Research paper

Effects of melatonin administration on mental health parameters, metabolic and genetic profiles in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Objective: The aim of this study was to evaluate the effect of melatonin supplementation on mental health parameters, metabolic and genetic parameters in women suffering from polycystic ovary syndrome (PCOS).

Methods: This randomized, double-blinded, placebo-controlled clinical trial was performed on 58 subjects, aged 18–40 years old. Subjects were randomly allocated to take either 10 mg melatonin (2 melatonin capsules, 5 mg each) ($n = 29$) or placebo ($n = 29$) once a day 1 h before bedtime for 12 weeks. Glycemic control and lipid profiles were measured at baseline and after the 12-week intervention. Using RT-PCR method, gene expression related to insulin and lipid metabolism was conducted on peripheral blood mononuclear cells (PBMCs) of PCOS women.

Results: Melatonin supplementation significantly decreased Pittsburgh Sleep Quality Index (β −2.15; 95% CI, −3.62, −0.68; $P = 0.005$), Beck Depression Inventory index (β −3.62; 95% CI, −5.53, −1.78; $P < 0.001$) and Beck Anxiety Inventory index (β −1.95; 95% CI, −3.41, −0.48; $P = 0.01$) compared with the placebo. In addition, melatonin administration, compared with the placebo, significantly reduced serum insulin (β −1.20 µIU/mL; 95% CI, −2.14, −0.26; $P = 0.01$), homeostasis model of assessment-insulin resistance (HOMA-IR) (β −0.28; 95% CI, −0.50, −0.05; $P = 0.01$), serum total- (β −7.96 mg/dL; 95% CI, −13.75, −2.17; $P = 0.008$) and LDL-cholesterol levels (β −5.88 mg/dL; 95% CI, −11.42, −0.33; $P = 0.03$), and significantly increased the quantitative insulin sensitivity check index (QUICKI) (β 0.008; 95% CI, 0.002, 0.014; $P = 0.007$). Moreover, melatonin supplementation upregulated gene expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) ($P = 0.004$) and low-density lipoprotein receptor (LDLR) ($P = 0.01$) compared with the placebo.

Conclusions: Overall, melatonin administration for 12 weeks had beneficial effects on mental health parameters, insulin levels, HOMA-IR, QUICKI, total- and LDL-cholesterol levels, and gene expression of PPAR-γ and LDLR among women with PCOS.

1. Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy that occurs in up to 10% of women during their reproductive years (Casadei et al., 2018). It is characterized by hyperandrogenism, ovulatory dysfunction and metabolic disturbances such as dyslipidemia, insulin resistance, obesity, and increased inflammatory markers (Antonio et al., 2018; Dumesic et al., 2019). Although the etiology of PCOS is not yet fully understood, extensive evidence suggest that insulin resistance plays a pivotal role in this condition (Dumesic et al., 2019). Insulin resistance and impaired lipid profiles are present in 50–75% and 70% of subjects with PCOS, respectively (Kahal et al., 2018; Pluta et al., 2018). Both abnormalities are main components of metabolic syndrome (MetS), and a major risk factor for cardiovascular disease and type 2 diabetes mellitus (Anwar and Shikalgar, 2017; Gunning and Fauser, 2017). The majority of subjects with PCOS

suffer from symptoms related to hyperandrogenism, including hirsutism, oligomenorrhea, acne, and androgenic alopecia (Franik et al., 2018). Furthermore, people with PCOS have increased sleep disorders, depression, and anxiety (Fernandez et al., 2018). The negative impacts of these symptoms impair the quality of life in PCOS patients (Chaudhari et al., 2018).

