

Circulating Kisspeptin Levels Regulate LH Rise in PCOS

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Abstract

Aim: The study was planned to determine the relationship between serum kisspeptin levels and LH elevation in PCOS patients.

Materials and Methods: A total of 40 women were divided into two groups as PCOS and control. Patients in PCOS group consisted of 20 women. The control group consisted of 20 BMI-matched women without PCOS. Women in the control group were randomly selected from patients admitted with our clinic for routine gynecological examination. Venous blood samples for hormone, glucose and insulin analysis were taken following a 12 hour fasting during the early follicular phase of spontaneous or progesterone withdrawal bleeding. Serum kisspeptin levels were measured by using the Human ELISA kit.

Results: The kisspeptin values of PCOS patients were found to be significantly higher than the control group ($p < 0.01$). Serum testosterone, LH, insulin and HOMA-IR of PCOS patients were significantly higher than the control group ($p < 0.02$, $p < 0.01$, $p < 0.03$ and $p < 0.01$, respectively). Serum kisspeptin levels are positively correlated with the serum levels of LH ($r = 0.644$, $p < 0.01$) and negatively correlated with HOMA-IR ($r = 0.431$, $p < 0.02$).

Conclusion: The increase in serum kisspeptin levels is one of the reasons for the increase of LH in PCOS patients.

Keywords: PCOS; Kisspeptin; LH; HOMA-IR

Introduction

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. PCOS is characterized by three key features including hyperandrogenism, oligo-anovulation, and associated insulin resistance [1,2]. Since each woman with PCOS does not exhibit high serum levels of androgens, hyperandrogenemia may not be the only underlying etiological factor in the occurrence of PCOS. One possible culprit in PCOS aetiology may be central or peripheral peptides [1,2]. In addition to hyperandrogenism and insulin resistance studies demonstrated that there was dysregulated expression of central and peripheral peptides in PCOS [1,2]. Isolated studies have investigated the relation between circulating levels of peptides and PCOS [1,2]. Interaction between peptides, ovary and pituitary gland may be disrupted in PCOS [1]. In a recent comprehensive review, the relationship between the peripheral/central peptides and PCOS was comprehensively discussed by Celik, *et al* [1,2]. However, there are isolated studies discussing the role of kisspeptin in PCOS aetiology.

Kisspeptin, 54-amino acid protein, is isolated firstly from melanoma cell lines and named KISS1 [3]. Kisspeptin is a natural ligand of G protein coupled receptor (GPR54) [4,5]. KISS1/GPR54 system is expressed in many central and peripheral sites including hypothalamus, pituitary gland, testicle and ovaries suggesting a its role in the regulation of reproductive function [4,5]. When the literature is reviewed, it appears that many peripheral and central peptides are studied in PCOS patients. However, studies investigating central peptides including kisspeptin are scarce. There is a complex interaction between kisspeptin and hypothalamo-pituitary neurons. Fluctuation in circulating levels of kisspeptin can cause disturbed synthesis and release of GnRH and gonadotropins in PCOS. The reason for the height of LH, which is one of the main components of PCOS, is not clearly known. Androgen height is considered to be the main mechanism that increases LH. However, the effect of androgens on LH is unclear. It is thought that the effects of androgens on LH through kisspeptin [6]. However, the relationship between kisspeptin and LH in PCOS cases has not been clearly explained. This study was planned to determine the relationship between serum kisspeptin levels and LH elevation in PCOS patients.

Materials and Methods

Patient selection

This case-controlled study was conducted at the Faculty of Medicine, Department of Obstetrics and Gynecology, BAU University. A total of 40 women were divided into two groups as PCOS and control. Patients in PCOS group consisted of 20 women. The control group consisted of 20 BMI-matched women without PCOS. Women in the control group were randomly selected from patients admitted with our clinic for routine gynecological examination. They had no polycystic appearance on USG examination. They have also regular menstrual cycle, normal biochemical and hormonal profiles. The women were diagnosed with PCOS according to revised Rotterdam criteria two of the following three findings need to be identified: 1) oligo and/or anovulation, 2) clinical and/or biochemical hyperandrogenism, and 3) polycystic ovaries determined by ultrasonography. Twelve or more follicles with a diameter of 2 - 8 mm and/or increased ovarian volumes were used as ultrasonographic criteria. Biochemical hyperandrogenism was defined as total testosterone levels above the normal range. Oligomenore was defined as absence of menstruation for 45 days or more and amenorrhea was defined as absence of bleeding for 3 months or more. Women using antiandrogen, antidiabetic, insulin sensitizer, lipid-lowering drugs, glucocorticoids or other hormonal drugs were excluded from the study. Venous blood samples for hormone, glucose and insulin analysis were taken following a 12 hour fasting during the early follicular phase of spontaneous or progesterone withdrawal bleeding. Serum fasting blood glucose, insulin, follicle stimulating hormone (FSH), LH, estradiol (E2) and total testosterone levels were measured using an automated analyzer. A detailed history and demographic characteristics of each group of subjects such as age and BMI were recorded. The BMI was calculated using the following formula: weight [kg]/square meter height [m²]. Insulin resistance was calculated using the following formula: HOMA-IR = fasting serum insulin (μIU/mL) X fasting plasma glucose (mg/dL)/405.

