 cm for girls.

If GH treatment does not affect the onset of puberty, the age at the onset of puberty should be about the same. However, for patients who start therapy close to the average age of puberty, the duration of GH treatment is short, and it is impossible to evaluate whether it affects the onset of puberty. The relationship between GH treatment and onset of puberty cannot be evaluated in patients who start treatment after the mean age at the onset of puberty. Therefore, we selected patients who started GH treatment sooner than approximately –2 SD from the mean age.

### Table 1 Patients’ background factors

|                      | Boys (n = 135) | Girls (n = 89) |
|----------------------|---------------|---------------|
| n                    |               |               |
| Gestational weeks (weeks) | 124           | 84            |
| Birth weight (g)     | 124           | 85            |
| Birth weigh SDS (SD) | 124           | 85            |
| Birth length (cm)    | 123           | 81            |
| Birth length SDS (SD)| 123           | 81            |
| Height of father (cm)| 121           | 83            |
| Height of mother (cm)| 124           | 84            |

### Table 2 Clinical factors at start of GH treatment

|                      | Boys (n = 135) | Girls (n = 89) |
|----------------------|---------------|---------------|
| n                    |               |               |
| Age (years)          | 135           | 89            |
| Height (cm)          | 135           | 89            |
| Height SDS (SD)      | 135           | 89            |
| Body weight (kg)     | 133           | 88            |
| % overweight (%)     | 133           | 88            |
| Bone age (years)     | 122           | 82            |
| IGF-I (ng/mL)        | 119           | 81            |
| IGF-I SDS (SD)       | 119           | 81            |
| GH dose (mg/kg/week) | 123           | 85            |
age at the onset of puberty in these patients for the main and sub analyses, specifically those who started GH treatment at <10 years in boys and <9.5 years in girls. For the sub analysis, the selected patients were divided into two groups of nearly equal numbers and examined to assess whether there was a difference in age at the onset of puberty. In boys, Group A (n = 45), in which treatment was started at 2 to <8 years of age, and Group B (n = 39), in which treatment was started at 8 to <10 years, were defined. In girls, Group A (n = 26), in which treatment was started at 2 to <7 years of age, and Group B (n = 21), in which treatment was started at 7 to <9.5 years, were defined. Unselected patients for the main and sub analyses were defined as Group C, which included 51 boys who started treatment at 10 to <13 years and 42 girls who started treatment at 9.5 to <13 years.

In the main analysis, to examine the correlation between age at the start of GH treatment and age at the onset of puberty, Pearson’s correlation coefficient with Fisher’s Z-conversion of r was used, with the level of significance set at p < 0.05. In the sub analysis, the end-point was the difference in age at the onset of puberty for boys and girls in Groups A and B, and the data were analyzed using the Mann-Whitney U test and Kaplan-Meier log-rank test, with p values <0.05 indicating statistical significance. The Mann-Whitney U test was also used to analyze intergroup differences in other clinical factors in Groups A and B.

Predicted adult height was compared among Groups A, B, and C as a supplemental analysis. Adult height was predicted using the Growth Potential II method [12]. Factors in Groups A, B, and C were compared using the Bonferroni/Dunn test with the significance level set at p < 0.0167.

This study was approved by the Japan Medical Association Ethical Review Board (R2-15). We published information about the study content on the clinic’s notice board and homepage.

### Results

Table 4 (a) and (b) show the background factors and the clinical factors at the start of GH treatment in boys and girls by group. There were no significant intergroup differences in background factors. There were naturally significant differences in age, height, body weight, and bone age among the three groups but no differences in height SD score, or GH therapeutic dose.

In the main analysis, a significant positive correlation between age at the start of GH treatment and age at the onset of puberty was observed in boys and girls (boys: r = 0.427, p < 0.0001; girls: r = 0.302, p < 0.05) (Fig. 1(a) and (b)).

There were no significant correlations between age at the onset of puberty and background factors listed in Table 1, nor were there correlations among the boys or girls between age at the onset of puberty and clinical factors at the start of GH treatment, such as height SD score, % overweight, or IGF-I levels.

