

Assessment of the Serum Level of Melatonin and Its Correlation with Insulin, Insulin Resistance, and Glycated Hemoglobin in Iraqi Patients with Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is one of the most frequent gynecological endocrinopathy that occur in premenopausal females. The importance of melatonin (N-acetyl-5-methoxytryptamine) in human reproduction is still unidentified. A numerous study suggests that melatonin and reproductive hormones are closely related. **Objectives:** The study aimed to evaluate the role of melatonin in women with PCOS and its correlation with insulin, insulin resistance (IR), and glycated hemoglobin (HbA1c) in a patient with PCOS. **Materials and Methods:** A prospective cross-sectional study was designed taking 60 PCOS patients and 30 controls women from January to April 2019. These patients admitted to obstetrics and gynecology unit at Babylon teaching hospital. Five milliliter of blood sample was taken on day 2 of menstrual cycle from each subject enrolled in this study. Blood samples were collected for testing serum melatonin, insulin, IR, and HbA1c estimation. **Results:** The study showed that there is the significant difference between PCOS women and the control group concerning melatonin level. Results also showed higher means of HbA1c in PCOS women than control women, and positive correlation between HbA1c and melatonin. The study showed higher means of insulin was shown in PCOS women when compared with control group, and positive correlation between insulin and melatonin. Furthermore, this study showed higher means of IR was recorded in PCOS women when compared with control group, and positive correlation between IR and melatonin. **Conclusions:** Women with PCOS have significant increase of serum melatonin in PCOS women. And, there were significant increases in serum levels of HbA1c, insulin, and IR in women with PCOS compared to healthy women. In addition, positive correlation was found between melatonin with insulin, IR, and HbA1c. This study could open the way for therapeutic role of melatonin in the treatment of PCOS women.

Keywords: Glycated hemoglobin, insulin, insulin resistance, melatonin, patients, polycystic ovarian syndrome

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is one of the most frequent gynecological endocrinopathy that occur in premenopausal females,^[1] with a predominance range from 6% to 10% among women of reproductive age.^[2] It is characterized by hyperandrogenism (male hormone in female), menstrual disturbance, excess body and facial hair (hirsutism), acne, temperament disorder, endometrial cancer, in addition, severe physiological disturbance are commonly detected among women with PCOS; for example, abdominal adiposity, inflammation, and infertility.^[3-5] PCOS diagnosis is based on two of the following three findings: Oligo- or anovulation, polycystic ovaries under

ultrasonography, and clinical or biochemical signs of hyperandrogenism.^[6]

PCOS etiology and pathogenesis are still unknown, but some causative factors play important role in this syndrome, such as hormonal disorders, adipose tissue dysfunction, oxidative stress have been blamed, but definitive consensus

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Submission: 24-09-2019 **Accepted:** 01-10-2019 **Published Online:** 23-12-2019

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How to cite this article: Hameed AA, Ahmeid MS. Assessment of the serum level of melatonin and its correlation with insulin, insulin resistance, and glycated hemoglobin in Iraqi patients with polycystic ovarian syndrome. *Med J Babylon* 2019;16:316-20.

Access this article online

Quick Response Code:



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DOI:
10.4103/MJBL.MJBL_75_19

has not been reached.^[7] However, in recent years, insulin resistance (IR) has been reported to play an important role in the progression of PCOS.^[8-10] PCOS may present with metabolic abnormalities such as IR and visceral obesity at a young age. Long-term exposure to these abnormalities during fertile life may increase the reverse impacts and expose these women to higher risks of metabolic syndrome (MetS), cardiovascular diseases and type II diabetes mellitus.^[11] While melatonin (N-acetyl-5-methoxytryptamine), a neurohormone synthesized from the aromatic amino acid tryptophan mainly by the pineal gland of humans.^[12]

The important of melatonin in human reproduction is still unidentified. A numerous study suggests that melatonin and reproductive hormones are closely related.^[13] This concept is based on observation of influence melatonin on sex steroid production at different stages of ovarian follicular maturation as melatonin receptors have been demonstrated at multiple sites in ovary and in intrafollicular fluid. In addition, several studies found that increased melatonin concentration in serum of women with PCOS, and also indicating a feedback mechanism due to reduced melatonin concentration at the level of ovarian follicles. This could interpretation role of melatonin in the pathogenesis of PCOS.^[14]

This study aimed to evaluate the role of melatonin in women with PCOS and its correlation with insulin, IR, and glycated hemoglobin (HbA1c).

