The Effect of Vitamin D Supplementation on Symptoms of Depression in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Background: *The effect of vitamin D supplementation on depressive symptoms in people with type 2 diabetes is still up for debate. The aim of this paper was to investigate the effect of vitamin D supplementation on symptoms of depression in type 2 diabetic patients.* ***Methods:*** *The protocol for this review has been registered in PROSPERO:CRD42021231713. Searching for literature was conducted using Pubmed, EBSCOhost, and EMBASE. Randomised controlled trials (RCTs) regarding vitamin D supplementation in type 2 diabetic patients with depression were retrieved through a systematic search. The outcome measured was a change in depressive symptoms evaluated with any validated rating scale. Independent data extraction was conducted, and the study quality was assessed. A meta-analysis was carried out to calculate the improvement in depressive symptoms in the group receiving vitamin D and the control group. The available evidence in RCTs was analysed using the PRISMA approach, and clinical significance was determined using the GRADE system. Risk of bias was assessed using the Cochrane Risk of Bias Tool.* ***Results:*** *Four RCTs were reviewed and three RCTs were meta-analysed. In two studies, vitamin D was statistically effective in improving depressive symptoms in type 2 diabetic patients. Three randomised controlled trials were included in the meta-analysis with 161 subjects using depression score as an outcome assessment. Vitamin D is significantly more effective than placebo (95% CI: -0.70 to - 0.08, p = 0.01).* ***Conclusion:*** *Vitamin D supplementation may improve the depressive symptoms in type 2 diabetic patients. Future research with different geographical areas and larger samples should be done to further assess the benefits.*

Keywords*: depression, type 2 diabetes mellitus, vitamin D.*

INTRODUCTION

Diabetes mellitus and depression are both significant chronic diseases that diminish life expectancy, reduce quality of life, and increase functional disability.[1] Diabetes and depression occur together approximately twice as frequently

as they would be predicted by chance alone. Comorbid diabetes and depression pose a significant clinical problem because the outcomes of both disorders are exacerbated by the presence of the other.[2] Despite the existence of biological, psychological, and environmental explanations, the underlying pathophysiology of depression is unknown, and several processes may be involved.[3]

A study by Holt et al. showed that diabetic patients have an increased risk of developing depression. This phenomenon can be caused by several factors, either by patients' perception of a disease or by biological changes that occur within the body. The diagnosis of diabetes mellitus often frightens patients. Some of the reasons are that they are afraid that the disease cannot be cured and that it requires high discipline and compliance to take medications regularly to prevent further complications. Moreover, diabetic patients should also change their lifestyle, which is not suitable and comfortable for some of them. On the other hand, diabetes can also cause decreased neurogenesis, which can further increase the risk of depression.[2,3] The symptoms of depression in diabetic patients are correlated with a decreased quality of life, a higher risk of developing further complications, and increasing mortality. Several solutions can be given to patients, and one of the solutions is giving anti-depressants. However, several anti-depressants have side effects of decreasing glycaemic control and causing weight gain, which are not suitable for diabetic patients. As a result, other solutions to this problem are being sought.[4,5]

In the past few years, other treatment options besides anti-depressants have been investigated to treat depressive symptoms. One of these treatment options is vitamin D. Vitamin D receptors are found on neurons and glia in various parts of the brain, including the cingulate cortex and hippocampus, which have been linked to depression pathophysiology.[6] Furthermore, vitamin D is a supplement that is easily accessible and inexpensive. These reasons serve as a foundation for utilizing vitamin D supplementation to treat depressive symptoms in patients with type 2 diabetes. Even though vitamin D is theoretically useful to treat depressive symptoms in type 2 diabetic patients, there are not many studies that are able to give conclusive conclusions regarding this matter.[7-9] This review aimed to compile all the available evidence on the effectiveness of vitamin D in type 2 diabetes patients with depression when compared to placebo or other vitamin D doses in relieving depressive symptoms.

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA).[10] The protocol for this review is registered with PROSPERO (CRD42021231713).[11]

Inclusion Criteria

We considered trials to be eligible if they included: (1) studies with the intervention of vitamin D supplementation and placebo as comparison – intervention can be single or combined with other drugs, such as anti-depressants, psychotherapy treatment, or other adjuvant therapies (micronutrients, probiotics, etc.); (2) the patients in the studies were older than 18 years old; (3) type 2 diabetes mellitus patients diagnosed based on ADA/WHO criteria with any depression questionnaire; (4) experimental studies; (5) studies in the form of randomized controlled trials (RCTs); (6) studies written in English; and (7) full-text articles; original articles; and (9) studies that were published between January 1, 2009 and December 31, 2021.

