Vitamin D Supplementation Affects the Beck Depression Inventory, Insulin Resistance, and Biomarkers of Oxidative Stress in Patients with Major Depressive Disorder: A Randomized, Controlled Clinical Trial

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Abstract

Background: Vitamin D may decrease depression symptoms through its beneficial effects on neurotransmitters, metabolic profiles, biomarkers of inflammation, and oxidative stress.

Objective: This study was designed to assess whether vitamin D supplementation can reduce symptoms of depression, metabolic profiles, serum high-sensitivity C-reactive protein (hs-CRP), and biomarkers of oxidative stress in patients with major depressive disorder (MDD).

Methods: This randomized, double-blind, placebo-controlled clinical trial was performed in 40 patients between 18 and 65 y of age with a diagnosis of MDD based on criteria from the Diagnostic and Statistical Manual of Mental Disorders. Patients were randomly assigned to receive either a single capsule of 50 kIU vitamin D/wk (n = 20) or placebo (n = 20) for 8 wk. Fasting blood samples were taken at baseline and postintervention to quantify relevant variables. The primary (Beck Depression Inventory [BDI], which examines depressive symptoms) and secondary (glucose homeostasis variables, lipid profiles, hs-CRP, and biomarkers of oxidative stress) outcomes were assessed.

Results: Baseline concentrations of mean serum 25-hydroxyvitamin D were significantly different between the 2 groups (9.2 ± 6.0 and 13.6 ± 7.9 μg/L in the placebo and control groups, respectively, P = 0.02). After 8 wk of intervention, changes in serum 25-hydroxyvitamin D concentrations were significantly greater in the vitamin D group (+20.4 μg/L) than in the placebo group (−0.9 μg/L, P < 0.001). A trend toward a greater decrease in the BDI was observed in the vitamin D group than in the placebo group (−8.0 and −3.3, respectively, P = 0.06). Changes in serum insulin (−3.6 compared with +2.9 μIU/mL, P = 0.02), estimated homeostasis model assessment of insulin resistance (−1.0 compared with +0.6, P = 0.01), estimated homeostasis model assessment of β cell function (−13.9 compared with +10.3, P = 0.03), plasma total antioxidant capacity (+63.1 compared with −23.4 mmol/L, P = 0.04), and glutathione (+170 compared with −213 μmol/L, P = 0.04) in the vitamin D group were significantly different from those in the placebo group.

Conclusion: Overall, vitamin D supplementation of patients with MDD for 8 wk had beneficial effects on the BDI, indicators of glucose homeostasis, and oxidative stress. This trial was registered at www.irct.ir as IRCT201412065623N29. J Nutr 2016;146:243–8.

Keywords: vitamin D supplementation, glucose metabolism, lipid profiles, oxidative stress, depression

Introduction

Major depressive disorder (MDD) is defined as a mental disorder characterized by a pervasive and persistent low mood that is accompanied by a loss of interest or pleasure in normally enjoyable activities (1). It affects ~20% of the population at some point during the lifetime of an individual (2). The overall estimation of current prevalence of MDD is 4.1% in Iran (3). Several factors, including psychological, hereditary, evolutionary, and biological, might contribute to the risk of MDD (4). This disorder may result in considerable morbidity, mortality, and decreased quality of life (5). Previous studies have linked depression to the increased risk of cardiovascular disease,
hypertension, dyslipidemia, and diabetes (6). Increased amounts of oxidative stress have been reported in MDD (7).

In addition to its role in calcium homeostasis and bone health (8), vitamin D is crucial for brain development and function (9). Deficiency of vitamin D was associated with an 8–14% increase in the prevalence of depression (10) and a 50% increase in the prevalence of suicide (11). Cross-sectional studies have indicated an inverse relation between serum 25-hydroxyvitamin D concentrations and depressive symptoms (12, 13). Few interventional studies have examined the effects of vitamin D administration on mood and depressive symptoms in overweight/obese subjects (14) and in patients with seasonal affective disorder (15). Findings from a recent meta-analysis indicated that patients with clinically significant depression had a reduction in depressive symptoms after vitamin D supplementation (16). Vitamin D may result in improvement of depressive symptoms through its effect on neurotransmitters, inflammatory markers, calcium homeostasis in the brain, and nerve growth factor synthesis (17, 18).

