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Research Article

The Influence of Kisspeptin1 on Polycystic Ovarian Syndrome in Iraqi Women

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is a serious gynecological condition that affects 3-10% of women of reproductive age. The defective ovulation and menstrual disorders seen in PCOS is in conjunction with abdominal obesity. Kisspeptins are peptides produced by the KISS1 gene that regulate the hypothalamic-pituitary-gonadal (HPG) axis. The aim of this study was to analyze the effect of Kisspeptin on PCOS features and obesity.

Materials and Methods: a case control study enrolled 105 participants of which 70 women have PCOS subdivide according to their BMI to 16 obese, 19 overweight, and 35 with normal weight. The remaining 35 represent the control group who were apparently healthy women. Patients with PCOS were selected from the Infertility Department/ Gynecology and Obstetrics Teaching Hospital in Karbala and from out clinic patients. Measurement of serum humane Kisspeptin1 was performed using ELISA technique as well the hormonal profile.

Results: Kisspeptin1showed significant difference among PCOS for obese, overweight and normal weight patients against control group, (396.320 ±137.266), (419.167 ±149.660), (370.853 ±86.257) and (23.601 ±52.250) respectively. The levels of LH were significantly higher ($P< 0.05$) among PCOS women more than control group. There is no significant difference ($P> 0.05$) in Kisspeptin1 levels between three age groups.

Conclusion: Our study suggests a higher concentration of serum kisspeptin1 appeared in PCOS groups as compared with control group as well, a substantial difference in its levels among different BMI of the study groups. Further experimental and clinical studies are needed to ascertain the role of kisspeptin in PCOS.

Keywords
Kisspeptin1; Polycystic ovary syndrome, Hormonal profile, Body mass index.

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Introduction

The PCOS is a common endocrine and metabolic disorder, which is characterized by chronic anovulation, polycystic ovaries and hyperandrogenism (A Al-Shamma and Z Al-Saedi, 2013), and it is one of the most common causes of female infertility, it affects 5–22% of women of reproductive age (Rutkowska and Diamanti-Kandarakis, 2016).Despite extensive research and studies on PCOS, the underlying etiology of the condition remains a mystery. PCOS is caused by a combination of genetic, endocrine, metabolic, and environmental factors (De Leo et al., 2016). Biochemically, the increased production of luteinizing hormone (LH) and a normal or low amount of follicular stimulating hormone (FSH) by the anterior pituitary reveal ovarian dysfunction in PCOS (Morgante et al., 2018).

PCOS is a complex, heterogeneous disorder of uncertain etiology, but there is strong evidence that it can, to a large degree, be classified as a genetic disease (Escobar-Morreale, 2018). PCOS is grouped into three sorts firstly; patients with hyperandrogenism and prolonged anovulation but normal ovaries were diagnosed with classic PCOS. The second sort is patients with polycystic ovaries and elevated LH levels. Finally, high level of LH and LH/FSH ratio but patient have normogenic phenotype, normal free androgen index, normal insulin sensitivity and normal BMI (Ibrahim, 2020).

Kisspeptins are peptides that regulate the HPG axis through their binding to GPR54, a G protein-coupled receptor. Kisspeptins' mechanism is to act directly on GnRH neurons, causing them to release GnRH into the portal circulation, which then stimulates LH and FSH, resulting in the release of androgens (Pinilla et al., 2012).Kisspeptin, also known as metastin, is a 54-amino-acid peptide encoded by the KISS1 gene (Albalawi et al., 2018). Kisspeptin stimulates LH secretion by triggering GnRH for inducing ovulation. Although ovarian kisspeptin expression has been observed in a variety of species, including humans, the specific mechanism through which kisspeptin is involved in ovulation is still unknown. Ovulatory dysfunction, hyperandrogenism, and metabolic changes are all symptoms of PCOS, a neuroendocrine condition. Because LH and GnRH levels have been shown to be high in PCOS patients, it was hypothesized that kisspeptin levels would be high as well. Many studies have been done on the function of kisspeptin in the pathogenesis of PCOS, and the same studies have found that PCOS patients have higher levels of kisspeptin than normal women (Chen et al., 2010, Nyagolova et al., 2016, Jeon et al., 2013, Gorkem et al., 2018). While other studies found no differences in kisspeptin levels (Panidis et al., 2006, Emekci Ozay et al., 2016, Yerlikaya et al., 2013).

