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UPDATE ON THE RELATIONSHIP BETWEEN VITAMIN D AND DEPRESSION: SYSTEMATIC REVIEW

*[1]Ilma Fitriana, [1]Dela Intan Permatasari

[1]*Faculty of Medicine, Trisakti University, Jakarta Special Region, Indonesia*

Correspondence Author:
ilmafitr@yahoo.com

ABSTRACT

Introduction: *Depression remains a significant global health challenge, affecting approximately one in ten individuals, and its multifaceted nature requires prolonged therapeutic interventions. Recent studies have explored the potential link between vitamin D deficiency and depression, highlighting the role of vitamin D in neurobiology and its plausible association with depressive symptoms. However, the exact nature of this relationship and its implications for depression management require further investigation, as outlined in the systematic review "Association of Vitamin D and Depression: An Update Systematic Review," aiming to provide clarity on the role of vitamin D in depression etiology and guide future research and clinical interventions.*

Method: *The researchers in this study followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure that their work met the required standards. This was done to ensure the precision and reliability of the conclusions derived from the research.*

Result: *Our search produced 13 results. After looking at the titles and summaries, we found 10 papers that fit our criteria. At first, we excluded several articles because they were written in review style and case reports. But after reading the full papers carefully, we included five papers in our final analysis. These papers included experimental study, observational study a randomized, double-blind, placebo controlled clinical trial, a cross-sectional analysis, and double-blind randomized clinical trial.*

Conclusion*: Some studies indicate improvements in mood, reductions in corticosterone levels, and prevention of serum vitamin D decreases with vitamin D and SSRI antidepressant combination. Another study in obese women with depression showed positive effects on mood, BDNF levels, inflammation, and SIRT1 with vitamin D and magnesium supplementation. However, no significant associations were found between baseline vitamin D levels and depression symptoms, and vitamin D supplementation did not improve depression symptoms in deficient but otherwise healthy individuals, suggesting caution in using it for depression management. Further research, especially in diverse populations, is needed to clarify the role of vitamin D in depression.*

Keywords: *BDNF level, depression, SSRI vitamin D*

INTRODUCTION

Depression presents a pressing public health challenge, lacking a universally effective remedy, with approximately one in ten individuals globally currently grappling with its burdens. Often referred to as major depressive disorder or clinical depression, this pervasive psychiatric condition manifests through symptoms including profound sadness, feelings of worthlessness, hopelessness, diminished interest, and at times, thoughts of life's futility.[1] Depression transcends mere melancholy; it's not a sign of weakness, nor is it something one can easily overcome. Rather, it frequently necessitates prolonged therapeutic interventions. Yet, there's reason for optimism; many individuals find relief through medication, psychological therapy, or a combination thereof. Nevertheless, the exact etiology of depression remains elusive, with a myriad of factors potentially contributing, such as biological variances, brain chemistry, hormonal imbalances, and genetic predispositions. In light of these uncertainties, researchers strive to unravel depression's underlying mechanisms. [2]

Recent investigations have tentatively linked depression to vitamin D deficiency, though the precise nature of this connection remains unclear. Furthermore, this correlation doesn't definitively establish whether low vitamin D levels precipitate depression or vice versa. What is apparent, however, is that insufficient serum vitamin D levels may heighten the risk of depression. Vitamin D, often dubbed the "sunshine" vitamin, is a fat-soluble nutrient crucial for various bodily functions. Its primary forms, D3 (cholecalciferol) and D2 (ergocalciferol), can be acquired through diet or synthesized in the skin upon exposure to sunlight. Following synthesis or ingestion, vitamin D undergoes metabolic processes involving liver and kidney enzymes, eventually yielding its active form, 1,25-dihydroxyvitamin D (1,25(OH)2D3).[3]

Emerging research suggests that vitamin D also functions as a neuroactive steroid, influencing neurotransmitter expression, neurotrophic factor regulation, neuroimmune modulation, antioxidant production, and neurotropic factor synthesis. This neurobiological role underscores the plausible association between vitamin D and depression. However, current findings on whether vitamin D insufficiency directly causes depression or results from depressive tendencies are inconclusive.[4] Moreover, discrepancies in vitamin D measurement methodologies across laboratories exacerbate this uncertainty. In this context, we delve into the neuroactive properties of vitamin D relevant to depression, alongside ongoing research and clinical endeavors, aiming to provide a comprehensive perspective on the role of vitamin D in depression treatment and prevention.[5]

