Relationship between vitamin D status and psychopathology in patients with first-episode schizophrenia: a cross-sectional study

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Received 14 March 2016
Accepted 31 October 2016

Middle East Current Psychiatry
2017, 24:43–48

Background
Deficient vitamin D is one of the implicated factors in the etiopathogenesis of schizophrenia and other mental disorders. However, there are scarce reports as regards its prevalence or associated problems among those with first-episode schizophrenia.

Objective
The aim of this study was to assess 25-hydroxyvitamin D [25(OH)D] serum concentrations in first-episode schizophrenia male patients as compared with healthy controls and to determine whether a correlation exists between serum levels of 25(OH)D and disease activity.

Methods
We enrolled 50 male patients with first-episode schizophrenia and compared them with 50 controls with no major psychopathology. The Positive and Negative Syndrome Scale for schizophrenia and the Montgomery–Asberg Depression Rating Scale for depression were administered on the same day. The blood samples were drawn and plasma 25(OH)D level was measured using immunoassay.

Results
Lower serum 25(OH)D concentrations were detected among patients with first-episode schizophrenia (24.8 ± 11.21 ng/ml) compared with controls (67.3 ± 22.91 ng/ml, $P < 0.05$). We found a negative correlation between duration of untreated psychosis (DUP), disease activity (measured using the Positive and Negative Syndrome Scale and Montgomery–Asberg Depression Rating Scale score), and vitamin D levels.

Conclusion
Serum 25(OH)D levels were lower in patients with schizophrenia as compared with healthy controls. A negative correlation was found between plasma vitamin D level, DUP, and severity of psychopathology. Future trials may investigate this association with longer follow-up. We suggested that plasma 25(OH)D levels should be measured in patients with first-episode schizophrenia, especially those with a longer DUP (> 10 weeks) and prominent negative and more severe depressive symptoms. Our finding may raise the suggestion that further treatment with add-on vitamin D supplements and diets that are rich in vitamin D may be beneficial.

Keywords:
first-episode schizophrenia, male inpatients, plasma vitamin D, psychotropic drugs naive and drug free

Middle East Curr Psychiatry 24:43–48

2090-5408

Introduction

The architecture of schizophrenia is still largely unknown and conventional categories for diagnosing schizophrenia and schizoaffective states are still based on the descriptions of symptoms and behaviors [1]. Although progress has been made as regards the underlying molecular biology and neuropathology of schizophrenia, characterization of discrete symptoms does not reflect underlying neurobiological mechanisms [2].

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 [3].

There is a growing interest in the relationship between vitamin D and mental health [4–6], and it has been proposed that the developmental deficiency of vitamin D may contribute to the etiology of schizophrenia [7–9]. Recently, there has been increasing evidence of the relationship between vitamin D receptors and mental diseases such as major depression [10],

 DOI: 10.1097/01.XME.0000508433.27202.4e

bipolar disorder [11], and schizophrenia [12]. It has been shown in many studies [13–15] that adults with schizophrenia have significantly lower serum concentrations of vitamin D compared with healthy controls and a trend for lower levels compared with other psychoses [12,14]. The vitamin D receptor and the enzyme needed for the hydroxylation of the precursor molecule 25-hydroxyvitamin D [25(OH)D] to the active form 1-α-hydroxylase have widespread expression in the adult human brain [16]. Many of these brain regions are implicated in schizophrenia, including the hippocampus, thalamus, hypothalamus, amygdala, prefrontal cortex, cingulate gyrus, and temporal lobe. A plausible role in schizophrenia pathology is also suggested by the finding that vitamin D acts to regulate the transcription of many genes involved in pathways implicated in schizophrenia, including genes involved in synaptic plasticity, neuronal development, and protection against oxidative stress [17]. Despite these, it is still unknown whether vitamin D deficiency is a cause or the result of schizophrenia. Present data as regards vitamin D deficiency in psychosis have been reported in those with established disorder, and therefore could be due to prolonged hospitalization, poor nutrition, or the prescription of anticonvulsant medications [18]. To our knowledge, no data exist on vitamin D levels at first onset of the disorder. We therefore tested the hypothesis that vitamin D levels in male patients with their first schizophrenia episode are lower than those in the general population, and that vitamin D deficiency may correlate with some symptoms displayed by patients.

