



The different effects of gonadotropin-releasing hormone agonist therapy on body mass index and growth between normal-weight and overweight girls with central precocious puberty

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Purpose: The effects of gonadotropin-releasing hormone agonist (GnRHa) treatment on body mass index (BMI) are controversial in girls with central precocious puberty (CPP). We therefore evaluated auxological parameters during GnRHa therapy in patients with CPP, specifically focusing on changes in BMI.

Methods: Seventy-seven girls with idiopathic CPP who underwent GnRHa therapy were retrospectively recruited. We investigated BMI changes during the treatment period after stratifying them according to baseline BMI status as follows: normal (BMI percentile of <85th) and overweight groups (BMI percentile of ≥85th).

Results: The incidence of overweight/obesity (40.3%/23.4%) was very high in the girls with CPP. In the overall study population, no significant BMI change was observed during the GnRHa treatment period. However, when stratified according to baseline BMI status, the normal-weight group showed a significant increase in BMI-standard deviation score (SDS), whereas the overweight group showed no change in BMI-SDS. Baseline BMI-SDS was an independent predictor of changes in BMI during the GnRHa treatment period. Changes in weight-SDS were similar, but changes in height-SDS were significantly greater in the overweight group than in the normal-weight group, which explains the observed difference in BMI-SDS.

Conclusion: Our results demonstrate that the difference in the pattern of BMI changes among our CPP patients suggests that delayed puberty induced by GnRHa treatment may have different effects on linear growth according to baseline body composition. This study underscores the importance of individualized lifestyle intervention in CPP children.

Keywords: Gonadotropin-releasing hormone agonist, Body mass index, Overweight, Obesity, Central precocious puberty

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Introduction

Central precocious puberty (CPP) in girls is defined as the development of sexual characteristics before the age of 8 years that result from premature activation of the hypothalamic-pituitary-gonadal axis¹. For over 30 years, gonadotropin-releasing hormone agonist (GnRHa) has been used in the treatment of CPP². Nonpulsatile administration of GnRHa effectively desensitizes the pituitary response to GnRH by downregulating the GnRH receptors, thereby suppressing the acceleration of bone maturation and premature pubertal development³. The benefits of GnRHa therapy include arrest or regression of secondary sexual characteristics, delayed menarche, and maximization of linear growth^{4,5}.

Childhood obesity has become a major health concern in recent decades since it was known

as an independent predictor of short- and long-term metabolic and cardiovascular morbidities⁶. In addition, excess adiposity during childhood is closely associated with growth and early pubertal development⁷. Although the prevalence of obesity was reported to be higher in children with CPP than in the general population^{8,9}, previous studies that evaluated the effect of GnRHa therapy on auxological parameters in CPP patients mainly focused on the improvement of final height^{10,11}, and less attention has been paid to its impact on body composition¹. In fact, limited, even somewhat controversial, data are available regarding the effects of GnRHa treatment on body mass index (BMI). Some studies demonstrated a significant increase in BMI during and after GnRHa treatment¹²⁻¹⁵, whereas others reported a lack of relationship between GnRHa administration and changes in body composition^{13,16-18}, or even a reduction in BMI^{19,20}. Despite the general agreement that GnRHa treatment does not pose an additional risk of developing obesity, a recent report suggested that baseline weight status might influence BMI parameters after treatment²¹.

In the present study, we retrospectively evaluated girls with CPP with different BMIs to (1) determine the factors that affect changes in body composition and (2) investigate whether serially assessed BMI differed between overweight and normal-weight patients during GnRHa treatment.

Materials and methods

1. Subjects

The hospital records of 77 girls diagnosed with idiopathic CPP at Hallym University Kangnam Sacred Heart Hospital were retrospectively reviewed. All the subjects received GnRHa, and the treatment was completed prior to the commencement of the study. CPP was diagnosed according to the following criteria: (1) objective breast budding appearing before the age of 8 years; (2) advanced bone age (BA), at least 1 year ahead of chronological

age (CA); (3) significantly higher peak luteinizing hormone values than the cutoff value of 5 IU/L, according to the result of a GnRH stimulation test conducted before the age of 9 years; and (4) the absence of pathology on a brain magnetic resonance imaging scan.