Exclusion Criteria

The exclusion criteria in this study include (1) children and adolescents as subjects; (2) pregnant and breast-feeding mothers; (3) subjects with progressive illness (such as: chronic kidney disease, hepatic cirrhosis, known history of seizure and other neurological disorders, and previous history of depression); (4) correspondence, reviews, editorials, and conference abstracts.

Outcomes

Our primary outcome for all studies was a change in depressive symptoms evaluated with any validated rating scale.

Table 1. Literature Search Strategy.

Database	Keywords	Results
PubMed	((((Depression[Title/Abstract] OR Depressive[Title/Abstract] OR Mood[Title/Abstract] OR Mental[Title/Abstract])))) AND ((Vitamin D[Title/Abstract] OR Vitamin- D2[Title/Abstract)) AND ((Diabetes Mellitus[Title/Abstract] OR Diabetes[Title/Abstract]))	135
EBSCOhost	("Depression" OR "Depressive" OR "Mood" or "Mental") AND "Vitamin D" AND ("Diabetes Mellitus" OR "Diabetes")	95
EMBASE	(Depression OR Mood OR Mental OR Affective Disorder*) AND (Vitamin D OR Cholecalciferol OR Vitamin D3 OR Ergocalciferol OR Vitamin D2 OR Alfacalcidol) AND (Type 2 Diabetes Mellitus OR Type II Diabetes Mellitus OR Diabetes Mellitus OR Diabetes)	69

Search Strategy

The literature search was conducted in six databases: PubMed, EBSCOhost, and EMBASE (up to 31 March 2022). The keywords used in the literature search were "depression" in conjunction with "diabetes mellitus" and "vitamin D". Synonyms used in the literature search keywords are obtained from the MeSH Terms (**Table 1**). Supplemental 2 provides the detailed search process. The search was limited to studies in English and was bound to articles that were published between January 1, 2009 and December 31, 2021. Studies that have no available full-text reports were not looked into further. Available full-text articles from the three databases were then screened based on their titles and abstracts. Eligibility criteria were applied to the articles for further screening. Suitable texts that fulfil all the criteria were taken into deeper analysis. In addition, all included publications' reference lists were thoroughly checked to ensure that no relevant studies were missed.

Study Selection

Following the removal of duplicates, all titles and abstracts were evaluated by three independent researchers (RP, KH, and SS). When studies were found eligible, the researchers collected full texts and conducted additional screening. Consensus was used to settle disagreements.

Data Extraction

To address the differences, the three researchers (RP, KH, and SS) did data extraction and reviewed the results. Some papers were eliminated from the data extraction process because they did not meet the study's objectives, and the remaining articles were extracted by two different researchers independently (EDS and SRFS).

Study characteristics (first author's name, year of publication, study location, publishing year, and study design), diagnosis, participant characteristics (mean age and gender of intervention and control group subjects, health condition of subjects, and the number of subjects in each group), types of intervention (type, dose, and duration of supplementation), mean and SD or percentage of clinical variables were collected from each study.

Quality Assessment

We assessed the risk of bias of RCTs using the Cochrane Risk of Bias Tool.[12] The following categories were examined: (1) method of randomisation, (2) allocation concealment, (3) blinding of subjects and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (8) other biases. Each domain was labelled as low risk of bias (+), high risk of bias (-) or unclear risk of bias (?). Two independent reviewers performed the quality assessment and resolved disagreements via discussion. Review Manager (RevMan) 5.4 software was used to assess the risk of bias.[13]We intended to assess publication bias using funnel plot techniques[14], Begg's rank test[15], and Egger's regression test[15], as appropriate, given the known limitations of these methods.

Statistical Analysis

On the basis of pre-to-post intervention changes, the effects of vitamin D supplementation were investigated. For all continuous outcomes, we utilized the standardized mean difference (SMD) and 95 percent confidence intervals (CIs). A fixed-effects model was applied to pool SMDs across studies by RevMan 5.4 software.[13] The chi-squared test and I-squared values were used to measure statistical heterogeneity. Moderate to substantial heterogeneity was indicated by I-squared >75 percent, mild heterogeneity by I-squared 50-75 percent, and low or no heterogeneity by I-squared ≤ 50 percent.

