ORIGINAL SCIENTIFIC ARTICLE

VITAMIN D DEFICIENCY IN PATIENTS RECEIVING ANTIDEPRESSANT MEDICATIONS

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ABSTRACT

This study aimed at exploring vitamin D levels in treated depressive patients in comparison to healthy individuals. The cross-sectional study included 20 ambulatory and inpatients with depressive episodes taking antidepressants and 30 healthy individuals. The serum concentration of 25(OH)D from collected blood samples was determined using biochemical analyzers. Serum 25(OH)D levels (ng/mL) in patients were significantly lower (the mean 13.1, standard deviation 7.3, median 11.4, minimal 3.8, maximal 35.9) then in control subjects (19.4, 9.1, 15.8, 7.6, 43.6) (p=0.004). Additional targeted research is needed because some lifestyle and dietary habits which are known to influence vitamin D status may confound observed effects.

Keywords: *vitamin D deficiency, antidepressants, depressive patients, serum vitamin D levels.*

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INTRODUCTION

There is a growing amount of epidemiological and other evidence that associates depression and bone metabolism disturbances with the consecutive development of osteoporosis and thus increased risks of bone fractures (1-4). Researchers proposed a variety of potential mechanisms for these causalities including the past, recent and current use of antidepressants. However, there is not enough scientific evidence for identifying any particular pharmacological subgroup or a single drug as a definite cause of vitamin D deficiency (5, 6). Taking into account the tremendous importance of vitamin D for bone health, the studies on the potential effects of antidepressants should become an issue of crucial interest for both scientists and physicians (7).

Surprisingly, the studies in relationships between individual antidepressants or drug classes and vitamin D levels are scarce. One of the earliest reports, published in the middle of the 1980s, focused on mianserin but some additional evidence has appeared only (8). In a trial that included several hundreds of elderly people (aged 60 or more) in which the patients with depression were compared to a control group without the depressive disorder, only the use of tricyclics (but not selective serotonin inhibitors or other antidepressants) was independently associated with significantly lower serum concentrations of $1,25(OH)_2D_3$, but not $25(OH)D_3$, after the adjustment for confounders (9).

METHODS

This study aimed at exploring 25(OH)D serum levels in patients with depressive disorder who took antidepressants in comparison to healthy individuals. In order to control the possible side-effects of concomitant psychotropics, only a limited amount of benzodiazepines was allowed as an additional medication.

The study has a cross-sectional design and, besides blood testing for measuring vitamin D levels, it follows the observational approach. The Ethics Committee of the Clinical Centre "Kragujevac", Kragujevac, Serbia, approved the research and all subjects signed the informed consent for the participation in the study. The study sites included the departments of psychiatry, clinical biochemistry, and clinical pharmacology.

In order to determine the sample size for this study, the input parameters were needed and they were obtained from the study conducted by Stanojević Pirković et al., 2012 (10). In addition, their results reveal the changes in 25(OH)D serum concentrations which also serve here as an argument for the hypothesis that there are differences between patients using antidepressants and healthy individuals. An appropriate software (www.gpower.hhu.de) was used with alpha=0.05, a study power of 0.8, and other necessary inputs. It provided the results that the total study sample should be at least 40 subjects – with 20 individuals in both an experimental and a control group. Our study included 50 adult subjects of both genders who were allocated to two groups: 20 patients with mental illnesses taking antidepressant medication (the experimental group) and 30 healthy individuals (the control group). The inclusion criteria were: adult patients (18 y of age or more), male or female gender, treated at the Clinic for Psychiatry of the Clinical Centre of Kragujevac (outpatients and inpatients) or Department of Neuropsychiatry of the Primary Health Care Centre Kragujevac (outpatients). Besides, the criteria were having only one diagnosis of mental disorder – a depressive episode (World Health Organization International Classification of Diseases version 10, code F32), and having given consent for voluntary participation in the study. The antidepressants had been the foundation of the treatment and only a limited amount of benzodiazepines was allowed to enhance sedative, anxiolytic effects. The use of antipsychotics, mood stabilizers, cognitive enhancers, and other psychotropic drugs was an exclusion criterion for participation in this study. The drug treatment for a concomitant somatic disease in stable phases or stages was allowed within both study groups.

