Original Article

The Association between Melatonin Hormone and Reproductive Hormones in Polycystic Ovary Syndrome: A Case–Control Study

Ban Jabir Edan, Zahid Mohammed-Ali Kadhim
Department of Physiology, College of Medicine, University of Babylon, Babylon, Iraq

Abstract

Background: One of the common endocrine disorders is polycystic ovary syndrome (PCOS) with prevalence of about 5%–15% of women within reproductive age. It is related to androgen disturbance, obesity, and irregular menstrual cycle. Pineal gland secretes melatonin hormone, which is involved in the regulation of the circadian rhythm. Melatonin receptors in the ovary adjust sex steroid secretion. Furthermore, it is considered a strong antioxidant, which protects ovarian follicles during follicular maturation. **Objectives:** To evaluate the level of melatonin in patients with PCOS and its relation with reproductive hormones and anthropometric measures. **Materials and Methods:** A case-control study included 200 women in reproductive age (20–40 years), including 100 PCOS patients and 100 controls who appeared to be in generally good health. Anthropometric measurements were evaluated. Reproductive hormones and anti-Müllerian hormone (AMH) were evaluated using the mini VIDAS method. Human MT (Melatonin) ELISA Kit from Elabscience source (USA) was used for measuring melatonin levels. **Results:** Luteinizing hormone/follicle-stimulating hormone (FSH) ratio, AMH, and melatonin were significantly higher in PCOS women, whereas FSH level was significantly lower in PCOS compared with controls. There was an adverse relationship between melatonin levels with thigh circumference, waist circumference, and waist/hip ratio ($P < 0.05$). There was a significant adverse correlation between melatonin and testosterone hormone in PCOS patients ($P < 0.05$). Melatonin level showed an AUC of 0.755 at a cutoff point of 20 ng/mL and more, giving a sensitivity (78%) and specificity (75%). **Conclusions:** Although PCOS women had higher serum melatonin concentrations, their effect on ovarian hormones is diminished. Melatonin had a connection with androgen, and melatonin supplements may improve metabolic dysfunction in PCOS patients.

Keywords: Melatonin, PCOS, reproductive hormones

Introduction

Polycystic ovarian syndrome is an endocrine disorder that affects 5%–15% of women. It is related to androgen disturbance, obesity, and irregular cycle.[1,2]

The diagnosis of polycystic ovary syndrome (PCOS) is achieved by demonstrating "1—the presence of oligo/anovulation, 2—clinical or biochemical markers of hyperandrogenism, and/or 3—appearance of polycystic ovaries."[3] PCOS is involved in a wide array of endocrine and metabolic derangements.[4]

Pineal gland secretes a neurohormone called melatonin hormone, which is involved in the regulation of the circadian rhythm and sleep. Melatonin secretion peaks during the dark hours, so it initiates sleep and declines greatly during the daytime. Therefore, it is said that it plays a key role in regulating the sleep–wakefulness cycle.[5] Melatonin is considered a strong antioxidant, which protects ovarian follicles during follicular maturation.[5] Melatonin hormone has an important antigonadal effect by directly inhibiting testosterone secretion.[6]

It is theorized that melatonin treatment may aid in maintaining testosterone and decrease the luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio in PCOS patients[7] through specific receptor proteins present in the ovaries.[8,9] It is also responsible for regulation

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_523_23

Address for correspondence: Dr. Ban J. Edan, Department of Physiology, College of Medicine, University of Babylon, Babylon, Iraq.
E-mail: med.ban.edan@uobabylon.edu.iq

Submission: 09-May-2023 **Accepted:** 30-Jun-2023 **Published:** 09-May-2024

How to cite this article: Edan BJ, Kadhim ZM-A. The association between melatonin hormone and reproductive hormones in polycystic ovary syndrome: A case–control study. Med J Babylon 2024;21:161-4.

special gene expression,"LH receptor gene expression, and gonadotropin- releasing hormone receptor gene" in human granulosa-lutein cells via the mitogen-activated protein kinase (MAPK) pathway.[10]

According to certain researches, the melatonin hormone has a direct impact on the quality and development of the embryo as well as ovulation, oocyte maturation, and embryonic quality. Melatonin level is higher in larger follicles compared with smaller ones, and this has a protective antioxidant activity of granulosa cells from free radicals that are formed during ovulation.[11,12]

Materials and Methods

A total of 200 women (100 women with PCOS and 100 controls) in reproductive age (20–40 years) were involved in this case–control study collected from the private clinic in Babylon province between March 2022 and end of December 2022.

History was taken from each participant including age, address, level of education, and job. Also, anthropometric measurements including "thigh circumference, arm circumference, waist circumference, hip circumference, waist/hip ratio, and body mass index (BMI)" were evaluated. FSH, LH, prolactin, testosterone, estradiol hormone, and anti-Müllerian hormone (AMH) were also measured on the 2nd or 3rd day of the cycle using the mini VIDAS (automated immunoanalyzer) method.