Sensitivity Analysis

We utilized a "leave-one-out" evaluation procedure to assess the stability of the estimated measures in the sensitivity analysis. This evaluation is an iterative procedure in which one trial was excluded from each iteration, and a meta-analysis was conducted on the remaining sample of studies. This analysis demonstrates how each study influences the overall estimate of the other studies.

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the certainty of depression score as the outcomes, which values certainty at one of four levels, to objectively analyse the power of the included research (high, moderate, low, and very low).[16]

RESULTS

After a thorough search and selection, our searches yielded 19,375 references. After duplicates were removed, 232 references remained for title and abstract screening. Of these, 6 were identified and retrieved for full-text screening; all were in English. After a full text review, four RCTs were included for the systematic review and three for the meta-analysis. The phases of the literature search are illustrated in **Figure 1**.

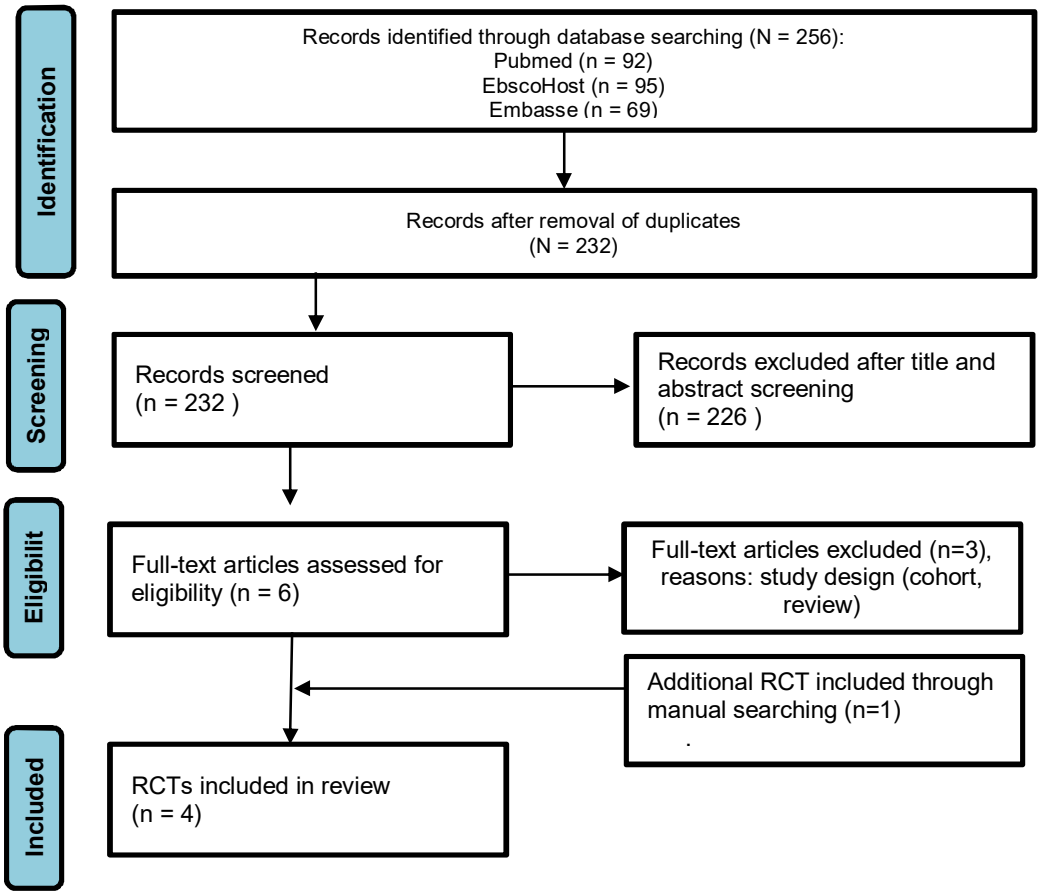

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Diagram of Study Selection

Table 2. Study Characteristics of Selected Articles.

