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THE EFFECT OF LONG-TERM MELATONIN SUPPLEMENTATION ON PSYCHOSOMATIC DISORDERS IN POSTMENOPAUSAL WOMEN

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Different psychosomatic disorders are observed in postmenopausal women. The decrease of estrogen production is believed to be the main cause of their severity. It is nowadays evident that the decreased melatonin release in women at this age who suffer from postmenopausal disorders might also contribute to the severity of the symptoms. The aim of the study was to evaluate the effect of melatonin supplementation on female hormones release and the alteration in climacteric symptoms. The study included 60 postmenopausal women, aged 51 – 64 years, who were randomly allotted into two equal groups. Group I was recommended placebo (2 × 1 tablet) and Group II - melatonin (3 mg in the morning and 5 mg at bedtime) for 12 months. Serum levels of 17β-estradiol, follicle-stimulating hormone (FSH), melatonin and urinary 6-sulfatoxymelatonin (aMT6s) excretion as well as Kupperman Index (KI) and body mass index (BMI) were determined before the start and at 12 months after placebo or melatonin administration. In Group I only the value of KI slightly decreased (28.4 ± 2.9 versus 25.6 ± 3.8 points, P = 0,0619). In Group II - KI decreased from 29.1 ± 2.9 to 19.7 ± 3.1 points ($P < 0.001$) and BMI from 30.9 ± 2.9 to 28.1 ± 2.3 kg/m² ($P < 0.05$). Melatonin supplementation failed to change significantly the serum concentration of female reproductive hormones 17β-estradiol and FSH. We conclude that melatonin supplementation therapy exerts a positive effect on psychosomatic symptoms in postmenopausal women and can be recommended as the useful adjuvant therapeutic option in treatment of these disorders.

Key words: *melatonin, estradiol, follicle-stimulating hormone, psychosomatic disorders, 6-sulfatoxymelatonin, menopause, climacteric disorders*

INTRODUCTION

Different psychosomatic disorders are observed in postmenopausal women. The severity of climacteric symptoms such as hot flushes, excessive sweating, sleep disorders, irritability, depressive mood, fatigue, headache, vertigo, myalgia, palpitation and paresthesia can be assessed using the Kupperman Index (1). This index as well as Menopause Rating Scale (2) do not take into account eating disorders which frequently may cause the metabolic syndrome and obesity in these patients. However, the nutritional disturbances constitute an important problem in postmenopausal women. The decrease of estrogen production is believed to be the major cause of excessive appetite in postmenopausal women (3-6). On the other hand, the treatment with estrogens has been shown to impair gastric motility (7, 8) and suppress gastric secretion (9). Thus, it is reasonable to introduce the conventional female steroid hormone replacement therapy or alternative hormones in the prevention of obesity in the postmenopausal women (10). Unfortunately, the use of female hormones has limitations due to their serious side effects including the activation of blood clotting factors, venous embolism, acute coronary syndromes, stroke or even cancer (11-15). Furthermore, long-term application of estrogens and/or hormones with progestational activity can lead to increase body weight gain (16). There is an ongoing search for new ways of treating of eating disorders, especially in postmenopausal women. However, the attention has recently been paid to the involvement of melatonin in the process of nutrition. Beneficial effects of melatonin on the carbohydrate and lipid metabolism after its administration have been observed in animals (17-19) as well as in humans (20, 21). Melatonin has been well recognized as hormonal factor improving the quality of sleep in humans (22, 23). Clinical studies have demonstrated also a correlation between low level of melatonin and obesity (24, 25) and suggested its use for therapeutic purposes (26, 27). The administration of melatonin and its analogues were shown to exert antidepressant activity (28, 29). The secretion of melatonin is suppressed in postmenopausal women which can result in development of emotional and eating disorders (30-34). All the above facts indicate the necessity of the use of this indoleamine in the complex therapy of climacteric disorders in women.

