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Changes in body composition and muscle strength in girls with idiopathic central precocious puberty during gonadotropin-releasing hormone agonist therapy

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ABSTRACT

Aims: Our objective is to explore changes in body fat distribution and muscle strength among a cohort of girls with idiopathic central precocious puberty (ICPP) undergoing the gonadotropin-releasing hormone analogs (GnRHa) therapy.

Methods: A total of 50 patients who were newly diagnosed with ICPP and treated with GnRHa were included in the study. Patients were investigated at baseline, 6th months and 12th months.

Results: Body-mass index (BMI) standard deviation score (SDS) was similar throughout the treatment duration. The percentage of body fat (PBF) increased from 24.2±5.1% at the beginning to 26.3±5.3% at the 6th month and to 27.7±5.43% at the 12th month ($p<0.001$). While lean body mass (LBM) increased during the treatment duration ($p<0.001$), there was a decrease in the LBM percentage in both the 6th month and 12th month ($p=0.001$, $p=0.005$). The change in PBF between 0 and 12 months was significantly higher in the group with PBF<97th percentile (p), with a median of 2.3 (3.3)%, compared to a median of 0.5 (0.5)% in the group with PBF>97th p ($p=0.005$).

Conclusion: Over the one-year duration of GnRHa treatment, no increase was observed in BMI SDS. While PBF increased, a decrease was noted in LBM percentage. Despite the decrease in LBM percentage, since LBM increased over the course of treatment, an increase in muscle strength was observed under GnRHa therapy. Additionally, the alteration in PBF during GnRHa treatment exhibited variations based on the initial PBF status.

Keywords: Central precocious puberty, GnRHa therapy, body composition, lean body mass, muscle strength

INTRODUCTION

Pubertal development involves the chemical maturation of body tissues, leading to changes in the quantity and distribution of adipose tissue, as well as increases in bone mass and fat-free lean tissue mass.[1] Key features of puberty include the appearance of secondary sex characteristics, accelerated skeletal maturation, and alterations in body fat distribution.[2] Central precocious puberty (CPP) results from the premature reactivation of the gonadotropin-releasing hormone (GnRH) pulse generator in the hypothalamus, causing the onset of secondary sexual characteristics before the age of eight in females and nine in males.[3] The idiopathic CPP (ICPP) diagnosis is established once all organic causes have been ruled out.[4] GnRH analogs (GnRHa) are the standard of care for treating CPP. However, despite their established safety and efficacy, significant questions persist, particularly concerning their impact on body-mass index (BMI).[3] The literature presents diverse data concerning the impact of GnRHa on BMI and raises concerns about body fat composition. There is variability in the findings, and particular attention has been drawn to the potential susceptibility of children with CPP to the development of adiposity.

Dual-energy lowercase letter (X-Ray) absorptiometry, bioelectrical impedance analysis (BIA), ultrasonography (USG), computed tomography, and magnetic resonance imaging (MRI) serve as essential tools for evaluating adiposity as well as the quantity and distribution of muscle mass in pediatric and adolescent patients.[1] Particularly, BIA stands out as a widely embraced method for assessing body composition, attributed to its user-friendly application, safety, non-invasiveness, cost-effectiveness, repeatability, and rapid result delivery.

During puberty, changes in hormone levels can lead to an increase in muscle mass and the development of muscle strength. However, the effects on muscle strength during puberty can vary from person to person. These effects may depend on various factors such as genetic factors, level of physical activity, dietary habits, and other environmental factors. The impact of early onset puberty and halting pubertal

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progression through the treatment on muscle strength is also a topic of interest. To measure muscle strength, various methods can be used including manual muscle testing, the Oxford Scale, isotonic, isokinetic, and isometric methods. Isometric methods measure the maximum static strength of the muscle. Evaluating muscle function, especially in children and adolescents, can be challenging. The most commonly used technique, due to its low cost and affordability, is hand dynamometry.[5]

This study aims to investigate alterations in BMI, body fat distribution with BIA and muscle strength with hand dynamometry in a group of girls with ICPP undergoing GnRHa therapy. Additionally, it aims to explore the factors influencing fat distribution during treatment.

