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ORIGINAL ARTICLE

Co-administration of probiotic and vitamin D significantly improves cognitive function in schizophrenic patients: A double-blinded randomized controlled trial

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Abstract

Aim: Manipulation of the intestinal microbiome and supplying vitamin D can attenuate psychiatric symptoms in schizophrenic patients. The current study tried to evaluate the effects of probiotic/vitamin D supplementation on the cognitive function and disease severity of schizophrenic patients.

Methods: In the present study, 70 patients (aged 18–65) with schizophrenia were recruited. Participants were randomly allocated to the placebo ($n=35$) and intervention (probiotic supplements+400 IU vitamin D, $n=35$) groups. Severity of disease and cognitive function (primary outcomes) were evaluated by Positive and Negative Syndrome Scale (PANSS) and Montreal Cognitive Assessment (MoCA) tests, respectively. Moreover, lipid profile, body mass index (BMI), gastrointestinal (GI) problems, serum C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were evaluated as secondary outcomes.

Results: A total of 69 patients completed the study. The MoCA score was increased by 1.96 units in the probiotic-containing supplement group compared to the placebo ($p=0.004$). Also, the percentage of subjects with MoCA score ≥ 26 rose significantly in the intervention group ($p=0.031$). Moreover, TC ($p=0.011$), FBS ($p=0.009$), and CRP ($p<0.001$) significantly decreased in the supplement group compared to the placebo. Although the probiotic supplement reduced PANSS score by 2.82 units, the difference between the study groups was not statistically significant ($p=0.247$).

Conclusion: Co-administration of probiotics and vitamin D has beneficial effects on the improvement of cognitive function in schizophrenic patients.

KEYWORDS
cognitive function, probiotics, schizophrenia, vitamin D

1 | BACKGROUND

Schizophrenia is among the most common severe mental disorders and one of the top 25 leading causes of disability around the world. However, schizophrenia's essential nature remains to be clarified. So, it is sometimes called a syndrome, a group of disorders, or a spectrum disorder in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). There is no laboratory test for diagnosis of schizophrenia and clinicians should appreciate that the diagnosis of schizophrenia is entirely based on the psychiatric history and mental status examination.[1,2] We can divide the symptoms of schizophrenia into three groups including: positive, negative, and cognitive symptoms. The Positive and Negative Syndrome Scale (PANSS) is a medical scale used for measuring the severity of symptoms in patients with schizophrenia.[3] The Montreal Cognitive Assessment (MoCA) is another score that is widely used for the assessment of cognitive impairment.[4]

Medications that block the dopamine system are effective in delusions and hallucinations. However, they are less effective in the improvement of cognitive and motivational disorders. Some specific occupational and psychological interventions along with antipsychotic medications can improve functional outcomes in these patients. Unfortunately, these types of interventions are not widely available. There are several ongoing research to understand the underlying biological mechanisms of schizophrenia symptoms as well as the psychosocial factors that moderate their expression. Most of these methods lead to the control of the disease instead of treatment.[5,6]

Taking antipsychotic drugs, which have anticholinergic and anti-histaminergic effects, increases the prevalence of constipation and weight gain-related disorders in schizophrenic patients. It should be noted that depression is a predictor of rapid weight gain in these patients. Weight gain can cause dyslipidemia and inflammation. Both these factors have the main role in disease progression and decrement in quality of life. Increment of C-reactive protein (CRP) is related to the increasing the risk of schizophrenia, positive symptoms, and cognitive impairment.[7–9] It has been suggested that anti-inflammatory strategies can be effective in the treatment of schizophrenia. Also, there is some evidences on the relationship and the effect of gastrointestinal (GI) tract microbiota on the brain activity of these patients. It should be noted that the antipsychotic medications, themselves, can affect gut microbiota.[10]