2. Methods

All the patients were treated with leuprolide acetate at 75–100 µg/kg every 28 days. The patients were encouraged to visit the hospital regularly, and changes in height, weight, and sexual maturity were monitored every 3 months. Height was measured by using the Harpenden stadiometer (Seca, Hamburg, Germany), and body weight was measured by using a digital scale (Dong-Sahn Jenix, Seoul, Korea). BMI was calculated as weight (kg) divided by the square of height (m²). We evaluated height, weight, BMI, and BA at the onset of GnRHa treatment, 12 months later, and at the end of the treatment. The subjects were divided into 2 groups, the normal-weight and overweight groups, based on baseline BMI. Patients with BMI percentiles ≥85th were allocated to the overweight group. Height, weight, and BMI were expressed as a standard deviation score (SDS) according to age- and sex-matched Korean standards 2007. BA was evaluated every 6 months by a single observer based on a X-ray of the left hand, according to the Greulich and Pyle method. Predicted adult height was estimated using the Bayley-Pinneau method²². Sexual maturity rating according to the Tanner staging system was assessed by one pediatric endocrinologist. This study was approved by the Institutional Review Board of Hallym University Medical Center, Seoul, Korea (approval number: 2016-02-07).

3. Statistical analyses

Values are expressed as mean±standard deviation or estimated mean±standard error. All SDS values are expressed relative to CA. Comparisons of the results were assessed by using

Table 1. Baseline characteristics of the 77 girls with central precocious puberty

Variable	Total (n=77)	Normal-weight (n=46)	Overweight (n=31)	P-value
CA (yr)	8.6±0.5	8.6±0.3	8.4±0.6	0.047
BA (yr)	10.3±0.6	10.3±0.5	10.4±0.8	0.841
BA advancement (yr)	1.8±0.5	1.7±0.5	2.0±0.6	0.020
MPH (cm)	165.4±4.6	165.9±4.3	164.6±4.9	0.207
PAH (cm)	160.3±5.6	160.3±5.3	160.3±6.0	0.988
Treatment duration (mo)	30.7±8.4	29.1±7.3	33.1±9.4	0.049
Height (cm)	136.0±5.6	136.0±4.8	135.9±6.8	0.960
Height-SDS	1.3±0.8	1.2±0.7	1.5±0.9	0.177
Weight (kg)	35.1±6.1	31.9±3.7	39.8±5.9	<0.001
Weight-SDS	1.2±0.8	0.7±0.6	1.9±0.5	<0.001
BMI (kg/m ²)	18.9±2.6	17.2±1.4	21.4±1.8	<0.001
BMI-SDS	0.8±1.0	0.2±0.7	1.7±0.4	<0.001

Values are presented as mean±standard deviation.

CA, chronological age; BA, bone age; MPH, mid parental height; PAH, predicted adult height; SDS, standard deviation score; BMI, body mass index.

the Student *t*-test or Mann-Whitney test, according to data distribution. The chi-square test was also used. For longitudinal comparisons, repeated-measures analysis of variance was performed. Analysis of covariance was used to determine the covariate-adjusted differences across the weight groups. Stepwise multiple linear regression analyses were performed to evaluate the factors that affect change in BMI-SDS during the GnRHa treatment. Statistical analyses were performed by using IBM SPSS Statistics ver. 19.0 (IBM Co., Armonk, NY, USA), and a *P*-value of <0.05 was considered statistically significant.

Results

1. Baseline characteristics of the patients

The baseline characteristics of the patients at the onset of GnRHa therapy are shown in Table 1. In our overall study population, the mean CA and BA were 8.6 ± 0.5 and 10.3 ± 0.6 years, respectively, and the mean treatment duration was 30.7 ± 8.4 months. Of the 77 patients, 46 (59.7%) were in the normal-weight group and 31 (40.3%) were in the overweight group. Among the baseline variables, except for body composition indexes, CA and BA advancement were significantly different between the normal-weight and the overweight groups (age: 8.6 ± 0.3 years vs. 8.4 ± 0.6 years, $P=0.047$; BA advancement: 1.7 ± 0.5 years vs. 2.0 ± 0.6 years, $P=0.020$). The mean treatment duration was slightly longer in the overweight group than in the normal-weight group (33.1 ± 9.4 months vs. 29.1 ± 7.3 months, $P=0.049$).

