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**Association between bipolar affective disorder, use of antidepressants
and osteoporosis**

Повезаност биполарног афективног поремећаја, употребе антидепресива
и остеопорозе

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SUMMARY

Introduction/Objective Osteoporosis is one of the most common comorbid disorders in depressive mood disorder. The aim of this study was to assess the association between use of antidepressants and osteoporosis in patients with bipolar affective disorder (BPAD).

Methods The study included 73 inpatients, aged 50-72 years, male and female, hospitalized with depressive episode of BPAD from 2016-2020 at Clinic of psychiatry, Clinical centre of Vojvodina, divided in two groups: a) first group (40) was treated with selective serotonin reuptake inhibitors (SSRIs) in combination with mood stabilizer (lithium carbonate/lamotrigine), b) second group (33) was treated with mood stabilizer only. Study included two control groups, too. Clinical measurements of bone mineral density at lumbal spine and hip was made using dual energy X-ray absorptiometry. CrossLaps and level of calcium and vitamin D were collected from blood sample. Data was analyzed by Analysis of variance and Kruskal-Wallis test.

Results Osteoporosis was registered in 25% of patients in the first group and in 18% of patients in second group, while osteopenia was observed within 40% of patients in the first group and in 37% of patients in the second group. There was significant difference in value of CrossLaps, and level of 25 (OH) D vitamin between control groups and first two groups, as well as in prevalence of osteoporosis and osteopenia.

Conclusion Depressive episode in BPAD is connected with higher prevalence of osteoporosis. Patients treated with SSRIs have higher prevalence of osteoporosis than patients treated with mood stabilizers only.

Keywords: bone mineral density; depression; selective serotonin reuptake

САЖЕТАК

Увод/Циљ Остеопороза је један од најчешћих коморбидних поремећаја међу болесницима са депресивним поремећајем. Циљ овог истраживања је био да се процени повезаност употребе антидепресива са остеопорозом код болесника лечених од биполарног афективног поремећаја (БАП).

Метод Ова студија је обухватила 73 болесника, стара 50-72 године, оба пола, хоспитализована због депресивне епизоде биполарног афективног поремећаја, између 2016. и 2020. године, на Клиници за психијатрију Клиничког центра Војводине. Болесници су подељени у две групе: а) прва група (40) је лечена селективним инхибиторима поновног преузимања серотонина (ССРИ) у комбинацији са стабилизатором расположења (литијум-карбонат/ламотригин), б) друга група (33) је третирана само стабилизатором расположења. Студија је такође обухватила и две контролне групе испитаника. Клиничка мерења минералне густине кости на лумбалној кичми и куку изведена су методом абсорпциометрије рендгенских зрака двоструке енергије. Измерени су нивои калцијума и Д-витамина из узорака крви болесника. Подаци су статистички обрађени анализом варијансе и Крускал-Волис тестом.

Резултати Остеопороза је регистрована код 25% болесника у првој и код 18% болесника у другој групи, док је остеопенија установљена код 40% у првој и код 37% болесника у другој групи. Постоји статистички значајна разлика у вредностима нивоа *CrossLaps* и нивоа 25 (OH) D-витамина, као и у заступљености остеопорозе и остеопеније у односу на контролне групе.

Закључак Депресивна епизода у БАП је повезана са већом преваленцом остеопорозе у односу на контролну групу. Болесници лечени са ССРИ имају већу преваленцу остеопорозе у односу на болеснике лечене само стабилизатором расположења.

Кључне речи: минерална густина кости; депресија; селективно преузимање серотонина

INTRODUCTION

Depression has been reported as the most common mental disorder in the 21st century based on its incidence and prevalence that have been increasing constantly over the last decades not only in Serbia, but in the majority of other countries with valid health statistics [1, 2]. Besides incidence rate, depression is significant, because numerous metabolic disorders can result from untreated or inadequately treated mental disorder. Osteoporosis is one of the most common comorbid disorders, especially in bipolar and unipolar mood disorders. Nowadays, there is a risk of osteoporosis becoming a “silent epidemic,” just like mood disorders, which are both metabolic disorders. According to the official statistics, every third woman and every sixth man over 60 is affected by osteoporosis [3]. The risk of these health problems is growing substantially considering the common comorbidity of mood disorders and osteoporosis [4, 5]. Well-known risk factors are: biological predisposition, gender, age, positive family history, low body weight and bad habits (smoking, taking alcohol, fast food, greasy and poor-quality food, lack of physical activity) as well as the use of certain medications (etc. corticosteroids) [6, 7]. In addition to those risk factors, it is not clear whether the same pathophysiological processes take place in mood disorders and osteoporosis [1, 2].