METHODS

Study Design

Approval was obtained from the Akdeniz University Faculty of Medicine Clinical Researches Ethics Committee prior to the commencement of the study (Date: 16.03.2022, Decision No: KAEK-195). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study was designed as a single-center, descriptive, longitudinal investigation. The cohort comprised 50 girls newly diagnosed with ICPP and treated with GnRHa at the pediatric endocrinology clinic of our hospital between September 2020 and January 2022. The research focused on examining these patients' clinical and laboratory findings at the initiation of GnRHa therapy, as well as at the 6th and 12th months of treatment, with subsequent comparisons. Exclusion criteria encompassed patients diagnosed with peripheral precocious puberty, those with concurrent chronic illnesses, and patients using medications that could impact puberty and growth. Additionally, boys diagnosed with ICPP were excluded from the study due to distinct growth and body composition patterns.

Patients were divided into two groups based on whether their percentage of body fat (PBF) was above or below the 97th percentile (p) upon the diagnosis of ICPP, and subgroup analyses were conducted. PBF reference curves for healthy Turkish children and adolescents were utilized for PBF percentiles according to age from the study by Kurtoğlu et al.[6]

Diagnosis and Treatment Procedure of ICPP Patients

The diagnosis of patients with ICPP was established based on the following criteria (3): (I) the presence of breast buds before the age of 8, (II) a basal luteinizing hormone (LH) level exceeding 1.0 IU/L or a peak LH level surpassing 5 IU/L in response to the LH-releasing hormone stimulation test, (III) evidence of accelerated growth and advancement of bone age (BA) by at least one year compared to chronological age (CA), and (IV) the absence of lesions in the hypothalamus-pituitary region as confirmed by MRI scans. Every subject diagnosed with ICPP received subcutaneous injections of 3.75 mg (initial dose) of GnRHa (Leuprolide acetate, Lucrin depot®) every 28 days. However, during follow-up, the treatment interval was adjusted to 21 days if there was an escalation in pubertal symptoms.

Clinical and Laboratory Investigations

Height, weight, and BMI standard deviation scores (SDS) were determined based on the reference values for Turkish children.[7] BMI was computed as the weight ratio to the square of height (kg/m^2). Overweight status was defined as having a BMI above the 85th percentile for age and sex, referencing Turkish children's norms, while cases exceeding the 95th percentile were classified as obese.[7] Pubertal staging followed the criteria established by Marshall and Tanner,[8] and BA was assessed using the Greulich and Pyle method.[9] For subjects with BA exceeding six years, predicted adult height (PAH) was calculated using the Bayley-Pinneau method.[10] Conversely, for subjects with of BA less than six years, the Roche-Wainer-Thissen (RWT) method was employed to estimate PAH.[11] Additionally, mid-parenteral height (MPH) was determined using the formula: (height of mother + height of father - 13)/2.

Luteinizing hormone levels were assessed through chemiluminescence immunoassay, while estradiol (E2) levels were determined using the electrochemiluminescence immunoassay method, both conducted by Roche in Mannheim, Germany. After treatment was initiated, the levels of LH, FSH, and E2 in the cases were measured 90 minutes later the GnRHa injection. Pelvic USG was carried out by a qualified radiologist for all subjects. Ovarian volume was computed using the formula: (D1×D2×D3/1000)×0.523, where D1 represents the longest longitudinal diameter, D2 denotes the largest anteroposterior diameter, and D3 signifies the largest transverse diameter, all measured in centimeters (cm) for each ovary. The total volume was then calculated as the sum of the volumes of both ovaries, expressed in milliliters. Similarly, uterus volume was determined using the same formula.