MATERIALS AND METHODS

Study design

A prospective cross-sectional study was designed taking 60 PCOS patients and 30 controls women whose ages were between 15 and 35 years old, from the beginning of January 2019 to the ending of April 2019. These patients admitted to obstetrics and gynecology unit at Babylon Teaching Hospital. An interview was carried out with these patients using questionnaire form designed by the investigator, including their demographic characteristics, age, weight, length, body mass index... etc.

Inclusion criteria for selection of cases women

These studies depend on the Rotterdam European Society for Human Reproduction, and Embryology/American Society for Reproductive Medicine these criteria were used to diagnose PCOS and women with presence of any two of the following three features were included in the study:

- Menstrual disturbance or irregular
- Clinical and/or biochemical hyperandrogenism (hirsutism, acne, and alopecia)
- Polycystic ovaries morphology under ultrasound.

Inclusion criteria for selection of controls women

- Regular menstrual cycle
- Normal androgen, without (hirsutism, alopecia, and acne)
- Absence of polycystic ovary morphology under ultrasound
- Normal biochemical parameters including (S. Melatonin, S. Insulin, S. HbA1c, and IR).

Exclusion criteria

All patients with metabolic or endocrinology disorders, including thyroid disorder, diabetes mellitus, hypertension, Cushing's syndrome, acromegaly, premature ovarian failure, virilizing adrenal or ovarian tumors, and history of using contraceptive through the past 6 months were excluded from this study.

Sampling

Five milliliter of the blood sample was taken on day 2 of the menstrual cycle by vein puncture from each subject enrolled in this study. Blood samples were collected between 07:00 a.m. and 08:00 a.m., and placed into sterile test tubes, after blood clotting, centrifuged at 2500 RPM for 15 min then clot removed and remain re-centrifuged at 2500 RPM for 10 min and the obtained serum were aspirated using mechanical micropipette and transferred into clean test tubes which labeled and stored in deep freeze at -20°C for serum melatonin, insulin, IR, and HbA1c measurement.

Statistical analysis

Computerized statistically analysis was performed using SPSS statistical program version 24 (SPSS, IBM Company, Chicago, USA). Comparison was carried out using; Chi-square and *t*-test probability (*P* value).

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with a patient's verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee.

RESULTS

Comparison of age in polycystic ovarian syndrome and control women

A total of 60 PCOS women and 30 non-PCOS women (control group) were examined for (melatonin, insulin, IR, and HbA1c). Their age range group was between 15 and 35 years [Table 1].

The study showed that there is the significant difference between PCOS women and the control group concerning melatonin level, and the highest mean of melatonin was occurred in PCOS women (61.21 ± 13.78 vs. 28.61 ± 6.73) [Table 2].

The correlation between melatonin and HbA1c was positive in PCOS women in this study. Higher Mean values of HbA1c were

Table 1: Comparison of age in polycystic ovarian syndrome and control women

Age	PCOS group	Control group
<i>n</i>	60	30
Mean $\pm$ SD	24.25 $\pm$ 5.12	23.63 $\pm$ 4.06
<i>P</i>	NS	

SD: Standard deviation, PCOS: Polycystic ovarian syndrome, NS: Not significant

observed in PCOS women than in control group (5.11 ± 0.13 vs. 4.25 ± 0.18) with significant relation [Figure 1 and Table 3].

Positive correlation between insulin and melatonin was observed in PCOS women involved in this study, and higher mean of insulin was shown in PCOS women when compared with control group (18.99 ± 3.75 vs. 8.23 ± 1.88) with significant relation between them [Figure 2 and Table 4].