Common facts that prove the existence of common pathophysiological processes in both disorders are considered to be hypercortisolemia, increased activity of the hypothalamic-pituitary-adrenal axis, increased cytokine activity (interleukin-6 (IL-6) and tumor necrosis factor (TNF)), and decrease in anti-inflammatory interleukin activity (IL-10, IL-13) as well as an increase in oxidative stress factors, increase in parathyroid hormone levels with consecutive decrease of 25 (OH) D vitamin, and the decrease in estrogen levels in plasma [6, 8–11].

Although the association between depression and osteoporosis has not been clearly explained, recent studies suggest that depression should be considered as an official risk factor for osteoporosis [12]. Depressive disorder can be represented as unipolar (depressive episodes only), or within bipolar disorder, when depressive symptoms are replaced, or it can overlap with manic/hypomanic symptoms. Only few clinical studies have been focused on monitoring the risk for osteoporosis within bipolar patients [13].

The aim of this study was to assess the association between developing osteoporosis and taking antidepressants in patients with diagnosis of bipolar affective disorder.

METHODS

The study included 73 patients, aged 50–72 years, both male and female, hospitalized with diagnosis of bipolar affective disorder (middle, recurrent, depressive episode, Hamilton Depression Scale (HAMD) more than 20), from 2016-2020 at Clinic of Psychiatry, Clinical Centre of Vojvodina. Also, two control groups were included: a) the first control group (30) included depressive patients without psychopharmacotherapy; b) the second control group (30) was formed of healthy volunteers.

Patients with psychopharmacotherapy (73) were divided into two groups: a) the first group (40) was treated with selective serotonin reuptake inhibitors (SSRIs) antidepressants (escitalopram, fluoxetine, sertraline) in combination with mood stabilizers (lithium carbonate and/or lamotrigine). Antidepressants were added to therapy due to non-reactive depression; b) the second group (33) was treated with mood stabilizers only, without antidepressants.

Sociobiographic and sociodemographic data were collected, including information about all medication. Diabetes mellitus, hypothyroidism, hyperlipidaemia and hypertension were the most common comorbidities. Patients were under medication control. Diagnosis of osteoporosis was based on the ICD 10 code. Clinical measurements and assessment of BMD at lumbar spine (L2-L4) and hip was made, using dual energy X-ray absorptiometry (DXA/DEXA). Also, CrossLaps and vitamin D and calcium level were collected from blood sample [14].

All patients signed the consent according to the Declaration of Helsinki. The study has been approved by competent ethics committee of the Clinical Center of Vojvodina, and conforms to the legal standards. For the purpose of statistical analysis, SPSS (version 21.0) and JASP (version 0.14.1.0) were used. Results were statistically analyzed by one-way analysis of variance – ANOVA and Tukey's Honest Significant Difference (HSD) post-hoc test as parametric method of testing and by Kruskal–Wallis test with post-hoc Mann–Whitney U tests as non-parametric method of testing. The presence of osteoporosis or osteopenia was done using analysis of contingency tables. A p-value less than 0.05 was considered statistically significant.

RESULTS

Average age in the first group was 56.2 ± 7.8 , and in the second group was 55.9 ± 4.3 . In both control groups, average age was similar (55 ± 3.3 in the first control group and 56.1 ± 4.1 in the second control group). Women were represented in a larger percentage in all groups: 66% vs 34% and 67% vs 33% (control groups 68% vs 32% and 75% vs 25%). Mood stabilizers such as lithium carbonate and lamotrigine were included: 7.8 years \pm 3.6 in the first group, and 8.4 years \pm 3.2 in the second group. Patients with comorbid physical disorders: hypothyroidism, diabetes mellitus and arterial hypertension were also included in this study. All comorbidities were adequately treated. Forty patients were administered with SSRI antidepressants, which are indicated in the treatment of moderate depressive episodes in combination with mood stabilizer. Thirty-three patients were treated with mood stabilizers as monotherapy. These SSRI antidepressants were administered: sertraline in 68% of patients in an average dose of 75 mg/day, escitalopram in 20% of patients- average dose of 10 mg/day and fluoxetine in 12% of patients in an average dose of 20 mg/day. The average length of SSRI was 72 days (Table 1).