Aim

The aim of the present study, therefore, was to test serum vitamin D levels in male patients with first-episode schizophrenia compared with healthy controls. We also aimed to investigate the possible correlations between plasma concentrations of vitamin D and the severity of psychopathology in schizophrenia patients, to detect its possible involvement in the emergence of schizophrenia.

Methods

Design

This work was a cross-sectional case–control study conducted during the period between March 2014 and February 2015.

Setting

This study was performed at the Department of Psychiatry, Cairo University Hospital, Egypt, after being approved by the scientific and ethical committee. Written informed consent was obtained from all patients and/or their caregivers.

Participants

Patients were recruited from those admitted in the psychiatry inpatient unit according to certain inclusion and exclusion criteria. Inclusion criteria were as follows: (a) first-episode schizophrenia male patients admitted in the Psychiatry Department in Cairo University Hospitals; (b) diagnosis of schizophrenia according to ICD-10 [19] assessed by administering the Mini International Interview [20]; (c) psychotropic drug naive and drug free; (d) age between 21 and 30 years; and (e) consent to participate in the study. Patients with any of the following ICD-10 diagnosis were excluded: schizoaffective disorder, bipolar disorder, major depression, and substance-induced psychotic disorder, in addition to exclusion of cases of known organic pathology and patients with a past history of epilepsy or endocrine disorders. Controls were selected from among hospital workers ($n = 50$). These individuals were selected so that the age, sex, educational level, marital status, and employment in the control group were similar to that of individuals in the patient group (case–control 1-to-1 matching). Individuals with current or prior mental health problems or serious physical health problems were excluded. Additional exclusion criteria for both the control group and cases were as follows: a diagnosis of intellectual disability, terminal cancer, and end-stage renal failure. They were administered the Mini International Interview [19] to confirm the absence of a current or prior mental disorder. Overall, 50 male patients and 50 healthy male controls completed the study. All participants were administered a comprehensive demographic data form. Individuals in the patient group were also administered the Positive and Negative Syndrome Scale (PANSS) [21] and the Montgomery–Asberg Depression Rating Scale (MADRS) [22] at the time of enrollment.

Measures

The sociodemographic data form used in the study was prepared by the authors; it assessed the age, sex, education, marital status, economic status, occurrence of other medical disorders, and family psychiatric history of all participants. The patient group was also asked about the duration of illness and their medication history. Duration of untreated psychosis (DUP) was defined as the time from the appearance of the first prodromal symptoms to initiation of antipsychotic treatment.

The PANSS [21]: the PANSS is a scale used for measuring symptom severity of patients with schizophrenia. The PANSS is a relatively brief interview, requiring 45–50 min to administer.

The MADRS was used to evaluate depressive symptoms, considering a score of up to 9 as indicative of clinical remission of depression [22].

Biochemical assays

Venous blood samples were collected from all participants. This procedure was carried out before any pharmacological treatment in the patient group. All biochemical testings were conducted by independent

laboratories that were blinded to participants' case or control status.

Vitamin D measurement

After obtaining informed consent, 5 cm^3 of venous blood sample was drawn from each participant after an overnight fast of 12 h. Serum was separated and stored at −20°C until assayed. Serum samples were assayed for 25(OH)D using quantitative enzyme immunoassay [23]. Serum 25(OH)D is the major circulating form of vitamin D and a standard indicator of vitamin D status [24]. The 25(OH)D cutoffs to define deficiency and insufficiency have most recently been framed by the 2011 desirable levels of the Institute of Medicine Report and the Endocrine Society Guidelines [25,26]. According to these guidelines, vitamin D deficiency was defined in the present study as a concentration of 25(OH)D less than 20 ng/ml, that between 20 and 29.9 ng/ml as insufficiency, and a concentration of at least 30 ng/ml as sufficient.

Statistical analysis

SPSS 18.0 (SPSS Inc., Chicago, Illinoisa, USA) for Windows was> used for data analysis. Student's *t*-test was used to compare normally distributed continuous measures between cases and controls. The Mann–Whitney *U*-test was used to compare non-normally distributed continuous variables, and the χ^2-tests or Fisher's exact tests were used to compare dichotomous or categorical variables. The relationship between plasma vitamin D level and DUP, the total scores for PANSS subscales, and MADRS Score was assessed using correlation coefficients. The level of statistical significance was set at *P* value less than 0.05.