In the sub analysis, the Mann-Whitney U test for Groups A and B of age at the onset of puberty showed a significant difference in both boys and girls (boys, p < 0.01; girls, p < 0.05) (Fig. 2(a) and (b)).

There were no significant correlations between age at the onset of puberty and background factors listed in Table 1, nor were there correlations among the boys or girls between age at the onset of puberty and clinical factors at the start of GH treatment, such as height SD score, % overweight, or IGF-I levels.

In the sub analysis, the Mann-Whitney U test for Groups A and B of age at the onset of puberty showed a significant difference in both boys and girls (boys, p < 0.01; girls, p < 0.05). Fig. 2(a) and (b) show the Kaplan-Meier analysis of Groups A and B in boys and girls. The log-rank test showed a significant difference in both boys and girls (boys, p < 0.01; girls, p < 0.05).

Clinical factors at the onset of puberty and predicted adult height by group are shown for boys and girls in Tables 5 (a) and (b). The mean height at the onset of puberty was not significantly different between Groups A and B, although there were significant differences in the period from the start of GH treatment to the onset of puberty.

### Table 3 Clinical factors at onset of puberty

|                  | Boys (n = 135) | Girls (n = 89) |
|------------------|----------------|---------------|
| n                | Mean ± SD      | n = Mean ± SD |
| Age (years)      | 135 11.7 ± 0.8 | 89 11.4 ± 1.1 |
| Height (cm)      | 135 135.2 ± 4.2 | 89 133.8 ± 5.6 |
| Height SDS (SD)  | 135 −1.63 ± 0.53 | 89 −1.79 ± 0.63 |
| Body weight (kg) | 134 30.9 ± 4.2 | 89 28.5 ± 3.7 |
| % overweight (%) | 134 1.6 ± 11.1 | 89 −3.5 ± 10.2 |
| Bone age (years) | 130 10.5 ± 2.2 | 88 10.2 ± 0.9 |
| IGF-I (ng/mL)    | 116 277 ± 87 | 85 301 ± 69 |
| IGF-I SDS (SD)   | 116 −0.05 ± 0.87 | 85 −0.27 ± 0.75 |
| GH dose (mg/kg/week) | 126 0.210 ± 0.014 | 88 0.212 ± 0.020 |
puberty among groups of the boys and girls. Among Groups A, B, and C, the mean height at the onset of puberty and predicted adult height were not significantly different in boys but were significantly higher in girls in Group C.

Discussion

During the phGH treatment period, the onset of puberty was delayed because many patients had multiple pituitary hormone deficiencies accompanied by an

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Table 4  (a) Patients' background and clinical factors at the start of GH treatment by study group of boys

| Group A (45) | Group B (39) | Group C (51) | Significance* |
|-------------|--------------|--------------|---------------|
| N | Mean ± SD | N | Mean ± SD | N | Mean ± SD |
| Gestational weeks (weeks) | 40 | 38.8 ± 2.4 | 38 | 38.6 ± 2.4 | 46 | 38.6 ± 3.6 | NS |
| Birth weight (g) | 40 | 2,782 ± 503 | 39 | 2,884 ± 462 | 45 | 2,830 ± 646 | NS |
| Birth weight SDS (SD) | 40 | −0.55 ± 1.26 | 39 | −0.29 ± 1.16 | 45 | −0.42 ± 1.62 | NS |
| Birth length (cm) | 40 | 47.5 ± 3.1 | 39 | 48.3 ± 2.9 | 45 | 47.7 ± 3.5 | NS |
| Birth length SDS (SD) | 40 | −0.71 ± 1.50 | 39 | −0.32 ± 1.40 | 44 | −0.63 ± 1.64 | NS |
| Height of father (cm) | 40 | 168.1 ± 4.5 | 36 | 167.9 ± 5.2 | 45 | 167.9 ± 5.8 | NS |
| Height of mother (cm) | 40 | 153.3 ± 5.8 | 38 | 153.4 ± 5.2 | 40 | 155.1 ± 5.3 | NS |
| Age (years) | 45 | 6.2 ± 1.3 | 39 | 9.0 ± 0.6 | 51 | 11.3 ± 0.8 | a, b, c |
| Height (cm) | 45 | 102.4 ± 7.8 | 39 | 117.5 ± 3.1 | 51 | 127.6 ± 4.2 | a, b, c |
| Height SDS (SD) | 45 | −2.52 ± 0.45 | 39 | −2.35 ± 0.30 | 51 | −2.68 ± 0.35 | NS |
| Body weight (kg) | 43 | 161.6 ± 2.8 | 39 | 21.8 ± 2.1 | 51 | 26.8 ± 4.1 | a, b, c |
| % overweight (%) | 43 | 2.8 ± 10.3 | 39 | 8.9 ± 9.0 | 51 | 7.8 ± 13.7 | a |
| IGF-I (ng/mL) | 34 | 71.8 ± 32.8 | 36 | 118.1 ± 35.8 | 49 | 141.4 ± 59.4 | a, c |
| IGF-I SDS (SD) | 34 | −1.31 ± 0.83 | 36 | −1.18 ± 0.63 | 49 | −1.57 ± 0.84 | NS |
| Bone age (years) | 36 | 4.1 ± 1.4 | 37 | 7.2 ± 1.2 | 19 | 9.6 ± 1.4 | a, b, c |
| GH dose (mg/kg/week) | 36 | 0.210 ± 0.017 | 37 | 0.205 ± 0.023 | 45 | 0.204 ± 0.013 | NS |