Manipulation and change in intestinal microbiota by probiotics can be useful to relieve GI diseases, improve lipid profile and inflammation, and attenuate psychiatric symptoms in schizophrenic patients.[11,12] Probiotics can change the balance of the gut microbiota and prevent inappropriate immune responses to the harmful antigens originated from the gut lumen. Regulation of the inflammatory responses is the proposed mechanism of action for the probable therapeutic effects of probiotics in schizophrenia.[13,14] Among nutrients, vitamin D can regulate anti-inflammatory processes itself.[15] In the pathogenesis of schizophrenia, vitamin D deficiency (VDD) is an important factor. So, correcting VDD in schizophrenic patients is very crucial, especially in communities with high VDD. Iran is a developing country with high prevalence of VDD. So, considering vitamin D supplement in treatment regimens can increase therapy effectiveness.[16–18] Many studies suggest the synergistic effects of combined vitamin D and probiotics on mental health. It has been hypothesized that probiotics can increase vitamin D levels. In addition, probiotics improve the expression of vitamin D receptors. Vitamin D may improve mental health via induction of tyrosine hydroxylase expression and augmentation of the bioavailability of dopamine. Therefore, targeting the microbiota-gut-brain axis with probiotic and vitamin D might provide a novel approach to promote mental health.

The current study aimed to investigate the effects of co-administration of probiotic and vitamin D supplementation on the MoCA and PANSS scores, lipid profile, body mass index (BMI), and serum level of CRP in schizophrenic patients.

2 | METHODOLOGY

2.1 | Study design and participants

In this randomized double-blind placebo-controlled clinical trial (RCT), 70 patients with Schizophrenia were recruited from the Razi Psychiatric Hospital of the University of Social Welfare and Rehabilitation Sciences from December 2021 to April 2022. The written informed consent was obtained from all patients. The criterion for diagnosis of schizophrenia was the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5).

All participants were from the long-stay ward and were informed about the study details and aim. The written informed consent was also taken following the National Health and Medical Research Council guideline. All participants were free to withdraw their participation at any time. Inclusion criteria were as follows: age range of 18–65 years, capacity for signing the written informed consent, having at least a fifth-grade elementary education, having no GI problem at the study baseline, and being stable on the current psychotropics for at least 6 months. On the other hand, exclusion criteria were having a history of brain injury, head trauma, mental retardation, Parkinson's disease, using opioid or stimulant substances in the last 3 months, taking antidepressant or stimulant medications, having an allergy to probiotic supplements, receiving antibiotics in 14 days before the study beginning, pregnancy and lactation, having a history of significant medical disorder (such as epilepsy, diabetes, hypertension, thyroid, heart or liver disease), having criteria for substance-related disorders, being involved in specific medications with metabolic side effects except for the second-generation antipsychotics, having a history of exposure to the weight-loss medicines and/or change in treatment regimen during the study period.

This research project was approved by the Ethics Committee of the University of Social Welfare and Rehabilitation Sciences

(Ethical code: IR.USWR.REC.1400.219). This clinical trial study is also registered in the Iranian Registry of Clinical Trials (IRCT ID: IRCT20211118053100N1) and the trial protocol can be accessed on the IRCT website.

The sample size was calculated with a 95% confidence interval (CI) and a statistical power of 80%, considering the schizophrenia score.[11,19] Finally, a total sample size of 70 participants was calculated. These patients were randomly allocated, using shuffled cards, to one of the two treatment groups: "A" was the probiotic group ($n=35$), and "B" was the placebo group ($n=35$). Patients in the probiotic and placebo groups received probiotic or starch capsules (1 capsule per day), respectively. The duration of treatment was 12 weeks for both groups.

2.2 | Probiotic supplement and placebo

Probiotic and placebo supplements were produced and supplied by Tak Gen Zist Pharmaceutical Company, Tehran, Iran. Probiotic/vitamin D supplement (BioZenD) was containing *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Lactobacillus paracasei Bifidobacterium longum*, *Bacillus coagulans* (2×10^9 CFU), and 400 IU vitamin D per one capsule. Both placebo and probiotic capsules were identical in appearance and packaged in bottles labeled as either capsule A or capsule B. All capsules were stored at −20°C until dispensed to the participants. The identity of the capsules was unknown to the participants, researchers, and primary investigator. Randomization was conducted by an independent researcher using shuffled cards in a ratio of 1:1.