Regarding the effect of vitamin D on metabolic status, a 6 wk study in pregnant women with gestational diabetes mellitus demonstrated that vitamin D supplementation had beneficial effects on glucose homeostasis and total and LDL cholesterol concentrations, but it did not affect inflammation and oxidative stress (19). Taking vitamin D supplements did not affect insulin sensitivity, inflammation, and lipid profiles in patients with type 2 diabetes mellitus (20). Vitamin D administration might influence metabolic profiles, inflammatory factors, and biomarkers of oxidative stress through its effect on apolipoprotein gene expression (21), parathyroid hormone suppression (22), and upregulation of antioxidant systems, including glutathione peroxidase and superoxide dismutase (23). Although there is no specific data on vitamin D concentrations in patients with MDD in the Iranian population, an earlier study (24) showed that 95% of patients with MDD had serum 25-hydroxyvitamin D concentrations of <30 μg/L. We are not aware of a study that has examined the effect of vitamin D supplementation on metabolic profiles, inflammatory factors, and biomarkers of oxidative stress in patients with MDD. The current study was undertaken to investigate the effects of vitamin D supplementation on the clinical and metabolic status of patients with MDD.

Methods

Participants. This randomized, double-blind, placebo-controlled clinical trial was performed in Kashan, Iran, from October 2014 to December 2014. Kashan, located at 51° 27’ east longitude and 33° 59’ latitude, with an average temperature of 25°C, lies at the center of Iran (IRCT201412063623N29). The UV index of Kashan varies from 7 to 3 between October and December. In our study, the primary outcome variable was the Beck Depression Inventory (BDI). For estimating sample size, we used the standard formula suggested for parallel clinical trials by considering the type 1 error (α) of 0.05 and type 2 error (β) of 0.20 (power = 80%). Based on a previous study (24), we used 8.6 as the SD and 8.6 as the difference in mean of the BDI as a key variable. Therefore, we needed 16 participants in each group. Considering 4 dropouts in each group, the final sample size was determined to be 20 participants per group. Individuals aged 18–65 y diagnosed with MDD based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, who had a score of ≥15 on the 17-item Hamilton Depression Rating Scale were included in the current study. All patients were selected from Kargarneghad Hospital, Kashan University of Medical Sciences (KUMS), Kashan, Iran. Individuals with a history of coronary infarction, angina pectoris, stroke, or renal stone disease, as well as pregnant or lactating women, smokers, those with liver problems or substance abuse, or those having non-normal creatinine concentrations or taking dietary supplements during the last 2 mo were excluded. All study phases were followed in accordance with the ethical standards set by the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. In addition, the ethical committee of KUMS approved the study and we obtained written informed consent from all participants.

Study design. After stratification for preintervention BMI (in kg/m²; >25 or ≤25) and age (>40 or ≤40 y), patients were randomly assigned to receive weekly either a single capsule of 50 kIU vitamin D (n = 20; 17 women and 3 men) or a placebo (n = 20; 17 women and 3 men) for 8 wk. Random assignment was conducted by the use of computer-generated random numbers. Randomization and allocation were concealed from the researcher and participants until the main analyses were completed. All participants were instructed to take the supplements and placebos once per week at a standardized time point. Vitamin D and placebo capsules were provided by Zahravi Pharmaceutical Company and Barij Essence Pharmaceutical Company, respectively. The appearance of the placebo capsules, including color, shape, size, and packaging, was identical to that of the vitamin D capsules. Vitamin D and placebo capsules were in the same form of packaging, and neither the patients nor the investigators were aware of the content of the package until the end of the data analysis. At study baseline, patients were requested not to change their routine physical activity or usual dietary intake throughout the study. The use of vitamin D supplements and placebos throughout the study was checked by asking the participants to return the empty medication packages. In addition, to increase compliance, all patients received a short message on their cellular telephones to remind them to take the supplements. All participants provided 3 dietary records (1 weekend day and 2 weekdays) and 3 physical activity records. Both dietary and physical activity records were obtained at weeks 2, 4, and 6 of the intervention. Physical activity was expressed as metabolic equivalents in hours per day through multiplying the times (in hours per day) reported for each physical activity by their relevant metabolic equivalent coefficients obtained from standard tables (25). To obtain the nutrient intake for the study participants, we used Nutritionist IV software (First Databank) modified for Iranian foods.