Results

The study included two groups of male patients experiencing their first schizophrenia episode and a control group comprising healthy male individuals. The mean age in the schizophrenic group was 23.8 ± 9.7 years, and that in the control group was 24.2 ± 10.3 years. Both groups were matched as regards age, educational attainment, marital status, and employment (mean age 28.05 ± 8.17 years, $P > 0.05$) (Table 1).

The mean serum 25(OH)D level was significantly lower in first-episode schizophrenia patients (24.8 ± 11.21 ng/ml) than in controls (67.3 ± 22.91 ng/ml) ($t = -3.864$, $d.f. = 22$, $P < 0.001$) (Table 2).

The disposition of patients based on plasma 25(OH)D status showed that, of total first-episode schizophrenia patients, only eight (16%) had sufficient 25(OH)D level, 31 (62%) had insufficient plasma 25(OH)D, and 11 (22%) showed 25(OH)D deficiency (Table 3).

As shown in Table 4, among the first-episode schizophrenia patients, insufficient plasma 25(OH)D level was associated with a longer DUP, more severe psychopathology as measured using the PANSS, and more prominent depressive symptoms assessed using the MADRS ($P < 0.05$) (Table 4).

Table 1 Demographic characteristics of participants

Characteristics	Patients ($n=50$)	Controls ($n=50$)	Statistics	*P*-value
Age [mean (SD)] (years)	23.8 (9.7)	24.2 (10.3)	$t=0.03$	0.976
Education [mean (SD)] (years)	11.9 (5.8)	12.1 (6.2)	$t=0.01$	0.342
Marital status [*n* (%)]			$\chi^2=0.163$	**0.862**
Single	32 (64)	31 (62)		
Married	18 (36)	19 (38)		
Employment [*n* (%)]			$\chi^2=0.163$	0.436
Full paid	12 (24)	14 (28)		
Part time	38 (76)	36 (72)		

Clinical characteristics of schizophrenic patients	Mean (SD)
Duration of untreated psychosis (weeks)	11.2 (4.1)
PANSS	
Total PANSS	75.3 (18.9)
PANSS negative subscale	26.9 (9.1)
PANSS positive subscale	28.4 (8.2)
MADRS	19.6 (9.3)

MADRS, Montgomery–Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale.
Bold non significant $P > 0.5$.

We observed negative correlations between plasma 25(OH)D and DUP ($r = -0.604$; $P < 0.001$), plasma 25(OH)D levels and PANSS negative symptoms scores ($r = 0.432$, $P < 0.001$), and plasma 25(OH)D level and depressive symptoms score ($r = -0.508$, $P < 0.001$) (Table 5).

Discussion

To the best of our knowledge, this is the first study that demonstrated a significant association between vitamin D deficiency or insufficiency and severity of psychopathology in first-episode schizophrenia male inpatients in an Arab culture.

Our study found that vitamin D levels were significantly lower in schizophrenia cases than in controls. In our sample, vitamin D deficiency was present in 11% of cases, and 62% of the cases had insufficient vitamin D levels. Our findings support previous associations between first-episode schizophrenia and vitamin D deficiency and indicate that even at the first onset of schizophrenia in drug-naive male patients, the mean vitamin D levels were significantly lower than that in controls [8,12,13,15,27]. A series of large cohort studies have implicated insufficiency of vitamin D in the susceptibility to both psychosis and schizophrenia [28–30]. Three factors may underlie this. The first relates to the long prodromal phase in some patients with schizophrenia, lasting up to 5 years [31], which may include a tendency toward withdrawal from day-to-day activities, thus reducing exposure to sunlight and lowering vitamin D level. Second, longstanding low vitamin D levels may be a risk factor for developing psychosis [32]. This possibility is raised by research showing that both high and low neonatal vitamin D levels are associated with the development of schizophrenia in adult life and also by birth cohort studies, suggesting an increased risk of developing schizophrenia in Finnish

Table 2 Plasma 25(OH)D levels in patients with first-episode schizophrenia and healthy controls

Serum parameters	Patients ($n=50$)	Controls ($n=50$)	Paired *t*-tests	*d.f.*	*P* value
25(OH)D [mean (SD)] (ng/ml)	24.8 ± 11.21	67.3 ± 22.91	−3.864*	0.22	<0.001

25(OH)D, 25-hydroxyvitamin D.
*Statistically highly significant $P<0.001$.

