ISSN: 0067-2904

Assessment of Neurokinin B and Galanin Levels in Women with Polycystic Ovarian Syndrome

Maryam A. Malik*, Sura F. Alsaffar
Department of Biology, College of Science, University of Baghdad, Iraq

Received: 27/6/2024 Accepted: 9/9/2024 Published: 30/9/2025

Abstract:
Polycystic ovarian syndrome (PCOS) is a common endocrine disorder that predominantly affects women of reproductive age, impacting their hormonal balance and fertility. The present study was conducted to evaluate the levels of neurokinin B and galanin in women with PCOS. The study recruited PCOS patients who visited infertility consultation at the Medical City of Baghdad Hospital, Baghdad, Iraq. Patients were categorized into two groups based on their body mass index (BMI): thirty healthy control women, whose average age was between 20 and 35 years, and sixty PCOS patients, who were overweight group (BMI less than 30 kg/m^2) or obese group (BMI more than 30 $kg/m^{2)}$. The diagnosis of PCOS in women was based on the presence of at least two of the three characteristic criteria: hyperandrogenism, oligo- or anovulation, and polycystic ovaries. Weight measurements were recorded in kg, while height, waist, and wrist circumferences were recorded in cm. Serum samples were obtained from women with PCOS and a control group during the early follicular phase. The neurokinin B, galanin, anti-mullerian hormone (AMH), and testosterone levels in the blood samples were determined. The results indicated that galanin levels were higher in PCOS patients in both groups. The PCOS patients showed a significant increase in neurokinin B levels in the obese group, and there was a positive correlation between neurokinin B and wrist circumference in the same group. However, this elevation was not statistically significant. The group that was obese had significantly higher levels of AMH and testosterone. In the group of obese patients, there was also a positive correlation with waist circumference. The results of the present study revealed that neuropeptides (neurokinin B and galanin) were elevated in obese PCOS patients, which confirms the positive correlation between obesity and PCOS incidence. neuropeptide (neurokinin b and galanin) was elevated in obese PCOS patient that confirm the positive correlation between obesity and PCOS incidence.

Keywords: Polycystic ovarian syndrome, Neurokinin B, Galanin, AMH, Obesity.

تقييم Neurokinin Bو Galanin لدى النساء المصابات بمتلازمة تكيس المبايض

مريم اياد مالك *, سرى فؤاد الصفار
قسم علوم الحياة، كلية العلوم، جامعة بغداد، بغداد، العراق

الخلاصة

*Email: mariam.ayad1602a@sc.uobaghdad.edu.iq

متلازمة تكيس المبايض هي اضطراب في الغدد الصم ينتشر بصورة واسعة في النساء خلال العمر الانجابي. الدراسة الحالية شملت تقييم مستويات هرموني galanin، neuorokinin b في النساء المصابات بمتلازمة تكيس المبايض اللاتي زرن استشارية العقم في مستشفى بغداد التعليمي في مدينة الطب ببغداد. شملت الدراسة النساء الاصحاء (30 امرأة) وقسمت المريضات اعتمادا على مؤشر كتلة الجسم: المريضات البدينات (أكثر من 30 كغم\م2) ومريضات غير بدينات (أكثر من 30 كغم\م2) اللاتي يتراوح متوسط أعمارهن بين 20 و35 عامًا. شخصت حالات تكيس المبايض اعتمادا على وجود اثنين من معايير التشخيص الثلاثة (فرط الأندروجين، قلة الإباضة، وتكيس المبايض). وقيس الوزن والطول ومحيط الخصر والمعصم. وجمع مصل المريضات والاصحاء ضمن فترة الجريبية. قيست هرمونات galanin، neuorokinin b، وكذلك مخزون المبايض والهرمون الذكري في المريضات. اظهرت النتائج أن الهرمون galaninمرتفع في كلا مجاميع المرضى ولوحظ أيضا ارتفاعا معنويا في مريضات تكيس المبايض البدينات وهنالك علاقة موجبة بين هرمون neuorokinin b ومحيط المعصم في كلا المجموعتين. كما ارتفع مستوى هرمون AMH وهرمون testosteroneفي المريضات البدينات. وكذلك يوجد علاقة طردية في الهرمون الذكري مع محيط الخصر. نستنتج من الدراسة ان البيبتيدات العصبية ترتفع مستوياتها في المريضات المصابات بمتلازمة تكيس المبايض البدينات وهذا يعزز العلاقة الطردية مع السمنة.

