Egyptian Journal of Psychiatry

Vol. 45, No. 2, 2024
ISSN: 1110-1105 (print)
ISSN: 2090-2425 (online)
DOI: 10.21608/EJPSY.2025.406244

# ORIGINAL ARTICLE

## Effect of Vitamin D Supplementation on Cognitive Functions, Positive and Negative Symptoms Among an Egyptian Sample of Patients with Schizophrenia

**Mina M. Mikhail[a]; Ibtihal M.A. Ibrahim[a]; Farha Elshennawy[b]; Salwa S. Tobar[a]; Hala A. El boraie[a]**

*[a]Psychiatry Department; [b]Clinical Pathology Department, Mansoura Faculty of Medicine, Mansoura University, Egypt.*

**Correspondence to** *Ibtihal M.A. Ibrahim, Assistant Professor Psychiatry Department, Mansoura Faculty of Medicine, Mansoura University, Egypt.*
*E-mail: drpossy2002@yahoo.com.*

**Background** A role for vitam in D in brain development and function has been gaining support over the last decade. Early deficiencies have been linked with neuropsychiatric disorders, such as schizophrenia.

**Aim** Is to assess whether correcting vitamin deficiency in patients with schizophrenia results in improvement in cognitive function and improve positive and negative symptoms.

**Subjects and Methods** This is a Randomized double-blind placebo-controlled study. 74 patients were interviewed; 14 patients did not meet inclusion criteria and were excluded and the remaining 60 patients were divided in two groups: 30 patients with normal level of serum vitamin D and 30 patients with low serum vitamin D. Then 30 patients with low vitamin D were blindly divided into 13 patients received vitamin D plus antipsychotic medications and 17 patients received antipsychotic medications plus placebo. Cognitive functions, positive and negative symptoms were compared between groups.

**Results** Vitamin D treatment helped to improve attention by 15.2%, memory by 36.14% and emotion recognition by 43.7%. Also, improvement in positive scale by 66.2% in treatment group versus 46.5% in untreated group. Improvement in negative scale by 51.2% in treatment group versus 28.8% in untreated group. Improvement in pathology scale by 65.4% in treatment group versus 40.7% in untreated group.

**Conclusions** Vitamin D injection helped to improve attention, memory, emotion recognition, positive and negative symptoms of schizophrenia when given with antipsychotic medications.

**Keywords** CNB, Cognitive function, Schizophrenia, Vitamin D.

### INTRODUCTION

Schizophrenia is a chronic and complicated disorder with multiple mental and behavioral abnormalities. There are numerous genetic and environmental factors that may be responsible for occurrence of schizophrenia, including maternal malnutrition, maternal exposure to influenza, and a range of vitamins and minerals malnutrition such as vitamin D, B vitamins, and zinc deficiencies (Sheikhmoonesi *et al.,* 2016).

Some epidemiological evidences suggest that vitamin D deficiency in the third trimester is a risk factor for schizophrenia. Possible roles for vitamin D in the brain development and regulation are thought to be effective in pathogenesis of schizophrenia. Vitamin D levels have been shown to be lower in schizophrenic patients compared to healthy individuals or even depressed patients. Whether hypovitaminosis D is a causative factor of schizophrenia

or a result of poor nutrition of psychotic patients or a side effect of antipsychotics is the focus of intense research (Sheikhmoonesi *et al.,* 2016).

Low levels of vitamin D are prevalent among patients with schizophrenia and have been linked to the risk and outcome of the disorder. Vitamin D has a regulatory effect on the inflammatory system, which is dysfunctional in schizophrenia. Within clozapine- treated schizophrenia patients, high levels of vitamin D are associated with lower serum levels of the proinflammatory cytokine IL-6. This relationship may indicate an immunomodulatory effect of vitamin D in treatment-resistant patients with schizophrenia maintained on clozapine (Krivoy *et al.,* 2020).

Vitamin D is involved in brain development and functioning, as well as in regulation of neurotrophic factors. Changes in the expression of those factors are possibly responsible for morphologic abnormalities and symptoms in patients suffering from schizophrenia (Peitl *et al.,* 2020).

