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Effects of Ketogenic Diet on Neuropeptides (Kisspeptin and Phoenixin-14) in Obese Polycystic Ovarian Syndrome

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ABSTRACT

Purpose: The detrimental effects of irregularities in reproductive indicators in polycystic ovarian syndrome (PCOS) are increased due to obesity. The outcomes of reproductive characteristics in PCOS are affected by the ketogenic diet. Dysregulation of the neuropeptide is a key mechanism in the PCOS pathogenesis. Despite the impact of the ketogenic diet on many neuropeptides being established in various diseases, its impact on neuropeptide indicators has not yet been established in PCOS. Thus, a specific objective of the current pilot observational report was to investigate whether the ketogenic diet has a significant impact on the neuropeptide indicators (Kisspeptin and Phoenixin-14) in obese PCOS.
Methods: The present work is a pilot observational study conducted over 1 year (2025) on 100 obese PCOS women at private clinics in Baghdad City. Only fifty obese PCOS women completed and concluded our study. The impact of adhering to a 3 and 6-month ketogenic diet has been investigated by measuring the routine reproductive and neuropeptide levels (Kisspeptin and Phoenixin-14).
Results: From the baseline (before obese PCOS women adhered to the ketogenic diet), the ketogenic diet for 3 and 6 months had a significant impact, resulting in a significant reduction in the kisspeptin (1861.9±139.8 pg/mL vs. 1801.8±193.5 pg/mL vs. 1775.9±287.7 pg/mL), and a significant reduction in the phoenixin-14 (79.5±29.1 ng/mL vs. 62.7±22.3 ng/mL vs. 54.9±33.2 ng/mL).
Conclusion: The current findings highlight the importance of the ketogenic diet as adjunctive management for the reproductive and neuropeptide indicators to manage PCOS complications, particularly neuropeptide dysregulation.

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Introduction

Polycystic ovary syndrome (PCOS) is a classic endocrine disorder in women during the reproductive age, with an approximate estimate of 8% to 13%.[1] The recent clinical criteria to diagnose PCOS require at least 2 of 3 major symptoms after other possible causes have been ruled out: oligo-ovulation or anovulation, signs of hyperandrogenism (HA), and the presence of many cysts in the ovaries by ultrasound detection.[2] Although the exact PCOS etiology remains in question, much of the literature describes the role of family history, an improper lifestyle, using cosmetics containing cancerous preservatives, obesity, and dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis as potential factors associated with the causes of this syndrome.[3] Obesity has been the subject of many studies in PCOS because approximately fifty percent of PCOS women have a body weight go towards the category of overweight or even obesity.[4] On the other hand, obesity is a classic problem that causes elevation of adaptive hyperinsulinemia (HI) and insulin resistance (IR), diabetes mellitus type 2 (DM-T2), glucose intolerance, dyslipidemia, and other various complications related to PCOS.[5] The HPO axis permits the cyclic production of gonadotropic and steroid hormones, and its imbalance is another significant pathophysiological mechanism of PCOS.[6] Recently, the association between obesity and ovulatory disorders caused by changes in the neuroendocrine of the HPO axis is well documented, even though the precise pathophysiological mechanisms underlying this linkage are unknown.[7]

A ketogenic diet (KD) is a dietary regimen that involves consuming low amounts of carbohydrates, high fat, and adequate protein.[8] KD is a key strategy for promoting the generation of ketone bodies and replicating the metabolic state of fasting.[9] KD is one of the practical dietary approaches widely recognized for the management of intractable epilepsy. In recent years, KD has gained widespread recognition in treating various conditions like malignancies and DM-T2, IR, as well as dyslipidemia associated with obesity and metabolic syndrome.[10] Over the past decade, most researchers have emphasized that KD is an effective approach to managing the outcomes of anthropometric, metabolic, and reproductive variables in PCOS.[11] Moreover, the HPO axis is thought to benefit from KD via improvement of insulin sensitivity, which causes overall endocrine function.[12]

Kisspeptin (KISS) is one of the most important neuropeptides that has been identified to exist in an inactive form, pre-pro-KISS, containing 145 amino acids. Although different mature forms of KISS range from 10 to 54 amino acids in sequence, KISS-54 is the most abundant and active form of KISS isoforms in human circulation.[13] KISS activates its cognate receptor GPR-54 in various target tissues to exert disparate functions, including the puberty onset, gonadotropin hormone secretion, and ovulation.[14] KISS neurons are located in the posterior part of the hypothalamus, where they form the gonadotropin-releasing hormone (GnRH) pulse generator and stimulate GnRH secretion. Thus, KISS enhances luteinizing hormone (LH) release in women.[15] A considerable amount of literature has been published on KISS among PCOS phenotypes regarding BMI. These studies have noted that KISS is raised in obese PCOS compared with normal-weight PCOS.[16] Phoenixin (PNX) is one of the novel neuropeptides that has been recently identified as a cleaved product from a small integral membrane protein 20 called Smim-20, containing 67 amino acids.[17] In spite of the different mature forms of PNX, which range from 14 to 46 amino acids in sequence, PNX-14 and -20 are the most abundant and active forms of PNX isoforms in human circulation.[18] PNX-14 exerts disparate functions in different tissues via activating its cognate receptor GPR-173, including gonadotropin hormone secretion, ovarian periodicity, adipocyte growth, and body weight regulation. PNX-14 controls pituitary gonadotropin secretion by altering the expression of the GnRH receptor. Therefore, PNX-14 proves to be an essential mediator in regulating ovarian periodicity through controlling the

LH secretion.[19] There is a large volume of published studies describing the role of PNX-14 in contributing to obesity due to PCOS through the hypertrophy and hyperplasia it creates in adipose tissue (AT).[17]

Although the impacts of KD adherence have been established on multiple neuropeptides in various conditions, its impacts on neuropeptides have not been investigated in PCOS. Thus, the present pilot observational study was to ascertain how well adhering to 3 and 6 months of KD affects routine reproductive and neuropeptide (KISS and PNX-14) markers in obese PCOS.

