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ÖZGÜN ARAŞTIRMA/ORIGINAL ARTICLE

İdiyopatik Santral Puberte Prekokslu Kızlarda Luteinizan Hormon Seviyeleri ile Vücut Kitle İndeksi Arasındaki İlişkinin Değerlendirilmesi

Evaluation of the Relationship Between Luteinizing Hormone Levels and Body Mass Index in Girls with Idiopathic Central Precocius Puberty

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ÖZ

Amaç: Puberte başlangıç ve menarş yaşı gibi pubertal gelişimdeki değişikliklerin en önemli nedenlerinden biri adipositede artış olabilir. Çalışmamızda, santral puberte prekokslu kız hastalarda vücut kitle indeksinin (VKİ) standart İV GnRH testi ile uyarılmış pik LH düzeyleri üzerindeki etkisinin saptanması amaçlanmıştır.

Gereç ve Yöntemler: İdiyopatik santral puberte prekoks tanısı alan 59 kız hasta çalışmaya dahil edilmiştir. GnRH uyarı testi sırasındaki antropometrik ölçümler ve bazal/uyarılmış LH düzeyleri incelendi. VKİ ve gonodotropinler arasındaki ilişki araştırıldı.

Bulgular: Katılanların ortalama yaşı 7,11±1,01 (3,20-7,94) yıldı. Olguların %67,8'i (n=40) meme büyümesi şikâyeti ile başvurmuştu ve %64,4'ü (n=38) evre 2, %35,6'sı (n=21) evre 3 pubertedeydi. Farklı puberte seviyelerindeki olgularda, VKİ SDS ile bazal/uyarılmış LH (sırasıyla evre 2 puberte için p=0,531, p= 0,598 ve evre 3 puberte için p=0,126, p=0,827), tüm çalışma grubunda da VKİ/VKİ SDS ve pik LH arasında korelasyon yoktu. Bazal LH, FSH, E2 ve pik LH seviyeleri normal ağırlıklı, fazla kilolu ve obez gruplar arasında farklılık göstermiyordu.

Sonuç: Farklı puberte evrelerine sahip santral puberte prekokslu kızlarda vücut kitle indeksi ile bazal/uyarılmış gonadotropin düzeylerine arasında ilişki saptamadık.

ABSTRACT

Objective: Excess adiposity has effects on various aspects of pubertal development as the timing of pubertal initiation and hormonal parameters during puberty. We aimed to determine the effect of BMI on peak LH (luteinizing hormone) levels obtained by standard GnRH (Gonadotropin Releasing Hormone) stimulation test in girls with central precicous puberty.

Materials and Methods: A total of 59 female patients who were diagnosed as idiopathic central precicous puberty were included in the study. Anthropometric measurements at the time of GnRH stimulation test and basal/stimulated gonadotropin levels were evaluated. The relationship between BMI and gonadotropins was investigated.

Results: The mean age of the participants was 7.11±1.01 (3.20-7.94) years. 21 cases (35%) were overweight/obese. 67.8% (n = 40) of the cases were presented with breast development and 64.4% (n = 38) were in stage 2, 35.6% (n = 21) were in stage 3 puberty. There was no significant correlation between BMI SDS and basal/peak LH levels (p=0.531, p= 0.598 for stage 2 and p=0.126, p=0.827 for stage 3 puberty respectively), peak LH / FSH (follicle-stimulating hormone) ratio (p=0.408 for stage 2 and p=0.797 for stage 3 puberty) in patients according to both puberty stages. There was not also any correlation between BMI /BMI SDS and peak LH in total study group. Basal LH, FSH, estradiol and peak LH levels did not vary among normal weight, overweight and obese cases.

Conclusion: We could not find a relationship between basal and stimulated gonadotropin levels in girls with central precicous puberty in different stages of puberty.

Introduction

Childhood obesity threats public health. There is an increase in obesity prevalence worldwide (1-3). In studies performed in 6-16 years old children in Turkey, prevalence rates of 10.3%-17.6% and 1.9%-7.8% for overweight and obesity, are reported respectively (4). Excess adiposity is associated with various medical complications like insulin resistance, hyperglycemia, hypertension and dyslipidemia (5). Obesity is also an important contributing factor to the earlier onset puberty in girls (6-9). Excess fat mass may lead or be a contributing factor in the course of early puberty (7).

Precocious puberty is defined as the progressive onset of secondary sexual characteristics before the age of 8 years in girls (10,11). Idiopathic central precocious puberty (ICCP) results from premature activation of the hypotalamic-pituitary-gonadal axis (11). Girls with central precocious puberty have high LH levels and high LH/FSH ratio for age and increased secretion of GnRH. In early puberty, there is also sleep-entrained increase in LH pulse frequency and amplitude with a subsequent decrease of LH release during waking hours (12,13). The gold standard biochemical diagnosis of ICPP is based on the assessment of gonadotropins after stimulation with GnRH10. The peak value of LH has the highest specifity and sensitivity to ICPP diagnosis (14,15).