Assessment of outcomes. The primary outcome in the current study was the BDI, by which we examined depressed mood at study baseline and postintervention. The BDI is a self-compiled questionnaire of 21 items in multiple-choice format (26). Our secondary outcome variables were indicators of glucose homeostasis, lipid profiles, high-sensitivity C-reactive protein (hs-CRP), and biomarkers of oxidative stress. A trained nutritionist at the psychiatry clinic obtained anthropometric measurements at pre- and postintervention. Body weight was measured in an overnight fasting state, without shoes and with minimal clothing with the use of a digital scale (Seca). Height was measured with the use of a nonstretch tape measure (Seca). BMI was calculated as weight in kilograms divided by height in meters squared. Fasting blood samples (10 mL) were obtained at baseline and 8 wk after intervention at the KUMS reference laboratory in the early morning after an overnight fast. Blood samples were immediately centrifuged (Hettich D-78332) at 1465 × g for 10 min at room temperature to separate serum. The samples then were stored at −80°C before analysis at the KUMS reference laboratory. Serum 25-hydroxyvitamin D concentrations were evaluated with the use of a commercial ELISA kit (IDS). The inter-
analyses for baseline values, age, and baseline BMI to avoid potential subject factor. To control for the effect of confounders, we adjusted all points (baseline and 8 wk after intervention) was considered as a within-placebo) was regarded as a between-subject factor and time with 2 time ANOVA. In this analysis, the treatment (vitamin D compared with biomarkers of oxidative stress, we used 1-factor repeated measures glucose homeostasis variables, lipid profiles, serum hs-CRP, and determine the effects of vitamin D supplementation on the BDI score, square test was used for the comparison of categorical variables. To examine the normal distribution of variables. An independent samples Student’s t test was used to examine the normal distribution of variables. An independent samples Student’s t test was used to detect differences at study baseline between the 2 groups. Comparison of means at the end of the trial, as well as FIGURE 1 Summary of patient flow. The intervention was supplementation with 50 kIU vitamin D/wk.

intra-assay CVs for serum 25-hydroxyvitamin D assays ranged from 5.2% to 7.2%. Commercial kits were used to measure fasting plasma glucose (FPG); serum calcium; TGs; and total-, VLDL, LDL, and HDL cholesterol concentrations (Pars Azmun). All inter- and intra-assay CVs for FPG and lipid profiles were <5%. Serum insulin concentrations were determined by ELISA kit (Monobind). The intra- and inter-assay CVs for serum insulin were 2.9% and 5.0%, respectively. Serum antioxidant capacity (TAC) was assessed by the method developed by Benzie and Strain (28). Total glutathione was measured by the method of an ELISA kit (LDN) with intra- and inter-assay CVs of 2.4% and 3.6%, respectively. Total antioxidant capacity (TAC) was assessed by the use of the ferric reducing/antioxidant power method developed by Benzie and Strain (28). Total glutathione was measured by the method modified by Beutler et al. (29).

Statistical analysis. The Kolmogorov-Smirnov test was used to examine the normal distribution of variables. An independent samples Student’s t test was used to detect differences at study baseline between the 2 groups. Comparison of means at the end of the trial, as well as dietary intake between the vitamin D and placebo groups, was also done by the use of an independent samples Student’s t test. A Pearson’s chi-square test was used for the comparison of categorical variables. To determine the effects of vitamin D supplementation on the BDI score, glucose homeostasis variables, lipid profiles, serum hs-CRP, and biomarkers of oxidative stress, we used 1-factor repeated measures ANOVA. In this analysis, the treatment (vitamin D compared with placebo) was regarded as a between-subject factor and time with 2 time points (baseline and 8 wk after intervention) was considered as a within-subject factor. To control for the effect of confounders, we adjusted all analyses for baseline values, age, and baseline BMI to avoid potential bias. This analysis was done using ANCOVA. A P value < 0.05 was considered to be statistically significant. All statistical analyses were done with the use of SPSS.

Results
Among individuals in the vitamin D group, 2 patients met the exclusion criteria. The placebo group also had 2 exclusions. Ultimately, 36 patients [vitamin D (n = 18) and placebo (n = 18)] completed the trial (Figure 1). On average, the rate of compliance was high, such that >90% of capsules were taken throughout the study in the 2 groups.