In Table 2 are presented values of indicators of osteoporosis in the patients of all four groups: osteoporosis was registered in 25% of patients treated with mood stabilizers and SSRI antidepressants and in 18% of patients treated with mood stabilizers, while osteopenia was observed within 40% of patients treated with the combination of SSRI and a mood stabilizers and in 37% of patients treated with a mood stabilizers only. In the first control group, osteoporosis was detected in 16% of patients and osteopenia was presented in 32% of patients. In the group of healthy volunteers, osteoporosis was presented in 10% of examinees, while osteopenia was detected in 20% of examinees. There was no significant difference in value of CrossLaps and 25 (OH) D vitamin between first two groups of patients. There was a significant difference between both control groups and other two groups in prevalence of osteoporosis and osteopenia as well as in value of CrossLaps and 25 (OH) D vitamin.

Smokers in all groups of patients were in high level (98% in patients treated with SSRI vs 99% in patients treated just with mood-stabilization medicaments). In control groups, smokers presented 86.5% of sample.

DISCUSSION

Numerous results indicate strong relationship between use of antidepressants and osteoporosis. In addition to undoubtedly common comorbidity of depression and osteoporosis, the measures for prevention and early diagnosis need to be taken in order to have an early detection, treatment and lowering of the complication and mortality rate of both disorders [1, 4, 10, 11, 14].

According to the World Health Organization (WHO) reports, mood disorders represent a huge health problem in comorbidity with osteoporosis and there is no doubt that unrecognized and untreated symptoms of depression, as well as anxiety symptoms, extensive use of certain types of antidepressants have been associated with increased risk of osteoporosis in the last decade [4, 15, 16]. Osteoporosis is related to higher incidence of hip fracture in women over 60 who were treated by therapeutic doses of SSRI in comparison to the depressive patients treated by other antidepressants [17, 18]. The most supported assumption in literature nowadays is that depression, as a separate mood disorder, triggers the development of osteoporosis through neuroendocrine and immune mechanisms as well as through bad habits (poor nutrition, alcohol, smoking, lack of physical activity) [3-5, 7, 15, 16]. The results have been controversial up to now, even though there is still a large number of studies that do not support the assumption that SSRI antidepressants play neuroendocrine role in bone metabolism. However, all the data require adequate choice of antidepressants for each individual patient together with consideration of all comorbidities and received therapies.

Bone architecture and the risk of osteoporosis can be assessed in a timely manner during therapy by measuring the bone density, determining vitamin D status in bones, and determining ionized calcium and other parameters of osteoporosis. Vitamin D is very important for physical and mental health. It is one of the key hormones in the regulation of bone metabolism. Vitamin D deficiency could increase the risk for low bone mineral density, or osteoporosis. During last years, lot of issues point out that vitamin D has important role in vulnerability for depression [10, 15, 17]. It is interesting that insufficient level of 25-hydroxy vitamin D (less than 50 nmol/l) could be associated with depressive disorder. Interestingly, lower level of vitamin D is found in 40-50% of depressive patients. This is probably due to lifestyle in depression.

Depressive patients very often smoke a lot, sometimes they abuse alcohol or other psychoactive substances. Such behavior may lead to hypovitaminosis [6, 19]. On the other side, some issues point that people with lower level of vitamin D could be at greater risk of developing depressive disorders [20, 21]. Until now, the relationship between hypovitaminosis D and depression remains unclear. Probably, the association between low level of D vitamin and depression lies in homostatic, trophic and immunomodulatory effects of vitamin D [22, 23, 24]. New investigations also show that vitamin D receptors are identified in the same area of the brain associated with depression. Anyway, hypovitaminosis D may represent an underlying biological vulnerability for depression [1, 17, 18, 23]. Although there is still no evidence that treatment with vitamin D supplements can reveal depressive symptoms, there is possibility that some subgroup of depression may maximally benefit from treatment with vitamin D. Anyway, it is clear that vitamin D has marked place in treatment of depressive patients with low level of vitamin D. In such patients, long-term supplementation of vitamin D and calcium can increase bone mass and prevent fracture and long-term invalidity. In depressive patients with osteopenia/osteoporosis most benefit is combination of adequate antidepressant therapy, psychotherapy, and, if indicated, therapy with vitamin D supplements. Also, there are some issues suggested that more intensive depression is associated with lower level of vitamin D [23, 24]. In this sample, there was no relationship between level of vitamin D and severity of depressive symptoms measured with HAMD. In the future, further investigation should be made on larger sample of patients to concern if there is connection between low level of vitamin D in blood and severity of depressive symptoms.

