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Original Article

Effect of melatonin in reducing second-generation antipsychotic metabolic effects: A double blind controlled clinical trial

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ABSTRACT

Introduction: The use of second-generation atypical antipsychotics has an increasing role in the development of metabolic syndrome. However, these medications due to metabolic disorders can lead to an increased risk of cardiovascular disease and subsequently mortality as well as reduced adherence to treatment. The main objective of current study was to determine the ability of melatonin to reduce the metabolic effects of second-generation antipsychotics.
Methods: This double blind controlled clinical trial was conducted on 100 patients aged 18–64 years old were treated with the second-generation antipsychotics for the first time. The patients were divided randomly into two groups of 50. The case group received slow-release melatonin at a dose of 3 mg and the control group was given oral placebo at 8 p.m.
Results: The findings in melatonin group indicated significantly increase of HDL and decreased fasting blood sugar and systolic blood pressure, as well as had statistically significant increase in waist circumference, weight and BMI compared with placebo group.
Conclusion: According to the findings, it can be claimed that the addition of melatonin to atypical antipsychotics has led to a reduction in some of the metabolic effects of these drugs. In this study, HDL level was increased, and the mean systolic blood pressure and FBS were decreased in the melatonin group. Considering that these factors are contributing to cardiovascular disease as a leading cause of mortality in psychiatric patients, so the use of melatonin can reduce some of the medical effects of long-term treatment of atypical antipsychotics.

1. Introduction

The second-generation antipsychotics (SGAs) are a group of medications introduced to clinical psychiatry in the early 1990s. The SGAs are currently the most prescribed drugs for schizophrenia and other psychosis-related illnesses in most parts of the world. These drugs are also called SDAs (serotonin-dopamine antagonists) due to the high affinity for D2 and 5-HT2A receptors [1].

Clozapine was the first drug introduced in 1990 in the United States, although it has been available since the early 1970s in some European countries. The clozapine is known as the atypical antipsychotics due to negligible extrapyramidal side effects. In addition, it is effective in a group of mood and anxiety symptoms that are common in schizophrenia. Following the clozapine, other drugs with fewer side effects were released to the market, including risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole [1].

All SGAs are recommended for the treatment of schizophrenia, most of them are suitable for monotherapy or supportive therapy in bipolar disorder, and some have been confirmed for the treatment of major depression [2].

The first-generation antipsychotics are the D2 receptor antagonists, while the second-generation antipsychotics are the antagonists of D2 and serotonin receptors [3,4]. The use of first-generation antipsychotics has been limited due to severe and intolerable complications, especially in the elderly [5]. The use of second-generation antipsychotics is on the rise among elderly people around the world. The use of these drugs has been

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questioned in recent years due to the risk of dementia in the elderly and the possibility of sudden death [6]. These drugs are also increasingly applied in adolescents, and their administration rates have increased significantly [7].

People with mental illness, such as bipolar disorder and schizophrenia, are more likely to be exposed to metabolic disorders such as obesity, hypertension, diabetes, and lipid disorders; for example, obesity among them is 1.5–5 times more prevalent compared to the general population [8].

Although the second-generation antipsychotics have proven effects on the acute and long-term treatment of these disorders, and are the first choice of treatment, but unfortunately in turn cause weight gain [9]. Numerous studies have demonstrated an association between these medications and increased triglycerides [10]. An increasing incidence of metabolic syndrome has been reported because of using the atypical antipsychotics [11]. Three or more of the following symptoms characterize the metabolic syndrome: increased waist circumference, increased triglycerides, decreased HDL, hypertension and high FBS [12]. Among these drugs, the olanzapine and clozapine have the highest risk of developing metabolic syndrome [13]. However, these medications due to metabolic disorders can lead to an increased risk of cardiovascular disease and subsequently mortality, as well as reduced adherence to treatment [1].

Various studies have been conducted to reduce these metabolic complications; for example, the addition of melatonin (*N*-acetyl-5-methoxytryptamine) to the therapeutic regimen of patients. This hormone is secreted in the pineal gland, whose effect is well known to regulate circadian rhythm of sleep and wakefulness [14,15]. The hormone secretion is stimulated by darkness and inhibited by light. Maximum secretion of the melatonin hormone occurs at 2am, so that is sometimes called "the hormone of darkness" [16]. Its synthesis is controlled by light under the body circadian clock located in the suprachiasmatic nucleus [17]. The melatonin is synthesized from the amino acid precursor "tryptophan", which initially converts into serotonin and eventually into the melatonin [18]. Exogenous melatonin reportedly ameliorates the disturbances of the sleep and wakefulness rhythm [19]. The melatonin also affects basic metabolism, oxidative stress, inflammation, apoptosis [20,21], cognitive behavior [22], mood and behavior [23], and the regulation of metabolic processes such as insulin, leptin and lipid [24]. The beneficial metabolic effects of melatonin were first shown in mice, in which the administration of exogenous melatonin prevented the increase in visceral fat, insulin and leptin in the aging process [25]. The animal model suggests that melatonin, regardless of food intake and total body fat, reduces weight gain as well as increases the leukomotor activity [26].