Study	Country	Year	Subjects	N,Gender	Design	Intervention	Comparison	Duration	Validated scale used	Outcomes
Raygan et al.[17]	Iran	2018	Type 2 diabetic people with CHD, 45-85 years old	60 (30 Male, 30 Female)	RCT	50,000 IU vitamin D + probiotic	Placebo	12 weeks	Beck Depression Inventory (BDI II) scale	Improvements in BDI total score (-2.8 vs -0.9, p=0.01)
Omidian et al.[18]	Iran	2019	People with type 2 DM and mild- moderate depressive symptoms, 30-60 years old	68 (40 Male, 28 Female)	RCT	4000 IU	Placebo	3 months	Beck Depression Inventory (BDI II) scale	BDI-II scores decreased from 15.2 to 9.8 (p value <0.001)
Fazelian et al.[19]	Iran	2019	Women with type 2 diabetes and vitamin D deficiency, 20 – 60 years old	51 women	RCT	50,000 IU vitamin D3	placebo	16 weeks	Depression, Anxiety, Stress Scales (DASS-21)	Depressive changes were not significantly different between groups (p>0.05). Within group-analysis, it showed significant decrement in depression score in vitamin D group (p=0.03)
Mirzavandi et al.[20]	Iran	2020	Patients with type 2 diabetes mellitus and vitamin D deficiency, 30 – 60 years old	50 (Male 15, Female 35)	RCT	200,000 IU vitamin D injection at week 0 and week 4	none	8 weeks	Beck Depression Inventory (BDI II) scale	No significant difference in depression score between groups

In **Table 2**, we summarized the characteristics of the four RCTs. The samples ranged from 50 to 68 subjects and the mean sample size was 57.25. A total of 229 patients within the studies were evaluated. Among all subjects, 85 were men and 144 were women. The age of subjects included in these studies ranged from 30 to 85 years old, with a mean age of 52.7 in the experimental group and 54 in the placebo group. All of them were diagnosed with type 2 diabetes mellitus based on the American Diabetes Association or World Health Organization criteria. Only subjects in the study by Raygan et al. [15] had a comorbidity of coronary heart disease. The dose of vitamin D used ranged from 4000 IU to 200000 IU. The extracted scales used to measure depression in the selected studies included the BDI [17,16,20] and DASS -21.[19] For the post-intervention score, means and SD values were calculated from medians and ranges. Two of the studies reported no adverse events, while the other two did not report anything regarding side effects.

Assessment of Risk of Bias

The risk of bias of included RCTs was assessed using the Cochrane risk- of-bias tool for randomized trial (RoB 2).[21] Two reviewers independently assessed the risk of bias of the included RCTs using the technique developed by Higgins and Green in the Cochrane Handbook for Systematic Reviews of Interventions.[12] Selection bias (random sequence generation and concealment of allocation), performance bias (blinding of subjects and personnel), detection bias (blinding of researchers conducting outcome assessments), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other sources of bias were all assessed. A judgement of 'low risk' of bias, 'high risk' of bias, or 'unclear risk' of bias was made for each domain. Any disagreements were resolved by discussion or by involving a third reviewer until consensus was reached (**Figure 2** and **3**). There were insufficient numbers of included studies to appropriately assess a funnel plot or more advanced regression-based assessments; hence, publication bias was not assessed.[22]

Outcome Evaluation and Meta-Analysis

There was a statistically significant improvement in depressive symptoms in the vitamin D supplementation group as compared to the control group (95% confidence interval: -0.70 to - 0.08, p = 0.01). Only three studies were included because one study did not report the mean and SD, so it was not estimable.[18] Statistical heterogeneity was assessed using the chi-squared test and I-squared values. Our meta-analysis showed 0% ≤ I-squared ≤50 % low or no heterogeneity.