2.3 | Outcomes

Disease severity and cognitive symptoms were evaluated (as primary outcomes) by PANSS and MoCA tests at the baseline, end of the trial, and every 2 weeks during the study period. The MoCA test assesses seven cognitive domains as follows: visuospatial abilities (5 points), naming (3 points), attention (6 points), language (3 points), abstract reasoning (2 points), the short-term memory recall task (5 points), and orientation to time and place (6 points). MoCA scores range between 0 and 30. A score of 26 or over is considered normal. Also, the validity of MoCA test was previously assessed in Iranian schizophrenic patients.[20] Symptom severity was measured by PANSS scale. The scale is composed of three subscales as follows: a positive scale (seven Items; minimum score = 7; maximum score = 49), a negative scale (seven Items; minimum score = 7; maximum score = 49), and a General Psychopathology Scale (16 Items; minimum score = 16; maximum score = 112). Each subscale is rated with 1 to 7 points ranging from absent to extreme. Validity of PANSS has been previously assessed in Iranian schizophrenia patients.[21] In the current RCT, lipid profile, BMI, GI problems, serum CRP, and erythrocyte sedimentation rate (ESR) were evaluated as secondary outcomes. Data related to the GI problems were recorded weekly.

2.4 | Blood analyses

Five milliliters of fasting blood sample was collected from all participants at the baseline and the end of the intervention. Blood samples were centrifuged at 1400 g for 10 min and then the serum samples were stored at −70°C to analyze the level of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood sugar (FBS), CRP, and ESR. The serum levels of TC, HDL-C, and TG were measured by enzymatic colorimetric methods with a commercially available kit (Pars Azmoon, Tehran, Iran) by an automatic analyzer (Abbott, modelAlcyon 300, USA). Serum LDL-C was calculated by the Friedewald equation.[22] The concentration of serum CRP was measured using ELISA assay by laboratory kits (Pars Azmoon, Tehran, Iran). Before and after the intervention, FBS and ESR were analyzed immediately by the auto-analyzer (Mindray auto hematology analyzer, China) in fresh blood.

2.5 | Statistical analyses

All statistical analyses were performed with SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA). Independent sample T-test and chi-square test were initially used to analyze differences in baseline characteristics between the study groups for continuous and categorical variables, respectively. Statistical analysis of primary and secondary outcomes was conducted using the repeated measure analysis of variance (ANOVA) and analysis of covariance (ANCOVA) test with baseline values as the covariate. To analyze data from participants who withdrew from the trial for any reason, the intention-to-treat (ITT) analysis[23] was used. In the current work, marginal mean (MM) and MM difference (MMD) are statistics to report the effect size. The MM is a mean for a variable that the effects of potential confounders are adjusted on. Also, MMD is the difference between two groups in terms of an MM. p-value <0.05 was considered statistically significant.

3 | RESULTS

The study flowchart is shown in Figure 1. A total of 69 patients completed the study. One patient was excluded from the probiotic receiving group due to some personal reasons. Also, no adverse effects were observed during the study period. There was no significant difference in anthropometric and demographic characteristics including age, weight, height, BMI, gender, and marriage status between the study groups at the baseline (Table 1).

The study results showed that the marginal mean for MoCA score after adjustment for baseline values were 19.47 ± 0.43 and 21.43 ± 0.44 for placebo and probiotic/vitamin D receiving groups, respectively (Table 2). This means that the probiotic/vitamin D supplement increased MoCA score by 1.96 units compared to the placebo group and this difference was significant ($p=0.004$). Also,