In a randomized double blind placebo control study conducted by Francisco Romo-Nava et al. on 20 patients with bipolar disorder and 24 patients with schizophrenia, the patients were divided into two groups of 24 (control) and 20 (melatonin) and were studied for 8 weeks. In the melatonin group, there was a decrease in diastolic blood pressure and weight gain compared to the control group [27].

As well, Koziróg et al. in 2011 in Netherlands studied 33 healthy volunteers and 30 patients with metabolic syndrome who were not treated with lifestyle interventions for 3 months. In this study, the subjects with metabolic syndrome were prescribed daily 5 mg/day melatonin two hours before bedtime. Significant changes occurred in systolic blood pressure, diastolic blood pressure, LDL and antioxidant defense two months after treatment compared to the baseline. It was found that melatonin might be effective in treating people with metabolic syndrome [28].

Due to the limited studies carried out and pivotal need for the therapeutic regimen to reduce or prevent the metabolic effects of second-generation antipsychotics, the main objective of this study was to determine the ability of melatonin to ameliorate the metabolic effects of second-generation antipsychotics.

2. Materials and methods

This double blind controlled clinical trial was conducted for eight weeks on the patients aged 18–64 years old who were referred as outpatients or hospitalized in Karegarnejad Hospital in Kashan (Iran) in 2014–2015 and were recently treated with the second-generation antipsychotics. Exclusion criteria were hypertension, diabetes, lipid disorders, thyroid dysfunction, liver diseases, history of melatonin allergy, pregnancy, lactation and history of drug dependence or abuse in the last 6 months. After explaining the research objectives, possible complications and related issues to the patient or caregivers, written consent was obtained from all patients and their relatives.

The patients were randomly assigned to two groups by blocked randomization procedures. The case group received slow-release melatonin at a dose of 3 mg and the control group was given oral placebo at 8 pm. According to the study, in order to compare the effect of melatonin and placebo on the reduction of metabolic complications of second-generation antipsychotics, the mean change in diastolic blood pressure after treatment was -4.6 ± 5.9 in the melatonin group and 1.8 ± 5.8 in the placebo group.

In terms of LDL, these two measures were 18.6 ± 19.5 and 1.6 ± 21.4, respectively. With regard to 95% confidence interval and 90% test power, the minimum sample size was calculated to be 30 in each group. Considering other measured parameters, this study was performed on two groups of 50.

The change in the type of antipsychotics was prohibited, but the dose adjustment was allowed and recorded. The second-generation antipsychotics are divided into two groups of high-risk (olanzapine and clozapine) and low-risk (risperidone and quetiapine) in terms of the development of metabolic complications. Other prescription drugs, such as antidepressants, hypnotics and mood stabilizers are allowed in the presence of clinical indications. The choice of antipsychotic type was introduced as a confounding variable, and in case of dose change in each drug, they were compared to a single criterion. If there was any change in blood lipids, sugar and pressure profiles (possible side effects), these patients were treated routinely for these parameters in spite of

Table 1
Frequency distribution of descriptive variables in the studied groups.

Variables		Groups		P value*
		Melatonin	Placebo	
Gender	Male	22 (44%)	29 (58%)	0.161
	Female	28 (56%)	21 (42%)	
	Total	50	50	
Educational level	Illiterate	3 (6%)	5 (10%)	0.21
	Primary school	15 (30%)	16 (32%)	
	Secondary school	18 (36%)	8 (16%)	
	High school	9 (18%)	15 (30%)	
	Academic	5 (10%)	6 (12%)	
	Total	50	50	
marital status	Single	18 (36%)	18 (36%)	0.897
	Married	30 (60%)	29 (58%)	
	Deceased spouse	2 (4%)	3 (6%)	
	Total	50	50	
Age (year)	≤29	11 (22%)	15 (30%)	0.36
	30–34	25 (50%)	18 (36%)	
	≥45	14 (28%)	17 (34%)	
	sd$\bar{x}\pm$	37.4 ± 10.3	37.46 ± 12.42	0.986

* P value: significance level related to the used test "Chi".

receiving the studied drugs. This factor was also included in the study as an outcome variable (Table 1).

The patients were requested to be fasting for 12 h before each assessment. At first, laboratory tests and then the measurements of weight, height and body mass index were performed, as well as waist circumference and blood pressures were measured. These evaluations were performed at baseline, fourth week of treatment and end of treatment.

Moreover, the patients were asked to maintain constant diet during treatment, but it was introduced into study as a confounding factor in case of the changes in physical activity (Table 2).

2.1. Statistical analysis

Data was analyzed in SPSS software (version 21) using Kolmogorov-Smirnov test to evaluate the normality of data, calculating the mean and standard deviation for metabolic disturbances, and determining the trend of changes during treatment in the two groups [29–34].