Accumulating data show that there may be an association between vitamin D deficiency and schizophrenia. In an updated meta-analysis to investigate the relationship between schizophrenia and blood vitamin D level, all published observational articles have been searched from five databases until September 2019. In total, 36 articles with a total of 12528 participants were included in this study. Patients with schizophrenia have significantly lower levels of vitamin D than controls (Zhu *et al.,* 2020).

So, in this study we aim to assess whether correcting vitamin D deficiency in patients with schizophrenia results in improvement in cognitive function and improve positive and negative symptoms.

## SUBJECTS AND METHODS

This is a Randomized double-blind placebo-controlled study; randomization was done by independent person other than who was doing assessment. Patients were given placebo or vitamin D according to sealed envelope randomization. examiner was blinded from who took placebo and who took vitamin D. This study took part from 17th April 2020 to 10th February 2021.

The study was conducted in psychiatry department of Mansoura university hospital. The study was approved by the ethical committee and Institutional Review Board of faculty of medicine Mansoura University. Written Consent was taken from the patients or their relatives to participate in the study.

**Inclusion criteria**

1. Both sexes aged 19–50 years (to minimize the influence of aging on cognitive functions and to exclude cases of early dementia).
2. Those fulfilling DSM V criteria for schizophrenia.
3. Schizophrenia with illness duration (<7 years) (recent onset psychosis to avoid severe cognitive impairment that happens with chronic cases).
4. Vitamin D deficiency: Serum OH (25) D below (≤30 ng/ml).
5. Written informed consent.

**Exclusion criteria**

1. Past history of head trauma, brain tumor, brain infection, or delirium.
2. Chronic medical condition (end stage renal disease, malabsorption syndromes, or corticosteroid therapy).
3. Comorbid substance use disorder.
4. Patients already on vitamin D supplementation.
5. Women who have reached menopause as they have higher dietary requirements.

The diagnosis was made using schedule for clinical assessment of neuropsychiatry (SCAN) and was confirmed by consensus diagnosis made by two senior psychiatrists.

**Measuring serum vitamin D**

A sample of 3ml of venous blood was collected into a test tube that does not contain anticoagulant at the baseline. Each sample was centrifuged (3500xg) for 15min Then the serum was separated and the serum vitamin D concentration was analyzed using a commercially available 25-OH Vitamin D ELISA kit. According to the manufacturer's instructions. This ELISA kit is designed for the in vitro determination of 25-OH vitamin D in human serum or plasma samples (Sheikhmoonesi *et al.,* 2016).

Patients with schizophrenia who met the inclusion criteria and who agreed to participate in the study were enrolled. Sociodemographic and clinical data was collected from the patients and then blood sample was withdrawn from them to test for serum level of vitamin D. depending on the results, patients were divided in two groups.

**Group one**

Thirteen patients with diagnosis of schizophrenia took antipsychotic drugs plus vitamin D supplementation. Each patient received 400,000 IU Vitamin D injection along their antipsychotic regimen (Sheikhmoonesi *et al.,* 2016). Patients received (2 ampoules of devarol-s 200,000 IU IM injection, available in Egypt) one shot at baseline. Vitamin D injection was administered by a fully trained nurse in a private room within the department of Psychiatry at Mansoura Hospital.

The injection was given in the upper arm of the non-dominant hand (deltoid muscle) of the participant after antiseptic preparation. After injection is administered, participants were monitored by study staff for any side effects, including allergic reaction, for a total of one hour. Positive and Negative syndrome scale and cognitive battery were administered at the baseline and after one month (Sheikhmoonesi *et al.,* 2016). A checklist was prepared consisting of the common and adverse effects associated with vitamin D supplementation which are mainly related to raised serum calcium levels.

**Group two (control group)**

Seventeen patients with diagnosis of schizophrenia took antipsychotic drugs plus placebo (saline injection because its similar in shape to vitamin D). Positive and Negative syndrome scale and cognitive battery were administered at the baseline and after one month.

