The Effect of Gonadotropin-releasing Hormone Analog Treatment on Body Mass Index and Height in Female Patients with Central Precocious Puberty

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ABSTRACT

Aim: Gonadotropin-releasing hormone agonists (GnRHa) are widely used in the treatment of central precocious puberty (CPP). There is concern that GnRHa treatment, whose positive effects on the adult height are known, may cause weight gain and body mass index (BMI) increase. The aim of this study was to assess the effect of the GnRHa treatment on BMI and height in female patients with CPP.

Materials and Methods: Ninety-two patients diagnosed with idiopathic CPP and 22 patients diagnosed with organic CPP, who received GnRHa treatment were included in the study. Data taken on the treatment start date, 6th month, 1st and 2nd year for height, weight, BMI and bone age were obtained retrospectively from the file records.

Results: BMI standard deviation score (SDS) increased during the treatment period in all the patients. In the second year of GnRHa treatment, BMI SDS was higher in the organic CPP, compared to the idiopathic CPP (0.66±0.84 and 1.35±0.72, p=0.007). In both groups, at the beginning of GnRHa treatment, the BMI SDS increase was higher in those patients with normal weight compared to those who were overweight/obese. In both groups, the prevalence of obesity was higher than the reference population at the beginning of treatment. An increase was determined in the height SDS and predicted adult height in both groups according to bone age.

Conclusion: In patients with CPP, the prevalence of obesity was higher in the first application compared to the reference population. In CPP, BMI SDS increased with GnRHa treatment. The weight of the patients at the beginning of the treatment affected the weight and BMI change with GnRHa treatment. Those patients with organic CPP were more prone to weight gain and BMI increase.

Keywords: Central precocious puberty, gonadotropin-releasing hormone analogues, obesity

Introduction

Precocious puberty (PP) is defined as the initiation of secondary sex characters before the age of eight in girls and nine in boys. PP may be true (central-gonadotropin dependent) or pseudo (peripheral-gonadotropin independent). Central PP (CPP) occurs with sex steroids released by the gonads as a result of an early activation of the hypothalamic-pituitary-gonadal (HPG) axis. Increased sex steroids cause an acceleration in pubertal progression, height increase and bone maturation and may lead to a reduced final adult height, early menarche, and psychological disorders (1). The purpose of treatment in CPP is to stop the progression of secondary sex characters by suppressing the HPG axis, to slow the skeletal maturation, to slow the bone epiphyseal closure, to increase adult height, and to benefit
psychosocial well-being (2). For this purpose, gonadotropin-releasing hormone agonists (GnRHa) have been widely used for the treatment of CPP for more than 30 years. GnRHa treatment that effectively inhibits gonadotropin secretion is generally a reliable treatment in children (2). In long-term follow-up studies, it was shown to increase final adult height in children with CPP but it did not show significant changes in reproductive activity (3). Studies on the efficacy and the auxological effects of GnRHa treatment in CPP are mainly related to revealing adult height gain (4). The results in the studies conducted about the effect of GnRHa treatment on body weight are contradictory. While it is reported in some studies that GnRHa treatment is linked with body fat mass, body weight and body mass index (BMI) increases (4-10), it is reported not to be linked in other studies (3,5,9,11,12). Even some studies reported that it was associated with a decrease in BMI (12,13).

Nutrition and body fat mass during childhood are closely related to PP. Considering the increasing prevalence of obesity all over the world and the higher prevalence of PP in obese people compared to the normal population (14-17), the importance of the effects of GnRHa treatment used for PP on body weight is increasing day by day.

The aim of this study was to evaluate the effects of the GnRHa treatment on BMI and height in female patients with central PP.

**Materials and Methods**

In this study, the records of patients who were diagnosed with PP in the Konya Training and Research Hospital, Clinic of Paediatric Endocrinology Outpatient between 2010 and 2018 were retrospectively reviewed. The study was approved by the Necmettin Erbakan University Faculty of Medicine Local Ethics Committee (approval number: 2017/1100). Informed consent was obtained. A total of 114 female patients, who received GnRHa treatment and were followed up in this context and were diagnosed with PP (organic CPP) were included in the study.

Patients with a history of central nervous system disease and/or pathological cranial MRI symptoms were accepted as central PP (organic CPP) developing secondarily to central nervous system pathologies. Patients who used drugs that might affect anthropometric measures and had a systemic disease such as hypothyroidism, congenital adrenal hyperplasia or Cushing’s disease were excluded from the study.

