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The effect of tryptophan and serotonin levels on the severity of depressive and climacteric symptoms in perimenopausal women

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Abstract. – OBJECTIVE: The dysfunctional serotonergic system is a factor contributing to the development of depression. The aim of this study was to assess the effect of serotonin and tryptophan on the severity of climacteric and depressive symptoms in perimenopausal women.

PATIENTS AND METHODS: The study involved data collection and biochemical analysis. The research instruments were: the Blatt-Kuppermann index, the Beck Depression Inventory, and the proprietary questionnaire.

RESULTS: There was no significant effect of tryptophan (r=0.05; *p*=0.219) and serotonin (r= -0.03; *p*=0.537) on the severity of depressive symptoms, or tryptophan on the severity of climacteric symptoms (r=0.019; *p*=0.657). However, a weak negative correlation was found between the level of serotonin and the severity of climacteric symptoms (r=-0.09; *p*=0.022). Additionally, it was found that severe depressive symptoms were associated with a significant exacerbation of climacteric symptoms (β=0.379; *p*<0.001), while higher serotonin levels alleviated them (β=-0.604; *p*=0.005).

CONCLUSIONS: Higher severity of depressive symptoms may exacerbate climacteric symptoms. Serotonin levels may influence the severity of climacteric symptoms. Moreover, the higher the serotonin level, the lower the odds of depressive disorders, irrespective of the severity of climacteric symptoms. Tryptophan levels had no effect on the severity of depressive and climacteric symptoms in the perimenopausal women.

Key Words:
Tryptophan, Serotonin, Perimenopausal women, Depressive symptoms, Climacteric symptoms.

Introduction

Perimenopause, also called the menopausal transition, usually begins around the age of 45, and lasts approximately five years. In Western countries, the average age of the last menstruation is around 50 years[1]. This is a time in a woman's life that is characterized by various physical and psychological changes. A decline and fluctuations in ovarian hormone levels may result in numerous physical complaints, such as hot flashes, night sweats, urogenital atrophy with urinary incontinence, vaginal dryness, sexual dysfunction, and osteoporosis[2]. The literature also provides many reports on psychological disorders[3], including irritability, anxiety, insomnia[4], and depressive mood[5].

The available findings suggest that the perimenopausal period is associated with an increased risk of depressive symptoms[6-8] and depression[9,10]. The hormonal changes that then occur involve a decrease in the level of estradiol (E2), and a corresponding increase in the levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH)[11]. However, the research results concerning the relationship between sex hormone levels and depressive mood are ambiguous. While some studies show that depression is related to the levels of E2, FSH, and LH[7], others suggest a relationship with elevated testosterone levels[12]. There are also reports which do not confirm a direct connection between the blood E2: FSH ratio and depression[13,14]. Nevertheless, there is a correlation between sex hormones, fluctuating in the perimenopausal period, and the serotonergic system[15,16].

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Although the etiology of depressive disorders is not fully understood, for over sixty years, research on the pathophysiology of depression has focused mainly on serotonin (5-HT) and serotonergic neurotransmission. An organic chemical compound, serotonin is the 5-hydroxy derivative of tryptamine. It belongs to the group of biogenic amines, is a tissue hormone and an important neurotransmitter in the central nervous system. Three major families of serotonin receptors (5-HT1, 5-HT2 and 5-HT3) have been described, which differ in binding affinity for selective ligands, receptor coupling mechanisms with effectors, and behavioral processes regulated by them. 5-HT1A and 5-HT2 receptors may be involved in the etiology of major depression and the therapeutic effects of antidepressant treatment[17].

Studies in rats have shown that estrogen modulates the expression of both 5-HT1A and 5-HT2A receptor density, and mRNA levels in several areas related to the limbic system. 5-HT1AR and its related functions have been shown to dominate serotonin transmission under normal conditions, but the 5-HT2AR signaling pathway plays an important role in extreme situations, when the release of serotonin is elevated[18]. Serotonin mediates stress relief and adaptation, thus facilitating relaxation, mental flexibility[19-22], and a positive mood[23,24].

Tryptophan (TRP) is the only circulating amino acid in serum that is partly related to the transport protein, albumin. It is capable of crossing the hematoencephalic barrier and converting into serotonin in the brain through enzymatic processes of hydroxylation and decarboxylation. It has been shown that total tryptophan (TT) and free tryptophan (FT) have cyclic variability during the menstrual cycle, and that their levels are negatively correlated with gonadotropin levels in a very significant way. In the mid-cycle, when the levels of FSH and LH are elevated, the TT/FT ratio is low, while in the mid-follicular and the mid-luteal phases, when gonadotropin levels are low, the TT/FTs ratio in serum reaches its maximum value[25].