The purpose of the systematic review titled "Association of Vitamin D and Depression: An Update Systematic Review" is to provide an updated and comprehensive analysis of the relationship between vitamin D levels and depression. Through a systematic and rigorous examination of existing literature, the review aims to shed light on the potential association between vitamin D deficiency and depressive symptoms. By synthesizing current research findings and addressing methodological inconsistencies, the review seeks to offer insights into the neurobiological mechanisms linking vitamin D to depression. Ultimately, this systematic review endeavors to contribute to a better understanding of the role of vitamin D in depression etiology and inform future research directions and clinical interventions aimed at managing and preventing depression.

METHODS

Protocol

The researchers in this study followed the 2020 Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines to ensure that their work met the required standards. This was done to ensure the precision and reliability of the conclusions derived from the research.

Criteria for Eligibility

For inclusion in the study, published articles had to meet particular requirements. They had to be research papers written in English, focusing on relationship between vitamin D and depression. The studies had to meet the following criteria: articles need to have been published after 2019 but within the applicable timeframe for this systematic review. Articles falling into categories like editorials, lacking a DOI, review articles that were already published, or duplicating previously published journal papers were excluded from the assessment.

Search Strategy

We conducted a comprehensive literature search using PubMed, Wiley Journal Database, and ScienceDirect focusing on studies published from 2018 to 2024. The search terms employed were as follows ("relationship"[All Fields] OR "relationships"[All Fields]) AND ("vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]) AND ("depressed"[All Fields] OR "depression"[MeSH Terms] OR "depression"[All Fields] OR "depressions"[All Fields] OR "depression s"[All Fields] OR "depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depressivity"[All Fields] OR "depressive"[All Fields] OR "depressively"[All Fields] OR "depressiveness"[All Fields] OR "depressives"[All Fields]). Moreover, we performed cross-referencing of relevant articles to reveal additional research. The evaluation of study quality, methodology, interventions, and results was undertaken independently by the researchers, resolving any differences through discussion and agreement. Furthermore, both researchers collected and compared discoveries from all studies, considering the potential for conducting a meta-analysis if deemed feasible.

Inclusion and exclusion criteria

Inclusion criteria for the studies were as follows: (1) original research that assesses relationship between vitamin D and depression; (2) Randomized Controlled Trials (RCTs) or observational studies (cohort or case-control studies); (3) availability of relevant data. Exclusion criteria were as follows: (1) ongoing studies or studies without available data; (2) duplicate publications. In cases of duplicate publications, the most recent article was chosen; (3) Non-English language studies were excluded.

Data Retrieval

The authors conducted a thorough examination of relevant studies, specifically selecting those that met precise inclusion criteria. They focused on original, unpublished papers in English to ensure a refined and high-quality selection. The analysis covered essential information, such as study particulars, authors, publication dates, locations, and research methodologies, aligning with the study's objectives.

