

The effect of gonadotropin-releasing hormone analog treatment (leuprolide) on body fat distribution in idiopathic central precocious puberty

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SUMMARY: Taşçılar ME, Bilir P, Akıncı A, Köse K, Akçora D, İnceoğlu D, Fitöz SÖ. The effect of gonadotropin-releasing hormone analog treatment (leuprolide) on body fat distribution in idiopathic central precocious puberty. *Türk J Pediatr* 2011; 53: 27-33.

Gonadotropin-releasing hormone analog (GnRHa) therapy is used in idiopathic central precocious puberty (ICPP) worldwide. It has also been shown that during this therapy, body mass index (BMI) increases slightly as a side effect. We investigated the side effects of GnRHa treatment in ICPP on body composition and insulin resistance (IR). Twenty girls (7.55 ± 1.02 y) with ICPP were treated with GnRHa (leuprolide) for an average of 20.83 ± 4.8 months. Bioelectrical Impedance Analysis (BIA) was used to measure the body's fat balance. Nine patients out of 20 (45%) had significant gain weight. We showed a significant elevation in trunk fat mass compare to baseline values ($p < 0.01$). These nine patients had high homeostasis model assessment (HOMA)-IR and low glucose/insulin (G/I) index. This study showed a slight increase in BMI, moderate increase in total body fat, and exaggerated elevation in trunk fat mass and IR in GnRHa-treated ICPP children.

Key words: leuprolide, precocious puberty, obesity, body fat composition, body mass index, hyperinsulinism.

Central precocious puberty (CPP) is characterized by premature activation of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator, with subsequent pulsatile gonadotrophin secretion. Its prevalence is estimated at 1:5,000 to 1:10,000 and it is 5 to 10 times more common in girls than in boys¹⁻⁶.

In CPP, treatment is mainly indicated for two reasons. The first is the major psychosocial stress on the affected child resulting from the very early appearance of signs of puberty and generally wrong but frequent assumption by others that the child possesses a correspondingly early mental and emotional maturity. The second reason for treatment is the risk of reduced adult height due to disproportional acceleration of skeletal age^{2,3}. Significant impairment of final height in untreated CPP

has dominated the rationale for intervening with GnRH analogue (GnRHa) treatment⁷. It has been calculated that height loss is of the order of 20 cm and 12 cm in boys and girls, respectively⁸. Few studies have evaluated the psychosocial outcome following early or precocious puberty^{7,8}. There is evidence that normal, early-maturing adolescents are more likely to have sexual intercourse and engage in substance abuse at an earlier age than normal or late-maturing adolescents⁷⁻¹⁰.

The treatment involves the administration of GnRHa where there is prolonged suppression of pituitary gonadotropins - luteinizing hormone (LH) and follicle-stimulating hormone (FSH) - and thorough down-regulation of the pituitary GnRH receptors^{2,3}. Several preparations of GnRHa are currently available. These include leuprorelin, triptorelin and goserelin, which are

Table I. Summary of BMI and Fat Distribution of All Cases

Patients (n:20)	Onset of the GnRHa therapy	At the end of first year	P
BMI	16.66 ±1.65	18.12±4.11	>0.05
Total body fat (%)	22.38±2.41	29.52±4.28	<0.05
Trunk body fat (%)	15.47±1.35	22.75±4.28	<0.01

BMI: body mass index.

each available as monthly and three-monthly depot preparations¹¹⁻¹³. A 12-month implant (histrelin) is also available¹⁴. Like with every new therapy, the long-term effects of GnRHa therapy began to be discussed by researchers. Most of them were about catch-up growth and final height of the affected child. There is also some variable evidence about the promotion of weight gain and bone metabolism¹⁵⁻²⁷. At this point, it is important to evaluate whether or not this weight gain aggravates the metabolic syndrome (MetS) risk.

