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Original Article

BMI-SDS Changes During GnRHa Therapy in 150 Girls with Idiopathic Central Precocious Puberty: Follow-up Through Final Height

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What is known on the subject?
Studies on the effect of GnRHa treatment on weight and BMI-SDS have reported conflicting results (increased, unchanged, or decreased BMI during therapy). Most did not account for baseline BMI-SDS category or birthweight status when evaluating BMI-SDS changes. Data on BMI-SDS trajectories through final adult height remain limited.

What this study adds?
This is one of the largest cohorts with follow-up to final adult height, stratified by pretreatment BMI-SDS and birthweight status. BMI-SDS showed no sustained increase at final height across baseline weight groups, and early SGA–AGA differences were not maintained. Baseline BMI-SDS was the key independent predictor of ΔBMI-SDS during treatment.

Abstract
Objective: To evaluate longitudinal changes in body mass index standard deviation score (BMI SDS) in girls with central precocious puberty (CPP) treated with gonadotropin-releasing hormone analogues (GnRHa) from treatment initiation to final adult height.
Methods: This retrospective study included 150 girls with idiopathic CPP treated with leuprolide acetate and followed to final adult height. BMI SDS was assessed at treatment initiation, at 1 year of therapy, at treatment completion, and at final adult height. Patients were categorized according to BMI SDS at the time of diagnosis as underweight, normal weight, overweight, or obese. BMI SDS was evaluated at predefined time points and examined within baseline weight groups, and transitions between BMI SDS categories were analyzed across the follow-up period. In addition to baseline weight status, participants were categorized as SGA or AGA based on birth weight for gestational age.
Results: In normal-weight girls, BMI-SDS increased significantly during the first treatment year and then declined toward final height, with no difference between baseline and final height. BMI-SDS remained stable in those overweight or obese at treatment initiation. BMI-category distribution changed over follow-up (overall $p = 0.014$), OW+OB prevalence increased during treatment (48.6%→56.6%) and decreased by final height (45.3%) (baseline vs final $p = 0.533$). By final height, obesity increased ($p = 0.0076$) and overweight decreased ($p = 0.006$), while normal-weight prevalence did not differ from baseline ($p = 0.098$). In multivariable analysis, baseline BMI-SDS was inversely related to ΔBMI-SDS (treatment end − baseline) ($\beta = -0.174$, 95% CI −0.291 to −0.057; $p = 0.004$)
Conclusion: In this large cohort of girls with idiopathic CPP followed through final adult height, BMI SDS showed no sustained increase at final height across baseline weight groups, and the SGA–AGA differences observed earlier were not maintained. Baseline BMI-SDS was the key independent determinant of ΔBMI-SDS (treatment end − baseline), with lower baseline values predicting greater increases.
Keywords: Central precocious puberty; gonadotropin-releasing hormone analog; body mass index; long-term follow-up

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Introduction

Nutritional status during childhood plays an important role in pubertal timing and progression and may explain a substantial proportion of the variability in pubertal onset (1-4). In particular, overnutrition and obesity have been associated with earlier pubertal development, while impaired fetal growth and neonatal thinness have also been linked to earlier pubertal maturation (2). Central precocious puberty (CPP) is defined as the premature activation of the hypothalamic–pituitary–gonadal axis before the age of 8 years in girls and 9 years in boys, leading to early secondary sexual characteristics, accelerated growth velocity, and advanced bone maturation (5). Gonadotropin-releasing hormone analogues (GnRHa) have been used in the treatment of CPP since the early 1980s and are currently considered the standard therapy. GnRHa therapy is generally safe and well tolerated. The most frequently reported adverse effects include local or systemic hypersensitivity reactions and mild hypoestrogenic symptoms such as hot flushes, headache, and nausea (6,7).
Despite the well-established efficacy of GnRHa in controlling pubertal progression, its effects on body weight and body mass index (BMI) remain controversial. Some studies have reported an increase in body weight during GnRHa treatment (8,9), whereas, other studies have demonstrated no significant change in BMI SDS (10,11) or have even reported a decrease in BMI during therapy (12,13). Furthermore, most studies did not take the effect of initial pretreatment BMI category or birthweight status on changes in BMI SDS during GnRHa therapy into account. Finally, data evaluating BMI SDS trajectories extending to final adult height are limited.
Therefore, we aimed to evaluate longitudinal changes in BMI SDS from treatment initiation through treatment completion and into final adult height in girls with idiopathic CPP treated with GnRHa. Additionally, we investigated the effects of BMI SDS at the beginning of therapy and being born SGA on BMI trajectories during GnRHa treatment.