Human MT (Melatonin) ELISA Kit from Elabscience source (Houston, Texas, USA) was used for measuring melatonin levels. The melatonin reference was 15.63–1000 pg/mL.

Statistical analysis

All statistical analyses were performed using SPSS (IBM, Chicago, USA) software (version 23). The *t* test was employed for continuous data, and the Chi-square test was utilized for categorical data. The Pearson correlation was done for the detection of correlation between measured variables. The binary logistic regression analysis for PCOS versus healthy control was also done. The receiver operating characteristic (ROC) curve for PCOS against healthy control in the studied group was done to detect the sensitivity and specificity of the melatonin hormone. A *P* value of less than 0.05 was considered significant.[13]

Ethical approval

Verbal informed consent was taken from participant according to the guiding principle of the University of Babylon under the reference No. number 1789 on Dec 30, 2021.

Results

In this study, 200 women (100 with PCOS and 100 controls) were participated, and their demographic characteristics [Table 1] demonstrate insignificant differences between patients and controls concerning age, level of education, job, and address ($P > 0.05$). Regarding anthropometric characteristics, there were significant differences regarding waist (cm), waist/hip ratio, and BMI ($P < 0.05$).

The hormonal level at day 2 or 3 of menstrual cycle (MC) was measured and shown in Table 2. LH/FSH ratio, AMH, and melatonin were higher significantly in patients than those in the control group, whereas FSH level was lower significantly in patients than those in the control group ($P < 0.05$).

Table 3 shows the correlation of melatonin with patient age and anthropometric measurements in PCOS women, and there was a negative correlation between melatonin levels with thigh circumference (TC), waist circumference (WC), and waist/hip (W/H) ratio ($P < 0.05$).

A diagnostic evaluation was performed using logistic regression. Women with PCOS can compare the effects of various hormones using the control group as the benchmark, as demonstrated. Table 5 lists the melatonin level, AMH, and LH/FSH ratios. Ratio appeared to be important diagnosing factors. The higher odds ratio (OR) reported, though, was for PCOS with a significant LH/FSH ratio (OR = 2.01). For melatonin, the odds ratio is

Table 1: Demographic and anthropometric data of study groups

Variable	PCOS patients (100)	Control (100)	*P* value
	No. (%)	No. (%)	
Age (mean ± SD) years	28.35 ± 6.11	30.50 ± 7.92	0.078
Education			
Primary school	20 (20)	30 (32)	0.145
Secondary school	48 (48)	48 (48)	
Higher education	32 (32)	22 (20)	
Job			
Housewife	77 (77)	68 (68)	0.15
Employer	23 (23)	32 (32)	
Address			
Urban	59 (61)	63 (63)	0.77
Rural	41 (39)	37 (37)	
Thigh circumference (cm)	50.18 ± 5.75	50.83 ± 5.11	0.48
Arm circumference (cm)	32.90 ± 4.82	31.38 ± 5.88	0.19
Waist (cm)	98.80 ± 8.72	81.77 ± 9.81	0.023*
Hip (cm)	118.55 ± 9.23	05.85 ± 7.67	0.09
Waist/hip ratio	0.93 ± 0.21	0.79 ± 0.17	0.044*
BMI (kg/m²)	28.25 ± 3.85	26.30 ± 4.41	0.005*

BMI: body mass index, PCOS: polycystic ovary syndrome, SD: standard deviation

*$P < 0.05$ was significant

Table 2: Hormonal level at day 2 of the menstrual cycle of the studied groups

Hormones	PCOS	Controls	*P* value
	No. 100	No. 100	
FSH (mIU/mL)	5.83 ± 1.81	7.30 ± 4.77	0.024*
LH (IU/L)	7.35 ± 4.05	7.01 ± 1.94	0.54
LH/FSH	1.28 ± 0.48	1.06 ± 0.28	<0.01*
Prolactin (ng/mL)	22.46 ± 9.46	20.01 ± 6.97	0.07
Testosterone (ng/mL)	0.66 ± 0.41	0.62 ± 0.41	0.76
AMH (ng/mL)	3.68 ± 1.54	2.61 ± 1.21	0.017*
E2 (pg/mL)	33.43 ± 10.85	37.54 ± 21.61	0.18
Melatonin (ng/mL)	28.91 ± 7.96	25.24 ± 5.09	0.02*

AMH: anti-Müllerian hormone, E2: estradiol hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, PCOS: polycystic ovary syndrome

*$P < 0.05$ was significant

Table 3: Correlation between melatonin levels with patient age and anthropometric measurements in polycystic ovary syndrome women