Although the close relationship between MetS and obesity is accepted, it is still not clear why not all obese children have MetS. Morbidities associated with obesity are mostly related to the body's fat distribution, but body mass index (BMI), which is a criterion in MetS, does not show the body's fat distribution. Thus, it is important to evaluate the body's fat balance with other techniques. Abdominal perimeter measurements and Bioelectrical Impedance Analysis (BIA) are promising methods that can be used in children to measure the increase in the body's fat balance, which is an indication of high cardiovascular and metabolic risks^{28,29}. Although there is variable data about the GnRHa effect on BMI, there is little information about fat distribution and insulin resistance (IR). The aim of this prospective and multicentre study was to investigate longitudinally BMI changes and body fat distribution in a group of girls with idiopathic CPP (ICPP) during the GnRHa therapy. This is the preliminary report of an ongoing study.

Material and Methods

Patients

This prospective ongoing study covers 20 girls (7.55±1.02 y) with ICPP. Based on the main inclusion criteria of the study, ICPP girl

patients with normal BMI were included. The criteria for diagnosis of ICPP (30) were: (a) onset of breast development before 8 years and/or menses before 9 years of age (mean 7.55±1.02 y), (b) pubertal LH response to exogenous GnRH, (c) a ratio of stimulated LH: stimulated FSH of more than 1.0 (31,32), (d) no clinical signs and/or history of organic CPP, and (e) no evidence of hypothalamopituitary lesions on magnetic resonance imaging (MRI). Patients who had regular physical activity were excluded from the study. Girls with a family or personal history of diabetes mellitus, or who presented evidence of thyroid dysfunction, glucose intolerance, or late-onset congenital adrenal hyperplasia, and those receiving any other medication known to affect gonadal function or carbohydrate metabolism were also excluded from the study.

Auxologic and hormonal data were recorded for all patients combined with body fat distribution evaluated with BIA at the beginning and during follow-up. In all cases, bone age and pelvic ultrasonography were obtained. Variations in dietary intake and physical activity level were assessed with validated questionnaires at the beginning of and during the study. A specialist dietician prepared the dietetic list for each case according to their appropriate calorie needs. All kids were cautioned not to eat carbohydrate-rich food. Informed consent was obtained from parents and assent from the girls.

At treatment onset, all patients had a history of increased growth velocity (GV) and a breast development of Tanner stage 2 or more. In all cases, bone age (BA) was advanced more than one year beyond chronological age (CA), and the average BA:CA ratio was more than 1.

All cases were treated with GnRHa (leuprolide) 3.75 mg intramuscular (IM) every three weeks for an average of 20.83±4.8 months. Clinical examination and auxologic measurements including body fat distribution were performed

Table II. The First Year Glucose Metabolism and Lipid Profile Results of All Cases

	Fasting glucose (mg/dl)	Fasting insulin (mmol/L)	G/I	HOMA-IR	Total cholesterol (mg/dl)	HDL (mg/dl)	VLDL (mg/dl)	LDL (mg/dl)	Triglyceride (mg/dl)
Patients with weight gain (N:9)	97.40 ± 12.20	29.22 ± 7.08	3.35±0.65	4.85±0.95	156.30 ± 12.70	42.90 ± 9.80	21.00 ± 2.00	89.90 ± 9.70	92.70 ± 6.70
Patients without weight gain (N:11)	83.70 ± 13.30	6.70 ± 3.10	12.87 ± 3.89	1.37 ± 0.76	159.40 ± 18.90	47.80 ± 4.90	22.40 ± 3.00	84.10 ± 70	98.40 ± 5.10

G/I: Glucose/insulin index. HOMA-IR: Homeostasis model assessment-insulin resistance. HDL: High-density lipoprotein. VLDL: Very low-density lipoprotein. LDL: Low-density lipoprotein.

every three months (Tanita Body Composition Model No: BC-480); assessment of serum LH, FSH and estrogen levels was done during the follow-up. Blood samples for hormonal evaluation (LH, FSH) were analyzed with immunochemiluminometric assay (ICMA). BMI was calculated as weight (kg) divided by height square (m²). BMI higher than 95th percentile was defined as obesity and higher than 85th percentile was defined as overweight. Turkish standards for BMI percentile values were used (33). Fasting blood glucose and fasting insulin levels were obtained from the patients at every follow-up. Glucose/insulin ratio (G/I) [glucose (mg/dl)/insulin (mmol/L)] and homeostasis model assessment (HOMA)-IR [glucose (mmol/L) X insulin (mmol/L)/22.5] were calculated for patients, and 7 was determined as a cut-off value for G/I and 3.16 for HOMA-IR³⁴⁻³⁶.

