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ORIGINAL PAPER

THE SEVERITY OF DEPRESSIVE AND ANXIETY SYMPTOMS IN POSTMENOPAUSAL WOMEN DEPENDING ON THEIR MAGNESIUM, ZINC, SELENIUM AND COPPER LEVELS*

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Abstract

Women, especially in the peri- and postmenopausal periods, undergo many organic and functional changes. Fluctuation and ultimately a decline in the levels of female reproductive hormones is a long-lasting process, potentially leading to regulatory disorders of the autonomic nervous system. In consequence, postmenopausal women experience depressive mood disorders and more severe anxiety symptoms. The aim of this study was to assess the severity of anxiety and depressive symptoms in postmenopausal women in connection with the serum levels of zinc (Zn), magnesium (Mg), selenium (Se), and copper (Cu). The study involved 102 healthy postmenopausal women. It was divided into two parts: the first part was based on a survey performed using standardized research instruments and a questionnaire developed by the authors. The second part involved a biochemical serum analysis, whose aim was to determine the levels of selected elements. The mean level of anxiety as a state was 4.53±1.79, and the mean level of anxiety as a trait was 3.86±2.03. The mean level of depression according to the Beck Depression Inventory was 6.77±6.82. As many as 77.5% of the women had no depressive symptoms. The mean serum levels of the studied elements were as follows: magnesium (19.41±02.81 mg dm^{-3}), zinc (0.94±0.22 mg dm^{-3}), selenium (0.06±0.03 mg dm^{-3}), and copper (0.40±0.57 mg dm^{-3}). No relationship was demonstrated between the levels of selected elements and the development of depressive and anxiety disorders in the studied postmenopausal women.

Keywords: depressive disorder, postmenopause, micronutrients.

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INTRODUCTION

The monitoring of the population's health status, both in Poland and worldwide, indicates a regular growth in the incidence of mental diseases. In today's world, stress is no longer understood only as a physiological reaction to life-threatening events but is popularly perceived as a specific and negative psychological experience that can have adverse effect on one's mental health. According to the World Health Organization (WHO), nearly 450 million people worldwide are affected by stress-related conditions (WHO 2001). Although both women and men suffer from mental disorders, there are apparent differences in susceptibility to such diseases between sexes. In modern society, women are believed to be more predisposed to experience increased stress. Especially an increase in the rate of depression, leading to many social and health complications, is a serious public health problem. The causes of mental disorders, such as depression, remain unclear. Therefore, large-scale research is needed to understand them. It seems reasonable to take actions aiming at the identification of potential markers of depressive disorders. Numerous studies suggest that macro- and microelements play a role in the activation of enzymes involved in catecholamine transmission, whose disturbances are related to the pathogenesis of depression (Eby, Eby 2010, Sanhueza et al. 2013).

Magnesium (Mg) is a microelement that is necessary for normal activity of biochemical and physiological processes. This intracellular cation activates a number of enzymes crucial for the proper functioning of the brain (Wang et al. 2018). The role of magnesium ions in modulatory processes within many neurotransmitter and enzymatic systems and the occurrence of depressive symptoms in people with magnesium deficiency substantiate research on magnesium ion levels in blood seems (Yamanaka et al. 2019). Studies of the association between the levels of magnesium and the parts of the brain's limbic system show that this element is involved in the etiology and progression of depression. Changes in magnesium levels have also been observed during depressive episodes. Numerous studies confirm that magnesium deficiency can substantially contribute to the development of both depression and mood disorders (Camardese et al. 2012, Yary et al. 2013, Jurczak et al. 2013).

Zinc (Zn) is another trace element essential for many biochemical and physiological processes associated with the function of the brain (Jurowski et al. 2014), as well as the metabolism of cells (Maret 2017). It serves as a modulator of synaptic conduction and maintains homeostasis in many areas of the brain, including those responsible for the pathophysiology of depression, namely the hippocampus, amygdala, and cerebral cortex. Its deficiency leads to nerve conduction disorders and changes in neuropsychological behavior. Research on the relationship between zinc and depression has been conducted since the late 1980s, providing evidence that its

levels are decreased in patients (especially women) with this condition (Maserejian et al. 2012).