Table 3 Distribution of patients with first-episode schizophrenia based on plasma 25(OH)D level status

	Sufficient (≥30 ng/ml)	Insufficient (20 and 29.9 ng/ml)	Deficient (<20 ng/ml)
n (%)	8 (16)	31 (62)	11 (22)

25(OH)D, 25-hydroxyvitamin D.

male population not given vitamin D supplements during the first year of life [8]. Further support to this link between vitamin D deficiency and psychosis is provided by a prospective birth cohort study, which showed an inverse relationship between serum vitamin D levels and psychotic experiences during childhood. In addition, maternal vitamin D deficiency may be a risk factor for psychosis [7,9], a finding supported by preclinical models [33]. Third, vitamin D has recently been identified as a negative acute phase reactant [34], and, as a consequence of this, there can be marked fall in serum vitamin D levels during a systemic inflammatory response. Variations in acute phase responses, with aberrations in cytokine levels, independent of antipsychotic medications have been demonstrated in acute schizophrenia [33], which may simply be an indicator of immune activity [35,36].

This study is the first, to our knowledge, to report an association of vitamin D insufficiency and a longer DUP, more severe negative symptoms, and more severe depressive symptoms in patients with first-episode schizophrenia in our culture. It is possible that schizophrenic patients with more severe negative and/or cognitive symptoms would have lifestyles that lead to lower vitamin D status. These symptoms, including social isolation and amotivation, would be associated with a lower overall level of functioning, potentially leading to poorer nutrition and less time spent outdoors that would contribute to lower 25(OH)D. Our findings are in agreement with some previous studies. They found that lower vitamin D levels in schizophrenic patients were associated with more severe negative symptoms and overall cognitive deficits [5,37]. A continuum for vitamin D levels across the spectrum of psychotic illness has been suggested [12], with schizophrenia patients manifesting the lowest levels. Correlations between 25(OH)D levels and some negative/depressive symptoms have also been reported among patients with psychotic symptoms and depressive disorders [5,38].

Some researchers observed negative and moderate correlations between total vitamin D levels and clinical global impression scores, total vitamin D levels and PANNS scores, and total vitamin D levels and negative symptom scores [39]. Vitamin D deficiency has been

Table 4 Clinical characteristics in first-episode schizophrenia patients based on plasma 25(OH)D levels vitamin D status (sufficient vs. insufficient)

Characteristics	Patients with sufficient 25(OH)D [8 (16%)]	Patients with insufficient 25(OH)D [42 (84%)]	*P* value
DUP [mean (SD)] (weeks)	8.4 (3.2)	12.6 (5.8)	0.03
PANSS total score [mean (SD)]	62.3 (11.8)	76.0.9 (12.1)	0.001
PANSS negative subscale score [mean (SD)]	13.6 (5.9)	24.7 (8.4)	0.001
PANSS positive subscale score [mean (SD)]	14.3 (8.7)	23.1 (11.2)	0.02
MADRS score [mean (SD)]	12.3 (6.9)	19.1 (7.4)	0.001

DUP, duration of untreated psychosis; MADRS, Montgomery–Asberg Depression Rating Scale; 25(OH)D, 25-hydroxyvitamin D; PANSS, Positive and Negative Syndrome Scale.

Table 5 Correlation between plasma 25(OH)D level and some clinical characteristics

	Plasma 25(OH)D levels	
Variables	Correlation coefficient (*r*)	*P* value
Duration of untreated psychosis	−0.604	<0.001
PANSS negative score	−0.432	<0.001
MADRS	−0.508	<0.001

MADRS, Montgomery–Asberg Depression Rating Scale; 25(OH)D, 25-hydroxyvitamin D; PANSS, Positive and Negative Syndrome Scale.

investigated as a mediator of depression. Some randomized clinical trials found that adults deficient in vitamin D had a significantly higher likelihood of depression compared with those who were not [40]. In patients with seasonal affective disorder randomized to either phototherapy or vitamin D supplementation, the patients who received vitamin D treatment showed improvement in psychological tests, whereas the phototherapy group remained the same [41]. Our results are in contrast to some earlier studies including patients with established psychotic disorders. These previous studies, however, have methodological limitations, including lack of adjustment for ethnicity [42–44], comparison between hospitalized patients and healthcare workers [13] or hospitalized patients and healthy controls recruited using advertisements without control for place of residence [14].