Melatonin is an indoleamine that regulates various important actions related to circadian rhythms, reproduction, and the sleep cycle (Reiter et al., 2010). Environmental stress leads to a disturbance of diurnal rhythm of corticosterone and melatonin levels (Yuan et al., 2016). The favorable effects of melatonin administration on oocyte maturation and embryo development have been confirmed by in vitro and in vivo studies (Tamura et al., 2009, 2012). In addition, both animal and human studies have demonstrated that melatonin intake may have beneficial effects on components of MetS, including hyperglycemia and insulin resistance, increased blood pressure, dyslipidemia and obesity (Peschke et al., 2010; Raygan et al., 2017). In addition, epidemiologic studies displayed an inverse association between insulin resistance and nocturnal melatonin secretion (McMullan et al., 2013). Reduction in the intrafollicular melatonin levels and significantly increased excretion of 6-sulfatoxymelatonin, the main excretory metabolite of melatonin, has been reported in patients with PCOS (Spinedi and Cardinali, 2018). Normal melatonin concentrations in the follicular fluid are necessary for high oocyte quality, follicular growth, and ovulation, whereas decreased follicular melatonin levels may be responsible for poor quality of oocyte and anovulation in these patients (Spinedi and Cardinali, 2018). In a recent randomized, controlled trial, combined melatonin and myo-inositol administration, compared with myo-inositol alone, significantly improved oocyte and embryo quality in PCOS patients who were candidates for in vitro fertilization (IVF) (Pacchiarotti et al., 2016).

To our knowledge, no investigation is currently on-going to evaluate the impact of melatonin supplementation on mental health parameters, metabolic and genetic profiles in women with PCOS who candidates for IVF. Therefore, the present study was done to investigate the effects of melatonin administration on mental health parameters, glycemic homeostasis, lipid profiles and its related gene expression in these patients.

2. Materials and methods

2.1. Trial design and subjects

The current randomized, double-blinded, placebo-controlled trial, registered in the Iranian website for registration of clinical trials (http://www.irct.ir: IRCT2017090533941N23), was carried out among 58 women with PCOS aged 18–40 years old who were referred to the Taleghani Hospital in Tehran, Iran, between December 2017 and July 2018. Diagnosis of PCOS was performed according to the Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004): those with the two of the following criteria were considered as having PCOS: oligo- and/or anovulation (defined as delayed menses >35 days or <8 spontaneous hemorrhagic episodes/year), clinical (hirsutism using modified Ferriman-Gallwey score of ≥ 8) and/or biochemical signs of hyperandrogenism and polycystic ovaries (12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume >10 ml³). The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (SBUMS). Written informed consent was obtained from all participants prior to the intervention. Exclusion criteria were as follows: pregnancy, adrenal hyperplasia, androgen-secreting tumors, hyperprolactinemia, thyroid dysfunction, diabetes and other metabolic disorders at enrollment, inflammatory and malignant diseases, those taking melatonin supplements, antioxidant and/or anti-inflammatory supplements within 3 months prior to the enrollment in the study, the night shift workers.

2.2. Supplementation

Initially, patients were randomly divided into two groups to take either 10 mg melatonin (2 melatonin capsules, 5 mg each) ($n = 29$) or placebo ($n = 29$) once a day 1 h before bedtime for 12 weeks. Melatonin and its placebo were produced in the same capsule shape and packaged by Zahravi Pharmaceutical Company (Tabriz, Iran) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. During the study, the use of melatonin or placebo was examined by asking subjects to return the medication containers and through brief daily cell phone reminders to take the supplements. All subjects completed 3-day diet recall at weeks 0, 3, 6, 9 and 12 of the intervention. Daily macro- and micro-nutrient intakes were calculated by nutritionist IV software (First Databank, San Bruno, CA).

2.3. Anthropometric measures

A trained staff took anthropometric measurements in the clinic at baseline and after the 12-week intervention. Height and weight (Seca, Hamburg, Germany) were determined with light clothing and the shoes removed. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared.

2.4. Assessment of outcomes

Glycemic control was considered as the primary outcome. Lipid profiles, gene expression of peroxisome proliferator-activated receptor gamma (PPAR-γ), glucose transporter 1 (GLUT-1) and low-density lipoprotein receptor (LDLR) were recognized as the secondary outcomes.

2.5. Mental health parameters

Quality of sleep was determined using Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). Beck Depression Inventory index (BDI) was assessed using a self-compiled questionnaire of 21 items in multiple choice format (Beck et al., 1961). Anxiety was measured using the Beck Anxiety Inventory (BAI)-21 questionnaire developed by Beck et al. (Beck et al., 1988) to determine the frequency of anxiety symptoms in adults.