Selenium (Se), involved in antioxidant defense mechanisms of the nervous system, plays a neuromodulatory role in the functioning of the brain. The available results have confirmed that selenium levels are linked to depression and other affective disorders, such as anxiety, disorientation and hostility. Selenium deficiency is associated with decreased levels of brain-derived neurotrophic factor (BDNF), which plays a major part in the pathophysiology of depression (Camardese et al. 2012, Björkholm, Monteggia 2016).

Copper (Cu) is an element whose both deficiency and excess can substantially contribute to the development and functioning of the brain. Therefore, the brain has mechanisms that regulate copper metabolism. The processes in which this element plays an important part include neurotransmission, cognitive functions, the processes of learning and remembering, neurogenesis, synaptogenesis. Copper determines the proper functioning of dopamine beta-hydroxylase, converting dopamine into noradrenaline in synaptic vesicles (Stefańska et al. 2014). Its concentration in the blood correlates with the severity of depressive episodes, measured on the Hamilton Depression Rating Scale (HDRS) (Zięba et al. 2000). The outcomes of the studies concerning serum copper levels in people suffering from depression are ambiguous. Nonetheless, in most cases elevated copper levels in patients with depressive episodes have been confirmed and normalized after effective pharmacological treatment. The identification of biological markers of depression and other affective disorders may help prevent the recurrence of these health problems in the future.

The purpose of the study was to analyze the severity of anxiety and depression in postmenopausal women in connection with the serum levels of zinc, magnesium, selenium, and copper.

MATERIALS AND METHODS

The study group

The study involved 102 healthy women from West Pomeranian province. The mean age of the women was 56.69 years (±6.0). The youngest respondent was 45 years old, and the oldest was 75. The criteria for inclusion in the study sample were female sex, age, at least one year from the last menstruation, no diagnosis of endocrine disease, cancer, or mental disorder, voluntary signed consent to take part in the study, and residence in West Pomeranian province. The participants were characterized by non-smoking, moderate physical activity, low alcohol intake, not using elimination diets, and not taking any vitamin/mineral supplements. In all the patients, axis

I psychiatric disorders according to the ICD-10 classification were excluded by means of the Primary Care Evaluation of Mental Disorders (PRIME-MD) questionnaire. All patients were informed in writing about the purpose and course of the study and assured that they could resign at any stage of the research procedure without giving a reason. All the women received detailed information about the purpose and scope of the research and gave written consent to take part in it. The protocol of the study was approved by the Bioethical Commission of the Pomeranian Medical University, Szczecin (approval number KB-0012/135/18).

The study was divided into two parts: the first part was based on a survey performed using standardized research instruments and a questionnaire concerning sociodemographic and medical data. Anxiety was assessed by the State-Trait Anxiety Inventory (STAI). The inventory consists of two parts: STAI (X-1) measuring the level of anxiety as a state, and STAI (X-2) measuring anxiety as a trait. Scores for each part of the questionnaire range from 20 to 80 points: the score of 20 reflects a low level of anxiety, and the score of 80-a high level of anxiety. Raw data are converted into standard scores (stens). The interpretation of the 10-unit sten scale used in our study is as follows: scores of 1-4-a low level of anxiety, scores of 5-6-a medium level of anxiety, scores of 7-10-a high level of anxiety. The severity of depression was measured by a standardized research instrument, the Beck Depression Inventory-II (BDI-II). Statistical analysis of women without depression (0-11), with mild depression (12-26), moderate depression (27-49), and severe depression (50-63) was performed. The second part involved biochemical blood serum analysis. After obtaining their consent to take part in the study, and in accordance with the protocol, samples containing no more than 5 ml venous blood were taken from each patient on an empty stomach (minimum 8 hours from the last meal) on a one-off basis, using the Monovette system to determine serum levels of magnesium (Mg, norm 20-25 mg dm^{-3}), zinc (Zn, norm 0.66-1.1 mg dm^{-3}), selenium (Se, norm 0.07-0.15 mg dm^{-3}), and copper (Cu, norm 0.8-1.6 mg dm^{-3}). The levels of these elements were measured by absorption spectrometry. Laboratory tests were performed in the Department of Biochemistry and Chemistry, Pomeranian Medical University in Szczecin (Poland) in accordance with the guidelines PN-EN ISO 15189.