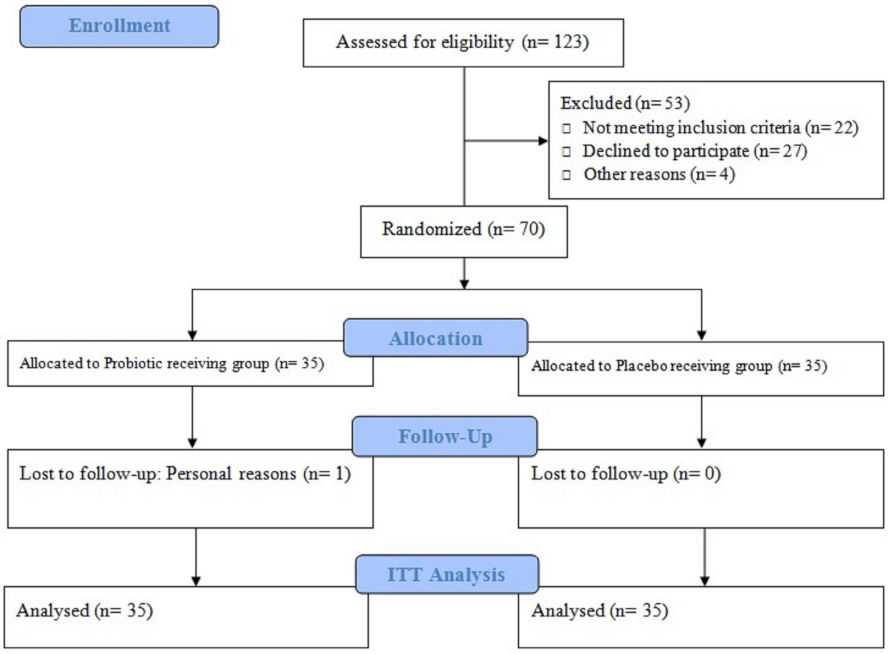

FIGURE 1 The study Flow diagram. ITT, Intention-to-treat.

TABLE 1 General and anthropometric variables in the study groups.

Variables	Groups		
	Probiotic ($n=35$)	Placebo ($n=35$)	p-Value
Age (years)	50.29 ± 9.61	52.02 ± 8.32	0.426*
Weight (kg)	79.36 ± 16.15	74.51 ± 18.15	0.246*
High (cm)	170.53 ± 10.46	167.77 ± 9.59	0.258*
BMI (kg/m^2)	27.26 ± 5.03	25.50 ± 6.37	0.208*
Gender			
Male	25 (73.5)	25 (71.4)	0.530**
Female	9 (26.5)	10 (28.6)	
Marriage			
Single	27 (79.4)	23 (65.7)	0.213**
Married	5 (14.7)	8 (22.9)	
Divorced	2 (5.9)	4 (11.4)	

Note: *p-Value was reported based on independent sample T-test; **p-Value was reported based on chi-square test.
Abbreviation: BMI, body mass index.

the percentage of subjects with MoCA score ≥ 26 significantly increased in probiotic group ($p=0.031$); while there were no significant changes in placebo-receiving patients ($p=0.625$; Figure 2). On the other hand, baseline adjusted values for PANSS score were 51.20 ± 1.50 and 48.36 ± 1.53 for placebo and intervention groups, respectively. Although the probiotic supplement reduced PANSS score by 2.82 units the difference between the study groups was not statistically significant ($p=0.247$; Table 2).

The combined probiotic and vitamin D supplementation significantly decreased TC ($p=0.011$), FBS ($p=0.009$), and CRP ($p<0.001$) compared to the placebo-receiving group (Table 3). The differences in baseline-adjusted MM between the probiotic and placebo groups for the mentioned variables were −17.79, −8.63, and −2.33, respectively. Although the probiotic supplementation reduced TG and LDL-C by 12.43 and 6.73 units compared to the placebo group, the differences were not statistically significant ($p=0.317$ and $p=0.104$, respectively). On the other hand, the study results showed that intervention with probiotic had no significant effects on LDL-C/HDL-C and ESR ($p>0.05$) levels. The findings of the current study showed that there was no significant change in the probiotic-receiving group in terms of serum HDL-C. However, the level of serum HDL-C significantly reduced in the placebo group and this made the between-group difference significant ($p=0.002$).