From the outpatient clinic file records of patients, their weight, height, puberty phase according to Marshall and Tanner (19), basal serum LH, follicle stimulating hormone (FSH), and estradiol studied from venous blood samples taken between 08.00-12.00 after 12-hour fasting, peak serum LH level after exogenous GnRH (gonadorelin 100 µg) intravenous injection, bone age assessment according to the Greulich and Pyle (20) method, and cranial imaging results were recorded. BMI of the patients was calculated with weight (kg) / height (cm)^2 by using their weight and height measurements; height standard deviation score (SDS), BMI SDS, BMI percentile values were obtained using standardized data prepared for Turkish children based on age and gender (21). BMI ≥95 percentile was considered as obese, 85-95 percentile as overweight, and <85 percentile as normal body weight. Predicted adult height (PAH) according to bone age was calculated according to the Bayley and Pinneau (22) method. Height SDS, BMI SDS, BMI percentile, and PAH value were calculated from the height, weight and bone age data for the 6th month, 1st year and 2nd year of the treatment in the follow-up of patients.

In the routine protocol of the clinic of paediatric endocrinology outpatient; for the treatment of PP, GnRHa leuprolide (Lucrin 3.75 mg depot) or triptorelin (Decapeptyl 3.75 mg depot) is intramuscularly administered every 28 days with a dose of 3.75 mg if the patient has a weight >20 kg and with a dose of 1.875 mg if the patient has a weight <20 kg (2). Patients undergoing treatment are followed up with anthropometric measurements, pubertal symptoms, and serum LH levels every 3 months. During the follow-up, serum LH level <3 mIU/mL at 60th minute after GnRH injection is accepted as suppressed HPG axis; serum LH level ≥3 mIU/mL is accepted as non-suppressed axis (23) and the axis is checked again in terms of suppression with a standard GnRH test in the 3rd week of GnRHa injection. A peak LH level <2 mIU/mL in the standard GnRH test is considered as suppressed HPG axis, while a peak LH ≥2 mIU/mL is considered as non-suppressed axis (24) and GnRHa treatment dose is increased to 7.5 mg/28 days. The data of the patients, who were followed up in this context and were diagnosed with central PP, and received GnRHa treatment, were included in the study.
Serum LH, FSH, and estradiol levels were studied in the Biochemistry Laboratory of Konya Training and Research Hospital using an ADVIA Centaur XP (Siemens Healthcare Diagnostics, Camberley, UK) device with a chemiluminescence immunoassay method.

Statistical Analysis
For statistical analyses, the IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY, United States of America) program was used. The data were determined as mean ± standard deviation and the significance limit for all statistics was accepted as p<0.05. In order to decide the appropriate test statistics in the evaluation of data, first the suitability of data to normal distribution was tested by applying Kolmogorov-Smirnov test statistics. In the numeric data, Student’s t-test in two-group comparisons for the data meeting normal distribution; Mann-Whitney U test for comparison of data that did not show normal distribution; ANOVA in the comparison of repeated measurements in the same group; chi-square and Fisher’s exact tests in the comparison of qualitative data were used.

Results
The admission average age was 7.84±1.01 years in the idiopathic CPP group and 7.57±0.13 years in the organic CPP group. The bone age at the beginning of the treatment was 9.99±1.13 years in the idiopathic CPP group and 9.44±1.5 years in the organic CPP group. Admission age, age at beginning of treatment, bone age, bone age-age at beginning of treatment difference, basal LH, FSH, estradiol and peak LH responses to classical GnRH test were similar in the idiopathic and organic CPP groups (Table I).

The mean BMI SDS increased during treatment in all patients receiving GnRHa treatment. BMI SDS statistically significantly increased in the 1st year (0.67±0.12 and 0.88±0.12, p<0.001) and 2nd year (0.67±0.12 and 0.89±0.11, p=0.005) compared to the beginning of treatment, in the 1st year (0.73±0.12 and 0.88±0.12, p=0.014) and 2nd year (0.73±0.12 and 0.89±0.11, p=0.023) compared to the 6th month of treatment (Table II).

When examining the mean BMI SDS values of the patients in the groups, it was determined that there was a significant increase in BMI SDS in the 1st year compared to the beginning of treatment in patients with idiopathic CPP (0.63±0.88 and 0.76±0.84, p=0.006). A significant increase was found in BMI SDS in the 2nd year compared to the beginning of treatment in the organic CPP group (0.80±0.97 and 1.35±0.72, p=0.029). Although BMI SDS was not different between the two groups in the 6th month and 1st year of GnRHa treatment, BMI SDS was significantly higher in the organic CPP group compared to the idiopathic CPP group in the 2nd year of the treatment (0.66±0.84 and 1.35±0.72, p=0.007) (Table III).