* Bonferroni/Dunn  a: A vs. B, p < 0.0167  b: B vs. C, p < 0.0167  c: C vs. A, p < 0.0167
NS, not significant

Table 4  (b) Background factors and clinical factors at start of GH treatment in groups A, B, C in girls

| Group A (26) | Group B (21) | Group C (42) | Significance* |
|-------------|--------------|--------------|---------------|
| N | Mean ± SD | N | Mean ± SD | N | Mean ± SD |
| Gestational weeks (weeks) | 23 | 38.9 ± 1.1 | 20 | 39.2 ± 1.1 | 41 | 39.0 ± 1.1 | NS |
| Birth weight (g) | 23 | 2,779 ± 250 | 21 | 2,841 ± 208 | 41 | 2,899 ± 3,245 | NS |
| Birth weight SDS (SD) | 23 | −0.55 ± 0.63 | 21 | −0.40 ± 0.52 | 41 | −0.25 ± 0.86 | NS |
| Birth length (cm) | 23 | 47.6 ± 1.6 | 19 | 48.2 ± 1.6 | 39 | 48.1 ± 1.7 | NS |
| Birth length SDS (SD) | 23 | −0.39 ± 0.74 | 19 | −0.11 ± 0.68 | 39 | −0.15 ± 0.80 | NS |
| Height of father (cm) | 22 | 167.7 ± 4.3 | 20 | 166.7 ± 4.6 | 41 | 169.0 ± 5.9 | NS |
| Height of mother (cm) | 22 | 154.2 ± 5.1 | 20 | 154.4 ± 4.2 | 42 | 155.4 ± 4.1 | NS |
| Age (years) | 26 | 5.7 ± 1.3 | 21 | 8.5 ± 0.6 | 42 | 11.0 ± 0.8 | a, b, c |
| Height (cm) | 26 | 98.1 ± 8.4 | 21 | 113.2 ± 4.3 | 42 | 126.8 ± 4.2 | a, b, c |
| Height SDS (SD) | 26 | −2.73 ± 0.75 | 21 | −2.51 ± 0.47 | 42 | −2.52 ± 0.32 | NS |
| Body weight (kg) | 25 | 14.3 ± 2.7 | 21 | 18.7 ± 1.5 | 42 | 25.2 ± 2.8 | a, b, c |
| % overweight (%) | 24 | 1.2 ± 10.4 | 21 | 1.5 ± 7.5 | 42 | 4.4 ± 10.7 | NS |
| IGF-I (ng/mL) | 23 | 82.0 ± 32.3 | 19 | 129.4 ± 32.5 | 39 | 152.2 ± 38.4 | a, c |
| IGF-I SDS (SD) | 23 | −1.540 ± 1.02 | 19 | −1.640 ± 0.69 | 39 | −2.34 ± 0.800 | b, c |
| Bone age (years) | 24 | 4.4 ± 1.5 | 17 | 6.7 ± 0.9 | 41 | 5.3 ± 0.8 | a, b, c |
| GH dose (mg/kg/week) | 25 | 0.211 ± 0.024 | 19 | 0.210 ± 0.015 | 42 | 0.210 ± 0.019 | NS |