There were no significant differences between the vitamin D and placebo groups in terms of mean age, height, physical activity, baseline weight, baseline BMI, and changes in weight and BMI during the study. The distribution of participants in terms of gender and their educational levels was not significantly different between the 2 groups (Table 1).

Based on 3 d dietary records obtained throughout the intervention, no statistically significant difference was seen between the 2 groups in terms of dietary intake of energy, carbohydrates, proteins, fats, SFAs, PUFAs, MUFAs, cholesterole, dietary fiber, vitamin D, calcium, magnesium, manganese, and zinc (Table 2).

After 8 wk of intervention, changes in serum 25-hydroxyvitamin D concentrations were greater in the vitamin D group than in the placebo group (P < 0.001) (Table 3). A trend toward a greater decrease in the BDI was observed in those who took vitamin D supplements compared with those in the placebo group (P = 0.06). Changes in serum insulin concentrations (P = 0.02), HOMA-IR (P = 0.01), HOMA-B (P = 0.03), TAC (P = 0.04), and glutathione concentrations (P = 0.04) in the supplemented group were also significantly different from the changes in these indicators in the placebo group. Changes in serum calcium concentrations, lipid profiles, FPG, QUICKI, and hs-CRP concentrations in the vitamin D group were not significantly different from changes in the placebo group.

Baseline concentrations of serum 25-hydroxyvitamin D were significantly different between the 2 groups (P = 0.02). Therefore, we controlled the analyses for the baseline values, age, and

<table>
<thead>
<tr>
<th>TABLE 1 General characteristics of patients with MDD</th>
<th>Placebo group</th>
<th>Vitamin D group</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36.1 ± 6.9</td>
<td>36.5 ± 8.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.60 ± 0.05</td>
<td>1.64 ± 0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Weight at study baseline, kg</td>
<td>69.1 ± 10.5</td>
<td>69.1 ± 12.1</td>
<td>0.99</td>
</tr>
<tr>
<td>Weight at end of trial, kg</td>
<td>69.9 ± 9.5</td>
<td>69.9 ± 12.1</td>
<td>0.99</td>
</tr>
<tr>
<td>Body weight change, kg/8 wk</td>
<td>0.8 ± 2.8</td>
<td>0.8 ± 2.4</td>
<td>0.93</td>
</tr>
<tr>
<td>BMI at study baseline, kg/m²</td>
<td>26.9 ± 3.8</td>
<td>25.8 ± 5.2</td>
<td>0.44</td>
</tr>
<tr>
<td>BMI at end of trial, kg/m²</td>
<td>27.3 ± 3.5</td>
<td>26.0 ± 5.1</td>
<td>0.38</td>
</tr>
<tr>
<td>BMI change, kg/m² - 8 wk</td>
<td>0.4 ± 1.1</td>
<td>0.2 ± 0.9</td>
<td>0.81</td>
</tr>
<tr>
<td>MET/h/d</td>
<td>23.1 ± 4.6</td>
<td>23.6 ± 3.8</td>
<td>0.72</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>M</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>17 (85)</td>
<td>17 (85)</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>3 (15)</td>
<td>3 (15)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
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<td></td>
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<tr>
<td>Elementary school</td>
<td>5 (25)</td>
<td>4 (20)</td>
<td></td>
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<tr>
<td>High school</td>
<td>13 (65)</td>
<td>14 (70)</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td></td>
</tr>
</tbody>
</table>

1 Values are means ± SDs or n (%); n = 18 in each group. MDD, major depressive disorder; MET, metabolic equivalent.
2 Obtained from an independent samples Student’s t test, except for gender and educational level, which were obtained from a Pearson’s chi-square test.
TABLE 2 Dietary intake of patients with MDD throughout the study

