Endokrynologia Polska
DOI: 10.5603/EP2016.0012
Tom/Volume 67; Numer/Number 3/2016
ISSN 0423–104X

Serotonin and melatonin secretion in postmenopausal women with eating disorders

Wydzielanie serotoniny i melatoniny u kobiet po menopauzie z zaburzeniami odżywiania

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Abstract

Introduction: Postmenopausal women manifest emotional disorders associated with an increase in appetite.
The aim of the study was to assess the serotonin and melatonin secretion and metabolism in postmenopausal women in relation to eating disorders.

Material and methods: Sixty postmenopausal women and 30 women without hormonal disturbances were enrolled into the study and divided into three groups: group I (control) – women without menstrual disorders, group II — postmenopausal women without appetite disorders and change in body weight, and group III — postmenopausal women with increased appetite and weight gain. Serum melatonin, serotonin, urinary 6-sulfatoxymelatonin (aMT6s), and 5-hydroxyindoleacetic acid (5-HIAA) excretion were measured.

Results: Serum serotonin and melatonin levels in groups II and III were lower compared to group I. Urinary 5-HIAA and aMT6s excretion was lower in overweight women. In group III the correlation between the serum level of serotonin, melatonin, and BMI was negative; a high statistical significance was found between BMI and urinary aMT6s excretion.

Conclusions: Melatonin supplementation and use of drugs modulating the serotonin homeostasis together with female hormones have a beneficial effect in complex treatment of disorders of eating in postmenopausal women. **(Endokrynol Pol 2016; 67 (3): 299–304)**

Key words: *serotonin; melatonin; postmenopausal women; disorders of eating*

Streszczenie

Wstęp: U kobiet po menopauzie często spotykamy zaburzenia emocjonalne oraz wzrost apetytu.
Celem badań była ocena wydzielania i metabolizmu serotoniny i melatoniny u kobiet w okresie pomenopauzalnym z zaburzeniami odżywiania.

Materiały i metody: Badanie przeprowadzono w grupie 60 kobiet po menopauzie i 30 przed menopauzą (grupa kontrolna). Wśród kobiet po menopauzie wyodrębniono dwie podgrupy — kobiety ze wzrostem apetytu i masy ciała oraz bez nich. Procedury diagnostyczne obejmowały ocenę stanu odżywienia, określenie stężenia melatoniny i serotoniny w surowicy krwi oraz ich matabolitów — siarczanu 6-metoksymelatoniny (aMT6s) oraz kwasu 5-hydroksy-indolooctowego (5-HIAA) w moczu.

Wyniki: Stwierdzono, że stężenie serotoniny i melatoniny w surowicy krwi w grupach pacjentek po menopauzie było niższe niż u kobiet przed menopauzą. Wydalenie metabolitów serotoniny i melatoniny z moczem było najniższe u otyłych kobiet po menopauzie. U tych pacjentek stwierdzono ujemną korelację między stężeniem serotoniny w surowicy krwi, stężeniem melatoniny oraz BMI; a także istotną statystycznie zależność pomiędzy wydalaniem aMT6s z moczem a BMI.

Wnioski: U kobiet w okresie pomenopauzalnym wydzielanie serotoniny i melatoniny jest zmniejszone, co należy uwzględnić w kompleksowej terapii i prewencji zaburzeń łaknienia i odżywienia. **(Endokrynol Pol 2016; 67 (3): 299–304)**

Słowa kluczowe: *serotonina; melatonina; kobiety po menopauzie; zaburzenia odżywiania*

Introduction

Postmenopausal women often manifest emotional disorders associated with weakness or increase in appetite [1, 2]. These changes may lead to reduction in body weight or more frequently to obesity [3–5].

Perimenopausal depression and obesity are important health problems [6]. The temporal relationship of mental disorders and appetite does not raise doubts, but common pathogenetic factors are still searched for. Among them, not only the decrease of the level of oestrogen is taken into account but also the disruption

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of homeostasis of other hormones and neuromodulators [7]. Alterations in serotonergic neuronal function in the central nervous system are commonly considered to be one of the causes of depression [8]. Serotonin also plays an important role in the regulation of appetite [9]. For these reasons drugs modulating serotonin reuptake have found application in the treatment of both depression and obesity [10, 11].