Variables	Melatonin hormone	
	Correlation coefficient, *r*	*P* value
Age	0.064	0.83
Thigh circumference (cm)	−0.653*	0.016
Arm circumference (cm)	−0.333	0.266
Waist circumference t (cm)	−0.531*	0.02
Hip circumference (cm)	−0.101	0.62
Waist/hip ratio	−0.381*	<0.01
BMI	−0.206	0.50

There was a significant negative correlation between melatonin and testosterone in PCOS patients ($P < 0.05$) [Table 4]

*$P < 0.05$ was significant

Table 4: Correlation between melatonin levels with reproductive hormones in polycystic ovary syndrome women

Hormones	Melatonin hormone	
	Correlation coefficient (*r*)	*P* value
FSH (mIU/mL)	0.110	0.720
LH (IU/L)	−0.147	0.632
LH/FSH ratio	−0.211	0.128
Testosterone (ng/mL)	−0.46	0.02
Prolactin (ng/mL)	0.08	0.91
AMH (ng/mL)	−0.433	0.212
E2 (pg/mL)	0.020	0.949

AMH: anti-Müllerian hormone, E2: estradiol hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone

1:83. Women who produce more melatonin levels have an increased chance of having PCOS.

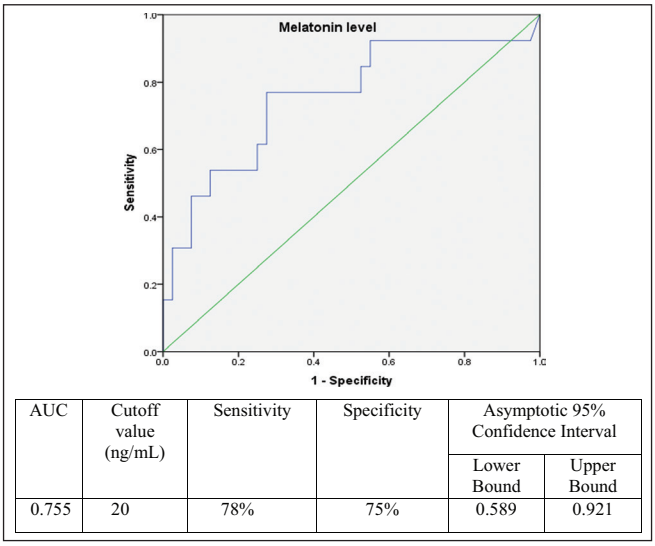
ROC curve was done to assess the validity of melatonin in PCOS diagnosis [Figure 1]. Melatonin level showed an AUC of 0.755 at a cutoff point of 20 ng/mL, giving a sensitivity (78%) and specificity (75%), which indicate that melatonin level is a moderate diagnostic factor in PCOS independent of other parameters.

Table 5: Binary logistic regression analysis for the diagnosis of polycystic ovary syndrome

PCOS	*P* value	Odds ratio (95% CI) (lower limit–upper limit)
Melatonin	0.026*	1.83 (0.926–1.908)
FSH	0.051	0.657 (0.322–1.340)
LH	0.15	1.89 (0.750–2.389)
AMH	0.03*	1. 88 (0.417–2.841)
E2	0.524	1.028 (0.944–1.119)
LH/FSH ratio	0.03*	2.01 (0.93–2.48)
Testosterone	0.64	1.12 (0.91–1.48)
Prolactin	0.92	1.01 (0.81–1.02)

AMH: anti-Müllerian hormone, CI: confidence interval, E2: estradiol hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, PCOS: polycystic ovary syndrome

*$P < 0.05$ was significant



AUC	Cutoff value (ng/mL)	Sensitivity	Specificity	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
0.755	20	78%	75%	0.589	0.921

Figure 1: Receiver operating characteristic (ROC) curve for the validity of melatonin level in PCOS diagnosis

Discussion

The study found that melatonin level is higher in PCOS patients compared with control groups and that its level correlated with the level of testosterone and with many anthropometric measures such as TC, WC, and W/H ratio.

These findings are explained as many patients with PCOS had high body weight, and this will induce insulin resistance, which will stimulate the secretion of testosterone that can decline sex hormone-binding globulin. Hyperandrogenemia will cause derangement of the hormonal hypothalamic-ovarian axis, which leads to amplified LH/FSH, arrest of follicular development, and, finally, anovulation.[14,15]

Some authors found that melatonin supplements defence mechanism against metabolic abnormalities in PCOS. Giving it to them affects body features such as decreased weight, BMI, and fat.[16]

The hormonal level at day 2 or 3 of MC was measured and shown in Table 2, and LH/FSH ratio, AMH, and melatonin were higher significantly in patients than in the control group, whereas FSH level was lower significantly in patients than in the control group ($P < 0.05$).