While the study results revealed that probiotic supplementation had no significant effects on BMI values compared to the placebo group and baseline values, before-after data analysis showed that BMI significantly increased in the placebo-receiving group ($p=0.004$). The evaluation of GI symptoms, including diarrhea and constipation, during the study period, showed that no GI problem was observed in probiotic receiving group while the GI symptoms were observed in about 29 percent of subjects in the placebo group ($p<0.001$; Figure 3).

4 | DISCUSSION

In the current study, MoCA and PANSS scores were evaluated as primary outcomes. Findings showed that probiotic/vitamin D supplementation significantly increased MoCA score compared to the placebo-receiving group. Also, the number of patients with MoCA score ≥ 26 significantly increased in probiotic group. On

TABLE 2 The effects of probiotic/vitamin D supplementation on PANSS and MoCA.

Variables	Groups	Time points							Baseline adjusted MM	MMD	*p*-Value**
		Baseline	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks			
PANSS	Placebo ($n=35$)	43.49 ± 11.48	44.94 ± 12.98	42.40 ± 11.09	41.69 ± 10.16	42.54 ± 10.79	42.94 ± 11.66	42.17 ± 9.14	51.20 ± 1.50	−2.82 ± 2.41	0.247
	Probiotic ($n=34$)	63.09 ± 12.02	61.09 ± 13.64	61.32 ± 15.26	59.18 ± 14.73	56.15 ± 16.88	54.47 ± 18.51	50.15 ± 16.03	48.36 ± 1.53		
	p-Value*	<0.001	<0.001	<0.001	<0.001	<0.001	0.003	0.015			
MoCA	Placebo ($n=35$)	20.60 ± 6.18	21.06 ± 5.55	21.83 ± 5.42	21.43 ± 6.27	21.57 ± 5.53	21.26 ± 5.84	21.69 ± 5.50	19.47 ± 0.43	1.96 ± 0.65	0.004
	Probiotic ($n=34$)	15.23 ± 4.27	15.38 ± 4.48	17.50 ± 4.15	19.17 ± 3.92	20.29 ± 4.18	21.29 ± 4.19	22.58 ± 3.60	21.43 ± 0.44		
	p-Value*	<0.001	<0.001	<0.001	0.078	0.283	0.976	0.423			

Note: *p-value was reported based on independent sample T-test; **p-value was reported based on repeated measure ANOVA test after adjustment of baseline values.
Abbreviations: MM, marginal mean; MMD, marginal mean difference; MoCA, montreal cognitive assessment; PANSS, Positive and Negative Syndrome Scale.

the other hand, intervention with probiotic-containing supplement decreased PANSS score. However, this decrement was not statistically significant compared to the placebo group. In a similar study, Ghaderi et al. (2020) showed that 12 weeks supplementation with probiotic (8×10^9 CFU/day; Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri, and Lactobacillus fermentum) plus vitamin D (50,000 IU every 2 weeks) significantly decreased PANSS score in Iranian schizophrenic patients compared to placebo group.[24] In a systematic review by Ng et al. (2019), three clinical studies that investigated the effect of probiotic supplementation on schizophrenia symptoms were enrolled.[19] The obtained results by Ng et al. showed that probiotic supplementation has no significant effects on PANSS score and its sub-scales. It should be noted that all enrolled studies in the systematic review used the same probiotic species (Lactobacillus rhamnosus strain GG and Bifidobacterium animalis subsp. lactis strain Bb12), dosage (2×10^9 CFUs), and intervention duration (14 weeks).[19] So, variables including probiotic species, dosage, and using vitamin D along with probiotic are the main reasons for the observed controversies related to the probiotic supplementation and disease severity among schizophrenic patients. In the current RCT, vitamin D with dosage of 400 IU/day was used. In another study, Ghaderi et al. used supplementation of vitamin D with dosage of 50 000 IU per 2 weeks (about 3600 IU/day).[24] Prevalence of VDD among Iranian people is high and correcting this status may have beneficial effects on the symptoms of depression and schizophrenia.[25] The difference between our findings and the results reported by Ghaderi et al.[24] could be rooted in the dosage of vitamin D.