Method and Materials

Study Design and Participants

The present work is a pilot observational study conducted over 1 year (2025) on 100 obese PCOS women at private clinics in Baghdad City, ages 18 to 25. Fifty obese PCOS women were excluded from our pilot observational study; 13 did not meet the inclusion criteria, 12 refused to participate, 10 were on current PCOS therapy, nine lost to follow-up, and six withdrew after 4 months of adhering to KD. Thus, only 50 obese PCOS women completed and concluded the study as presented in Figure 1. The present study utilizes the revised Rotterdam criteria to diagnose PCOS,[2] which calls for at least 2 of 3 major symptoms to be required: (1) oligo/or amenorrhea; (2) signs of biochemical hyperandrogenism; (3) polycystic ovary morphology (each ovary has ≥12 follicles with 2-9 mm in diameter and a raised volume ≥10 mL, seen through ultrasonography). Obese women with other possible conditions, rather than PCOS, were ruled out in our study, including Cushing's syndrome, congenital adrenal hyperplasia, tumors that secrete androgens, diabetes mellitus, and hypertension. Also, obese women who have taken any drug except potassium citrate (Kalinor), an anti-drug for calcium oxalate and uric acid stones, were ruled out in our study. To obtain their ethical consent, a short questionnaire was designed to ascertain women's understanding of the brief information about the current study, including its aim and benefits, methods, and confidentiality.

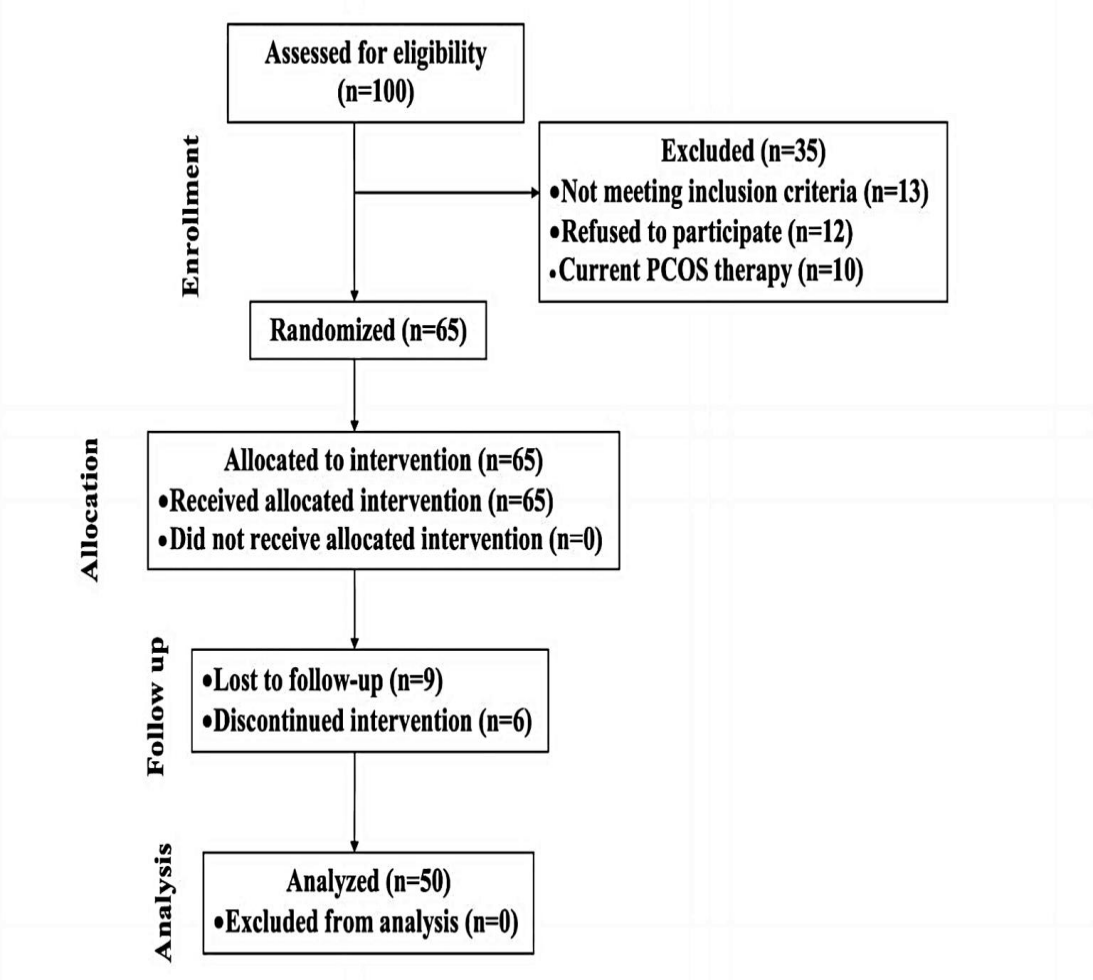

Figure1. Flowchart of obese PCOS selection in the study.