In the patients who had normal weight at the beginning of GnRHa treatment in both groups, the BMI SDS increase

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CPP: Central precocious puberty, BMI: Body mass index, tb: GnRHa treatment beginning, †p=0.005: Second year BMI SDS change compared to the beginning of treatment, ‡p=0.014: First year BMI SDS change compared to 6th month of treatment, §p=0.023: Second year BMI SDS change compared to 6th month of treatment

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CPP: Central precocious puberty, BMI: Body mass index, SDS: Standard deviation score, tb: Gonadotropin-releasing hormone agonists treatment beginning, *p=0.006: First year BMI SDS change compared to the beginning of treatment, †p=0.029: Second year BMI SDS change compared to the beginning of treatment, ‡statistical difference between groups
was higher in these patients compared to overweight-obese ones. BMI SDS at the beginning of treatment in patients who had a normal weight at the beginning of treatment in the idiopathic CPP group significantly increased in the 1st year (0.02±0.57 and 0.26±0.66, p=0.008) and 2nd year (0.02±0.57 and 0.28±0.65, p=0.011) of the treatment. Likewise, BMI SDS at the beginning of treatment in patients who had a normal weight at the beginning of treatment in the idiopathic CPP group significantly increased in the 1st year (0.02±0.57 and 0.26±0.66, p=0.008) and 2nd year (0.02±0.57 and 0.28±0.65, p=0.011) of the treatment. Likewise, BMI SDS at the beginning of treatment in patients who had a normal weight at the beginning of treatment in the idiopathic CPP group significantly increased in the 1st year (0.02±0.57 and 0.26±0.66, p=0.008) and 2nd year (0.02±0.57 and 0.28±0.65, p=0.011) of the treatment. No significant change was observed in the BMI SDS during treatment of those patients who were overweight-obese at the beginning of GnRHa treatment in both groups (Table IV).

While 34% of the patients in the idiopathic CPP group were overweight-obese (21%, 13%) at the beginning of the treatment, this rate was determined as 45% (25%, 20%) in the organic CPP group. An increase was observed in the frequency of overweight-obese patients undergoing GnRHa treatment in the organic CPP group (50%, 59%, and 64%, respectively in the 6th month, 1st year, and 2nd year of treatment). The frequency of obese patients with BMI >95 percentile was higher in the organic CPP group compared to the idiopathic CPP group both in the 1st year (47% and 18%, p=0.039) and 2nd year (57% and 19%, p=0.02) of GnRHa treatment (Figure 1).

In patients with idiopathic CPP, the 2nd year height SDS was significantly lower compared to the beginning of treatment (1.05±1.03 and 0.74±1.06, p=0.024); whereas, height SDS according to bone age was significantly higher in the 2nd year compared to the beginning of treatment (-1.01±0.95 and -0.68±0.72, p=0.03). Similarly, the height SDS of patients with organic CPP was significantly higher based on bone age compared to the beginning of treatment (-1.19±0.82 and -0.69±0.68, p=0.025). No difference was found in the height SDS in the organic CPP group in the 1st and 2nd years compared to the beginning of treatment.

PAH was determined as 158.7±6.5, 162.3±6.1, and 164.4±6.6 cm, respectively for the beginning, 1st year and 2nd year of treatment (p>0.05) in patients with idiopathic CPP, and as 159.9±6.1, 161±5.3, and 164.7±4.6 cm, respectively (p>0.05) in the organic CPP group. There was no significant difference between the two groups in terms of 1st and 2nd year PAH. ∆PAH was determined to be on average 5.7 cm in the idiopathic CPP group and 4.8 cm in the organic CPP group following 2 years of GnRHa treatment. No difference was determined in both groups in terms of ∆PAH (Table V).