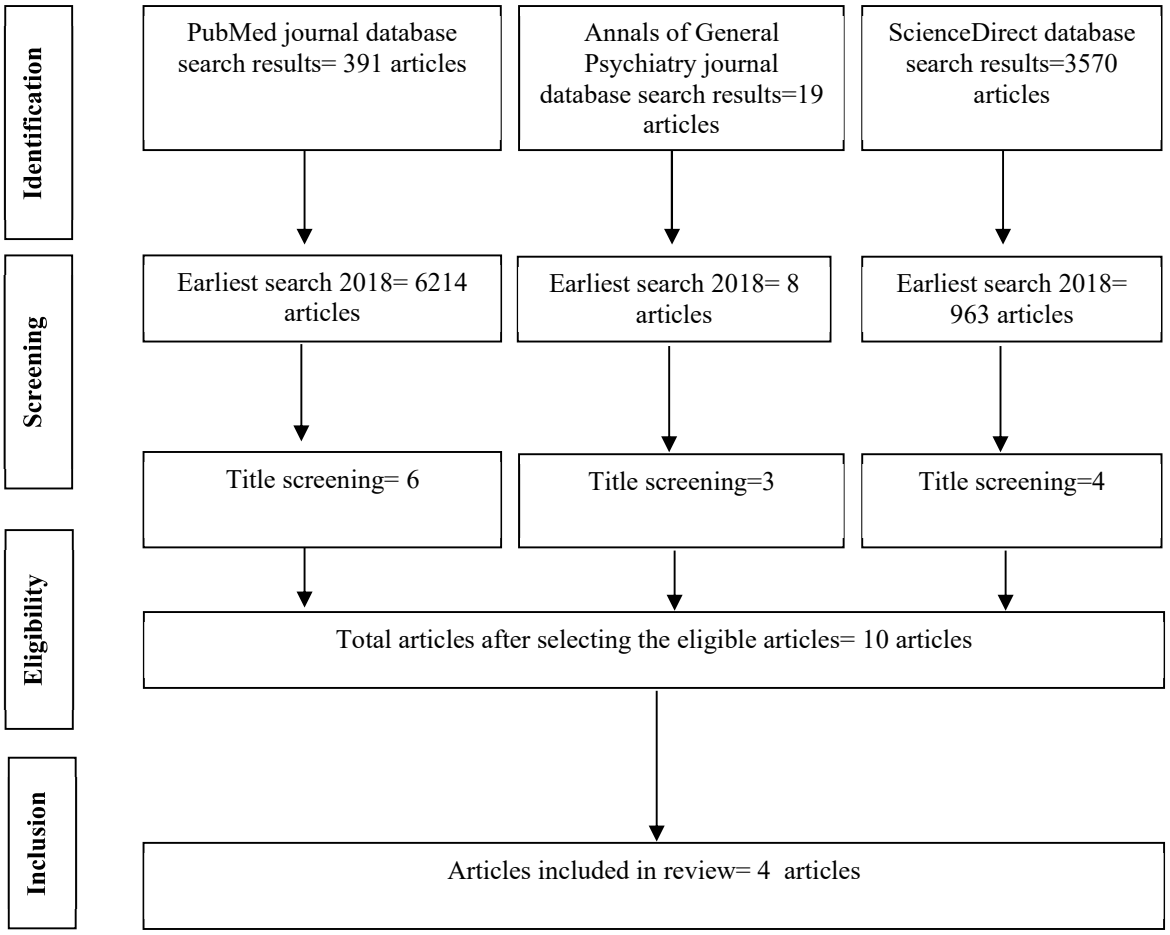

Figure 1. Article search flowchart

Author	Origin	Method	Sample Size	Result
Al-Ramadhan, 2023.[6]	Saudi Arabia	Experimental study.	A total of 40 male Wistar rats (224–296 g).	Our results show that VD3 had effects similar to fluoxetine on the depressive behavior of the rats when measured by three behavioral tests, namely SPT, FST, and OFT ($p < 0.001$). Additionally, VD3 had a protective effect against depression similar to that of fluoxetine. Corticosterone levels were lower in the CUMS group that received vitamin D and the CUMS group that received both vitamin D and fluoxetine than in the CUMS group ($p < 0.000$)
Khan B et al., 2022.[7]	Saudi Arabia	Observational study	Vitamin D levels of 100 healthy and 100 depressed subjects were determined.	Study has reported a higher percentage of vitamin D deficiency in the Peshawar region. The results of our study indicated that depression was common in individuals having vitamin D deficiency
Behnaz et al., 2021.[8]	Iran	A randomized, double-blind, placebocontrolled clinical trial.	108 obese women with mild to moderate depressive symptoms.	At the end of the study, ANCOVA demonstrated significant differences between the 4 groups in 25(OH)-D, magnesium, TNF-α, IL-6, and BDNF levels. But, we found no significant differences in terms of hs-CRP and SIRT1 levels. A significant reduction in depression score was observed in 3 intervention groups and also in control group. No significant differences in BDI-II score were shown among the 4 groups at the end of the intervention.
Mousa et al., 2018.[9]	Australia	Cross-sectional analyses.	63 (39M/24F) overweight or obese (body mass index (BMI) ≥25 kg/m2) and vitamin D-deficient (25(OH)D ≤50 nmol/l) adults (mean age=31.3 ± 8.5), without clinical depression.	At baseline, mean 25(OH)D concentration was 32.9 ± 11.3 nmol/l and total BDI score was 6.6 ± 6.3 (range=0 - 33). There were no associations between 25(OH)D concentrations and total BDI scores or BDI subscales (all $p>0.1$). After the 16-week intervention, 25(OH)D concentrations increased in the vitamin D group compared to placebo (56.0 ± 20.8 versus 2.7 ± 13.9 nmol/L, respectively; $p<0.0001$). Change in total BDI scores did not differ between vitamin D and placebo groups (-2.0 ± 4.5 versus -1.5 ± 2.9, respectively; $p=0.7$). There were no differences in BDI subscales between groups (both $p>0.1$). Results remained non-significant after adjusting for multiple covariates including sun exposure, physical activity, and dietary vitamin D intake (all $p>0.1$).
Mina et al., 2020.[10]	Iran	Double-blind randomized clinical trial.	56 subjects with mild to moderate depression, aged 43.0 ± 1.15yrs.	Following intervention, significant changes were observed in the intervention group compared to the controls: 25(OH)D concentrations increased (+40.83±28.57 vs. +5.14±23.44 nmol/L, $P<0.001$) and BDI scores decreased (-11.75±6.40 vs. -3.61±10.40, $P = 0.003$). Oxytocin concentrations were significantly reduced in controls (-6.49±13.69 ng/mL, $P = 0.01$), but between -group differences were insignificant. Within- and between-group differences of platelet serotonin concentrations were not significant; however, the increment in controls was higher (+0.86±10.82 vs. +0.26±9.38 ng/mL, $P = 0.83$).