The rationale behind the therapy with melatonin of postmenopausal women was justified by our and other previous studies proving the good tolerability and safety of melatonin in human subjects (34-36). For instance, Andersen *et al.* (37) have observed that melatonin administered intravenously at the dose

of 10 mg or 100 mg to 12 healthy volunteers, reached its peak serum concentrations within the time shorter than 50 minutes with the complete absence of any side effects. Moreover, the oral administration of melatonin to the volunteers resulted in the rise in serum melatonin already within the time less than one hour (38). Similar results of the melatonin pharmacokinetics were proved the usefulness of this indoleamine applied in oral dose of 0.4 mg and 4 mg in older adults (39) and the larger dose of 80 mg of melatonin in young male volunteers (40). In contrast, a single administration of melatonin to human subjects raised its level for only a few hours. We have also reported that melatonin administered in human studies at the dose of 3 mg in either daily hours or bedtime failed to cause drowsiness and did not limit nor impair the patient psychophysical activities (36). This justifies the usefulness of melatonin administered in splitted doses presenting a full advantage and the safety, particularly, in patients who suffer from metabolic disorders.

Based on the studies with an oral administration of melatonin published in evidence based medicine, we aimed to evaluate the effect of long-term melatonin supplementation on psychosomatic disorders in postmenopausal women.

MATERIAL AND METHODS

Ethics

The study was performed in accordance with the Declaration of Helsinki and with the principles of Good Clinical Practice. Written consent was obtained from each subject enrolled into the study and the study protocol was approved by the Bioethics Committee of the Medical University in Lodz (RNN/596/11/KB).

Patients

The study included 60 women, aged 51 – 64 years, 4 – 10 years after the last menstrual period, with average and severe climacteric symptoms and without steroid hormonal replacement therapy. Patients were recruited from two units of Medical University in Lodz, Poland, the Menopause Outpatient Clinic and from Gastroenterological Outpatient Clinic. This clinical research was performed in the years 2012 – 2016 at the Department of Clinical Nutrition and Gastroenterological Diagnostics and at the Department of Gastroenterology of the Medical University in Lodz.

The patients exclusion criteria from these studies were: the metabolic, mental or organic diseases, particularly of the liver and kidney, and other diseases which had required the pharmacotherapy.

Study design and procedures

The intensity of psychosomatic disorders was estimated by Kupperman Index (KI) by adding up the score for the individual symptoms after multiplying from 0 to 3 average of its severity; the points between 15 and 20 being interpreted as mild climacteric syndrome, the points between 21 and 35 as average severity symptoms, and the points more than 35, as severe psychosomatic disorders (1).

All patients recruited for this study underwent the routine laboratory tests including blood cells count, serum levels of urea, creatinine, glucose, glycosylated hemoglobin, cholesterol, triglycerides, amylase, lipase, bilirubin, alanine aminotransferase and aspartate aminotransferase.

Serum level of 17β-estradiol was determined by immunoassay (antibodies Ortho-Clinical Diagnostics, Inc., Raritan, NY, USA), and follicle-stimulating hormone (the specific antibodies purchased from Vitros Product Inc., Rochester NY, USA).

Serum melatonin level and urinary concentration of 6-sulfatoxymelatonin were measured by the ELISA method utilizing IBL antibodies (RE-54021 and RE-54031, IBL International GmbH, Hamburg, Germany) and Expert 99 MicroWin 2000 Reader (GmbH Labtech, Offenburg, Germany).

Seven days prior to the evaluations the patients were on the same diet. On the day of the study initiation, all patients were administered the same liquid diet (Nutridrink-Nutritia) in the amount of 3 × 400 ml, containing 18.9 g carbohydrate, 6.0 g protein, 5.8 g lipid/100 ml, of the total caloric value of 1800 kcal, and 1500 ml of isotonic water.

Blood samples of 15 ml were drawn from the antecubital vein at 9:00 a.m. and then the samples were frozen at minus 70ºC. Blood samples were collected before melatonin administration and 48 has after completion of this supplementation. On the same day, the 24-hour urine collection was performed and the samples were kept at 4ºC. Next morning, the volume of urine was measured and the samples were frozen at minus 70ºC.