2. Prevalence of overweightness and obesity

At the onset of treatment, 13 of all the patients (16.9%) were overweight (85th percentile \leq BMI < 95th percentile) and 18 (23.4%) were obese (BMI \geq 95th percentile). At 12 months later, the proportion of overweight children increased (+5.2%), while the number of children with overt obesity decreased (-1.3%). At the end of the GnRHa treatment, 15 (19.5%) were overweight, and another 15 were obese. However, the overall difference in BMI-SDS between before and after treatment was not statistically significant (Table 2).

3. Changes in BMI-SDS and height-SDS during GnRHa treatment

In the overall study population, a slight, but not significant, increase in BMI-SDS was noted (from 0.83 ± 0.95 at the start of therapy to 0.87 ± 0.85 at the end of therapy, $P=0.492$). When stratified according to baseline weight status, the normal-weight group showed a significant increase in BMI-SDS at 12 months (0.36 ± 0.63 , $P=0.027$) and at the end of treatment (0.39 ± 0.67 , $P=0.025$) as compared with the pretreatment BMI-SDS (0.24 ± 0.73). On the other hand, the overweight group had a stable BMI-SDS during the treatment period (from 1.73 ± 0.38 at the start of therapy to 1.60 ± 0.52 at the end of therapy, $P=0.065$) (Table 2, Fig. 1A). In the multiple linear regression analysis, baseline BMI-SDS was the only factor that affected the change in body composition (delta-BMI-SDS; Table 3).

Suppression of the pituitary-gonadal axis by GnRHa administration led to a significant decrease in linear growth rates (height-SDS: from 1.32 ± 0.81 at baseline to 0.82 ± 0.83 at the end of therapy, $P<0.001$) (Table 2). This downward trend was consistent in both groups (height-SDS: normal-weight, from 1.21 ± 0.70 to 0.70 ± 0.72 , $P<0.001$; overweight, from 1.47 ± 0.94 to 1.00 ± 0.96 , $P<0.001$).

4. Intergroup difference in variation of BMI-SDS (delta-BMI-SDS) during GnRHa treatment

The changes in BMI-SDS (delta-BMI-SDS) during the entire GnRHa treatment period were significantly different between the normal-weight and overweight groups (0.15 ± 0.44 vs. -0.14 ± 0.40 , $P=0.005$) (Fig. 1B). The results were similar after adjustment for baseline covariates such as age, BA advancement,

Table 3. Multiple regression analysis of factors that influence changes in BMI-SDS (Δ BMI-SDS) during gonadotropin-releasing hormone agonist treatment

Covariate	Δ BMI SDS		
	B \pm SE	β	<i>P</i> -value
Age	-0.114 \pm 0.132	-0.133	0.392
Treatment duration	-0.004 \pm 0.009	-0.074	0.653
BA advancement	-0.009 \pm 0.102	-0.011	0.930
PAH	-0.007 \pm 0.009	-0.091	0.417
Baseline BMI-SDS	-0.220 \pm 0.055	-0.472	<0.001

BMI-SDS, body mass index-standard deviation score; SE, standard error; BA, bone age; PAH, predicted adult height.

Table 2. Changes in BMI-SDS and height-SDS in girls treated with gonadotropin-releasing hormone agonist at the start of therapy, 12 months later, and at the end of therapy

Duration	Total (n=77)		Normal-weight (n=46)		Overweight (n=31)	
	BMI-SDS	Height-SDS	BMI-SDS	Height-SDS	BMI-SDS	Height-SDS
Start of therapy	0.83 ± 0.95	1.32 ± 0.81	0.24 ± 0.73	1.21 ± 0.70	1.73 ± 0.38	1.47 ± 0.94
12 Months later	0.91 ± 0.86	1.18 ± 0.79	0.36 ± 0.63	1.06 ± 0.68	1.73 ± 0.41	1.35 ± 0.91
End of therapy	0.87 ± 0.85	0.82 ± 0.83	0.39 ± 0.67	0.70 ± 0.72	1.60 ± 0.52	1.00 ± 0.96

Values are presented as mean \pm standard deviation. All SDS values are expressed relative to chronological age. BMI, body mass index; SDS, standard deviation score.