The semi-structured questionnaire for the assessment of vitamin D status was designed based on the previous studies in the field and the study was conducted within the same geographical area (10, 11). The other data were extracted from the patients' medical files or were obtained through an interview with healthy subjects. The blood samples were obtained from May to June 2016 which is a season with adequate and approximately the same sunshine exposure. The serums were sent to the hospital laboratory where the vitamin D (in 25(OH)D form), calcium, phosphorus, magnesium, sodium, and potassium concentrations were determined with "Cobas e601" analyzer (*Roche Diagnostics*, Mannheim, Germany) and "Beckman Coulter AU 680" biochemical analyzers, as appropriate. The vitamin D measurements were performed with the manufacturer's reagent testing kit (electrochemiluminescence binding assay), providing regular internal and external controls according to the laboratory quality assurance procedures.

The vitamin D status types were defined as: deficiency (below 20 ng/mL), insufficiency (21-29 ng/mL) and sufficiency (30-100 ng/mL) (12).

The statistical analyses of the collected data included testing the sample distribution for normality (Normal Q-Q Plot, Histogram, Kolmogorov-Smirnov test, Shapiro-Wilk test), descriptive statistics as well as Wilcoxon rank-sum test, Pearson $?^2$ test, and Fisher exact test for analyzing the differences between the groups. The level of probability for statistical significance was predetermined at $p<0.05$. The data were processed and analyzed in the statistical program R – version 3.1.1 (2014-07-10).

RESULTS

The demographic and other clinical variables are presented in detail in Table 1. There were 2 inpatients and 18 outpatients in the antidepressant group. The mean duration of their primary mental illness was 3.6 (4.9) years (median 1.5, from one month to 19.9 years). The most frequently prescribed antidepressant drug was sertraline (in 10 patients) followed by escitalopram (4), mirtazapine (5), paroxetine (4), venlafaxine (2) and amitriptyline (1), maprotiline (1), and trazodone (1). Eight patients used a combination of two antidepressants and twelve had antidepressants prescribed as a monotherapy. Only concomitant psychotropic medications allowed for the participation in this study were benzodiazepines and similar drugs such as lorazepam (in 8 patients), bromazepam (5), alprazolam (4), zolpidem (3), and diazepam (1). Arterial hypertension was the most frequent somatic disease in both study groups and it was significantly more frequent in depressive patients. Other chronic illnesses were osteoporosis (3 patients, 1 control subject), diabetes mellitus type 2 (in 3 patients), and breast cancer (one patient). Thus, a somatic disease burden was significantly higher in the patient group than in the control group.

The data confirmed that there was a statistically significant difference between the study groups in 25(OH)D serum concentrations (Figure 1) (Table 1). The patients taking antidepressants had significantly lower 25(OH)D serum levels than healthy subjects both in the overall study sample (n=50, p=0.004) and in the subgroup with vitamin D deficiency (n=36, p=0.020) by 22 – 32% on average.

However, some socio-demographic and most of the habitual and dietary characteristics that might directly or indirectly impact vitamin D status were also statistically different between the study groups (Table 1).

The results presented in this paper, in addition to other reliable evidence, confirm that individuals on antidepressant drugs used for treating a depressive disorder are a vulnerable population group for developing inadequate vitamin D serum concentrations. The additional drugs used by the subjects in this study included benzodiazepines and antihypertensive medications (ace inhibitors, beta-blockers, and calcium channel blockers) but we are currently unaware of any valid data about their potential impacts on vitamin D metabolism in humans and antidepressants thus remain here the only agents of possible causalities.

