

## Serum Vitamin D Deficiency and Risk of Schizophrenia: A Case Control Study

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### ABSTRACT

**Background:** Schizophrenia is a mental illness with symptoms like delusions and hallucinations. A recent study concluded that individuals with vitamin D deficiency are twice more likely to have schizophrenia than optimum level vitamin D people.

**Objective:** To measure schizophrenic patients' serum vitamin D concentration and compare it to healthy controls (non schizophrenics), and to investigate the relationship between serum schizophrenia and related potential risk factors.

**Subjects and Methods:** Twenty patients with schizophrenia were recruited and compared to 20 controls with no major psychopathology using age and sex matched case control study. The SCID-1 (semi-structured interview for making major DSM-IV Axis 1 diagnoses), was administered and the blood samples were withdrawn after patient consent on the same day.

**Results:** Schizophrenic patients showed a significantly lower mean vitamin D level ( $14.8 \pm 4.5$  IU) compared to control group ( $19.6 \pm 3.3$  IU) ( $P < 0.001$ ). Higher vitamin D level participants were nearly 80% less likely to have schizophrenia compared to low level ones. Being older and female were 80% and 40% less likely to have schizophrenia respectively. Individuals with large body mass index were 1.2 times more likely to have schizophrenia compared to normal body weight. Smokers were 10% less likely to be schizophrenic compared to non-smoker participants.

**Conclusions:** Patients with schizophrenia showed lower serum vitamin D level compared to healthy controls. Further studies are needed to explore the role of vitamin D in the pathogenesis of schizophrenia.

**Keywords:** Vitamin D and Schizophrenia, low vitamin D as a risk of schizophrenia, role of vitamin D in Schizophrenia.

### INTRODUCTION

Schizophrenia is a group set of neuropsychiatric treatable disorders including symptoms like hallucinations, delusions, confused thinking, and disorganized speech.<sup>(1)</sup> This could impose great costs to the health care system.

Prevalence of schizophrenia is widely different across geographic regions. It affects more than 21 million people worldwide. One in two people living with schizophrenia does not receive optimum care, though care of persons with schizophrenia can be provided at community level with active family and community involvement.<sup>(2)</sup>

Epidemiological evidence suggests that the etiology of schizophrenia could be due to 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. Until recently, less was known about the role of vitamin D in brain function. Growing evidence implicates sunlight, or vitamin D in the etiology of neuropsychiatric diseases.<sup>(3)</sup>

Vitamin D<sub>3</sub> (cholecalciferol) and vitamin D<sub>2</sub> (ergocalciferol) are considered to be the two most important forms of vitamin D.<sup>(4)</sup> Both forms are at hand in dietary form however; vitamin D<sub>3</sub> is synthesized in the skin by ultraviolet B (UVB) radiation from sunlight. In part, the human body cannot produce vitamin D<sub>2</sub> which is driven up with fortified food or given as supplements. Vitamin D binding protein are bound to both forms in plasma and then transported to the liver where both are

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hydroxylated to form vitamin D (25-OH), that is, 25-hydroxyvitamin D. It is commonly agreed that vitamin D (25-OH) is the metabolite which determines the overall vitamin D status, as it is the major storage form of vitamin D in the human body.<sup>(5)</sup>

Vitamin D is engaged in neurotransmitter synthesis, neuro-protection from injury and inflammation, regulation of circadian rhythms and sleep, and also has a key role in neurodevelopment.<sup>(6)</sup>

Schizophrenia, autism, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and multiple sclerosis are examples of psychiatric and neurological diseases with potential connections to vitamin D deficiency.<sup>(7)</sup> Though vitamin D receptors and the vitamin D-activating enzyme 1 $\alpha$ -hydroxylase are found in most human body organ systems, including the brain. Moreover the hypothalamus and the dopaminergic neurons of the substantia nigra showed a high density of vitamin D receptors as well as the vitamin D-activating enzyme.<sup>(8)</sup>

The link between vitamin D and schizophrenia explained by a "season-of birth effect" as a greater proportion of individuals with schizophrenia are born in late winter and early spring and thus most probably exposed to lower levels of vitamin D in their peri-natal period. There is also an increased incidence and prevalence of schizophrenia at latitudes farther from the equator.<sup>(7)</sup> This is supported by the fact that individuals with darker skin are particularly more vulnerable to schizophrenia when they live at higher latitudes.<sup>(9)</sup>