Essentially, The patients were randomly divided into two equal groups, and double blind was on medications. Group I (n = 30) was administered placebo (2 × 1 tablet) while the Group II (n = 30) received melatonin at a dose of 3 mgat the morning and of 5 mg at the bedtime, for the time period of 12 months. For entire length of the time, the patients consumed the same balanced diet of total caloric value of 1600 – 2200 kcal depending on the nature of professional work. As principle, all patients were advised a balanced diet composed of 50-55% carbohydrates, 15-25% protein, 20-25% fat. Every month, the patients were controlled by a physician and the dietitian.

Follow-up clinical examinations of these patients were performed after 2, 4, 6, 8, 10 and 12 months and laboratory tests (including 17β-estradiol, FSH, melatonin, and aMT6s) were performed after 12 months of placebo or melatonin supplementation.

Statistical analysis

Data are expressed as means ± SD. Student's t-test was used to compare the means for normal distribution or Kruskal-Wallis and Mann-Whitney nonparametric test to compare the results of two different parameters. The linear correlation coefficient r was used to determine the relationship between the value of urinary aMT6s excretion and severity of clinical symptoms. The differences between the results were regarded as statistically significant when a P value was < 0.05. Calculations were made using Statistica 9.1(StatSoft, INC USA) and MS Exel@007 (Microsoft Co., USA).

RESULTS

In group I and group II patients demonstrated similar initial levels of body mass index (BMI), Kupperman Index (KI) as well as the diagnostic parameters of liver and kidney function (*Table 1*).

Frequency of occurrence of psychosomatic symptoms also was no statistically different in both groups (*Table 2*).

After 12-months of placebo administration (Group I) as well as melatonin supplementation (Group II) no statistically significant changes were notified in biochemical parameters (*Table 3*).

After placebo administration (group I) the value of Kupperman Index was significantly decreased from 28.4 ± 2.9 points to 25.3 ± 2.8 points ($P > 0.05$), while after melatonin supplementation (group II) this index has significantly decreased

from 29.1 ± 2.9 to 19.7 ± 3.1 points ($P < 0.001$, *Fig. 1*). The difference of results between I and II group reached a statistical significance at $P < 0.01$. After melatonin ingestion, the majority of frequently observed symptoms in postmenopausal women such as sleep disorders, heart palpitation, sweating and headaches completely disappeared or were significantly decreased in 93.3%, 90.0%, 80.0% and 76.6%, respectively, in patients subjected to the treatment with melatonin.

The value of BMI after placebo administration (group I) was not significantly changed, while in patients receiving melatonin

Table 1. General characteristic of the age and biochemical parameters analyzed in postmenopausal women enrolled in the study; body mass index (BMI), Kupperman Index (KI), bilirubin, alanine aminotransferase (ALT), asparagine aminotransferase (AST), glomerular filtration rate (GFR).

Feature	**Group I** (r = 30)	**Group II** (r = 30)
Age (years)	56.2 ± 4.1	57.3 ± 6.4
BMI (kg/m^2)	30.7 ± 3.8	30.9 ± 3.5
KI (points)	28.5 ± 2.9	29.1 ± 2.8
Bilirubin (μmol/L)	0.9 ± 0.2	0.8 ± 0.3
ALT (IU/L)	26.2 ± 4.3	24.9 ± 6.1
AST (IU/L)	25.1 ± 3.8	23.8 ± 5.9
GFR (ml/min)	98.7 ± 12.1	101.6 ± 11.9

Frequency of occurrence of psychosomatic symptoms also was not statistically different in both groups (*Table 2*).

Table 2. Frequency of occurrence of psychosomatic symptoms in the examined patients.

Symptoms	**Group I** (r = 30) Number of patients (%)	**Group II** (r = 30) Number of patients (%)
Hot flashes	18 (60.0)	17 (56.6)
Sweating	27 (90.0)	29 (96.6)
Sleep disorders	29 (96.6)	28 (93.3)
Irritability	28 (93.3)	27 (90.0)
Depressed mood	24 (80.0)	26 (86.6)
Dizziness	11 (36.6)	14 (46.6)
Weakness	19 (63.3)	23 (76.6)
Joint pains	16 (53.3)	14 (46.6)
Headaches	18 (60.0)	17 (56.6)
Heart palpitations	21 (70.0)	23 (76.6)
Paresthesia	9 (30.0)	11 (36.6)

Table 3. Serum levels of 17β-estradiol, follicle-stimulating hormone (FSH) and melatonin, and urinary 6-sulfatoxymelatonin (a $MT6_s$) excretion before (a) and after (b) placebo (group I) or melatonin (group II) administration; differences inside of the groups and between the groups were not statistically significant.