1. Introduction

A complicated endocrine condition recognized as polycystic ovarian syndrome (PCOS) is characterized by several clinical features, such as irregular menstruation, elevated testosterone levels, and the appearance of cystic ovaries [1,2]. According to guidelines from the National Institutes of Health (NIH), the incidence of PCOS worldwide is currently 6% (classified as 5 to 8%). However, according to Rotterdam (2003), the prevalence of PCOS is pegged at 10% [3]. The POCS is an endocrine imbalance observed in females of reproductive age, with a prevalence rate ranging from 5 to 10% among fertile females [4]. Obesity, characterized by an excessive accumulation of body fat, is a common metabolic issue [5]. The World Health Organization (WHO) and the Centre for Disease Control and Prevention (CDC) define overweight, obese, and severely obese as having a body mass index (BMI) of more than 25, 30, and 40 kg/m^2, respectively [6]. There is compelling evidence that obesity raises the risk of sub-fertility and infertility in both men and women. Obesity in women increases endometrial dysfunction, lowered oocyte quality, and dysregulation of the hypothalamus-pituitary-ovary pathway [7,8].

The anti-mullerian hormone (AMH) is one of the transforming growth factor groups. Granulosa cells in the tiny and antral follicles of the ovary produce and release this reliable indicator of ovarian reserve [9–10]. Anti-mullerian hormone regulates follicular growth, plays a critical role in the pathophysiological process of PCOS, and is strongly connected with the severity of the condition [11]. Moreover, serum AMH levels are more sensitive and are not influenced by the menstrual cycle [11,12]. Various factors, such as environment and heredity, can affect blood AMH levels [10,13]. Androgens are produced by several tissues. The adrenal gland, gonads, and peripheral tissues - including the liver, skin, and adipose tissue - are the primary sites for the synthesis of pre-androgens such as androstenedione and dehydroepiandrosterone (DHEA). Testosterone is primarily produced in the ovaries, adipose tissue, and other peripheral tissues like the liver and skin in women [14]. The ovaries begin producing testosterone at the onset of ovulation. This cyclical production peaks in the middle of the cycle and continues to be high during the luteal phase.

The peptide family known as tachykinins, which includes neurokinin B, is linked together by the amino acid sequence Phe-X-Gly-Leu-Met-NH2 at the C-terminus. The neurokinin 3 receptor (NK3R; encoded by the TAC3R gene) is the preferred binding site for neurokinin B

(NKB), which is produced by the human TAC3 gene. The human nervous system contains both NK3R and NKB [15]. A study was conducted in 1991 on women who reached menopause and those who had not provided the first evidence of NKB's role as a regulator of reproductive function [16]. NKB is considered to be an essential GnRH secretion regulator. The factor causes an increase in thecal androgen secretion and a decrease in the ovulation ratio, which is the clinical manifestation in PCOS patients [17]. Ovarian testosterone levels rise in response to pituitary production of luteinizing hormone (LH), which also prevents ovulation.

Premenopausal women were studied to examine the effects of NK3R antagonism on LH secretion and ovarian follicle development during the follicular phase of the menstrual cycle. The results showed that NKB-NK3R signaling plays a critical role in the physiological regulation of GnRH-driven follicle growth and, in turn, the timing of ovulation [18]. The identification of the involvement of the hypothalamic neuropeptides kisspeptin and neurokinin B (NKB) and their receptors has greatly advanced our knowledge of the regulation of gonadotropin-releasing hormone (GnRH) secretion and, by extension, the hypothalamic-pituitary-gonadal axis. Numerous investigations have established that kisspeptin positively regulates LH release in both men and women. In healthy women, the response to kisspeptin varies and depends on the sex steroid milieu at different stages of the menstrual cycle. Also, there is a positive correlation between kisspeptin and estradiol concentrations. The administration of NKB did not affect LH secretion in either men or women [19].

