Effect of gonadotropin-releasing hormone agonist therapy on body mass index and growth in girls with idiopathic central precocious puberty

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ABSTRACT

Objective: The study aimed to assess the effect of gonadotropin-releasing hormone (GnRH) agonist therapy on body mass index (BMI) and growth in girls diagnosed with idiopathic central precocious puberty (CPP). Materials and Methods: Hospital records of 32 girls with idiopathic CPP who have been receiving GnRH agonist therapy for at least 12 months were retrospectively reviewed and auxological, clinical and laboratory parameters of the patients were recorded. BMI, body mass index standard deviation score (BMI SDS) for chronological age body mass index standard deviation score (CA-BMI SDS), BMI SDS for bone age body mass index standard deviation score (BA-BMI SDS), ratios of obesity and overweight were assessed before treatment and on the 12th month of therapy in patients diagnosed with idiopathic CPP. Results: The study comprised of 32 girls diagnosed with idiopathic CPP. BMI values showed statistically significant increase in the 1st year of treatment (19.16 ± 2.8 vs. 20.7 ± 3.4, \(P = 0.001\)). Despite a mild increase in CA-BMI SDS in the 1st year of treatment versus before treatment, it was no statistically significant (1.0 ± 0.8 vs. 1.1 ± 0.9, \(P = 0.061\)). However, significant increase was observed in BA-BMI SDS in the 1st year of treatment versus before treatment (0.8 ± 0.7 vs. 0.4 ± 0.8, \(P < 0.001\)). Before treatment, 37.5% (12/32) of the patients were overweight and 21.9% (5/32) were obese, whereas in the 1st year, 34.4% (11/32) of the patients were overweight and 31.3% were obese (\(P = 0.001\)). Conclusion: Whilst 1/3 of the cases diagnosed with idiopathic CPP were overweight and obese at the time of diagnosis, GnRH agonist therapy caused statistically significant weight gain in patients diagnosed with CPP. Therefore, these patients should be closely monitored and weight control should be provided by diet and exercise programs in the course of treatment.

Key words: Body mass index, central precocious puberty, gonadotropin-releasing hormone agonist

INTRODUCTION

Idiopathic central precocious puberty (CPP) is defined as development of secondary sex characteristics before the age of 8 in girls and 9 in boys due to early activation of gonadotropin-releasing hormone (GnRH)-secreting neurons without the presence of an organic reason.\(^1\)\(^2\) GnRH agonist therapy used in the treatment of CPP inhibits stimulating effects of endogenous GnRH by desensitizing hypophyseal gonadotropic cells and thus acceleration in bone maturation and early puberty is suppressed. This therapy delays the onset of puberty and leads to delay in menarche and provides an increase in final stature.\(^3\)\(^4\)

Many previous studies evaluating the effect of GnRH agonist therapy on anthropometric parameters in CPP patients particularly investigated the effect on adult height, however, effect on body weight has been rarely investigated.\(^5\) Nevertheless, some studies demonstrated positive and negative effects of GnRH agonist therapy on weight gain.\(^6\)\(^7\) It has been also demonstrated that weight gain continues to increase after discontinuation of therapy and may lead to obesity.\(^8\) Considering the importance of nutrition and weight gain on moving the onset of puberty to earlier, this likely side-effect becomes
Results of the studies investigating the effect of GnRH agonist therapy on body weight are quite variable. Although some studies have demonstrated weight gain resulted from GnRH agonist therapy, some studies concluded that there is no effect on body mass index (BMI). Unlike these studies, two studies demonstrated a decrease in BMI with GnRH agonist therapy. In the present study, we aimed to investigate the effect of GnRH agonist therapy on height gain and BMI in girls diagnosed with CPP.

Materials and Methods

Hospital records of 32 girls with idiopathic CPP who have been receiving GnRH agonist therapy for at least 12 months were retrospectively reviewed and auxological, clinical and laboratory parameters of the patients were recorded. Eligibility criteria were: (a) breast development before the age of 8 years, (b) presence of pubertal growth spurt, (c) bone age at least 1 year advanced than the chronological age, (d) peak luteinizing hormone (LH) ≥5 IU/L, (e) absence of history for hypothalamic/hypophyseal disease suggestive of organic CPP and normal brain magnetic resonance imaging, (f) suppressed gonadotropins and sex steroids in the course of treatment, or (g) premature menarche (≤10 years of age).