Positive correlation between melatonin and IR levels was observed in PCOS women included in this study, and higher mean of IR was recorded in PCOS women when compared with control group (4.70 ± 1.09 vs. 1.54 ± 0.44) with significant relation [Figure 3 and Table 5].

DISCUSSION

This study found that there was no significant difference between PCOS women and control group concerning age (24.25 ± 5.12 vs. 23.63 ± 4.06) [Table 1]. This agreement

Table 2: Comparison of melatonin and polycystic ovarian syndrome

Serum melatonin (ng/ml)	PCOS group	Control group
<i>n</i>	60	30
Mean $\pm$ SD	61.21 ± 13.78	28.61 ± 6.73
<i>P</i>	<0.05	

SD: Standard deviation, PCOS: Polycystic ovarian syndrome

Table 3: Comparison between glycated hemoglobin and polycystic ovarian syndrome

Serum HbA1c	PCOS group	Control group
<i>n</i>	60	30
Mean $\pm$ SD	5.11 ± 0.13	4.25 ± 0.18
<i>P</i>	<0.05	

SD: Standard deviation, PCOS: Polycystic ovarian syndrome, HbA1c: Glycated hemoglobin

Table 4: Comparison between insulin and polycystic ovarian syndrome

Serum insulin (μ U/L)	PCOS group	Control group
<i>n</i>	60	30
Mean $\pm$ SD	18.99 ± 3.75	8.23 ± 1.88
<i>P</i>	<0.05	

SD: Standard deviation, PCOS: Polycystic ovarian syndrome

Table 5: Comparison of insulin resistance with polycystic ovarian syndrome

Serum IR (μ U/ml)	PCOS group	Control group
<i>n</i>	60	30
Mean $\pm$ SD	4.70 ± 1.09	1.54 ± 0.44
<i>P</i>	<0.05	

SD: Standard deviation, PCOS: Polycystic ovarian syndrome, IR: Insulin resistance

with^[15] study, that found PCOS affects women of childbearing age without higher prevalence by ethnic groups, but the signs and symptoms may differ by ethnicity, and disagreed with^[16] who reported that PCOS varies with age but continues to be more common among women aged <35 years than in those above 35 years, this finding could be attributed to that the women in that age are physiological active concerning the fertility and ovulation.

The study also showed that there is the significant difference between PCOS women and the control group concerning melatonin level, and the highest mean of melatonin was occurred in PCOS women compared with control group (61.21 ± 13.78 vs. 28.61 ± 6.73), [Table 2].

Melatonin is normally synthesized in the ovary, as both melatonin synthesizing enzymes arylalkylamine N-acetyltransferase and hydroxyindole-O-methyltransferase are present in ovarian tissue.^[17] The study by Tenorio *et al.*^[18] found that the presence of melatonin receptors in the follicular cells of rats and mice, suggests possible melatonin production in the ovary. Its well-documented role as an antioxidant may be associated with follicular development and oocyte quality, interfering in processes such as oocyte maturation and ovulation.^[19] This study agreement with,^[20] Experimental studies with female rats and hamsters reported that removal of the pineal gland leads to a decrease in melatonin levels with consequent premature vaginal opening, ovarian hypertrophy, increased cornification of vaginal cells and chronic anovulation, effect that can be reversed after the administration of melatonin.^[21]

The reduction of melatonin ovary can decrease embryo implantation, as well as interfere with pregnancy when rats are subjected to short photoperiods, showing an increase in melatonin levels accompanied by depressions in follicle-stimulating hormone and reduction in follicle development, becoming anestrus,^[18] and also with Woo *et al.*^[22] study, found the expression of receptors for melatonin MT1 and MT2 has been identified in human reproductive tissues, including the mammary epithelium, myometrium, ovary, and granulosa-luteal cells. In females, the influence of melatonin on the reproductive function can be inferred