Galanin is a 29-amino acid neuropeptide that belongs to the galanin peptide family, which also includes galanin, galanin-like peptide, and alarin. It regulates insulin resistance, hunger, obesity, hypertension, metabolism, mood, memory, learning, addiction, and appetite [20]. This neurohormone indicates a role for galanin in GnRH regulation by sending a signal through the G-protein coupled receptor GAL1-3, which is generated by arcuate nucleus gonadotropin-releasing hormone neurons. Galanin is a molecular motif that links metabolism and the neuroendocrine-reproduction axis. Additionally, it is connected to the regulation of glucose metabolism and thermogenesis [21,22]. The peptide galanin (GAL) is found in the stomach, pancreas, pituitary, adrenal medulla, hypothalamus, and placenta [23]. Galanin contributes to the GAL peptide, which modulates pancreatic insulin release and enhances insulin sensitivity [24]. The hypothalamus and the GnRH-producing GT1-7 cells release GnRH in response to galanin [25]. Body weight, food consumption patterns, and energy metabolism are all regulated by the neuropeptide GALP (galanin-like peptide).

2. Materials and methods

2.1 Study population

The study included PCOS patients who visited the Medical City of Baghdad Hospital, Baghdad, Iraq, for infertility consultations. These included ninety women in total: thirty patients without PCOS (control group) and sixty PCOS patients (overweight and obese PCOS patients). The average age of the patient and control groups was between 20 and 35. Based on their BMI: overweight PCOS with a BMI <30 kg/m^2 and obese female with PCOS with a BMI ≥30 kg/m^2. Weight was measured in kg, while height, waist circumference, and wrist circumference were measured in cm. The formula used to calculate BMI was "BMI = weight (kg) / height (m^2)." The PCOS patients that was non obese their BMI less than 24 Kg/ m^2 A consultant physician used the 2003 Rotterdam criteria to diagnose PCOS [26].

2.2. Ethical approval

The study received ethical clearance from the College of Science's Ethics Committee at the University of Baghdad, located in Baghdad, Iraq, with the reference number (Ref.: CSEC/1123/0098, dated October 2023). All patients and controls provided written informed consent before participating in the study.

2.3. Sample analysis

The enzyme-linked immunoassay (ELISA) kit (Elabscience Company, USA) was used to assess the neurokinin B, galanin, and AMH levels in the blood samples, Catalog No: E-EL-H1885 E, EL-H1301, E-EL-H6189). A universal microplate reader (ELX 800, UK) was used to measure the optical density of the final ELISA plates. The level of testosterone hormone was measured by a competitive enzyme immunoassay using a TOSOH AIA analyzer (Cat. No. 0025204).

2.4. Statistical analysis

The statistical analysis was performed using the Statistical Analysis System (SAS) software (2018). Values were expressed as mean $\pm$ standard error of the mean (SE). A one-way analysis of variance (ANOVA) was utilized to compare the means and correlation of some parameters. The degree of probability was less than 0.05.

3. Results and discussion

As shown in Table 1, the mean Body Mass Index (BMI) of the obese PCOS group (34.15±0.76) was found to be significantly higher ($P<0.05$) compared to the control group (25.92±0.58). Compared to the control group, the waist circumference of the obese group was significantly higher (97.75 ±1.45). There was no significant difference in the mean wrist circumference between the groups. Table 2 showed that there was a positive significant correlation between wrist circumference, waist circumference, and BMI in the obese group. Also, there was a positive, non-significant correlation between BMI and galanin in the same group. Neurokinin B had a positive, non-significant correlation with wrist circumference in obese PCOS. AMH and BMI had a positive correlation in obese PCOS compared with control females. Testosterone and BMI were positively significantly correlated in the obese PCOS group compared with the control. As illustrated in Table 3, neurokinin B significantly increased obese PCOS (1273.10 ±233.12) compared with the control (1040.42±307.85) $p<0.05$. There was no significant difference in galanin levels when comparing the obese PCOS group (20.87 ±2.32) to the control female (14.66±3.69). The levels of testosterone hormone and anti-mullerian hormones were significantly higher in the obese PCOS group (6.12 ±0.42) compared with the control group (4.18 ±0.38). The present study found that the obese PCOS group had a high body mass index, wrist circumference, and waist circumference. This is consistent with several studies [27]. Given the association between IR and PCOS, all females with PCOS should have their risk of developing metabolic syndrome and its associated conditions, such as type 2 diabetes, hypertension, and hyperlipidemia, as well as their potential risk of clinical events, such as acute myocardial infarction and stroke, evaluated [32]. The BMIs of the research group participants differed significantly from one another. In PCOS women, abdominal obesity can lead to both localized and systemic oxidative stress. Furthermore, there is a higher chance that problems caused by PCOS could get worse if there is abdominal fat. Obesity is considered to be one of the reasons for PCOS because it leads to a large accumulation of cholesterol and other lipids, which are then converted to testosterone in the skin and fat cells as well as in the ovaries and adrenal glands, which change the balance between the hormones FSH and LH. Fat accumulates in the femoral and gluteal fat pads, but in women with PCOS, this changes to the visceral depots, increasing the waist circumference and BMI [33]. The neurokinin B level was elevated in the