	Group I		**Group II**	
Feature	**a**	**b**	**a**	**b**
Estradiol (pg/ml)	18.2 ± 5.1	17.2 ± 4.8	17.5 ± 5.9	17.0 ± 5.6
FSH (IU/ml)	87.5 ± 12.1	92.8 ± 11.2	84.5 ± 15.9	88.4 ± 9.9
Melatonin (pg/ml)	6.9 ± 1.3	6.5 ± 1.3	7.1 ± 1.3	7.2 ± 1.2
$aMT6_s$ (μg/24h)	9.16 ± 1.6	8.6 ± 1.4	9.2 ± 1.7	9.6 ± 1.5

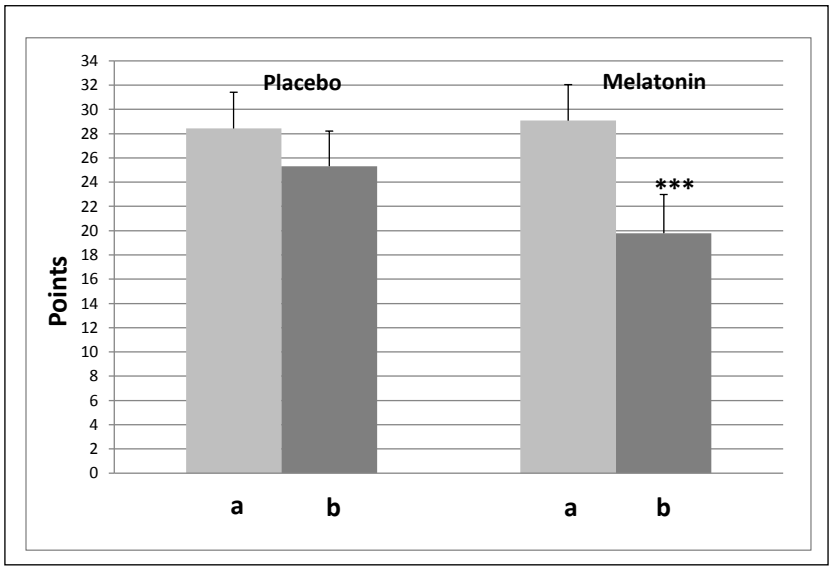

Fig. 1. The value of Kupperman Index (points) before (a) and after (b) placebo administration or melatonin supplementation in postmenopausal women, *** $P < 0.001$; Statistically significant difference of results between placebo group and melatonin group at $P < 0.01$.

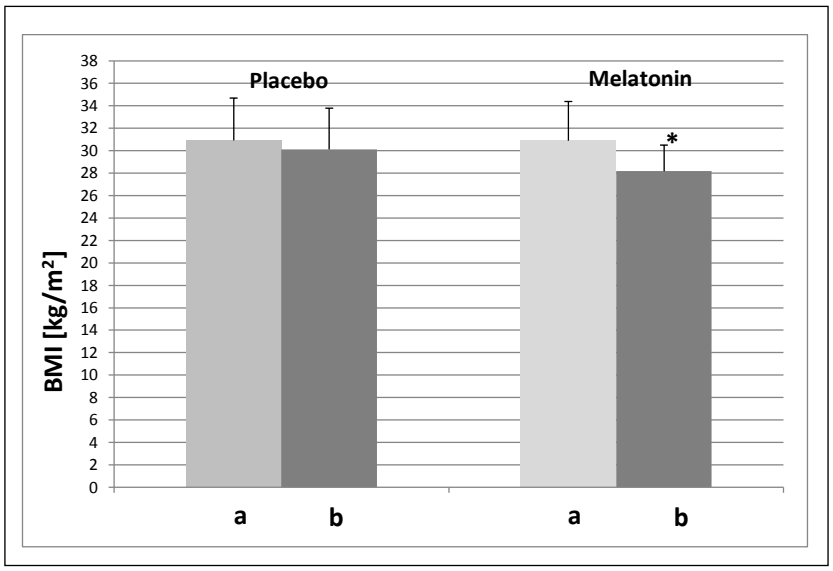

Fig. 2. The value of body mass index (BMI) before (a) after(b) placebo administration or melatonin supplementation in postmenopausal women, *$P < 0.05$; difference of results between placebo group and melatonin group was statistically significant; $P < 0.05$.