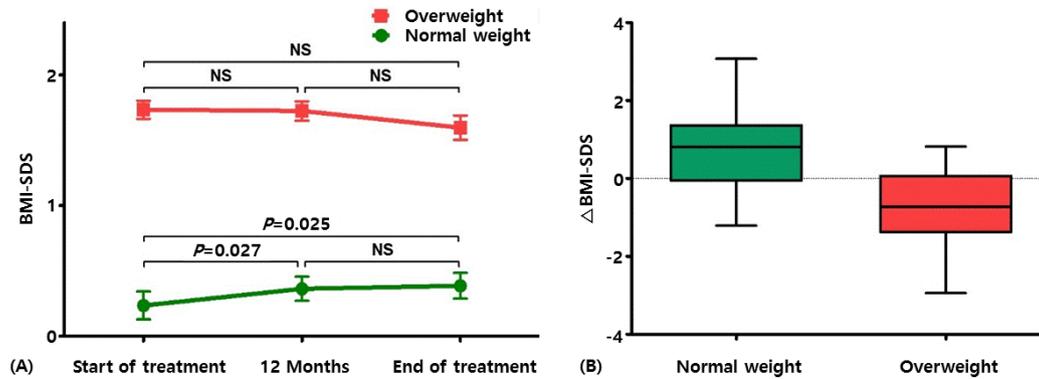


Fig. 1. (A) Serial changes in body mass index-standard deviation score (BMI-SDS) during gonadotropin-releasing hormone agonist treatment. (B) Comparison of variations in BMI-SDS (Δ BMI-SDS) between the normal-weight and overweight groups. NS, not significant.

Table 4. Changes (Δ) in height and weight parameters during the gonadotropin-releasing hormone agonist treatment period

Variable	Normal-weight (n=46)	Overweight (n=31)	P-value
Δ Height	13.26 \pm 0.28	14.37 \pm 0.35	0.019
Δ Weight	11.42 \pm 0.53	13.36 \pm 0.65	0.028
Δ BMI	2.15 \pm 0.21	2.04 \pm 0.25	0.732
Δ Height SDS	-0.55 \pm 0.04	-0.41 \pm 0.05	0.033
Δ Weight SDS	0.78 \pm 0.81	-0.01 \pm 0.99	0.549
Δ BMI SDS	0.53 \pm 0.14	-0.70 \pm 0.17	<0.001

Values are presented as estimated mean \pm standard error after Bonferroni adjustment for multiple comparisons of the following baseline covariates: age, treatment duration, and bone age advancement.

BMI, body mass index; SDS, standard deviation score.

and treatment duration. We further analyzed height and weight parameters to elucidate the intergroup difference in delta-BMI-SDS. Gains in stature (delta-height) and weight (delta-weight) were both greater in the overweight group than in the normal control (Table 4). As for variations in height- and weight-SDS, statistical significance was observed only for delta-height-SDS ($P=0.033$) (Table 4), indicating that the reduction in BMI was because statural growth outweighed weight gain in the overweight girls (Table 4).

Discussion

In the present study to address the effect of GnRHa treatment on body composition, we evaluated girls with CPP with different body compositions and demonstrated a significant difference in the patterns of the changes in BMI between the normal-weight and overweight CPP patients. Through stepwise regression analyses, we reaffirmed that weight status at the onset of treatment was the only factor that affected GnRHa-related changes in body composition. Unlike the overweight patients who maintained a relatively stable body composition, the girls with normal weight at baseline showed a significant increase in BMI-SDS during the treatment period, which was mainly

attributable to the difference in statural growth between them.

Childhood obesity, an important predictor of morbidity and premature mortality in adulthood²³, was reported to be quite common in children with CPP^{8,9}. Likewise, the overall incidence of obesity and overweightness was alarmingly high in our study population. The prevalence of overt obesity (23%) was also higher than that in the general pediatric population of Korea (8% for girls)²⁴. Considering its metabolic and cardiovascular complications such as impaired glucose tolerance, dyslipidemia, fatty-liver disease, hypertension, and systemic inflammation and its negative impact on psychosocial health, special cautions are required for these patients.

In the present study, the changes in BMI-SDS during GnRHa treatment showed a significant difference according to baseline BMI status. In fact, a similar finding was reported by some researchers, although the mechanism behind this phenomenon remains elusive^{14,15,21}. Wolters et al.²¹ found that BMI-SDS increased during GnRHa treatment only in normal-weight children but not in overweight children. Two other studies that demonstrated an increase in BMI-SDS in both groups showed that the change in BMI-SDS was significantly greater in normal-weight patients than in overweight patients^{14,15}. In line with the findings of previous studies, our findings strongly support that GnRHa treatment may have different effects on the body composition of CPP patients according to baseline BMI status. Based on our results, it appears reasonable to assume that this difference was attributable to the inhomogeneity in statural growth across the weight groups. Our findings, however, need more validation in a larger study population.