* Bonferroni/Dunn  a: A vs. B, p < 0.0167  b: B vs. C, p < 0.0167  c: C vs. A, p < 0.0167
NS, not significant
insufficient secretion of other pituitary hormones, particularly gonadotropins [2]. However, among idiopathic GHD patients receiving GH treatment, the onset of puberty is also delayed compared with healthy children [7-9].

If GH treatment does not affect the onset of puberty, the age at the onset of puberty should generally be nearly the same if the treatment is started before the onset of puberty, whether earlier or later. However, if GH is involved in ovarian and testicular development and is necessary for the onset of puberty, an early start of treatment is expected to lead to an earlier onset of puberty. Table 6 shows the age at the start of GH treatment and the age at the onset of puberty in this study and in the literature in Japan [4, 9, 13, 14]. Although the severity of GHD is not the same among these reports, the age at onset of puberty in those reports with late start of GH [4, 9] is very late compared with that of normal children in boys (11.5 years [15], 10.8 years [16]) and girls (9.74 years [17], 10.0 years [16]). This strongly suggests that GHD develops delayed puberty without GH treatment. As GH treatment is started earlier, the age at the onset of puberty becomes earlier. This suggests that GH treatment accelerates the onset of puberty.

GH reportedly produces insulin-like growth factor I (IGF-I) locally in the ovaries and testes, which increases responsiveness to gonadotropin [18-21]. GH has been used as an adjunctive therapy in clinical infertility treatment [22-25]. Therefore, if decreased secretion of GH-IGF-I leads to decreased responsiveness of the ovaries and testes to gonadotropin in the setting of GH deficiency, a delayed onset of puberty in patients with idiopathic GHD is understandable.

Many reports on GH treatment efficacy have been prepared based on cases in which treatment was started...
before the start of puberty because the influence of sex hormones in puberty cannot be ruled out. However, when patients who start GH treatment in prepuberty are examined, the age at the start of treatment is always younger than the average age at the onset of puberty. Therefore, a positive correlation is always observed when the correlation is examined in all patients. Therefore, in this study, the correlation was examined only in patients sufficiently younger than the average age at the onset of puberty, and a significant correlation was observed between the age at the start of GH treatment and the age at the onset of puberty. And the age at the onset of puberty was examined before the start of puberty because the influence of sex hormones in puberty cannot be ruled out. However, when patients who start GH treatment in prepuberty are examined, the age at the start of treatment is always younger than the average age at the onset of puberty. Therefore, a positive correlation is always observed when the correlation is examined in all patients. Therefore, in this study, the correlation was examined only in patients sufficiently

Table 5  (a) Clinical factors at onset of puberty and predicted adult height by study group of boys

