Effect of Vitamin D Supplementation on Cardio-metabolic Indices and the Severity of Symptoms in Male Patients With Chronic Schizophrenia

Parinaz Kalejahi¹, Sorayya Kheirouri¹*, Seyed Gholamreza Noorazar²

Abstract

**Objectives:** Hypovitaminosis D is suggested to be related to the high risk of metabolic disorders and symptoms of schizophrenia. Therefore, this study aimed to evaluate the effect of vitamin D supplementation on cardio-metabolic indices and the severity of symptoms in schizophrenic patients.

**Materials and Methods:** Patients with schizophrenia (N = 42) were randomly assigned to 2 groups, i.e., intervention (2000 IU of vitamin D daily; n = 21) and placebo groups (n = 21). The intervention was administered for 8 weeks. Anthropometric, clinical, and laboratory measures were assessed at both baseline and end of the trial. The Positive and Negative Syndrome Scale (PANSS) was performed to assess the schizophrenia symptoms.

**Results:** Vitamin D supplementation leads to a significant decrease in low-density lipoprotein cholesterol (LDL-C) levels (P = 0.006). In addition, a significant improvement was found in the PANSS negative subscale score (PANSS-NSS) and PANSS total score (PANSS-TS; P = 0.005 and P = 0.015, respectively). At the baseline, there was a significant negative correlation between PANSS-NSS, PANSS positive subscale score (PANSS-PSS), and PANSS-TS with serum levels of vitamin D (r = -0.42, P = 0.010; r = -0.34, P = 0.041; and r = -0.47, P = 0.004, respectively).

**Conclusions:** Vitamin D supplementation may have helpful efficacy on some cardio-metabolic indices and schizophrenia severity.

**Keywords:** Schizophrenia, Cardio-metabolic indices, Cardiovascular disease, PANSS, Severity

**Introduction**

Schizophrenia is a chronic and complex mental disorder affecting about 1% of the world’s population. The disorder occurs in all populations with an incidence rate of 0.07 to 7.1 per 1000 (1,2). The exact etiology of schizophrenia is unknown; however, it seems to be a multifactorial disorder involving genetic, psychological, hormonal, and environmental factors (3). According to the literature, the high prevalence of metabolic abnormalities, including obesity, hyperlipidemia, hypertension, and glucose intolerance, in schizophrenia patients leads to an increased incidence of cardiovascular disease (CVD) and other chronic diseases, contributing to premature death and lower life expectancy (4,5). Antipsychotic medications, especially atypical antipsychotics (APPs), can have a wide range of side effects on patients, probably resulting in cardio-metabolic and endocrine disorders (6).

APPs are antagonists for receptors such as serotonin 2C and muscarinic M3 (7). The antagonistic effect of APPs on these receptors is linked to weight gain and insulin dysregulation (8). Other causes of these abnormalities include nutritional factors, such as vitamin D deficiency (9). Vitamin D, as a fat-soluble vitamin, can be stored in adipose tissue, involving inflammatory processes (10). Inflammation is known as a key regulator in the development of cardio-metabolic complications and disorders (11). The role of vitamin D in modulating inflammation is through its effect on innate and adaptive immunity and the activity of antigen-presenting cells, secretion of cytokines, and inflammatory mediators, which can affect inflammatory responses (12). Further, vitamin D receptors (VDRs) have been reported to positively affect body composition by improving the ability to control calcium homeostasis (13). Vitamin D is also a negative moderator of renin activity (14). Experimental studies have shown that rats with VDR deletion have high blood pressure, cardiac hypertrophy, and increased renin-angiotensin-aldosterone system activation (15,16). Based on the results of a systematic review and meta-analysis of 36 observational studies with a total of 12,528 patients and controls, it was found that schizophrenic patients have lower levels of vitamin D compared to healthy people (17). Vitamin D deficiency was also linked to the severity of symptoms of schizophrenia due to its role in various brain functions (18,19). Findings of a study on psychosis patients showed that 62.7% of patients had inadequate vitamin D levels, besides the significant relationship of the vitamin D level with the risk of metabolic parameters and negative symptoms of schizophrenia (20).

Despite numerous descriptive studies that have shown...
In the present study, 8 weeks of vitamin D supplementation (2000 IU/d) resulted in a significant reduction in LDL-C levels.