The disease process of schizophrenia is associated with activation of cell-mediated and inflammatory pathways. There are strong associations between schizophrenia and smoking, obesity, sleep disorders, and poor oral health may further augment this inflammation.<sup>(10)</sup> Leukocyte Telomere length (LTL) is a marker of oxidative stresses. These stresses shorten telomere length and eventually trigger earlier cell senescence and apoptosis<sup>(11)</sup>. As vitamin D has documented with modulator effects on reduction of oxidative stress and inflammation, the relationship of vitamin D to telomere length, particularly in schizophrenia, is an important channel to tag as a biomarker

for neuroprotection that may have therapeutic entanglement.<sup>(12)</sup> This significant relationship between vitamin D and LTL would advocate that the association is not simply spurious, resulting from decreased outside activity, but that it could also play a role in pathogenesis.<sup>(13)</sup>

Although the role of vitamin D in schizophrenia has been investigated in several epidemiological studies, data are inconsistent. Finnish birth cohort observed that, vitamin D supplementation during the first year of life was associated with a reduced risk of schizophrenia in male subjects<sup>(14)</sup> Also, in the dried blood samples of a Danish neonatal biobank, low concentrations of 25-hydroxyvitamin D<sub>3</sub> in neonates was associated with two fold increased risk of developing schizophrenia later in life.<sup>(15)</sup> Moreover, findings from most case control studies have revealed significant inverse association between vitamin D status and schizophrenia.<sup>(16)</sup> On the other hand, some studies have failed to find a significant association,<sup>(17)</sup> and some others have found that higher vitamin D concentrations are associated with increased risk of schizophrenia.<sup>(15)</sup>

To our knowledge few studies have been done on the relationship between vitamin D deficiency and risk of schizophrenia in Egypt, so we conducted this study to spot the light more on this relationship.

**Objective:** To measure schizophrenic patients' serum vitamin D concentration and compare it to healthy controls (non schizophrenics), and to investigate the relationship between serum schizophrenia and related potential risk factors.

## SUBJECTS AND METHODS

**Subjects:** Age and sex matched case control study was carried out in AL-Zahraa University Hospital on a total of 40 subjects (20 patients with schizophrenia and 20 individuals as a control group). The schizophrenic patients included in the study were those attending the psychiatric outpatient clinic for follow up and taking medication, and their age was more than 18 years old. The control subjects were those accompanying the attendants from other outpatient clinics and employees at AL-Zahraa University Hospital. All individuals having major illness were excluded.

**Methodology:** All individuals were subjected to the following steps:

. **Complete History taking:** Personal history was taken from the participants which consisted of the basic socio-demographic characteristics including; age, sex, residence, level of education, occupation, marital status and smoking habit. This is followed by complete medical history and examination. Next anthropometric measurements were recorded: weight and height measurements, weight was measured to the nearest 0.5 kg and height to the nearest 1.0 cm and body mass index was calculated as weight in kg / height in square meters<sup>(18)</sup>. Then each participant was subjected to a complete psychiatric interview: A Full psychiatric history and sheet including present and past history of schizophrenia, mental state examination and diagnosis using Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) criteria for diagnosis of schizophrenia.<sup>(19)</sup>

. **Semi-Structured Interview For Diagnostics and Statistics Manual (DSM-IV) {SCID-1}** for confirmation of diagnosis and assessment of symptoms, the SCID-1 is conducted and it is a valid reliable semi-structured interview<sup>(20)</sup> for diagnosing psychiatric disorders along major DSM-IV Axis. The subjects may either be psychiatric or general mental patients, or individuals who do not identify themselves as patients, such as subjects in a community survey of mental illness or family members of psychiatric patients. The SCID for DSM-IV is available in two versions: Clinician and Research. The used version in this study is the Research Version, it contains more disorders, subtypes, severity and course specifics, and provisions for coding the specific details of the past mood episodes.<sup>(21)</sup>

. **Biochemical investigations:** after taking an informed consent, a blood sample was collected from each participant and analyzed for vitamin D level LIAISON® for the quantitative determination of the autoantibody titers. This is a two-step immunoluminometric sandwich assay that employs directly coated magnetic microparticles.<sup>(22)</sup> Vitamin D status is readily assessed by measuring serum 25-hydroxyvitamin D (25OHD Total) with most

authorities defining Deficiency, insufficiency, sufficiency and Toxicity levels as <10.0 ng/ml, 10–30 ng/ml, 30–100 ng/ml and >100 ng/ml, respectively.