Genetic, nutritional, enviromental and socioeconomic factors can effect the beginning of puberty (11,16). Sleep related LH rise is found blunted in healthy premenarchial pubertal girls with elevated BMI (17). Obesity in prepubertal and early pubertal girls is associated with reduced LH secretion, low morning LH values and reduced nocturnal changes of LH. It is linked with reduced LH amplitude and elevated LH frequency in later pubertal girls (18,19). Fu et al., reported that higher BMI is associated with lower LH response to GnRH (20). In another study, no association was found between obesity and basal/stimulated LH values (21). In the study of Zhao et al. (22), the relationship between BMI SDS (standard deviation score) and peak LH value differed according to stages of puberty. In our study, we aimed to determine the effect of BMI on peak LH levels obtained by standard GnRH stimulation test in girls with idiopathic central precocious puberty.

Materials and Methods

59 girls diagnosed with ICPP in pediatric endocrinology clinics of Hitit University, Medeniyet University and Gaziosmanpaşa Taksim Training and Research Hospital from January 2016 to January 2019 enrolled into the study. Detailed medical histories of all patients and anthropometric evaluations were recorded. The study protocol was approved by the Ethics Commitee of Hitit University (28.02.2019, number: 2019-102). Parents of all participants signed in our informed consent forms.

Following criteria were used in the diagnoses of central precicous puberty in girls (11,14,23):

- Breast development before 8 years
- Advanced bone maturation
- Accelerated somatic development according to age and gender
- Increased basal and stimulated (with standard GnRH test) gonadotropin levels (LH:0.3 and 5 mIU/ml, respectively).
- Enlarged ovaries and uterus (ultrasound criteria)

Patients with any other endocrinopathy, systemic disease, having an organic etiology were excluded. Height, weight, BMI values and their standard deviation scores were calculated referring to national charts (24). Overweight was defined as BMI > +1 SDS and obesity was defined as BMI > +2 SDS above the mean(25). Pubertal evaluation was made by pediatric endocrinologists by using Tanner – Marshall criteria (26). Breast development was evaluated with palpation and confirmed with ultrasound to distinguish from adipomastia if necessary. We compared anthropometric findings and hormonal status of the two groups in Tanner Stage 2 (B2/BREAST 2) and Stage 3 (B3). Bone age was assessed according to Greulich- Pyle atlas (27).

LH, FSH and estradiol (E2) levels were measured by chemiluminescence method (Cobas 601®, Roche Diagnostics, Switzerland). The samples of FSH and LH were also taken at 30, 45, 60, 90 minutes after intravenous 100 µcg GnRH (LH-RH Ferring® 0.1 mg/ml, Ferring Ilac, Istanbul).

Statistical Analysis

All analysis were performed using SPSS Version 22.0 (IBM SPSS, Chicago, IL). Categorical variables were presented as numbers (n) and percentages (%). Descriptive statistics were expressed as mean ± standard deviation for variables with a normal distribution, and as median (minimum-maximum) for variables without a normal distribution. Normal distribution was assessed by the Shapiro-Wilks test. Spearman's Correlation Test was used to evaluate the relationship between BMI, BMI SDS and gonadotropins. Statistical significance was set at $p<0.05$.

Results

59 girls participated in this study. The mean age of the group was 7.11±1.01 (3.20-7.94) years. 67.8% (n = 40) of the cases presented with breast development, 18.6% (n=11) with breast development and pubic/ axillary hair, 6.8% (n=4) with pubic/axillary hair and the remaining 6.8% presented with breast development, pubic/axillary hair and long stature.38 cases were in stage 2 and 21 cases were in stage 3 puberty. There were 8 overweight (21 %), 1 obese (0.04%) in B2 and 8 overweight (38%), 4 obese (19%) patients in B3 group, respectively. Clinical and anthropometric characteristics, laboratory findings of patients according to pubertal stage are shown in Table 1.

There were no statistically significant correlations between BMI SDS and basal/peak LH levels, peak LH / FSH ratio in patients according to both puberty stages (Table 2). There was not any correlation between BMI/BMI SDS and peak L

H in all participants, also (p=0.764, r=-0.040 and p=0.705, r=-0.051 respectively (Figure1,2).

Basal LH, FSH, E2 and peak LH levels did not also vary among normal weight, overweight and obese cases (p=0.089, p=0.244, p=0.308 and p=0.873, respectively) after we excluded the effect of pubertal stage.