These findings lead us to hypothesize that inadequate vitamin D status may account for some portion of the symptom burden experienced by individuals with schizophrenia. As much of the disability experienced by individuals with schizophrenia is related to the severity

of negative and cognitive symptoms [45] and there are currently no approved pharmacologic methods to treat these symptoms, we hypothesize that correcting vitamin D insufficiency in schizophrenia could fill a critical role. It has been shown that dietary intake of vitamin D is associated with a decreased risk for moderate and high-level psychotic symptoms in women from the general population in Sweden [46].

Our data may suggest the existence of an unknown interaction between the severity of psychopathology and plasma vitamin D level. In the hope of coming nearer to answering this question, we have added to the published work describing vitamin D deficiency in established psychosis [5] to focus specifically on vitamin D levels in first-episode schizophrenia. Further work is needed to answer the question of causality. There is a growing body of evidence that vitamin D is neuroprotective, and experimental evidence from animal studies show a link between a lack of vitamin D and behavioral and cognitive dysfunction [47,48]. Vitamin D is a neuroprotective and patients with psychosis have a reduced life expectancy of up to 18 years, largely due to cardiovascular disease, for which vitamin D deficiency is a known risk factor [49–51].

Furthermore, some studies reported that, besides inadequate calcium intake, lower levels of vitamin D and high levels of smoking would contribute to the low bone mineral density in schizophrenic patients [52], and an increased risk for osteoporosis has been found to be more marked in schizophrenic patients than in the general population [53]. The high rates of vitamin D deficiency in our patients, given the postulated neuroprotective role of vitamin D, raise the possibility that the judicious treatment of low serum vitamin D in first-episode schizophrenia may have potential benefit. This is in agreement with recent renewed interest in the protective benefits of nutritional agents, both in the prevention of the development of psychotic illnesses [32] and the progression from subthreshold psychosis to psychotic disorders [54]. Nevertheless, there is a clear need for new schizophrenia therapies. There are currently no medications approved for the treatment of negative or cognitive symptoms. On the other hand, vitamin D supplementation is well tolerated with minimal side effects, and the findings reported here support the possibility that supplementation might reduce symptoms or augment recovery of patients with schizophrenia, particularly targeting those with vitamin D insufficiency.

Although the results of our study raise important questions for patients with first-episode schizophrenia, it is premature to draw any conclusions on whether vitamin D supplementation can improve schizophrenia symptoms.

Limitations

This work has several limitations:

(1) The study is a cross-sectional one, and hence follow-up period is needed to test whether low plasma vitamin D level is a state marker or trait marker for schizophrenia.
(2) Being a cross-sectional study, the question of reverse causality (worse negative and depressive symptoms leading to lower vitamin D status) can never be conclusively answered. Future cohort studies may investigate the association with longer follow-up.
(3) We did not screen specifically for malabsorption problems, which confer a higher risk of vitamin D deficiency [55].

Clinical therapeutic implications for schizophrenia therapeutics

Vitamin D deficiency is highly prevalent in patients with schizophrenia, especially those in acute episodes. Low serum vitamin D concentrations may have an effect on the pathogenesis of schizophrenia, or schizophrenia and vitamin D deficiency may have a genetic co occurrence.

Conclusion

We found lower plasma vitamin D level in first-episode schizophrenic patients compared with matched controls. Vitamin D is a neuroprotective and patients with psychosis have a reduced life expectancy of up to 18 years, largely due to cardiovascular disease, for which vitamin D deficiency is a known risk factor. In addition, low vitamin D may increase the risk for reduced bone mineral density. Addressing vitamin D deficiency may thus provide a potential avenue to reduce cardiovascular risk and minimize the risk for osteoporosis in schizophrenic patients. Our findings suggest routine testing of vitamin D concentrations in patients with schizophrenia. These findings may support the need to develop guidelines to prevent vitamin D deficiency from occurring, and how to manage it when it is detected or suspected in first-episode schizophrenia. This may serve to modify psychopathology, the course of schizophrenia, or improve longevity and quality of life.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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