**Statistical Analysis:**

Data were fed to the computer using STATA version 13. Possible entry errors were checked for by a serial range, minimum and maximum values as well as frequency distribution and cross tabulations to ensure that all questions had valid codes and values. Many variables were created for re-categorization of variables. Also, all the used SCID 1 scale was scored according to the instructions of the authors.

Simple descriptive statistics as frequency and percentage distribution for categorical variables and mean with the standard deviation for quantitative variables were used.

For comparative purposes, McNemar Chi-square ( $\chi^2$ ) was used for categorical variables, paired t test was used for quantitative variables. Spearman correlation coefficient was utilized to assess association between vitamin D and age and BMI. For comparison between cases and controls analysis was initially carried out based on a series of univariate comparisons. Appropriate inferential statistics was done with  $\leq 0.05$  level of significance. Multiple Logistic Regression model of schizophrenia predictors among the studied population was constructed containing the following predictors; vitamin D, age, sex, BMI and smoking.

**Ethical Considerations:**

All the necessary approvals for carrying out the research were obtained including ethical approval. An informed written consent, explaining the purpose of the research was prepared and signed by the participants after explaining the aim and procedures of the study and before filling the questionnaire. Complete confidentiality was ensured. Participants had the right to withdraw from the study whenever they want without affection of their long term care plan was also ensured.

**RESULTS**

**Table 1**

The sample included 40 participants 20 patients with schizophrenia and 20 control. The Schizophrenic patients tended to be younger (24.7±4.9 years) compared to control group

(26.4±4.1 years) in non-significant way ( $p>0.05$ ). On the other hand, when comparing BMI, it was found that schizophrenic patients had a significant higher mean BMI (24.9±5.8) compared to control group (21.1±3.0) ( $p<0.05$ ). Schizophrenic patients showed a significantly lower mean vitamin D level (14.8±4.5 IU) compared to control group (19.6±3.3 IU) ( $P<0.001$ ).

#### Figure (1)

Half of the studied population “schizophrenic patients and control group” was females. Almost all the schizophrenic patients (95%) were non-smokers compared to 80% of the control group and this difference was significant statistically ( $p<0.05$ ). Half of the schizophrenic patients and control group were single while the other halves were either widowed or divorced but this difference was not significant statistically ( $p>0.05$ ). Schizophrenics seemed to be significantly less educated as quarter of the patients were holding university degree compared to half of the control group ( $p=0.05$ )

#### Table 2

Females are more likely to have higher mean serum vitamin D level compared to males. Smokers tended to have lower mean serum vitamin D compared to non smokers. Divorced participants had the least mean serum vitamin D level. Participants holding university degrees recorded as being with the highest mean serum vitamin D level. All these differences were statistically non-significant ( $P>0.05$ ).

#### Table 3

There is a significant negative correlation between BMI and mean serum vitamin D level ( $r=-0.05$ ,  $p=0.002$ ). However, there is a non-significant negative correlation between age and mean serum vitamin D level ( $r=-0.02$ ,  $p=0.9$ ).

#### Table 4

It shows results from a logistic regression model of schizophrenia predictors among the studied population. Vitamin D was significantly associated with schizophrenia ( $p\leq 0.05$ ). Controlling for other variables; high vitamin D level participants were nearly 80% less likely to have schizophrenia compared to low level ones. Being older and female were

80% and 40% less likely to have schizophrenia respectively. Large body mass index was 1.2 times more likely to be schizophrenic compared to normal body weight. Smokers were 10% less likely to be schizophrenic compared to non-smoker participants.

## DISCUSSION

Vitamin D is not only an essential element in perpetuating bone integrity, but it also an integral in several other biochemical procedures within the human body.

Vitamin D receptors are placed in bone, skeletal muscle, immune cells, and other body tissues including the brain, prostate, breast, and colon. The associated cell signaling by vitamin D may explain the mounting evidence that links vitamin D deficiency with an increased risk for a variety of diseases, including cancer, autoimmune disorders, bone disease, cardiovascular disease, and psychiatric disorders.<sup>(23)</sup>

Among the forty participants in the current study, schizophrenic patients tended to be younger with larger body mass index compared to control group.