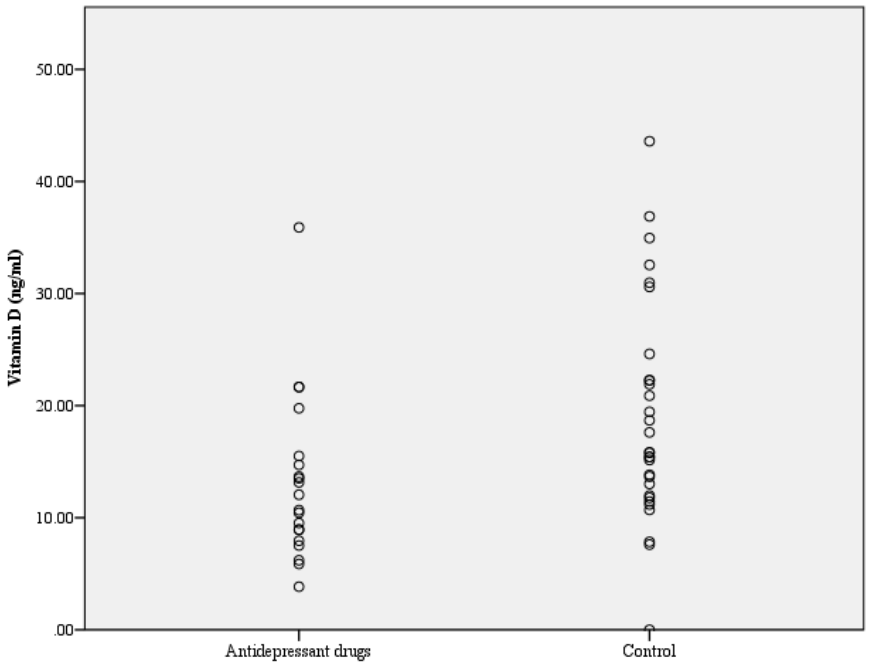
Table 1. Characteristics of study subjects and the status of vitamin D and bone minerals

Variable	Antidepressant group (n=20)	Control group (n=30)	Statistics
Male gender	4 (20.0)	12 (40.0)	Fisher Exact Test p=0.216
Age (years)	52.5 (13.3)	49.2 (14.6)	Wilcoxon rank sum test W=330.0, p=0.559
Body mass index (kg/m^2)	25.0 (3.4)	25.7 (4.0)	Wilcoxon rank-sum test W=284, p=0.766
Urban inhabitancy	13 (65.0)	30 (100)	Fisher Exact Test, p<0.001
Higher education*	4 (20.0)	20 (66.7)	Fisher Exact Test, p=0.002
Good life condition*	5 (25.0)	30 (100)	Fisher Exact Test, p<0.001
Smoking	10 (50.0)	9 (30)	Fisher Exact Test p=0.168
Coffee consumption*	6 (30.0)	5 (16.7)	Fisher Exact Test p=0.277
Physical activity	14 (70.0)	30 (100)	Fisher Exact Test, p=0.002
Sedentary lifestyle	9 (45.0)	0 (0)	Fisher Exact Test, p<0.001
Meat consumers	20 (100)	30 (100)	n.a.
Fish consumers	17 (85.0)	27 (90.0)	Fisher Exact Test p=0.672
Eggs consumers	15 (75.0)	19 (63.3)	Pearson χ^2 test, χ^2_1=0.8, p=0.387
Bread consumption (g/day)	258.3 (170.8)	185.8 (151.9)	Wilcoxon rank sum test, W=324, p=0.027