The Protocol for Ketogenic Diet Adherence

Obese PCOS in our pilot observational study have adhered to a standard KD. The daily calories consumed by each obese PCOS woman were measured by a certified nutritionist doctor through determining her body composition, basal metabolic rate, and daily home physical activity, which provides daily kilocalories of approximately 1300-1700 kcal/day. Two meals were included to compute the net daily energy. The net daily energy consumption was taken as 6% vegetable carbohydrate sources (like green pepper, lettuce, cabbage, tomato, and garlic), 20% animal protein sources (like shrimp, fish, chicken, eggs, and meat), and 74% fats from avocado fruit, olive oil, animal tallow, and coconut oil. Each PCOS woman was contacted through mobile phone during the 6 months of KD intervention to monitor compliance, resolve any issues, and take food dietary diaries. KD adherence was assessed using urinary ketone body measurements (≥ +1.5 mmol/L) on urine strips (CYBOW, Republic of Korea) three times a day.

Blood Sample Collections

Five milliliters by using a disposable syringe were withdrawn from the venous obese PCOS after overnight fasting for 10-12 hours during days 2, 3, or 4 (early follicular phase of the menstrual cycle). Five milliliters were left to clot at room temperature (25 ℃) in tubes containing gel for 10 minutes and then centrifuged to separate the sera.

The sera obtained by centrifugation were stored until the routine reproductive hormonal and neuropeptide parameters were measured.

Anthropometric and Biochemical Characteristics Determination

The woman's body weight and height were measured through the InBody-270S (InBody, UK) electronic scale, nearest 0.1 kg, and the BSM-270B (InBody, UK) stadiometer, nearest 0.1 cm. To measure a woman's body mass index (BMI), her weight (kg) was divided by her height squared (m^2).

Fasting sera of hormonal tests, including insulin (INS, µIu/mL), luteinizing hormone (LH, mIU/mL), follicle-stimulating hormone (FSH, mIU/mL), total testosterone (TT, ng/mL), dehydroepiandrosterone-sulfate (DHEA-SO_4, µg/dL), estradiol (E_2, pg/mL), and sex hormone-binding globulin (SHBG, nmol/L), were measured by commercial kits (Roche Diagnostics, Switzerland) and the Cobas e-411 autoanalyzer system (Roche-Hitachi Diagnostics, Japan) through the Electro-Chemi-Luminescence-Immuno-Assay (ECLIA). One of the most well-known equations for calculating free androgen index (FAI) percentage is TT (ng/mL) × 2.5 / SHBG (nmol/L) × 100%.[20]

The kisspeptin (KISS, 31.25-2000 pg/mL) and phoenixin-14 (PNX-14, 1.563-100 pg/mL) levels were determined using commercial kits (FineTest, China) through the Enzyme-Linked-Immune-Sorbent Assay (ELISA).

Statistical Analysis

One-way ANOVA (analysis of variance) and Tukey's tests were performed to assess the P-value (probability of differences) between before and after-KD adherence in obese PCOS via the Prism computer program, version 8.0.1 (GraphPad Software, New York, USA). The Shapiro–Wilk normality test was employed to assess whether the study parameters follow a Gaussian (normal distribution). Mean ± standard deviation (SD) was used to present the study results. To investigate whether there were significant associations between neuropeptides (KISS and PNX-14) and reproductive parameters at baseline (before KD adherence), Pearson intercorrelations were employed.

Results and Discussion

Table 1 presents the linear regression analysis among KISS and PNX-14 with anthropometric and reproductive parameters at baseline (pre-KD). The correlational analysis regarding KISS showed a significant positive association with LH, TT, and DHEA-SO_4, and a significant inverse association with SHBG. The correlational analysis regarding PNX-14 reveals significant positive associations with BMI, LH, LH/FSH ratio, TT, and E_2. On the other hand, further statistical tests revealed no significant association between KISS and PNX-14 (r=0.299, P=0.421).

Table 1. The intercorrelations among the studied parameters in obese PCOS women at baseline.

Parameter	KISS		PNX-14	
	r	P	r	P
Weight, Kg	0.223	0.203	0.501	0.097
BMI, Kg/m^2	0.131	0.189	**0.597**	**0.007****
INS, µIu/mL	0.412	0.389	0.811	0.078
LH, mIU/mL	**0.722**	**0.001****	**0.422**	**0.039***

FSH, mIU/mL	0.021	0.914	0.078	0.933
LH/FSH ratio	0.152	0.526	**0.297**	**0.034***
TT, ng/mL	**0.720**	**0.001****	**0.612**	**0.001****
DHEA-SO_4, µg/dL	**0.692**	**0.001****	0.634	0.349
E_2, pg/mL	0.167	0.507	**0.311**	**0.032***
SHBG, nmol/L	**-0.489**	**0.005****	-0.454	0.557
FAI, %	0.412	0.389	0.222	0.159

:** significant association between the two parameters; *:** highly significant association between the two parameters.