All participants completed base line examinations that included measurement of serum 25-hydroxyvitamin D [25(OH)D] levels. Although one would expect that vitamin D levels in Egyptian schizophrenic patients would be higher due to the sunny climate. However, Egyptian population spent lots of time indoor and even their recreational and social activities. Though, the study demonstrated an overall low serum vitamin D levels. Schizophrenic patients showed a significantly lower mean vitamin D level (14.8±4.5 IU) compared to control group (19.6±3.3 IU). Despite that few researchers have dealt with the putative association between serum vitamin D concentration and mental illnesses. In two studies that primarily aimed to explore the link between vitamin D and osteoporosis in patients with schizophrenia, low vitamin D concentrations were recorded.<sup>(24)</sup> This is also supported with what was reported by a recent mini meta-analysis showing lower vitamin D levels in individuals with psychotic disorders, particularly schizophrenia, as compared to healthy controls.<sup>(25)</sup> This is also consistent with other researchers<sup>(26)</sup> reported that

vitamin D deficiency has been linked to an increased risk for schizophrenia. Therefore, the current results are in line with a great body of work reviewing 19 studies, which included more than 2800 participants, suggesting that those with vitamin D deficiency were more than twice as likely to be diagnosed with schizophrenia compared with their counterparts who were not vitamin D deficient. In addition, 65% of the patients who had schizophrenia also had lower levels of vitamin D.<sup>(26)</sup> Surprisingly, a study conducted in Denmark showed that neonates with excessive concentrations of vitamin D had an elevated risk for this disorder.<sup>(15)</sup>

Interestingly, schizophrenics seemed to be significantly less educated as quarter of the patients was holding university degree compared to half of the control group. This could be explained by the fact that those with higher education level may find many ways for recreation and have better social life compared to those with lower educational level.

The current study demonstrated a significant inverse relationship between smoking and schizophrenia as almost all the schizophrenic patients were non-smokers compared to two third of the control group and the plausible explanation of this situation could be the small sample size. Fortunately, there is no significant relation between marital status and schizophrenia and this could be attributed to the young age of both groups.

Individuals with psychotic disorders often have vitamin D deficiency as recorded by previous researches. However, this could be attributed to long hospital stays, use of anticonvulsant medications, or poor diet. In case, it was expected that vitamin D levels may be to some extent low even in early psychosis, as people may be a bit little bound in their day-to-day activities in the period before their first presentation and this results in less sunlight exposure. However,<sup>(27)</sup> did not record any correlation between vitamin D levels and length of hospitalization in the patient group.

Despite this, 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.<sup>(28)</sup>

Turning to the relation between sex and level of vitamin D, the present study demonstrated that schizophrenic females are more likely to have higher mean serum vitamin D level compared to males. Kristina *et al.*<sup>(29)</sup> also showed that low vitamin D level among schizophrenic males was associated with increased overall negative symptoms and decreased premorbid adjustment. These findings prove that low vitamin D among males may be one of the responsible factors account for the burden of increased symptoms severity. In schizophrenic females vitamin D supplementation could afford valuable neuroprotective effects as a buffer of oxidative stress.

The present study revealed that schizophrenic patients significantly tended to be with large weight compared to control group. Saneei *et al.*<sup>(30)</sup> reported similar finding through previous meta-analysis; an inverse relationship between serum vitamin D levels and BMI. This could be attributed to direct relation between severities of disorders and decreased physical activity, increased body mass index, smoking, hypertension and other factors that may be independently associated with mental disorders.

In terms of the significant association between vitamin D deficiency and schizophrenia, controlling for other variables; high vitamin D level, being female and older age and with smaller body mass index are less likely to have schizophrenia.

Although socio-demographic and psychological risk factors are now well established, there is mounting interest in the search for modifiable risk factors that simultaneously affect mental disorders and other chronic co-morbidity as hypertension especially in the elderly.<sup>(31)</sup>

## CONCLUSION

Vitamin D deficiency is eminently swinging and has a lead in the pathogenesis of schizophrenia. We recommend that schizophrenic patients have to assess regularly

their serum vitamin D level. According to their vitamin D levels, these patients should have appropriate exposure to sunlight, activity and dietary adjustments to normalize vitamin D levels. Also, we excogitate that prenatal vitamin D supplements during pregnancy may depress the risk of schizophrenia in the offspring.