Evaluation of Body Composition and Muscle Strength

The Bioelectrical Impedance Analysis method was employed to assess total body fat (TBF) and lean body mass (LBM) using a segmental body composition analyzer, specifically the Tanita BC-418MA (Tanita Corporation, Tokyo, Japan), with adjustments made for minimal indoor clothing. Before the measurement, participants were instructed to abstain from consuming food or beverages for at least one hour, empty their bladders, and wear lightweight clothing. The analyzer, accounting for age, sex, height, and weight, provided precise percentage of body fat (PBF) measurements to the nearest 0.1%. During the assessment, children and adolescents stood barefoot on the analyzer while gripping handholds with each hand. Muscle strength measurements of the cases were conducted using a dynamometer tool that measures isometric contraction force (GRIP-D dynamometer). Three measurements were taken for each hand, and the average was calculated. Total muscle strength was determined by dividing the sum of the average forces of the right and left hands by two.

Statistical Analysis

We conducted the statistical analysis using The Statistical Package for the Social Sciences (SPSS for Windows, Version 23.0, Chicago, IL, USA). Continuous measurements were reported as either median [Interquartile range (IQR)] or mean ± standard deviation, while categorical data were presented as counts and percentages. We employed Pearson's chi-square and Fisher's exact tests to compare categorical variables. The Shapiro-Wilk test was used to assess normality, and distribution was also checked when comparing continuous measurements. Normally distributed parameters were compared using the t-test, while non-normally distributed parameters were compared using the Mann-Whitney U test. A mixed-design repeated measures ANOVA test was employed to determine the time-by-group interaction. In cases where measurements taken at more than two-time points violated the assumption of normal distribution, the Friedman test was utilized for comparisons. The Spearman correlation test assessed relationships between ordinal or non-normally distributed continuous variables. In contrast, the Pearson correlation test was employed for continuously distributed variables conforming to normal distribution. A p-value less than 0.05 was considered indicative of statistical significance.

RESULTS

The results of a total of 50 girls diagnosed with ICPP who were included in the study were analyzed. Changes in anthropometric measures and clinical parameters during the GnRHa therapy are given in Table 1. The mean CA of the cases at the beginning of treatment was 7.37±0.68 years, and the median BA was 8.75 (1.0) years. The maturation degree of BA was decreased at the 12th month of treatment compared to the beginning of treatment (p=0.039). After the initiation of treatment, the Tanner stages of the cases generally remained stable, and no progression in pubertal development was observed. Height SDS was similar at the beginning of treatment, at the 6th month, and at the 12th month. Although BMI was higher at the 6th month and 12th month of treatment compared to the beginning (p=0.003, p<0.001), BMI SDS was similar throughout the treatment duration. While the prevalence of overweight was 26% both at the beginning of GnRHa therapy and at the 12th month, the prevalence of overt obesity was 14% at the beginning and 10% at the 12th month. A statistically significant increase in PAH SDS at the 12th month of treatment was observed due to the decrease in BA maturation compared to the CA (p=0.031).

Changes in body composition during GnRHa therapy are presented in Table 2. Compared to the beginning of treatment, a statistically significant increase in TBF was observed at both the 6th month and 12th month (p<0.001). The PBF increased from an average of 24.2±5.1% at the beginning to 26.3±5.3% at the 6th month and 27.7±5.43% at the 12th month (p<0.001). While LBM increased during the treatment duration (p<0.001), there was a decrease in the LBM percentage in both the 6th month and 12th month (p=0.001, p=0.005). Ten cases had a PBF above the 97th p at the beginning of GnRHa treatment. A comparison of those cases with those whose PBF was below 97th p is presented in Table 3. The CA, BA, height SDS, and PAH SDS levels of the two groups were similar at the beginning of treatment and at the 12th month. Similarly, basal and stimulated LH levels, basal E2 level, and ovarian and uterine volumes were similar at the beginning of treatment in the two groups. In the group with PBF>97th p, the mean PBF

Table 1. Changes in antropometric measures and clinical parameters during the GnRHa therapy