2.6. Biochemical assessment

Fasting blood samples were taken from participants (15 mL) at baseline and after the 12-week intervention. To determine fasting plasma glucose (FPG) and lipid profiles, enzymatic kits (Pars Azmun, Tehran, Iran) with inter- and intra-assay coefficient variances (CVs) below 5% were used. Serum insulin levels were assessed using an ELISA kit (Monobind, California, USA) with the intra- and inter-assay CVs below 6%. The homeostatic model assessment for insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were determined according to the suggested formulas (Pisprasert et al., 2013).

2.7. Isolation of lymphocyte cells

Lymphocytes were extracted from blood samples of women with PCOS with a 50% percoll (Sigma-Aldrich, Dorset, UK). Samples were taken for cell count and viability testing using trypan blue, and RNA and DNA extraction (Dunkley et al., 2008).

2.8. RNA extraction and real-time PCR

RNA extraction was performed with use of the RNX-plus kit (Cinnacolon, Tehran, Iran). Following extraction of the total RNAs from each sample, the RNA quantification was evaluated with an UV spectrophotometer. Samples OD 260/280 ratio was standardized between

Table 1

Specific primers used for real-time quantitative PCR.

Gene	Primer	Product size (bp)	Annealing temperature (°C)
GAPDH	F: AAGCTCATTTCCTGGTATGACAACG	126	61.3
	R: TCTTCCTCTTGTGCTCTTGCTGG		
PPAR-γ	F: ATGACAGACCTCAGACAGATTG	210	54
	R: AATGTTGGCAGTGGCTCAG		
GLUT-1	F: TATCTGAGCATCGTGGCCAT	238	62.1
	R: AAGACGTAGGGACCACACAG		
LDLR	F: ACTTACGGACAGACAGACAG	223	57
	R: GGCCACACATCCCATGATTC		

GAPDH, glyceraldehyde-3-Phosphate dehydrogenase; GLUT-1, glucose transporter 1; LDLR, low-density lipoprotein receptor; PPAR-γ, peroxisome proliferator-activated receptor gamma.

1.7 and 2.1 showing no contamination for either protein or DNA (Dunkley et al., 2008). The isolated RNA was reverse transcribed to cDNA library using the moloney murine leukemia virus reverse transcriptase (M-MLV RT). Gene expressions of PPAR-γ, GLUT-1 and LDLR were evaluated by quantitative RT-PCR, using the LightCycler technology (Roche Diagnostics, Rotkreuz, Switzerland) with SYBR green detection and Amplicon Kit (Table 1). Glyceraldehyde-3-phosphate dehydrogenase primers were used as a housekeeping gene. To design primers, Primer Express Software (Applied Biosystems, Foster City) and Beacon designer software (Takaposizt, Tehran, Iran) were utilized. Relative transcription levels were calculated using the methods of Pffafi.

2.9. Sample size

We used a randomized clinical trial sample size calculation formula where type one (α) and type two errors (β) were 0.05, and 0.20 (power = 80%), respectively. Based on a previous trial (Raygan et al., 2017), we used 2.20 as the SD and 1.75 as the change in mean (d) of HOMA-IR as a primary outcome. Based on the formula, 25 subjects per group treatment were needed; after allowing for 20% dropouts per each group, the final sample size was 30 subjects in each group.

2.10. Randomization

Randomization assignment was performed using computer-generated random numbers. Randomization and allocation were concealed from the researchers and participants until the final analyses were completed. The randomized allocation sequence, enrolling participants and allocating them to interventions were conducted by a trained staff at the clinic.

2.11. Statistical analyses

The Kolmogorov-Smirnov test was done to determine the normality of data. Differences in anthropometric measures, dietary intakes and gene expression related to insulin and lipid between treatment groups were detected with independent-sample *t*-tests. Multiple linear regression models helped to assess the treatment effects on study outcomes after adjusting for confounding parameters including; age, and BMI. Significance of the treatment effects was presented as the mean differences with 95% confidence interval. P-values < 0.05 were considered statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

3. Results

As demonstrated in the study flow diagram (Fig. 1), during the enrollment phase of the study, there were 64 women with PCOS;

however, 4 participants did not meet the inclusion criteria and thus were excluded. During the follow-up, 2 participants dropped out of the study due to personal reasons (one participant in each group). Finally, 58 participants [placebo (n = 29) and melatonin (n = 29)] completed the trial.