Statistical methods

Statistical analysis was performed in the R environment, version 3.5.0. Descriptive statistics (number of valid cases, arithmetic mean, standard deviation, median, minimum, maximum), as well as percentage shares and mathematical statistics (normal distribution tests, nonparametric correlations, difference significance tests) were applied. Using the Shapiro-Wilk test, it was confirmed that the distribution of the analyzed variables is different from the normal one ($p<0.05$). The level of significance was assumed as $p\leq0.05$ (statistically significant) and $p\leq0.01$ (highly statistically significant).

RESULTS

The median age was 56 years. Nearly half of the participants (53.9%) had completed third-level education, 38.2% had completed secondary education, and 7.9% had completed vocational education. 83.3% of the women lived in cities with a population of more than 100.000. A vast majority of the women (92.1%) had life partners (marriage or cohabitation), and were employed (79.4%). 80.4% were non-users of menopausal hormone therapy (MHT) – Table 1.

Table 1

The structure of the study sample with regard to sociodemographic and medical data

Sociodemographic data	*n*	(%)
Education		
Vocational	8	7.9
Secondary	39	38.2
Tertiary	55	53.9
Total	102	100.0
Place of residence		
Village	8	7.9
City < 10.000 residents	2	1.9
City 10.000-100.000 residents	4	3.9
City > 100.000 residents	88	86.3
Total	102	100.0
Marital status		
Married or cohabiting	94	92.1
Single	8	7.9
Total	102	100.0
Employment		
Employed	81	79.4
Unemployed	21	20.6
Total	102	100.0
Physical activity		
Yes	56	54.9
No	46	45.1
Total	102	100.0
Medical data	*n*	%
Menopausal hormone therapy		
Yes	20	19.6
No	82	80.4
Total	102	100.0

The median level of anxiety as a state (STAI X-1) was at the level 4.00 (3.0-6.0) and was similar to the median level of anxiety as a trait (STAI X-2) - 4.00 (2.0-5.0). The median level of depression according to the BDI was 5.00 (1.0-11.0) – Table 2.

Table 2

Analysis of the STAI and the BDI-II results

Variable	Min-Max	Q_1-Q_3	Me	*p*
STAI				
STAI (X-1) anxiety as a state	2.0-9.0	3.0-6.0	4.0	0.000
BECK–II				
STAI (X-2) anxiety as a trait	1.0-9.0	2.0-5.0	4.0	0.000
BDI–II	0.0-30.0	1.0-11.0	5.0	0.000

Me – median, Min – minimum, Max – maximum, Q_1 – first quartile, Q_3 – third quartile

51.5% of the women had moderate levels of anxiety as a state, and 48.5% had low levels of anxiety as a trait. 77.5% of the participants had no depressive symptoms. Mild depression was only observed in 16.7%, while both moderate and severe depression were noted in 2.9% (Table 3).

Table 3

Analysis of the severity of anxiety and depressive disorders

STAI									
STAI (X-1) anxiety as a state	low level of anxiety		moderate level of anxiety		high level of anxiety		total	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
	35	34.7	52	51.5	14	13.9	101	100.0
STAI (X-2) anxiety as a trait	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
	49	48.5	37	36.6	15	14.9	101	100.0
BDI–II									
No depression		mild depression		moderate depression		severe depression		total	
n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
79	77.5	17	16.7	3	2.9	3	2.9	102	100.0

The median serum level of magnesium was 19.13 (17.941-20.56) mg dm^{-3}, zinc 0.94 (0.815-1.06) mg dm^{-3}, selenium 0.06 (0.043-0.08) mg dm^{-3}, and copper 0.13 (0.073-0.37) mg dm^{-3} (Table 4).

The majority of the women with normal levels of selected elements had moderate anxiety as a state (STAI X-1). The women with reference levels of

Table 4

Analysis of the levels of selected elements

Serum levels	Min-Max	Q_1-Q_3	Me
Mg (mg dm^{-3})	8.733-28.55	17.941-20.56	19.13
Zn (mg dm^{-3})	0.090-1.48	0.815-1.06	0.94
Se (mg dm^{-3})	0.001-0.16	0.043-0.08	0.06
Cu (mg dm^{-3})	0.001-2.54	0.073-0.37	0.16

Explanation see Table 2.

selenium, magnesium, and zinc were mostly characterized by low anxiety as a trait (STAI X-2). The normal levels of selected elements were mainly observed in the women without depressive disorders, and with mild depressive symptoms (Table 5).