Discussion

It is well known that major determinants of the timing of puberty are genetic origin. However, there are prominent roles of different enviromental factors such as nutritional status, different stressors, endocrin disruptors, chronic diseases, etc. A balance between endogenous and exogenous regulators determine the proper timing of puberty, or its deviations (28,29). There is a trend that beginning of puberty decreases in last decades. Obesity is an important contributing factor to this fact. Overweight children tend to undergo earlier sexual maturation. Using NHANES III (National Health and Nutrition Examination Survey) data, it was reported that %32 of early maturers and %20 of average/ late maturing children were overweight. Overweight was 1.5 fold and obesity was 2 fold prevalent in early maturing girls (30).

	Pubertal Stage	
	B2 (n=38) Mean±SD (min-max)	B3 (n=21) Mean±SD (min-max)
Chronological age (years)	7.33±0.70 (4.75-7.94)	6.73±1.34 (3.20-7.90)
Bone age (years)	8.66±1.29 (6.00-11.00)	8.18±1.97 (3.50-11.00)
Weight SDS	0.58±0.93 (-1.36-3.09)	1.44±1.13 (-0.23-3.43)
Height SDS	0.68±1.17 (-1.32-3.739	1.01±1.26 (-0.67-3.15)
BMI SDS	0.42±0.89 (-1.36-2.02)	1.27±0.87 (-0.12-2.95)
Basal LH (IU/ml)	0.36±0.20 (0.05-0.86)	0.42±0.22 (0.10-0.83)
Basal E2 (pg/ml)	15.85±11.62 (4.00-49.00)	10.42±7.51 (2.00 -30.00)
Peak LH (IU/ml)	11.09±7.73 (5.18-38.00)	11.93±9.41 (5.06-45.00)
Peak LH/FSH ratio	0.94±1.26 (0.22-7.61)	0.85±0.85 (0.23-3.15)
Over volume (ml)	1.84±1.12 (0.40-5.42)	1.24±0.94 (0.26-3.60)
Uterine length (mm)	30.75±7.95 (14.00 -50.00)	29.46±12.87 (11.00-57.00)

Table 1. Clinical and anthropometric characteristics, laboratory findings of patients according to puberty stage

(SDS:standard deviation score, BMI:body mass index, LH: luteinizing hormone, follicle-stimulating hormone, E2:estradiol)

	Pubertal Stage			Peak LH	Peak LH /FSH ratio
Spearman's rho	B2	BMI SDS	R	-0.090	0.140
			P	0.598	0.408
	B3	BMI SDS	R	0.051	0.060
			P	0.827	0.797

Table 2. Correlation between BMI SDS and basal/peak LH levels, peak LH / FSH ratio in according to puberty stages

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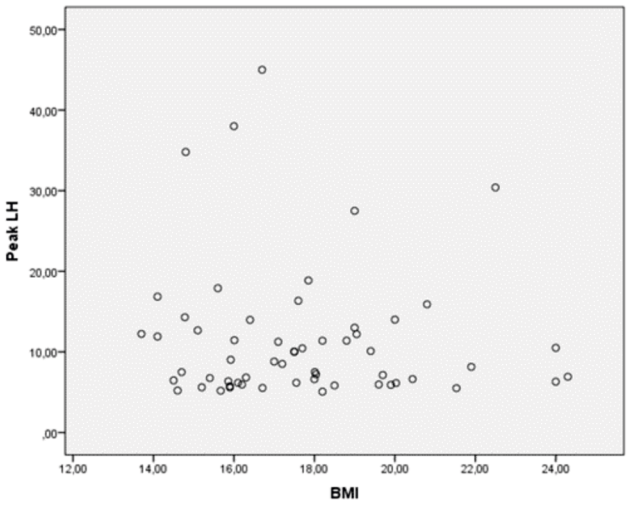

Figure 1: Correlation between BMI and peak LH values (whole study group)

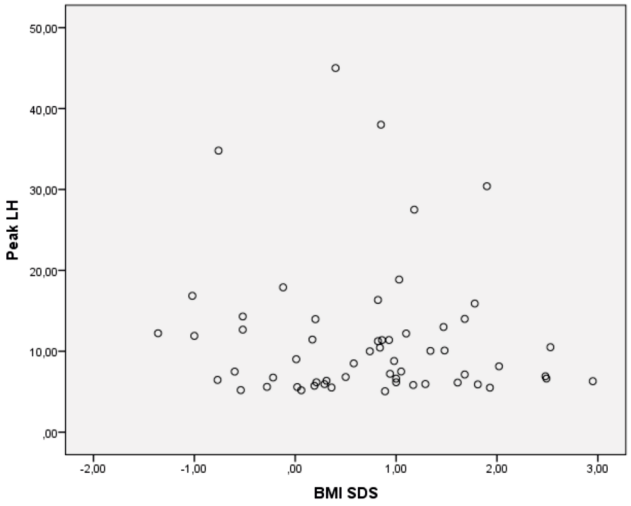

Figure 2: Correlation between BMI SDS and peak LH values (whole study group)