Statistics

Statistical analyses were performed with SPSS 11.5 (SPSS, Inc., Chicago, IL) at Ankara University Medical Faculty, Department of Biostatistics. The differences between the obese and normal cases were evaluated by Student’s t test. The differences between results at the onset and at the end of the first year [BMI (adjusted for age), total body fat (%), trunk body fat (%)] were analyzed by paired t test. The level of statistical significance was set at p<0.05.

Results

The main results of the study are summarized in Tables I and II. None of our patients was overweight or obese at the beginning of the therapy. Nine patients out of 20 (45%) had significant weight gain compared to the others. The elevation in BMI values in these nine patients was significantly high compared to values at the onset of the therapy (Fig. 1). The maximum weight gain was seen at the third and sixth months of therapy, but nine patients showed slight increase in their BMI values. Although these patients became overweight and slightly obese, there were no significant differences in this BMI elevation, but they did have an elevation in BMI percentile.

Total body fat percentage was elevated in those nine patients compared to at the beginning of therapy (Fig. 2). However, it was interesting

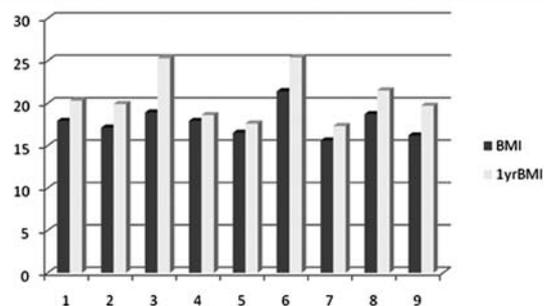


Fig. 1. BMI values of 9 cases who had insulin resistance are given patient by patient. There was a slight elevation in BMI values compared to the beginning but the difference was not significant ($p>0.05$).

to see a significant fat percentage elevation at the trunk in those nine patients ($p<0.01$) (Fig. 3). It was also correlated with the high HOMA-IR and low G/I index that resembles IR (Fig. 4).

Discussion

The aims of this prospective study were to evaluate whether obesity occurs at a high rate in ICPP during the treatment with GnRHa, and if so, do these kids carry MetS risk or IR? Variable reports were found in the literature about BMI in this group of patients^{6,9-11,17,20}. In 2004, Arrigo et al.²² published a large series of patients with CPP who showed a decrease in BMI during therapy with GnRHa. In this published data, 23.8% of the girls were obese before they started drug administration. They showed a significant decrease in both average

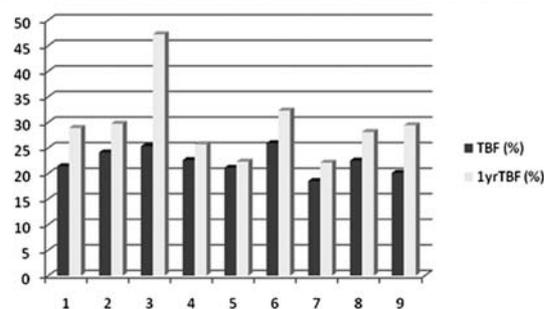


Fig. 2. Total body fat value of 9 patients with insulin resistance: total body fat (%) values of these 9 patients compared to the end of one year results are shown patient by patient. Total body fat values (%) were significantly elevated compared to the beginning ($p<0.05$).