In the perimenopausal period, as a result of hormonal changes, serotonin and tryptophan levels may fluctuate, thus potentially increasing the severity of depressive and climacteric symptoms. The aim of this study was to assess the effect of serotonin and tryptophan levels on the severity of climacteric and depressive symptoms in perimenopausal women.

Patients and Methods

The research was carried out in the West Pomeranian Voivodeship, Poland. The inclusion criteria for the study were: female sex, 40-65 years of age, and no history of inflammatory, psychiatric, or neoplastic diseases. The mental health of the respondents was assessed using the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire 9 (PRIME-MD PHQ-9) screening tool.

The research was conducted in accordance with ethical standards and the Declaration of Helsinki. The study protocol was approved by the Bioethics Committee of the Pomeranian Medical University in Szczecin, Poland (No. KB-0012/181/13). Informed written consent was obtained from all study participants.

The study consisted of two stages: the collection of data by means of the questionnaires, and biochemical analysis. Based on the proprietary questionnaire, we obtained information on sociodemographic data (age, sex, education, place of residence, marital status and employment status) and basic medical data (date of the last menstruation, date of the first menstruation, the use of MHT, current test results, body weight and height, use of medications and stimulants, and past diseases).

The Blatt-Kuppermann index was used to measure the severity of climacteric symptoms. The respondents assessed the severity of particular climacteric symptoms, such as hot flashes, sweating, sleep disorders, nervousness, depression, dizziness, general weakness, joint pain, headache, heart palpitations, and paresthesia. The results were interpreted as follows: 0-16 points— no climacteric symptoms, 17-25 points –mild symptoms, 26-30 points – moderate symptoms, and more than 30 points – severe climacteric symptoms.

The severity of depression was evaluated using the Beck Depression Inventory. This research instrument consists of 20 statements, graded according to the intensity of symptoms scored from 0 to 3. The result (ranging from 0 to 60 points) is obtained after summing up the points and comparing it with the norm table defining the severity of depression (0-11 points – no depression; 12-19 points – mild depression; 20-25 points – moderate depression; over 26 points – severe depression).

Blood for biochemical analysis was collected from a venous vessel in accordance with the pro-

cedure for collecting, storing, and transporting biological material from a peripheral vein. Blood was drawn between 7.00 a.m. and 9.30 a.m. after an overnight fast and a 10-minute rest in a sitting position. Blood was collected into Vacutainer tubes (Sarstedt, Nümbrecht, Germany) for serum biochemical analysis (7 ml).

Statistical Analysis

Statistical analysis was performed using the Statistica v. 13.3 (TIBCO Software, Palo Alto, CA, USA). In the case of quantitative variables, the following methods of descriptive statistics were used: arithmetic mean (M), minimum (Min), maximum (Max), standard deviation (SD), coefficient of variation (CV). Non-numerical variables were presented using number (n) and per cent (%). Pearson's correlation coefficient was used to determine the strength of correlations between two quantitative variables. To assess the impact of selected factors on the severity of climacteric symptoms, a multivariate linear regression model with the evaluation of the potential influence of moderators was used. The regression model was fitted to the empirical data by the Ordinary Least Squares (OLS) method. All factors were introduced to the model at the same time. The model statistics was calculated for each factor. The vector and strength of significant correlations were interpreted by determining β standardized regression coefficients.

To evaluate the influence of selected factors on the odds of developing depressive symptoms (yes / no), we used a nonlinear estimation model for the logistic regression function with the evaluation of the potential influence of moderators. The Rosenbrock and the quasi-Newton estimation methods were used, and asymptotic standard errors were determined. For each predictor, an odds ratio (OR) was determined along with a 95% confidence interval (CI).

In all analyzes, the effects for which the probability value p was lower than the adopted significance level of 0.05 ($p < 0.05$) were considered significant.

Results

The study involved 566 women at the mean age of 53.5 years (Table I). 46.29% of the women had third-level education, 40.46% had secondary education, 10.78% had vocational education, and 2.47% had primary education. 71.38% of the respondents came from a city with more than 100,000 inhabitants, 17.14% came from smaller towns, and the remaining respondents (11.48%) came from rural areas. 71.55% of the women were married, 8.66% lived in cohabitation, and 19.79% were single. The vast majority of the respondents were employed (86.22%).