Methods

Medical records of 150 girls diagnosed with central precocious puberty (CPP) who were treated with GnRHa therapy using leuprolide acetate and followed until reaching final adult height were retrospectively reviewed.

CPP was defined as progressive breast development starting before 8 years of age, associated with accelerated growth (>6 cm/year) and skeletal maturation (advanced by at least one year) (3); biochemical evidence of HPG-axis activation, defined as either basal LH >0.6 mIU/mL or a GnRH-stimulated peak LH ≥5 mIU/mL, as previously accepted in the literature and consensus statements (6,14). Uterine length >34 mm and ovarian volume >2 cm³ were taken as supportive criteria (6,15). Fasting venous blood samples were obtained from all girls in the morning for FSH, LH and E2 measurements using chemiluminescent methods (Beckman Coulter Diagnostics, CA, USA).

Patients with organic causes of CPP or comorbid conditions known to affect body mass index or pubertal development were excluded from this study. All patients received depot leuprolide acetate at a dose of 3.75 mg intramuscularly every 28 days. Height and weight were measured using a Harpenden stadiometer (Holtain Ltd. Crosswell, Crymyh, Pembs, UK) and a calibrated digital scale (seca GmbH & Co. KG, Hamburg, Germany). BMI was calculated as weight divided by height squared (kg/m²), and BMI SDS were calculated using national reference data (16-18). Patients were classified according to baseline BMI-SDS into three weight groups: normal weight (NW; BMI-SDS ≥ −1 and < +1), overweight (OW; BMI-SDS ≥ +1 and < +2), and obese (OB; BMI-SDS ≥ +2). No patients had a BMI SDS < –1 at treatment initiation. No structured lifestyle intervention (diet or supervised exercise program) was prescribed as part of the treatment protocol. Bone age was assessed by left-hand radiography according to the Greulich and Pyle method (19). Age at menarche and auxological measurements at menarche were recorded when available from the medical records. Final adult height was defined as a growth velocity of less than 1 cm/year together with a bone age of at least 15 years, in accordance with previously published criteria (20). BMI SDS was evaluated at four predefined time points: treatment initiation, the first year of treatment, treatment completion, and final adult height. Birth weight and gestational age data were obtained from medical records, and small for gestational age (SGA) was defined as a birthweight < −2 standard deviations for gestational age (21). The primary outcome measure was the longitudinal change in BMI SDS assessed at four predefined time points. BMI-category distributions were compared across follow-up using paired categorical methods. In addition, BMI SDS trajectories were analyzed according to baseline weight status and birthweight status to identify potential modifiers of BMI SDS changes.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 5.00 (GraphPad Software, San Diego, CA, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test, and data are presented as mean±standard deviation. Within-group changes in BMI-SDS over time were analyzed using repeated-measures ANOVA. Comparisons between independent groups were performed using the independent-samples t test or Mann–Whitney U test, as appropriate. Changes in BMI-category prevalence (underweight/normal/overweight/obese and OW+OB) across treatment initiation, treatment completion, and final adult height were analyzed using Cochran's Q test. post hoc pairwise comparisons using McNemar's test with exact p values.A p value <0.05 was considered statistically significant. Baseline predictors of change in BMI-SDS (ΔBMI-SDS; end of treatment minus baseline) were assessed using multiple linear regression.

