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VITAMIN D STATUS IN PATIENTS WITH MENTAL DISORDERS: A CROSS-SECTIONAL ANALYSIS OF SINGLE COHORT FROM ROUTINE PRACTICE

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Abstract

Context. Clinical research suggests that vitamin D deficiency correlates with mental illnesses.

Objective. The aim was to prove that the patients from the psychiatric health care service in Serbia had higher vitamin D deficiency than patients from general practice.

Design. The study had a cross-sectional design.

Methods. The study included 47 patients aged 19 – 76 of both sexes with different mental disorders. We performed sample size calculation on available data for vitamin D deficiency in patients in health care facilities compared with the general population. The concentrations of vitamin D in serums were measured by HPLC (high performance/pressure liquid chromatography).

Results. The mean value of vitamin D (standard deviation) in the whole group of study subjects was 16.27(10.62) ng/mL; 68.1% of the patients had a deficiency of vitamin D (25(OH)D<20 ng/mL). The difference is statistically significant from expected proportion of people with vitamin D deficiency in general practice (p=0.040). Serum concentrations of 25(OH)D were significantly correlated with serum concentrations of phosphorus (ϱ=0.336, p=0.024) and sodium (ϱ=0.304, p=0.038).

Conclusions. The patients of psychiatry health care had significantly higher frequency of vitamin D deficiency than expected. There is a significant association between serum levels of vitamin D, and phosphate and sodium.

Key words: vitamin D, mental disorders, deficiency.

INTRODUCTION

The World Health Organization (WHO) estimates that several hundred million people in the world suffer from a mental or behavioral disorder at the beginning of the new millennium. In addition, mental illnesses are the second leading cause of disability worldwide (1). Depression, the most common mental disorder, is one of the major global public health problems and projected to become the second leading cause of burden of disease by 2030 (2, 3).

Scientific findings about the role of vitamin D in healthy people and patients with numerous diseases increasingly accumulate in medical literature (4). The fact that, taking into account recommended optimal values, about a third or more of adult population in societies with higher life standard had a deficiency of vitamin D, raises additional, widespread concern (5, 6). Such circumstances might have consequences for mental functions because there is evidence of the association between vitamin D and the nervous system functioning. For example, vitamin D receptors (VDR) were found in neurons and glial cells in brain areas responsible for the development of depression and suggesting a role of vitamin D for development of some mental disorders (7-9). In addition, a systematic review of 14 epidemiological studies found that the prevalence of low vitamin D serum concentrations was about 30% higher in patients with depression, who, during the course of the disease, are twice more likely to develop hypovitaminosis D than general population (10). The results of the most recent meta-analysis indicated that two-thirds of patients with schizophrenia had significant vitamin D serum deficiency (11). Moreover, some researchers found connection between 1.25-hydroxyvitamin D concentrations, dietary sodium intake and regulation of blood pressure by both salt sensitive and plasma renin-activity mechanism in humans rising awareness about possible biological link of vitamin D and electrolytes other than bone minerals (12). However, there were several studies

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that did not support the connection between vitamin D deficiency and mental disorders: no significant vitamin D deficiency was found in large groups of adult population aged 20 years, and women aged 18 to 24 years with depression (13, 14) and in the elderly and middle-aged adults aged 50 to 70 years with symptoms of schizophrenia and depression (15). This is in line with some evidences about the lack of efficacy of vitamin D supplementation for improving depression symptoms (16).

Based on the above mentioned facts and conflicting results, the relationship of vitamin D, and mental disorders needs further clarification. The existence of chronic mental illness could, itself, increase the risk for the deficit of vitamin D in patients either through lifestyle (e.g. inadequate nutrition, physical inactivity, lack of sun exposure) or exposure to psychotropic drugs. Conversely, a low concentration of vitamin D could either trigger or contribute to pathophysiological mechanisms of development of psychiatric illness.

The topic is of particular importance for the people in Serbia. During the past two decades, the residents in this country have experienced a long lasting socio-economic transition and they have being exposed to severe stress. This was associated with an increase of wide variety of mental disorders and problems of somatic health in the population, which had significant impact on public health in the country (17, 18). Therefore, the primary aim of our study was to verify that patients attending the psychiatric health care services in Serbia had significantly higher frequency of vitamin D deficiency than expected for patients in general practice from literature data. The secondary study aim was to investigate the correlation between the concentration of vitamin D and concentrations of major serum electrolytes including cations and anions others than those involved directly in bone metabolism pathways.

