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Association between plasma kisspeptin levels and adolescent gynecomastia

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ABSTRACT

Background: Gynecomastia is defined as benign proliferation of male breast glandular tissue. To date, the pathophysiology of adolescent gynecomastia (AG) remains unclear. Kisspeptin is a polypeptide that plays an important role in the regulation of the hypothalamic-pituitary-gonadal hormonal axis. In this study, we investigated whether there is a relationship between kisspeptin and AG. **Materials and Methods:** This study included 40 males between 9 and 18 years of age diagnosed with gynecomastia. The control group consisted of 30 young healthy males in the same age range. The participants were evaluated with respect to anthropometric measurements (age, height, body weight, body mass index, breast and pubic stages and testicular volume). The levels of kisspeptin, follicle-stimulating hormone, luteinizing hormone, estradiol (E2), testosterone (T), and ratio of E2 to T were measured in both groups. **Results:** The mean age was 13.8 years. There were no differences between the groups in terms of anthropometric parameters, plasma gonadotropin levels, estrogen levels, and E2/T ($P > 0.05$). Plasma kisspeptin (0.77 and 0.54 ng/mL, $P < 0.05$) and T (253.9 ng/dL and 117.9 ng/dL) levels were significantly higher in the AG group than in the control group ($P < 0.001$). **Conclusion:** Kisspeptin levels are an important factor in AG.

Key words: Adolescent, gynecomastia, kisspeptin

INTRODUCTION

Gynecomastia is may be unilateral or bilateral, and is diagnosed on exam as a palpable mass at least 0.5 cm in diameter.[1] The prevalence of physiological gynecomastia is 70% in male adolescents and in 90% of subjects, it disappears spontaneously in 2–3 years.[2] In cases of macrogynecomastia (up to 6 cm in diameter) surgery is often the only solution due to a poor response to drug therapy.[2] Based on a careful medical history and physical examination, many patients are found to actually have pseudogynecomastia.[1-3]

There is no single cause of gynecomastia. The factors involved may include tumors, syndromes, hormones, diseases, or drugs.[4-8] The most common cause of gynecomastia is puberty.[1] The underlying pathogenesis of adolescent gynecomastia (AG) is unclear but in general gynecomastia is caused by increased levels of estrogens, decreased levels of androgens, or any process that increases the ratio of available estrogens to androgens. Gynecomastia is presumably caused by an excess of circulating estrogens due to the conversion of androgens to estrogens by peripheral aromatase enzymes. Gynecomastia may also be caused by increased histological sensitivity to the female hormones prolactin, estrogen, and progesterone. In these cases, kisspeptin, a protein that directly stimulates gonadotropin-releasing hormone release via G protein-coupled receptor 54, may play a role. Kisspeptin has an important functional role in the onset of puberty. Pubescent changes occur as a consequence of the activation of the hypothalamic-pituitary-gonadal axis and hypothalamic-pituitary-adrenal axis.[9-18] To the best of our knowledge, no clinical or experimental research as assessed the effects of kisspeptin on AG.

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In the present study, we compared data between adolescents with gynecomastia and those without it, and identified a relationship between kisspeptin and AG.

PATIENTS AND METHODS

The AG group included children aged 9–18 years (n = 40) who presented to the outpatient clinic of our pediatric endocrinology unit with a complaint of breast development. The control group included healthy children in the same age range (n = 30) who were admitted to the hospital for routine health examination and who were not on any medications. This study was approved by the Institutional Ethics Review Board and written informed consent was obtained from all of the families. Breast development was staged according to Tanner's criteria. Anthropometric measurements (age, height, body weight, body mass index [BMI], breast and pubic stages, and testicular volume), hormonal levels (kisspeptin, follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol [E2], testosterone [T]), and the E2/T ratio were obtained in both groups. All except one were follow-up conservatively for 6 between 2 years and spontoneusly resolved. One underwent surgery for liposuction because he was not satisfied with his breast appearance and he was 17-year-old.

Kisspeptin analysis

To measure kisspeptin levels, 2 mL blood samples were drawn into tubes containing K_2EDTA from each subject in the AG and control groups. The tubes were immediately centrifuged at 5000 rpm at 4°C for 5 min and the samples were stored at −80°C until needed. Kisspeptin levels were measured using a KiSS-1 (112–121) Amide/Kisspeptin-10/metastin (45–54) Amide (Human) EIA Kit, (Catalog# EK-048-56) in the Department of Biochemistry according to the directions provided by the manufacturer (Phoenix Pharmaceuticals Inc., Burlingame, California, USA). The results were calculated according to standards (ng/mL).

Statistical analysis

Statistical analyses were performed using SPSS for Windows, version 16.0. Chicago: SPSS Inc. Normality for continued variables in the groups was determined using the Shapiro–Wilk test. The independent-samples t-test was used for age, height, E2, and T that showed normal distribution ($P > 0.05$). Mann-Whitney U-test was used for body weight, BMI, breast and pubic stages, testicular volume, and levels of kisspeptin, FSH, and LH that showed abnormal distribution ($P < 0.05$). Spearman's rho test was used to measure correlations between the variables.