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Vitamin D group</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, Mcal/d</td>
<td>2.1 ± 0.2</td>
<td>2.1 ± 0.2</td>
<td>0.55</td>
</tr>
<tr>
<td>Carbohydrates, g/d</td>
<td>282 ± 47</td>
<td>270 ± 30</td>
<td>0.34</td>
</tr>
<tr>
<td>Protein, g/d</td>
<td>77 ± 13</td>
<td>84 ± 23</td>
<td>0.34</td>
</tr>
<tr>
<td>Fat, g/d</td>
<td>75 ± 12</td>
<td>75 ± 15</td>
<td>0.86</td>
</tr>
<tr>
<td>SFAs, g/d</td>
<td>25 ± 6</td>
<td>25 ± 6</td>
<td>0.77</td>
</tr>
<tr>
<td>PUFAs, g/d</td>
<td>23 ± 4</td>
<td>22 ± 6</td>
<td>0.44</td>
</tr>
<tr>
<td>MUFAs, g/d</td>
<td>21 ± 5</td>
<td>21 ± 6</td>
<td>0.93</td>
</tr>
<tr>
<td>Cholesterol, mg/d</td>
<td>223 ± 115</td>
<td>196 ± 95</td>
<td>0.45</td>
</tr>
<tr>
<td>TDF, g/d</td>
<td>17 ± 4</td>
<td>18 ± 3</td>
<td>0.58</td>
</tr>
<tr>
<td>Vitamin D, μg/d</td>
<td>2.8 ± 0.9</td>
<td>2.7 ± 0.6</td>
<td>0.58</td>
</tr>
<tr>
<td>Calcium, g/d</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>0.52</td>
</tr>
<tr>
<td>Magnesium, mg/d</td>
<td>246 ± 54</td>
<td>232 ± 47</td>
<td>0.42</td>
</tr>
<tr>
<td>Manganese, mg/d</td>
<td>1.8 ± 0.9</td>
<td>1.6 ± 0.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Zinc, mg/d</td>
<td>10.0 ± 2.7</td>
<td>9.8 ± 3.3</td>
<td>0.78</td>
</tr>
</tbody>
</table>

1 Values are means ± SDs; n = 18 in each group. MDD, major depressive disorder; TDF, total dietary fiber.
2 Obtained from an independent samples Student's t test.

baseline BMI. However, after adjustments for baseline values, age, and baseline BMI, reductions in the BDI (P = 0.04) were significantly greater in the vitamin D group that in the placebo group (Table 4). Except for the BDI, other findings did not alter after these adjustments.

Discussion

We assessed the effects of high-dose vitamin D supplementation on the BDI total score, indicators of glucose homeostasis, lipid profiles, hs-CRP, and biomarkers of oxidative stress in patients with MDD. Taking vitamin D supplements improved insulin function and decreased oxidative stress in these patients. To our knowledge, this is the first study to report the effect of high-dose vitamin D supplementation on the clinical and metabolic status of patients with MDD. It must be taken into account that, because of cultural issues, the time span of outdoor activities is limited, in particular for women. Furthermore, the study participants were patients with MDD who have normally low limited physical activity levels and sun exposure than others, which in turn would result in the poor impact of UV exposure on 25-hydroxyvitamin D concentrations.

MDD is associated with complications that include morbidity, mortality (5), increased risk of cardiovascular disease, dyslipidemia, and impaired insulin function (6). This study showed that after controlling for the baseline values of age and BMI, vitamin D supplementation significantly decreased BDI total scores. Previous studies, in terms of the effects of vitamin D supplementation on mood and depression symptoms, have shown inconsistent results. It was demonstrated that a single 300-kIU dose of vitamin D led to a decreased severity of depression in elderly patients with MDD (30). Furthermore, some studies have reported a favorable effect from vitamin D supplementation on symptoms of depression in overweight and obese people (14) and patients with MDD (24). However, a large randomized trial in older women showed that a single annual dose of 500 kIU vitamin D for 3–5 y had no significant impact on mood (31). The exact mechanism of the effect of vitamin D on brain and mood is not completely understood. Increased expression of the tyrosine hydroxylase gene (the rate-limiting enzyme of the catecholamine synthesis pathway) and enhancement of the bioavailability of some neurotransmitters such as dopamine, norepinephrine, and epinephrine might explain some of the beneficial effects of taking vitamin D supplements on mood and depression (24, 32).

