

Correlation between total vitamin D levels and psychotic psychopathology in patients with schizophrenia: therapeutic implications for add-on vitamin D augmentation

Rabia Nazik Yüksel, Neslihan Altunsoy, Baise Tikir, Merve Cingi Külük, Kubranur Unal, Sema Goka, Cigdem Aydemir and Erol Goka

Ther Adv Psychopharmacol

2014, Vol. 4(6) 268–275

DOI: 10.1177/
2045125314553612

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Abstract

Objectives: Vitamin D deficiency is one of the implicated factors in ethio-pathogenesis of schizophrenia. Low serum vitamin D levels have been reported in many schizophrenia studies. However, the question is still not answered: Is there a correlation between disease activity and serum vitamin D levels? This is the first study evaluating the relationship between serum total vitamin D levels and disease activity, by comparing total vitamin D levels in two schizophrenia groups abruptly different in terms of disease activity.

Methods: 41 patients with schizophrenia in remission, 40 patients with schizophrenia those in an acute episode and 40 age- and sex -matched controls with no major psychopathology were recruited in this study. Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression – Severity scale (CGI-S) were used to evaluate disease activity. A demographic data form that included entries on age, gender, ethnicity, weight, skin color, daily duration of sun exposure and nutritional assessment were used. Blood samples were taken from all patients and controls. Total vitamin D (D2+D3), calcium, phosphor, parathyroid hormone values were measured.

Results: Patients in an acute episode had significantly lower vitamin D levels compared to patients in remission and to healthy controls (in terms of median values respectively, 7.18, 15.03, 15.02, $p < 0.001$). We observed negative and moderate correlations between vitamin D levels and CGI scores ($r = -0.624$, $p < 0.001$), vitamin D levels and PANNS scores ($r = -0.508$, $p < 0.001$). There were no significant differences between groups in terms of serum P, Ca and PTH levels ($p = 0.099$, $p = 0.943$, $p = 0.762$). We could not detect any significant impact of weekly duration of sun exposure, skin color, ethnicity or nutrition on total vitamin D levels.

Conclusions: Even though important factors for vitamin D synthesis were similar, there was severe vitamin D deficiency in patients presenting with an acute episode, significantly different from those in remission. Is vitamin D deficiency the result or the cause of an acute episode? Our results contribute to the idea that vitamin D deficiency and schizophrenia may have interactions with an unknown pathway. Present data points out a possible influence at a genomic level. Future trials may investigate this association with longer follow up. We recommend that, serum vitamin D levels should be measured in patients with schizophrenia especially in long term care. Appropriate further treatment with add-on vitamin D supplements and diets that are rich in vitamin D should be considered.

Keywords: Schizophrenia, vitamin D, vitamin D deficiency, psychosis, total vitamin D, 25-OH vitamin D

Introduction

Epidemiological evidence suggests that the etiology of schizophrenia may involve both the influence of genetic factors specific to the individual and the impact of the environment. It is quite

likely that a crucial role in disease development is played by molecular mechanisms mediating the interaction between genes and the environment [Popov *et al.* 2012]. Until recently, little was known about the role of vitamin D in brain

Correspondence to:
Rabia Nazik Yüksel, MD
Ankara Numune Eğitim
ve Araştırma Hastanesi,
D Blok, Psikiyatri Doktor
odaları, Altındağ, Ankara,
06100, Turkey
rabia.nky@gmail.com

Neslihan Altunsoy, MD
Baise Tikir, MD
Merve Cingi Külük, MD
Sema Goka, MD
Cigdem Aydemir, PhD
Erol Goka, PhD
Department of Psychiatry,
Ankara Numune Training
and Research Hospital,
Ankara, Turkey

Kubranur Unal, MD
Department of
Biochemistry, Ankara
Numune Training and
Research Hospital,
Ankara, Turkey

function. Growing evidence implicates sunlight, or vitamin D, is a key environmental factor in the etiology of neuropsychiatric diseases.