Both groups received the same antipsychotic (on a stable dose of Resperidone ranging from 4-8mg/day) (Sheikhmoonesi *et al.,* 2016).

**Assessment of positive and negative symptoms using PANSS (Kay *et al.,* 1987)**

The 30-item PANSS provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology. It thus constitutes four scales measuring positive and negative syndromes, their differential, and general severity of illness.

**Assessment of cognitive functions using Penn Computerized Neurocognitive Battery (CNB) (Arabic version)(Ibrahim *et al.,* 2015):**

The Arabic Penn CNB consists of 14 tests: Motor Praxis Test for assessment of sensorimotor integration speed; the Penn Continuous Performance Test–Number for assessment of attention; face memory (immediate and delayed) with the Penn Face Memory Test and Penn Face Memory Test–Delayed Memory; the Penn Conditional Exclusion Task for assessment of abstraction and mental flexibility; Short Computerized Finger-Tapping Task; Short Visual Object Learning Test and Short Visual Object Learning Test Delayed Memory for assessment of spatial memory; the Penn Matrix Reasoning Test for assessment of nonverbal reasoning; the Short Penn Line Orientation Test for spatial orientation; the Age Differentiation Test; Penn Emotion Recognition Task; the Measured Emotion Differentiation Test for social cognition; and, finally, the Short Fractal N-Back for assessment of working memory.

**Statistical Analysis**

Data were analyzed by IBM SPSS software version 20.0. Qualitative statistics were labeled using number and percent. the sample size was calculated using G*Power. Univariate differences between groups were assessed using Student's *t*-test. To compare outcomes between two independent groups we used the Mann Whitney Wilcoxon test. Wilcoxon signed-rank test was used to conduct a paired difference test of repeated measurements.

## RESULTS

Data were analyzed by IBM SPSS software version 20.0. Qualitative statistics were labeled using number and percent. the sample size was calculated using G*Power. Univariate differences between groups were assessed using Student's *t*-test. To compare outcomes between two independent groups we used the Mann Whitney Wilcoxon test. Wilcoxon signed-rank test was used to conduct a paired difference test of repeated measurements.

Table (1) shows that the group of patients with normal vitamin D and the group of patients with low vitamin D were matched regarding age, sex, years of education, residence, family history of psychiatric disorders and consanguinity.

Table (2) shows that patients with normal vitamin D level took more time to reach correct choice in short visual object learning test delayed memory (for assessment of delayed memory) than patients with low level of vitamin D. There is no statistically significant difference between treated and untreated groups regarding sensorimotor integration speed, emotion differentiation and face memory test (immediate and delayed), also no difference between patients with normal and low serum vitamin D levels. There is statistically significant difference between treated and untreated group regarding the Penn Continuous Performance Test–Number (PCPT-n) for assessment of attention being more accurate in treated group. Patients with normal vitamin D level took more time in short visual object learning test (for assessment of memory) compared to people with low vitamin D level. There is statistically significant difference between patients with normal and patients with low vitamin D level regarding Short Visual Object Learning Test Delayed Memory being more accurate in patients with normal vitamin D but took much more time compared to patients with low vitamin D.

Table (3) shows that vitamin D treatment helped to improve attention by 15.2%. Table (4) shows improvement in memory by 36.14% after vitamin D treatment. Table (5) shows improvement in emotion recognition by 43.7% after treatment by vitamin D.

Table (6) shows improvement in positive scale by 66.2% in treatment group versus 46.5% in untreated group. Improvement in negative scale by 51.2% in treatment group versus 28.8% in untreated group. Improvement in

pathology scale by 65.4% in treatment group versus 40.7% in untreated group.