The benefits as well as possible adverse effects of received therapy should be examined in every patient and useful advice should be given to them on their way of lifestyle and physical activity. In case it is necessary, bisphosphonates can be used for treating osteoporosis without any risk of interaction with SSRI antidepressants. Schweiger (2010) argues that osteoporosis of the spine has been diagnosed in almost 15% of patients who suffer from depression - unipolar or bipolar, while numerous recent studies show a considerably higher incidence of depressive symptoms in women with vertebral and hip fractures [2, 8, 9]. In the adolescent population, girls who suffer from anorexia and mood disorders are significantly more affected by osteoporosis than the general population. In addition to undoubtedly common comorbidity of depression and osteoporosis, the measures for prevention and early diagnosis need to be taken in order to have an early detection, treatment and lowering of the complication and mortality rate of both disorders. For the purpose of screening for osteoporosis, the National Osteoporosis

Foundation recommends using the DXA/DEXA technique in women, aged 65 and above and men aged 70 and above or in people who are older than 50 and are at increased risk of fracture [1, 3, 4, 9, 10].

Hypercortisolemia in depression is meant to be the possible neurobiological base for such hypothesis [8, 9, 19]. Depression causes activation of HPA axis (Hypothalamo-pituitary-adrenal) and this alteration, which could be the crucial factor for increased risk of osteoporosis in depressed patients [1, 10]. Actual hypothesis considers that corticotropin-releasing hormone (CRH) and persisting high level of cortisol in depressed patients lead to secondary hypogonadism, which present one of the crucial risk factors for bone loss [1, 8, 14, 15, 21]. Such negative influence could be responsible for higher incidence of osteoporosis in patients with depressive symptoms, both in unipolar and bipolar affective disorders compared to general population [1, 15, 17, 22]. According to the definition provided by the WHO, osteoporosis is a progressive systemic skeletal disease characterized by reduced bone mineral density and bone microarchitecture alteration, which contributes to the risk of fracture and disability [1, 2]. The incidence of osteoporosis is 8–10%, but it is 10 times more common in women who reach menopause – the osteoporosis has been diagnosed in almost 22 million women and about 5.5 million men in the European Union [6]. The reduced bone mass and demineralization cause the bone to lose its strength and elasticity which significantly increases the risk of fracture even with minimal trauma. According to the majority of the world's statistics, it is considered that almost 70% of fractures occur due to osteoporotic bones. Bone demineralization occurs as a result of bone remodeling process due to increased catabolic processes (increased osteoclast function and reduced osteoblast function). The osteoporosis is diagnosed by using the bone densitometry or dual-energy X-ray absorptiometry (DXA/DEXA scan) and bone mineral density (BMD) described as a T-score and Z-score. A T-score represents standard deviation of a patient's BMD from the average value of BMD of a person of the same gender and constitution aged between 20 and 30. Having the T-score between -1 to -2.5 is osteopenia and the T-score lower than -2.5 is osteoporosis [3, 20].