BMI-SDS and obesity prevalence during the treatment period and a further decrease after withdrawal of the therapy in their study group. Their patients were obese at the beginning of their study compare to ours, and the authors did not mention the diet or exercise habit of these cases. Heger et al.⁶ reported that obesity in CPP does not seem to be either caused or aggravated during the treatment. Although some individuals may experience significant increases and decreases during the course of therapy, Palmert et al.²⁷ found that BMI did not change significantly during therapy. Van der Sluis et al.¹⁵ published that although there was an initial aggravation of adiposity, which follows GnRHa therapy onset, no prolonged negative effects were detectable. Pasquino et al.¹¹ published that there was an increase in BMI values during and after the treatment, but it was not significant, like our results. The differences between all these studies can be explained by individual differences and different drug administration. Recently, Carel et al.²⁰ published the consensus statement on the use of GnRH in children. That conference did not endorse commonly voiced concerns regarding the use of GnRHa, such as promotion of weight gain. Our outcome data showed parallelism with the literature by showing a slightly higher BMI but not significant values^{6,11}. Even though our study group was small in comparison with other studies, this is an ongoing study and it is the preliminary report of our results. The advantage of this study is that with the programmed diet and exercise habit, our group seems more homogeneous. During therapy with GnRHa, we assumed that these patients had a kind of harmless transient pseudomenopause. Pescovitz et al.³⁷ described other side effects such as headache, hot flashes and nausea during GnRHa therapy. They also used the terminology of menopause while explaining these side effects. Cardiovascular disease risk rises sharply with menopause, likely due to the coincident increase in IR and related atherogenic changes that together comprise the metabolic or IR syndrome, a cluster of metabolic and hemodynamic abnormalities strongly implicated in the pathogenesis and progression of cardiovascular disease³⁸. In our study group, the kids who had weight gain showed IR (45%). Not all women gain weight in the menopausal period but some do,

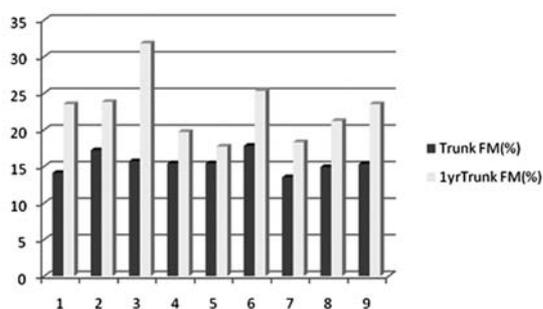


Fig. 3. Trunk fat percentage of 9 patients with insulin resistance: trunk fat (%) of those patients was significantly increased compared to the beginning ($p < 0.01$).

as did these kids. Although it is a subjective observation, there was an increase in these kids' appetite. It is hard to determine which mechanism triggered the appetite in our study group. More studies, which are focused on the mechanisms of appetite, need to be done in this area. Since the 1970's, medroxyprogesterone acetate has been used in the management of ICPP, and an increased weight gain in patients was reported, as in our study^{39,40}. From this point of view, it can be suggested that this is not a drug side effect, but probably the result of the pause of pubertal development that mimics menopause. There can also be other unknown mechanisms affecting weight gain in those kids. Because this study is ongoing, we also cannot say what will happen after the cessation of therapy. We suggest that larger studies would be more helpful to evaluate this point. The most important data that we want to highlight is the IR results of the cases. To assess body fat composition by BIA is a promising and harmless method compared to other methods, which contain the risk of radiation and are hard to use^{28,29}. We suggest that using Tanita BC 480 will be helpful in regular longitudinal

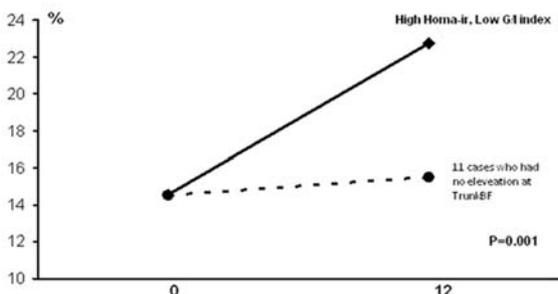


Fig. 4. Comparison of the 9 cases with insulin resistance (+) to the others.

follow-up during the therapy with GnRHa. Metformin appears to have a direct effect on ovarian steroidogenesis, specifically to reduce both androgen and estradiol production and as a therapeutic agent in IR cases⁴¹. New approaches in ICPP therapy may need to include the discussion of the combination of GnRHa therapy with metformin in those patients with an elevation in trunk fat percentage. We also cannot predict what will happen after the recess of GnRHa therapy. Will this IR continue in those patients or will it resolve; at this point, it is hard to say with certainty. We suggest that our later results will be informative, but other future investigations with larger numbers might need to be done in this area.

In conclusion, this preliminary report of our study showed a slight increase in BMI and moderate increase in total body fat percentage. It was interesting to find an exaggerated elevation in trunk fat mass and IR in these patients. We suggest that further investigations need to be done in this area; combination of metformin therapy will be helpful in avoiding this complication.

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