Growth during childhood and adolescence is controlled by many factors such as nutritional status, genes, physical activity, and hormones such as growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis, thyroid, and gonadal steroids. CPP, a clinical condition characterized by an unusually early pubertal onset, initially can cause a tall stature, but rapid bone maturation that causes premature epiphyseal fusion leads to short adult stature. Therefore, the fundamental goal of GnRHa treatment is to delay puberty until a more appropriate age so that prepubertal

growth can continue while slowing bone maturation²⁵). A number of studies have demonstrated that during the prepubertal phase, obese children exhibit higher growth velocity than lean subjects. However, this prepubertal advantage in growth is counterbalanced by an attenuated pubertal growth spurt and earlier pubertal maturation, achieving final heights similar to those in non-obese children²⁶). This unique growth pattern of obese children provides an insight on why our overweight/obese CPP patients, while still in prolonged prepubertal phase via GnRHa therapy, grew taller than the normal-weight patients did. More rapid bone maturation (delta BA: normal-weight vs. overweight, 1.31 ± 0.06 vs. 1.66 ± 0.07 ; $P < 0.001$) in our overweight group also supports this hypothesis. In addition, GnRHa-driven GH/IGF-1 axis modulation and subsequent decrease in levels of biologically active IGF-I²⁷) might have played a role because somatic growth in obese children appeared to be largely GH independent^{26,27}). Further well-designed prospective studies are required to validate our findings and to investigate whether delaying puberty with GnRHa treatment results in more favorable long-term outcome particularly in CPP patients who are overweight or obese at baseline.

Controversy persists regarding the effect of GnRHa treatment on body fat and composition in CPP patients. Several studies have demonstrated that the percentage of fat mass or body fat-SDS and BMI-SDS increased during GnRHa treatment^{14,15,28-30}). Conversely, some studies reported that GnRHa treatment had no effect on change in BMI^{13,16,18,31}). Another study found that BMI-SDS and obesity prevalence decreased during GnRHa therapy in girls with idiopathic CPP¹⁹). Inconsistency in the literature may be affected by several factors such as lack of a control group, and differences in population age, treatment duration, and sex distribution. However, it should be noted that previous studies that demonstrated an increase in BMI-SDS during GnRHa treatment included mostly normal-weight children^{14,28,29}), while studies with negative results were based predominately on overweight children^{13,18,31}). Our findings that support the novel notion that GnRHa treatment-derived delayed puberty may lead to dissimilar linear growth according to individual body fat status would provide a plausible explanation for the observed inconsistencies.

Our study has some limitations. First, we had no control group because most of the CPP children underwent GnRHa treatment. Our population was relatively well-balanced (46 normal-weight patients vs. 31 overweight patients). As for a retrospective study, however, the present results could be confounded by a small, unequal sample size. Furthermore, although we performed analysis of covariance, one of the most commonly used statistical methods to adjust baseline covariates (e.g., age, BA advancement, and treatment duration), nonrandomized retrospective design of this study inevitably has a risk of introducing hidden bias³²). The present findings could not be applied to the general CPP population because we only analyzed girls. On the other hand, however, unisexuality can be a forte considering the heterogeneities in growth pattern across sexes. Finally, although neither lifestyle modification nor strict

dietary restriction was recommended during the treatment period, obese children, who are more likely to be self-conscious about fatness, may behave in different ways from normal-weight children, which might have biased our results.

The present study, which demonstrated a significant difference in the patterns of BMI changes between the normal- and overweight/obese CPP patients, strongly suggests that delaying puberty with GnRHa treatment has different effects on growth according to baseline body composition. Moreover, our systematic analyses based on auxological parameters provided a mechanistic insight into this phenomenon. Given the high incidence of obesity in CPP children, the present finding prompted further study to determine whether establishing an individualized treatment strategy based on pretreatment body composition has clinically relevant roles in promoting healthy growth and in preventing obesity in CPP patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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