Variable	Basal	6th month	12th month	p
CA (year)	7.37±0.68	7.90±0.68	8.41±0.75	
BA (year)	8.39±1.07	-	9.03±1.08	<0.001[b]
BA/CA	1.12±0.11	-	1.08±0.12	0.039[b]
Statural age (years)	8.43 (1.73)	8.98 (1.09)	9.42 (1.43)	<0.001[a,b]
Tanner stage				
2	46 %	50%	55%	
3	52%	48%	43%	
4	2%	2%	2%	
Weight (kg)	28 (7)	30.5 (8.4)	33.4 (7.9)	<0.001[a,b]
Weight SDS	0.73 (1.56)	0.95 (1.37)	0.88 (1.01)	0.153[a] 0.047[b]
Height (cm)	128 (8.30)	132 (6.4)	134.7 (8.2)	<0.001[a,b]
Height SDS	1.01 (1.29)	1.07 (0.17)	1.02 (1.5)	0.131[a] 0.752[b]
BMI (kg/m^2)	17.40±2.78	17.90±2.73	18.3±2.88	0.003[a] <0.001[b]
BMI SDS	0.61 (1.53)	0.71 (1.20)	0.73 (1.34)	0.103[a] 0.053[b]
Overweight prevalance (%)	26	32	26	
Overt obesity prevalance (%)	14	10	10	
MPH (cm)	162.5±4.6	-	-	
MPH SDS	0.07 (0.97)	-	-	
PAH (cm)	162.5±7.11	-	163.9±7.13	0.011[b]
PAH SDS	0.01 (1.6)	-	0.06 (1.24)	0.031[b]
LH (mIU/ml)	0.72 (0.77)	0.99 (1.0)	1.05 (0.85)	0.183[a] 0.271[b]
LH (peak on LHRH test, mIU/ml)	6.87 (5.63)	-	-	
FSH (mIU/ml)	3.57 (2.90)	1.71 (1.69)	2.05 (1.52)	<0.001[a] 0.001[b]
E2 (pg/ml)	14.7 (23.1)	5.0 (6.8)	5.0 (6.6)	0.003[a] 0.002[b]

Data are expressed as mean or mean±standard deviation or median (IQR) or as number (percent), [a]Comparison of 0-6th month, [b]Comparison of 0-12th month, CA: Chronological age, BA: Bone age, SDS: Standard deviation score, BMI: Body-mass index, MPH: Midparenteral height, PAH: Predicted adult height, GnRHa: Gonadotropin-releasing hormone analog

Table 2. Changes in body composition during the GnRHa therapy

Variable	Basal	6th month	12th month	p
TBF (kg)	7.11±2.72	8.3±2.8	9.41±3.51	<0.001[a,b]
PBF (%)	24.2±5.1	26.3±5.3	27.7±5.43	<0.001[a,b]
LBM (kg)	20.5±3.53	21.6±3.9	22.8±3.62	<0.001[a,b]
LBM percentage (%)	72.1±5.73	69.4±5.0	68.5±5.18	0.001[a] 0.005[b]
Muscle strength (Newton)	8.06±2.04	8.36±2.29	10.60±2.56	<0.001[a,b]

Data are expressed as mean±standard deviation, [a]Comparison of 0-6th month, [b]Comparison of 0-12th month, TBF: total body fat, PBF: percentage of body fat, LBM: Lean body mass, GnRHa: Gonadotropin-releasing hormone analog

Table 3. Subgroup analyzes of subjects according to PBF at the beginning of the GnRHa therapy

Variable	PBF >97 p (n=10)	PBF <97 p (n=40)	p
At the beginning of the treatment			
CA (year)	7.30±0.93	7.37±0.62	0.786
BA/CA	1.08±0.10	1.13±0.12	0.214
Height SDS	0.76 (2.05)	1.0 (1.2)	0.874
BMI SDS	2.05 (0.64)	0.38 (1.2)	<0.001
PAH SDS	0.39 (1.49)	-0.17 (1.6)	0.308
PBF (%)	31.9±4.8	22.2±2.8	<0.001
LBM	22.1±4.8	20.3±3.1	<0.001
LBM percentage (%)	64.1±4.6	74.2±3.8	<0.001
Muscle strength (Newton)	8.57±2.2	7.93±2.0	0.371
LH (basal, mIU/ml)	0.34 (1.2)	0.50 (0.86)	0.582
E2 (basal, pg/ml)	14.1 (22.5)	14.9 (20.8)	0.760
LH (peak on LHRH test, mIU/ml)	6.3 (6.9)	7.3 (5.3)	0.325
Uterus volume (ml)	2.64 (3.4)	3.09 (3.5)	0.333
Total ovarian volume (ml)	3.90 (2.5)	4.05 (3.1)	0.787
At the end of the 12th month of the treatment			
BA/CA	1.07±0.07	1.08±0.13	0.842
Height SDS	1.2 (2.1)	1.01 (1.1)	0.871
BMI SDS	1.91 (1.1)	0.57 (1.2)	<0.001
PAH SDS	0.1 (1.7)	0.02 (1.2)	0.890
PBF (%)	32.6±5.5	26.0±4.2	0.002
LBM	24.5±6.83	22.3±2.5	0.157
LBM percentage (%)	64.1±5.3	70.1±4.0	<0.001
Muscle strength (Newton)	10.2±1.9	10.5±2.6	0.677
Change in BFP (0-12th months)	0.5 (0.5)	2.3 (3.3)	0.005