Although the precise mechanism for kisspeptin's role in the etiology of PCOS is still unknown, it has been demonstrated that metabolic problems in PCOS may lead to kisspeptin level changes. Any fluctuation in serum kisspeptin levels could be due to the varied nature of the genetic etiology of PCOS (Branavan et al., 2019). Determining the kisspeptin 1, LH and FSH levels in PCOS affected women may be useful in determining the multifactorial etiology of PCOS (Coutinho and Kauffman, 2019).The study was aimed to analyze the effect of Kisspeptin on PCOS features and obesity.

Materials and methods

The present work included a case control study for a group of (105) samples: 16 obese, 19 over weight, and 35 normal weight women who have PCOS and 35 apparently healthy subjects serve as control. The study was conducted from February 2021 to June 2021, with age ranged between (18-40) years. Patients with PCOS were selected from the Infertility Department in Karbala Gynecology and Obstetrics Teaching Hospital and out clinic patients. History of patients, clinical and biochemical features, also weights and heights were taken from each patient. The sociodemographic aspects of the patients were collected through the self-reported questionnaire that includes age, residency, BMI, education, social status, type and duration of infertility, and having any

current chronic diseases. All patients were diagnosed as PCOS by consultant gynecologist according to Rotterdam criteria. Biochemical parameters were measured to all patients participated in this study in the follicular phase (2-5) days of cycle. The levels of LH, FSH, Free Testosterone, and prolactin were measured by using Cobas e 411. Measurement of serum human Kisspeptin1 were performed using ELISA kit.

Results and Discussion

There were substantial differences in BMI among the participants in the study groups, as shown in Table (1). In women with PCOS, abdominal obesity can cause both local and systemic oxidative stress. The abdominal obesity increases the likelihood of PCOS-induced problems being more severe in the context of abdominal obesity. The increase of visceral fat appears to be a significant factor in the development of PCOS (Nasiri et al., 2015) .

Table 1:
The distribution of demographic data of study group.

Characteristics	PCOS (Obese) Mean ± SD	PCOS (Over weight) Mean ± SD	PCOS (Normal weight) Mean ± SD	Control Mean ± SD	P value
Number	16	19	35	35	-
Age (years)	27 ±4.73	24.21 ±4.4	24.7 ±4.12	24.91 ±3.33	> 0.05
BMI kg/m²	33.9 ±3.09	27.46 ±1.55	23.30 ±1.96	22.79 ±2.38	< 0.01
Residency/Kerbala (number: and percentage):					> 0.05
Inside	12: (75%)	16: (84.21%)	24: (68.57%)	26: (74.28 %)	
Outside	3: (18.75%)	3: (15.78%)	11: (31.42%)	9: (25.71%)	
Occupation (number: and percentage):					< 0.01
Employed	3: (18.75%)	4: (21.05%)	3: (8.57%)	23: (65.71 %)	
Student	4: (25%)	2: (10.52%)	10: (28.57%)	7: (20%)	
House wife	9: (56.25%)	13: (68.42%)	22: (62.85%)	5: (14.28%)	