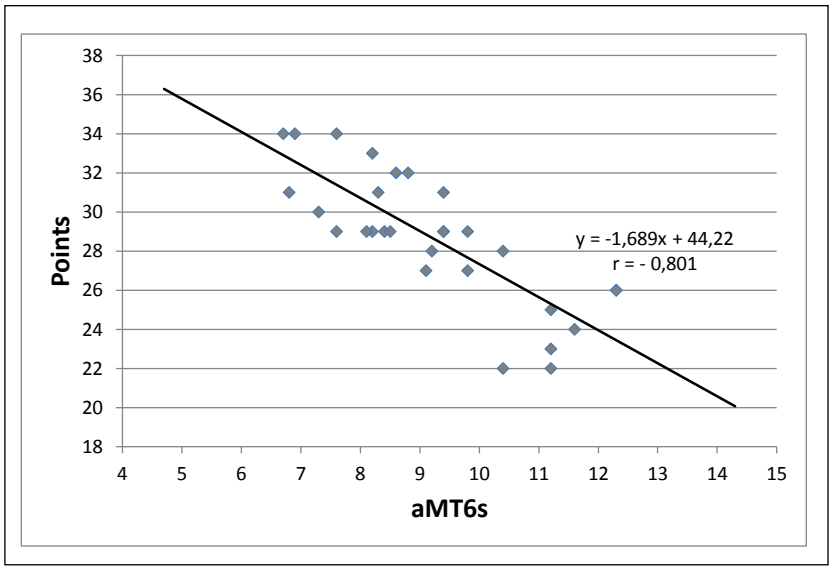

Fig. 3. Correlation between urinary 6-sulfatoxymelatonin excretion ($aMT6_s$, mg/24 h) and the value of Kupperman Index (points) before melatonin supplementation in postmenopausal women; $P < 0.001$.

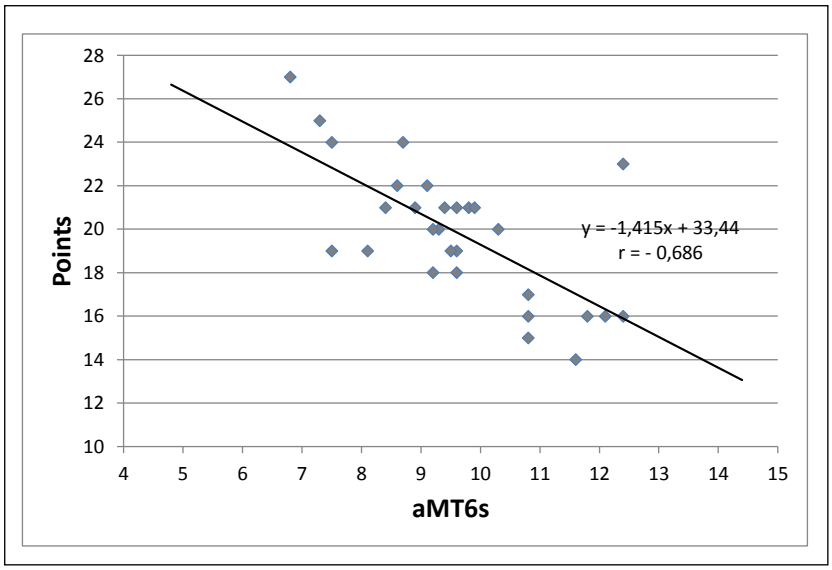

Fig. 4. Correlation between urinary 6-sulfatoxymelatonin excretion ($aMT6_s$, mg/24 h) and the value of KI (points) after melatonin supplementation in postmenopausal women; $P < 0.001$.

suplementation (group II), it significantly decreased from 30.8 ± 3.4 kg/m^2 to 28.1 ± 2.3 kg/m^2 ($P < 0.05$, *Fig. 2)*.