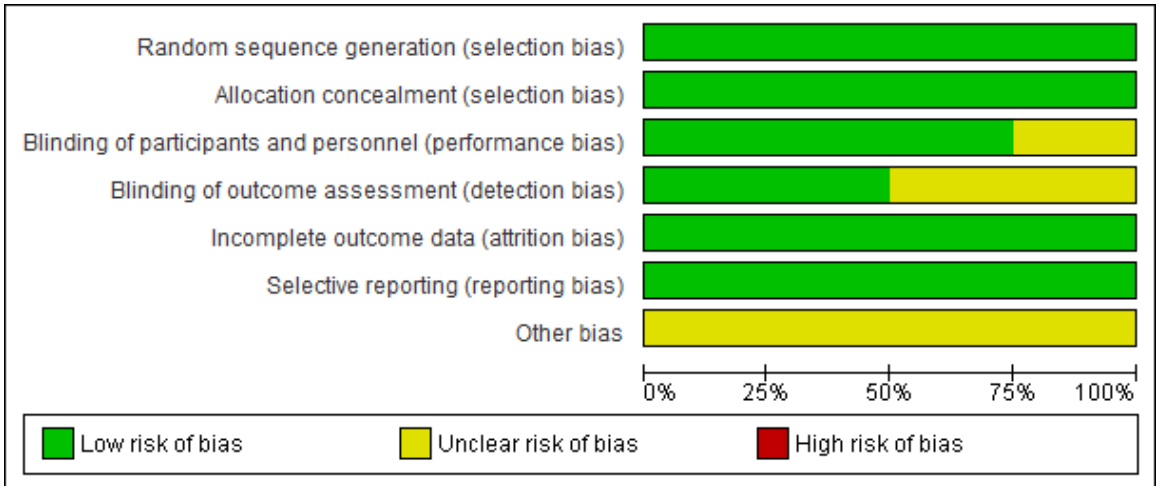

Figure 2. Risk of bias graph: review author's judgements about each risk of bias item presented as percentages across all included studies

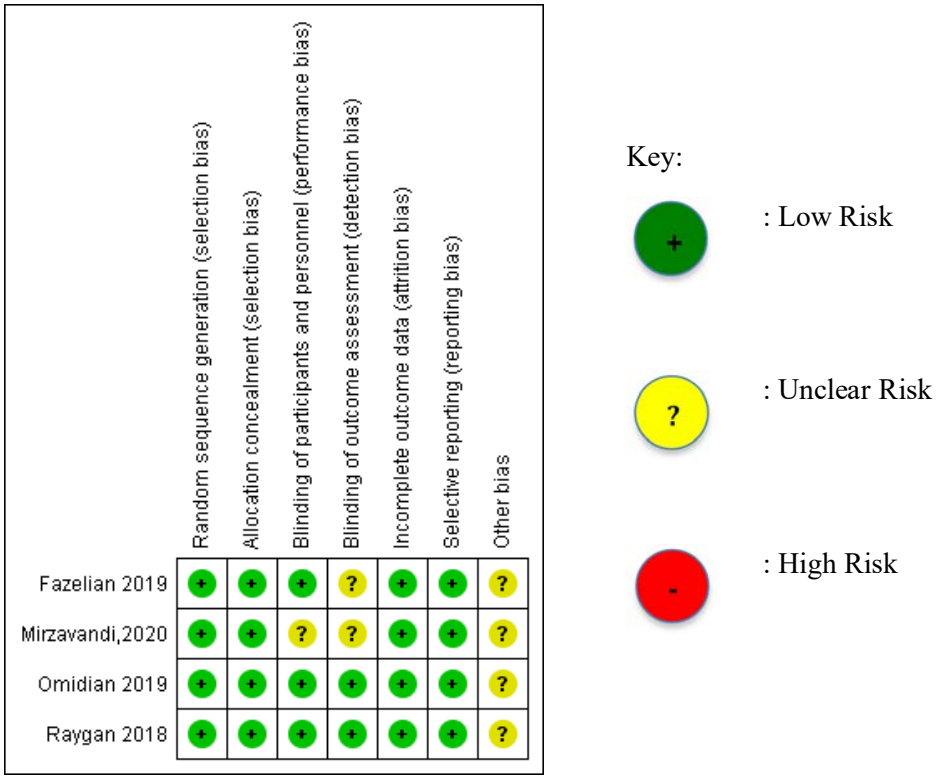

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

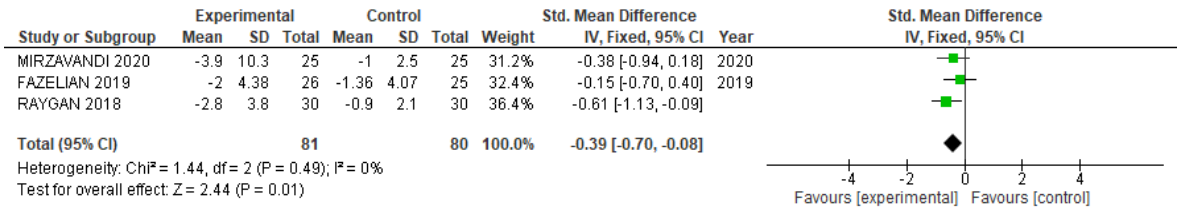

Figure 4. Meta-analysis of Randomised Controlled Trials of the Effect of Vitamin D Supplementation in Improving Depressive Symptoms in Patients with Type 2 Diabetes Mellitus.