In the study population, the mean age was (25.15) years, with a range of (18 – 40) years. The study revealed non- significant differences (P> 0.05) among women with PCOS, inside and outside the city of Kerbala, the study found that most common women that admitted to women's hospital obstetrics education inside Kerbala, this result disagree with (R Hussein et al., 2021) study which found residence investigation among the patients showed higher proportion in urban population in comparison to rural one with more response is in urban residents about (51.9%) compared to (33.3%) in rural population. The result also found the occupational status higher percentage of patients were house wife 22(62.85%) for normal weight women with PCOS and 13 (68.42%), 9 (56.25%) overweight and obese women with PCOS, respectively.
The precise mechanism by which PCOS manifests itself is still unknown, the syndrome appears to be caused by genetic, environmental, dietary, and metabolic factors (Merkin et al., 2016). The origin of PCOS begins in the birth and continues throughout the lifecycle, and environmental insults and lifestyle issues may affect vulnerable

women, resulting in the occurrence of PCOS phenotypic characteristics. Diet appears to be one of the most important environmental determinants of PCOS occurrence, women with PCOS have an imbalance in their hormone levels (Kshetrimayum et al., 2019) .
Table 2 shows non-significant differences (P> 0.05) concerning the economic status of Iraqi women.

Table 2:
The living conditions of women in this study.

Characteristics	PCOS (Obese) (Number: percentage)	PCOS (Over weight) (Number: percentage)	PCOS (Normal weight) (Number: percentage)	control (Number: percentage)	P value
Number	16	19	35	35	-
Economic status					
High	2: (12.5%)	3: (15.78%)	4: (11.24 %)	3: (8.57 %)	P > 0.05
Moderate	13: (81.85%)	16: (84.21%)	30: (85.71%)	32: (91.42%)	
Low	1: (6.25%)	0	1: (2.85 %)	0	
Social status					P < 0.01
Married	15: (93.75%)	17: (89.47%)	25: (71.42 %)	20: (57.14%)	
Unmarried	1: (6.25%)	2: (10.52%)	10: (28.57%)	15: (42.85 %)	
Education					
Illiterate	0	1: (5.26%)	3: (8.57 %)	0	P < 0.01
Primary	3: (18.75 %)	3: (15.78%)	4: (11.24 %)	1: (2.85 %)	
secondary	6: (37.5%)	10: (52.63%)	12: (34.28%)	1: (2.85 %)	
University	6: (37.5%)	5: (26.31%)	16: (45.71 %)	32: (91.42%)	
Institute	1: (6.25%)	0	0	1: (2.85 %)	

The present study showed that women admitted to hospital were married. The number of obese PCOS women was 15(93.75%), and overweight women with PCOS were 17(89.47%), PCOS with normal weight 25(71.42%) and control 20(57.14%).

Clinical parameters

Hirsutism is a common clinical manifestation of hyperandrogenism in PCOS patients (Wang et al., 2019). Hirsutism, which is characterized by excessive hair growth in women, was shown to have the greatest impact on patients' quality of life, and it is generally characterized by the presence of terminal hair with male distribution in women, with PCOS being the most common etiology of hirsutism (Mara Spritzer et al., 2016) .In Table (3), we found that most cases of women who have baldness are the PCOS with normal weight 31 (88.57%), followed by 17(89.47%) and 12(75%) women of PCOS with overweight and obese respectively, the study found only nine women (25.71%) with baldness from the control group. Hair loss is one of the symptoms of PCOS that has been reported. Women with PCOS frequently experience acne, thinning hair, and hair loss, as well as limp, lackluster hair that break easily and are dry and damaged. This is primarily due to the high levels of androgenic hormones present in the body of these individuals. Androgenic alopecia, also known as male pattern baldness, can be caused by a hormonal imbalance and manifest itself as the following characteristics: The frontal and parietal (side) areas of the scalp are the most commonly affected by hair loss. As a result, the hair in the parting area becomes noticeably thinner (Shum et al., 2002).

Table (3):
The distribution of demographic data among study groups.