In Group II, the negative correlation between the value of urinary 6-sulfatoxymelatonin excretion and KI has been observed before as well as after melatonin supplementation ($r = –0.801$ and $r = –0.686$, respectively) ($P < 0.001$, $P < 0.001$, *Fig. 3*, *Fig. 4*).

Melatonin was well tolerated, only three women (about 10% of total number of patients) reported the increased fatigue in the morning at the first week of the treatment but without the need of discontinuation of the therapy or the necessity of the reduction of the dose of melatonin.

DISCUSSION

Melatonin is a biogenic amine of pleiotropic and still not completely recognized properties, which has been shown to exhibit the antioxidant, the anti-inflammatory and the immunomodulatory activities (41, 42). The pineal gland is considered as the major source of endogenous melatonin but this indoleamine can also be produced and released from multiple extrapineal tissues, including the cells of gastrointestinal tract and the reproductive organs (42). The alterations in secretion of melatonin have been observed in many pathological conditions (43-45) and during aging process, particularly in postmenopausal women (30, 32-34). Interestingly, melatonin synthesis is reduced in these patients not only in pineal gland but also in peripheral organs including those in gastrointestinal tract. That is why we have designed our present study in order to provide melatonin supplementation at night and during daily hours. It is strongly emphasized that melatonin applied in a dose of 3 mg at daily hours did not induce neither the patients drowsiness nor the psychophysical activity of subjects enrolled for this study (34, 36, 46, 47).

The correlation between melatonin and the secretion of female hormones has not conclusively been established (48-50). For instance, Schernhammer *et al.* (31) have indicated significantly lower urinary aMT6s excretion in healthy women at age of 49 years and older, compared to women at younger age averaging 39 years. Bodis *et al.* (51) have demonstrated that melatonin decreased secretion of female reproductive hormones, estradiol and progesterone. In turn, Luboshitzky *et al.* (52) reported that 4-month treatment with estradiol reduced urinary 6-sulfatoxymelatonin (aMT6s) excretion. Gruber *et al.* (53) have observed a negative correlation between serum estradiol level and urinary aMT6s excretion. Similarly, Okatani *et al.* (54) detected a negative correlation between the night peak of melatonin secretion and the level of estradiol. In another study, Toffol *et al.* (55) found that the secretion of estrogens and melatonin is significantly inhibited in postmenopausal women. In study by Vakkuri *et al.* (56) a negative correlation between the level of FSH and urinary melatonin excretion in postmenopausal women at night has been observed. Furthermore, they suggested that reduced melatonin secretion could be an important biomarker which may initiate the menopause (56).

Previously, we have reported (57) that there is no significant correlation between the serum level of melatonin, estradiol and FSH. Furthermore, we have found a negative correlation between aMT6s excretion and body mass index (57). Moreover, the the 6-month administration of melatonin in the daily dose of 5 mg significantly reduced the body weight (46).

The results of the present study are corroborative with the above observations and further extend the notion that melatonin exerted a beneficial effect and improved the majority of psychosomatic symptoms regardless of the deficiency of female gonadal steroid hormones in postmenopausal women. Simultaneously, melatonin failed to alter the concentration of female hormones suggesting that melatonin-induced improvement of climacteric disorders involves a different mechanism unrelated to direct effect of this indoleamine on the secretion of female gonadal hormones. This seems to justify the implementation of melatonin in the therapy of postmenopausal disorders. However, we are aware that the final outcome of clinical studies depend on choice of patients, inclusion and exclusion criteria and good compliance.