The role of melatonin is less known in this aspect. First research studies revealed that secretion of melatonin was higher in women with both anorexia nervosa and bulimia than in the control groups [12]. However, experimental studies demonstrated increased insulin resistance, development of glucose intolerance, and weight gain in pinealectomised rats [13]. It was also shown that melatonin supplementation in animals with induced obesity had a positive effect on the secretion of leptin and adiponectin and on the level of glucose, cholesterol, and triglycerides [14, 15]. Melatonin and its analogues have been introduced into the treatment of mood disorders and hyperalimentation in humans [16].

Serotonin is the substrate in the synthesis of melatonin. Its secretion is subject to similar processes of circadian and seasonal variations, and it also shows correlation with the age of the respondents [17] and the secretory activity of the gonads, but opinions on this subject are not consistent [18] and it requires further research.

The aim of our study was to assess serotonin and melatonin secretion and metabolism in postmenopausal women in relation to eating disorders.

Material and methods

Sixty women were enrolled into the study, a minimum of three years after their menopause, aged 53–63 years and 30 women in whom clinical examinations excluded hormonal disturbances and any diseases.

Three groups were distinguished:

— Group I (control, n = 30) — healthy women without menstrual disorders
— Group II (n = 30) — postmenopausal women without appetite disorders and change in body weight
— Group III (n = 30) — postmenopausal women experiencing, at that time, increased appetite by minimum 3 points in a 10-point VAS scale and weight gain by minimum 10% of the due weight.

The clinical examination determined, among other things, the level of anxiety using the Hamilton Anxiety Rating Scale (HARS) and the severity of depression using the Beck Depression Inventory (BDI), and imaging examinations were performed (endoscopy, USG, CT) as well as the following laboratory tests: blood cell count, CRP, bilirubin, alanine (ALT) and aspartate (AST) aminotransferase, gamma-glutamyl transpeptidase (GGT), amylase, lipase, urea, creatinine, cholesterol, triglycerides, and glycated haemoglobin.

17-β-oestradiol concentration in serum was measured by the ELISA test (antibodies Ortho — Clinical Diagnostic) and follicle-stimulating hormone (FSH) concentration in serum was also measured by Elisa test (antibodies Vitros Products).

Exclusion criteria: other organic and metabolic diseases, past surgeries, severe anxiety (over 24 points in HARS) and/or depression (more than 15 points in BDI) according to the German criteria, *Helicobacter pylori* infection, the use of hormone replacement therapy, or other pharmacotherapy.

Seven days prior to the evaluations, all medications were withdrawn and the patients remained on the same diet containing tryptophan-rich products. On the day of the study the patients were administered the same liquid diet (Nutridrink-Nutricia) in the amount of 3 × × 400 ml, containing 18.9 g carbohydrate, 6.0 g protein, 5.8 g lipid/100 mL, of total caloric value 1800 kcal, and 1500 ml of isotonic still water. Blood samples were drawn from the antecubital vein at 08:00 and serum was frozen at –70°C. On the same day, the 24-hour urine collection was performed and the samples were kept at 4°C. At the end of 24-hour collection, the volume of urine was measured and the samples were frozen at –70°C. Serum melatonin and urinary 6-sulfatoxymelatonin (aMT6s) concentration were measured by the ELISA method applying IBL antibodies (RE-54021 and RE-54031, Nordic Immunological Laboratories, Tilburg, Holland) and Expert 99 MicroWin 2000 Reader (BMG Labtech, Offenburg, Germany)

Serum serotonin and urinary 5-hydroxyindoleacetic acid (5-HIAA) were measured using the ELISA method applying an IBL kit (RE 59121 and RE 59131).

Statistical analysis

The nonparametric Kruskal-Wallis test was used in the statistical analysis to compare serotonin and melatonin levels and urinary 5-HIAA and aMT6s excretion. The Mann-Whitney test was applied for median comparison. The correlation between the above parameters and the body mass index was estimated with the Pearson's correlation coefficient and linear regression equation. STATISTICA 9.1 software (AxAP106E735914191-F license) was used for the calculations.

