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

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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

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Key Messages

- Cardio-metabolic disorders and hypovitaminosis D are common problems in schizophrenic patients that may be related to each other.
- 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

the role of vitamin D deficiency in the development of schizophrenia symptoms and cardiometabolic disorders associated with schizophrenia, clinical trials related to the efficacy of vitamin D supplementation in these patients are very limited, in addition, there is no proposed therapeutic dosage for vitamin D to improve the symptoms severity and cardiometabolic outcomes in chronic schizophrenic patients who are treated with various antipsychotic medication and have low serum levels of vitamin D. Therefore, this study was designed to evaluate the of 8-week effect vitamin D supplementation on cardio-metabolic indices and the severity of schizophrenia symptoms, according to the Positive and Negative Syndrome Scale (PANSS), in chronic schizophrenic patients with vitamin D deficiency.

Materials and Methods

Study Design and Subjects

This single-center, randomized, double-blind, placebo-controlled trial was conducted at the Razi Hospital of Tabriz University of Medical Sciences, Iran. The inclusion criteria for participants were: having schizophrenia based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria; being between 18 to 65 years old; having vitamin D deficiency (≤20 ng/mL); having PANSS score of 70 or higher. The exclusion criteria were having mental retardation (intelligence quotient <70); receiving nutritional supplements, including vitamin D3 and calcium, over the past year; engaging with other major psychiatric disorders, such as bipolar disorder, simultaneously; changing treatment methods and medication during the intervention.

Forty-two patients were recruited and randomly assigned into two groups of intervention (n = 21) and control (n = 21). The intervention group received 2000 IU vitamin D every day, and the control group received a placebo (paraffin soft gel capsules) for 8 weeks. The Dana Pharmaceutical Company (Tabriz, Iran) manufactured Vitamin D and placebo capsules. All researchers and patients were blinded to the intervention type during the study until the end of the statistical analysis.

Biochemical measurements

At the baseline, demographic information was collected from study participants. 5 mL venous blood samples were collected from each participant after 12-hour fasting at the beginning and after the 8-week intervention. The samples were centrifuged, and serums were isolated and stored at −80°C until analysis. Serum levels of vitamin D were measured by the quantitative chemiluminescent immunoassay (CLIA) method. Further, serum levels of fasting blood sugar (FBS), cholesterol (CHOL), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were determined by enzymatic methods.

Anthropometric Measurements

The height and weight of patients were measured using a scale-mounted stadiometer and a calibrated scale (Seca, Hamburg, Germany); with an accuracy to the nearest 0.5 cm, and 0.1 kg, respectively. Body mass index (BMI) was calculated accordingly. Waist circumference (WC) was measured using a non-extendable measuring tape (Seca, Hamburg, Germany) by placing the tape at the midpoint of the lower margin of the last palpable rib and the top of the iliac crest to the nearest 0.5 cm. Blood pressure was measured by the mercury sphygmomanometer to the nearest 1 mm Hg. All the measurements were performed by one person to minimize the error rate.

Measurement of the Disorder Severity

The disorder symptoms (severity) were assessed using PANSS at the pre-supplementation phase and the end of the trial. This tool is a 30-item scale that includes three subscales (positive, negative, and general psychopathology). The positive subscale was composed of seven symptoms, the negative one included seven symptoms, and the general subscale was composed of 16 symptoms.

Statistical Analyses

Data were analyzed using SPSS version 16.0 (SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used for assessing the normality of the variable distributions. Variables with normal distribution were reported as mean and standard deviations, and categorical data were presented as frequency and percentage. Independent samples *t* test, chi-square test, Fisher exact test, and Mann-Whitney U test were used to compare continuous and categorical variables between groups. The paired *t* test was used for assessing changes in each group during the treatment phase, and the analysis of covariance (ANCOVA) test was used to control the effect of confounding variables and determine the differences between the two groups post-intervention. Pearson's correlation coefficient test and partial correlation analysis were performed to study the correlation between serum levels of vitamin D and other parameters in the baseline. All statistical tests were two-tailed, and statistical significance was set at $P < 0.05$.