Data are expressed as mean±standard deviation or median (IQR), CA: Chronological age, BA: Bone age, SDS: Standard deviation score, BMI: Body-mass index, PAH: Predicted adult height, PBF: Percentage of body fat, LBM: lean body mass, LH: Luteinizing hormone, E2: Estradiol, LHRH: Luteinizing hormon releasing hormone, GnRHa: Gonadotropin-releasing hormone analog

was 31.9±4.8 % at the beginning of treatment and 32.6±5.5% at the 12th month, whereas in the group with PBF<97th p, the mean PBF was 22.2±2.8% at the beginning of treatment and 26.0±4.2% at the 12th month. The change in PBF between 0 and 12 months was significantly higher in the group with PBF<97th p, with a median of 2.3 (3.3) %, compared to a median of 0.5 (0.5) % in the group with PBF>97th p (p=0.005).

No significant correlation was observed between the age at the initiation of GnRHa treatment and the 12th month PBF in the correlational analysis, as shown in Table 4. A reverse relationship was found between the maturation degree of BA at the beginning of treatment and the 12th month of PBF. It was observed that significant determinants of the 12th month PBF were the BMI and LBM percentage at the beginning of treatment, at the 6th month, and at the 12th month of the GnRHa treatment (p<0.001).

As shown in Table 5, muscle strength exhibited a positive correlation with LBM during all months within the same period (p<0.05).

Table 4. Correlational analysis of 12th month PBF with other clinical parameters

	12th month PBF	
CA at diagnosis (year)	p=0.455	r=0.132
BMI at diagnosis	p<0.001*	r=0.832
BA/CA at diagnosis	p=0.03*	r=-0.373
PBF at diagnosis	p<0.001*	r=0.839
LBM percentage at diagnosis	p<0.001*	r=-0.829
BMI at 6th month	p<0.001*	r=0.800
PBF at 6th month	p<0.001*	r=0.815
LBM percentage at 6th month	p<0.001*	r=-0.818
BMI at 12th month	p<0.001*	r=0.866
LBM percentage at 12th month	p<0.001*	r=-0.937

*Statistically significant correlation, r=correlation coefficient, CA: Chronological age; BA: Bone age; BMI: Body-mass index; PBF: Percentage of body fat; LBM: Lean body mass

Table 5. Correlational analysis of muscle strength with LBM

	Muscle strength at basal		Muscle strength at 6th month		Muscle strength at 12th month	
LBM at basal	p<0.001*	r=0.539	p=0.002*	r=0.473	p=0.003*	r=0.505
LBM at 6th month	p<0.001*	r=0.541	p<0.001*	r=0.565	p<0.001*	r=0.611
LBM at 12th month	p=0.094	r=0.296	p=0.007*	r=0.481	p=0.006*	r=0.465

*Statistically significant correlation, r=correlation coefficient, LBM: Lean body mass

DISCUSSION

Puberty is characterized by significant hormonal fluctuations and rapid growth in body size, accompanied by noticeable alterations in body composition.[12] Both sexes undergo substantial increases in adiposity, although the body fat the proportion growth rate is comparatively slower in boys due to a simultaneous rapid surge in lean mass.[1] While the BMI proves to be a reliable measure of adiposity in adulthood, its applicability is intricate when applied to children and adolescents due to its dependence on factors such as stature, the relative difference between trunk and leg length, fat-free mass, and maturity level. The sensitivity of BMI in identifying children with excess TBF or PBF is only low to moderate. This implies that using BMI to detect overweight children is characterized as poor to fair.[13,14] Therefore, monitoring body composition rather than solely tracking BMI changes during this developmental stage holds significance, as various aspects of body composition during puberty serve as predictors for subsequent measurements of these traits in adulthood.