Variable	Antidepressant group (n=20)	Control group (n=30)	Statistics
Sun exposure (>60 minutes/day)*	12 (60.0)	15 (50.0)	Fisher Exact Test, p=0.108
Any somatic disease	12 (60.0)	7 (23.3)	Pearson χ^2 test, χ^2_1=6.8 p=0.009
Arterial hypertension	11 (55.0)	6 (20.0)	Pearson χ^2 test, χ^2_1=6.5 p=0.010
Prevous bone fracture	1 (5.0)	1 (3.3)	Fisher Exact Test, p=1.000
Serum 25(OH)D (ng/mL)[1]	13.1 (7.3, 11.4, 3.8, 35.9)	19.4 (9.1, 15.8, 7.6, 43.6)	Wilcoxon rank-sum test W=156, p=0.004
Deficiency/ Insufficiency/ Sufficiency of vitamin D	17 (85.0) / 2 (10.0) / 1 (5.0)	19 (63.3) / 5 (16.7) / 6 (20.0)	Fisher Exact Test, p=0.254
Serum 25(OH)D in patients with deficiency (ng/mL)[1]	10.7 (4.0, 10.4, 3.8, 19.8)	13.7 (3.2, 13.8, 7.6, 19.4)	Wilcoxon rank-sum test W=87.5, p=0.020
Serum 25(OH)D in patients with insufficiency (ng/mL)[1]	21.7 (0.1, 21.7, 21.7, 21.8)	22.4 (1.4, 22.2, 20.9, 24.7)	Wilcoxon rank-sum test W=2, p=0.381
Serum 25(OH)D in patients with sufficiency (ng/mL)[1]	35.9 (n.a., 35.9, 35.9, 35.9)	34.9 (4.9, 33.8, 30.6, 43.6)	Wilcoxon rank sum test W=4, p=0.857
Serum calcium (mmol/L)[2]	2.38 (0.22)	2.40 (0.11)	Wilcoxon rank sum test W=295, p=0.929
Serum magnesium (mmol/L)[2]	0.76 (0.09)	0.90 (0.05)	Wilcoxon rank sum test W=37, p<0.001
Serum phosphorous (mmol/L)[2]	1.06 (0.25)	1.11 (0.17)	Wilcoxon rank-sum test, W=246, p=0.423

Numbers represent the frequency (percent), [1]the mean (standard deviation, median, minimum, maximum), and [2]the mean (standard deviation); *>2 categories: n.a.-not applicable, due to single observation

Figure 1. The serum concentrations of 25(OH)D in patients taking antidepressant drugs (n=20) and in healthy, control subjects (n=30)



DISCUSSION

The published data which were systematized some years ago identified patients with depressive disorders to be a population susceptible to developing vitamin D deficiency (13, 14). In addition, several trials suggested that vitamin D supplementation could improve patients' depressions to some extent (15, 16, 17). This is in compliance with our knowledge about the significance of vitamin D for normal brain development and functioning (18, 19). The statistical significance of the observed differences between depressive patients and the healthy control group found in our study was expected. However, we are still unable to claim that there is a definite causality between antidepressant use and vitamin D deficiency since we noted significant differences between the study groups in some lifestyle and dietary habits which are known to influence vitamin D status and which may intervene with the effects of antidepressants (20). This is the major limitation of this study. A multivariable analysis is needed but was not performed due to the limited sample size and preliminary nature of our study design. Consequently, the issue is yet to be addressed in the future.

It is pretty unlikely that the question about potential antidepressant-induced vitamin D deficiency and/or bone metabolism disturbances could be resolved without a carefully selected research approach targeted at individual drugs. The pharmacology of antidepressant drugs is very complex since they target plenty of neurotransmitter receptors, transporters, and other biologically active molecules and there are significant differences even within the same drug subclass which may result in a wide variety of effects and outcomes within the single class (21). For example, the analysis of group effects of selective serotonin reuptake inhibitors, which excluded their influence on bone mineral density, has revealed that fluoxetine affects cultivated human bone cells while citalopram and sertraline influence the development of human embryonic bone (22, 23, 24). Therefore, there is a possibility that methodological approaches used in previous studies focused on the effects of a drug class had no power to detect small but important differences which exist among individual drugs in terms of their influence on bone health parameters, including vitamin D status.

CONCLUSION

In conclusion, patients with depressive episodes who take antidepressants have a higher probability of inadequate levels of 25(OH)D serum in comparison to healthy individuals. However, the true nature of the relations between the disease, disturbances, antipsychotic drugs, and other plausible contributors is currently unknown. Taking into account the significance and the scope of medical and public health issues related to mental disorders, further research into nutrition and pharmacotherapy is needed in near future in order to finally resolve the issues of potential drug causalities.

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CONFLICT OF INTEREST

All authors have no conflicts of interest.

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