Chi-square test was applied to study the descriptive variables of the research (gender, age, education and marital status) in two groups. Independent *t*-test and repeated measures ANOVA were exploited to examine the differences between the existing variables (triglyceride, HDL, cholesterol, FBS, diastolic blood pressure, systolic blood pressure, waist circumference, weight and BMI) between the two groups along with the effect of time [35–42].

In this study, the p value or significance level (test error value) was considered to be 0.05 with 95% confidence interval [43–49].

3. Results

In this study, 100 patients taking atypical antipsychotics (olanzapine, clozapine, risperidone and quetiapine) were studied for complications of metabolic syndrome (50 in the melatonin group and 50 in the placebo group), including 51 males and 49 females. All patients were in the age range of 18–64 years with the mean age of 37.4 ± 11.35 years. The highest frequency was related to the age group of 30–45 years, 36% in the melatonin group and 50% in the placebo group.

The males and females were 44% and 56% in the melatonin group, as well as 58% and 42% in the placebo group, respectively. No significant correlation was found between the treatment groups with the gender of the patients (P = 0.161). In addition, the highest frequency was in the educational level of primary school in the melatonin group, and secondary school in the placebo group. There was no significant relationship between the treatment groups and the educational status of the patients (P = 0.21). Considering the above table, there was no statistically significant relationship between marital status of patients and treatment groups (P = 0.897). In the melatonin group, 30% of patients were under 29 years of age, 36% were between 30 and 44 years, and 34% were over 45 years of age. In the placebo group, 22% were younger than 29 years of age, 50% between 30 and 44 years old and 28% over 45 years of age. There was no statistically significant relationship between age and treatment groups (P = 0.36). Moreover, the mean age in both groups was 37.46 and 37.4, respectively (P = 0.986).

After four weeks of treatment, the mean triglyceride was increased by 23.3 units in the melatonin group and 20 units in the placebo group; this difference was not statistically significant (P = 0.65). This difference was not significant after eight weeks of treatment as well (P = 0.162).

After four weeks of treatment, the mean HDL was increased by 2 units in the melatonin group, and was decreased by 0.32 units in the placebo group; this difference was statistically significant (P = 0.04). This significant difference was observed after eight weeks of treatment (P = 0.001).

After four weeks of treatment, the mean cholesterol was increased by 13.2 units in the melatonin group and 8.5 units in the placebo group; this difference was not statistically significant (P = 0.219). This difference was not also significant after eight weeks of treatment (P = 0.784).

After four weeks of treatment, the mean FBS was increased by 2.2 units in the melatonin group and 0.5 units in the placebo group; this difference was not statistically significant (P = 0.32). The mean FBS was reduced by 3 units in the melatonin group and was increased by 1.3 units in the placebo group; this difference was significant (P = 0.002).

After four weeks of treatment, the mean diastolic blood pressure was increased by 0.4 units in the melatonin group and 0.6 units in the placebo group; this difference was statistically significant (P = 0.9). This significant difference was not observed after eight weeks of treatment (P = 0.112).

After four weeks of treatment, the mean systolic blood pressure was decreased by 0.1 units in the melatonin group and 1.2 units in the placebo group; this difference was not statistically significant (P = 0.596). The mean systolic blood pressure was reduced by 1.4

Table 2
Mean and standard deviation of variables in the two groups after four and eight weeks of treatment.

Variables		Groups		P value
		Melatonin (Mean ± SD)	Placebo (Mean ± SD)	
Triglyceride	Four weeks after treatment	23.38 ± 31.80	20.22 ± 38.34	0.655
	Eight weeks after treatment	16.32 ± 24.91	23.62 ± 26.89	0.162
HDL	Four weeks after treatment	2.0 ± 5.13	−0.32 ± 5.98	0.04
	Eight weeks after treatment	3.34 ± 6.88	−1.58 ± 6.94	0.001
Cholesterol	Four weeks after treatment	13.24 ± 20.91	8.5 ± 17.2	0.219
	Eight weeks after treatment	11 ± 22.67	9.88 ± 17.72	0.784
FBS	Four weeks after treatment	2.24 ± 9.47	0.56 ± 7.29	0.323
	Eight weeks after treatment	−3.02 ± 7.08	1.32 ± 6.42	0.002
Diastolic blood pressure	Four weeks after treatment	0.4 ± 7.87	0.6 ± 7.93	0.900
	Eight weeks after treatment	−0.1 ± 7.85	2.30 ± 7.08	0.112
Systolic blood pressure	Four weeks after treatment	−0.1 ± 9.60	−1.2 ± 10.99	0.596
	Eight weeks after treatment	−1.4 ± 9.03	2.9 ± 10.5	0.031
Waist circumference	Four weeks after treatment	1.6 ± 3.28	0.52 ± 1.18	0.031
	Eight weeks after treatment	1.97 ± 2.96	0.78 ± 1.31	0.011
Weight	Four weeks after treatment	0.93 ± 1.2	0.29 ± 0.62	0.001
	Eight weeks after treatment	1.1 ± 1.11	0.51 ± 0.71	0.003
BMI	Four weeks after treatment	2.51 ± 3.11	0.84 ± 1.71	0.001
	Eight weeks after treatment	2.95 ± 3.07	1.48 ± 2.06	0.006

units in the melatonin group and was increased by 2.9 units in the placebo group; this difference was significant (P = 0.031).