Table 2 compares the results from the preliminary analysis of KD adherence at 3 and 6 months. From the baseline (pre-KD), a significant reduction was demonstrated in the levels of body weight (-12.5 kg *vs.* -25.5 kg), BMI (-6.1 kg/m^2 *vs.* -10.2 kg/m^2), INS (-2.8 µIu/mL *vs.* -5.3 µIu/mL), LH (-6.5 mIU/mL *vs.* -9.3 mIU/mL), LH/FSH ratio (-1.6 *vs.* -2.2), TT (-0.6 ng/mL *vs.* -0.8 ng/mL), DHEA-SO_4 (-28.3 µg/dL *vs.* -45.7 µg/dL), E_2 (-26.6 pg/mL *vs.* -71.8 pg/mL), and FAI (-3.3% *vs.* -6.3%). At the same time, significant improvement in the levels of FSH (1.3 mIU/mL *vs.* 2.5 mIU/mL) and SHBG (5.6 nmol/L *vs.* 12.4 nmol/L).

Table 2. Anthropometric and reproductive parameters changes before and after KD adherence in obese PCOS.

Parameter	Pre-KD (Baseline) Mean ± SD	Post-3 months of KD Mean ± SD	Post-6 months of KD Mean ± SD	P-value
Weight, Kg	88.9 ± 12.7	76.4 ± 14.3	63.4 ± 11.9	<0.0001
BMI, Kg/m^2	34.9 ± 3.8	28.8 ± 3.3	24.7 ± 4.1	<0.0001
INS, µIu/mL	16.7 ± 2.2	13.9 ± 4.6	11.4 ± 3.6	0.0025
LH, mIU/mL	18.9 ± 5.5	12.4 ± 2.9	9.6 ± 2.4	<0.0001
FSH, mIU/mL	5.6 ± 1.9	6.9 ± 1.5	8.1 ± 2.1	0.0254
LH/FSH ratio	3.4 ± 2.9	1.8 ± 1.9	1.2 ± 1.1	0.0388
TT, ng/mL	1.9 ± 0.7	1.3 ± 0.4	1.1 ± 0.2	<0.0001
DHEA-SO_4, µg/dL	230.8 ± 75.5	202.5 ± 88.1	185.1 ± 92.6	<0.0001
E_2, pg/mL	266.4 ± 62.4	239.8 ± 77.7	194.6 ± 93.9	<0.0001
SHBG, nmol/L	42.5 ± 22.6	48.1 ± 18.5	54.9 ± 20.4	<0.0001
FAI, %	11.1 ± 4.6	7.8 ± 1.4	4.8 ± 1.7	<0.0001

KD: Ketogenic Diet; **SD:** Standard Deviation; **FAI:** Free Androgen Index.

Figures 2 and 3 show the effects of adhering to KD for 3 and 6 months on the level of neuropeptides (KISS and PNX-14). The levels of KISS (-60.1 pg/mL *vs.* -86 pg/mL) and PNX-14 (-16.8 ng/mL *vs.* -24.6 ng/mL) were significantly reduced from the baseline.

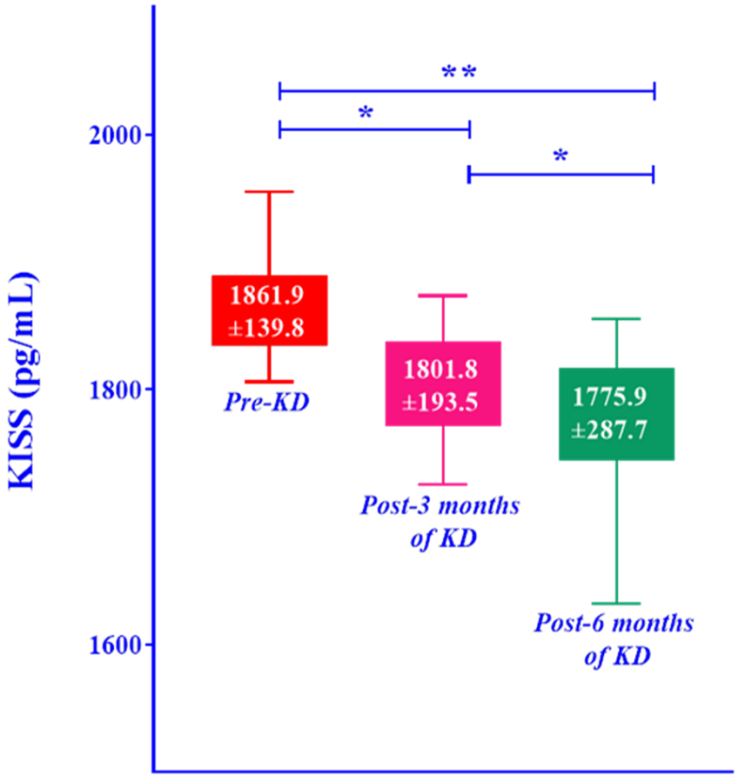

Figure 2. Changes in kisspeptin levels before and after KD adherence. */**: reveal that the means difference is significant (P<0.05).