To the best of our knowledge, no interventional studies have evaluated the effects of probiotic supplementation on MoCA score in schizophrenic patients until now. Shi et al. in an RCT examined the effects of Bifidobacterium longum supplementation on MoCA score in healthy older adults. The study results showed that the probiotic significantly improved cognitive function in the study population.[26] On the other hand, eliminating VDD in patients with schizophrenia had positive effects on the efficacy of treatment with antipsychotic medications. Neriman et al. reported the same results in schizophrenic patients after 8 weeks of vitamin D supplementation with dosage of 50 000 IU per week.[27] Vitamin D supplementation in vitamin D deficient individuals improves mental health but such beneficial effects in healthy adults are not provided by literature. It has been shown that the co-administration of vitamin D and probiotic had higher health benefits, such as mental health, than its comparators did.[28]

Probiotics can modulate neurotransmitters in the brain through the gut–brain axis. Immunomodulatory effect of probiotics is another important mechanism for the effects of probiotic supplementation on decreasing disease severity and improving cognitive function in schizophrenic patients.[14] The results obtained from the current RCT also showed that the intervention considerably decreases serum levels of CRP (an indicator of general inflammation) in probiotic + vitamin D group compared to the placebo-receiving patients.

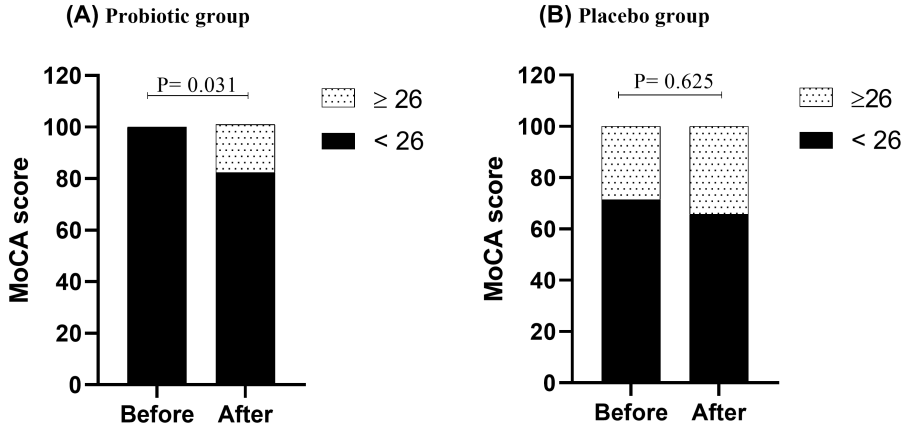

FIGURE 2 The percentage of subjects with MoCA score ≥ 26 before and after of the study in probiotic/vitamin D (A) and placebo (B) groups. MoCA, The Montreal Cognitive Assessment. Data are presented as percentage. Data analysis was done by sign test.