After four weeks of treatment, the mean waist circumference was increased by 1.6 units in the melatonin group and 0.52 units in the placebo group; this difference was statistically significant (P = 0.031). This difference was also significant after eight weeks of treatment (P = 0.011).

After four weeks of treatment, the mean BMI was increased by 0.93 units in the melatonin group and 0.29 units in the placebo group; this difference was statistically significant (P = 0.001). This difference was also significant after eight weeks of treatment (P = 0.003).

After four weeks of treatment, the mean weight was increased by 2.5 units in the melatonin group and 0.84 units in the placebo group; this difference was statistically significant (P = 0.001). This difference was also significant after eight weeks of treatment (P = 0.006).

The results of this table show the effect of time on changes in triglyceride levels in the patients (P = 0.049). However, no significant interaction was observed between treatment groups and triglyceride changes in the presence of time effect (P = 0.15).

In addition, the findings in this table indicate that the time was not effective on changes in HDL in the patients (P = 0.91). However, the interaction of treatment groups in the presence of time factor on HDL changes was significant (P = 0.001).

On the other hand, the effect of time on cholesterol changes in the patients was not significant (P = 0.704). As well, no significant interaction was observed between treatment groups and cholesterol changes in the presence of time factor (P = 0.582).

The results of this table indicate that the factor of time was ineffective on changes in FBS (P = 0.670), but the interaction of treatment groups was significant on changes in FBS in the presence of time (P = 0.004).

Based on the results of Table 3, the time factor was ineffective on the diastolic blood pressure changes in the patients (P = 0.754) and also the interaction of treatment groups and diastolic blood pressure changes was not significant in the presence of time factor (P = 0.163).

The results of this table show that the time factor was not effective on changes in systolic blood pressure in the patients (P = 0.747). However, the interaction of treatment groups and systolic blood pressure changes was significant in the presence of time factor (P = 0.013).

The effect of time factor on waist circumference was positive (P = 0.001). There was also a significant correlation between the treatment groups and waist circumference in the presence of time factor (P = 0.025).

Additionally, the time factor affects the weight of patients (P = 0.000). The interaction of treatment groups and the changes in weight was significant in the presence of time factor (P = 0.002). Finally, the results of this table show the effect of time factor on BMI changes in the patients (P = 0.001). Furthermore, the interaction of treatment groups and the changes in BMI was significant in the presence of time factor (P = 0.001).

4. Discussion

The present study examined the effect of melatonin supplementation on metabolic complications of second-generation antipsychotics. The drugs were olanzapine, clozapine, risperidone and quetiapine. None of the subjects under study, who were newly treated, was treated with clozapine. In this study, 100 patients aged 16–64 years were divided randomly in two groups of 50. The case group received the antipsychotics and the melatonin, and the control group was administered with the placebo. The study variables were calculated at weeks 4 and 8 and analyzed by SPSS 21. The age and gender were compared in the two groups to ensure a lack of confounding factors. The melatonin group included 30% of people younger than 29 years of age, 36% between 30 and 44 years old and 34% over 45 years of age, while the placebo group consisted of 22% less than 29 years old, 50% between 30 and 44 years old and 28% over 45 years old.

The melatonin group also had 44% male and 56% female. The placebo group included 58% male and 42% female. However, there was no significant difference in age and gender in the study groups.

Due to the increased administration of these drugs, there are concerns about the long-term use of these drugs. Various studies have shown that the atypical antipsychotics could increase weight, BMI and some metabolic syndrome components in the patients. These complications not only are important in terms of general health due to increased risk of diabetes mellitus, cardiovascular disease and blood pressure, but also can lead to a lack of patient adherence for effective treatment. Therefore, proper solutions should be considered to minimize these adverse effects.

According to the results of studies showing the regulatory role of melatonin secreted by the pineal gland in the sleep/wakefulness

Table 3
One-way ANOVA results to measure the time difference in variables in two groups.

Source of changes		Sum of squared errors	Degrees of freedom	Mean squared error	F value	P value
Triglyceride	Time	2792.650	1.560	1790.108	3.357	0.049
	Time × group	1595.667	2	797.833	1.918	0.150
HDL	Time	85.442	1.806	47.306	2.491	0.091
	Time × group	252.834	1.806	139.986	7.371	0.001
Cholesterol	Time	111.582	1.848	60.375	0.328	0.704
	Time × group	373.634	1.848	202.167	1.098	0.582
FBS	Time	25.513	1.727	14.769	0.355	0.670
	Time × group	451.898	1.727	261.597	6.286	0.004
Diastolic blood pressure	Time	13.781	1.882	7.333	0.265	0.754
	Time × group	95.919	1.882	50.971	1.846	0.163
Systolic blood pressure	Time	19.371	1.638	11.826	0.223	0.747
	Time × group	407.569	1.638	248.826	4.912	0.013
Waist circumference	Time	35.428	1.540	22.998	8.255	0.001
	Time × group	18.208	1.540	11.820	4.243	0.025
Weight	Time	51.338	1.730	29.683	9.273	0.000
	Time × group	38.426	1.730	22.271	6.940	0.002
BMI	Time	5.743	1.695	3.389	7.638	0.001
	Time × group	5.662	1.695	3.341	7.530	0.001

cycle, metabolic activities of the body, energy regulation and lipid distribution, it is hypothesized that daily administration of melatonin may prevent the metabolic effects of these drugs by regulating the circadian rhythm of the body. Particularly, the melatonin is a natural substance without any reported toxicity.