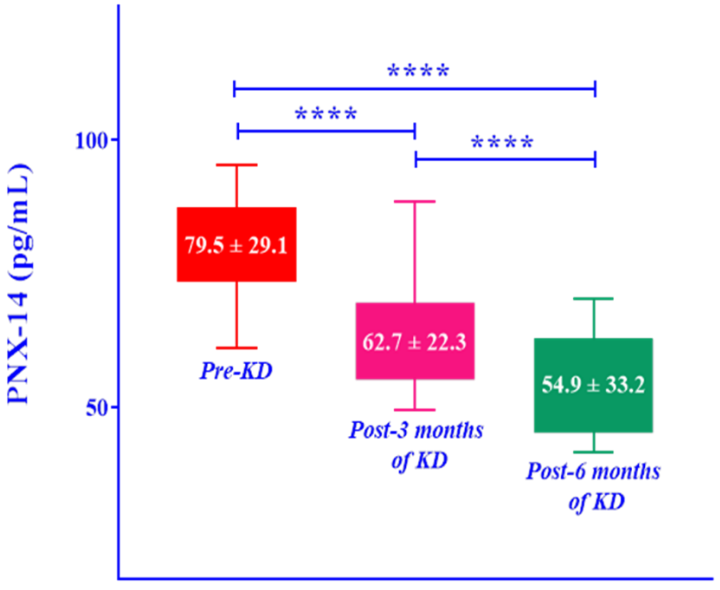

Figure 3. Changes in the phoenixin-14 level before and after KD adherence. ****: reveal that the means difference is substantial and significant (P<0.0001).

The most intriguing findings that emerged from Table 2 in the current pilot observational study were that intervention for 3 and 6 months of KD had a statistically significant impact (P<0.005) on routine anthropometric and reproductive parameters among obese PCOS women. Our results accord with earlier observations by Harbi and colleagues,[21] who demonstrated that 6 months of KD intervention substantially and significantly alter routine

anthropometric, metabolic, and reproductive parameters in obese PCOS individuals. Limiting daily carbohydrate intake to ≤ 50g causes the gluconeogenesis pathway in the liver to be stimulated. Moreover, when endogenous glucose synthesis is depleted, circulating insulin levels decrease, thereby exhausting body fat storage through the ketogenesis pathway. Thus, recent years have seen renewed interest in KD as a significant weight-loss regimen because of its pivotal role in reducing ghrelin (hunger hormone) and increasing satiety peptides through the ketone bodies' appetite-suppressing properties, and then dramatically lowering calorie intake.[22,23] Additionally, the existing literature on many obesity-related diseases, particularly PCOS, is extensive and focuses particularly on the central correlation between obesity and dyslipidemia prevalence and ovulatory dysfunction in PCOS.[24] One of the main phenomena seen in obese PCOS women is dyslipidemia due to IR with compensatory HI. Dyslipidemia is recognized to be related to central and liver fats in obese PCOS.[25] Recent studies demonstrate a significant association between dyslipidemia and HA in PCOS through reduced apolipoprotein A1 (Apo A1), a key aspect for numerous androgenic and steroidogenic enzymes in the ovarian granulosa cell.[26] Also, liver fat is a dominant contributor to HA in PCOS, which causes an adverse reproductive dysregulation risk. [27] KD was found to reduce liver fat and regulate the lipid profile in obese PCOS via improving hepatic IR and reducing circulating glucose and insulin.[21] Likewise, HI has significant effects on the ovaries' ability to synthesize and release more androgen through reducing SHBG secretion by the liver in obese conditions.[28] SHBG, a central biologically and bioavailability regulator for androgens and sex steroids in the circulation, is used to evaluate the severity of HA in PCOS. SHBG is mainly produced by hepatocytes, and its synthesis and secretion are substantially affected by HI due to obesity.[29] According to our results regarding the effect of KD intervention on SHBG levels, we may infer that decreased HI enhances SHBG synthesis and secretion by hepatocytes via limiting the stimulation of ovarian androgen synthesis, which together restrict the free androgen levels in the bloodstream. On the other hand, a dominant feature of disrupted ovulation in PCOS is a relatively elevated LH-to-FSH ratio, and a significant reduction in this ratio is frequently prescribed for menstrual cycle regulation, hormonal balance normalization, ovulatory improvement, and chances of conceiving.[30] It can thus be suggested that KD intervention is typically helpful for PCOS women to reduce the LH/FSH ratio, which may restore normal function of the endocrine system.

On the question of the impact of KD on neuropeptide levels (KISS and PNX-14), our study found that KISS and PNX-14 levels were significantly reduced after 3 and 6 months of KD adherence, as displayed in Figures 2 and 3. To our knowledge, our study is the first pilot observational report to observe whether the KD intervention significantly impacts circulating neuropeptides (KISS and PNX-14) in obese PCOS. While the potential mechanisms by which KD regulates neuropeptides in PCOS remain unclear, our study results may be explained by four primary suggestions. First, weight loss is important in obesity and can help to regulate neuropeptides in PCOS. Recent studies have established that substantial weight loss results in significant regulation of neuropeptides circulating in the bloodstream.[31] Although KISS does not show a significant correlation with BMI, PNX-14 had a significant positive association with BMI, as shown in Table 1. Therefore, it seems possible that this finding is due to an implication of the current pilot observational results, which suggest a link between KD-support weight loss and neuropeptide regulation in obese PCOS. Second, the KD reduces visceral adipose tissue (VAT) and regulates blood biochemical variables.[32] Recently, considerable evidence has accumulated to show that VAT releases various neuropeptides and can trigger reproductive disorders.[33,34] Several lines of evidence suggest that a significant reduction in the VAT level by KD results in reduced abdominal obesity and improves its complications.[35] Although VAT was not measured in the current pilot observational study, earlier observation by Paoli and colleagues reported that VAT was significantly reduced by 36.5% among overweight PCOS women who

