Original Article

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

Ahmet Anık, Gönül Çatlı, Ayhan Abacı, Ece Böber

Department of Pediatric Endocrinology, Faculty of Medicine, Dokuz Eylül University, Izmir, Turkey

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.[6] Considering the importance of nutrition and weight gain on moving the onset of puberty to earlier, this likely side-effect becomes

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.131770

Corresponding Author: Dr. Ayhan Abacı, Department of Pediatric Endocrinology, Dokuz Eylül University, Faculty of Medicine, Izmir, Turkey. E-mail: ayhanabaci@gmail.com

more important.[8-10] 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,[6,7,11,12] some studies concluded that therapy has no effect on body mass index (BMI).[13,14] Unlike these studies, two studies demonstrated a decrease in BMI with GnRH agonist therapy.[8,15] 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 chemiluminescent microparticle immunoassay (CMIA) method after exogenous intravenous administration of luteinizing-hormone releasing hormone (LHRH) (gonadorelin 100 μg), (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 body weight and administered through intramuscular route every 28 days. Suppression of hypothalamus-pituitary-gonad axis was checked every 3 months and adequate suppression was considered in patients with clinically paused or regressed pubertal signs and a serum LH level < 0.4 IU/L and estradiol level <20 pg/ml before GnRH agonist injection.[16] The height was measured by Harpenden stadiometer of 0.1 cm sensitivity and the body weight was measured by SECA scale of 0.1 kg sensitivity. BMI was calculated using weight (kg)/height^2 (m) formula. BMI was assessed according to the data of Center for Disease Control. Cases with a BMI percentile of 85-95 were considered overweight and >95 were considered obese. Weight, height, BMI and bone ages of the patients were recorded before treatment and on the 12th month of treatment. Height standard deviation score (SDS) was calculated both for bone age height standard deviation score and for chronological age height standard deviation score. Likewise, body mass index standard deviation score (BMI SDS) was calculated both for bone age body mass index standard deviation score (BA-BMI SDS) and for chronological age body mass index standard deviation score (CA-BMI SDS). Bone age was assessed by Greulich-Pyle method,[17] whereas sexual maturation was assessed by Marshall-Tanner method.[18] Predicted adult height (PAH) was calculated according to Bayley-Pinneau method.[19] Targeted adult height was calculated by subtracting 6.5 to the mean of parental heights.

Statistical analysis

Statistical analyses were performed by Statistical Package for Social Sciences version 19.0 (Inc., Chicago, IL, USA). All data were presented as mean ± standard deviation and paired *t*-test was used for the comparison of data. In the case of longitudinal comparisons of the same parameter, repeated-measures ANOVA was performed. A *P* value of less than 0.05 was considered statistically significant.

Results

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

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.

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.[3,4] 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.[20] 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.[5] 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.[21] 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,[6,14,22-24] as well as studies expressing just the opposite, reporting that GnRH agonist therapy

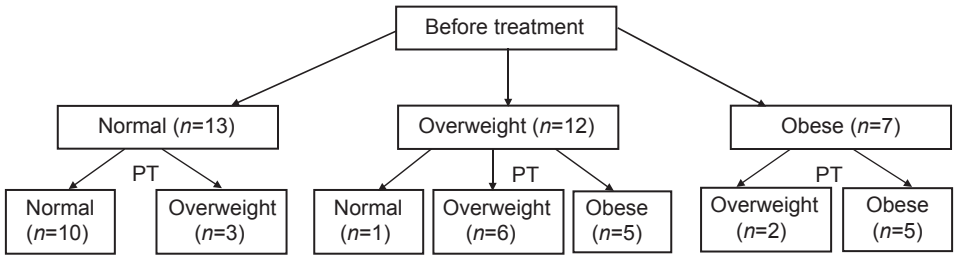

Figure 1: Change in body weight of the patients in the 1st year of treatment versus before treatment (PT: Post-treatment)

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.