The average treatment durations were 2.8±0.84 and 2.6±0.51 years, respectively for the patients with idiopathic CPP and organic CPP (p>0.05). In both groups, 65% of the patients were using leuprolide and 35% were using triptorelin and there was no difference between the groups in terms of the frequency of medication usage. Cranial imaging was performed in 104 patients from 114 patients included in the study and pathological findings were determined in 22 of them (organic CPP). Pathologies detected in cranial imaging were: septum pellucidum anomaly (n=1), hypothalamic

| Table IV. Body mass index standard deviation score changes with treatment in patients who were normal weight and overweight-obese before the gonadotropin-releasing hormone agonists treatment |
|---------------------------------|------------------|-----------------|------------------|------------------|
|                                | **Idiopathic CPP** | **Organic CPP**  |
|                                | BMI ≥85p, (n=61)  | Normal BMI, (n=31) | BMI ≥85p, (n=12) | Normal BMI, (n=10) |
| BMI SDS tb                     | 1.49±0.37        | 0.02±0.57        | 1.70±0.45        | 0.02±0.56        |
| BMI SDS 6th month              | 1.40±0.59        | 0.14±0.62        | 1.76±0.45        | 0.13±0.49        |
| BMI SDS 1st year               | 1.58±0.54        | 0.26±0.66*       | 1.82±0.22        | 0.36±0.36*       |
| BMI SDS 2nd year               | 1.47±0.56        | 0.28±0.65+       | 1.89±0.24        | 0.63±0.43+       |

CPP: Central precocious puberty, BMI: Body mass index, SDS: Standard deviation score, tb: Gonadotropin-releasing hormone agonists treatment onset, *p=0.008: First year BMI SDS change compared to the beginning of treatment; †p=0.011: Second year BMI SDS change compared to the beginning of treatment; ‡p=0.048: First year BMI SDS change compared to the beginning of treatment; ‡p=0.03: Second year BMI SDS change compared to the beginning of treatment.
Possible causes may include different designs of studies, heterogeneous etiology including idiopathic and organic etiology, different gender and age ranges, different body weights at the beginning of GnRHa treatment, different treatment strategies, and different follow-up intervals. In a recent study conducted in Spain to evaluate BMI SDS of 333 patients with CPP who received GnRHa treatment, a significant increase was determined in BMI SDS during treatment and this increase was reported to continue after the interruption of the GnRHa treatment and reaching adult height (10). Similarly, in the present study, the average BMI SDS of all our patients who received GnRHa treatment increased both in the 1st and 2nd years compared to the beginning of treatment and in the 1st and 2nd years compared to the 6th month (Table II). These results suggest that GnRHa treatment is associated with an increase in BMI and weight gain. The mechanism of GnRHa treatment causing an increase in body weight and BMI is not exactly known. There is a need for further studies on this subject that will explain the mechanism and evaluate adipokine levels involved in the energy-gonad axis such as leptin, neuropeptide Y, insulin and ghrelin.

In the present study, 1st year BMI SDS in the idiopathic CPP group and 2nd year BMI SDS in the organic CPP group showed a significant increase compared to the beginning of treatment. In the organic CPP group, the 2nd year average BMI SDS values were higher than the idiopathic CPP group (0.66±0.84 and 1.35±0.72, p=0.007) (Table III). These results revealed that GnRHa treatment caused an increase in weight and BMI in patients with both idiopathic CPP and organic CPP and the weight gain and prevalence of overweight-obesity were higher in the organic CPP group compared to the idiopathic CPP group. In the literature, there are a limited number of studies comparing the effects of GnRHa treatment on body weight and BMI in idiopathic and organic CPP groups. Feuillan et al. (26) reported in their study conducted with 18 patients with CPP caused by hypothalamic hamartoma HH-CPP and 32 patients with idiopathic CPP who received GnRHa treatment that BMI SDS was higher in patients with HH-CPP compared to the idiopathic CPP group at the beginning of the treatment, termination of the treatment and during the follow-up period after the treatment. In another study conducted to evaluate the patients with HH-CPP who received GnRHa treatment, the prevalence of overweight and obesity was reported to be high in female patients with HH-CPP (34). The structural central disorder causing organic pathology in patients with organic CPP is likely to cause more weight gain by causing changes in the neuronal network of the central nervous system.
associated with obesity and in neurotransmitters. There is a need for more related studies which include more organic CPP and control groups.

In addition to the studies reporting that the increase in BMI SDS and obesity prevalence for patients receiving GnRHa treatment is observed in those children who were overweight before the treatment (5,35), there are also other studies reporting that the patients who had normal weight at the beginning of treatment had more weight gain with GnRHa treatment compared to the overweight-obese patients (11,36,37). In the present study, a significant increase was observed in BMI SDS in both the 1st year and 2nd year of the treatment in patients who had normal weight at the beginning of treatment in both groups (Table IV). No significant change was observed in BMI SDS during the treatment period in those patients who were overweight-obese at the beginning of treatment in both groups. The present study showed that patients who had a normal weight at the beginning of treatment had the tendency to have more weight gain during the treatment and the weight at the beginning of the treatment affected the weight gain associated with GnRHa treatment. The fact that the patients who were overweight and obese at the beginning of the treatment, and their parents, were more susceptible to the possible weight gain that could develop with the treatment and so had the tendency to take measures such as diet, physical activity, and sleep regulation to prevent obesity is believed to contribute to the lower weight gain in this group.