Mean age, height, and baseline, end-of-trial and change body weight and BMI were not statistically different between the two groups (Table 2).

Considering the 3-day dietary records obtained during the intervention, there was no statistically significant difference in terms of dietary macro- and micro-nutrient intakes between melatonin and placebo groups (Data not shown).

Melatonin supplementation significantly decreased PSQI (β −2.15; 95% CI, −3.62, −0.68; P = 0.005), BDI index (β −3.62; 95% CI, −5.53, −1.78; P < 0.001) and BAI index (β −1.95; 95% CI, −3.41, −0.48; P = 0.01) compared with the placebo (Table 3). In addition, melatonin administration, compared with the placebo, significantly reduced serum insulin (β −1.20 μIU/mL; 95% CI, −2.14, −0.26; P = 0.01), HOMA-IR (β −0.28; 95% CI, −0.50, −0.05; P = 0.01), serum total- (β −7.96 mg/dL; 95% CI, −13.75, −2.17; P = 0.008) and LDL-cholesterol levels (β −5.88 mg/dL; 95% CI, −11.42, −0.33; P = 0.03), and significantly increased QUICKI (β 0.008; 95% CI, 0.002, 0.014; P = 0.007). Melatonin supplementation did not affect FPG and other lipid profiles.

Melatonin supplementation upregulated gene expression of PPAR-γ (1.14 ± 0.17-fold increase vs. 1.00 ± 0.15-fold change, P = 0.004) and LDLR (1.09 ± 0.13-fold increase vs. 0.98 ± 0.17-fold reduction, P = 0.01) compared with the placebo (Figs. 2 and 3).

Melatonin supplementation did not affect gene expression of GLUT-1 (1.08 ± 0.20-fold increase vs. 1.02 ± 0.18-fold increase, P = 0.27) compared with the placebo (Fig. 2).

4. Discussion

The current study is the first report of the effects of melatonin administration on mental health parameters, metabolic and genetic profiles in women with PCOS. We found that melatonin supplementation for 12 weeks to women with PCOS had favorable effects on BDI, BAI, PSQI index, insulin concentrations, HOMA-IR, QUICKI, and gene expression of PPAR-γ and LDLR, but did not affect other metabolic profiles and gene expression of GLUT-1.