Results

A total of 150 girls with CPP who completed GnRHa treatment and reached final adult height were included in the analysis. The mean age at treatment initiation, completion of treatment, age of menarche and at final height were 8.0±1.2, 10.8±0.6, 12.4 ± 1.2, 18.6±2.4 years, respectively. At treatment initiation, most girls were of normal weight (n = 77, 51.3%), while 57 girls (38.0%) were classified as overweight and 16 (10.7%) as obese. Although no girls were underweight at baseline, 18/150 (12.0%) were classified as underweight at final height, reflecting downward transitions during follow-up, primarily from baseline normal weight (n = 15) and less commonly from baseline overweight (n = 3) (Figure 1).

No patient required dose escalation during therapy. The mean duration of GnRHa treatment was 2.8 ± 1.2 years. The mean age at treatment initiation differed significantly among the NW, OW, and OB groups (8.1 ± 1.1, 8.1 ± 1.0, and 7.1 ± 1.8 years, respectively; $p = 0.01$), whereas bone age at treatment initiation was comparable (9.6 ± 1.6, 9.9 ± 1.6, and 9.5 ± 2.0 years, respectively; $p = 0.70$). Compared with normal-weight girls, obese girls exhibited a more advanced bone age relative to chronological age and greater stature at treatment initiation. First-year growth velocity SDS did not differ significantly between baseline BMI groups, 0.4 (−0.5 to 0.8) in normal-weight girls, 0.2 (−0.6 to 0.7) in overweight girls, and 0.1 (−0.8 to 1.6) in obese girls (p = 0.8). The baseline auxological characteristics of the cohort according to BMI category are summarized in Table 1.

When all patients were evaluated together, BMI SDS changed significantly over time (p = 0.001), with higher values at treatment completion compared with baseline (p = 0.009), followed by a significant decrease toward final adult height (p = 0.006). BMI SDS at final adult height did not differ from baseline (p = 0.13). When BMI SDS changes were evaluated according to pre-treatment BMI categories, in the normal-weight group, BMI SDS increased during the first year of treatment and remained elevated at treatment completion (p < 0.01), followed by a significant decrease toward final adult height, resulting in comparable BMI SDS with baseline. In contrast, BMI SDS remained stable throughout treatment and follow-up in both the overweight and obese groups, with no significant overall change across the four time points (p = 0.4 and p = 0.3, respectively) (Table 2 and Table 3).

Figure 1 demonstrates bidirectional BMI-category transitions over follow-up. Although some girls who were overweight/obese at baseline shifted to a lower category by final height, a subset of girls with baseline normal weight transitioned to overweight/obesity. Accordingly, the prevalence of overweight/obesity (OW+OB) varied across treatment initiation, treatment end, and final height (overall p = 0.014), increasing from 73/150 (48.6%) at baseline to 85/150 (56.6%) at treatment end (p = 0.029) and decreasing to 68/150 (45.3%) at final height (p = 0.012 vs treatment end), while baseline and final-height prevalences were not different (p = 0.533). The normal-weight proportion decreased during treatment from 77/150 (51.3%) to 63/150 (42.0%) (p = 0.013) and was 64/150 (42.7%) at final height (baseline vs final p = 0.098). When examined separately, overweight prevalence increased numerically during treatment (57/150 [38.0%] to 69/150 [46.0%]) but did not reach statistical significance (baseline vs treatment end p = 0.081), and decreased by final height (35/150 [23.3%]; treatment end vs final p < 0.001; baseline vs final p = 0.006). Obesity prevalence did not change during treatment (16/150 [10.7%] at both baseline and treatment end; p = 1.00) but increased at final height (33/150 [22.0%]; treatment end vs final p = 0.006; baseline vs final p = 0.0076). Underweight was absent at baseline and remained rare at treatment end (2/150 [1.3%]; baseline vs treatment end p = 0.50) but increased at final height (18/150 [12.0%]; treatment end vs final p < 0.001). In the multivariable model, girls who started treatment with a lower BMI SDS experienced a larger increase in BMI SDS during follow-up (ΔBMI SDS = nd of treatment minus baseline) (β = −0.174, 95% CI −0.291 to −0.057; p = 0.004). (Table 4).