The next stage of the study involved analysis of the correlation between the severity of anxiety (STAI X-1 and STAI X-2) and depressive symptoms (BDI) and the levels of selected elements (Table 6). No significant correlations were noted ($p>0.05$).

Our analysis did not demonstrate any correlations between the levels of magnesium ($p>0.05$), zinc ($p>0.05$), selenium ($p>0.05$), or copper ($p>0.05$) and depressive disorders in the studied women.

DISCUSSION

The part of trace elements in the functioning of a human body is a frequent subject of clinical studies. They undeniably contribute to many physiological processes essential for living and proper development, and their deficiencies can lead to serious metabolic and mental disorders. Elements that play a key role in the etiology of mental diseases and the regulation of the immune system are magnesium, zinc, selenium, and copper. Despite global, large-scale research on affective disorders, biological markers of the risk of depression have not yet been determined. The identification of laboratory markers of depression and other affective disorders would help detect susceptibility to these diseases and enable their early diagnosis.

Magnesium, zinc, and copper are known to be factors in glutamatergic neurotransmission, but their role in the etiopathogenesis of depression remains unclear (Siwek et al. 2007, Zawadzki et al. 2009). Studies of plasma magnesium levels in people suffering from depression have provided very ambiguous results, and the impact of this element on the therapy and prevention of this health problem has not been fully elucidated. It has been demonstrated that low magnesium levels often entail depressive symptoms, and supplementation with this element can improve their treatment (Derom

Table 5

Analysis of anxiety and depressive disorders with regard to the reference levels of selected elements

Variable		Cu				Se				Mg				Zn			
		reference values		deviation from normal values		reference values		deviation from normal values		reference values		deviation from normal values		reference values		deviation from normal values	
		n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
(STAI X-1)	low level of anxiety	2	25.0	34	34.7	13	27.1	23	39.7	11	35.5	25	33.3	24	32.9	12	36.4
	moderate level of anxiety	4	50.0	51	52.0	28	58.3	27	46.6	14	45.2	41	54.7	37	50.7	18	54.5
	high level of anxiety	2	25.0	13	13.3	7	14.6	8	13.8	6	19.4	9	12.0	12	16.4	3	9.1
	Phi; *p*	.094; .628				.135; .380				.109; .535				.098; .602			
(STAI X-2)	low level of anxiety	3	37.5	49	50.0	24	50.0	28	48.3	15	48.4	37	49.3	33	45.2	19	57.6
	moderate level of anxiety	4	50.0	35	35.7	16	33.3	23	39.7	10	32.3	29	38.7	30	41.1	9	27.3
	high level of anxiety	1	12.5	14	14.3	8	16.7	7	12.1	6	19.4	9	12.0	10	13.7	5	15.2
	Phi; *p*	.079; .718				.081; .707				.101; .581				.135; .382			
BDI	no depression	5	62.5	74	78.7	40	81.6	39	73.6	23	74.2	56	78.9	58	81.7	21	67.7
	mild depression	3	37.5	14	14.9	7	14.3	10	18.9	6	19.4	11	15.5	10	14.1	7	22.6
	moderate depression	0	0.0	3	3.2	1	2.0	2	3.8	2	6.5	1	1.4	1	1.4	2	6.5
	severe depression	0	0.0	3	3.2	1	2.0	2	3.8	0	0.0	3	4.2	2	2.8	1	3.2
	Phi; *p*	.172; .388				.102; .788				.183; .330				.181; .340			

Table 6

Analysis of the correlations between the severity of anxiety and depressive disorders and the levels of selected elements

Variable	STAI X-1 Anxiety as a state		STAI X-2 Anxiety as a trait		BDI	
	rho	*p*	rho	*p*	rho	*p*
Mg	0.098	0.319	0.159	0.104	0.082	0.413
Zn	0.038	0.702	0.090	0.361	0.075	0.457
Se	-0.020	0.837	-0.040	0.680	-0.055	0.581
Cu	0.116	0.238	0.075	0.444	0.128	0.198

rho – Spearman's nonparametric correlation coefficient, *p* – level of significance for *r*