Results

Fasting serum serotonin level differed in the group of postmenopausal women compared to the control group and it was in group I — 142.3 ± 38.1 ng/mL, in group II — 129.6 ± 23.7 ng/mL ($p < 0.05$), in group III — 117.7 ± 27.9 ng/mL ($p < 0.01$) (Table I, Fig. 1).

Table I. *General characteristics of women enrolled in the study*

Tabela I. *Charakterystyka ogólna kobiet uczestniczących w badaniu*

Feature	Group I	Group II	Group III
Age (years)	32,4 ± 3,1	57,2 ± 1,8	56,9 ± 4,0
BMI [kg/m^2]	21,7 ± 1,7	21,6 ± 1,8	30,5 ± 3,6
HARS (points)	10,5 ± 6,1	19,2 ± 3,4	18,4 ± 2,9
BDI (points)	6,6 ± 2,9	16,2 ± 2,4	17,1 ± 2,0
17-β-oestradiol [pg/mL]	51,0 ± 16,3	16,8 ± 4,9	18,3 ± 5,2
FSH [mIU/mL]	14,5 ± 5,4	80,3 ± 19,0	76,5 ± 17,6
GFR [ml/min]	104,8 ± 10,2	98,8 ± 6,9	96,5 ± 12,3

BMI — body mass index; HARS — Hamilton Anxiety Rating Scale; BDI — Beck Depression Inventory; FSH — follicle stimulating hormone; GFR — glomerular filtration rate

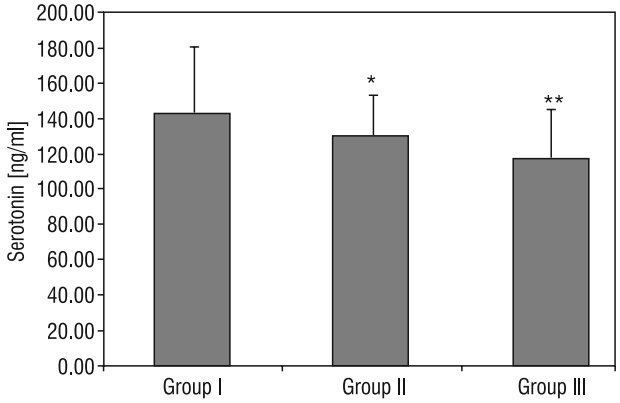

Figure 1. *Serum levels of serotonin in healthy women (group I), postmenopausal women without disorders of eating (group II), and with overweight (group III);* $\overline{x}$ *± SD, *p < 0.05, **p < 0.01*

Rycina 1. *Stężenie serotoniny w surowicy zdrowych kobiet (grupa I), u kobiet po menopauzie bez zaburzeń odżywiania (grupa II) oraz kobiet z nadwagą (grupa III);* $\overline{x}$ *± SD, *p < 0,05, **p < 0,01*

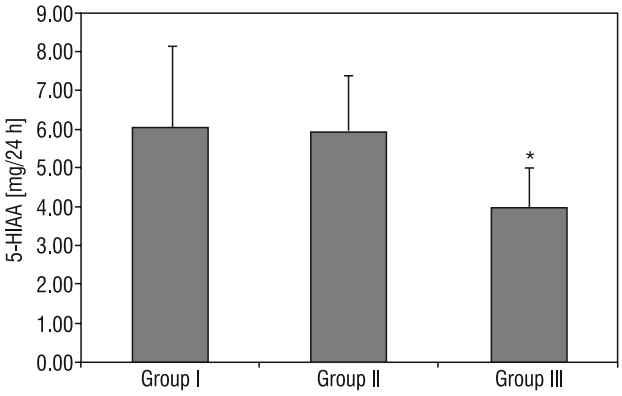

Figure 2. *Urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion in healthy women (group I), postmenopausal women without disorders of eating (group II), and with overweight (group III);* $\overline{x}$ *± SD, *p < 0.05*