Vitamin D supplementation for 8 weeks, decreased PANSS-NSS and PANSS-TS.
Results

Participants Description
Figure 1 shows the flow chart of the study design and process. Of 74 individuals initially recruited to the study, 42 ones completed the study (intervention group: n = 21; placebo group: n = 21).

The baseline characteristics, serum levels of vitamin D, and the rate of metabolic diseases in the patients are summarized in Table 1. There was no statistically significant difference in baseline demographic information, including age, level of education, duration of illness, marital status, smoking, and antipsychotic treatment, between the two groups (P > 0.05). Serum levels of vitamin D were 12.75 ± 4.56 and 15.19 ± 5.06 ng/mL in the intervention and placebo groups, respectively, with no significant difference (P = 0.109). In addition, the prevalence of current metabolic diseases (dyslipidemia, diabetes mellitus, overweight or obesity, and hypertension) did not significantly differ between the two groups (P > 0.05).

Cardio-metabolic Indices
As shown in Table 2, the cardio-metabolic indices, including body weight (BW), WC, BMI, FBS, TG, HDL, LDL, CHOL, systolic blood pressure (SBP), and diastolic blood pressure (DBP), were compared between the two groups at the baseline. There was no significant difference between the two groups in all the variables (P > 0.05); however, serum CHOL and TG levels were significantly different (P = 0.020 and P = 0.045, respectively). At the end of the study, there were no significant changes in all the indices between the two groups except the HDL level, which was significantly higher in the vitamin D-supplemented group (P = 0.040; Table 2). At the endpoint, according to the comparisons done within the intervention and placebo groups using paired t-test, a significant decrease was observed in WC (MD = -1.99, 95% CI [-3.65, -0.32], P = 0.022), TG (MD = -8.71, 95% CI [-15.91, -1.51], P = 0.020), and LDL (MD = -9.85, 95% CI [-14.26, 5.25], P < 0.001) levels in the intervention group. There was a significant increase in LDL (MD = 1.33, 95% CI [1.00, 1.66], P = 0.001) in the intervention group, but this was not observed in the placebo group (MD = -0.98, 95% CI [-2.34, 0.38], P = 0.159).

Data are shown by mean ± SD for continuous variables and number (percent) for categorical variables.

Dyslipidemia was defined as any one of triglyceride ≥150 mg/dL, total cholesterol ≥200 mg/dL, low-density lipoprotein cholesterol ≥160 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, and/or using cholesterol-lowering medicines during the last 2 weeks, diabetes mellitus as defined, fasting blood glucose level of ≥ 126 mg/dL or drug use, overweight or obesity as defined BMI ≥25 (kg/m²) and hypertension as defined ≥140/90 mm Hg for SBP/DBP or drug use.

Table 1. Baseline Demographic Characteristic and Prevalence of Metabolic Disorders In Schizophrenic Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (n = 21)</th>
<th>Placebo (n = 21)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>41.80 ± 8.77</td>
<td>41.42 ± 8.72</td>
<td>0.889‡</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td>0.535</td>
</tr>
<tr>
<td>Less than diploma</td>
<td>20 (95.20)</td>
<td>21 (100.0)</td>
<td></td>
</tr>
<tr>
<td>Diploma and more</td>
<td>1 (4.80)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Duration of disorder (y)</td>
<td>8.38 ± 4.64</td>
<td>6.23 ± 4.11</td>
<td>0.205§</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>2 (9.50)</td>
<td>4 (19.0)</td>
<td>0.226</td>
</tr>
<tr>
<td>Smoking</td>
<td>15 (71.40)</td>
<td>16 (76.20)</td>
<td>0.726</td>
</tr>
<tr>
<td>Serum levels of vitamin D (ng/mL)</td>
<td>12.75 ± 4.56</td>
<td>15.19 ± 5.06</td>
<td>0.109∥</td>
</tr>
<tr>
<td>Antipsychotic treatment</td>
<td></td>
<td></td>
<td>0.196∥</td>
</tr>
<tr>
<td>Typical antipsychotics</td>
<td>9 (42.90)</td>
<td>9 (42.30)</td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>8 (38.10)</td>
<td>5 (23.80)</td>
<td></td>
</tr>
<tr>
<td>Combined antipsychotics</td>
<td>4 (19.0)</td>
<td>7 (35.00)</td>
<td></td>
</tr>
<tr>
<td>Current prevalence of metabolic diseases¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>18 (85.70)</td>
<td>11 (61.90)</td>
<td>0.159</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (4.80)</td>
<td>3 (14.30)</td>
<td>0.606</td>
</tr>
<tr>
<td>Overweight or obesity</td>
<td>9 (42.10)</td>
<td>11 (52.38)</td>
<td>0.758</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (19.0)</td>
<td>2 (9.50)</td>
<td>0.663</td>
</tr>
</tbody>
</table>

Data are shown by mean ± SD for continuous variables and number (percent) for categorical variables.