The changes in body composition in girls experiencing precocious puberty and the effects of GnRHa treatment on this process are also a subject of curiosity. The impact of GnRHa treatment on body composition in girls experiencing early puberty can vary. The suppression of sex hormone production can affect the typical patterns of fat accumulation and muscle development.[15,16] Studying changes in body composition over time -before, during, and after the administration of GnRHa- offers a distinctive lens through which we can unravel the intricate physiological mechanisms governing growth amid the targeted and reversible suppression of gonadal sex steroids. This analysis allows us to delve into the nuanced regulation of

growth and serves as a valuable avenue to address a common clinical concern: the potential inclination of children with CPP towards developing obesity during GnRHa therapy.[17,18]

Data obtained from 297 healthy Caucasian girls in the Fels Longitudinal Study reveals a steady increase in TBF levels, starting at a mean of approximately 5.5 kg at age 8 and reaching around 15 kg at age 16.[19] In our study, it is noteworthy that at the end of the 12th month of GnRHa treatment in cases of ICPP, the mean TBF was found to be considerably higher at 9.4 kg compared to this study when cases were average 8.4 years old. However, interpreting this finding as an increase in adiposity due to GnRHa treatment is challenging, as the patients already had a fat content of a mean of 7.1 kg at the onset of treatment when they were a mean of 7.3 years old. The potential influence of the early onset of pubertal changes on variations in body composition analysis makes it challenging to unequivocally attribute the observed differences to the effects of GnRHa treatment. On the other hand, increased PBF during treatment in the present study is consistent with numerous studies in the literature.[20-22] As reported in a more extended follow-up study, elevated PBF was observed both at the initiation and cessation of GnRHa treatment, and it normalized two years after the discontinuation of therapy. After an initial aggravation of adiposity, no prolonged adverse effects on PBF were found.[20]

In our study, despite an increase in LBM during treatment, a decrease in LBM percentage was demonstrated due to a comparatively higher increase in TBF, consistent with studies.[20,21] The reported decrease in growth hormone (GH) and insulin-like growth factor-I (IGF-I) levels during GnRH-a therapy may contribute to the increase in PBF and decrease in LBM percentage.[22-24] An inverse correlation between GH levels and BMI was also noted in the study by Kamp et al.[23]

The impact of GnRHa treatment on height extends beyond reduced GH and IGF-1 levels. Despite reports of a decrease in height SDS during the treatment period, GnRHa therapy can positively influence final adult height by slowing down the skeletal growth rate and delaying the closure of growth plates.[3] Although there was an observed decrease in linear growth during GnRHa administration, there is an improvement in growth potential owing to a reduction in the rate of bone maturation induced by prior exposure to high estrogen levels. In our study, a decrease in bone maturation and an increase in PAH were observed, aligning with the findings in the existing literature during the first year of GnRHa treatment.[4,15,16]