In the SGA group, no girls were obese at baseline (9 normal weight, 4 overweight). BMI SDS was lower in SGA than AGA at baseline, year 1, and treatment completion (p = 0.04, 0.04, and 0.01, respectively), but not at final adult height (p = 0.6). Within the SGA, BMI SDS group remained stable over follow-up, with no significant changes observed between year 1, treatment completion, and final adult height (all p > 0.05), (Table 5).

Discussion

In this longitudinal cohort of 150 girls with CPP who received GnRHa therapy and were followed until attainment of final adult height, we characterized BMI-SDS trajectories across treatment and post-treatment periods. Childhood obesity has been linked to earlier pubertal milestones, including earlier onset of breast development and pubic hair growth (22,23). At treatment initiation, nearly half of our cohort had

excess weight (overweight/obesity: 48.6%), consistent with other CPP series. Palmert et al. reported prevalences of overweight and obesity of 48% and 26%, respectively, and Arrigo et al. likewise noted a substantial burden of excess weight among CPP patients (12,24). The absence of underweight patients at baseline supports the well-established association between greater adiposity and earlier pubertal activation. In our cohort, girls who were obese at treatment initiation commenced GnRHa at a younger chronological age than their normal-weight or overweight peers, despite similar absolute bone ages. This pattern suggests greater skeletal advancement relative to age (higher BA–CA) at presentation, consistent with reports that obesity is associated with taller stature and advanced skeletal maturation for chronological age (25).

We evaluated treatment-related BMI-SDS changes stratified by weight status at initiation. The observed increase in BMI-SDS at treatment completion in the overall cohort was mainly attributable to changes in the normal-weight group in the first year of treatment, whereas BMI-SDS remained stable in patients who were overweight or obese at treatment initiation. However, at final height BMI SDS was comparable to BMI SDS at the beginning of GnRHa therapy in the overall cohort as well as in the subgroups of BMI categories. Categorical analyses added nuance to the continuous BMI-SDS findings: although OW+OB prevalence at final height was similar to baseline ($p = 0.533$), BMI-category distribution changed over follow-up (overall $p = 0.014$), reflecting bidirectional transitions across BMI-SDS cut-offs.

Most studies have not followed participants through adult height and have reported either increased BMI-SDS during treatment (26,27) or no change (28,29). Among the studies which reported data on final/nearfinal height (20, 30-36), only four of them categorized the subjects according to their BMI SDS prior to the commencement of the GnRHa therapy (30-33). Sinthuprasith et al. (30) reported in 58 subjects that BMI-SDS increased significantly at the first and second treatment years in the overweight/obesity group, whereas in the normal-weight group the increase was observed only during the first year. At near-final height, however, BMI-SDS did not differ significantly from baseline in either group. Arcari et al. (31) similarly noted BMI-SDS increases during treatment in normal-weight girls at both year 1 and year 2; in contrast, overweight girls showed a significant increase only at year 1, and obese girls showed no significant change. Notably, in the subgroup followed to final height (n=60), BMI-SDS decreased significantly at final height compared with treatment initiation.

Bruzzi et al. (32) reported in 57 girls that BMI-SDS increased during GnRHa therapy in normal-weight subjects, but not in overweight or obese subjects; importantly, when near-final or final height was reached, BMI-SDS returned toward pretreatment values across the cohort. In Lee et al.'s (33) study, 35 patients followed to final height showed no significant BMI-SDS change across follow-up within the normal-weight (n=26) or overweight/obese (n=9) subgroups; BMI-SDS increased significantly only during the first year in normal-weight girls, with no further change between years 1 and 2, and no difference between overweight and obese groups during treatment. Bruzzi et al. and Arcari et al.), our study adds several important elements. First, we report one of the largest single-center iCPP cohorts with follow-up to final adult height**,** with final-height data available for the entire treated cohort (n=150)**,** whereas earlier reports included smaller final-height subsets (e.g., Arcari et al. reported adult-height data for n=60 of 117; Bruzzi et al. analyzed n=57). Second, we present BMI-SDS at predefined longitudinal time points and complement continuous BMI-SDS analyses with paired categorical analyses of BMI-category redistribution/transition over follow-up (Figure 1), addressing the clinically relevant question of who moves between normal weight, overweight and obesity despite stable group-level BMI-SDS.