Future work is needed to figure out how the expanding problem of vitamin D deficiency may be affecting the overall health integrity adding to randomized clinical trials on vitamin D supplementation to focus on dosing and sustainability in schizophrenic patients as they did not know yet what the protective optimum dose of vitamin D.

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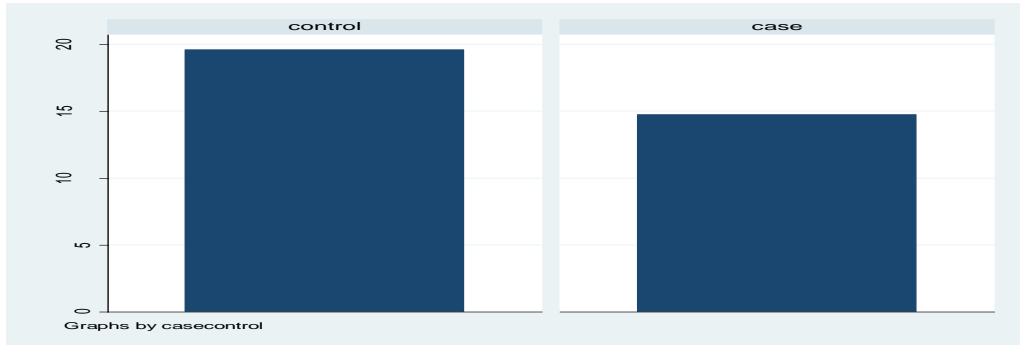
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**Table (1): Basic characteristics of the studied population**

Variables	Schizophrenia patients		Controls		Test	P
	Mean	SD	Mean	SD		
<b>Age</b>	24.7	4.9	26.4	4.1	1.2	0.3
<b>BMI</b>	24.9	5.8	21.1	3.0	-2.6	0.01
<b>VitD</b>	14.8	4.5	19.6	3.3	3.9	0.0004
	<b>N</b>	<b>%</b>	<b>N</b>	<b>%</b>	<b>McNemar<sup>x2</sup></b>	<b>P</b>
<b>Sex</b>						
Male	10	50.0	10	50.0	0.00	1.00
Female	10	50.0	10	50.0		
<b>Smoking</b>						
Smoker	1	5.0	4	20.0	9.8	0.002
Non-Smoker	19	95.0	16	80.0		
<b>Marital Status</b>						
Single	10	50.0	10	50.0	5.1	0.2
Married	7	35.0	8	40.0		
Divorced	3	15.0	0	0.0		
Widowed	0	0.0	2	10.0		
<b>Education</b>						
Preparatory	4	20.0	0	0.0		
Secondary	11	55.0	10	50.0		
University	5	25.0	10	50.0	5.7	0.05



**Graph (1): Relationship between mean serum vitamin D level and schizophrenia among the studied population**

**Table (2): Distribution of serum vitamin D level according to basic characteristics of the studied population**

Variables	Vitamin D		Test	P
	Mean	SD		
<b>Sex</b>				
Male	17	4.9	-0.2	0.8
Female	17.4	4.4		
<b>Smoking</b>				
Smoker	16.9	4.2	-0.7	0.5
Non-Smoker	18.6	4.2		
<b>Marital Status</b>				
Single	18.4	5.2	1.4	0.3
Married	16.7	3.8		
Divorced	13.3	2.9		
Widowed	15	0		
<b>Education</b>				
Preparatory	13.8	4.8	2.6	0.09
Secondary	16.6	4.9		
University	18.9	3.6		

**Table (3): Correlation between serum vitamin D level and age and BMI**

Variables	Vitamin D	
	R	P
Age	-0.02	0.9
BMI	-0.05	0.002

**Table (4): Logistic regression of predictors of schizophrenia among the studied participants**

Variables	Odds Ratio	SE	Z	P
Vitamin D	0.8	0.1	-2.2	0.03
Age	0.8	0.1	-1.7	0.08
Female	0.4	0.4	-0.9	0.4
BMI	1.2	0.2	1.7	0.09
Smoker	0.1	0.1	-1.7	0.09