Schizophrenic patients are at the risk of metabolic-related complications of antipsychotic medications. These complications include blood sugar-related metabolic disorders, hyperlipidemia, and weight gain. The risk of heart disease and death from obesity can increase due to antipsychotic drugs. At least 50 percent of death cases among schizophrenic patients are related to cardiovascular diseases. It has been shown that the risk of heart disease and death can increase in the next 10 years of life in schizophrenic patients because of antipsychotics' side effects.[29,30] Other findings of the current RCT were a decrease in TC, FBS, TG, and LDL-C by the combined supplement. As mentioned in the result section, there was no considerable change in the probiotic-receiving group in terms of serum HDL-C. However, serum HDL-C significantly reduced in the placebo group and this made the between-group difference significant. This means that probiotic supplementation inhibited HDL reduction during the study period in comparison to the placebo group. The effects of probiotic supplementation on the reduction of TC, TG, LDL-C, and FBS have been widely reported.[31] The beneficial effects of probiotics on lipid profile are likely related to several different mechanisms. De-conjugation of short-chain fatty acids, especially propionate, and bile salt are the main reasons involved in the improvement of lipid profile. Probiotics decline serum cholesterol through the activation of several regulatory proteins. Probiotics assimilate cholesterol and therefore can reduce cholesterol levels. Microbiome have a role in the release of bioactive compounds from foodstuffs. Some of these compounds could affect the lipid profile.[32,33] Our results also showed that the vitamin D-containing supplement reduced FBS compared to the placebo. Several mechanisms may explain the effects of probiotics on glucose metabolism. The antioxidant function of probiotics through inhibiting lipid peroxidation and induction of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase is one of the main proposed mechanisms for the glucose-lowering effects of probiotics.[34] On the other hand, vitamin D can regulate anti-inflammatory and insulin transcription itself. Also, vitamin D can regulate calcium levels in the cytoplasm. It has been suggested that vitamin D can increase glucose entrance into the cells by the elevation of intracellular calcium.[15]

The synergistic effects of co-administration of vitamin D and probiotics on mental health have been suggested by many studies. It has been hypothesized that probiotics increase vitamin D levels. In addition, probiotics can improve the expression of vitamin D receptors. Vitamin D may improve mental health via induction of tyrosine hydroxylase expression, augmentation of the bioavailability of dopamine, neuroprotection, and neuroimmunomodulation.[35,36] Also, microflora has role in the biosynthesis and regulation of gamma-aminobutyric acid (GABA) and serotonin.[37,38] Therefore, targeting the microbiota-gut-brain axis with co-administration of probiotics and vitamin D might provide a novel approach to promote mental health.

5 | LIMITATIONS

To the best of our knowledge, the combined supplement of probiotic along with vitamin D has been used for the first time in the current study. This type of supplement is more popular and more accessible to prescribe than the previous types of interventions. Also, for the first time, we evaluated the effects of probiotic supplementation on the MoCA score in schizophrenic patients. On the other hand, the most important limitation of the current study was a failure to consider vitamin D status in the study population. Also, the lack of more detailed information about the administered medications in the study groups can be considered as another limitation of the current work. Moreover, to control potential covariates, such as administered medications, it is better to use block randomization instead of simple randomization in future works.

6 | CONCLUSION

Although the current RCT revealed that probiotic supplementation along with vitamin D improves the cognitive function of schizophrenic patients, considering the limitations mentioned before, similar studies should be conducted to achieve a final decision.

TABLE 3 The effects of probiotic supplementation on BMI, lipid profile, CRP, FBS, and ESR.