In a study conducted in 2007 in the United States on female rats weighing 240–250 g for 8 weeks, increasing the body weight and visceral fat in mice may be related to at least to a lesser extent secondary to reducing the plasma melatonin levels due to the olanzapine. In this study, concomitant administration of the melatonin was able to prevent weight gain induced by olanzapine [50].

In a study in Netherlands (2011), the lipid and blood pressure profiles were declined significantly two months after administration of melatonin in the patients with metabolic syndrome [28].

In our study, the mean triglyceride was increased in the melatonin group significantly after 4 weeks, and was decreased after 8 weeks compared to the fourth week. In the placebo group, the mean triglyceride was increased after 4 weeks and was increased at week 8 as compared to week 4, indicating the effect of time on triglyceride changes in the patients ($P = 0.049$). However, no significant interaction was observed between treatment groups and triglyceride changes in the presence of time factor ($P = 0.15$).

In a study in Shafa Hospital in Rasht (Iran) in 2014, 48 patients with the first episode of schizophrenia candidate for treatment with olanzapine were randomly assigned to two groups. One of the groups was treated with olanzapine and melatonin, and another group was treated with olanzapine and placebo for 8 weeks. In the group receiving concurrent melatonin, an increase in triglyceride levels was significantly less than the placebo group [51], inconsistent with our study. In a study in 2014 in Rouzbeh Hospital in Tehran (Iran), 38 teenagers aged 17–11 years with the first episode of bipolar disorder treated with olanzapine and melatonin or olanzapine and placebo [52], it was found that the levels of triglyceride did not differ significantly between the two groups after 12 weeks, similar to this study in terms of the level of changes in triglyceride in the two groups.

In this study, the mean cholesterol level was increased also in the melatonin and placebo groups at week 8 compared to the baseline level, but was not significant ($P = 0.704$). Moreover, the interaction between treatment groups and cholesterol changes was not significant in the presence of time factor ($P = 0.582$). The results of this study were in line with the result of the study carried out in Shafa Hospital of Rasht concerning the cholesterol changes in the two groups of melatonin and placebo. In the study in the Roozbeh Hospital, the increased level of cholesterol in the melatonin group compared with the placebo group was reported close to significant.

In our study, the HDL level was increased in the melatonin group at weeks 4 and 8, while the decrease in the HDL level was observed in the placebo group; these changes were significant ($P = 0.001$). No changes in the HDL level have been mentioned in other studies. In this study, the mean diastolic blood pressure was increased in the melatonin group at week 4 and then decreased at week 8. In the placebo group, the mean diastolic blood pressure was elevated at weeks 4 and 8; these changes were not significant ($P = 0.163$). In a study for 8 weeks in Mexico in 2014, 44 patients (20 bipolar patients and 24 schizophrenic patients) were diagnosed with a reduction in diastolic blood pressure in the melatonin group [27], no matched with the outcome of this study. However, the result of this study was similar to the study in the Roozbeh Hospital and no significant changes in diastolic blood pressure were reported in melatonin and placebo groups.

The mean systolic blood pressure was decreased at weeks 4 and 8 in the melatonin group in this study, but firstly was decreased at week 4 in the placebo group and was increased at week 8; these changes in the mean systolic blood pressure were significant ($P = 0.013$). The result of this study is consistent with the study in the Roozbeh Hospital in Tehran.

In our study, the FBS level also was increased in the 4th week of the melatonin group, but decreased by 8 weeks compared to the baseline; and was increased in the 4th and 8th weeks in the placebo group; this difference was statistically significant ($P = 0.004$). However, this factor showed no significant difference in the study of the Shafa Hospital of Rasht. In addition, the difference in the FBS level due to melatonin was not significantly higher in the study in the Roozbeh Hospital, as opposed to the outcome of this study.

In our study, the mean waist circumference was increased in the melatonin and placebo groups at weeks 4 and 8, but this increase was higher in the melatonin group, which was statistically significant ($P = 0.025$). However, the mean changes in waist circumference in the melatonin group were significant in comparison to the placebo group in the study in the Shafa Hospital of Rasht.

In this study, the mean weight gain was also increased in both groups at weeks 4 and 8; this increase was higher in the melatonin group and was statistically significant ($P = 0.002$). In a study by Francisco Romo-Nava in Mexico, a decrease was observed in weight gain in the melatonin group in bipolar patients, and not in the schizophrenic group [27].