Rycina 2. *Wydalanie kwasu 5-hydroksyindolooctowego (5-HIAA) z moczem u zdrowych kobiet (grupa I), u kobiet po menopauzie, bez zaburzeń jedzenia (grupa II) oraz z nadwagą (grupa III);* $\overline{x}$ *± SD, *p < 0,05*

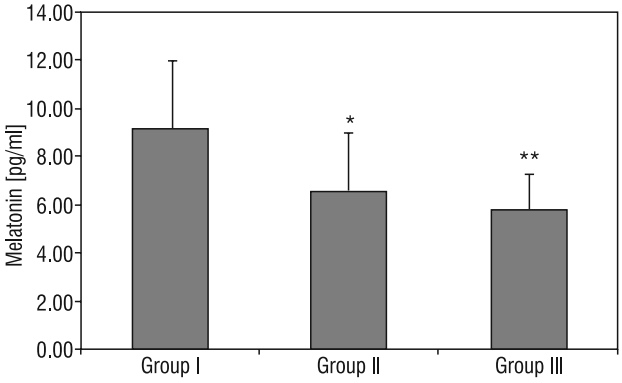

Figure 3. *Serum levels of melatonin in healthy women (group I), postmenopausal women without disorders of eating (group II), and with overweight (group III);*
$\overline{x}$ *± SD, *p < 0.05; **p < 0.01*

Rycina 3. *Stężenia melatoniny u zdrowych kobiet (grupa I), u kobiet po menopauzie bez zaburzeń jedzenia (grupa II) oraz z nadwagą (grupa III);* $\overline{x}$ *± SD, *p < 0,05; **p < 0,01*

However, urinary 5-HIAA excretion was lower only in overweight women, and it was: in the control group 6.05 ± 2.11 mg/24 hours and in group III — 3.99 ± 1.04 mg/24 h ($p < 0.05$) (Fig. 2).

Serum melatonin level was: in group I — 9.13 ± 2.87 pg/mL, in group II — 6.55 ± 2.47 pg/mL ($p < 0.05$), and in group III — 5.75 ± 1.53 pg/mL ($p < 0.01$) (Fig. 3).

Similar differences were observed in relation to urinary aMT6s excretion — respectively –11.32 ± 4.42 μg/24 hours, 8.84 ± 2.76 μg/24 hours ($p < 0.01$), 7.90 ± ± 2.97 μg/24 hours ($p < 0.001$) (Fig. 4).

In the control group, a weak, statistically insignificant negative correlation was noted between the above-mentioned parameters and body mass index (Table II).

In the group of postmenopausal women with normal body weight, a similar negative correlation was detected, but it was of significance only in relation to the urinary aMT6s excretion ($r = –0.5662$, $p < 0.05$) (Table II, Fig. 5).

In group III (women with overweight), the correlation between the serum level of serotonin and melatonin and BMI was also negative, and it was, respectively: $r = –0.5241$ and $r = –0.4906$ (Table II). However, a high statistical significance ($r = –0.87632$)

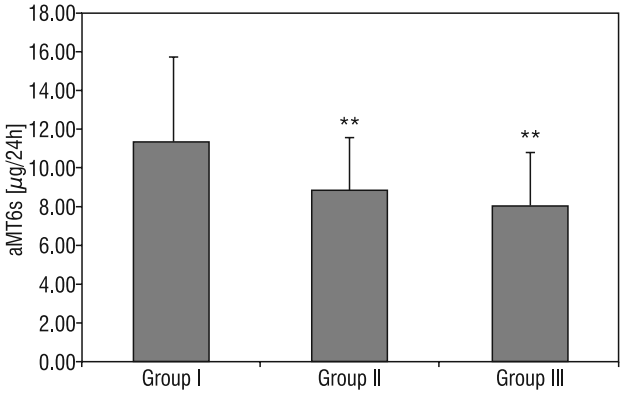

Figure 4. *Urinary 6-sulfatoxymelatonin (aMT6s) excretion in healthy women (group I), postmenopausal women without disorders of eating (group II), and with overweight (group III);* $\overline{x}$ *± SD, **p < 0.01*