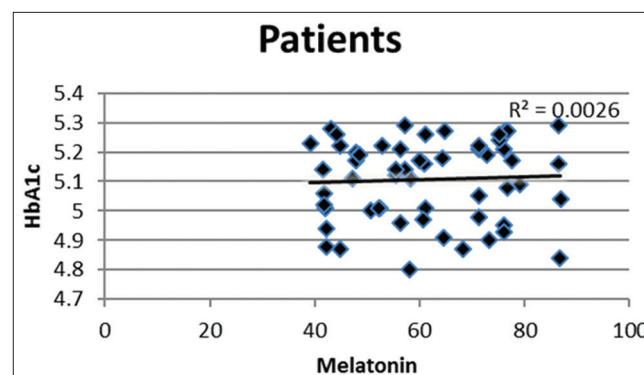


Figure 1: Correlation of melatonin and glycated hemoglobin level

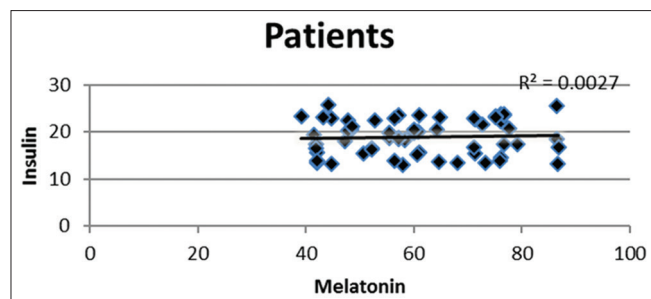


Figure 2: Correlation between melatonin and insulin

from studies that indicate that high levels of melatonin cause amenorrhea,^[23] disturbance in gonadotropin secretion, and the secretion of prolactin in response to the photoperiod.^[24] Studies have suggested that melatonin has a role in ovarian physiology, given that high concentrations of melatonin have been detected in follicular fluid.^[18]

IR and compensatory hyperinsulinemia can be triggered by obesity with visceral fat accumulation. Hyperinsulinemia affects granulosa cells in small follicles and theca cells. This condition induces early response to luteinizing hormones on granulosa cells of small follicles and causes premature differentiation of these cells, which eventually results in anovulation. Hyperinsulinemia may adversely affect the endometrial functions and environment, and evoke implantation disturbance.^[25] Our study disagreed with^[26] study, they found supplementation with 3 mg/day of melatonin after 8 weeks did not influence glucose control and IR in patients with schizophrenia.

These varied results of different studies may be associated with the differences in the type of diseases, dosage of melatonin consumption, and duration of the studies. Increased ovarian androgen production in PCOS includes hyperinsulinemia due to IR and increased volume of theca cells in an expanded ovarian stroma. A negative correlation has been seen with fasting glucose/insulin ratio. This can be explained by diverse mode of action of melatonin, firstly by a direct action at receptors MT1 and MT2 leading to alteration in ovarian steroidogenesis and secondly by its action at follicular level as antioxidant.^[27,28] They showed that melatonin supplementation to patients with PCOS for 12 weeks significantly decreased serum insulin levels, homeostatic model assessment-IR, total- and low-density lipoprotein-cholesterol levels of women with PCOS.

On the basis of existing evidence, melatonin administration may have some beneficial effects on glucose homeostasis and lipid profiles. And also demonstrated that melatonin intake (5 mg/kg) in MetS rats for 6 weeks significantly improved IR and dyslipidemia.

CONCLUSIONS

There were significant increases in serum levels of (melatonin, HbA1c, insulin, and IR) in women with PCOS compared

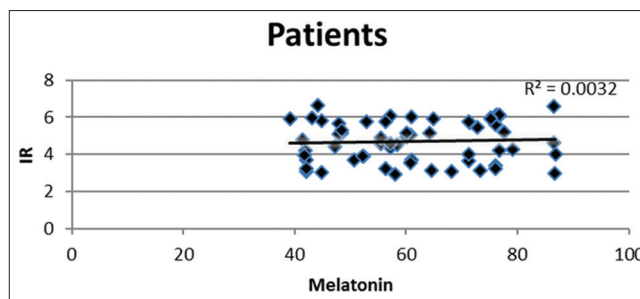


Figure 3: Correlation between melatonin and IR level

to healthy women (control group). In addition, there was a positive correlation of melatonin with insulin, IR, and HbA1c.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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