†Obtained from χ² test.
‡Obtained from Student’s t test.
∥Obtained from Mann-Whitney U test.
¶Dyslipidemia was defined as any one of triglyceride ≥150 mg/dL, total cholesterol ≥200 mg/dL, low-density lipoprotein cholesterol ≥160 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, and/or using cholesterol-lowering medicines during the last 2 weeks, diabetes mellitus as defined, fasting blood glucose level of ≥ 126 mg/dL or drug use, overweight or obesity as defined BMI ≥25 (kg/m²) and hypertension as defined ≥140/90 mm Hg for SBP/DBP or drug use.

Figure 1. Study Flowchart.
CI [-6.34, 3.67], P = 0.002) level in the placebo group. Considering confounding factors (age, medications, and smoking), the LDL level significantly decreased in the vitamin D-supplemented group (Table 2).

### Disorder Severity

As observed in Table 3, there was no significant difference at the baseline in terms of PANSS-PSS, PANSS-NSS, PANSS-GPSS, and PANSS-TS between the two groups (P > 0.050). At the end of the study, there was a significant decrease in PANSS-GPSS and PANSS-TS in the intervention group compared with the placebo group (P = 0.036 and P = 0.049, respectively). Further, all subscales of PANSS significantly decreased in both groups compared to the baseline (P < 0.05). After adjusting for confounders, only PANSS-NSS and PANSS-TS significantly differed between the two groups (P = 0.005 and P = 0.015, respectively) (Table 3).

### Association Between Serum Levels of Vitamin D and Cardio-metabolic Indices

The association between serum levels of vitamin D with BW, WC, BMI, FBS, TG, HDL, CHOL, LDL, SBP, and DBP for all of the subjects are provided in Table 4. Baseline serum levels of vitamin D did not show any correlation with cardio-metabolic indices (P > 0.05).

### Association Between Serum Levels of Vitamin D and PANSS Subscales

At the baseline, serum levels of vitamin D were negatively correlated with PANSS-NSS and PANSS-TS based on the Pearson’s correlation coefficient test (r = -0.33, P = 0.030 and r = -0.034, P = 0.024, respectively). After adjustment for age, medication, and smoking, a statistically significant negative association was found between serum levels of vitamin D with PANSS-PSS, PANSS-NSS, and PANSS-GPSS.
The role of vitamin D in increasing cytosolic calcium levels and stimulating 5'-AMP-activated protein kinase/acetyl-CoA carboxylase (AMPK/ACC) phosphorylation is of great importance that may inhibit the formation and secretion of hepatic TG, consequently decreasing serum levels of TG; also, calcium may increase the synthesis of bile acids from cholesterol and reduce serum levels of cholesterol (23,24).

Discussion

The literature shows that vitamin D levels in schizophrenic patients are lower than in healthy subjects, probably associated with disorder severity (21). On the other hand, cardio-metabolic diseases, possibly correlated with hypovitaminosis D, were the common cause of premature death in these patients (22). The current research findings showed that after 8 weeks of vitamin D supplementation (2000 IU/day), the levels of TG, LDL-C, and WC significantly decreased in the intervention group. In addition, HDL-C was significantly different between the 2 groups. It has been proposed that different vitamin D-dependent mechanisms may play a role in decreasing the serum TG and LDL or increasing HDL levels (23).

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WC is an authentic indicator of abdominal obesity. Some studies have suggested that vitamin D supplementation can lead to a significant reduction in WC (25,26). Vitamin D deficiency is associated with enhanced parathyroid hormone synthesis that could lead to an increase in lipogenesis, fat accumulation, and weight gain. Moreover, with increased adiposity, the storage of vitamin D, similar to other fat-soluble vitamins, can increase adipose tissue, leading to hypovitaminosis D (27,28).