RESULT

Our search produced 13 results. After looking at the titles and summaries, we found 10 papers that fit our criteria. At first, we excluded several articles because they were written in review style and case reports. But after reading the full papers carefully, we included five papers in our final analysis. These papers included experimental study, observational study a randomized, double-blind, placebo controlled clinical trial, a cross-sectional analysis, and double-blind randomized clinical trial.

The objective of this investigation by Al-Ramadhan et al was to assess the impacts of intraperitoneal (IP) doses of VD3, fluoxetine, and a combination of VD3 + fluoxetine on depressive behaviors and corticosterone levels. Before the experiment, there were no notable differences in rat weights among the study groups. Similarly, the results of all pre-experiment behavioral assessments did not reveal any significant distinctions between the groups, except for the Forced Swim Test (FST). Notably, a significant difference was observed in the FST between the CUMS group and the VD3 + fluoxetine + CUMS group ($p = 0.030$).[6]

There were no significant weight-related variations among the five study groups. However, in terms of the FST, the CUMS group exhibited significantly different results compared to three other groups: the control group, the VD3 + CUMS group, and the VD3 + fluoxetine + CUMS group. Additionally, post-experiment Tail Suspension Test (TST) outcomes showed a significant difference between the control group and the CUMS group, as well as among the different treatment groups. [6]

Notable changes in weight, TST, and Elevated Plus Maze (EPM) outcomes were observed across the groups ($p < 0.05$). However, the CUMS group did not exhibit a significant change in weight. Most of the behavioral test results for this group demonstrated significant alterations. In contrast, only the EPM test showed a significant change ($p < 0.05$) for the VD3 + fluoxetine + CUMS group, indicating that the combined treatment may mitigate stress in various behavioral assessments. Pearson's correlation analysis revealed a significant inverse correlation between serum 25-OH-VD levels and sucrose preference test results in the VD3 + fluoxetine + CUMS group. However, no other significant correlations were found between serum 25-OH-VD levels and behavioral test outcomes in the other study groups. [6]

This study by Khan et al in 2022 aimed to investigate the relationship between vitamin D levels and depression by analyzing the vitamin D levels of individuals with depression. The objective was to ascertain the significance of vitamin D levels in association with depression. To establish this relationship, we measured the vitamin D levels of 100 healthy subjects and 100 depressed subjects. These subjects were categorized into three age groups: Group-I included individuals below 20 years, Group-II encompassed those aged between 21 and 60 years, and Group-III consisted of individuals aged 61 years and above. [7]

Among the male subjects, the mean age was 39.28 ± 2.27, with a coefficient of variation (CV) of 44.42%, while the mean vitamin D level was 34.65 ± 3.84, with an 84.84% CV. Similarly, among the female subjects, the mean age was 45.82 ± 2.3, with a CV of 31.79%, and the mean vitamin D level was 61.45 ± 7.16, with a CV of 74.62%. Significant differences were observed in age ($p < 0.05$) and vitamin D levels ($p < 0.05$). For male subjects, the mean age was 38.87 ± 2.089, with a CV of 34.41%, and the mean vitamin D level was 24.17 ± 1.32, with a CV of 34.96%. The mean depression level on the BDI scale was 25.8 ± 1.49, with a CV of 37.17%. Among female subjects, the mean age was 45.5 ± 1.87, with a CV of 31.56%, the mean vitamin D level was 23.36 ± 1.81, with a CV of 59.76%, and the mean depression level was 28.06 ± 0.95, with a CV of 25.86%. Significant differences were observed in age ($p < 0.05$), but not in vitamin D levels ($p > 0.05$). [7]