4.1. Effects on mental health parameters

This study demonstrated that the intake of melatonin by patients with PCOS for 12 weeks significantly decreased BDI, BAI, and PSQI index. Circadian rhythms have been documented to be significantly disrupted in people with depression (Germain and Kupfer, 2008). Sleep disturbances such as early-morning awakening and insomnia are prominent manifestations of depressed mood (Srinivasan et al., 2009), indicating a close relationship between the melatonergic system and clinical depression (Malhi and Kuiper, 2013; Srinivasan et al., 2009). In addition, melatonin production from the pineal gland is modulated by norepinephrine, suggesting a link been melatonin and mental health disorders as well (Huang et al., 2015). Earlier, it was reported that melatonin could be used as a potential candidate drug to improve the neuropsychiatric behaviors via modulating the expression of the proteins involved in anxiety and depression behaviors such as glutathione S-transferase P 1 and complexin-1 (Nie et al., 2017). In agreement with our findings, Ghaderi et al., al.(2018) showed that melatonin supplementation to patients under methadone maintenance treatment for 12 weeks improved mental health parameters, including sleep quality, anxiety, and depression indices. In another trial, melatonin consumption at a daily dosage of 6 mg for 6 weeks in children with atopic dermatitis had a favorable impact on quality of sleep (Taghavi Ardakani et al., 2018). In addition, Rahman et al., al.(2010) observed that
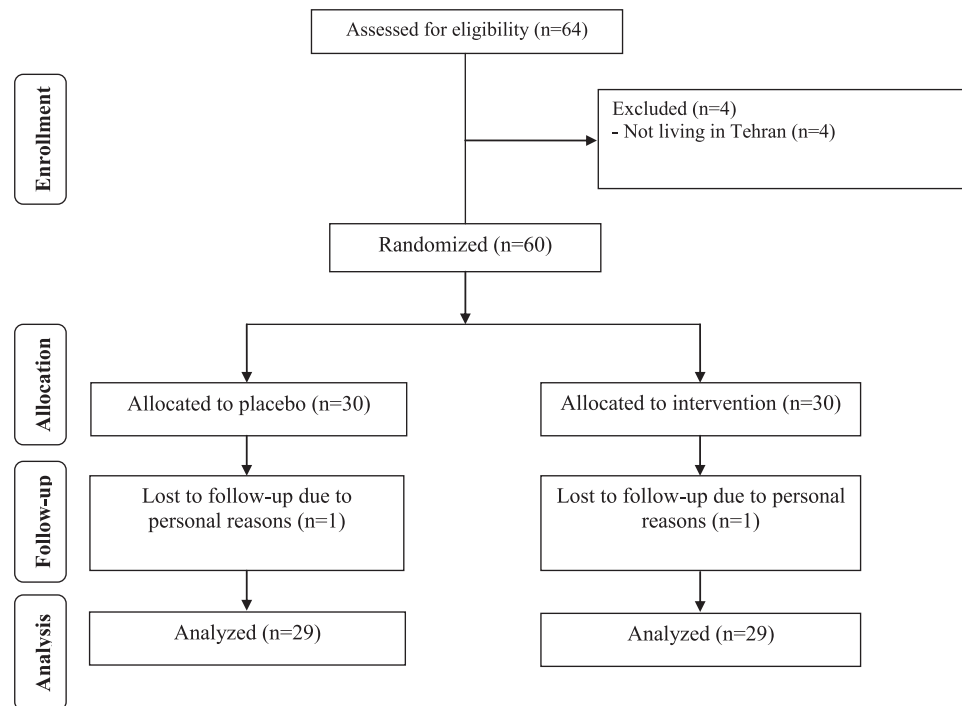
Fig. 1. Summary of patient flow diagram.

Table 2
General characteristics of study participants[a].

	Placebo group ($n = 29$)	Melatonin group ($n = 29$)	P[b]
Age (years)	26.0 ± 3.3	26.5 ± 3.5	0.59
Height (cm)	162.9 ± 5.2	163.0 ± 4.2	0.91
Weight at study baseline (kg)	73.7 ± 13.1	72.1 ± 12.9	0.63
Weight at end-of-trial (kg)	73.6 ± 12.3	71.9 ± 12.6	0.61
Weight change (kg)	−0.1 ± 1.5	−0.2 ± 1.2	0.81
BMI at study baseline (kg/m^2)	27.8 ± 4.7	27.1 ± 4.6	0.58
BMI at end-of-trial (kg/m^2)	27.8 ± 4.7	27.1 ± 5.0	0.57
BMI change (kg/m^2)	−0.04 ± 0.6	−0.05 ± 0.5	0.92

[a] Data are means ± SDs.
[b] Obtained from independent *t*-test.

Table 3
Metabolic profiles at baseline and after the 12-week intervention in women with polycystic ovary syndrome that received either melatonin supplements or placebo[a].