The two most important forms of vitamin D are vitamin D₃ (cholecalciferol) and vitamin D₂ (ergocalciferol) [Holick, 2007]. Vitamins D₂ and D₃ are both available in dietary form but only vitamin D₃ is synthesized in the skin by ultraviolet B (UVB) radiation from sunlight. The human body cannot produce vitamin D₂ which is taken up with fortified food or given as supplements. In human plasma vitamin D₃ and D₂ are bound to the vitamin D binding protein and transported to the liver where both are hydroxylated to form vitamin D (25-OH), that is, 25-hydroxyvitamin D. It is commonly agreed that vitamin D (25-OH) is the metabolite to determine the overall vitamin D status as it is the major storage form of vitamin D in the human body [Hart *et al.* 2006].

In 2004, McGrath stipulated that low prenatal vitamin D (especially during the third trimester) may be a risk factor for development of schizophrenia in offspring. Similarly, a lack of vitamin D supplementation during the first year of life in Finnish boys correlated with an increased risk of developing schizophrenia [McGrath *et al.* 2004].

In a laboratory study, brain development was assessed in neonatal rats whose mothers were made vitamin D deficient by eliminating vitamin D from the diet and eliminating UVB radiation from the lighting in the animal holding room [Eyles *et al.* 2003]. The effects on the brain of the offspring were dramatic. Vitamin D deficiency changed the size and shape of the neonatal brain, altered growth factor expression, and altered cell proliferation. These data confirm that vitamin D deficiency can have effects on the structure of brain, like enlarged ventricles [Lawrie and Abukmeil, 1998] and cortical thinning [Selemon *et al.* 1995] that are associated with schizophrenia.

Furthermore, evidence that vitamin D regulates nerve growth factor and glial cell line-derived neurotrophic factor suggests that it may be neuroprotective [Garcion *et al.* 1998]. Vitamin D can protect the brain against reactive oxygen species via upregulation of antioxidant molecules, such as glutathione, in nonneuronal cells [Garcion *et al.* 1999].

It has been reported that vitamin D₃ receptors and 1 α hydroxylase, the enzyme responsible for active

vitamin D in the human brain, were found in both neurons and glial cells in the human brain. The strongest immunohistochemical staining for both the receptor and enzyme was in the hypothalamus and in the large (presumably dopaminergic) neurons within the substantia nigra. This report suggests that vitamin D may have autocrine/paracrine properties in the human brain [Kalueff and Tuohimaa, 2007].

Recently, there has been increasing evidence of the relationship between vitamin D receptors and mental diseases like major depression [Spedding 2014], bipolar disorder [Cherniack *et al.* 2009] and schizophrenia [Belvederi Murri *et al.* 2013]. It has been shown in many studies [Itzhaky *et al.* 2012; Crews *et al.* 2013; Jamilian *et al.* 2013] that adults with schizophrenia have significantly lower serum concentrations of vitamin D compared with healthy controls.

A meta-analysis of seven studies on vitamin D and psychosis reported that schizophrenia had a medium effect size for lower vitamin D levels than healthy controls and a trend for lower levels than other psychoses [Belvederi Murri *et al.* 2013].

Higher rates of vitamin D deficiency in people with first episode psychosis are also reported in a study from London [Crews *et al.* 2013]. Despite these, it is still unknown whether vitamin D deficiency is a cause or the result of schizophrenia. Present data of vitamin D deficiency in patients with schizophrenia and first episode psychosis raise the following questions. Can vitamin D deficiency be a risk factor for relapse and have an impact on disease activity? Can vitamin D deficiency and schizophrenia be coexisting conditions based on genetic predisposition?

The aim of this study was to examine total vitamin D (vitamin D₂ + vitamin D₃ levels) concentrations in patients with schizophrenia and to investigate possible correlations between serum vitamin D concentrations and disease activity in the course of illness.