All patients have undergone a standard LHRH test. Both basal and peak LH and follicle stimulating hormone (FSH) levels were recorded. Serum LH, FSH and estradiol levels were studied by CMIA method (Abbott Architect i2000, USA). Measurable lowest limits for LH, FSH and estradiol were 0.1 IU/L, 0.6 IU/L and 20 pmol/L, respectively. All patients were treated with leuprolide (Lucrin Depot®; Takeda Pharmaceutical, Japan) or triptorelin (Decapeptyl Depot®; Ferring Pharmaceuticals, Kiel, Germany), which are depot forms of GnRH agonist, at a dose of 3.75 mg regardless of forms of GnRH agonist, at a dose of 3.75 mg regardless of

The mean age at the onset of patients’ complaints was 7.6 ± 1.2 years, whereas the mean age at the onset of treatment was 8.5 ± 1.2 years. The mean pre-treatment bone age was 2.7 ± 1.1 years higher than the chronological age (10.9 ± 1.2). At the time of diagnosis, height SDS for chronological age was 1.3 ± 1.1 and BMI SDS was 1.0 ± 0.8, whereas BMI SDS for bone age was 0.4 ± 0.8. Before treatment, mean PAH was 156.0 ± 9.2 cm and targeted height was 159.4 ± 5.4 cm. Mean basal LH and FSH levels were 1.6 ± 1.1 and 4.5 ± 1.9 respectively; mean stimulated peak LH, FSH and LH/FSH ratio were 18.8 ± 13.6, 15.7 ± 3.2 and 1.1 ± 0.6, respectively [Table 1].

It was observed that the difference between bone age and chronological age was decreased from 2.7 ± 1.1 years to 1.9 ± 1.1 years in the 1st year of treatment. No difference

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**Table 1: Characteristics of treated patients before treatment**

| Parameters                          | Mean±SD    |
|-------------------------------------|------------|
| Age at the onset of complaints (year) | 7.6±1.2    |
| Age at the beginning of treatment (year) | 8.5±1.2    |
| Bone age at the time of diagnosis (year) | 10.9±1.2   |
| Target height                       | 159.4±5.4  |
| Basal LH (IU/L)                     | 1.6±1.1    |
| Basal FSH (IU/L)                    | 4.5±1.9    |
| Peak LH (IU/L)                      | 18.8±13.6  |
| Peak FSH (IU/L)                     | 15.7±3.2   |
| Peak LH/Peak FSH (IU/L)             | 1.1±0.6    |

LH: Luteinizing hormone; FSH: Follicle stimulating hormone; SD: Standard deviation
between the pre-treatment height SDS for chronological age and height SDS in the 1st year of treatment was observed (1.3 ± 1.1 vs. 1.3 ± 1.1, \( P = 0.477 \)). However, height SDS for bone age showed statistically significant increase in the 1st year of treatment versus before treatment (−1.1 ± 1.0 vs. −0.4 ± 1.1, \( P < 0.001 \)). Although PAH was increased up to 158.9 ± 7.0 cm in the 12th month of treatment versus 156.0 ± 9.2 cm before treatment, this increase was not statistically significant (\( P = 0.113 \)). Despite tendency toward increment in CA-BMI SDS in the 1st year of treatment versus before treatment, this increase as well was no statistically significant (1.0 ± 0.8 vs. 1.1 ± 0.9, \( P = 0.061 \)). Nevertheless, statistically significant increase was observed in BA-BMI SDS in the 1st year of treatment versus before treatment (0.4 ± 0.8 vs. 0.8 ± 0.7, \( P < 0.0001 \)) [Table 2].

Before treatment, 37.5% (12/32) of the cases were overweight and 21.9% (7/32) were obese, whereas in the 1st year, 34.4% (11/32) were overweight and 31.3% (10/32) were obese (\( P = 0.001 \)) [Figure 1].

**Discussion**

The present study investigated the effect of GnRH agonist therapy on BMI in a relatively homogeneous group of girls with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP. Significant increase was observed in BMI SDS for bone age in the 1st year of treatment with idiopathic CPP.