MATERIAL AND METHODS

Study design

The study had a cross-sectional design and it included patients with a wide range of mental disorders, being treated in everyday psychiatric practice. The study procedures did not incorporate active assessment of mental status by the study researchers (diagnostic and therapeutic procedures for mental illness). Instead, study researchers used existing medical (psychiatric) records filled previously by the patients' psychiatrists in order to extract necessary study data. The study approach was primarily observational; the only intervention was blood sampling in order to measure vitamin D and other study analyses. The study was approved by the Ethics Board of the Clinical Centre "Kragujevac" and the Ethics Board of Primary Health Care Centre of Kragujevac. It was performed during the period from May to June, 2014, which approximately corresponds to season with adequate sunshine (late spring, early summer).

Study population

The study included 47 patients treated at the Clinic for Psychiatry of the Clinical Centre "Kragujevac" (outpatients and inpatients) and at the Department of Neuropsychiatry of the Primary Health Care Centre (outpatients), Kragujevac, Serbia, with the following characteristics: adults aged 19 to 76 years, of both sexes, with a diagnosis of a mental disorder, as established previously by the patient's psychiatrist. In general, there is no particular limitation about the phase of a mental disease. The patient could be at the first episode or he or she could have stable chronic disease or had exacerbation phase (relapse) of chronic diseases. The mental disorders included three categories: schizophrenia spectrum disorders (schizophrenia, schizotypal and delusional disorders), mood (affective) disorders and other mental diseases (organic, including symptomatic mental disorders; mental and behavioral disorders due to psychoactive substance use; neurotic, stress-related and somatoform disorders; disorders of adult personality and behaviour; poisoning by sedative-hypnotic drugs without previously documented psychopathological background).

Each patient gave the consent for voluntary participation in the study. There were 6 (12.8%) patients with the first episode, 8 (17.0%) with stable disease and 33 (70.2%) with the relapsing episode of mental illness. The following subjects were excluded from participation: people with any medically documented somatic disease which disturbed homeostasis of bone and related minerals and hormones including vitamin D, the illness which prevented study conduction (e.g. medically uncontrolled disease, chronic organ failure or significant disability) and those subjects who refused to participate in the study. The respondents who participated in the study were sampled from the overall population of patients with mental disorders during successive, random study visits. All subjects were from a narrow geographical area - territory of the city of Kragujevac and its surroundings.

Data collection, study procedures and vitamin D status

The researchers collected data from three sources: medical records, study questionnaire and biochemical analysis of patients' serum samples. The questionnaire designed for assessment of vitamin D status was based on a previous study (19). It consisted of several topics that related to: demographic characteristics, previous medical personal and family history, current psychiatric and, if appropriate, somatic illness, dietary and living habits representing the known risk factors for vitamin D deficiency and/or bone metabolic diseases (e.g. low-calcium intake, inadequate sun exposure, physical inactivity, smoking, alcohol, drug-induced osteoporosis), and information on drugs and substance abuse.

Blood sampling was performed according to common standards in clinical biochemistry. Immediately after collection, the samples were centrifuged and the serum has been stored in the freezer (at -30˚C) until determination of the biochemical parameters (usually within a week from date of sampling) in the Biochemistry Department of the hospital. The serum concentration of vitamin D, in the form of 25(OH)D, calcium, phosphorus, magnesium, sodium and potassium were measured using Cobas e 411 analyzer (Roche Diagnostics, Mannheim, Germany) and "Olympus AU 400" biochemical analyzers, as appropriate. Determination of vitamin D was done by HPLC (high performance/pressure liquid chromatography).

The primary dependent variable was the vitamin D status defined by cut-off serum concentration as deficiency (≤20 ng/mL), insufficiency (21-29 ng/mL), sufficiency (30-80 ng/mL) or toxicity (>80 ng/mL) (20). For the sake of clarity, the analysis of socio-demographic and clinical characteristics of the patients take into account only two subgroups: deficient (≤20 ng/mL) and non-deficient (>20 ng/mL) study subjects. Different variables were identified as independent or confounding factors for vitamin D status such as psychotropic drugs and somatic comorbidities connected with osteoporosis (21-24). In addition, we measured serum concentration of ions of calcium (total), phosphorus and magnesium (secondary outcome variables), as well as sodium and potassium (confounding variables). Determination of serum electrolytes was based on well-known facts about direct and indirect connections to their metabolism, both mutually and with the homeostasis of vitamin D (25, 26).