**Table 1:** Socio-demographic characteristics of the studied groups:

| | Low vitamin D | Normal vitamin D | Test of significance |
|---|---|---|---|
| Age/years | | | |
| mean±SD | 31.57±6.85 | 29.80±7.81 | *t*= 0.932<br>*P*= 0.355 |
| (%)Sex N | | | |
| Female | 12(40.0) | 8(26.7) | $\chi^2$= 1.20 |
| Male | 18(60.0) | 22(73.3) | *P*= 0.273 |
| Duration of education/years | | | |
| mean±SD | 14.70±3.87 | 14.63±3.61 | *t*= 0.069<br>*P*= 0.945 |
| Residence | | | |
| Urban | 12(40.0) | 16(53.3) | $\chi^2$= 1.07 |
| Rural | 18(60.0) | 14(46.7) | *P*= 0.301 |
| Family History of psychiatric disorders | | | |
| Negative | 24(80.0) | 26(86.7) | $\chi^2$= 0.480 |
| Positive | 6(20.0) | 4(13.3) | *P*= 0.488 |
| Consanguinity | | | |
| Negative | 29(96.7) | 24(80.0) | $\chi^2$= 1.07 |
| Positive | 1(3.3) | 6(20.0) | *P*= 0.301 |

*t*: Student t test; $\chi^2$= Chi-Square test.

**Table 2:** Cognitive assessment after vit D treatment among studied groups:

| | Normal vitamin D group | Cases with low vit D not treated | Cases with low vit D after treatment | Test of significance |
|---|---|---|---|---|
| Motor Praxis Test (MPRAXIS) reaction time | 1144(516–4255) | 1468(639.5–4021.5) | 903.0(512–4279) | *P1*= 0.121<br>*P2*= 0.239<br>*P3*= 0.950 |
| Penn facial memory test. total correct responses | 29.5(20–35) | 26(20–35) | 30(21–34) | *P1*= 0.253<br>*P2*= 0.671<br>*P3*= 0.163 |
| Penn facial memory test. median reaction time | 1602(834–5108) | 1654(984–4010) | 1304(1026–3972) | *P1*= 0.580<br>*P2*= 0.916<br>*P3*= 0.917 |
| Penn matrix reasoning test accuracy | 7(1–21) | 4(0–16) | 13(3–18) | *P1*= 0.282<br>*P2*= 0.283<br>*P3*= 0.817 |
| Penn matrix reasoning test reaction time | 5028(1054–70227.5) | 7055.75(631–18136) | 5216(2183–12279.5) | *P1*= 0.623<br>*P2*= 0.535<br>*P3*= 0.658 |
| Measured emotion differentiation test accuracy | 22(9–31) | 21(11–31) | 23(4–30) | *P1*= 0.790<br>*P2*= 0.374<br>*P3*= 0.721 |
| Measured emotion differentiation test speed | 1335.5(808.5–7912) | 1577(976–6256) | 1191.5(944–6504) | *P1*= 0.108<br>*P2*= 0.412<br>*P3*= 0.572 |
| Short penn continuous performance task. true positive responses | 81.5(21–119) | 70(15–108) | 111(37–119) | *P*1= 0.126<br>*P2*= 0.483<br>*P3*= 0.426 |

(Continued)