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 ($P>0.05$).

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

Characteristic	Intervention (n = 21)	Placebo (n = 21)	*P* [a]
Age (y)	41.80 ± 8.77	41.42 ± 8.72	0.889 [b]
Level of education			0.535
Less than diploma	20 (95.20)	21 (100.0)	
Diploma and more	1 (4.80)	0 (0)	
Duration of disorder (y)	8.38 ± 4.64	6.23 ± 4.11	0.205 [b]
Marital status			
Married	2 (9.50)	4 (19.0)	0.226
Smoking	15 (71.40)	16 (76.20)	0.726
Serum levels of vitamin D (ng/mL)	12.75 ± 4.56	15.19 ± 5.06	0.109 [b]
Antipsychotic treatment			0.196 [c]
Typical antipsychotics	9 (42.30)	9 (42.30)	
Atypical antipsychotics	8 (38.10)	5 (23.80)	
Combined antipsychotics	4 (19.0)	7 (35.00)	
Current prevalence of metabolic diseases [#]			
Dyslipidemia	18 (85.70)	13 (61.90)	0.159
Diabetes mellitus	1 (4.80)	3 (14.30)	0.606
Overweight or obesity	9 (42.10)	11 (52.38)	0.758
Hypertension	4 (19.0)	2 (9.50)	0.663

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

[a] Obtained from χ^2 test.

[b] Obtained from Student's *t* test.

[c] 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 glocuse level of ≥ 126 mg/dL or drug use, overweight or obesity as defined BMI ≥25 (kg/m^2) and hypertension as defined ≥140/90 mm Hg for SBP/DBP or drug use.

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 ($P>0.050$); 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%

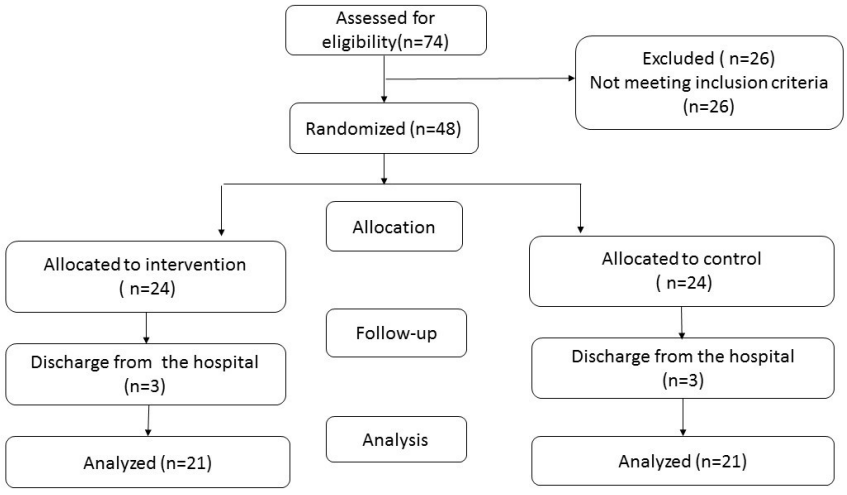

Figure 1. Study Flowchart.

Table 2. Effects of Vitamin D Supplementation (2000 IU/day) or Placebo on Cardio-metabolic Indices in Patients With Schizophrenia