As well, in the study in the Shafa Hospital of Rasht, the melatonin group had less weight gain than the placebo group, which was reported significantly inconsistent with the results of this study. In the study in the Roozbeh Hospital, weight gain was also significantly lower in the melatonin group.

Regarding the increased waist circumference and weight gain in both groups, the BMI was increased in both groups at weeks 4 and 8; the increase was higher in the melatonin group ($P = 0.001$). In the study in the Roozbeh Hospital, the decrease in BMI in the melatonin group was close to significant compared to the placebo group.

Additionally, in a randomized double blind placebo-controlled study in 2006 on adult female rats, the cases receiving olanzapine for 35 days showed significant weight gain compared to the control group. Then they were divided into three groups and were administered 20, 60 or 200 mg/day of Mifepristone (a potent glucocorticoid antagonist). On day 21, the rats had significant weight loss. The rats taking 200 mg/day had significantly less abdominal fat than the control group [53].

In another study in 2009, 57 men aged 19–38 years had weight gain and waist circumference significantly higher in the group receiving olanzapine and placebo than those taking the olanzapine and mifepristone [54].

Deng in 2012 indicated that co-administration of betahitne with olanzapine reduced the weight gain induced by the olanzapine [55].

A study was conducted in 2013 on rats regarding the fact that olanzapine causes a change in the intestinal microflora. A group of rats were given olanzapine + antibiotics (a cocktail of neomycin, metronidazole, and polymyxin B), and the control group received olanzapine and placebo. The antibiotic cocktail was shown to cause weight loss in the rats. Thus, it was hypothesized that the change in intestinal microflora plays a role in metabolic disorders caused by olanzapine [56].

In a study conducted in 2008, it was observed that adding metformin for 12 weeks into olanzapine in 40 patients with schizophrenia, the increase in weight, waist circumference and BMI was found to be lower n the metformin group than in the control group [57].

In another double blind study in 2010 for 12 weeks, 72 schizophrenic patients were divided into two groups of

olanzapine + placebo and olanzapine + topiramate (100 mg/day). At the end of study, it was shown that topiramate can prevent weight gain resulting from olanzapine and its metabolic effects, as well as causes a reduction in weight, glucose, cholesterol, triglycerides and systolic and diastolic blood pressure [58].

In summary, the increase in HDL and the decrease in FBS and systolic blood pressure were observed significantly in the melatonin group in our study, as well as the elevation in waist circumference, weight and BMI were statistically significant higher than the placebo group.

5. Conclusion

According to the results obtained from the current research, it can be concluded that the addition of melatonin to atypical antipsychotics decreased some of the metabolic effects of these drugs. In this study, the HDL level was increased, and the mean systolic blood pressure and FBS were decreased in the melatonin group. Considering that these factors are contributing to cardiovascular disease as a leading cause of mortality in psychiatric patients, so the use of melatonin can reduce some of the medical effects of long-term treatment of atypical antipsychotics.

Competing interests

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

This study was approved by Kashan University of Medical Sciences in 28th July 2015. The informed consent form was signed by all parents. All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Authors' contributions

All authors reviewed the final form of the paper and approved it for publication. MA was responsible for the data collection, analysis, and interpretation besides the literature review. MA and GA were responsible for organizing and supervising the work and revising it critically for important intellectual content.