**Table 2: (Continued)**

| | Normal vitamin D group | Cases with low vit D not treated | Cases with low vit D after treatment | Test of significance |
|---|---|---|---|---|
| Short penn continuous performance task. true negative responses | 228.5(104–239) | 231(171–240) | 237(187–239) | *P1*= 0.478<br>*P2*= 0.039*<br>*P3*= 0.075 |
| Short penn continuous performance task. median response time for true positive responses | 494.25(403–687.5) | 471(416–718) | 433(416–539) | *P1*= 0.543<br>*P2*= 0.771<br>*P3*= 0.691 |
| Penn Face Memory Test–Delayed Memory accuracy | 32(16–37) | 30(20–35) | 34(19–38) | *P1*= 0.579<br>*P2*= 0.652<br>*P3*= 0.967 |
| Penn Face Memory Test–Delayed Memory median response time | 1266.5(958–414) | 1464(244–3012) | 1156(982–2576) | *P1*= 0.232<br>*P2*= 0.526<br>*P3*= 0.572 |
| Age differentiation test Accuracy | 22(8–30) | 19(12–29) | 24(4–26) | *P1*= 0.456<br>*P2*= 0.411<br>*P3*= 0.950 |
| Age differentiation test Speed | 1364.75(936–3858) | 1296(999.5–5021) | 1073(165–1434) | *P1*= 0.324<br>*P2*= 0.234<br>*P3*= 0.983 |
| Penn Conditional Exclusion Task. median response time for correct responses | 1866.75 (1096.5–4342.5) | 2026.75(1314–2141) | 1223(1117.5–1349.5) | *P1*= 0.40<br>*P2*= 0.579<br>*P3*= 0.818 |
| Penn Conditional Exclusion Task Accuracy | 2.44(0.08–3.67) | 1.68(0.33–3.38) | 3.1(0.08–3.75) | *P1*= 0.859<br>*P2*= 0.606<br>*P3*= 0.738 |
| Short Computerized Finger-Tapping Task | 102.33(42–133) | 97.33(65.33–129.33) | 118.33(57–131) | *P1*= 0.868<br>*P2*= 0.731<br>*P3*= 0.615 |
| Short Visual Object Learning Test accuracy | 16(9–20) | 15(7–18) | 18(9–19) | *P1*= 0.894<br>*P2*= 0.894<br>*P3*= 0.899 |
| Short Visual Object Learning Test. median response time | 1425.5(440–3624) | 1544(786–2464) | 1256(731.5–3944) | *P1*= 0.016*<br>*P2*= 0.153<br>*P3*= 0.315 |
| Short Visual Object Learning Test Delayed Memory accuracy | 15(10–18) | 13(9–18) | 16(9–19) | *P1*= 0.02*<br>*P2*= 1.0<br>*P3*= 0.055 |
| Short Visual Object Learning Test Delayed Memory. median response time for correct responses | 1225.5(603.5–3944) | 1160(784–2955.5) | 1012(296–5399) | *P1*= 0.150<br>*P2*= 0.261<br>*P3*= 0.834 |
| Penn Emotion Recognition Task accuracy | 33(15–40) | 34(22–38) | 36(19–38) | *P1*= 0.773<br>*P2*= 0.671<br>*P3*= 0.785 |
| Penn Emotion Recognition Task. median response time | 1604(1112–8464) | 1496(1103–5952) | 1243(1151–2032) | *P1*= 0.241<br>*P2*= 0.672<br>*P3*= 0.517 |
| The Short Fractal N-Back. true positive responses | 22(8–29) | 21(10–28) | 23(13–29) | *P1*= 0.602<br>*P2*= 0.176<br>*P3*= 0.411 |
| The Short Fractal N-Back. median response time for MRC | 605.5(411.5–1144) | 659.25(498–1057) | 502.5(413.75–1018.5) | *P1*= 1.0<br>*P2*= 0.139<br>*P3*= 0.305 |

Used tests: Mann Whitney U test with paired comparison between 2 groups by Wilcoxon signed rank test; P1: Difference between normal Vit D group and Cases with low vit D; P2: Difference between normal vit D group and treated cases with low vit D; P3: Difference between cases with low vit D treated and not treated.

**Table 3:** Shows percentage of improvement in attention between baseline and follow up assessments:

| Short penn continuous performance task | True positive | | False positive | | True negative | | False negative | | True positive reaction time | |
|---|---|---|---|---|---|---|---|---|---|---|
| Control | | | | | | | | | | |
| Z | −0.562[a] | | −0.041[b] | | −0.041[a] | | −0.562[b] | | −0.864[b] | |
| Asymp. Sig. (2-tailed) | 0.574 | | 0.967 | | 0.967 | | 0.574 | | 0.388 | |
| Low Vit D untreated | | | | | | | | | | |
| Z | −0.947[a] | | −0.625[b] | | −0.625[a] | | −0.947[b] | | −0.260[b] | |
| Asymp. Sig. (2-tailed) | 0.344 | | 0.532 | | 0.532 | | 0.344 | | 0.795 | |
| Low Vit D treated | | | | | | | | | | |
| Z | −2.040[b] | 20.4% | −1.958[b] | 55.6 | −1.958[a] | 7.2 | −2.040[a] | 43.3 | −2.667[b] | 15.2 |
| Asymp. Sig. (2-tailed) | 0.041 | | 0.050 | | 0.050 | | 0.041 | | 0.008 | |

Wilcoxon signed rank test. Percent of improvement= pre − post/pre.