It has been reported that obesity is more common in girls with CPP.[25] Studies conducted in different geographical regions of our country found the prevalence of overweight to be 9.9-14.3% and obesity to be 1.6-7.8% in children.[29] In the present study, 37.5% of the cases were overweight and 21.9% were obese before treatment so as to corroborate that overweight-obesity is frequent in cases with precocious puberty and was consistent with the literature. It is not clear whether weight gain leads to precocious puberty or pubertal development leads to weight gain. It is known that an adequate amount of leptin is required for the initiation of puberty and leptin initiates pubertal development by increasing gonadotropin secretion.[30] Nevertheless, gonadal steroids secreted in case of precocious puberty also cause increment in body fat.[31] In the light of this information, the present study failed to explain weight gain in cases in which synthesis of sex steroids was suppressed with GnRH agonist therapy. It will also be important to determine in future studies whether the subjects with CPP had elevated BMI SDS before the onset of precocious pubertal development or only after exposure to a pubertal gonadal steroid milieu.

Limitations of the present study are: (a) Absence of a control group due to ethical concern; (b) absence of information about BMI SDS values after discontinuation of therapy; (c) probability of different therapy responses among patients due to the use of standard dose of GnRH agonist (regardless of body weight) and thus absence of standardization; (d) unavailability for the auxologic data of the parents.

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.

References

1. Carel JC, Léger J. Clinical practice. Precocious puberty. N Engl J Med 2008;358:2366-77.
2. Nebesio TD, Eugster EA. Current concepts in normal and abnormal puberty. Curr Probl Pediatr Adolesc Health Care 2007;37:50-72.
3. Carel JC, Lahlou N, Roger M, Chaussain JL. Precocious puberty and statural growth. Hum Reprod Update 2004;10:135-47.
4. Kauli R, Galatzer A, Kornreich L, Lazar L, Pertzelan A, Laron Z. Final height of girls with central precocious puberty, untreated versus treated with cyproterone acetate or GnRH analogue. A comparative study with re-evaluation of predictions by the Bayley-Pinneau method. Horm Res 1997;47:54-61.
5. Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, ESPE-LWPES GnRH Analogs Consensus Conference Group, *et al*. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics 2009;123:e752-62.
6. Feuillan PP, Jones JV, Barnes K, Oerter-Klein K, Cutler GB Jr. Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: Long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. J Clin Endocrinol Metab 1999;84:44-9.
7. Lee SJ, Yang EM, Seo JY, Kim CJ. Effects of gonadotropin-releasing hormone agonist therapy on body mass index and height in girls with central precocious puberty. Chonnam Med J 2012;48:27-31.
8. Arrigo T, De Luca F, Antoniazzi F, Galluzzi F, Segni M, Rosano M, *et al*. Reduction of baseline body mass index under gonadotropin-suppressive therapy in girls with idiopathic precocious puberty. Eur J Endocrinol 2004;150:533-7.
9. Głab E, Barg E, Wikiera B, Grabowski M, Noczyńska A. Influence of GnRH analog therapy on body mass in central precocious puberty. Pediatr Endocrinol Diabetes Metab 2009;15:7-11.
10. Heger S, Partsch CJ, Sippell WG. Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: Final height, body proportions, body composition, bone mineral density, and reproductive function. J Clin Endocrinol Metab 1999;84:4583-90.
11. Carel JC, Roger M, Ispas S, Tondu F, Lahlou N, Blumberg J, *et al*. Final height after long-term treatment with triptorelin slow release for central precocious puberty: Importance of statural growth after interruption of treatment. French study group of decapeptyl in precocious puberty. J Clin Endocrinol Metab 1999;84:1973-8.
12. Chiumello G, Brambilla P, Guarneri MP, Russo G, Manzoni P, Sgaramella P. Precocious puberty and body composition: Effects of GnRH analog treatment. J Pediatr Endocrinol Metab 2000;13 Suppl 1:791-4.
13. Messaaoui A, Massa G, Tenoutasse S, Heinrichs C. Treatment of central precocious puberty with Gonadotropin-Releasing Hormone agonist (triptorelin) in girls: Breast development, skeletal maturation,