Variables	Group	Baseline	End	MD (95% CI)	*P* [b]	*P* [c]
BW (kg)	Intervention	69.80 ± 9.93	69.33 ± 9.69	-0.47 (-0.28, 1.23)	0.204	0.626
	Placebo	74.61 ± 14.72	74.31 ± 14.72	0.30 (-0.23, 0.83)	0.257	
	P [a]	0.189	0.626			
WC (cm)	Intervention	86.61 ± 6.11	84.62 ± 7.25	-1.99 (-3.65, -0.32)	0.022*	0.748
	Placebo	87.62 ± 10.91	86.07 ± 10.63	-1.55 (-3.12, 0.02)	0.058	
	P [a]	0.508	0.612			
BMI (kg/m^2)	Intervention	23.76 ± 3.06	23.49 ± 3.02	-0.27 (-4.59, 0.05)	0.094	0.407
	Placebo	25.29 ± 4.67	25.07 ± 4.58	0.14 (-0.03, 0.32)	0.006	
	P [a]	0.387	0.431			
FBS (mg/dL)	Intervention	94.66 ± 9.87	94.23 ± 11.00	-0.42 (-5.10, 4.24)	0.850	0.858
	Placebo	90.0 ± 7.36	89.95 ± 10.07	-0.04 (-4.00, 3.91)	0.980	
	P [a]	0.670	0.952			
TG (mg/dL)	Intervention	156.90 ± 0.28	148.19 ± 28.36	-8.71 (-15.91, -1.51)	0.020*	0.076
	Placebo	159.57 ± 68.60	166.10 ± 58.50	6.52 (-7.90, 20.95)	0.357	
	P [a]	0.045*	0.675			
CHOL (mg/dL)	Intervention	159.38 ± 8.97	152.81 ± 22.52	-6.57 (-14.31,1.16)	0.092	0.424
	Placebo	152.71 ± 3.91	149.10 ± 14.33	-3.61(-7.57, 0.34)	0.071	
	P [a]	0.020*	0.076			
HDL (mg/dL)	Intervention	34.57 ± 4.15	35.80 ± 4.22	1.23 (-0.18, 2.66)	0.085	0.942
	Placebo	36.28 ± 5.36	36.95 ± 3.59	0.71 (-0.83, 2.25)	0.346	
	P [a]	0.101	0.040*			
LDL (mg/dL)	Intervention	96.04 ± 16.33	86.19 ± 12.18	-9.85 (-14.26, 5.25)	< 0.001*	0.006*
	Placebo	90.09 ± 14.10	91.42 ± 10.50	1.33 (-6.34, 3.67)	0.002*	
	P [a]	0.214	0.144			
SBP (mm Hg)	Intervention	120.95 ± 8.13	121.62 ± 8.08	0.14 (-3.32, 3.61)	0.932	0.624
	Placebo	121.10 ± 6.90	122.60 ± 8.30	1.55 (-0.94, 4.04)	0.209	
	P [a]	0.724	0.427			
DBP (mm Hg)	Intervention	77.42 ± 5.57	77.80 ± 4.94	4.90 (-5.27, 15.08)	0.327	0.297
	Placebo	82.33 ± 21.99	78.57 ± 6.15	0.05 (-3.42, 3.52)	0.664	
	P [a]	0.816	0.343			

MD, median of differences; CI, confidence interval; BW, body weight; WC, waist circumference; BMI, body mass index; FBS, Fasting blood sugar; TG, Triglyceride; CHOL, Cholesrtol; HLD, high-density lipoprotein; LDL, low-density lipoprotein; SBP, Systolic blood pressure; DBP, diastolic blood pressure.
The number of patients in the intervention group was 21 and the number of placebo group was 21.
All values are means ± SD.
[a] *P* values represent Student's *t* test.
[b] *P* values represent paired *t* test.
[c] *P* values represent ANCOVA (adjusted for age, medication and smoking).

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-

Table 3. Effects of Vitamin D Supplementation (2000 IU/day) or Placebo on Severity of Symptoms, According to PANSS in Patients With Schizophrenia