In the current study, the efficacy of vitamin D supplementation on other metabolic factors was not confirmed. Similar to our results, using vitamin D supplementation (14 000 IU/wk) for 8 weeks, Krivoy et al found no significant change in metabolic parameters in chronic patients with schizophrenia (29). In another study of 19 patients with schizophrenia or schizoaffective levels and stimulating 5'-AMP-activated protein kinase/acetyl-CoA carboxylase (AMPK/ACC) phosphorylation is of great importance that may inhibit the formation and secretion of hepatic TG, consequently decreasing serum levels of TG; also, calcium may increase the synthesis of bile acids from cholesterol and reduce serum levels of cholesterol (23,24).

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disorder treated with APPs, 8 weeks of a 2000 IU daily dose of vitamin D supplementation had no statistically significant changes in FBS and weight (30). Probably, the relatively short period of supplementation was the cause of this ineffectiveness. Patients in our study were chronic patients undertreated with antipsychotic medications for years and affected by the metabolic side effects of the treatment; thus, possibly, the improvement in these complications required a longer period of supplementation. It was also observed that all subscales of PANSS decreased in two groups compared to pre-supplementation levels. After adjusting for confounding variables, the mean PANSS-NS and PANSS-TS in the intervention group were significantly lower than in the placebo group. Ghaderi et al observed significant improvements in PANSS-TS after 12 weeks of vitamin D supplementation (50,000 IU every 2 weeks) and probiotics (31). However, in Krivoy and colleagues’ research, the 8 weeks of vitamin D supplementation did not affect schizophrenia symptoms in chronic patients under treatment with clozapine (29). Regarding the relationship between vitamin D supplementation and the severity of schizophrenia symptoms, the data obtained from studies are contradictory (29,31,32). It seems that the heterogeneity of data (in terms of length of illness and hospitalization, severity, nutritional status, serum levels of vitamin D, skin color, and race) has led to conflicting results in this area. For instance, Sheikhmoonesi et al did not find a correlation between serum vitamin D level changes and the decrease of PANSS-NS in schizophrenic patients, and they concluded that the lack of correlation was due to the low score of PANSS-NS (33).

In addition, in the present study, there was a significant inverse correlation between the serum levels of vitamin D and the PANSS positive subscale score (PANSS-PSS), PANSS-NS, and PANSS-TS. Consistent with our observation, some studies have reported a reverse correlation between the vitamin D level and total score or subscales of PANSS in both acute and chronic schizophrenia. Results achieved by Fund et al. showed that 27.5% of schizophrenic patients had hypovitaminosis D (<25 nM); low levels of vitamin D have been significantly associated with negative symptoms and decreased functioning (34). In a study conducted in Turkey on patients with schizophrenia, serum vitamin D levels were significantly inversely related to PANSS-PS, PANSS-NS, and PANSS-T (35). The association of serum vitamin D deficiency with the severity of symptoms has been observed even in patients in the first-episode psychosis. In a study by Yee et al, the bioavailable vitamin D level was statistically lower in schizophrenia patients than in controls, and they found an inverse relationship between serum total and bioavailable vitamin D and negative symptoms (36). In a study conducted by Yüksel et al, on schizophrenic patients, it was stated that bringing vitamin D levels up to normal levels due to the neuroprotective effect of this vitamin could be an effective approach in schizophrenia treatment and prevention. Since schizophrenia patients are in psychiatric hospitals and rehabilitation units for a long time, they should be exposed to sunlight, fed with vitamin D-fortified foods, and have their vitamin D levels checked regularly (35).

Since the negative symptoms of schizophrenia disorder are not more responsive to routine medications (37), supplementary treatment with vitamin D can be considered a successful approach to reduce these symptoms.

In this study, there were some limitations, such as the relatively short duration of intervention and disagreement on the appropriate dose of vitamin D in patients with mental disorders; it was possible to see more significant results in the cardio-metabolic indices if high doses were used.

Conclusions
The findings indicate that vitamin D supplementation may reduce some cardio-metabolic complications in patients with schizophrenia, thus contributing to decreased symptoms of the disorder. Further, serum levels of vitamin D are negatively correlated with the subscales of PANSS.

Authors’ Contribution
SKH and PK: concept and design the study. SGN: diagnosis and introduction of patients. PK: data collection and interpretation of the data. SKH, PK, and SGN: wrote the manuscript with input from all authors. All authors discussed the results and contributed to the final manuscript.

Conflict of Interests
Authors have no conflict of interest.

Ethical Issues
The trial protocol was approved by the Ethics Board of the Tabriz University of Medical Sciences and was registered at the Iranian Registry of Clinical Trials (identifier: IRCT20190313043039N1). Written informed consent was taken from a first-degree relative of each patient before the study.

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References


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