Statistical analysis

We performed sample size calculation based on published data about expected level of vitamin D deficiency in patients attending health care facilities from the general population. We found no similar study for Serbian population and, therefore, used data of recent research from European country in the same climatic zone (blood sampling in the sunshine-reach season, as in our study) in which 45.1% of patients had vitamin D deficiency (27). Taking expected difference of at least 20% in the group of patients with mental illnesses, using appropriate computer program (www.g-power.de), we calculated one sample cohort of at least 40 study subjects having sufficient power (α=0.05, β=0.2) for proving higher frequency of vitamin D deficiency as statistically significant.

Statistical analyses included primarily the descriptive measures (frequencies, percentages, mean, median, standard deviation [SD] and range). Spearman rank correlation test was used to evaluate the correlation between 25(OH)D with other numeric variables of interest, and linear regression was used for a model of their relationship. The level of probability for statistical significance was established at $p<0.05$. Data processing and analysis were done in the statistical program R - version 3.1.1 (2014-07-10) - "Sock it to Me" Copyright (C) 2014 The R Foundation for Statistical Computing (took over: 22nd of October 2014).

RESULTS

The mean value of vitamin D (standard deviation) in the whole group of study subjects was 16.27(10.62) ng/mL (median 13.21, min 3.75, max 59.48). Thirty-two patients (68.1%) had a deficiency of vitamin D (25(OH)D < 20 ng/mL), which was significantly higher than expected based on data from general practice (χ^2=4.21, df=1, p=0.040). The mean serum concentration of vitamin D in patients with the deficiency was 10.58(4.19) ng/mL (median 10.60, min 3.75, max 19.9). Eleven patients (23.4 %) had the insufficiency of vitamin D (25(OH)D = 20-29.9 ng/mL), with the mean serum concentrations of 24.1(2.88) ng/mL (median 22.4, min 20.38, max 28.41). Only four patients (8.5%) had sufficient vitamin D serum concentrations (25(OH)D ≥30 ng/mL) with the mean serum concentrations of 40.21(13.64) ng/mL (median 35.48, min 30.4, max 59.48). Socio-demographic and clinical characteristics of patients are described and analyzed in detail in Tables 1 and 2 and Fig. 1.

Correlation analysis showed statistically significant relationships between serum concentrations

Table 1. General and other patient's characteristics according to 25(OH)D categories

Characteristics	Total	25 (OH)D status	
		Deficient	Non-deficient
General			
Gender			
Male	20 (42.6%)	11 (34.4%)	9 (60.0%)
Female	27 (57.4%)	21 (65.6%)	6 (40.0%)
*Age (*yrs*)*			
Mean (SD)	45.68 (13.26)	46.12 (12.29)	44.73 (15.56)
Median (range)	47 (19-76)	47 (19-76)	48 (22-66)
*Body mass index (*kg/m^2*)*			
Mean (SD)	24.65 (4.06)	24.26 (3.3)	25.45 (5.36)
Median (range)	24.2 (17.3-35.2)	24.2 (17.3-31)	24.1 (17.6-35.2)
Education and conditions of life			
Education			
Uncompleted primary school	3 (6.4%)	1 (3.1%)	2 (13.3%)
Primary school	11 (23.4%)	5 (15.6%)	6 (40.0%)
Secondary school	30 (63.8%)	24 (75.0%)	6 (40.0%)
College or faculty	3 (6.4%)	2 (6.3%)	1 (6.7%)
Inhabitance status			
Urban	35 (74.4%)	25 (78.1%)	10 (66.7%)
Rural	12 (25.6%)	7 (21.9%)	5 (33.3%)
Life conditions			
Good	22 (46.8%)	13 (40.6%)	9 (60.0%)
Average	5 (10.6%)	4 (12.5%)	1 (6.7%)
Poor	20 (42.6%)	15 (46.9%)	5 (33.3%)
Habits			
Smoking (yes)	31 (66.0%)	22 (68.8%)	9 (60.0%)
Physical activity (yes)	32 (68.0%)	19 (59.4%)	13 (86.7%)
Proper nutrition (yes)	8 (17.0%)	3 (9.4%)	5 (33.3%)
Illness & treatment			
Illness duration, current primary mental disorder (yrs)			
Mean (SD)	10.72(8.65)	12.28(8.93)	7.5(7.29)
Treatment status			
Inpatient	38(80.9%)	27(84.4%)	11(73.3%)
Outpatient	9 (19.1%)	5(15.6%)	4(26.7%)
Mental disorers*			
Schizophrenia spectrum disorders	29 (61.7%)	21 (65.6%)	8 (53.3%)
Mood (affective) disorders	14 (29.8%)	10 (31.3%)	4 (26.7%)
Other mental disorders	16 (34.0%)	9 (19.1%)	7 (14.9%)
Psychotropic drugs*			
Antipsychotics (yes)	33 (70.2%)	24 (75.0%)	9 (60.0%)
Antidepressants (yes)	12 (25.5%)	9 (28.1%)	3 (20.0%)
Sedative-anxiolytics (yes)	43 (91.5%)	29 (90.6%)	14 (93.3%)
Mood stabilizers (yes)	8 (17.0%)	6 (18.8%)	2 (13.3%)