Confidence in Cumulative Evidence

For the effectiveness of treatment, the confidence in the cumulative evidence was considered moderate (Table 3). The possibility that the actual effect may be significantly different from the estimated effect reduced our confidence in the efficacy of the treatment effect estimate.

Potential limitations, such as even rates and a small sample size, failure to assess compliance, and a non- representative sample are likely to reduce confidence in the effect estimate. In addition, we found disparities in treatment effect estimates, unexplained heterogeneity in subgroup analyses, and minimal overlap of confidence ranges (CI). Some of the findings were consistent with substantial benefit and substantial harm, implying that imprecision should be rated lower.

DISCUSSION

In this meta-analysis of 3 randomized controlled trials with a total of 161 subjects, vitamin D supplementation was significantly associated with improving depressive symptoms ($p = 0.01$). All four studies analysed have strong points and were conducted with a high level of evidence, adequate duration of therapy, multiple disguises, proper randomization using computer-generated randomization, similarities between groups during baseline, and similarities in the

Table 3. The three studies included in the meta-analysis were graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profile for the role of vitamin D supplementation for depression symptoms.

Certainty Assessment							Effect		
Number of studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Relative (95%CI)	Certainty	Importance
Outcome: Depressive symptoms score									
3	RCT	Not serious	Not serious	Not serious	Not serious	None	- 0,70 - 0,08	Moderate	Important

given therapy (high dose of vitamin D). All studies had similar sample size of around 50–68 patients. There were a number of patients who were not available for a follow-up, but none were attributable to the side effects or complications of the regimen given. The number of samples was low due to restrictive inclusion and exclusion criteria applied to these four studies.

Lower serum vitamin D levels have been linked to an increasing risk of depression. Depressive symptoms in those with very low vitamin D levels could be alleviated with vitamin D supplementation.[23-25] Vitamin D supplementation increased the well-being in three pilot studies, and symptoms of depression were reduced when high doses of vitamin D3 (100 mcg per day) were given for 1 to 3 months.[23]

The studies by Raygan et al.[17] and Omidian et al.[18] showed that vitamin D supplementation led to significant improvement in depressive symptoms compared to placebo. In contrast, the study by Fazelian et al.[19] and Mirzavandi et al.[20] resulted in no statistically significant decrement of depression scores between groups. Nevertheless, the study by Mirzavandi et al. used non-experimental groups rather than the placebo group – control groups were not given intervention. This methodology makes the blinding process impossible to carry out, which may lead to an increasing risk of bias.[20] Moreover, the study by Fazelian et al. stated that according to the within-group analysis, patients who had a low serum vitamin D level at baseline had a significant decrement in their depressive symptoms score.[19] Therefore, further research to assess the effect of vitamin D supplementation on the improvement of depressive symptoms in patients with low levels of serum vitamin D is still needed.

The studies results by Omidian et al.[18] and Mirzavandi et al.[20] is highly applicable in type 2 diabetes mellitus patients with depression. Raygan et al.[17] did a study in diabetic patients with the comorbidity of coronary heart disease, while Fazelian et al.[19] did a study on depressed diabetic patients with low, moderate, or severe anxiety disorder. Nevertheless, the generalizability of these studies to a larger population is still questionable since all of the studies were performed in Iran.

The studies by Omidian et al.[18] and Mirzavandi et al.[20] reported that vitamin D supplementation did not show any significant side effects, while Raygan et al.[17] and Fazelian et al.[19] did not report anything about adverse effects. These findings show that the benefits of vitamin D are much greater than the potential losses.