Material and methods

Participants

This study was performed at the Department of Psychiatry of Ankara Numune Training and Research Hospital, Turkey. We recruited 41 patients with schizophrenia in remission who came to the outpatient clinic between June and November 2013, and 40 patients with schizophrenia in an

acute episode, hospitalized in our inpatient clinic between June and November 2013. Forty age- and sex-matched controls with no major psychopathology were recruited from the Family Medicine Clinic at Ankara Numune Training and Research Hospital. Inclusion criteria were a diagnosis of schizophrenia according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR), and 18–65 years of age. An additional inclusion criterion for outpatients was being in remission for at least 6 months according to Andreasen criteria [Andreasen *et al.* 2005]. Patients in an acute episode were included if they had a score of 4 or more (moderate or severe) on the Positive and Negative Syndrome Scale (PANSS) target item either for delusions (P1) or hallucinations (P3) and a score of 4 or more on the Clinical Global Impression (CGI) scale.

Individuals were excluded if they had a diagnosis of alcohol or substance dependence, organic mental disorder or learning disability, or a metabolic disease that may affect serum vitamin D concentrations.

Design and procedure

We did a case–control study to examine the association between disease activity and serum total vitamin D levels in patients with schizophrenia. The sample consisted of three groups: patients with schizophrenia in remission, those in an acute episode, and controls. Considering the seasonal fluctuation of vitamin D, patients were enrolled during the summer and fall of 2013. Trained physicians administered all the clinical assessments. The study received approval by the local ethics committee.

Instruments

All patients were given an informed consent form, the PANSS, the CGI – Severity scale (CGI-S) and a demographic data form that included entries on age, sex, ethnicity, occupation, marital status, weight, skin color, daily duration of sun exposure and nutritional assessment. Blood samples were taken from all patients and controls.

PANSS and CGI scales

We assessed the remission status using the PANSS and the CGI-S. The scales were administered on the same day that the blood sample was drawn.

Blood samples and laboratory analysis

With informed consent of patients, 10 cm³ peripheral venous blood samples were taken, placed in gel-containing tubes and centrifuged at 4000 rpm for 10 min to analyze the separated serum. Hemolysed and icteric serums were not used in this study.

Calcium and phosphorus values were evaluated photometrically in a Roche P800 autoanalyzer (Roche Diagnostics Turkey A.S, Ankara) using original commercial kits.

Parathyroid hormone (PTH) and total vitamin D (25-hydroxyvitamin D) values were measured by electrochemiluminescence with a Roche Cobas e-601. This assay is used as an aid in the assessment of vitamin D sufficiency. The electrochemiluminescence binding assay is intended for use on Elecsys (Elecsys 2010 Roche Immunoassay Analyzer, Turkey) and Cobas e immunoassay analyzers.

A sufficient level of total vitamin D was considered to be 20–100 ng/ml; an insufficient level, 10–20 ng/ml; a deficient level, less than 10 ng/ml [Holick, 2007].

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 20.0 was used for the analysis. In the statistical review of the results, the Kolmogorov–Smirnov test was used to determine whether the parameters were normally distributed. While descriptive statistics for continuous variables were shown as mean \pm standard deviation, categorical variables were expressed as number of cases (*n*) and %. The Student *t* test was used for the comparison of the two groups, one-way analysis of variance (ANOVA) was used for the comparison of the three groups for parametric variables. The Mann–Whitney *U* test and Kruskal–Wallis test were used for nonparametric variables. The Pearson correlation test was used to determine the association between the continuous parametric variables, and the Spearman correlation test was used to determine the association between the continuous nonparametric variables. The results were evaluated for a significance level of $p < 0.05$.

Results

Patients with schizophrenia in acute episode

Overall, 40 patients with schizophrenia in an acute episode were enrolled. Their average age was 38.08 ± 11.26 years (range 20–60 years).

Table 1. Baseline characteristics of study sample by disease activity in three groups ($n=121$).