obese PCOS group compared with obese PCOS females and the control group. The findings of the present study agree with several investigations [23]. Neurokinin B is one of several neuronal and endocrine variables that control GnRH secretion. Clinically, NKB causes an increase in adrenocortical androgen secretion and a decrease in the ovulation ratio, which is a typical presentation in polycystic individuals. In healthy women, NKB regulates the development of follicles, the release of gonadotropins, and the timing of ovulation. NKB and kisspeptin signaling affect the control of estrogen-negative feedback, which is altered in PCOS. Furthermore, elevated LH pulse frequency and amplitude are associated with PCOS, likely due to increased GnRH pulsatile production. Ovulation fails, and ovarian testosterone production rises as a result of increased pituitary LH output. According to recent investigations, the NKB–kisspeptin–GnRH pathway is essential for controlling LH secretion. Patients with genetically compromised NKB signaling were shown to produce lower LH and a lower LH pulse frequency. Consequently, the underlying pathophysiology of LH hypersecretion and hyperandrogenism observed in PCOS may be targeted by pharmacological NKB inhibition [34]. The obese PCOS group showed an increase in galanin, which is consistent with Pazderska *et al*. [35]. Increased levels of galanin and vaspin in the blood of obese individuals may be associated with weight gain or could represent one of several factors that contribute to the pathophysiology of obesity. Galanin affects both the central and peripheral nervous systems, but it is most strongly associated with endocrine functions, such as reproduction, inflammation, glucose metabolism, and anterior pituitary hormone regulation. It is uncertain how galanin functions in the pathophysiology of PCOS or whether it has any potential therapeutic benefits. However, considering the well-established neuroendocrine changes in PCOS patients, one might speculate that galanin, through its effects on gonadotropin-releasing hormone (GnRH) secretory neurons, could play a significant role in the onset of PCOS. Galanin, an intraovarian regulatory peptide, regulates steroidogenesis in ovarian tissue and controls the rise in LH and prolactin before menstruation. It can both co-secrete and control gonadotropin-releasing hormone (GnRH) secretion. In addition to raising FSH production, galanin can significantly reduce LH, insulin, glucose, insulin resistance (IR), and testosterone levels. Galanin also regulates the hormones that are produced by steroids. It may control the expression of genes related to metabolic, inflammatory, and hormonal issues in PCOS [36]. Numerous investigations have been reported a considerable increase in both AMH and testosterone in the obese group [37-38]. Two significant types of obesity are typically assessed using BMI and Waist circumference. These are central (abdominal) obesity and general (peripheral) obesity. The comorbidities of obesity and the distribution of body fat are tightly linked. There may be a connection between central obesity and AMH concerning some factors. Firstly, central or abdominal obesity is associated with higher levels of insulin resistance (IR) than general or peripheral obesity. Free fatty acids and the paracrine actions of the abdominal depot most likely mediate this association. Furthermore, central obesity exacerbates the insulin-related metabolic and reproductive characteristics of PCOS (39-40). The hyperinsulinemia caused by IR increases the availability of free androgens, which in turn stimulates ovarian steroidogenesis and inhibits the production of sex hormone-binding globulin in the liver. Adipose tissue also serves as a source of metabolism and storage for several lipid-soluble hormones, including androgens, which exacerbate hyperandrogenism. Therefore, a poorer clinical reproductive presentation is more prevalent in obese and overweight PCOS women. The build-up of small follicles and granulosa cell proliferation caused by excess testosterone is most likely the cause of the association between AMH and androgen levels [44]. The accumulation of fat in the subcutaneous adipose depots (SAD) is more common in women than in men. There is an overabundance of androgen in these people because the thickness of the intraperitoneal fat depots is significantly correlated with circulating androgen levels. Further research has provided evidence supporting androgens' participation in female body fat distribution and