66.61% of the women were postmenopausal, and 33.39% were still menstruating. 63.07% of the respondents had no climacteric symptoms, 25.44% had mild climacteric symptoms, 6.90% had moderate climacteric symptoms, and 4.59% had severe climacteric symptoms. 74.38% of the women did not show any symptoms of depression, and 25.62% had such symptoms (18.9% – mild, 3.89% – moderate, and 2.83% – severe) (Table II).

Table I presents descriptive statistics for age, the Blatt-Kuperman index, the Beck Depression Inventory, as well as serum serotonin and tryptophan levels. The mean score on the Blatt-Kupperman Index was 14.09 (SD = 8.95), and the mean score on the Beck Depression Inventory was 8.29 (SD = 7.11). The mean levels of tryptophan and serotonin were 13.14 µg/ml (SD = 5.58 µg/ml) and 151.59 ng/ml (SD = 104.01 ng/ml), respectively (Table II).

Correlation analysis did not demonstrate a significant effect of tryptophan (r = 0.05; p = 0.219) and serotonin (r = -0.03; p = 0.537) on the severity of depressive symptoms measured

Table I. Descriptive statistics of the studied variables.

	N	M	SD	Mdn	IQR	Mini	Maks	CV [%]
Kupperman Index	566	14.09	8.95	13.00	13.00	0.00	47.00	63.5
Beck Depression Inventory	566	8.29	7.11	7.00	9.00	0.00	40.00	85.8
Tryptophan [µg/ml]	566	13.14	5.58	12.62	6.01	1.89	43.06	42.5
Serotonin [ng/ml]	566	151.59	104.01	122.00	108.94	9.97	765.80	68.6
Age	566	53.53	5.36	54.00	8.00	37.00	66.00	10.0

M: mean, SD: standard deviation, Mdn: median, IQR: interquartile range, CV: coefficient of variation.

Table II. Characteristics of the study sample (N = 566).

Variable	Variant	N	%
Education	Primary	14	2.47
	Vocational	61	10.78
	Secondary	229	40.46
	Third-Level	262	46.29
Age	40-45	33	5.83
	46-50	148	26.15
	51-55	172	30.39
	56-60	159	28.09
	61-65	50	8.83
Place of residence	Village	65	11.48
	City of up to 10,000	25	4.42
	City of 10,000-100,000	72	12.72
	City of more than 100,000	404	71.38
Marital status	Married	405	71.55
	Live in cohabitation	49	8.66
	Single	112	19.79
Employment status	Unemployed	78	13.78
	Employed	488	86.22
Does she menstruate?	No	377	66.61
	Yes	189	33.39
Climacteric symptoms	No Symptoms	357	63.07
	Mild Symptoms	144	25.44
	Moderate Symptoms	39	6.90
	Severe symptoms	26	4.59
Severity of depressive symptoms	No Depression	421	74.38
	Mild Depression	107	18.90
	Moderate Depression	22	3.89
	Severe depression	16	2.83
Presence of depressive symptoms	No	421	74.38
	Yes	145	25.62

by the Beck Depression Inventory. There was also no significant correlation between the level of tryptophan and the severity of climacteric symptoms assessed by the Blatt-Kupperman index (r = 0.019; p = 0.657). However, a weak negative correlation was found between the level of serotonin and the severity of climacteric symptoms (r = -0.09; p = 0.022), which means that a decline in the level of serotonin was associated with a moderate increase in the severity of climacteric symptoms.

A multivariate regression analysis of the influence of selected factors (serotonin, tryptophan, depression) on the severity of climacteric symptoms according to the Blatt-Kuperman index was performed. It was found that greater severity of depressive symptoms caused significant exacerbation of climacteric symptoms (β = 0.379; p < 0.001), while higher serotonin levels alleviated them (β = -0.604; p = 0.005) (Table III).

The logistic regression model was used to assess the odds of developing depressive symptoms depending on the severity of climacteric

Table III. Regression analysis of the impact of the tested variables on the severity of climacteric symptoms according to the Blatt-Kupperman Index.