|                | Group A (45) | Group B (39) | Significance* Group A vs. B | Group C (51) | Significance** Group A, B, C |
|----------------|-------------|-------------|-----------------------------|-------------|-----------------------------|
| Age (years)    | 45: 11.2 ± 0.7 | 39: 11.7 ± 0.7 | p < 0.01                   | 51: 12.2 ± 0.8 | a, b, c                     |
| Height (cm)    | 45: 134.9 ± 4.7 | 39: 135.4 ± 3.5 | NS                         | 51: 135.2 ± 4.4 | NS                          |
| Height SDS (SD)| 45: −1.28 ± 0.43 | 39: −1.52 ± 0.41 | p < 0.01                   | 51: −2.02 ± 0.43 | b, c                        |
| Body weight (kg)| 45: 30.6 ± 4.0 | 38: 31.7 ± 3.8 | NS                         | 51: 30.7 ± 4.5 | NS                          |
| % overweight   | 45: 0.1 ± 10.2 | 38: 3.0 ± 10.7 | NS                         | 51: 1.9 ± 12.2 | NS                          |
| Bone age (years)| 42: 10.0 ± 3.6 | 38: 10.6 ± 1.0 | NS                         | 50: 10.8 ± 1.1 | NS                          |
| IGF-1 (ng/mL)  | 36: 255.7 ± 78.1 | 35: 279.2 ± 85.4 | NS                         | 46: 290.8 ± 92.9 | NS                          |
| IGF-1 SD (SD)  | 36: −0.10 ± 0.91 | 35: −0.38 ± 0.86 | NS                         | 46: −0.04 ± 0.87 | NS                          |
| GH dose (mg/kg/week) | 39: 0.211 ± 0.016 | 37: 0.207 ± 0.014 | NS                         | 50: 0.211 ± 0.014 | NS                          |
| Duration from GH TX till onset of puberty (years) | 44: 5.0 ± 1.3 | 39: 2.7 ± 0.9 | p < 0.001                   | 52: 1.0 ± 0.6 | a, b, c                      |
| Predicted adult height (cm) | 40: 161.6 ± 4.3 | 37: 161.5 ± 2.2 | NS                         | 47: 160.7 ± 2.9 | NS                          |

* Mann-Whitney U test  
** Bonferroni/Dunn
a: A vs. B, p < 0.0167  
b: B vs. C, p < 0.0167  
c: C vs. A, p < 0.0167
NS, not significant

Table 5  (b) Clinical factors at onset of puberty in groups A, B, C in girls

|                | Group A (26) | Group B (21) | Significance* Group A vs. B | Group C (42) | Significance** Group A, B, C |
|----------------|-------------|-------------|-----------------------------|-------------|-----------------------------|
| Age (years)    | 26: 10.4 ± 0.7 | 21: 11.0 ± 0.9 | p < 0.05                   | 42: 12.2 ± 0.9 | a, b, c                     |
| Height (cm)    | 26: 132.2 ± 4.7 | 21: 131.0 ± 0.6 | NS                         | 42: 136.1 ± 4.7 | b, c                        |
| Height SDS (SD)| 26: −1.14 ± 0.52 | 21: −1.81 ± 0.47 | p < 0.001                  | 42: −2.19 ± 0.39 | a, b, c                     |
| Body weight (kg)| 26: 27.9 ± 2.7 | 21: 26.7 ± 3.8 | NS                         | 42: 29.7 ± 3.9 | b, c                        |
| % overweight   | 26: −1.6 ± 9.2 | 21: −2.3 ± 8.5 | NS                         | 42: −5.3 ± 11.3 | NS                          |
| Bone age (years)| 25: 10.2 ± 0.7 | 21: 10.0 ± 0.7 | NS                         | 42: 10.4 ± 1.0 | NS                          |
| IGF-1 (ng/mL)  | 24: 294.0 ± 57.5 | 21: 295.9 ± 67.8 | NS                         | 40: 308.5 ± 77.0 | NS                          |
| GH dose (mg/kg/week) | 25: 0.208 ± 0.011 | 21: 0.216 ± 0.023 | NS                         | 42: 0.213 ± 0.023 | NS                          |
| Duration from GH TX till onset of puberty (years) | 26: 4.8 ± 1.3 | 21: 2.5 ± 1.1 | p < 0.001                  | 42: 1.1 ± 0.8 | a, b, c                      |
| Predicted adult height (cm) | 25: 149.2 ± 3.4 | 21: 148.1 ± 4.8 | NS                         | 42: 151.4 ± 2.7 | b, c                        |

* Mann-Whitney U test  
** Bonferroni/Dunn
a: A vs. B, p < 0.0167  
b: B vs. C, p < 0.0167  
c: C vs. A, p < 0.0167
NS, not significant
Whether GH treatment affects the onset of puberty in GHD can be scientifically examined by comparison with untreated controls in GHD. However, this is not possible because of ethical issues in clinical settings. Kamp et al. [26] treated idiopathic short stature (ISS) with high-dose GH up to 6.0 IU/m²/day (=0.5 mg/kg/week) for at least 2 years and reported that, compared with untreated ISS, bone age was significantly accelerated in the GH treatment group and the onset of puberty was significantly early, a factor that limited improvements in adult height. This clearly shows that high-dose GH treatment leads to an early onset of puberty in patients with ISS. Kawai et al. [27] treated ISS boys with a normal dose (0.17 mg/kg/week) for GHD in Japan, but their adult height was lower than that of untreated patients, suggesting that GH treatment in ISS patients may accelerate the onset of puberty even at a normal dose.