increased visceral adiposity. Women with higher visceral adiposity are thought to be at risk for developing metabolic syndrome, which may make the metabolic problems linked to this endocrinopathy worse. However, little is known about the molecular mechanisms behind the increased abdominal adiposity associated with long-term androgen therapy. Numerous studies have examined the hormones related to obesity. Obesity is thought to be a risk factor for arthritis, which is characterized by joint stiffness, discomfort, inflammation, and decreased mobility. Infections that could cause osteoarthritis, rheumatoid arthritis, and gout are more common in obese female PCOS patients with a high BMI [41,42,43].

Table 1: Comparison between body mass index, waist circumference, and wrist circumference in the study population

Group	BMI (kg/m^2)	Waist circumference (cm)	Wrist circumference (cm)
Control	25.92 ±0.58 b	73.62 ±1.97 b	15.37 ±0.34
Overweight PCOS	29.02 ±3.81 ab	76.33 ±2.35 b	17.56 ±0.22
Obese PCOS	34.15 ±0.76 a	97.75 ±1.45 a	17.98 ±2.51
P-value	0.042	0.0001	0.613

Values are presented as mean ± standard error of the mean; The mean having different alphabets a, b in the same column differed significantly; BMI: Body mass index; PCOS: Polycystic ovarian syndrome; * $p \leq 0.05$; **: $p \leq 0.01$; NS: Non-significant; SE: Standard error of the mean;

Table 2: Correlation coefficient between body mass index and other parameters

Parameter	Correlation coefficient-r with BMI	
	Obese PCOS	Control
Waist circumference	0.5**	0.04 NS
Wrist circumference	0.42*	0.03*
Galanin	0.02 NS	-0.3 NS
Neurokinin B	0.143 NS	0.29 NS
AMH	0.17 NS	-0.09 NS
Testosterone	0.4*	-0.12 NS

PCOS: Polycystic ovarian syndrome; BMI: Body mass index; AMH: Anti-mullerian hormone; $p \leq 0.05$; **: $p \leq 0.01$; NS: Non-significant

Table 3: Comparison between galanin, neurokinin B, AMH, and testosterone in the study population

Group	Mean ± SE (mg/dl)			
	Testosterone (ng/d)	Galanin (pg/ml)	Neurokinin B (pg/ml)	AMH (ng/ml)
Control	28.86 ±1.67 c	14.66 ±3.69	1040.42 ±307.85 ab	4.18 ±0.38 b
Overweight PCOS	39.93 ±2.37 b	17.15 ±3.16	863.07 ±86.87 b	5.79 ±0.63 ab
Obese PCOS	51.47 ±2.66 a	20.87 ±2.32	1273.10 ±233.12 a	6.12 ±0.42 a
P-value	0.0001	0.370	0.246	0.0415

Values are presented as mean ± standard error of the mean; The mean having different alphabets in the same column differed significantly; BMI: Body mass index; PCOS: Polycystic ovarian syndrome; AMH: Anti-mullerian hormone; *: $p \leq 0.05$; **: $p \leq 0.01$; NS: Non-significant; SE: Standard error of the mean.

Conclusion

The results of this study demonstrated a significant positive association between the prevalence of PCOS and obesity, suggesting a potential link between the two conditions, as evidenced by the elevated levels of neuropeptides (neurokinin B and galanin) in obese PCOS patients.

Acknowledgments

The authors would like to thank Dr. Khetam Malik Abd Alhameed and the medical team at the Medical City of Baghdad Hospital, Bagdad, Iraq, for their assistance with patient diagnosis and sample collection.

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