Rycina 4. *Wydalanie 6-sulfatoksymelatoniny (aMT6s) z moczem u zdrowych kobiet (grupa I), u kobiet po menopauzie bez zaburzeń jedzenia (grupa II) oraz u kobiet po menopauzie z nadwagą (grupa III);* $\overline{x}$ *± SD, **p < 0,01*

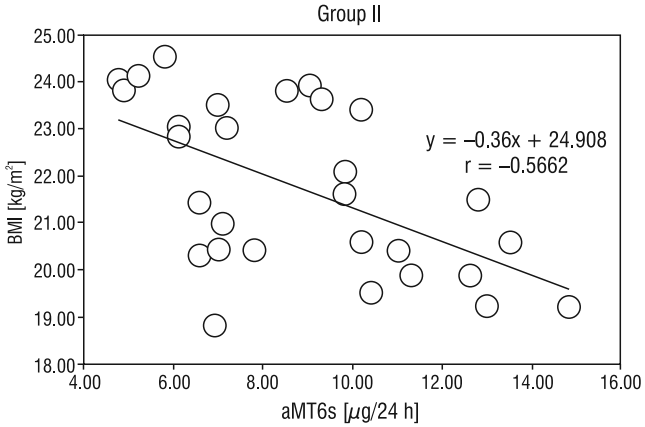

Figure 5. *Correlation between urinary 6-sulfatoxymelatonin (aMT6s) excretion and body mass index (BMI) in postmenopausal women without disorders of eating (group II);* $\overline{x}$ *± SD, *p < 0.05*

Rycina 5. *Korelacja między wydalaniem 6-sulfatoksymelatoniny (aMT6s) z moczem a wskaźnikiem masy ciała (BMI) u kobiet po menopauzie bez zaburzeń odżywiania (grupa II;* $\overline{x}$ *± SD, *p < 0,05*

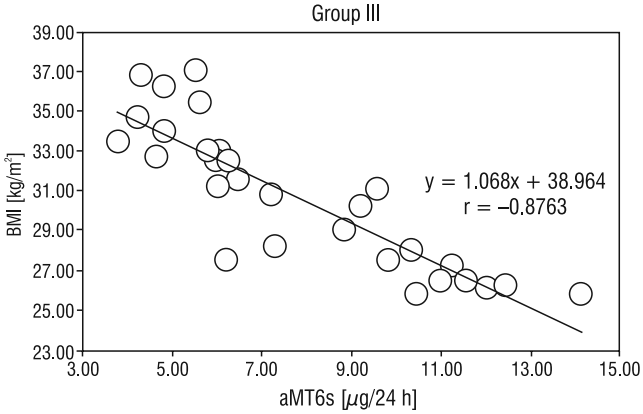

Figure 6. *Correlation between urinary 6-sulfatoxymelatonin (aMT6s) excretion and body mass index (BMI) in postmenopausal women with overweight (group III);* $\overline{x}$ *± SD, *p < 0.05*

Rycina 6. *Korelacja między wydalaniem 6-sulfatoksymelatoniny (aMT6s) z moczem a wskaźnikiem masy ciała (BMI) u kobiet po menopauzie z nadwagą (grupa III);* $\overline{x}$ *± SD, *p < 0,05*

Table II. ***Correlation between body mass index (BMI) and serotonin (SER) and melatonin (MEL) serum levels as well as urinary excretion of 5-hydroxyindoloacetic acid (5-HIAA) and 6-sulfatoxymelatonin (aMT6s);*** $\overline{x}$ ***± SD, *p < 0.05, **p < 0.001***

Tabela II. ***Korelacja między wskaźnikiem masy ciała (BMI) a stężeniem serotoniny (SER) i melatoniny (MEL) w surowicy oraz wydalaniem z moczem kwasu 5-hydroksyindolooctowego (5-HIAA) i 6-sulfatoksymelatoniny (aMT6s);*** $\overline{x}$ ***± SD, *p < 0,05, **p < 0,001***

Correlation		Correlation coefficient (r)		
		Group I	Group II	Group III
SER	BMI	–0.4042	–0.2379	–0.5241*
5-HIAA		–0.4881	–0.4326	–0.4483
MEL		–0.3318	–0.3563	–0.4906
aMT6s		–0.3774	–0.5662*	–0.8763**

was found between BMI and urinary aMT6s excretion, respectively (Table II, Fig. 6).