The impact of early exposure to gonadal sex steroids in children with CPP on the physiological interpretation of BMI remains uncertain. Undoubtedly, these children exhibit greater height and weight compared to their chronologically age-matched counterparts, potentially influencing their BMI SDS.[17] Although an increase in BMI was observed during our study, there was no significant increase in BMI SDS. Some studies do not report a significant increase in BMI during GnRH treatment.[25,26] On the other hand, several studies report increased BMI during the treatment.[27,28] The variability in results across different groups in the literature can be attributed to genetic factors and significant heterogeneity. For instance, in the study conducted by Boot et al.,[18] a notable increase in BMI SDS during GnRHa treatment was reported. However, the subjects in this study differ from those in other studies, as some girls experienced the onset of puberty after the age of 8 years. Investigating whether these older subjects had shorter treatment durations would be intriguing, considering the inverse relationship between therapy duration and BMI SDS observed in Palmert et al.[17] study. Furthermore, some studies emphasize that BMI changes depend on the initial BMI status. As reported in some studies, children with initially overweight/obese patients exhibited a more remarkable change in BMI compared to those with normal BMI.[4,17] Conversely, more studies reported that the change in BMI SDS was significantly greater in normal-weight patients than in overweight patients.[27,29-31] Aiming to assess the impact of the initial PBF on clinical and laboratory parameters in our study with the same logic, we categorized patients based on whether their PBF was above or below the 97th p at the time of diagnosis. Interestingly, we observed a statistically significant increase in PBF the group with PBF below 97th p when comparing to the higher group, over the 12 months. Throughout the pubertal course, an increase in adiposity in cases with lower fat percentages may stem from diverse dynamics in adipokines, presenting one of the plausible mechanisms. This aspect gains significance when considering data suggesting the necessity of adequate leptin levels for initiating puberty.[32] While elevated serum leptin concentrations have not been proven to induce precocious pubertal development in humans, evidence indicates that CPP occurs in the presence of pubertal stage-appropriate, or in other words, sufficient leptin levels.[33] During the treatment of precocious puberty, variations in adipokine secretion and their impact dynamics may occur based on the initial fat percentage status.

Before puberty, muscle mass shows a linear increase with age.[34] During this phase, the anabolic effects of GH and IGF1 drive physical growth.[35] However, muscle strength gains in this developmental stage appear to be more influenced by neural factors than by an increase in muscle mass.[36] In puberty, muscle strength becomes closely associated with muscle quantity. As physiological functions align more with biological age than chronological age, an early-maturing child likely holds an advantage in absolute strength measures compared to a later-maturing peer of the same sex with less muscle mass. In girls, peak strength gains typically occur after peak height velocity, although there is more individual variability in the strength-to-height and body weight relationship for girls compared to boys, owing to the close association between boys' muscle strength and androgens. Female adolescents generally reach a plateau in muscle strength gains around the age of 15 years.[37,38] In our study, we observed that muscle strength gains continued under GnRHa treatment. This phenomenon may be linked to an increase in LBM despite a decrease in LBM percentage, as muscle strength shows a positive correlation with LBM throughout all months.

Limitations

Our study has certain limitations. The follow-up data for the cases are confined to a one-year duration of the GnRHa

treatment. A more extended follow-up of cases, assessing body composition ratios at the end of the GnRHa treatment and in adulthood, could provide a clearer understanding of the long-term effects of initial PBF. Additionally, conducting studies with larger patient cohorts, including a greater number of cases with initial PBF >97th p, could enhance the reliability of subgroup analyses.

CONCLUSION

Over the one-year duration of GnRHa treatment in girls experiencing ICPP, no increase was observed in BMI SDS and overweight-obesity rates in the present study. While PBF increased, a decrease was noted in LBM percentage. Despite the decrease in LBM percentage, since LBM increased over the course of treatment, an increase in muscle strength was observed under GnRHa therapy. Additionally, the alteration in PBF during GnRHa treatment exhibited variations based on the initial PBF status.

Over the one-year duration of GnRHa treatment in girls with ICPP, no increase was observed in BMI SDS or the rates of overweight and obesity. While the PBF increased, a decrease in LBM percentage was noted. However, despite the reduction in LBM percentage, the overall increase in LBM during the treatment period led to an observed improvement in muscle strength under GnRHa therapy. Moreover, the changes in PBF during treatment varied depending on the initial PBF status. The greater increase in PBF observed in cases with PBF >97th percentile at baseline is important due to the lack of similar data in the literature and its potential to provide insights for future studies. Assessing the PBF at the initiation of GnRHa treatment and monitoring changes in PBF during follow-up may benefit patients for future risk of obesity and metabolic complications.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Akdeniz University Faculty of Medicine Clinical Researches Ethics Committee (Date: 16.03.2022, Decision No: KAEK-195).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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