According to the Cosi-Tur 2016 study conducted by the Ministry of Health (38), it was found that the prevalence of overweight and obesity was 24.2% in girls who were aged between 6-9 years in Turkey, the prevalence of overweight and obesity was higher with the rate of 34% in the idiopathic CPP group and 45% in the organic CPP group compared to the reference age group in our patients who were in a similar age group at the beginning of their treatment (Figure 1). Similar to the results of the present study, Anik et al. (35) reported that the overweight prevalence and obesity prevalence in patients with PP before GnRHa treatment were higher than the average of the population with rates of 37.5% and 21.9%, respectively. The high obesity prevalence determined at the beginning of GnRHa treatment in the present study shows a correlation between the obesity and PP.

In the literature, the results reporting on the prevalence of overweight-obesity in the follow-ups of GnRHa treatment in patients with CPP are contradictory similar to BMI and BMI SDS results (11,12,35). In the present study, the rate of overweight-obese patients in the idiopathic CPP group which was 34% before the treatment, increased by 42.2% in the 1st year and by 38% in the 2nd year but it was not found to be statistically significant. In the organic CPP group, the prevalence of overweight-obese patients showed a significant increase at the beginning, the 1st year, and the 2nd year of the treatment with 45%, 59% and 64%, respectively. The rate of overweight-obese patients was found to be higher in the 1st and 2nd year of the treatment in the organic CPP group compared to the idiopathic CPP group (Figure 1). Especially cases with organic CPP receiving GnRHa treatment should be monitored more carefully in terms of weight gain and risk factors that may contribute to weight gain should be eliminated during the follow-up.

In the present study, while height SDS did not change in the idiopathic and organic CPP groups in the 1st year of GnRHa treatment, it decreased in the 2nd year of treatment in the idiopathic group compared to the basal. In both groups, an increase was observed in height SDS according to bone age (Table V). Similarly, Weise et al. (39) reported that height SDS decreased according to age and height SDS increased according to bone age in 100 female patients with CPP receiving GnRHa treatment. Slowness in the rapid height increase, decrease in height SDS according to age and increase in height SDS according to bone age as a result of the rapid bone maturation stopping with GnRHa treatment are expected results and reflect the positive effect of this treatment on the height prognosis.

There are no randomized controlled studies evaluating the efficacy of GnRHa treatment in terms of height gain and most studies are conducted by comparing final height and the height before PAH treatment (4). Klein et al. (40) showed that a gain in adult height was achieved with basal PAH 149.3±9.6 cm, final height 159.8±7.6 cm compared to pre-treatment PAH in patients with PP receiving a 2-year GnRHa treatment and the height prognosis was affected positively by treatment. In the present study, an average of 5.7 cm height gain in the idiopathic CPP group and 4.8 cm height gain in the organic CPP group were obtained with a 2-year GnRHa treatment and the height prognosis was affected positively by treatment. In the present study, an average of 5.7 cm height gain in the idiopathic CPP group and 4.8 cm height gain in the organic CPP group were obtained with a 2-year GnRHa treatment, which is compatible with the literature (Table V). It was thought that GnRHa treatment was effective in terms of height gain in patients with CPP with the height SDS and PAH increase according to bone age.

**Study Limitations**

The limitations of the present study are that the study was retrospective, the number of patients was low especially in the organic CPP group, there was no control group, it included a relatively short duration of treatment, and there was a lack of follow-up after the completion of the treatment. There is a need for prospective studies which also include serum adipokine levels for the interpretation of
weight changes associated with GnRHa treatment including more patients and control groups.

**Conclusion**

The prevalence of obesity was higher in patients with CPP during the admission, and obesity is a risk factor for PP. BMI SDS increases with GnRHa treatment in CPP. Patients with organic CPP are more prone to weight and BMI increase. Patients with CPP receiving GnRHa treatment should be followed up for weight gain and obesity development and necessary precautions should be taken.

**Ethics**

**Ethics Committee Approval:** The study was approved by the Necmettin Erbakan University Faculty of Medicine Local Ethics Committee (approval number: 2017/1100).

**Informed Consent:** Informed consent was obtained.

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**


**Conflict of Interest:** No conflict of interest was declared by the authors.

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**References**