Table 2: Anthropometric data before treatment and in the first year of treatment

| Parameters                  | Before treatment | 1st year of treatment | \( P^* \) |
|-----------------------------|------------------|-----------------------|----------|
| BMI (kg/m²)                 | 19.2±2.8         | 20.7±3.4              | <0.001   |
| CA-BMI SDS                 | 1.0±0.8          | 1.1±0.9               | 0.061    |
| BA-BMI SDS                 | 0.4±0.8          | 0.8±0.7               | <0.001   |
| CA-Height SDS              | 1.3±1.1          | 1.3±1.1               | 0.477    |
| BA-Height SDS              | −1.1±1.0         | −0.4±1.1              | <0.001   |
| PAH (cm)                   | 156.0±9.2        | 158.9±7.0             | 0.113    |
| BA (year)                  | 10.9±1.2         | 11.3±1.3              | 0.031    |

*Paired sample t test, data were presented as mean±SD, CA-BMI SDS: Chronological age body mass index standard deviation score, BA-BMI SDS: Bone age body mass index standard deviation score, CA-BMI SDS: Chronological age height standard deviation score, CA-Height SDS: Chronological age height standard deviation score, BA-Height SDS: Bone age height standard deviation score, PAH: Predicted adult height, BA: Bone age

CPP is a clinical condition characterized by accelerated growth, advancement in bone age and increment in sex steroids, which may lead to premature menarche and loss in final height unless treated. GnRH agonists used for the treatment of CPP provides an increase in final adult height by inhibiting pubertal progression and advancement in bone age. Nevertheless, there is no randomized controlled study investigating the effect of GnRH agonist therapy on adult height. Many studies have compared pre-treatment PAH with final adult height. Pasquino et al. retrospectively evaluated 87 girls diagnosed with idiopathic CPP and treated with GnRH agonist for 3-8 years and found 9.5 ± 4.6 cm increase in adult height as compared with pre-treatment PAH calculated according to Bayley-Pinneau method. Bone age at the time of diagnosis, age at the beginning of treatment and therapy duration are the factors that influence adult height. Whereas, mean height gain is 9-10 cm in girls that have been treated before the age of 6 years, it is 7.2 ± 5.3 cm in those treated between 6 years and 8 years. Likewise, the present study as well found that PAH has been increased to 158.9 ± 7.0 from 156.0 ± 9.2 at the time of diagnosis. Weise et al. evaluated growth rate in 100 girls treated for CPP and found that growth rate for chronological age (height velocity) has decreased below normal values in the course of treatment (−1.6 ± 1.7 SDS) and that growth rate is inversely proportional to duration of exposure to high estrogen before treatment. Nevertheless, they found the growth rate for bone age to be normal, even increased, in girls aged less than 10 years and height SDS for bone age to be increased after treatment. In the present study, height SDS for chronological age showed no change in the 1st year of treatment versus before treatment (1.3 ± 1.1 SDS). However, height SDS for bone age has been increased to −0.4 ± 1.1 SDS in the 1st year of treatment from −1.1 ± 1.0 before treatment and this increment was statistically significant.

In the literature, results of the studies evaluating the effect of GnRH agonist therapy on BMI are conflicting. There are studies demonstrating that GnRH agonist therapy increases BMI SDS as well as studies expressing just the opposite, reporting that GnRH agonist therapy.

![Figure 1: Change in body weight of the patients in the 1st year of treatment versus before treatment (PT: Post-treatment)](image-url)
has no significant effect on BMI SDS and obesity.[8,10,25] The reason of this inconsistency between the studies is not clear. Likely causes of this inconsistency include different age, sex and body weight of study participants at the onset of GnRH agonist therapy. Oostdijk et al.[26] and Ko et al.[27] reported that BMI SDS was increased both for bone age and for chronological age in CPP patients receiving GnRH agonist therapy. Increase in BMI SDS with GnRH agonist therapy is mostly seen in children who are overweight before treatment.[14] Nonetheless, Wolters et al. found that BMI SDS was increased in children with normal body weight before GnRH agonist therapy and that unlike control group, BMI SDS remained stable in children who were overweight before treatment.[28] In the present study, it was observed that BA-BMI SDS was significantly increased in the 1st year of treatment versus before treatment and that CA-BMI SDS was also increased in the 1st year of treatment versus before treatment, but the difference was not statistically significant. Whilst obesity was not observed in the 1st year of treatment in the group with normal body weight before treatment, obesity was observed in 5 of 12 children who were overweight before the treatment.

In summary, the height SDS for bone age significantly increased during GnRH agonist treatment in our patients and the PAH was also increased after treatment. Furthermore, the BMI SDS for bone age increased significantly. It is difficult to determine whether increased BMI is a result of therapy or is an expected manifestation of the primary process. Preventive measures, such as increased physical activity, can be introduced to minimize possible alterations in body weight and a long-term follow-up study is required to elucidate whether GnRH agonist treatment in Turkish girls with CPP affects adult obesity.

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