Consistent with the results of our study, other clinical trials that have different population samples also showed that vitamin D supplementation was associated with improvement of depressive symptoms.[26,27] A study by Mozzafari et al. recruited depressed patients with vitamin D deficiency as their subjects and found that after 3 months of injected vitamin D, there was a significant improvement in depressive symptoms.[26] Penckofer et al. reported a significant effect of vitamin D supplementation on depressed diabetic women.[7] A further study by Penckofer et al. in the Sunshine 2 study showed that there was a significant improvement in depressive symptoms in diabetic women over time, regardless of the vitamin D3 dose.[28] Furthermore, Khoraminya et al. reported that

vitamin D supplementation as an adjunctive therapy to an anti- depressant drug was effective.[29] Moreover, two cross-sectional studies have also proved that there is a correlation between low serum vitamin D and depressive symptoms.[30,31] However, there are some observational studies that have found no association between these two variables.[32,33]

In this systematic review of RCTs, the effect of vitamin D supplementation was significant for improvement in depressive symptoms in patients with type 2 diabetes mellitus. Even though one of the RCTs showed no significant effect of vitamin D supplementation, the study did show a possible trend of depressive symptom improvement by giving a vitamin D injection. The decrement of the BDI score was higher in the experimental group (-3.9 10.3) than in the non-experimental group (-1.0 2.5) [20]

Limitations

To the best of our knowledge, this study is the first study to review the effect of vitamin D supplementation on the improvement of depressive symptoms in type 2 diabetic patients. Moreover, this systematic review only included RCTs with a high level of evidence, which ensured less study bias and was more reliable in assessing the effectiveness of medical treatment. In addition, the author also did some grey literature searching, which minimized the plausibility of missing evidence.

The limitations of this study include the questionable generalizability of the findings because of concentrated patient samples, i.e., all studies were conducted in Iran. Furthermore, even though the included articles were focused on the effect of vitamin D supplementation on the improvement of depressive symptoms in type 2 diabetic patients, most of the studies lacked detailed information on the mechanisms of how vitamin D may affect depressive symptoms.

Due to the limitations of the study, the authors provide recommendations as follows: (1) larger patient samples and more varied patient demographics since all available studies were conducted in Iran; (2) more studies that include within-group analysis, especially based on the level of serum vitamin D, are highly recommended to further explore the effect of vitamin D; (3) the addition of more different populations in the next research topic because the existing studies only examine specific populations, namely patients with type 2 diabetes mellitus who do not have complications from diabetes mellitus; and, (4) the dosing and form of vitamin D used should be more standardized for further studies.

CONCLUSION

The results of the systematic review and meta-analysis demonstrated that vitamin D supplementation may improve the depressive symptoms in type 2 diabetic patients.

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CONFLICT OF INTEREST

The authors report no declarations of interest.

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REFERENCES

1. Roy T, Llyod CE. Epidemiology of depression and diabetes: a systematic review. Journal of Affective Disorders. 2012;S8–S21. doi: 10.1016/S0165-0327(12)70004-6
2. Holt RIG, Groot M de, Golden SH. Diabetes and depression. Curr Diab Rep. 2014;14(6):491. doi: 10.1007/s11892-014-0491-3.
3. Anglin RES, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. British Journal of Psychiatry. 2013:202(2):100-7. doi: 10.1192/bjp.bp.111.106666
4. Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. Diabetologia. 2010;53(12):2480–6. doi: 10.1007/s00125- 010-1874-x. Epub 2010 Aug 14.
5. Fisher L, Glasgow RE, Strycker LA. The relationship between diabetes distress and clinical depression with