Variable	b	OR	-95% CI	+95% CI	Wald t	*p*
Beck Depression Inventory	**0.580**	**0.379**	**0.320**	**0.438**	**12.625**	**0.000**
Tryptophan [µg / ml]	-0.036	-0.031	-0.128	0.066	-0.624	0.533
Serotonin [ng/ml]	**-0.053**	**-0.604**	**-1.021**	**-0.188**	**-2.849**	**0.005**

b: non-standardized regression coefficient; OR: odds ratio; CI: confidence interval; Wald t: statistics value; *p*:level of probability.

symptoms and the levels of tryptophan and serotonin. It was shown that individuals with higher serotonin levels were significantly less likely to develop depression (OR = 0.992, p = 0.002). Moreover, the influence of climacteric symptoms on the odds of depression was moderated by the level of serotonin. Climacteric symptoms have a smaller impact on the odds of depression in subjects with higher serotonin levels (Table IV).

Discussion

The issue of a relationship between the severity of climacteric and depressive symptoms has been raised by many authors. In their study of 45-54-year-old women, Bosworth et al[26] observed that climacteric symptoms entailed a higher incidence of depressive disorders. Similarly, Delam and Bazrafshan[27] reported a link between the severity of depression and climacteric symptoms as measured by the modified Kupperman index. Ruan et al[28], who analyzed a group of 1,225 Chinese women, found that depression was one of the most common climacteric symptoms in both perimenopausal and postmenopausal women. Also, in our research, women with more serious depressive problems were characterized by a significantly higher severity of climacteric symptoms.

One of the main factors contributing to the development of depression is the dysfunctional serotonergic system. The intestinal microflora is believed to be able to regulate the level of tryptophan, which is the major precursor of serotonin, in the host. Lukić et al[29] examined the influence of the regulation of brain tryptophan and serotonin levels on depressive behavior in mice. They concluded that the microflora may contribute to depression-like behavior by affecting the availability of tryptophan in the brain and the serotonergic system.

Tryptophan is the only precursor to serotonin and kynurenine (KYN) produced both peripherally and centrally. Colle et al[30] assessed the levels of tryptophan and metabolites of serotonin and kynurenine in 173 patients with a current major depressive episode (MDE) compared with 214 healthy controls. Tryptophan levels did not differ between MDE patients and the control group. The levels of serotonin and its precursor (5-hydroxytryptophan) were lower in MDE patients than in the control group, while the levels of its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), were within the normal range. Although these results show a relationship between the studied metabolites and depression, researchers believe that the causes of these changes should be further investigated.

Baranyi et al[31] supported the hypothesis that tryptophan and serotonin deficiency is associated with major depressive disorder (MDD). Inadequate levels of the serotonin precursor (tryptophan) in patients with MDD suggests the dysfunction of serotonin neurotransmission. A two-stage hierarchical linear regression model showed that low tryptophan levels, insufficient social support, high job demands, personality traits, impaired physical functioning, and impaired vitality contribute to higher scores on the Beck Depression Inventory.

Tomioka et al[32] analyzed the levels of tryptophan metabolites in the plasma of patients with major monopolar depression (MMD) and healthy controls but did not detect any significant differences between these two groups. Serotonin levels were higher in MMD patients than in the control group, which may have been associated with the use of drugs inhibiting the transport of serotonin. At the same time, the plasma 5-HIAA levels were higher in control subjects than in MMD patients.

Takada et al[33] observed very low or undetectable serotonin levels in patients with monopolar depression. The 5-HIAA/TRP ratio and the KYN/TRP ratio did not differ between the control group and patients with depression. Furthermore, in depressed patients, serotonin was quickly metabolized to 5-HIAA, while the level of kynurenine did not change, which may indicate that the metabolism of tryptophan is modified by stress and depression.

Our study demonstrated a correlation between the level of serotonin and the severity of climacteric symptoms. What is more, higher serotonin levels decreased the odds of depression. The severity of climacteric and depressive symptoms was not correlated with the level of tryptophan.

This study concerning depressive problems experienced by perimenopausal women is not free from limitations. The vast majority of women in the study sample had either mild depressive and/or climacteric symptoms, or they had no such symptoms at all, which may have translated into a small relationship between the levels of serotonin and tryptophan and the severity of depressive symptoms and depression. It is nec-

essary to conduct further research in this field, especially among people with clinically diagnosed depression and with severe climacteric symptoms.

Conclusions

1. More severe depressive symptoms may exacerbate climacteric symptoms.
2. Serotonin levels may influence the severity of climacteric symptoms. What is more, the higher the serotonin level, the lower the odds of developing depressive symptoms, irrespective of the severity of climacteric symptoms.
3. The level of tryptophan had no effect on the severity of depressive or climacteric symptoms in the perimenopausal women.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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