Variables	Group	Baseline	End	MD (95% CI)	*P*[b]	*P*[c]
PANSS-PSS	Intervention	25.90 ± 5.21	22.23 ± 4.68	-3.66 (-5.41, -1.92)	< 0.001*	0.478
	Placebo	25.62 ± 4.71	23.04 ± 4.44	-2.57 (-4.07, -1.06)	0.002*	
	P[a]	0.853	0.562			
PANSS-NSS	Intervention	30.10 ± 5.24	24.85 ± 4.35	-5.23 (-7.44, -3.03)	< 0.001*	0.005*
	Placebo	28.48 ± 4.33	27.09 ± 3.94	-1.38 (-2.40, -0.35)	0.011*	
	P[a]	0.280	0.089			
PANSS-GPSS	Intervention	57.23 ± 5.09	50.76 ± 5.61	-6.47 (-8.55, -4.39)	< 0.001*	0.062
	Placebo	58.90 ± 6.17	54.80 ± 6.43	-4.09 (-6.85, -1.33)	0.006*	
	P[a]	0.346	0.036*			
PANSS-TS	Intervention	114.38 ± 11.50	97.85 ± 11.80	-16.51 (-21.84, -11.20)	<0.001*	0.015*
	Placebo	112.81 ± 11.79	104.81 ± 10.36	-8.00 (-12.50, -3.49)	0.001*	
	P[a]	0.664	0.049*			

PANSS, Positive and Negative Syndrome Scale; PANSS-NSS, PANSS negative subscale score; PANSS-PSS, PANSS positive subscale score; PANSS-GPSS, PANSS general psychopathology subscale score; PANSS-TS, PANSS total score; MD, median of differences; CI, confidence interval.
The number of patients in the intervention group was 21 and the number of placebo group was 21.
All values are mean ± SD.
[a] *P* values represent Student's *t* test; [b] *P* values represent paired *t* test; [c] *P* values represent ANCOVA (adjusted for age, medication and smoking).

TS (r = -0.42, *P* = 0.041, r = -0.34, *P* = 0.010 and r = -0.47, *P* = 0.004, respectively) (Table 5).

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/d), 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). 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).

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 (14000 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

Table 4. Correlation Between Baseline Serum Levels of Vitamin D and Cardio-metabolic Indices in Schizophrenic Patients

Variables	Unadjusted		Adjusted	
	r	*P*[a]	r	*P*[b]
BW (kg)	0.03	0.825	0.08	0.617
WC (cm)	-0.08	0.615	-0.01	0.921
BMI (kg/m^2)	0.87	0.582	0.17	0.321
FBS (mg/dL)	0.17	0.915	0.09	0.602
TG (mg/dL)	0.14	0.350	0.22	0.186
CHOL (mg/dL)	0.02	0.900	0.17	0.312
HDL (mg/dL)	-0.01	0.998	-0.19	0.253
LDL (mg/dL)	0.05	0.713	0.99	0.566
SBP (mm Hg)	-0.05	0.710	-0.10	0.537
DBP (mm Hg)	0.30	0.050	0.35	0.035

BW, Body weight; WC, Waist circumference; BMI, Body mass index; FBS, Fasting blood sugar; TG, Triglyceride; CHOL, Cholesrtol; HLD, high-density lipoprotein cholesterol; LDL, Low-density lipoprotein cholesterol; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.
[a] *P* values represent bivariate (unadjusted) and [b] *P* values represent partial (adjusted for age, medications and smoking) correlation coefficients.

Table 5. Correlation Between Baseline Serum Levels of Vitamin D and Severity of Symptoms, According to PANSS in Schizophrenic Patients

Variables	Unadjusted		Adjusted	
	r	*P*[a]	r	*P*[b]
PANSS-PSS	-0.23	0.137	-0.34	0.041*
PANSS-NSS	-0.33	0.030*	-0.42	0.010*
PANSS -GPSS	-0.15	0.324	-0.18	0.282
PANSS-TS	-0.34	0.024*	-0.47	0.004*

PANSS, Positive and Negative Syndrome Scale; PANSS-NSS, PANSS negative subscale score; PANSS-PSS, PANSS positive subscale score; PANSS-GPSS, PANSS general psychopathology subscale score; PANSS-TS, PANSS total score.
[a] *P* values represent Bivariate (unadjusted) and [b] *P* values represent partial (adjusted for age, medications and smoking) correlation coefficients.

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-NSS 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-NSS in schizophrenic patients, and they concluded that the lack of correlation was due to the low score of PANSS-NSS (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-NSS, 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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