*the numbers totaled beyond study sample due to comorbid symptoms/diagnoses.

of vitamin D and some bone mineral and other major electrolytes. Serum concentrations of 25(OH)D were significantly correlated with serum concentrations of phosphorus (ϱ=0.336, p=0.024) and sodium (ϱ=0.304, p=0.038) but not with total calcium (ϱ=0.222, p=0.134), magnesium (ϱ=0.153, p=0.328), and potassium (ϱ=0.185, p=0.212) (ϱ-Spearman's rank correlation, p-probability). The correlations between serum concentration of 25(OH)D with serum concentration of phosphorus (Fig. 2) and sodium (Fig. 3) had moderate positive and linear relationships.

DISCUSSION

The results of our research prove the primary hypothesis that the patients of psychiatry health care

Table 2. Serum electrolytes of patients according to 25(OH)D categories

Characteristics	Total	25 (OH)D status	
		Deficient	Non-deficient
*Calcium (*mmol/L*)*			
Mean (SD)	2.34(0.1)	2.33(0.1)	2.36(0.1)
Median (range)	2.35(2.07-2.6)	2.34(2.07-2.6)	2.37(2.16-2.52)
*Magnesium (*mmol/L*)*			
Mean (SD)	0.81(0.12)	0.8(0.11)	0.85(0.14)
Median (range)	0.82(0.51-1.2)	0.80(0.51-0.97)	0.83(0.55-1.2)
Phosphorus (mmol/L)			
Mean (SD)	1.14(0.23)	1.1(0.25)	1.22(0.18)
Median (range)	1.14(0.33-1.6)	1.12(0.33-1.6)	1.21(0.89-1.57)
*Sodium (*mmol/L*)*			
Mean (SD)	140.4(2.09)	140.1(2.28)	140.9(1.55)
Median (range)	140(135-145)	140(135-145)	141(137-143)
*Potassium (*mmol/L*)*			
Mean (SD)	4.48(0.43)	4.44(0.42)	4.56(0.46)
Median (range)	4.4(3.8-5.7)	4.4(3.9-5.7)	4.6(3.8-5.3)

have significantly higher frequency of vitamin D deficiency than expected. Namely, in the whole group of patients the mean value of vitamin D was far below optimal levels and about two thirds of study subjects had a deficiency. In fact, the level of vitamin D found in our study has approached the level observed in Serbian patients with other chronic diseases for which the highly disturbed metabolism of vitamin D is well-known fact like terminal kidney failure treated by hemodialysis (28).

Previous similar studies in the field have been mainly done by comparison of a group of the patients with one type of mental disorder (often postmenopausal women or elderly with depression or inpatient subjects with severe mental disease) with a control group of healthy individuals (13-15, 29). Our study included the hospitalized and some ambulatory-treated subjects of both genders, in a broad life-span of ages, suffering mostly from schizophrenia spectrum disorders (schizophrenia, schizotypal and delusional disorders), in lesser extent from mood (affective) disorders (as independent diagnoses) and, in the minority ones, from other mental disturbances. This structure of patients, with moderate-to-severe mental disorders, is similar to the one usually managed in routine psychiatric care settings. Therefore, it can be expected that the high frequency of inadequate vitamin

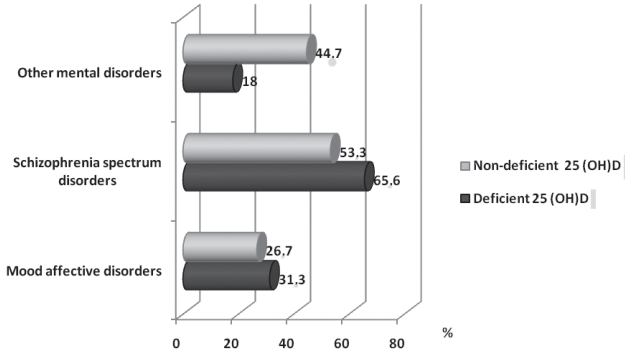

Figure 1. The most common mental disorders of patients according to 25(OH)D categories.