Variables	Placebo group ($n = 29$)		Melatonin group ($n = 29$)		Difference in outcome measures between melatonin and placebo groups[a]	
	Baseline	Week 12	Baseline	Week 12	β (95% CI)	P[b]
PSQI	7.7 ± 3.2	6.9 ± 3.3	8.1 ± 3.1	4.7 ± 2.1	−2.15 (−3.62, −0.68)	0.005
BDI score	21.7 ± 5.1	20.6 ± 5.1	22.1 ± 5.1	16.9 ± 3.6	−3.66 (−5.53, −1.78)	<0.001
BAI score	17.1 ± 4.1	16.5 ± 4.8	18.9 ± 4.7	16.3 ± 4.4	−1.95 (−3.41, −0.48)	0.01
FPG (mg/dL)	93.9 ± 6.6	93.0 ± 7.5	94.9 ± 6.8	93.2 ± 5.5	−0.44 (−2.38, 1.50)	0.65
Insulin (μIU/mL)	11.8 ± 1.6	11.7 ± 2.0	13.3 ± 2.9	11.6 ± 2.8	−1.20 (−2.14, −0.26)	0.01
HOMA-IR	2.7 ± 0.5	2.7 ± 0.5	3.1 ± 0.8	2.7 ± 0.7	−0.28 (−0.50, −0.05)	0.01
QUICKI	0.329 ± 0.007	0.329 ± 0.008	0.324 ± 0.012	0.332 ± 0.018	0.008 (0.002, 0.014)	0.007
Triglycerides (mg/dL)	147.8 ± 46.1	147.2 ± 46.9	149.5 ± 53.6	140.9 ± 54.4	−7.90 (−17.54, 1.72)	0.10
VLDL-cholesterol (mg/dL)	29.6 ± 9.2	29.4 ± 9.4	29.9 ± 10.7	28.2 ± 10.9	−1.58 (−3.50, 0.34)	0.10
Total cholesterol (mg/dL)	177.7 ± 31.8	175.1 ± 28.9	179.9 ± 24.3	168.9 ± 22.7	−7.96 (−13.75, −2.17)	0.008
LDL-cholesterol (mg/dL)	100.5 ± 32.6	98.3 ± 29.6	106.9 ± 22.5	97.1 ± 20.9	−5.88 (−11.42, −0.33)	0.03
HDL-cholesterol (mg/dL)	47.7 ± 6.9	47.4 ± 7.0	43.9 ± 7.9	43.7 ± 7.9	−0.39 (−2.46, 1.67)	0.70
Total-/HDL-cholesterol ratio	3.8 ± 0.9	3.8 ± 0.9	4.2 ± 0.8	4.0 ± 0.8	−0.15 (−0.36, 0.05)	0.13

Data are mean ± SDs.
BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; FPG, fasting plasma glucose; HOMA-IR, homeostasis model of assessment-insulin resistance; HDL-cholesterol, high density lipoprotein-cholesterol; LDL-cholesterol, low density lipoprotein-cholesterol; PSQI, Pittsburgh Sleep Quality Index; QUICKI, quantitative insulin sensitivity check index; VLDL-cholesterol, very low density lipoprotein-cholesterol.
[a] Outcome measures" refers to the change in values of measures of interest between baseline and week 12. β [difference in the mean outcomes measures between treatment groups (melatonin group = 1 and placebo group = 0)].
[b] Obtained from multiple regression model (adjusted for baseline values of each biochemical variables, age and baseline BMI).
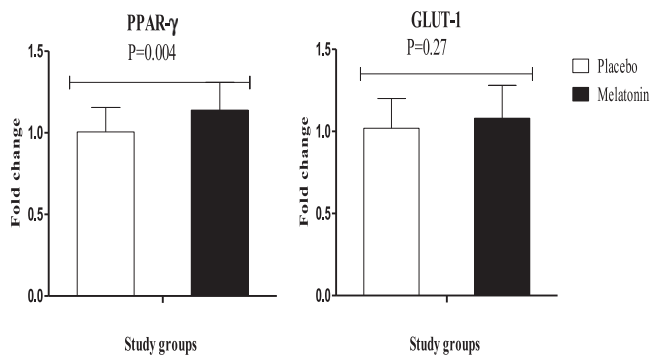
Fig. 2. Fold change (means ± SDs) in gene expression levels of PPAR-γ and GLUT-1 in women with polycystic ovary syndrome receiving melatonin supplements and placebo

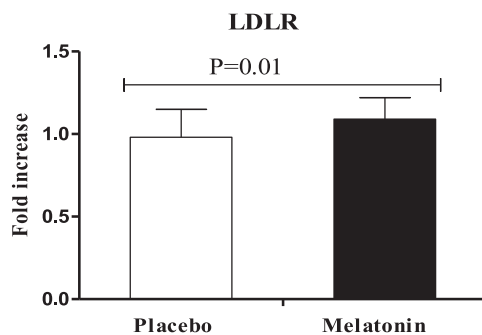P value was obtained from independent *t*-test. N = 29 in each group.