et al. 2013, Yary et al. 2013). The authors of some clinical studies, on the other hand, indicate that symptoms of depression are accompanied by elevated levels of magnesium (Frizel et al. 1969, Keitner, Mansfield 2012). Even though the results of available studies are ambiguous, they show that there is a relationship between changes in magnesium levels and the course of depression and depressive episodes (Sowa-Kucma et al. 2013). Some authors claim that the majority of patients with a diagnosis of depressive episodes had increased copper levels in blood, emphasizing, however, that the role of this element in the pathophysiology of serious depressive disorders and its potential usefulness as a clinical marker are insignificant (Zięba et al. 2000, Siwek et al. 2007). Some researchers suggest that zinc-copper imbalance is a factor that can lead to mental diseases (for example, depression, postnatal depression, schizophrenia, autism) and the zinc-copper ratio may be a more sensitive marker than the level of each of these elements separately (Osredkar, Sustar 2011). Studies of zinc so far have provided strong theoretical and experimental evidence for the association between its serum levels and depression. The relationship between serum zinc levels and the occurrence of depression was first mentioned in the 1980s (Hansen et al. 1983). Most researchers indicate that patients with depression and mood disorders have lower serum zinc levels (Siwek et al. 2007, 2010). The functioning of the nervous system is also determined by the level of selenium, whose deficiency negatively contributes to the function of some neurotransmitters. Individuals with low levels of this element more often suffer from depression and other affective disorders, as well as symptoms, such as anxiety, confusion, and hostile attitudes towards others (Pillai et al. 2014, Björkholm, Monteggia 2016). In our study, an overwhelming majority of the women had the element levels within the laboratory reference ranges, which may have resulted from the fact that most of them did not have depressive disorders. Demographic changes in the worldwide population include the constant lengthening of life expectancy of women and men. Women spend about 30% of their lives in the postmenopausal period, which is when they quite commonly experience mood disorders and depression.

There is a lot of scientific evidence that the risk of developing symptoms of depression in women rises with age and the change in the menopausal status. Many of the studies published so far describe an impact of a decline in sex hormone levels during this period on the development of depressive symptoms, however, this issue has not been fully explained yet (Jurczak et al. 2015). The incidence of depressive symptoms in postmenopausal women is undoubtedly related to deficiencies of the above-mentioned elements (Sawada, Yokoi 2010). In our study, the greater part of the postmenopausal women (77.5%) had no depressive disorders. Mild symptoms were only noted in 16.7% of cases. The women with moderate and severe disorders were in the definite minority.

Depressive moods often accompany anxiety disorders. According to Kessler, anxiety is a relatively common psychiatric affective disorder, underlain by various biological mechanisms (Kessler et al. 2009). Some of its major causes are defects of neurotransmission in the central nervous system (especially the serotoninergic and noradrenergic systems). Anxiety can be understood as a transitory and situationally conditioned state of an individual, or as a relatively permanent personality trait, which determines an individual's reactions to certain situations (Mielimąka et al. 2015). Our analysis of postmenopausal women did not demonstrate high levels of anxiety as a trait or as a state. Numerous researchers assert that supplementation with the elements involved in psychoendocrine processes may prevent the feelings of stress and anxiety, and consequently many anxiety disorders (Boyle et al. 2017, Wang et al. 2018).

A vast majority of clinical studies provide evidence for the decreased serum levels of magnesium, selenium, zinc, and copper in patients with depressive disorders. In our investigation, an attempt was made to assess the relationship between the levels of these elements and the severity of depressive disorders in postmenopausal women. Our results did not confirm statistically significant correlations between the levels of magnesium, zinc, selenium, and copper and the occurrence of affective disorders. Different results were obtained by Styczeń's team, who reported a positive correlation between the severity of depressive symptoms and blood magnesium levels (Styczeń et al. 2015). This connection was also observed by Derom et al., who, however, indicated the necessity for further investigation based on a larger study sample (Derom et al. 2013).

In recent years, the incidence of depressive disorders has increased, leading to many health complications, and thus posing a serious public health problem (Lakhan, Vieira 2008). Although the literature does not provide unequivocal clinical research results, the association between deficiency of selected elements and the development of depression is noticeable. Selected elements can serve as potential markers of depressive disorders.

CONCLUSIONS

1. No relationship was demonstrated between the levels of selected elements and the development of depressive and anxiety disorders in the studied postmenopausal women.

2. There is a need for further clinical research based on a large sample on the role of magnesium, zinc, selenium, and copper in the pathophysiology of depression and other affective disorders, as well as the usefulness of these biomarkers in the monitoring of these health problems.

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