	Control	Remission	Acute episode	<i>p</i>
Number of patients	40	41	40	
Age, mean \pm SD (min–max)	41.85 \pm 13.42 (17–58)	38.85 \pm 10.64 (19–66)	38.08 \pm 11.26 (20–60)	0.523*
Sex				0,125
Male	19 (47.5%)	27 (65.9%)	20 (50%)	
Female	21 (52.5%)	14 (34.1)	20 (50%)	
Education years (mean \pm SD)		8.98 \pm 3.67	8.93 \pm 3.89	0.952
Ethnicity				0.398
Turkish		36 (87.8%)	38 (95%)	
Kurdish		4 (9.8%)	1 (2.5%)	
Other		1 (2.4%)	1 (2.5%)	
Marital status				0.491
Married		14 (34.1%)	9 (22.5%)	
Divorced/single		27 (65.9%)	31 (77.5%)	
Duration of illness, median (25–75% quartiles)		10 (7.5–20)	5.50 (1–15)	0.003
Sun exposure				0.298
None		7 (17%)	11 (27.5%)	
<15 min, three times a week		13 (32%)	15 (37.5%)	
>15 min, three times a week		21 (51%)	14 (35%)	
Nutrition status				0.320
Sufficient intake of vitamin D		25 (61%)	20 (50%)	
Insufficient intake of vitamin D		16 (39%)	20 (50%)	
Skin color				0.597
White skinned		12 (29%)	14 (35%)	
Medium dark skinned		22 (54%)	17 (42.5%)	
Dark skinned		7 (17%)	9 (22.5%)	
CGI, mean \pm SD		2.66 \pm 0.83	5.85 \pm 0.86	<0.001
PANNS total, mean \pm SD		53.58 \pm 12.09	115.35 \pm 20.37	<0.001

* For age parameter, Bonferroni correction was made. *p* Value was 0.174 before the Bonferroni correction. CGI, Clinical Global Impression; SD, standard deviation.

Table 2. Vitamin D deficiency distribution according to groups.

	Acute episode (%)	Remission (%)	Control (%)	<i>p</i>
Total vitamin D				0.002
Deficient < 10 ng/ml	26 (65)	9 (22)	12 (30)	
Insufficient 10–20 ng/ml	12 (30)	28 (68.3)	22 (55)	
Sufficient 20–100 ng/ml	2 (5)	4 (9.8)	6 (15)	
Total	40 (100)	41 (100)	40 (100)	

There were 20 men (50%) and 20 women (50%). The median of schizophrenia disease duration was 5.5 years (1–15 years, as 25–75%).

The average PANSS score was 115.35 \pm 20.37; positive psychotic symptoms scored 31.35 \pm 7.91, negative psychotic symptoms scored

Table 3. Serum vitamin D, PTH, Ca and P levels according to groups.

	Acute episode	Remission	Control	<i>p</i>
Total vitamin D, median (25–75%)	7.18 [3.43–13.9]	15.03 [9.8–20.1]	15.02 [8–21.7]	<0.001
PTH, median (25–75%)	40.09 [27–47]	41.14 [30.9–48.05]	–	0.762
Ca, mean ± SD	9.33 ± 0.56	9.33 ± 0.43	–	0.943
P, mean ± SD	3.67 ± 0.72	3.43 ± 0.57	–	0.099

Ca, calcium; P, phosphorus; PTH, parathyroid hormone; SD, standard deviation.

Table 4. Association between serum total vitamin D levels and clinical evaluation.

	Total vitamin D levels	
	<i>r</i>	<i>p</i>
CGI-S mean	–0.624	<0.001
PANSS total	–0.508	<0.001
P mean	–0.373	0.001
N mean	–0.582	<0.001
G mean	–0.443	<0.001

CGI-S, Clinical Global Impression Severity subscale; PANSS, Positive and Negative Syndrome Scale; P, Positive Scale; N, Negative Scale; G, General Psychopathology Scale.

27.22 ± 10.00 and general psychopathology scored 56.77 ± 10.91 (Table 1).

Patients with schizophrenia in remission

For comparison, we enrolled 41 patients with schizophrenia in remission. Their average age was 38.85 ± 10.64 years (range 19–66 years). There were 27 men (65.9 %) and 14 women (34.1%). The median of schizophrenia disease duration was 10 years (7.5–20 years, as 25–75%). The average PANSS score was 53.58 ± 12.09; positive psychotic symptoms scored 11.48 ± 3.20, negative symptoms scored 17.0 ± 4.88 and general psychopathology scored 25.09 ± 7.88.