One of our major goal in this present study was to determine the efficacy of the daily dose of melatonin in addition to the bedtime dose of this indoleamine, the subject of controversy in the literature. Yet an optimal therapeutic dose which should be administered in different diseases is under the debate in literature. Harpsoe *et al.* (47) reviewed 392 literature records and found out that the applied daily doses were from 0.3 mg to 100 mg of this indoleamine. Similar range of melatonin dosages (from 0.1 to 50 mg/daily of melatonin) were presented by Vural *et al.* (58). Melatonin is sensitive marker for rhythmicity involving neurons at the central nervous system and the endogenous level of this indoleamine plays an important role in neuroprotection. This indoleamine has been shown to improve the neuronal survival and attenuate the oxidative stress,

inflammation and apoptosis (59). The alterations in both human circadian activity of hypothalamic-pituitary axis and endogenous melatonin secretion have been linked with the cognitive impairments, poor sleep quality and neurodegeneration (60). For instance the disruption of circadian sleep-wake cycle may predispose to neurodegeneration and the development of cognitive symptoms associated with Alzheimer disease (60). The formation of the pathogenic amyloid-β peptide in the brain is regulated by the sleep-wake cycle also essential for cardiovascular system and protection against inflammatory states. With this respect, the improvement of sleep quality by melatonin can reduce the cardiovascular risk, inflammation and amyloid-β accumulation slowing down the process of neurodegeneration (60). Thus, the supplementation of exogenous melatonin seems to be reasonable in patients with neurodegenerative diseases including Huntington disease (HD) who also suffer from disruptions of circadian rhythm and poor sleep quality (61). The patterns of circadian changes in HD patients shows similarities with elderly individuals. Moreover, the lowered blood melatonin concentration was associated with acute ischemic stroke of the extra-hypothalamic brain structures (61). In another human study in patients with multiple sclerosis (MS), the supplementation with melatonin applied during the day-time in a dose of 5 mg markedly lowered the plasma lipid hydroxyperoxides considered as biomarkers of the chronic fatigue syndrome commonly observed in these patients (61). This beneficial effect of melatonin in MS subjects was explained by the antioxidative properties of this indoleamine either by indirect stimulation of antioxidative enzymes, or direct inactivation of reactive oxidant species (61). The dose of 3 mg and 5 mg/daily were effectively used in the treatment of diseases of alimentary tract and inflammatory disorders such IBD (62-64) as well as climacteric disorders in women (65). In patients with nonalcoholic hepatitis melatonin applied twice daily of dose 5 mg was effective and safe (21, 66). Goyal *et al.* (67) used daily treatment with 8 mg of melatonin as an effective treatment of the metabolic syndrome. In another studies, Cardinali and Haderland (68) have suggested the dose of melatonin ranging from 50 mg up to 100 mg daily for the management of inflammatory and metabolic disorders. We have selected the daily dose of 3 mg at the morning and 5 mg at the night time and we did not observe any complaints from the patients site such as drowsiness and/or impairment of mental or physical activities in postmenopausal women.

Good tolerability and safety of melatonin has been confirmed by its pharmacokinetic properties. The administration of a single dose of melatonin raised its level for a few hours (57). Again, this seems to justify the rationale for administration of melatonin in divided doses (3 mg + 5 mg) in order to receive a clinical benefit of this indoleamine in women with postmenopausal disorders.

Study limitations

Our findings indicate that melatonin adminstered b.i.d might compensate for the deficit of this hormone without adverse influence on patients psychosomatic activity. Nevertheless, we are aware that melatonin dosages should be chosen based on to the patient age, severity of symptoms and concomitant diseases. The individual sleep complaints was not recorded by postmenopausal women but in fact, these symptoms were not assessed in detail, in our study. Therefore, we are fully aware on limitations of our study because we could not assess the sleep complaints to check how this treatment affected the symptoms by individual patients and finally, how it might impact the overall KI in points. A weaker correlation between KI and aMT6 concentration in subjects supplemented with melatonin suggests the existence of relationship between melatonin production and the severity of climacteric symptoms. The hypothesis cannot be ruled out that other psychosomatic symptoms in these patients are relieved besides the improvement of sleep disorders. Since separate examination of 11 menopausal symptoms tested in this trial including sleep quality was outside of the scope of present study, we certainly would address this issue in our future studies. Thus, the results of our present study indicate that melatonin supplementation improve not only sleep disorders but also other climacteric symptoms and we conclude that melatonin can be safely and permanently used in complex treatment of psychosomatic disorders in postmenopausal women.

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Conflicts of interest: Non declared.

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