		Groups					
		Probiotic ($n=35$)		Placebo ($n=35$)			
Variable	Time point	Mean ± SD	MD	Mean ± SD	MD	MMD	*p*-Value**
BMI (kg/m^2)	Before	27.26 ± 5.03	0.17 (−2.21; 1.96)	25.50 ± 6.67	0.43 (−0.83; 4.61)	−0.32	0.169
	After	27.53 ± 5.25		26.04 ± 6.61			
	p-Value*	0.086		0.004			
	Baseline adjusted MM	29.61 ± 0.16		29.93 ± 0.16			
TG (mg/dL)	Before	141.24 ± 75.56	−8.00 (−253.00; 212.00)	158.88 ± 101.50	1.00 (−107.00; 22.00)	−12.43	0.317
	After	131.36 ± 79.67		157.63 ± 92.46			
	p-Value*	0.453		0.705			
	Baseline adjusted MM	138.48 ± 8.83		150.91 ± 8.57			
TC (mg/dL)	Before	164.69 ± 40.72	−15.00 (−143.00; 78.00)	153.08 ± 43.83	4.00 (−10.00; 24.00)	−17.79	0.011
	After	146.21 ± 34.18		155.86 ± 45.91			
	p-Value*	0.019		0.044			
	Baseline adjusted MM	142.01 ± 4.88		159.81 ± 4.74			
LDL (mg/dL)	Before	90.71 ± 30.25	−7.00 (−56.00; 49.00)	78.09 ± 31.20	1.00 (−8.00; 25.00)	−6.73	0.104
	After	81.97 ± 25.62		78.80 ± 5.35			
	p-Value*	0.055		0.525			
	Baseline adjusted MM	76.71 ± 2.94		83.45 ± 2.76			
HDL (mg/dL)	Before	40.89 ± 7.98	1.00 (−7.00; 10.00)	41.82 ± 10.48	−7.00 (−36.00; 32.00)	5.68	0.002
	After	42.11 ± 6.90		36.82 ± 9.17			
	p-Value*	0.062		0.026			
	Baseline adjusted MM	42.30 ± 1.21		36.62 ± 1.25			
LDL/HDL	Before	2.28 ± 0.86	−0.01 (−1.76; 1.33)	1.91 ± 0.69	−0.04 (−0.53; 0.61)	0.20	0.135
	After	2.34 ± 0.78		1.88 ± 0.73			
	p-Value*	0.481		0.644			
	Baseline adjusted MM	2.21 ± 0.09		2.01 ± 0.08			
FBS (mg/dL)	Before	104.58 ± 13.60	−8.00 (−58.00; 30.00)	100.88 ± 12.02	3.00 (−12.00; 11.00)	−8.63	0.009
	After	96.09 ± 18.24		102.77 ± 10.46			
	p-Value*	0.018		0.036			
	Baseline adjusted MM	95.09 ± 2.29		103.73 ± 2.25			

(Continues)

TABLE 3 (Continued)

Variable	Time point	Groups					
		Probiotic ($n=35$)		Placebo ($n=35$)		MMD	*p*-Value**
		Mean ± SD	MD	Mean ± SD	MD		
CRP (mg/L)	Before	2.46 ± 8.48	0.00 (−42.00; 7.60)	3.66 ± 1.51	−0.50 (−3.20; 2.00)	−2.33	<0.001
	After	0.77 ± 2.15		3.19 ± 1.35			
	p-Value*	0.305		0.002			
	Baseline adjusted MM	0.82 ± 0.33		3.15 ± 0.29			
ESR (mm/h)	Before	14.10 ± 14.83	8.00 (−23.00; 47.00)	7.46 ± 4.33	3.00 (−4.00; 13.00)	0.63	0.694
	After	11.63 ± 12.02		7.09 ± 4.16			
	p-Value*	0.135		0.227			
	Baseline adjusted MM	9.52 ± 1.15		8.89 ± 1.06			

Note: *p-value was reported based on paired sample *T*-test; **p-value was reported based on ANCOVA test after adjustment of baseline values.

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MD, mean difference; MM, marginal mean; MMD, marginal mean difference; TC, total cholesterol; TG, triglyceride.

FIGURE 3 GIT problems during the study period in the investigated groups. GIT, Gastrointestinal tract. Data are presented as percentage. Data analysis was done by Chi-square test.

AUTHOR CONTRIBUTIONS

AM: Conceptualization, Methodology, Writing – original draft. GS: Conceptualization, Methodology, Writing. ANA: Conceptualization, Methodology, Writing – original draft, Supervision. MJ: Methodology, Writing. MTE: Methodology, Writing. TD: Methodology, Writing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available as Data S1.

ETHICS STATEMENT

Approval of the Research Protocol by an Institutional Reviewer Board: This research project was approved by the Ethics Committee of University of Social Welfare and Rehabilitation Sciences (Ethical code: IR.USWR.REC.1400.219). All methods were conducted in accordance with the ethical standards of the declaration of Helsinki.

Registry and the registration no. of the study/trial: This clinical trial study is also registered in the Iranian Registry of Clinical Trials (IRCT ID: IRCT20211118053100N1) and trial protocol can be accessed on the IRCT website.

Animal studies: N/A.

Informed consent: Informed consent was obtained from all living participants.

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