Healthy controls

For a second comparison we recruited 40 healthy controls, 19 men (47.5%) and 21 women (52.5%), and their mean age was 41.85 ± 13.42 years (range 17–58 years).

Serum total vitamin D levels

Patients with schizophrenia in an acute psychotic episode had significantly lower total vitamin D levels compared with patients with schizophrenia in remission and healthy controls (in terms of median values: 7.18, 15.03, 15.02, respectively, *p* < 0.001). One-way ANOVA showed significant differences in vitamin D levels of patients with schizophrenia and healthy controls. *Post hoc* analysis revealed that patients with schizophrenia in acute episode had lower vitamin D levels than either patients with schizophrenia in remission or control subjects. There was no significant difference between total vitamin D levels in the remission group compared with healthy controls.

When patients were grouped according to total vitamin D ranges (deficient < 10 ng/ml, insufficient 10–20 ng/ml, sufficient 20–100 ng/ml), the acute-episode group comprised a greater proportion of all patients who were vitamin D deficient compared with those who were vitamin D insufficient: 26/40 (60%) versus 12/40 (30%), respectively (Table 2).

We also evaluated serum phosphorus (P), calcium (Ca) and PTH levels in order to discriminate between other possible biological effects on total vitamin D serum concentrations. There were no significant differences between groups in terms of serum P, Ca and PTH levels (*p* = 0.099, *p* = 0.943, *p* = 0.762) (Table 3).

As presented in Table 1, we could not detect any significant impact of weekly duration of sun exposure, skin color and ethnicity, or nutrition on total vitamin D levels.

Total vitamin D levels and disease activity

We observed negative and moderate correlations between total vitamin D levels and CGI scores ($r = -0.624$, $p < 0.001$), total vitamin D levels and PANNS scores ($r = -0.508$, $p < 0.001$) and total vitamin D levels and negative symptom scores ($r = -0.508$, $p < 0.001$). Positive symptom scores and general psychopathology scores were also correlated with total vitamin D levels negatively, but mildly ($r = -0.373$, $p < 0.001$; $r = -0.443$, $p < 0.001$) (Table 4).

The level of total vitamin D did not correlate with disease duration and number of hospitalizations.

When we controlled for the effects of other variables (age, sex, disease duration, sun exposure, nutrition, skin color), we also detected a negative and moderate correlation between total vitamin D levels and CGI scores ($r = -0.566$, $p < 0.001$) and total vitamin D levels and PANNS scores ($r = -0.500$, $p < 0.001$).

Discussion

To our knowledge, this is the first report of a significant association between vitamin D deficiency and disease activity in adults with schizophrenia. Our results indicate that many of the patients with schizophrenia have vitamin D deficiency, similar to other studies [Belvederi Murri *et al.* 2013; Itzhaky *et al.* 2012; Jamilian *et al.* 2013]. Our results also indicate that patients in an acute episode have lower serum concentrations of total vitamin D compared with patients in remission, and there is an inverse association between total vitamin D concentrations and disease activity based on PANSS and CGI-S scores. This finding remained after evaluating the impact of various factors such as sex, ethnicity, skin color, self-reported sun exposure and diet composition.

Current data show that there are three adult studies and one adolescent study examining the association between serum concentrations of vitamin D and severity of psychotic symptoms. A cross-sectional study reported negative correlations between vitamin D concentrations and physical energy, psychomotor activity and somatic complaints [Berg *et al.* 2010], whereas Itzhaky and colleagues reported no correlation between vitamin D concentrations and PANSS scores [Itzhaky *et al.* 2012]. The other study examining this association was a case-control study from the UK [Crews *et al.* 2013]. This study reported that patients with first-episode psychosis

have significantly lower concentrations of vitamin D, similar to our findings, but did not find an association between vitamin D concentrations and the severity of illness, in contrast to our findings. Herein, it may be useful to review the sampling of the other studies. If the sample consisted of similar patient groups, such as all in remission or all in acute episode/hospitalized, this could cause a similarity in disease activity. In our study, to precisely determine the association between disease activity and vitamin D levels, we designed two patient groups strictly different in their disease activity. However, in the aforementioned study all of the patients were in acute episodes.