There are different plausible mechanisms about the relationship between fat mass and puberty (31). First of all, aromatase activity of adipose tissue lead to production of estrogen from adrenal androgen precursors. Obesity associated hyperandrogenemia and insulin resistance are risk factors for early sexual maturation. Insulin augments LH induced androgen production from ovarian theca cells. Hyperinsulinism decreases hepatic production of sex hormone binding globulin (SHBG) leading to increased androgen bioavailibility. Hyperandrogenemia impairs the sensitivity of the GnRH pulse generator to negative feedback, leading to persistantly rapid GnRH pulses and elevated LH. In hyperandrogenemic girls transition from sleep- predominant to wake- predominant LH concentrations occurs two years earlier during normal pubertal development. Obesity is also associated with decreased hepatic clearance of estrogens (7,28,31-33). Leptin is an important hormone produced by adipocytes. Moreover it has a role in pubertal development. Leptin communicates to the central nervous system that energy storage is adequate to start puberty. So that, it has a permissive role in activation of GnRH and gonadotropin secretion (28,31). Leptin levels were found to be much higher in obese children and the correlation efficient between leptin and BMI was 0.88, in a study(34). Rise of leptin is a preceding factor in the pubertal rise of LH and estradiol in girls. Circulating leptin concentration is related to age at menarche. Ghrelin is another hormone playing role in puberty onset. The data suggests that, it suppresses gonadotropin levels in condition of negative energy balance.

In contrast with the big data about the relationship between fat mass and puberty, there are not so many studies about how BMI affects stimulated gonadotropins in patients with precocious puberty. Fu et al. (20) carried out a retrospective study on 865 ICPP girls.19.4% of the participants were overweight and 10.2% were obese. They reported that higher BMI is associated with lower LH response to GnRH. Peak LH levels were 9.1, 8.5 and 6.2mIU/ml in normal weight, overweight, obese groups, respectively. They speculated that, excess adiposity may paradoxally inhibit gonadotropin secretion. Lee at al. (35), investigated GnRH stimulation test results of 981 girls with ICPP. In early stages of puberty (Tanner stage 2,3) increased BMI was related with lower peak LH values, but it was not valid in stage 4 cases. Our results were not concordant with those studies. We could not find a relationship between BMI SDS and stimulated gonadotropins in girls with stage 2 and 3 puberty. We also, could not find an association between basal gonadotropin and E2 levels similar with the report of Lee et al (35). Basal and stimulated gonadotropins were not different among normal weight, overweight and obese cases. However, we did not include stage 4-5 pubertal cases. In another study, no association was found between obesity and basal/stimulated LH values (21). In the study of Zhao et al., the relationship between BMI SDS (standard deviation score) and peak LH value differed according to stages of puberty (22). They reported that, in B2 stage, BMI SDS was negatively correlated with LH peak. However, there was a negative correlation between BMI SDS and LH peak in cases with BMI SDS <1.5, and a positive correlation whose BMI SDS ≥1.5 in stage 3-4 puberty. They concluded that, relationship had been affected by other factors as androgens, E2 and glucose metabolism after using regression models with different confounding factors.

Similar with us, there was not any association was recorded between BMI and basal/ stimulated LH, FSH and LH/FSH ratio by another group. Obesity seemed to be a risk factor for early adrenarche but not for maturation of hypothalamic- pituitary- gonadal axis (21).

There are some limitations of our study. First of all, we did not evaluated SHBG, insulin, androgen and leptin levels that have effects on pubertal devolepment. We did not use direct methods for defining fat mass as dual energy radiograph absorptiometry (DEXA), bioelectrical impe-dance analysis, etc. However, the correlation between BMI and fat mass/fat mass percentage is sufficient in girls (7,36). Also, we did not include the cases in later stages of puberty as GnRH stimulation test is not needed for diagnosis frequently. Another limitation was the small number of patients.

Conclusion

In conclusion, we could not find a relationship between body mass index and stimulated LH levels in early pubertal girls. However, existing literature has conflicting results. Therefore, fat mass should be considered when interpre-ting GnRH stimulation test results. The influence of body mass index on gonadopin levels in precicous puberty remains unclear. Further research is needed to investigate this topic.

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