glycaemic control among patients with type 2 diabetes. Diabetes Care. 2010;33(5):1034–6. doi: 10.2337/dc09-2175
6. Groves NJ, McGrath JJ, Burne TH. Vitamin D as a neurosteroid affecting the developing and adult brain. Annu Rev Nutr. 2014;34:117-41. doi: 10.1146/annurev-nutr-071813-105557
7. Penckofer S, Byrn M, Adams W, et al. Vitamin D supplementation improves mood in women with type 2 diabetes. J Diabetes Res. 2017;2017:8232863. doi: 10.1155/2017/8232863. Epub 2017 Sep 7.
8. Gowda U, Mutowo MP, Smith BJ, Wluka AE, Renzaho AMN. Vitamin D supplementation to reduce depression in adults: meta-analysis of randomized controlled trials. Nutrition. 2015;31:421-429S.
9. Spedding S. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. Nutrients. 2014;6:1501-18.
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/ 10.1136/bmj.n71
11. National Institute for Health Research. http://www.crd.york.ac.uk/PROSPERO, registration number CRD42021231713.
12. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ. 2011;343:d5928.
13. Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.
14. Sterne JAC, Sutton AJ, Loannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta- analyses of randomised controlled trials. BMJ. 2011;343:d4002. doi: https://doi.org/10.1136/bmj.d4002
15. Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018;74(3):785-94. doi:10.1111/biom.12817
16. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: Introduction GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64:, 383-94.
17. Raygan F, Ostadmohammadi V, Bahmani F, Asemi Z. The effects of vitamin D and probiotic co-supplementation on mental health parameters and metabolic status in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84(Pt A):50–5. Doi: 10.1016/j.pnpbp.2018.02.007
18. Omidian M, Mahmoudi M, Abshirini M, et al. Effects of vitamin D supplementation on depressive symptoms in type 2 diabetes mellitus patients: Randomized placebo-controlled double-blind clinical trial. Diabetes Metab Syndr: Clin Res Rev. 2019;13:2375-80. doi: 10.1016/j.dsx.2019.06.011
19. Fazelian S, Amani R, Paknahad Z, Khein S, Khajehali L. Effect of Vitamin D supplement on mood status and inflammation in Vitamin D deficient type 2 diabetic women with anxiety: A randomized clinical trial. Int J Prev Med. 2019;10:17. doi:10.4103/ijpvm.IJPVM_174_18
20. Mirzavandi F, Babaie S, Rahimpour S, et al. The effect of high dose of intramuscular vitamin D supplement injections on depression in patients with type 2 diabetes and vitamin D deficiency: A randomized controlled clinical trial. Obes Med. 2020;17:1-6. doi: 10.1016/j.obmed.2020.100192
21. Sterne JAC, Savović J, Elbers RG, et al. RoB 2: a revised tool for assessing risk of bias in randomized tools. BMJ. 2019;366:l4898.
22. abousetta (https://stats.stackexchange.com/users/24137/abousetta), Meta- analysis: dealing with bias with a small number of studies, URL (version: 2013- 08-03): https://stats.stackexchange.com/q/66408
23. Geng C, Shaikh AS, Han W, Chen D, Guo Y, Jiang P. Asia Pacific Journal of Clinical Nutrition. 2019;28 (4): 689 – 94. doi: 10.6133/apjcn.201912_28(4).0003.
24. Li G, Mbuagbaw L, Samaan Z, et al. Efficacy of vitamin D supplementation in depression in adults: a systematic review. Journal of Clinical Endocrinology and Metabolism. 2014;99(3):757-67. doi:10.1210/jc.2013-345
25. Anglin RE, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry. 2013 Feb;202:100-7. doi: 10.1192/bjp.bp.111.106666. PMID: 23377209.
26. Mozaffari-Khosravi H, Nabizade L, Yassini-Ardakani SM, Hadinedoushan H, Barzegar K. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. J Clin Psychopharmacol. 2013;33(3): 378-85.
27. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double-blind trial. J Intern Med. 2008;264(6):599-609. doi: 10.1111/j.1365-2796.2008.02008.x. Epub 2008 Sep 10. PMID: 18793245.
28. Penckofer S, Ridosh M, Adams W, et al. Vitamin D supplemetation for the treatment of depressive symptoms in women with type 2 diabetes: a randomized clinical trial. Journal of Diabetes Research. 2022; ID: 4090807: 1 – 10. https://doi.org/10.1155/2022/4090807
29. Khoraminya N, Therani-Doost M, Jayazeri S, Hosseini A, Djazayery A. Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. Aust NZJ Psychiatr. 2013;47(3): 271-5. doi: 10.1177/0004867412465022
30. Kjærgaard M, Joakimsen R, Jorde R. Low serum 25-hydroxyvitamin D levels are associated with depression in an adult Norwegian population.

Pyschiatr Res. 2011;190(2-3):221-5. doi: 10.1016/j.psychres.2011.06.024
31. Hoogendijk WJ, Lips p, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatr. 2008;65(5):508- 12. doi: 10.1001/archpsyc.65.5.508
32. Zhao G, Ford ES, Li C, Balluz LS. No associations between serum concentrations of 25-hydroxyvitamin D and parathyroid hormone and depression among US adults. Br J Nutr. 2010;104(11):1696-702. doi: 10.1017/S0007114510002588
33. Pan A, Lu L, Franco OH, Yu Z, Li H, Lin X. Association between depressive symptoms and 25-hydroxyvitamin D in middle-aged and elderly Chinese. J Affect Disord 2009;118(1-3):240-3. doi: 10.1016/j.jad.2009.02.002