	PCOS (Obese) Mean ± SD	PCOS (Over weight) Mean ± SD	PCOS (Normal weight) Mean ± SD	Control Mean ± SD	P value
Infertility Type				-	P > 0.05
Primary	11: (68.75%)	17: (89.47%)	25: (71.42%)		
Secondary	5: (31.25%)	2: (10.52%)	10: (28.57%)		
PCOS Duration				-	P > 0.05
≥ 1 year	7: (43.75%)	9: (47.36%)	13: (37.14%)		
< 1year	9: (56.25%)	10: (52.63%)	22: (62.85%)		
Hirsutism					P < 0.01
Positive	10: (62.5%)	12: (63.15%)	26: (74.28 %)	2: (5.71%)	
Negative	6: (37.5%)	7: (36.84%)	9: (25.71 %)	33: (94.28 %)	
Acne					P < 0.01
Positive	4: (25%)	16: (84.12%)	16: (45.71 %)	1: (2.85 %)	
Negative	12: (75%)	3: (15.78%)	19: (54.28%)	34: (97.14 %)	
Hair loss					P < 0.01
Positive	12: (75%)	17: (89.47%)	31: (88.57%)	9: (25.71 %)	
Negative	4: (25%)	2: (10.52%)	4: (11.24 %)	26: (74.28%)	
Menstrual cycle				-	P > 0.05
Regular	6: (37.5%)	6: (31.57%)	5: (14.28%)		
Irregular	10: (62.5%)	13: (68.42%)	30: (85.71%)		

Biochemical parameters

There was significant difference in the levels of Kisspeptin1 among PCOS for obese, overweight and normal weight when compared with control group, (396.320 ±137.266), (419.167 ±149.660), (370.853 ±86.257) and (23.601 ±52.250) respectively, as shown in Table (4). On the other hand, our results of LH levels were significantly (P< 0.05) higher among PCOS women more than control group, Table (4).

Table (4):
The differences of Kisspeptine1, and hormonal profile in women with PCOS and control groups.

Parameters	PCOS (Obese) Mean ± SD	PCOS (Over weight) Mean ± SD	PCOS (Normal weight) Mean ± SD	Control Mean ± SD	P value
Kisspeptin (ng/L)	396.320 ±137.266	419.167 ±149.660	370.853 ±86.257	323.601 ±52.250	P < 0.01
LH (mIU/ml)	10.89 ±6.19	10.48 ±5.24	6.94 ±1.32	5.08 ±1.23	P < 0.01
FSH (mIU/ml)	6.30 ±2.47	5.32 ±1.66	4.89 ±0.99	6.92 ±1.15	P < 0.01
LH/FSH Ratio	1.68 ±0.33	1.94 ±0.68	1.419 ±0.488	0.735 ±0.134	P < 0.01
Free Testosterone (ng/ml)	0.68 ±0.40	0.79 ±0.53	0.927 ±0.379	0.382 ±0.09	P > 0.05
Prolactin (ng/ml)	22.36 ±4.70	19.40 ±8.9	22.854 ±9.919	17.594 ±3.481	P > 0.05

Kisspeptin is a neuropeptide that increases the release of the GnRH. It is required for the production of LH and the occurrence of ovulation. Women who have PCOS have altered amounts of the hormones GnRH and LH secretion, respectively (Ibrahim et al., 2020).In agreement with our results, increase serum Kisspeptin level in PCOS patients were observed in several studies (Nyagolova et al., 2016, Yarmolinskaya et al., 2017, Gorkem et al., 2018). While , other studies didn't find this variation (Yerlikaya et al., 2013, Emekci Ozay et al., 2016). Pandis *et al.,* (2006) demonstrated that Kisspeptin in PCOS women was negatively correlated with BMI (Panidis et al., 2006).
The levels of kisspeptin in lean PCOS patients were significantly higher than non-obese healthy women suggesting that PCOS is the main etiological factor in raising serum kisspeptin. Several other metabolic markers, the plasma concentration of testosterone, dehydroepiandrosterone sulfate, and free androgen index have been reported to be positively correlated with kisspeptin but it seems that kisspeptin level is not associated with BMI because only one study found that it is negatively correlated with kisspeptin in logistic regression analysis (Tang et al., 2019, Araujo et al., 2020) (Tang et al., 2019, Araújo et al., 2020).

Conclusion

In this study the significant difference was appeared in serum kisspeptin1 levels between PCOS groups as compared with control group with respect to their BMI. The hormonal disturbance in PCOS patients affects serum level of kisspeptin. Kisspeptin1 may be used as a biomarker in response of infertility treatments.

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