Kisspeptin analysis

Serum kisspeptin levels were measured by using the Human (KISS1) ELISA kit (Sunred Bioscience, Shanghai, China). The measurement was made in accordance with the working procedures defined in the kit catalogue. The intra-(within day) and inter-assay (between days) coefficients of variation for serum KISS1 were < 10% and < 12%, respectively. The minimum detection limit of KISS1 was 5 pg/ml. Automatic washer Bio-Tek ELX50 (BioTek Instruments, USA) was used for plate washings. Absorbance measurements were taken with a Chromate 4300 Microplate Reader (Awareness Technology, Palm City, USA). The detection range of KISS1 was 5 to 1500 pg/L. KISS1 test results are expressed in pg/ml.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science version 25.0 program (SPSS, Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered as a significant. Normality of continuous variables were examined by the Kolmogorov-Smirnov test. Quantitative data were expressed as mean ± SD. Since variables were not distributed normally Spearman correlation test and Mann Whitney U Test were used. Associations between serum kisspeptin, biochemical, hormonal and demographic parameters were analysed with Pearson correlation method.

Results

The age and BMI of women with PCOS and control group were similar. Infertility duration of the PCOS group was longer than the control group. Women with PCOS had high serum levels of insulin, total testosterone, estradiol and HOMA-IR compared to control group. The kisspeptin values of PCOS patients were found to be significantly higher than the control group (*p* < 0.01). Serum testosterone, LH, insulin and HOMA-IR of PCOS patients were significantly higher than the control group (*p* < 0.02, *p* < 0.01, *p* < 0.03 and *p* < 0.01, respectively). No significant difference was found between the PCOS and control group in terms of other variables. Serum kisspeptin levels are positively

correlated with the serum levels of LH ($r = 0.644, p < 0.01$) and negatively correlated with HOMA-IR ($r = 0.431, p < 0.02$). Any correlation was not detected between the serum kisspeptin levels and measured hormonal and demographic parameters in control group.

Discussion

LH elevation and insulin resistance are two main components that guide the metabolic process in PCOS cases. Many opinions have been suggested about the cause of LH elevation. The first of these is the presence of high androgens. However, androgens do not directly perform their LH-enhancing effects but do the vehicle through peptides [6]. Kisspeptin is one of these peptides. Kisspeptin is a peptide that induces GnRH release from the brain and regulates the LH secretion [7]. Activation of kisspeptin stimulates LH secretion and leads to PCOS-like appearance in ovary [8]. In the present study we found significantly increased kisspeptin levels in the serum of PCOS. Conflicting results have been reported in terms of kisspeptin levels in PCOS. Emekci, *et al.* showed that circulating kisspeptin levels of PCOS and non-PCOS women similar [9]. In line with our results recent study has reported that PCOS increases the serum kisspeptin levels [10]. Panidis, *et al.* reported that lean and obese women with PCOS had higher kisspeptin levels compared to obese non-PCOS women [10]. In the present study, we also found that serum levels of kisspeptin in women with PCOS were correlated positively with serum LH levels. On the other hand, we found a negative correlation between serum kisspeptin levels and BMI of PCOS women. Our results was compatible with the results of previous study. Panidis, *et al.* showed a negative correlation between kisspeptin, BMI and insulin resistance [10]. However, we did not find any correlation between kisspeptin values and HOMA-IR in PCOS group. We did not also find any correlation between kisspeptin values, hormonal and demographic parameters of control subjects.

In PCOS cases, LH hypersecretion is regulated by three different molecules. Androgens regulate the release of these three molecules. Neurokinin B and leptin regulate LH release in prepubertal period, while kisspeptin regulates LH secretion after puberty [6]. Kisspeptin enhances LH secretion by enhancing the effect of neurokinin B and leptin peptides. However, LH release cannot be reduced by using the kisspeptin blocker [6]. This finding suggests that the LH enhancing effect of kisspeptin occurs via other pathways. In our study, positive correlation between kisspeptin levels and LH increase can be a result for more than one aetiological reason. This is a situation that requires further investigation.

Conclusion

Increased production of kisspeptin might be cause of PCOS related clinical and hormonal findings. However, whether LH increase in PCOS subjects is due to increased androgen or insulin production or high kisspeptin peptides action are not clear. Since kisspeptin mediates the functions of the other peptides on the acute neurons it may have dual effect on central neurons. As supportive, interaction between central leptin and the kisspeptin stimulates the production and release of GnRH [6]. We, therefore, strongly suggest that kisspeptin plays a critical role in the emergence of PCOS related LH rise. This may be realized by directly affecting GnRH neurons and regulating the effects of other peptides on the arcuate nucleus. Our findings raise the possibility that increased production and release of kisspeptin may be possible underlying aetiological factor in the occurrence of PCOS and its clinical and laboratory findings.

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