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References

[1] Sadock B, Sadock V. Pedro Ruiz comprehensive text book of psychiatry. 9th ed. New York: Lippincott Williams & Wilkins; 2009. p. 1432–5.
[2] Sadock BJ, Sadock VA. Kaplan and Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry. Lippincott Williams & Wilkins; 2011.
[3] Ashcroft DM, Frischer M, Lockett J, et al. Variations in prescribing atypical antipsychotic drugs in primary care: cross-sectional study. Pharmacoepidemiol Drug Saf 2002;11(4):285–9.
[4] Barak Y, Shamir E, Weizman R. Would a switch from typical antipsychotics to risperidone be beneficial for elderly schizophrenic patients? A naturalistic, long-term, retrospective, comparative study. J Clin Psychopharmacol 2002;22(2):115–20.
[5] Alexopoulos GS, Streim J, Carpenter D, et al. Using antipsychotic agents in older patients. J Clin Psychiatry 2004;65:5–99 discussion 100–102; quiz 103–104.
[6] Shin J-Y, Choi N-K, Jung S-Y, et al. Risk of ischemic stroke with the use of risperidone, quetiapine and olanzapine in elderly patients: a population-based, case-crossover study. J Psychopharmacol (Oxf) 2013;27(7):638–44.
[7] Cooper WO, Arbogast PG, Ding H, et al. Trends in prescribing of antipsychotic medications for US children. Ambul Pediatr 2006;6(2):79–83.
[8] Zimmet P. Epidemiology of diabetes mellitus and associated cardiovascular risk factors: focus on human immunodeficiency virus and psychiatric disorders. Am J Med Suppl 2005;118:3–8.
[9] Nihalani N, Schwartz TL, Siddiqui UA, et al. Weight gain, obesity, and psychotropic prescribing. J Obes. 2011;2011.
[10] Henderson DC, Cagliero E, Gray C, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. Am J Psychiatry 2000;157(6):975–81.
[11] Fiedorowicz JG, Palagummi NM, Forman-Hoffman VL, et al. Elevated prevalence of obesity, metabolic syndrome, and cardiovascular risk factors in bipolar disorder. Ann Clin Psychiatry 2008;20(3):131–7.
[12] Grundy SM, Brewer HB, Cleeman JI, et al. Definition of metabolic syndrome. Circulation 2004;109(3):433–8.
[13] Girgis R, Javitch J, Lieberman J. Antipsychotic drug mechanisms: links between therapeutic effects, metabolic side effects and the insulin signaling pathway. Mol Psychiatry 2008;13(10):918.
[14] Srinivasan V, Pandi-Perumal SR, Trahkt I, et al. Melatonin and melatonergic drugs on sleep: possible mechanisms of action. Int J Neurosci 2009;119(6):821–46.
[15] Fornaro M, Prestia D, Colicchio S, et al. A systematic, updated review on the antidepressant agomelatine focusing on its melatonergic modulation. Current Neuropharmacol 2010;8(3):287–304.
[16] Pandi-Perumal SR, Trakht I, Spence DW, et al. The roles of melatonin and light in the pathophysiology and treatment of circadian rhythm sleep disorders. Nat Rev Neurol 2008;4(8):436.
[17] Stehle J, Von Gall C, Korf HW. Melatonin: a clock-output, a clock-input. J Neuroendocrinol 2003;15(4):383–9.
[18] Klein DC. Arylalkylamine N-acetyltransferase:the timezyme. J Biol Chem 2007;282(7):4233–7.
[19] Russcher M, Koch BC, Nagtegaal JE, et al. Long-term effects of melatonin on quality of life and sleep in haemodialysis patients (Melody study): a randomized controlled trial. Br J Clin Pharmacol 2013;76(5):668–79.
[20] Pohanka M, Sobotka J, Jilkova M, et al. Oxidative stress after sulfur mustard intoxication and its reduction by melatonin: efficacy of antioxidant therapy during serious intoxication. Drug Chem Toxicol 2011;34(1):85–91.
[21] Jang SS, Kim HG, Lee JS, et al. Melatonin reduces X-ray radiation-induced lung injury in mice by modulating oxidative stress and cytokine expression. Int J Radiat Biol 2013;89(2):97–105.
[22] Corrales A, Martínez P, García S, et al. Long-term oral administration of melatonin improves spatial learning and memory and protects against cholinergic degeneration in middle-aged Ts65Dn mice, a model of Down syndrome. J Pineal Res 2013;54(3):346–58.
[23] Cardinali DP, Vigo DE, Olivar N, et al. Therapeutic application of melatonin in mild cognitive impairment. Am J Neurodegener Dis 2012;1(3):280.
[24] Espino J, Pariente JA, Rodríguez AB. Role of melatonin on diabetes-related metabolic disorders. World J Diabetes 2011;2(6):82.
[25] Rasmussen DD, Boldt BM, Wilkinson C, et al. Daily melatonin administration at middle age suppresses male rate visceral fat, plasma leptin, and plasma insulin to youthful levels. Endocrinology 1999;140(2):1009–12.
[26] Terrón M, Delgado-Adámez J, Pariente J, et al. Melatonin reduces body weight gain and increases nocturnal activity in male Wistar rats. Physiol Behav 2013;118:8–13.
[27] Romo-Nava F, Alvarez-Icaza González D, Fresán-Orellana A, et al. Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. Bipolar Disord 2014;16(4):410–21.
[28] Koziróg M, Poliwczak AR, Duchnowicz P, et al. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res 2011;50(3):261–6.
[29] Hosseini ES, Moniri R, Goli YD, et al. Purification of antibacterial CHAPK protein using a self-cleaving fusion tag and its activity against methicillin-resistant staphylococcus aureus. Probiot Antimicrob Prot 2016;8(4):202–10.
[30] Kashani HH, Nikzad H, Mobaseri S, et al. Synergism effect of nisin peptide in reducing chemical preservatives in food industry. Life Sci J 2012;9(1):496–501.
[31] Dehghani R, Sharif A, Madani M, et al. Factors influencing animal bites in Iran: a descriptive study. Osong Public Health Res Perspect 2016;7(4):273–7.
[32] Kashani HH, Fahimi H, Goli YD, et al. A novel chimeric endolysin with antibacterial activity against methicillin-resistant Staphylococcus aureus. Front Cell Infect Microbiol 2017;2017.
[33] Kamani M, Hosseini ES, Kashani HH, et al. Protective effect of lepidium sativum seed extract on histopathology and morphology of epididymis in diabetic rat model. Int J Morphol 201735(2).
[34] Piroozmand A, Haddad Kashani H, Zamani B. Correlation between epstein-Barr virus infection and disease activity of systemic lupus erythematosus: a Cross-Sectional study. Asian Pac J Cancer Prev 2017;18(2):523–7.
[35] Jalali HK, Salamatzadeh A, Jalali AK, et al. Antagonistic activity of Nocardia brasiliensis PTCC 1422 against isolated Enterobacteriaceae from urinary tract infections. Probiot Antimicrob Prot 2016;8(1):41–5.