adhered to a 12-week KD.[36] It can thus be suggested that a substantial reduction in VAT by KD may reflect regularities in the secretion of neuropeptides from AT. Third, there is a significant influence of obesity on neuropeptide dysregulation because of HI.[37] Despite the current pilot observational study lacking a direct assessment of insulin effects on KISS and PNX-14 neurons, a large volume of published studies has investigated how most neuropeptides are affected in metabolic syndromes, especially in PCOS, due to HI.[6] As Table 2 shows, a significant reduction in insulin levels when obese PCOS women follow KD may have caused an observable reduction in their KISS and PNX-14 levels. Therefore, it is probable that the effects of KD intervention on neuropeptide (KISS and PNX-14) levels in obese PCOS may support neuropeptide secretion and HI pathophysiological correlation. Fourth, the majority of the literature has established that KD intervention plays a significant role in gonadotropin hormone secretion regulation by enhancing insulin sensitivity and thereby controlling GnRH secretion.[38] As shown in Table 1, KISS and PNX-14 have a significant direct association with LH. Hyperstimulation of thecal cells, follicular maturation failure, and anovulation are all caused by LH overproduction and result in androgenic hypersecretion and the creation of a vicious circle that feeds on itself.[39] Therefore, these correlations likely indicate that a significant reduction in LH and TT via KD leads to a substantial decrease in circulating neuropeptides (KISS and PNX-14) in obese PCOS.

The findings in this report regarding neuropeptides (KISS and PNX-14) are subject to at least three limitations, thereby reducing their generalizability. First, the sample of obese PCOS was small, the duration of KD follow-up was brief by 6 months, and the evaluation of ketone bodies during the KD follow-up relied mainly on urine strips. Second, this pilot observational report lacks a non-KD-obese PCOS (control group). Third, it is unfortunate that the study did not include measurement of VAT and no direct assessment of insulin effects on KISS and PNX-14 neurons. At the same time, several questions remain unanswered. For instance, the duration and side effects of KD are still controversial. There is no evidence of short-term side effects, and they are thought to be safe for short periods. Information on long-term adherence to KD is limited. Hence, to demonstrate whether KD has the same impacts, further pilot studies utilizing controlled trials are necessary in a large sample of obese PCOS individuals. More broadly, studies are also needed to determine the safety of adhering to KD over time.

Conclusion

The findings from the present pilot observational study are suggestive of the role of KD and its positive effects on reproductive and neuropeptide characteristics in PCOS. It can therefore be assumed that KD may be considered an adjunctive management for the reproductive and neuropeptide indicators to manage PCOS complications, particularly neuropeptide dysregulation.

Authors' Contribution

Conceptualization: Talib Hussein Abdullah, Diana Hussein Abdullah.
Data curation: Malik Musa Sultan.
Formal analysis: Talib Hussein Abdullah, Malik Musa Sultan.
Investigation: Talib Hussein Abdullah.
Methodology: Talib Hussein Abdullah, Malik Musa Sultan.
Software: Talib Hussein Abdullah, Malik Musa Sultan.
Validation: Diana Hussein Abdullah.
Supervision: Diana Hussein Abdullah.
Visualization: Talib Hussein Abdullah, Malik Musa Sultan.
Writing-original draft: Talib Hussein Abdullah, Malik Musa Sultan.
Writing-review & editing: Talib Hussein Abdullah, Diana Hussein Abdullah, Malik Musa Sultan.

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Conflicts of interest

There is no conflict of interest among the authors.

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Ethical Approval

The ethics committee of the College of Science / Mustansiriyah University, approved our study (code: BCSMU/0505/1010CT) on 05/01/2025 in accordance with all tenets of the Declaration of Helsinki.