Our observations in this large cohort followed through adult height are in agreement with the latter two studies and indicate that BMI-SDS increases in normal-weight girls during treatment—particularly in the first year—remains higher until treatment completion, and then declines after discontinuation, returning toward baseline by adult height, whereas BMI-SDS tends to remain stable in girls who are overweight or obese at baseline.

Thus, it appears that changes in BMI during GnRHa therapy are strongly modified by baseline weight status, One proposed explanation for this observation is that apparent BMI-SDS changes may reflect altered linear growth rather than true adiposity gain, because pubertal suppression can reduce growth velocity and thereby increase BMI even when weight gain is modest. (37,38) Differences in growth response by baseline adiposity may also modulate this pattern; for example, an obese/overweight subgroup showed a smaller decline in height SDS for chronological age during treatment compared with normal-weight peers in one cohort, which could attenuate BMI-SDS increases (39). However, growth velocity SDS did not differ significantly in our cohort refuting this hypothesis. It was also proposed that estradiol influences body composition and may promote fat-mass accrual during normal pubertal progression. Suppression of gonadal steroid production with effective GnRHa therapy may therefore blunt this pubertal, steroid-related increase in adiposity, potentially contributing to the relatively stable BMI-SDS observed in girls who were overweight at baseline. Nonetheless, this explanation does not fully account for the transient BMI-SDS increase observed in normal-weight girls during treatment in our cohort (40). Among the more likely explanations, given the known association between adiposity and precocious puberty in girls, some studies note that families of overweight/obese children may improve diet and physical activity during therapy, potentially limiting additional weight gain.

Another plausible explanation is that established excess adiposity may be maintained by biologically defended weight-regulation (the 'settling-point' framework), which can be relatively resistant to short-term change. In this model, adiposity-related signals (e.g., leptin/insulin) engage hypothalamic appetite–expenditure circuits and trigger compensatory responses that oppose sustained weight loss, potentially contributing to the relative BMI-SDS stability observed in girls with baseline overweight/obesity (41). In multivariate analyses, our finding that lower baseline BMI SDS predicted a larger increase in BMI SDS during treatment ($\beta = -0.174$; $p = 0.004$) aligns with Wolters et al. (42) and Vuralli et al. (43) who likewise reported an inverse association between baseline BMI SDS and on-treatment ΔBMI-SDS. Together, these data suggest that BMI-SDS changes during GnRHa therapy are largely determined by starting adiposity, rather than treatment duration or other auxological factors.

Puberty tends to start slightly earlier and may progress with a slightly faster tempo in girls born small for gestational age (SGA) compared with those born appropriate for gestational age (AGA) (44). In our cohort, chronological age did not differ between the SGA and AGA groups. Evidence on longitudinal changes in BMI-SDS during GnRHa therapy stratified by birth size is limited. In a retrospective cohort followed to near-final/final height, Cho et al. (45) compared girls with idiopathic CPP born SGA (n=19) versus AGA (n=50) and reported no significant between-group differences in BMI-SDS across follow-up to completion of treatment. In our cohort, BMI-SDS was lower in SGA than AGA at treatment initiation, year 1, and treatment completion, but this difference was no longer evident at final adult height.

Study Limitations

BMI-SDS is a practical longitudinal marker but does not directly reflect body composition; detailed measures of fat and lean mass (e.g., DXA) and metabolic outcomes were not available. Dietary intake and physical activity, as well as socioeconomic variables, were not systematically recorded, and no structured diet or supervised exercise program was prescribed as part of the treatment protocol; therefore, residual confounding related to unmeasured lifestyle changes cannot be excluded. In addition, an untreated early puberty/control group was not available, so causal attribution of BMI-SDS and BMI-category changes specifically to GnRHa therapy is limited. Finally, subgroup analyses—particularly the SGA subgroup—and menarche-related anthropometric data were limited by small numbers or incomplete availability; thus, non-significant findings should be interpreted cautiously given the risk of Type II error."