In addition to depression being considered a risk factor for osteoporosis, in the last ten years, a considerable controversy has been caused by the results of the studies that show a possibility that certain types of antidepressants can cause osteoporosis as well. This assumption refers to the selective serotonin reuptake inhibitors (SSRIs) type of antidepressants [12]. The mechanism of the action of these "newer" antidepressants is based on preventing the reuptake

of serotonin at the presynaptic membrane, which leads to an increase in the level of serotonin in the synaptic cleft and its reuptake by receptors located at the postsynaptic membrane. The SSRIs achieve their antidepressant effect by binding to the serotonin transporter (SERT) in CNS. The possibility that these antidepressants trigger osteoporosis is based on the discovery that functional serotonin receptors such as SERT (for which SSRIs are bound to at allosteric sites) are identified in osteoblasts, osteoclasts and osteocytes. The second possibility is that SSRIs lead to a decrease in testosterone levels and an increase in prolactin level in both genders, which represents a risk for osteoporosis. The following risk factors have significant effect on the increased incidence of osteoporosis: chronic diseases – thyroid and parathyroid function disorders, hypogonadism, Cushing's and Addison's disease, insulin-dependent diabetes, neurological disorders and digestive disorders. [1, 14, 19, 21, 22].

Not only in the middle age and elderly patients, but also in the adolescent population, girls who suffer from anorexia and mood disorders are significantly more affected by osteoporosis than the general population. In addition to undoubtedly common comorbidity of depression and osteoporosis, the measures for prevention and early diagnosis need to be taken in order to have an early detection, treatment and lowering of the complication and mortality rate of both disorders [1, 4, 10, 21, 22, 25].

CONCLUSION

The results of this investigation indicate that depressive episode, middle intensity, in bipolar affective disorder is connected with higher prevalence of osteoporosis. Patients treated with SSRIs have higher prevalence of osteoporosis than patients treated with mood stabilizers only, without antidepressants. In the future, larger cohort of patients should be included in this kind of researches.

Certainly, prevention is better than treatment of osteoporosis, which, in case of treatment of depressive symptoms, implies the selection of adequate group of medicines with respect to the age, initial status of patient's skeleton, especially in case of people who have already been diagnosed with osteoporosis or other familiar risk factors for its development.

Conflict of interest: None declared.

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Table 1. Type of psychopharmacotherapy

Patients		First group	Second group	Third group	Fourth group	p
		SSRI and mood stabilizers in therapy (\pm SD)	Mood stabilizers in therapy (\pm SD)	Control group of patients with depressive disorder, without SSRI or Mood stabilizers in therapy (\pm SD)	Control group of healthy volunteers (\pm SD)	
n =133		n = 40	n = 33	n = 30	n = 30	No significant difference
Age		56.2 \pm 7.8	55.9 \pm 4.3	55 \pm 4.3	54.2 \pm 3.2	No significant difference
Gender	Male	34%	33%	32%	25%	No significant difference
	Female	66%	67%	68%	75%	No significant difference
Duration of therapy with mood stabilizers (in years)		7.8 \pm 3.6	8.4 \pm 3.9	-	-	No significant difference
Dose of SSRIs: Sertraline (68%) Escitalopram (20%) Fluoxetine (12%)		75 mg/day 10 mg/day 20 mg/day	-	-	-	-

Table 2. Parameters of bone metabolism

Bone metabolism parameters	First group	Second group	Third group	Fourth group	p
	SSRI and mood stabilizers in therapy (n = 40) (\pm SD)	Mood stabilizers in therapy (n = 33) (\pm SD)	Control group of patients with depressive disorder, without SSRI or mood stabilizers in therapy (n = 30) (\pm SD)	Control group of healthy volunteers (n = 30) (\pm SD)	
25 (OH) D vitamin (ng/ml)	24.5 \pm 6.7 ^a	29.1 \pm 8.5 ^a	37.5 \pm 7.2 ^b	51.1 \pm 11.4	< 0.001*
Ca ⁺⁺ (mmol/l)	1.1 \pm 0.1 ^c	1.0 \pm 0.1 ^a	1.1 \pm 0.1	1.1 \pm 0.1	< 0.001*
β -CrossLaps (ng/l)	760.9 \pm 129.4 ^a	780.5 \pm 84.0 ^a	583.7 \pm 48.3 ^b	380.0 \pm 84.9	< 0.001*
Osteopenia	40% ^d	37%	32%	20%	< 0.01*
Osteoporosis	25% ^e	18%	16%	10%	< 0.01*

^ap < 0.001 compared with group 3 and 4

^bp < 0.001 compared with group 4

^cp < 0.001 compared with group 2

^dp < 0.01 compared with group 4

^ep < 0.01 compared with group 2, 3, and 4

*significant difference