References

1. Singh S, Pal N, Shubham S, Sarma DK, Verma V, Marotta F, et al. Polycystic ovary syndrome: etiology, current management, and future therapeutics. *J Clin Med* 2023;12(4):1454. doi: 10.3390/jcm12041454
2. Christ JP, Cedars MI. Current guidelines for diagnosing PCOS. *Diagnostics (Basel)* 2023;13(6):1113. doi: 10.3390/diagnostics13061113
3. Gill L, Coborn JE, Hoovler AR, Sherif K. Polycystic ovary syndrome and obesity: a cross-sectional survey of patients and obstetricians/gynecologists. *J Womens Health (Larchmt)* 2023;32(6):723-731. doi: 10.1089/jwh.2022.0471
4. Marinelli S, Napoletano G, Straccamore M, Basile G. Female obesity and infertility: outcomes and regulatory guidance. *Acta Biomed* 2022;93(4):e2022278. doi: 10.23750/abm.v93i4.13466
5. Barber TM, Franks S. Obesity and polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 2021;95(4):531-541. doi: 10.1111/cen.14421
6. Lonardo MS, Cacciapuoti N, Guida B, Di Lorenzo M, Chiurazzi M, Damiano S, et al. Hypothalamic-ovarian axis and adiposity relationship in polycystic ovary syndrome: physiopathology and therapeutic options for the management of metabolic and inflammatory aspects. *Curr Obes Rep* 2024;13(1):51-70. doi: 10.1007/s13679-023-00531-2
7. Chen X, Xiao Z, Cai Y, Huang L, Chen C. Hypothalamic mechanisms of obesity-associated disturbance of hypothalamic–pituitary–ovarian axis. *Trends Endocrinol Metab* 2022;33(3):206-217. doi: 10.1016/j.tem.2021.12.004
8. Harbi NS, AL-Qaisi AHJ, Hairunisa N. Evaluating the Effect of the Ketogenic Diet on the Reproductive and Metabolic Parameters in Iraqi Females with Polycystic Ovary Syndrome. *Al-Nahrain J Sci* 2025;28(1):8-13. doi: 10.22401/ANJS.28.1.02
9. Zhu H, Bi D, Zhang Y, Kong C, Du J, Wu X, et al. Ketogenic diet for human diseases: the underlying mechanisms and potential for clinical implementations. *Signal Transduct Target Ther* 2022;7(1):11. doi: 10.1038/s41392-021-00831-w

10. Patikorn C, Saidoung P, Pham T, Phisalprapa P, Lee YY, Varady KA, et al. Effects of ketogenic diet on health outcomes: an umbrella review of meta-analyses of randomized clinical trials. *BMC Med* 2023;21(1):196. doi: 10.1186/s12916-023-02874-y
11. Pandurevic S, Mancini I, Mitselman D, Magagnoli M, Teglia R, Fazzeri R, et al. Efficacy of very low-calorie ketogenic diet with the Pronokal® method in obese women with polycystic ovary syndrome: a 16-week randomized controlled trial. *Endocr Connect* 2023;12(7):e220536. doi: 10.1530/EC-22-0536
12. Khalid K, Apparow S, Mushaddik IL, Anuar A, Rizvi SAA, Habib A. Effects of Ketogenic Diet on Reproductive Hormones in Women With Polycystic Ovary Syndrome. *J Endocr Soc* 2023;7(10):bvad112. doi: 10.1210/jendso/bvad112
13. Chen X, Yang S, Shaw ND, Xia M. Kisspeptin Receptor Agonists and Antagonists: Strategies for Discovery and Implications for Human Health and Disease. *Int J Mol Sci* 2025;26(10):4890. doi: 10.3390/ijms26104890
14. Habibi M, Mahmoudi F, Haghighat K, Khazali H. Therapeutic Effects of Phytoestrogen Naringenin in Polycystic Ovary Syndrome (PCOS): Involvement of Kisspeptin and Calcitonin Gene Related Peptide Signalling Pathways. *Rep Biochem Mol Biol* 2025;14(1):38-45. doi: 10.61882/rbmb.14.1.38
15. Sun P, Zhang Y, Sun L, Sun N, Wang J, Ma H. Kisspeptin regulates the proliferation and apoptosis of ovary granulosa cells in polycystic ovary syndrome by modulating the PI3K/AKT/ERK signalling pathway. *BMC Women's Health* 2023;23(1):15. doi: 10.1186/s12905-022-02154-6
16. Akad M, Socolov R, Furnică C, Covali R, Stan CD, Crauciuc E, et al. Kisspeptin Variations in Patients with Polycystic Ovary Syndrome-A Prospective Case Control Study. *Medicina* 2022;58(6):776. doi: 10.3390/medicina58060776
17. Billert M, Rak A, Nowak KW, Skrzypski M. Phoenixin: More than Reproductive Peptide. *Int J Mol Sci* 2020;21(21):8378. doi: 10.3390/ijms21218378
18. McIlwraith EK, Zhang N, Belsham DD. The Regulation of Phoenixin: A Fascinating Multidimensional Peptide. *J Endocr Soc* 2022;6(2):bvab192. doi: 10.1210/jendso/bvab192
19. Liang H, Zhao Q, Lv S, Ji X. Regulation and physiological functions of phoenixin. *Front Mol Biosci* 2022;9:956500. doi: 10.3389/fmolb.2022.956500
20. Abdalla MA, Deshmukh H, Mohammed I, Atkin S, Reid M, Sathyapalan T. The Effect of Free Androgen Index on the Quality of Life of Women With Polycystic Ovary Syndrome: A Cross-Sectional Study. *Front Physiol* 2021;12:652559. doi: 10.3389/fphys.2021.652559
21. Harbi NS, Al-Darkazali WN, Hamud WM. Assessment of the Efficacy of Adhering to the Ketogenic Diet on Adipokines (Betatrophin, Endotrophin, and Meteorin-Like Protein) in Obese Women with Polycystic Ovary Syndrome. *Iraqi J Pharm Sci* 2026;35(1):190-200. doi: 10.31351/vol35iss1pp190-200
22. Ernesti I, Baratta F, Watanabe M, Risi R, Camajani E, Persichetti A, et al. Predictors of weight loss in patients with obesity treated with a Very Low-Calorie Ketogenic Diet. *Front Nutr* 2023;10:1058364. doi: 10.3389/fnut.2023.1058364
23. Roekenes J, Martins C. Ketogenic diets and appetite regulation. Curr Opin *Clin Nutr Metab Care* 2021;24(4):359-363. doi: 10.1097/MCO.0000000000000760
24. Bila J, Dotlic J, Andjic M, Ivanovic K, Micic J, Tulic L, et al. Obesity as a Part of Polycysric Ovary Syndrome (PCOS)—A Review of Pathophysiology and Comprehensive Therapeutic Strategies. *J Clin Med* 2025;14(16):5642. doi: 10.3390/jcm14165642