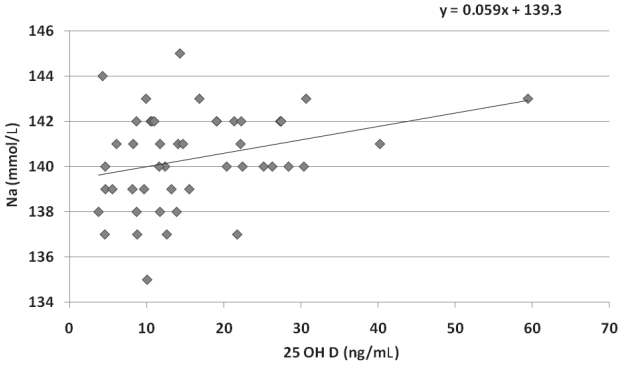

Figure 2. Correlation of vitamin D, in the form of 25(OH)D, and sodium serum concentrations.

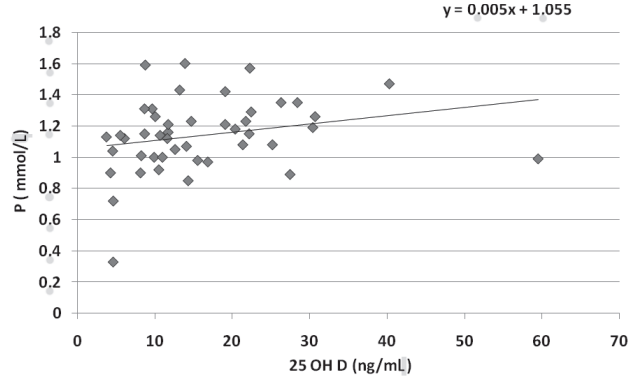

Figure 3. Correlation of vitamin D, in the form of 25(OH)D, and phosphorus serum concentrations.

D status described in our research would be observed in all similar population of patients elsewhere. This fact and the pattern of vitamin D status identified in our study justify further more targeted research on the topic (30). Deficiency of vitamin D might have significant impact on population health and should be addressed by recommendations for healthy life styles and other preventive medical measures that are significant parts of national health policy here and in other countries (31-33).

The correlation analysis taking into account serum levels of vitamin D and other electrolytes, in some regards, represents novelty in the field. Our results confirmed statistical significance for the positive, moderate correlation of vitamin D with phosphorus and sodium serum concentrations which, to our knowledge, is reported firstly for patients with mental disorders. Vitamin D is a direct regulator of the metabolism of calcium and, partly, phosphate and between them there are the feedback relationships which pathways affecting bone, intestine and kidney functions (26). In addition, it is known that excessive sodium intake represents a recognised risk factors for development of osteoporosis (often associated with vitamin D deficiency) due to interference with the renal excretion of calcium (23). Use of psychotropic medications could be associated with the increased risk for osteoporosis and bone fractures and in some patients who took these drugs researchers reported disturbances of major serum electrolytes (21, 22, 34, 35).

Evidence from basic research on experimental animals revealed the link between acitivity of vitamin D receptor (VDR) and some phosphate and sodium pathways, such as activity of type II sodium-phosphate contransportes. Many factors could regulate this transport molecule including targeted dietary interventions and humoral regulators like fibroblast growth factor 23 (FGF23) (36). In addition, paracalcitol, a metabolite of vitamin D regulates expression of dozens of genes including mRNA levels of atrial natriuretic factor in animals previously sensitized with high salt diet (37). At present, true clinical significance of these findings are difficult to understand. However, some recent clinical trials reported both the positive (e.g for blood pressure regulation) and the negative (e.g. people on a long-lasting, radical diet) correlations between serum vitamin D levels and dietary sodium intake (12, 38), making a fair rationale for future research of the topic.

The results of our study must be interpreted bearing in mind its limitations, primarily small sample size, absence of control group and heterogeneity of the patients. We believe that sample size calculation provided not only sufficient power for proving the primary research hypothesis, but also fair evidence of clinically meaningful difference of the vitamin D deficiency in subjects with mental illness in comparison with general population of patients. Investigators focused on psychiatric issues have already used historical controls and single-cohort subjects with multiple mental disorders, including questions about vitamin D (39, 40). Nevertheless, mentioned limitations of our research (originating primarily from logistic constraints) caution the general extrapolation of our results, requiring final confirmation in larger studies with more detailed designs.

In conclusion, the results of our study indicate that the prevalence of deficiency of vitamin D in patients with mental disorders was significantly higher than expected. The deficiency was also connected with disturbances in homeostasis of some electrolytes. Taking into account the importance of mental disorders for public health our findings justify the need for further researches in the field.

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Conflict of interest

The authors stated that they have no conflicts of interest regarding the publication of this article.

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