Conclusion

In this cohort of 150 girls with idiopathic CPP treated with leuprolide acetate—one of the largest series with follow-up to final adult height—In this cohort, BMI-SDS increased during therapy but returned toward baseline by adult height. This finding is reassuring regarding the long-term weight trajectory after GnRHa treatment. This pattern was mainly observed in normal-weight girls, whereas BMI SDS remained stable in those overweight or obese at baseline. Our study also provides rare data stratified by gestational age (SGA vs AGA), showing that early between-group differences in BMI SDS were not sustained at final height.

Baseline BMI-SDS was the key independent predictor of change in BMI-SDS during treatment, underscoring the importance of baseline weight status.

Ethics

Ethics Committee Approval: The study was approved by the Marmara University Ethics Committee. (Approval No: 09.2022.486)

Informed Consent: All eligible participants and their parents provided informed consent.

Authorship Contributions

Conflict of interest: None declared.

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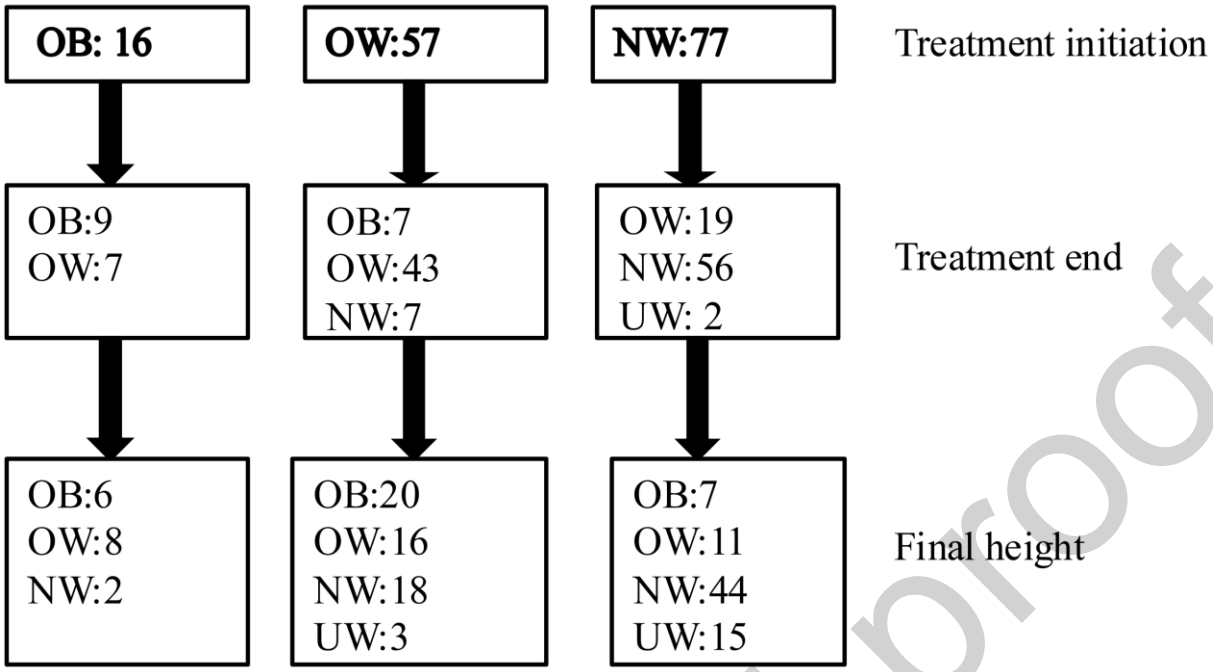

Figure 1. Transitions of BMI SDS categories from treatment initiation to end of treatment and final adult height (n = 150)