This is also the first study to report total serum vitamin D concentrations of patients with schizophrenia in Turkey. Our findings show that both patients with schizophrenia and the control group have significantly lower total serum vitamin D concentrations. In fact, Turkey is located at appropriate latitudes (36° 42' N) for the synthesis of vitamin D [Amato *et al.* 2010] and thus higher levels of total vitamin D would be expected. However, a study from Israel (31° 30' N), which is located at similar latitudes to Turkey, also reported low serum vitamin D concentrations in patients with schizophrenia.

Our results show that patients with schizophrenia in the remission group and control group have similar total serum vitamin D concentrations. For the control group, we recruited patients from the Family Medicine Clinic, and these patients had mild health problems, so the control group may not reflect the whole Turkish population. When it comes to patients with schizophrenia, especially in the acute episode group, there was severe vitamin D deficiency even though important factors for vitamin D synthesis such as sex, ethnicity, skin color, daily exposure to sunlight and nutrition were similar in both groups. This result may suggest the existence of an unknown interaction between disease activity and serum concentrations of total vitamin D. Why does the total vitamin D level fall during an acute period of disease? Is vitamin D deficiency the result or the cause of an acute episode? For the answer, we may look at the possible genetic interactions between schizophrenia and vitamin D, as well as the neuroprotective effects of vitamin D. Indeed, research from Italy published in 2010 reported a significant overlap of 70 genes between schizophrenia and vitamin D related genes (an overlapping gene is a gene whose expressible nucleotide sequence partially overlaps with the expressible nucleotide

sequence of another gene; in this way, a nucleotide sequence may make a contribution to the function of one or more gene products). This analysis provides the first hint, at a genomic level, of the existence of a relationship between schizophrenia and vitamin D related genes.

So, our findings contribute to the idea that vitamin D deficiency and schizophrenia may have been influenced at a genomic level.

Limitations of this study

For the understanding of whether vitamin D deficiency is a state marker or trait marker for schizophrenia, follow up should be conducted after the treatment of acute episodes.

Because this is a case-control study, it is not possible to understand if the vitamin D deficiency is a cause or result of schizophrenia. Future cohort studies may investigate the association with longer follow up.

Clinical therapeutic implications for schizophrenia therapeutics and conclusions

Vitamin D deficiency is highly prevalent in patients with schizophrenia, especially those in acute episodes. Low serum vitamin D concentrations may have an effect in the pathogenesis of schizophrenia, or schizophrenia and vitamin D deficiency may have a genetic cooccurrence. Our findings suggest routine testing of vitamin D concentrations in patients with schizophrenia. Given that vitamin D is neuroprotective, adequate serum vitamin D concentrations may be effective to prevent new acute episodes in the course of schizophrenia. Nevertheless, it is not known what dose of vitamin D is neuroprotective. So, future trials of vitamin D supplementation are needed to focus on dosing and tolerability in patients with schizophrenia. However, we recommended that patients with schizophrenia who are in long-term care in rehabilitation psychiatric units should be assessed with regard to their vitamin D levels. According to their vitamin D levels, these patients should have appropriate exposure to sunlight, activity and dietary adjustments to normalize vitamin D levels. Vitamin D containing foods are very few in nature. Fatty fish (such as tuna, salmon and mackerel) and fish liver oils are the best sources [Ross *et al.* 2011]. Beef liver, cheese, egg yolks and mushrooms are other vitamin D sources [Cranney *et al.* 2007]. Fortified foods such as milk and breakfast cereals often contain added vitamin D, as do some

brands of orange juice, yogurt, margarine and other food products. So diets that are rich in vitamin D can be given to these patients.

We believe that these interventions should be maintained during patients' stay in any such facilities where exposure to sunlight is limited. Appropriate further treatment with add-on vitamin D supplements should be considered based on patients' physical and mental health using the guidelines for vitamin D supplementation.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement


The author declares that there is no conflict of interest.

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