Fig. 3. Fold change (means ± SDs) in gene expression levels of LDLR in women with polycystic ovary syndrome receiving melatonin supplements and placebo

P value was obtained from independent *t*-test. N = 29 in each group.
GLUT-1, glucose transporter 1; LDLR, low-density lipoprotein receptor; PPAR-γ, peroxisome proliferator-activated receptor gamma; PCOS, polycystic ovary syndrome; PBMCs, peripheral blood mononuclear cells.

melatonin intake (5 mg/day) in subjects with delayed sleep phase syndrome ameliorated depressive symptoms and sleep continuity. However, 6 mg/day melatonin supplementation for 4 weeks did not affect mental health status in people with major depressive disorder (Serfaty et al., 2010). Finally, melatonin administration did not impact cognition and psychosocial functioning in subjects with severe mental disorder (Baandrup et al., 2017).

4.2. Effects on glycemic control and lipid profiles

We showed that melatonin supplementation to patients with PCOS for 12 weeks significantly decreased serum insulin levels, HOMA-IR, total- and LDL-cholesterol levels, and significantly increased QUICKI score, while it did not influence FPG and other lipid profiles. In addition, melatonin intake up-regulated gene expression of PPAR-γ and LDLR in PBMCs of women with PCOS, but did not affect gene expression of GLUT-1. On the basis of existing evidence, melatonin administration may have some beneficial effects on glucose homeostasis and lipid profiles. Ewida et al.(2016) demonstrated that melatonin intake (5 mg/kg) in MetS rats for 6 weeks significantly improved insulin resistance and dyslipidemia (Ewida and Al-Sharaky, 2016). In addition, melatonin intake in diabetic rats significantly ameliorated hypertension and insulin resistance and up-regulated PPAR-γ coactivator 1a and GLUT-4 gene expression (Rahman et al., 2017). Recently, we documented that 10 mg/day melatonin supplementation to diabetic people with coronary artery disease for 12 weeks had favorable impacts on glycemic control, insulin sensitivity, and HDL-cholesterol concentrations (Raygan et al., 2017). Also, melatonin consumption at a daily

dosage of 10 mg by patients with non-alcoholic fatty liver disease for 4 weeks significantly decreased median value of HOMA-IR (Gonciarz et al., 2013). In a meta-analysis, melatonin was shown to have a significant impact on triglycerides and total cholesterol concentrations, but did not affect HDL- and LDL-cholesterol levels (Mohammadi-Sartang et al., 2017). However, 6 mg/day melatonin administration for 14 days increased VLDL-cholesterol concentrations, but did not influence LDL- and HDL-cholesterol levels in postmenopausal women (Wakatsuki et al., 2001). In addition, supplementation with 3 mg/day of melatonin after 8 weeks did not influence glucose control and insulin resistance in patients with schizophrenia (Modabbernia et al., 2014). 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. A high-dose administration of melatonin or a longer intervention in women with PCOS may influence FPG, triglycerides, and HDL-cholesterol levels. Melatonin receptors (MT1 and MT2) have been identified on the cells of adipose cells and on the human pancreatic beta cells (Sharma et al., 2015). Melatonin reportedly inhibits insulin release via two G-protein-coupled receptors, MT1 (cAMP signaling pathway) and MT2 (cGMP signaling pathway), which modulate glucose homeostasis (Contreras-Alcantara et al., 2010). Furthermore, the favorable actions of melatonin on lipid concentrations may be due to increased esterification of cholesterol (Esquifino et al., 1997) mediated by higher lecithin-cholesterol acyltransferase activity (Tamura et al., 2008).

We encountered a few limitations in the current investigation. Due to budget limitations, we did not evaluate the effects of melatonin supplementation on serum and/or urinary melatonin. Secondly, we were unable to determine the impact of melatonin administration on expression other gene related to insulin and lipid metabolism.

4.3. Conclusions

Overall, melatonin supplementation for 12 weeks to PCOS women who were candidates for IVF had beneficial effects on mental health status, insulin levels, HOMA-IR, QUICKI, and gene expression of PPAR-γ and LDLR, but did not influence other metabolic profiles and gene expression of GLUT-1. This suggests melatonin supplementation may confer advantageous therapeutic potential for women with PCOS. Further research is needed in other participants and for longer periods to determine the beneficial effects of melatonin supplementation.

Conflicts of interest

None.

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