RESULTS

In all, 40 AG subjects (mean age 13.8 ± 2.1 years, range 9.1–17.8 years) and 30 controls (mean age 13.5 ± 2.1 years, range 9.3–16.9 years) were included. No differences were found between the groups regarding anthropometric parameters, breast and pubic stages, testicular volumes, levels of plasma gonadotropin and E2, and E2/T ($P > 0.05$). Levels of plasma kisspeptin and T were significantly higher in the AG group (0.77, range 0.2–2.5; 253.9 ng/dL, respectively) than in the control group (0.54, range 0.1–3.4 ng/mL, $P < 0.05$; 117.9 ng/dL, $P < 0.001$, respectively) [Tables 1 and 2].

DISCUSSION

Gynaecomasia is a part of normal pubertal development in about half of the males. There is no line of demarcation between normal and abnormal. The peak of gynecomastia occurs during puberty between the ages of 10 and 14 years with a prevalence ranging from 4% to 70%.[2] In our study, the mean age was

Table 1: Anthropometric parameters, breast and pubic stages, and testicular volumes in adolescent gynecomastia and control groups

	AG (n=40)	C (n=30)	P
Age±SD (year)	13.8±2.1 (9.1-17.8)	13.5±2.1 (9.3-16.9)	0.96
Height±SD (cm)	160.0±10.5 (140.0-187.0)	156.9±12.6 (128.5-185.0)	0.52
Body weight (kg)	52.8 (32.2-123.0)	51.4 (32.0-121.9)	0.35
BMI (kg/m^2)	21.4 (16.0-38.4)	20.9 (17.5-41.7)	0.35
PS (stage)	3.0 (1-5)	2.0 (1-5)	0.49
TVr (mL)	8.0 (4-25)	8.0 (4-25)	0.79
TVl (mL)	8.0 (4-25)	8.0 (4-25)	0.79
BSr (stage)	2.0 (1-5)	-	-
BSl (stage)	2.0 (1-5)	-	-

PG: Pubertal gynecomastia group, C: Control group, SD: Standart deviation, BMI: Body mass index, PS: Pubic stage, TVr: Right testicular volume, TVl: Left testicular volume, BSr: Right breast stage, BSl: Left breast stage

Table 2: Kisspeptin and hormonal levels in adolescent gynecomastia and control groups

	PG (n=40)	C (n=30)	P
Kisspeptin (ng/dL)	0.77 (0.2-2.5)	0.54 (0.1-3.4)	0.04
FSH (mIU/mL)	2.8 (0.2-14.0)	2.2 (0.1-8.9)	0.32
LH (mIU/mL)	2.0 (0.1-4.7)	1.2 (0.1-6.6)	0.18
E_2±SD (pg/mL)	30.5±8.2 (20.0-47.0)	29.7±8.0 (20.0-48.9)	0.49
T±SD (ng/dL)	253.9±166.2 (20.0-665.0)	117.9±109.2 (20.0-347.0)	<0.001
E_2/T±SD	0.25±0.0.31 (0.04-1.32)	0.46±0.55 (0.08-1.77)	0.07

PG: Pubertal gynecomastia group, C: Control group, SD: Standart deviation, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, E_2: Estradiol, T: testosterone), E_2/T: Ratio of estradiol/testosterone T

13.8 years in the AG group, 13.6 years in the control group, and the peak age was in agreement with the literature.[1-9,18] Anthropometric measurements in the AG group were within normal limits for age and the mean anthropometric values in the AG group were not different from the control group. As expected, positive correlations were observed with increasing age and other anthropometric parameters.

De Vries *et al*.[19] found that kisspeptin levels were significantly higher in adolescent females with central precocious puberty than in controls (14.62 ± 10.2 pmol/L vs. 8.35 ± 2.98 pmol/L, $P < 0.05$). In the present study, plasma kisspeptin levels were significantly higher in the AG group than in controls (0.77 and 0.54 ng/mL, respectively, $P < 0.05$). Because of the patient in AG more T aromatization may transform the T into E2 than the control group. Therefore in AG E2 caused high level kisspeptin.

The pathophysiology of gynecomastia remains poorly understood and various hypotheses have been proposed. The estrogen/androgen balance is generally accepted as an important factor in AG. Some reports have reported a transient increase in E2 concentration (or decrease in T concentration) at the onset of puberty in young males who develop gynecomastia.[3] In our study, we found higher levels of T in the AG group although E2/T levels were similar. In our opinion, the hypotheses are insufficient to explain the causes of the disease. Kisspeptin can play an important role in the pathophysiology of gynecomastia.

Because we found that plasma T levels were significantly higher in the AG group than in the control group (253.9 ng/dL and 117.9 ng/dL, respectively, $P < 0.001$) we suggest that T levels are not lower in AG subjects.

Kisspeptin plays a significant role in regulating the reproductive axis and kisspeptin signaling is essential for proper onset of puberty. Kisspeptin produced by Kiss-R1 neurons in the hypothalamus potently stimulates GnRH neurons via the kisspeptin receptor Kiss-1R, thereby activating the reproductive endocrine axis.

In the present has some limitations. One of them, assessing the testicular function is not justified by measuring only the serum T level but also requires assessment of spermatogenesis that may not be ethical in normal adolescents. Therefor we correlated kisspeptin level to T level. The second one, the gynecomasty have to screened for testicular function and sexual differantation, however we didn't screened these. This is a major limitation of this study.

CONCLUSION

In conclusion, the higher levels of kisspeptin in the AG group suggest that kisspeptin plays an important role in the development of AG. We suggest that the breast tissue of AG patients undergoing surgery should be evaluated for kisspeptin receptors. Further studies are necessary to better understand the role of kisspeptin in AG pathophysiology.

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Conflicts of interest
There are no conflicts of interest.

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