**Table 4:** Shows percentage of improvement in attention between baseline and follow up assessments:

| Short visual object learning test | Short visual object learning test total correct | | Short visual object learning test. median response time for total correct | | Short visual object learning test. true negative median response time | |
|---|---|---|---|---|---|---|
| CONTROL | | | | | | |
| Z | −2.335[a] | 15.4 | −2.273[a] | 20.6 | −1.742[a] | |
| Asymp. Sig. (2-tailed) | 0.020 | | 0.023 | | 0.081 | |
| Low Vit D untreated | | | | | | |
| Z | −0.569[a] | | −0.639[b] | | −0.310[b] | |
| Asymp. Sig. (2-tailed) | 0.569 | | 0.523 | | 0.756 | |
| Low Vit D treated | | | | | | |
| Z | −1.825[a] | | −0.734[a] | | −1.961[a] | 36.14 |
| Asymp. Sig. (2-tailed) | 0.068 | | 0.463 | | 0.050 | |

Wilcoxon signed rank test. Percent of improvement= pre − post/pre.

**Table 5:** Shows percentage of improvement in emotion recognition between baseline and follow up assessments:

| | Emotion recognition | |
|---|---|---|
| Control | | |
| Z | −1.806[a] | |
| Asymp. Sig. (2-tailed) | 0.071 | |
| Low Vit D untreated | | |
| Z | −0.260[a] | |
| Asymp. Sig. (2-tailed) | 0.795 | |
| Low vit D treated | | |
| Z | −2.760[a] | 43.7 |
| Asymp. Sig. (2-tailed) | 0.006 | |

Wilcoxon signed rank test. Percent of improvement= pre − post/pre.

## DISCUSSION

In our study we found no significant association between serum vitamin D level and positive symptoms of schizophrenia. However, during our work, we found that giving vitamin D bolus injection resulted in improvement of positive symptoms by percentage of 66.2% vs. 46.5% in patients who received antipsychotic medications alone.

This finding was supported by another study which concluded that there is increased severity of symptoms at lower levels of vitamin D, suggesting that treatment for schizophrenia should include assessment of patients' vitamin D levels (Dogan Bulut *et al.,* 2016).

Also, we found that giving vitamin D can improve negative symptoms by percentage of 51.2% versus 28.8% in patients who received antipsychotic medications alone. This finding was supported by another study found that vitamin D deficiency is strongly related to negative and depressive symptoms of schizophrenia (Nerhus *et al.,* 2016). Contrary to our findings, another study found that vitamin D deficiency is not related to symptoms of schizophrenia and not considered as risk factor for psychosis (Ozer *et al.,* 2004).

Regarding cognitive functions, we found statistically significant positive correlation between serum vitamin D

**Table 6:** Comparing improvement in PANSS scale between patients with low vitamin D who received vitamin D and who did not receive it:

| PANSS | Positive.scale.score | | Negative.score.scale | | Pathology.scale.score | |
|---|---|---|---|---|---|---|
| Control | | | | | | |
| Z | −4.128[b] | 50.8 | −3.574[b] | 37.6 | −4.270[b] | 49.2 |
| Asymp. Sig. (2-tailed) | 0.000 | | 0.000 | | 0.000 | |
| Low Vit D untreated | | | | | | |
| Z | −3.176[b] | 46.5 | −3.111[b] | 28.8 | −3.623[b] | 40.7 |
| Asymp. Sig. (2-tailed) | 0.001 | | 0.002 | | 0.000 | |
| Low vit D treated | | | | | | |
| Z | −3.185[b] | 66.2 | −3.187[b] | 51.2 | −3.180[b] | 65.4 |
| Asymp. Sig. (2-tailed) | 0.001 | | 0.001 | | 0.001 | |

Wilcoxon signed rank test. Percent of improvement= pre − post/pre.

and short visual object learning test which assess memory. We found that patients with normal vitamin D level took more time to complete test than patients with low level of vitamin D. The same correlation was found between serum vitamin D and Short Visual Object Learning Test Delayed Memory which assess delayed memory; we found that patients with normal vitamin D level took more time to complete test than patients with low level of vitamin D.