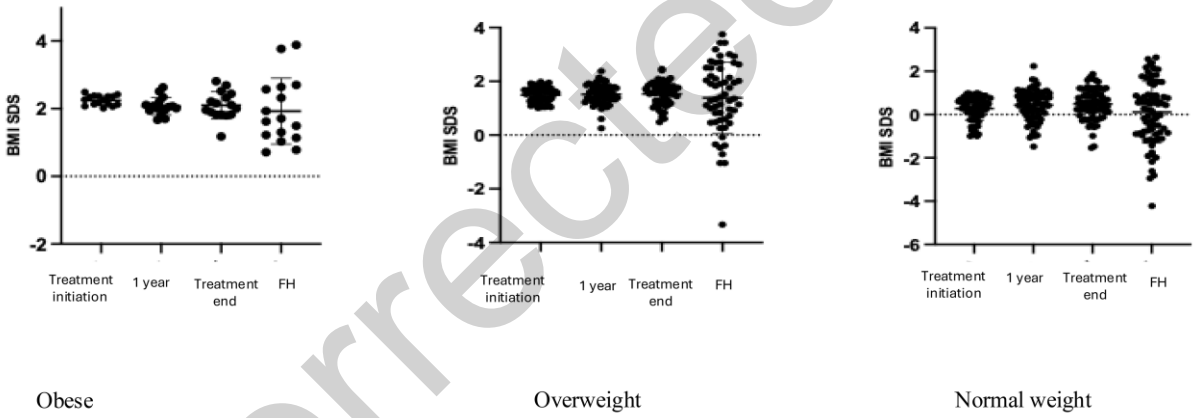

Figure 2. Changes in BMI SDS over time according to baseline weight status

Table 1. Baseline clinical and hormonal characteristics by BMI SDS category					
Variable	**All patients (n:150)**	**Normal weight (n: 77)**	**Overweight (n: 57)**	**Obese (n: 16)**	**p**
Age at treatment (years)	8.0±1.2	8.1±1.1	8.1±1.0	7.1±1.8	**0.01**
Height SDS	0.9±1.2	0.7±1.3	1.2±1.0	1.4±1.1	**<0.0001**
Weight SDS	1.1±1.0	0.5±0.8	1.7±0.5	2.5±0.6	**<0.0001**
BMI SDS	0.9±0.8	0.3±0.5	1.5±0.3	2.2 ±0.1	**<0.0001**
Bone age	9.7±1.6	9.6±1.6	9.9±1.6	9.5±2.0	0.7
BA-CA	1.6±1.3	1.4±1.0	1.6±1.7	2.4±0.6	**0.04**
Baseline LH (IU/L)	0.2(0.1-0.3)	0.2(0.1-0.3)	0.2(0.1-0.3)	0.3(0.1-0.5)	0.9
Peak LH (IU/L)	5.5(5.0-7.0)	6.4(4.8-8.3)	5.7(4.2-9.6)	7.4(3.7-10.2)	0.7
Peak LH/FSH	0.7±0.6	0.7±0.7	0.6±0.5	0.6±0.2	0.6
Uterine length (mm)	34.0±7.2	33.0±10.0	34.4±7.8	33.0±5.6	0.4
Uterine volume (cc)	4.0±3.7	4.0±3.7	4.2±4.1	3.3±1.5	0.7
Data are presented as mean±SD or median (IQR), as appropriate.					

Table 2. Changes in BMI-SDS and height-SDS from baseline to final height.					
	Baseline	**Year 1**	**Treatment end**	**Final height**	**p**
All patients **BMI SDS**	1.0(0.8-1.2)	1.1(1.0-1.3)	1.2(0.9-1.3)	0.8(0.6-1.1)	**0.001**
Height SDS	0.9(0.8-1.2)	1.0(0.9-1.2)	0.5(0.3-0.7)	-0.02(-0.3-0.2)	**<0.001**
Normal weight **BMI SDS**	0.3(0.3-0.6)	0.5(0.3-0.7)	0.5(0.3-0.7)	0.3(-0.3-0.6)	**<0.001**
Height SDS	0.8(0.4-1.0)	0.8(0.5-1.0)	0.3(0.1-0.5)	-0.4 (-0.6– -0.02)	**<0.001**
Overweight **BMI SDS**	1.5±0.2	1.5±0.4	1.5±0.4	1.4±1.3	0.4
Height SDS	1.2(0.8-1.6)	1.3(1.0-1.7)	0.7(0.3-1.2)	0.3(-0.05-0.6)	**<0.001**
Obese **BMI SDS**	2.2±0.1	2.0±0.2	2.1±0.4	1.9±1.0	0.3
Height SDS	1.5(0.8-2.3	1.6(1.1-2.3)	0.9(0.3-1.7)	0.1(-0.7-0.8)	**<0.001**
SGA **BMI SDS**	0.6(-0.5-1.4)	0.8(-0.1-1.6)	0.6(-0.3-1.1)	1.0(-0.1-1.9)	0.2
Height SDS	1.0(-0.6-2.4)	0.9(-0.7-2.3)	0.1(-1.0-1.5)	-0.7(-1.8-0.5)	**0.002**
Data are presented as mean±SD or median (IQR), as appropriate.					