The current study demonstrated that patients with MDD who took vitamin D supplements for 8 wk had a significant decrease in serum insulin concentrations, HOMA-IR, and HOMA-B compared with those who took the placebo, but vitamin D supplementation did not influence FPG, QUICKI, and lipid profiles. Although limited data are available evaluating the effects of vitamin D supplementation on metabolic status in MDD patients, observational studies have introduced hypovitaminosis D as a risk factor in the development of depressive symptoms in older persons (33). In patients without depression, as well as in animal models, the favorable effects of vitamin D supplementation on glucose homeostasis have been shown. In agreement with our study, insulin resistance was significantly reduced after supplementation with 4 kIU vitamin D/d in insulin-resistant female Asian subjects (34). In addition, 16 wk vitamin D supplementation (10 or 25 μg vitamin D/d) in healthy subjects with low vitamin D status did not affect lipid profiles (35). Some researchers did not observe any significant effect of vitamin D supplementation on markers of insulin metabolism. For instance, improvement in vitamin D status after the administration of 280 μg/d for 2 wk and 140 μg/d for 10 wk did not improve insulin resistance in patients with type 2 diabetes mellitus (20). In vitro studies have shown the existence of vitamin D receptors and 1-a-hydroxylase in pancreatic β cells (36). Several direct and indirect mechanisms for the beneficial effects of vitamin D on improved insulin action have been suggested; that is, via the activation of insulin receptor expression, the regulation of intra- and extracellular calcium concentrations, and the downregulation of cytokine generation (36). The absence of a significant effect from vitamin D supplementation on lipid profiles in the current study might be explained by the dosage of vitamin D supplementation, short duration of the intervention, and baseline concentrations of lipid profiles in study participants.

Findings from this study revealed that the administration of vitamin D supplements did not affect serum hs-CRP concentrations in patients with MDD compared with the placebo. In line with our study, Foroughi et al. (37) showed that supplementation with 50 kIU vitamin D/wk for 12 wk in patients with nonalcoholic fatty liver disease had no significant effect on CRP concentrations. In another study, oral vitamin D administration (1, 2, or 4 kIU vitamin D/d) for 3 mo did not influence inflammatory markers, including CRP concentrations (38). In contrast with these findings, we previously found that the administration of 400- IU vitamin D supplements for 9 wk in healthy pregnant women resulted in a significant decrease in serum hs-CRP concentrations (39). Different results might be mediated by different study designs, discrepancy in conditions of participants, different dosages of vitamin D supplementation, and duration of the study.

This study revealed that vitamin D supplementation led to a significant increase in TAC levels and glutathione concentrations in patients with MDD. Our findings were in accordance with those reported by other researchers, showing a significant decrease in the liver oxidative stress index and improved serum TAC levels in diabetic rats after vitamin D intake (40). However, supplementation with 50 kIU vitamin D every 14 d for 4 mo in adult patients with nonalcoholic fatty liver disease did not affect TAC levels (41). The accurate mechanisms by which the intake
of vitamin D supplements might influence biomarkers of oxidative stress are unknown. Improvement in cellular glutathione concentrations and a decrease in the production of reactive oxygen species and proinflammatory cytokines with vitamin D supplements may explain the beneficial effects on oxidative stress (42).

While interpreting our findings, some limitations need to be considered. The intervention in the current study was of relatively short duration. Long-term interventions might result in better effects on lipid profiles and inflammatory factors. Because all patients had a vitamin D deficiency (serum 25-hydroxyvitamin D concentrations <20 μg/L) in the current study, we were unable to examine whether the favorable effects of vitamin D supplementation were greater in vitamin D–deficient individuals than in those without a deficiency. Additional studies are required to provide some insights into this question. Furthermore, the beneficial effects of vitamin D supplementation on the BDI score might be explained by the fact that mean serum 25-hydroxyvitamin D concentrations were low at study baseline in both groups. Thus, a relatively short-term supplementation that was effective in this population might not be effective in others who have a better status.

Overall, supplementation with 50 kIU vitamin D/wk for 8 wk in patients with MDD had beneficial effects on markers of glucose metabolism and oxidative stress, but it did not affect FPG, QUICKI, lipid profiles, or serum hs-CRP concentrations.

Acknowledgments
ZA contributed to the conception, design, statistical analysis, and drafting of the manuscript, and supervised the study; and ZS, FK, FA, NM, AA, and AE contributed to the data collection and manuscript drafting. All authors read and approved the final manuscript.

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