This longer time taken by patients with normal vitamin D to reach more accurate responses as we noticed during our work may be related to that patients with poor cognition get anxious easily from having the test and may decide to choose any answer to finish the test. This finding was supported by another study which related vitamin D deficiency to changes in memory and even the onset of Alzheimer disease (Annweiler *et al.,* 2014).

Another review supports the hypothesis that hypovitaminosis D is associated with worse outcome on one or more cognitive function tests or a higher frequency of dementia (van der Schaft *et al.,* 2013). A more recent study confirmed that vitamin D concentrations are lower in individuals with cognitive impairment (Sultan *et al.,* 2020).

Also in support of our way of work which relies on giving high dose of vitamin D, another recent study found that giving high dose of vitamin D upgraded cognitive abilities tasks including memory, inhibitory control and selective attention, decision making, planning, sustained attention and cognitive flexibility (Bahrami *et al.,* 2021).

During our work, when we separated the patients with low vitamin D and gave bolus dose of vitamin D to only 13 patients of them, we found that vitamin D injection helped to improve results on Penn Continuous Performance Test–Number which is designed to assess attention. This finding is not matching with other study investigating effect of vitamin D on cognition in schizophrenia in general. This may be explained by difference in assessment tools, as in the other study, they relied on questionnaires in their assessment of cognitive functions while in our study; we used computerized battery for assessment (Graham *et al.,* 2015).

In comparison between patients who received antipsychotic medications plus vitamin D and patients who received antipsychotic medications plus placebo, the vitamin D group showed higher scores on second evaluation by Short Visual Object Learning Test Delayed Memory which assess delayed memory and this was done after one month of treatment. This finding is matching with the previous finding in our study, when we compared patients with low serum level of vitamin D with patients with normal serum level of vitamin D, the group with normal level showed higher scores in this test on baseline assessment.

By comparing our results between patients who received vitamin D plus antipsychotic medications and patients who received antipsychotic medications alone, we can say that vitamin D helped to improve attention by 15.2% and improved memory by 36.14% while improvement in emotional recognition was 43.7%.

## LIMITATIONS

Most of the patients in this study were from rural areas nearby Mansoura, we don't know the extent to which these findings would generalize to other urban populations. Another limitation to our study, that gender distribution among the subjects was not equal. We don't know to how extent this can affect the results. Unfortunately, we could not recruit larger number of patients because of covid-19 pandemic. Many patients were reluctant to seek help in public hospitals because of fear of the crowd and exposure time. Especially that assessment of cognition by our battery took more than one hour in most of the patients.

## CONCLUSION

Vitamin D injection helped to improve attention, memory, emotion recognition, positive and negative symptoms of schizophrenia when given with antipsychotic medications.

## RECOMMENDATIONS

1. More future studies on the effect of vitamin D supplementation on improving the symptoms of schizophrenia.

2. More future studies on relation between prenatal vitamin D deficiency and later risk of schizophrenia in offspring.

3. Routine screening for serum vitamin D level during pregnancy and early childhood.

4. More studies on mechanism of action of vitamin D as a neuroprotective factor.

5. Public awareness should be initiated to point out the high prevalence of vitamin D deficiency.

6. Public awareness should be initiated to point out that vitamin D is not only important for healthy bone growth but it plays important role in regulation of brain development and regulation of immunological response as well.

## ACKNOWLEDGEMENTS

Funding: there is no funding for this research.

## CONFLICTS OF INTEREST

There are no conflicts of interest.

## REFERENCE

Annweiler C., Maby E., Meyerber M., Beauchet O. (2014). Hypovitaminosis D and executive dysfunction in older adults with memory complaint: a memory clinic-based study. Dement Geriatr Cogn Disord 37:286–293. doi:10.1159/000356483.