Table 3. BMI SDS Changes Over Time: Pairwise P Values and Overall Four-Time-Point Comparison by Weight Group				
Comparison	**Normal-weight (n = 77)**	**Overweight (n=57)**	**Obese (n = 16)**	**All Patients (n = 150)**
Baseline ↔ 1st year	**p = 0.006 ↑**	p = 0.4	P=0.059	p = 0.067
1st year ↔ End of treatment	p = 0.3	p = 0.5	p = 0.7	p = 0.074
Baseline ↔ End of treatment	**p = 0.001 ↑**	p = 0.3	p = 0.1	**p = 0.009 ↑**
End of treatment ↔ Final adult height	**p = 0.008 ↓**	p = 0.2	p = 0.4	**p = 0.006 ↓**
Baseline ↔ Final adult height	p = 0.2	p = 0.3	p = 0.1	p = 0.1

Table 4. Baseline multivariable linear regression model for predictors of ΔBMI SDS during treatment (end of treatment − baseline)		
Independent variables	**β (95% CI)**	**p value**
Age at treatment initiation (years)	−0.005 (−0.239 to 0.229)	0.9
Baseline BMI SDS	**−0.174 (−0.291 to −0.057)**	**0.004**
Baseline height SDS	0.026 (−0.064 to 0.117)	0.5
Baseline BA–CA (years)	−0.002 (−0.030 to 0.026)	0.8
Birth weight SDS	0.218 (−0.137 to 0.574)	0.2
Treatment duration (years)	−0.029 (−0.230 to 0.173)	0.7

Table 5. Clinical data at baseline in SGA and AGA patients			
	SGA (n:13)	**AGA (n: 137)**	**p**
Birth weight SDS	-3.2±1.0	0.01±0.9	**<0,0001**
Age at treatment (years)	8.2±0.8	8.0±1.2	0.6
Height SDS	1.0 (-4.7-2.0)	1.0(0.2-1.6)	0.1
Weight SDS	0.6(-0.3-1.6)	1.2(0.5-1.9)	0.06
BMI SDS	0.5(-0.2-1.3)	1.0(0.4-1.6)	**0.04**
Bone age	9.9±1.4	9.7±1.6	0.6
BA-CA	1.7±1.2	1.6±1.4	0.8
Baseline LH (IU/L)	0.3(0.1-0.8)	0.2(0.1-0.6)	0.7
Peak LH (IU/L)	6.4+1.8	7.8+7.6	0.6
Peak LH/FSH	0.7+0.3	0.6+0.6	0.7
Uterine length (mm)	36.0±6.8	33.1±7.6	0.3
Uterine volume (cc)	8.0±6.7	3.7±3.2	0,8

Table 6. BMI SDS at Baseline, Year 1, Treatment Completion, and Final Height in SGA and AGA Subgroups			
	BMI SDS SGA (n:13)	**BMI SDS AGA (n:137)**	**p**
Baseline	0.5 ± 0.8	1.0 ± 0.8	**0.04**
Year 1	0.59 ± 0.83	1.06 ± 0.83	**0.04**
Treatment end	0.55 ± 0.72	1.10 ± 0.84	**0.01**
Final height	1.01 ± 1.07	0.77 ± 1.56	0.6

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