height and weight evolution during and after treatment. Rev Med Brux 2005;26:27-32.
14. Palmert MR, Mansfield MJ, Crowley WF Jr, Crigler JF Jr, Crawford JD, Boepple PA. Is obesity an outcome of gonadotropin-releasing hormone agonist administration? Analysis of growth and body composition in 110 patients with central precocious puberty. J Clin Endocrinol Metab 1999;84:4480-8.
15. van der Sluis IM, Boot AM, Krenning EP, Drop SL, de Muinck Keizer-Schrama SM. Longitudinal follow-up of bone density and body composition in children with precocious or early puberty before, during and after cessation of GnRH agonist therapy. J Clin Endocrinol Metab 2002;87:506-12.
16. Kunz GJ, Sherman TI, Klein KO. Luteinizing hormone (LH) and estradiol suppression and growth in girls with central precocious puberty: Is more suppression better? Are pre-injection LH levels useful in monitoring treatment? J Pediatr Endocrinol Metab 2007;20:1189-98.
17. Greulich WW, Pyle SI Radiographic Atlas of Skeletal Development of the Hand and Wrist. Stanford: Stanford University Press; 1959.
18. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44:291-303.
19. Bayley N, Pınneau SR. Tables for predicting adult height from skeletal age: Revised for use with the Greulich-Pyle hand standards. J Pediatr 1952;40:423-41.
20. Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: Impact on adult height, body mass index, bone mineral content, and reproductive function. J Clin Endocrinol Metab 2008;93:190-5.
21. Weise M, Flor A, Barnes KM, Cutler GB Jr, Baron J. Determinants of growth during gonadotropin-releasing hormone analog therapy for precocious puberty. J Clin Endocrinol Metab 2004;89:103-7.
22. Aguiar AL, Couto-Silva AC, Vicente EJ, Freitas IC, Cruz T, Adan L. Weight evolution in girls treated for idiopathic central precocious puberty with GnRH analogues. J Pediatr Endocrinol Metab 2006;19:1327-34.
23. Boot AM, De Muinck Keizer-Schrama S, Pols HA, Krenning EP, Drop SL. Bone mineral density and body composition before and during treatment with gonadotropin-releasing hormone agonist in children with central precocious and early puberty. J Clin Endocrinol Metab 1998;83:370-3.
24. Traggiai C, Perucchin PP, Zerbini K, Gastaldi R, De Biasio P, Lorini R. Outcome after depot gonadotrophin-releasing hormone agonist treatment for central precocious puberty: Effects on body mass index and final height. Eur J Endocrinol 2005;153:463-4.
25. Chiocca E, Dati E, Baroncelli GI, Mora S, Parrini D, Erba P, *et al*. Body mass index and body composition in adolescents treated with gonadotropin-releasing hormone analogue triptorelin depot for central precocious puberty: Data at near final height. Neuroendocrinology 2009;89:441-7.
26. Oostdijk W, Rikken B, Schreuder S, Otten B, Odink R, Rouwé C, *et al*. Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. Arch Dis Child 1996;75:292-7.
27. Ko JH, Lee HS, Lim JS, Kim SM, Hwang JS. Changes in bone mineral density and body composition in children with central precocious puberty and early puberty before and after one year of treatment with GnRH agonist. Horm Res Paediatr 2011;75:174-9.
28. Wolters B, Lass N, Reinehr T. Treatment with gonadotropin-releasing hormone analogues: Different impact on body weight in normal-weight and overweight children. Horm Res Paediatr 2012;78:304-11.
29. Bereket A, Atay Z. Current status of childhood obesity and its associated morbidities in Turkey. J Clin Res Pediatr Endocrinol 2012;4:1-7.
30. DiVall SA, Radovick S. Endocrinology of female puberty. Curr Opin Endocrinol Diabetes Obes 2009;16:1-4.
31. Kaplowitz PB. Link between body fat and the timing of puberty. Pediatrics 2008;121 Suppl 3:S208-17.

Cite this article as: Anik A, Çatli G, Abaci A, Böber E. Effect of gonadotropin-releasing hormone agonist therapy on body mass index and growth in girls with idiopathic central precocious puberty. Indian J Endocr Metab 2015;19:267-71.

Source of Support: Nil, **Conflict of Interest:** None declared.