Bahrami A., Rezaeitalab F., Farahmand SK., Mazloum Khorasani Z., Arabi SM., Bahrami-Taghanaki H., *et al.* (2021). High-dose vitamin D supplementation and improvement in cognitive abilities, insomnia, and daytime sleepiness in adolescent Girls. Basic Clin Neurosci 12:339–348. doi:10.32598/bcn.2021.1910.1.

Dogan Bulut S., Bulut S., Gorkem Atalan D., Berkol T., Gurcay E., Turker T., *et al.* (2016). The relationship between symptom severity and low vitamin D levels in patients with schizophrenia. Plos One 11:e0165284. doi:10.1371/journal.pone.0165284.

Graham KA., Keefe RS., Lieberman JA., Calikoglu AS., Lansing KM., Perkins DO., *et al.* (2015). Relationship of low vitamin D status with positive, negative and cognitive symptom domains in people with first-episode schizophrenia. Early Interv Psychiatry 9:397–405. doi:10.1111/eip.12122.

Ibrahim I., Tobar S., Elassy M., Mansour H., Chen K., Wood J., *et al.* (2015). Practice effects distort translational validity estimates for a Neurocognitive Battery. J. Clin Exp Neuropsychol 37:530–537. doi :10.1080/13803395.2015.1037253.

Kay SR., Fiszbein A., Opler LA. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13:261–276. doi:10.1093/schbul/13.2.261.

Krivoy A., Satz J., Hornfeld SH., Bar L., Gaughran F., Shoval G., *et al.* (2020). Low levels of serum vitamin D in clozapine-treated schizophrenia patients are associated with high levels of the proinflammatory cytokine IL-6. Int Clin Psychopharmacol 35:208–213. doi:10.1097/YIC.0000000000000303

Nerhus M., Berg AO., Kvitland LR., Dieset I., Hope S., Dahl SR., *et al.* (2016). Low vitamin D is associated with negative and depressive symptoms in psychotic disorders. Schizophr Res 178, 44–49. doi:10.1016/j.schres.2016.08.024.

Ozer S., Ulusahin A., Ulusoy S., Okur H., Coskun T., Tuncali T., *et al.* (2004). Is vitamin D hypothesis for schizophrenia valid? Independent segregation of psychosis in a family with vitamin-D-dependent rickets type IIA. Prog Neuropsychopharmacol Biol Psychiatry 28:255–266. doi:10.1016/j.pnpbp.2003.10.002.

Peitl V., Silic A., Orlovic I., Vidrih B., Crnkovic D., Karlovic D., *et al.* (2020). Vitamin D and neurotrophin levels and their impact on the symptoms of schizophrenia. Neuropsychobiology 79:179–185. doi:10.1159/000504577.

Sheikhmoonesi F., Zarghami M., Mamashli S., Yazdani Charati J., Hamzehpour R., Fattahi S., *et al.* (2016). Effectiveness of vitamin D supplement therapy in chronic stable schizophrenic male patients: a randomized controlled trial. Iran J. Pharm Res 15:941–950. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28243293.

Sultan S., Taimuri U., Basnan SA., Ai-Orabi WK., Awadallah A., Almowald F., *et al.* (2020). Low vitamin D and its association with cognitive impairment and dementia. J. Aging Res 2020:6097820. doi:10.1155/2020/6097820.

van der Schaft J., Koek HL., Dijkstra E., Verhaar HJ., van der Schouw YT., Emmelot-Vonk MH., *et al.* (2013). The association between vitamin D and cognition: a systematic review. Ageing Res Rev 12:1013–1023. doi:10.1016/j.arr.2013.05.004.

Zhu JL., Luo WW., Cheng X., Li Y., Zhang QZ., Peng WX., *et al.* (2020). Vitamin D deficiency and schizophrenia in adults: a systematic review and meta-analysis of observational studies. Psychiatry Res 288:112959. doi:10.1016/j.psychres.2020.112959.