25. Khan MS, Kim HS, Kim R, Yoon SH, Kim SG. Dysregulated liver metabolism and polycystic ovarian syndrome. *Int J Mol Sci* 2023;24(8):7454. doi: 10.3390/ijms24087454
26. Liu Q, Xie YJ, Qu LH, Zhang MX, Mo ZC. Dyslipidemia involvement in the development of polycystic ovary syndrome. *Taiwan J Obstet Gynecol* 2019;58(4):447-453. doi: 10.1016/j.tjog.2019.05.003
27. Arvanitakis K, Chatzikalil E, Kalopitas G, Patoulias D, Popovic DS, Metallidis S, et al. Metabolic dysfunction-associated steatotic liver disease and polycystic ovary syndrome: a complex interplay. *J Clin Med* 2024;13(14):4243. doi: 10.3390/jcm13144243
28. Magagnini MC, Condorelli RA, Cimino L, Cannarella R, Aversa A, Calogero AE, et al. Does the Ketogenic Diet Improve the Quality of Ovarian Function in Obese Women? *Nutrients* 2022;14(19):4147. doi: 10.3390/nu14194147
29. Qu X, Donnelly R. Sex hormone-binding globulin (SHBG) as an early biomarker and therapeutic target in polycystic ovary syndrome. *Int J Mol Sci* 2020;21(21):8191. doi: 10.3390/ijms21218191
30. Mitrašinović-Brulić M, Buljan M, Suljević D. Association of LH/FSH ratio with menstrual cycle regularity and clinical features of patients with polycystic ovary syndrome. *Middle East Fertil Soc J* 2021;26(1):40. doi: 10.1186/s43043-021-00085-0
31. Malik MA, Alsaffar SF. Assessment of Neurokinin B and Galanin Levels in Women with Polycystic Ovarian Syndrome. *Iraqi J Sci* 2025;66(9):3706-3714. doi: 10.24996/ijs.2025.66.9.17
32. Rondanelli M, Perna S, Ilyas Z, Peroni G, Bazire P, Sajuox I, et al. Effect of very low-calorie ketogenic diet in combination with omega-3 on inflammation, satiety hormones, body composition, and metabolic markers. A pilot study in class I obese subjects. *Endocrine* 2022;75(1):129-136. doi: 10.1007/s12020-021-02860-5
33. Tolson KP, Marooki N, De Bond JAP, Walenta E, Stephens SBZ, Liaw RB, et al. Conditional knockout of kisspeptin signaling in brown adipose tissue increases metabolic rate and body temperature and lowers body weight. *FASEB J* 2020;34(1):107-121. doi: 10.1096/fj.201901600R
34. Friedrich T, Stengel A. Current state of phoenixin-the implications of the pleiotropic peptide in stress and its potential as a therapeutic target. *Front Pharmacol* 2023;14:1076800. doi: 10.3389/fphar.2023.1076800
35. Gomez-Arbelaez D, Bellido D, Castro AI, Ordoñez-Mayan L, Carreira J, Galban C, et al. Body Composition Changes After Very-Low-Calorie Ketogenic Diet in Obesity Evaluated by 3 Standardized Methods. *J Clin Endocrinol Metab* 2017;102(2):488-498. doi: 10.1210/jc.2016-2385
36. Paoli A, Mancin L, Giacona MC, Bianco A, Caprio M. Effects of a ketogenic diet in overweight women with polycystic ovary syndrome. *J Transl Med* 2020;18(1):104. doi: 10.1186/s12967-020-02277-0
37. Hasan NT, Ali S. Impact of Obesity on Serum Levels of Neuropeptide–Y in Type 2 Diabetics in Relation to Glycemic Status. *Iraqi J Pharm Sci* 2024;33(4SI):282-289. doi: 10.31351/vol33iss(4SI)pp282-289
38. Eshaghhosseiny N, Ahmadi M, Izadi B, Vali M, Akbari M, Azari I, et al. The effects of ketogenic diet on metabolic and hormonal parameters in patients with polycystic ovary syndrome: a systematic review and meta-analysis of clinical trials. *J Diabetes Metab Disord* 2024;23(2):1573-1587. doi: 10.1007/s40200-024-01441-3
39. Longobardi S, Klinger FG, Zheng W, Campitiello MR, D'Hooghe T, La Marca A. Gonadotropin Activity during Early Folliculogenesis and Implications for Polycystic Ovarian Syndrome and Premature Ovarian Insufficiency: A Narrative Review. Int J Mol Sci 2024;25(14):7520. doi: 10.3390/ijms25147520