The mean age of boys and girls at the onset of puberty in this study was 11.7 and 11.4 years, respectively. The mean age of the treated boys was almost the same as that of the healthy boys (11.5 years [15], 10.8 years [16]). But the men age of the treated girls at the onset of puberty did not reach that of healthy girls (9.74 years [17], 10.0 years [16]). Although GH treatment was suggested to accelerate the onset of puberty, treatment normalized only the onset of puberty that was delayed without treatment and did not accelerate the onset of puberty as much as precocious puberty. However, this suggests that the height at the onset of puberty, which strongly correlated with adult height, will be almost the same in the group of patients who start GH treatment early and those who start GH treatment late and that there will be no difference in adult height. Therefore, an early start to GH treatment does not lead to improvements in adult height.

According to reports published in and after 2001, although the age at the start of GH treatment has been early, adult height remains around 160 cm (approximately –1.8 SD) for boys and around 147 cm (approximately –2.0 SD) for girls [3-6].

In the supplemental analysis, the lack of a significant difference in mean predicted adult height between Groups A and B suggests that an early start of GH treatment does not lead to a taller adult height. Among boys, there were no significant differences in predicted adult height among Groups A, B, and C; however, among girls, Group C showed a taller mean adult height than the other two groups because of a taller mean height at the onset of puberty. Thus, it seems that more female patients had delayed puberty since the mean age at the onset of puberty was >12 years. The predicted adult height in this study was almost the same as the adult height of GH-treated GHD reported above [3-6], suggesting no further improvements in adult height by the early start of GH treatment in patients with GHD.

The limitation of this study is that the age range of Group A was larger than that of Group B. It will be desirable to increase the number of patients to increase the number of groups and examine them within the same age range. The assessment of the onset of puberty may include subjective assessments by attending physicians. However, the strength of this study is its high objectivity because it was performed by a single physician, including the endocrinological assessments.

This study showed that GH treatment accelerates the onset of puberty. However, it is considered to normalize the timing of the onset of puberty in patients with GHD whose onset of puberty is originally delayed. The supplemental analysis demonstrated that the height at the onset of puberty and the adult height were nearly the same in the early versus late start of GH groups, suggesting that early treatment does not lead to an improved adult height. However, early diagnosis and treatment are recommended since the early achievement of a normal height by early treatment leads to the early improvement

| Reports          | Group*     | n  | Age at GH start | Age at onset of puberty | Group | n  | Age at GH start | Age at onset of puberty |
|------------------|------------|----|----------------|-------------------------|-------|----|----------------|-------------------------|
| Tanaka 2001      | Group A    | 541| 12.4           | 14.3                    | Group A | 398| 11.0           | 13.0                    |
|                  | Group B    | 75 | 11.9           | 13.5                    | Group B | 112| 10.5           | 12.1                    |
| Tanaka 1994      | Cohort II  | 219| 10.2           | 12.5                    | Cohort II | 94 | 10.3           | 12.1                    |
| Tanaka 2017      | GH alone   | 20 | 10.6           | 13                      |       |    |                |                         |
|                  | Combined   | 26 | 9.2            | 11.7                    |       |    |                |                         |
| Tanaka 2018      | 66         | 10.0| 12.0           |                         | 42    | 8.4 | 11.3           |                         |
| This study       | 135        | 8.9 | 11.7           |                         | 89    | 8.9 | 11.4           |                         |

* Cohort II is Japanese study. (Cohort I is Caucasian study: not shown).

Two groups in one report are divided according to the treatment methods after puberty.
of psychosocial problems due to short stature.

Disclosure

None of the authors have any potential conflicts of interest associated with this research.

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