[36] Sharif MR, Kheirkhah D, Madani M, et al. The relationship between iron deficiency and febrile convulsion: a case-control study. Glob J Health Sci 2016;8(2):185.
[37] Lotfi A, Shiasi K, Amini R, et al. Comparing the effects of two feeding methods on metabolic bone disease in newborns with very low birth weights. Glob J Health Sci 2016;8(1):249.
[38] Alavi NM, Madani M, Sadat Z, et al. Fatigue and vitamin D status in Iranian female nurses. Glob J Health Sci 2016;8(6):196.
[39] Saba M, Valeh T, Ehteram H, et al. Diagnostic value of neuron-specific enolase (NSE) and cancer antigen 15-3 (CA 15-3) in the diagnosis of pleural effusions. Asian Pac J Cancer Prev 2017;18:257.
[40] Sharif A, Kashani HH, Nasri E, et al. The role of probiotics in the treatment of dysentery: a randomized double-Blind clinical trial. Probiot Antimicrob Prot 2017;1–6.
[41] Hosseyni ES, Kashani HH, Asadi MH. Mode of action of medicinal plants on diabetic disorders. Life Sci J 20124(9).
[42] Moghaddasi Mohammad S, Kashani HH, Azarbad Z. Capparis spinosa L. propagation and medicinal uses. Life Sci J 2012;9(4):684–6.
[43] Sharif MR, Kashani HH, Ardakani AT, et al. The effect of a yeast probiotic on acute diarrhea in children. Probiot Antimicrob Prot 2016;8(4):211–4.
[44] Dehghani R, Sharif A, Assadi MA, et al. Fungal flora in the mouth of venomous and non-venomous snakes. Comp Clin Pathol 2016;25(6):1207–11.
[45] Kashani HH, Moniri R. Expression of recombinant pET22b-LysK-cysteine/histidine-dependent amidohydrolase/peptidase bacteriophage therapeutic protein in Escherichia coli BL21 (DE3). Osong Public Health Res Perspect 2015;6(4):256–60.
[46] Kashani HH, Moshkdanian G, Atlasi MA, et al. Expression of galectin-3 as a testis inflammatory marker in vasectomised mice. Cell J (Yakhteh) 2013;15(1):11.
[47] Nikzad H, Kashani HH, Kabir-Salmani M, et al. Expression of galectin-8 on human endometrium: molecular and cellular aspects. Iran J Reprod Med 2013;11(1):65.
[48] Dehghani R, Sharif MR, Moniri R, et al. The identification of bacterial flora in oral cavity of snakes. Comp ClinPathol 2016;25(2):279–83.
[49] Hosseini ES, Zeinoddini M, Kashani HH, et al. Intein as a novel strategy for protein purification. Life Sci J 2012;4:9.
[50] Raskind MA, Burke BL, Crites NJ, et al. Olanzapine-induced weight gain and increased visceral adiposity is blocked by melatonin replacement therapy in rats. Neuropsychopharmacology 2007;32(2):284.
[51] Modabbernia A, Heidari P, Soleimani R, et al. Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. J Psychiatr Res 2014;53:133–40.
[52] Mostafavi A, Solhi M, Mohammadi M-R, et al. Melatonin decreases olanzapine induced metabolic side-effects in adolescents with bipolar disorder: a randomized double-blind placebo-controlled trial. Acta Med Iran 2014;52(10):734.
[53] Beebe KL, Block T, DeBattista C, et al. The efficacy of mifepristone in the reduction and prevention of olanzapine-induced weight gain in rats. Behav Brain Res 2006;171(2):225–9.
[54] Gross C, Blasey CM, Roe RL, et al. Mifepristone treatment of olanzapine-induced weight gain in healthy men. Adv Ther 2009;26(10):959–69.
[55] Deng C, Lian J, Pai N, et al. Reducing olanzapine-induced weight gain side effect by using betahistine: a study in the rat model. J Psychopharmacol (Oxf) 2012;26(9):1271–9.
[56] Davey K, Cotter P, O'sullivan O, et al. Antipsychotics and the gut microbiome: olanzapine-induced metabolic dysfunction is attenuated by antibiotic administration in the rat. Transl Psychiatry 2013;3(10):e309.
[57] Wu R-R, Zhao J-P, Guo X-F, et al. Metformin addition attenuates olanzapine-induced weight gain in drug-naive first-episode schizophrenia patients: a double-blind, placebo-controlled study. Am J Psychiatry 2008;165(3):352–8.
[58] Narula PK, Rehan H, Unni K, et al. Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. Schizophr Res 2010;118(1):218–23.