Discussion

Serotonin plays an important role in the regulation of hunger and satiety. In the central and peripheral nervous system, its synthesis and secretion increase under the effect of β-adrenergic and muscarinic stimulation [19], but also under the influence of oestrogens [20]. In the gastrointestinal tract enterochromaffin cells are the main source of serotonin, and the changes of physical conditions during digestive processes stimulate its secretion [21].

Serotonin exerts an inhibitory effect on CNS hunger centres [22]. Both oestrogen and serotonin levels are reduced in ovariectomised experimental animals, which results in rapid weight gain. This change can be prevented by oestradiol supplementation [23]. Oestrogens exert an anorectic effect through increased production of serotonin in the CNS and cause increased satiety centre activity via cholecystokinin receptors [24]. An inhibitory effect of oestrogen on gastric motility [25], secretion [26], and stimulation of duodenal bicarbonate secretion are also possible.

Serotonin also demonstrates an inhibitory effect on the secretion of HCl [27], stimulating at the same time bicarbonate secretion [28]. This implies that the reduced levels of oestrogen and serotonin in postmenopausal women can stimulate gastric secretory and motor function and increase the feeling of hunger. The results of our research confirm such a direction and mechanism of changes.

Melatonin also plays an important role in the control of appetite. Melatonin biosynthesis is mainly regulated by light but also by norepinephrine via beta-1-adrenergic receptors. The involvement of other factors, including oestrogen, in the process of melatonin secretion is poorly recognised. Bodis et al. [29] demonstrated that melatonin suppresses oestradiol and progesterone secretion and may play a role in the regulation of the menstrual cycle. In turn, Luboshitzky et al. [30] found that a four-month oestradiol treatment reduces the urinary 6-6-sulfatoxymelatonin (aMT6s) excretion. Gruber et al. [31] noted in women with secondary amenorrhea a negative correlation between the serum level of 17-β-oestradiol and urinary aMT6s excretion.

The results of our study and other investigations do not confirm such a correlation. Okatani et al. [32] found a negative correlation between peak (night) melatonin secretion and secretion of 17-β-oestradiol. At the same time, they showed that oral intake of oestrogen reduces the nocturnal secretion of melatonin. The above observations indicate that low levels of oestrogen after menopause should result in increased secretion of melatonin.

Vakkuri et al. [33] detected in menopausal women a negative correlation between serum FSH and urinary melatonin secretion at night. Furthermore, they observed that reduced melatonin secretion begins immediately after the age of 40 years and can initiate menopause.

Bleicher et al. [34] observed in postmenopausal women lower urinary aMT6s excretion, particularly in the case of coexisting obesity and sleep disorders.

However, a beneficial effect of melatonin on carbohydrate and lipid metabolism indicators was demonstrated in many experimental studies [35, 36]. Regulation of these correlations leads to decreased appetite and weight reduction [37, 38].

The results of clinical studies also point to the correlation between a low level of melatonin and obesity [39]. For this reason, a lot of authors suggest using melatonin in therapeutic procedures in obesity [40, 41].

Moreover, experimental studies showed that melatonin inhibits the secretion of hydrochloric acid and pepsin [42], stimulates the secretion of duodenal and pancreatic bicarbonates, and thus acts synergistically with serotonin. As a consequence, its deficiency can also lead to a drop of pH in the duodenum, stimulation of insulin secretion, and increase of appetite. These changes are unfavourable and difficult to control, particularly at night. The coexisting sleep disorders, often occurring in postmenopausal women, can also promote the phenomenon of "night snacking" and the development of hyperalimentation syndrome.

Changes in appetite are more common in women than in men, which points to a significant effect of oestrogens on the physiology of eating [43]. Oestrogen deficiency after menopause and the associated reduction in the synthesis of serotonin can also be the cause of emotional disorders [44].

Conclusions

All of the above facts and the results of our studies point to the need of use of drugs modulating serotonin homeostasis and/or melatonin supplementation together with female hormones in the prevention and complex treatment of disorders of eating in postmenopausal women.

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