This result agree with Gocke and Gulnur who found that serum melatonin level in PCOS patients, was higher than healthy women which is considered as a sign of diagnosing PCOS.[12] Melatonin uptake from circulation is reduced and the number of atretic follicles increases in PCOS patients, both of which affect the melatonin level in follicular fluid.[17]

The melatonin deficiency affects gonadotrophin secretion, reduces FSH synthesis, and increases LH synthesis, the latter being the major change detected in PCOS patients.[18-19]

Melatonin level showed an AUC of 0.755 at a cutoff point of 20 ng/mL, giving a sensitivity (78%) and specificity (75%), which indicate that melatonin level is a moderate diagnostic factor in PCOS independent of other parameters.

This agrees with the results obtained by Jain *et al*.[9] in 2013.

In conclusion, although PCOS women had higher serum melatonin concentrations, their effect on ovarian follicles is diminished. Melatonin had a connection with androgen, and melatonin supplements may improve metabolic dysfunction in PCOS patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Alizadeh M, Karandish M, Asghari Jafarabadi M, Heidari L, Nikbakht R, Babaahmadi Rezaei H, *et al*. Metabolic and hormonal effects of melatonin and/or magnesium supplementation in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Nutr Metab (Lond) 2021;18:57.
2. Nawar AS, Alwan ZHO, Sheikh QI. Gene expression and plasma level of CuZn and Mn superoxide dismutase in Iraqi women with polycystic ovary syndrome. Med J Babylon 2022;19:691-6.
3. Dunaif A. Perspectives in polycystic ovary syndrome: From hair to eternity. J Clin Endocrinol Metab 2016;101:759-68.
4. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41-7.
5. Raygan F, Ostadmohammadi V, Bahmani F, Reiter RJ, Asemi Z. Melatonin administration lowers biomarkers of oxidative stress and cardio-metabolic risk in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial. Clin Nutr 2019;38:191-6.
6. Spinedi E, Cardinali DP. The polycystic ovary syndrome and the metabolic syndrome: A possible chronobiotic-cytoprotective adjuvant therapy. Int J Endocrinol 2018;2018:1349868.
7. Monastra G, Unfer V, Harrath AH, Bizzarri M. Combining treatment with myo-inositol and D-chiro-inositol (40:1) is effective in restoring ovary function and metabolic balance in PCOS patients. Gynecol Endocrinol 2017;33:1-9.
8. Bruni V, Dei M, Nannini S, Balzi D, Nuvolone D, *et al*. Polycystic ovary syndrome in adolescence. Ann N Y Acad Sci 2010;1205:175-84.
9. Jain P, Jain M, Haldar C, Singh TB, Jain S. Melatonin and its correlation with testosterone in polycystic ovarian syndrome. J Hum Reprod Sci 2013;6:253-8.
10. Woo MMM, Tai CJ, Kang SK, Nathwani PS, Pang SF, Leung PC. Direct action of melatonin in human granulosa-luteal cells. J Clin Endocrinol Metab 2001;86:4789-97.
11. Ahmadi M, Raizie J, Fathi F. The effect of melatonin on histological changes of ovary in induced polycystic ovary syndrome model in mice. Middle East Fertil Soc J 2017;22:255-9.
12. Gocke N, Gulnur T, Atiya S. Melatonin effective to reduce the microscopic symptoms of polycystic ovary syndrome-related infertility: An experimental study. Tissue Cell 2023;81:102015.
13. Daniel WW. Probability and t distribution biostatistics. In: A Foundation for Analysis in Health Science. 7th edition. Daniel WW, editor. Hoboken, NJ: John Wiley & Sons, Inc., 1999. p. 83-123.
14. Wang F, Dai W, Yang XH, Guo YH, Sun YP. Analyses of optimal body mass index for infertile patients with either polycystic or non-polycystic ovary syndrome during assisted reproductive treatment in China. Sci Rep 2016;6:34538.
15. Al-yasiry RZ, Jwad MA, Hasan MF, Alsayigh HA. How obesity affects female fertility. Med J Babylon 2022;19:111-4.
16. Lai SA, Majumdar AS. Protective effects of melatonin against metabolic and reproductive disturbances in polycystic ovary syndrome in rats. J Pharm Pharmacol 2014;66:1710-21.
17. Tamura H, Nakamura Y, Korkmaz A, Manchester LC, Tan D-X, Sugino N, *et al*. Melatonin and the ovary: Physiological and pathophysiological implications. Fertil Steril 2009;92:328-43.
18. Mojaverrostami S, Asghari N, Khamisabadi M, Khoei HH. The role of melatonin in polycystic ovary syndrome: A review. Int J Reprod Biomed 2019;17:865-82.
19. Rasheed SMH, Eidan AJ, Al-Dujaili AH, Abada LH, Al-Charrakh AH. Different cytokines and lipid profile in suicidal and non suicidal adults with major depression. Ann Trop Med Pub Health 2019;22:S282.