Further analysis was conducted within specific age groups. In Group-I (subjects aged 20 years and below), both normal and depressed subjects were evaluated for their vitamin D and depression levels. Normal subjects had a mean age of 15.9 ± 0.6, with a CV of 12.01%, and a mean vitamin D level of 17.67 ± 0.56, with a CV of 9.91%. Depressed subjects in this group had a mean vitamin D level of 23.2 ± 1.06, with a CV of 9.14%, and a mean BDI score of 19 ± 3.1. In Group-II (subjects aged between 21 and 60 years), the age, vitamin D, and depression profiles of both normal and depressed subjects. Normal subjects had a mean age of 39.18 ± 5.83, with a CV of 14.9%, and a mean vitamin D level of 44.51 ± 4.21 ng/mL, with a CV of 79.16%. Depressed subjects in this age group had a mean age of 39.35 ± 1.09, with a CV of 24.85%, a mean vitamin D level of 24.1 ± 1.44 ng/mL, with a CV of 32.1%, and a mean depression score of 26.78 ± 0.96. [7]

In Group III (subjects aged 61 years and above), the age, vitamin D, and depression profiles are summarized. Normal subjects had a mean age of 65.65 ± 1.06, with a CV of 7.2%, and a mean vitamin D level of 64.09 ± 11.96 ng/mL, with a CV of 83.5%. Depressed subjects in this age group had a mean age of 66.25 ± 1.2, with a CV of 16.6%, a mean vitamin D level of 21.8 ± 1.7 ng/mL, with a CV of 43.23%, and a mean depression score of 30.94. Among normal subjects, 38% had normal vitamin D levels, 36% had mild deficiency, 17% had severe deficiency, and 9% showed toxic levels of vitamin D. Among subjects with depression, 19% had normal vitamin D levels, 51% had mild deficiency, and 30% had severe deficiency. In terms of depression severity, 26% had mild depression, 24% had moderate depression, and 50% had severe depression. Overall, these findings highlight significant associations between vitamin D levels and depression, particularly among subjects aged 21 to 60 years, where vitamin D deficiency correlated with increased depression severity. [7]

Given the significance of exploring the effects of vitamin D and magnesium on mood, inflammation, and SIRT1, coupled with the unclear impact of their combined supplementation on these factors, and considering the widespread prevalence of

insufficiency/deficiency in these nutrients, particularly among obese and depressed individuals worldwide, this study by Abiri et al in 2021 aimed to assess the influence of vitamin D and/or magnesium supplementation on mood, serum levels of BDNF, SIRT1, and inflammatory markers in obese women exhibiting mild to moderate depressive symptoms. A total of 108 obese women with BDI-II scores ranging from 10 to 29 were initially recruited for the study. However, six participants were excluded due to unwillingness to continue the intervention or noncompliance with treatment, leaving 102 obese women for statistical analysis. [8]

The participants had a mean age of 34.30 ± 9.18 years, and there were no significant baseline differences among the four intervention groups in terms of age, height, weight, BMI, or waist circumference (WC). Dietary intake analysis during the intervention period revealed no significant differences in calorie, macronutrient, or micronutrient consumption, including magnesium and vitamin D, among the four groups. Moreover, no adverse effects were reported following vitamin D and/or magnesium supplementation throughout the study duration. [8]

Significant differences were observed in weight, BMI, and WC among the four groups after the intervention, with notable reductions observed within each intervention group compared to baseline values. Pairwise comparisons indicated significant differences in weight and BMI between the co-supplementation group and the vitamin D, magnesium, and control groups, as well as between the vitamin D group and the control group post-intervention. Additionally, a significant difference in WC was noted between the co-supplementation group and the control group after the intervention. [8]

Regarding serum biomarkers, no significant differences were found among the four groups at baseline. However, after adjusting for baseline values, significant differences were observed in serum levels of 25(OH)-D, magnesium, TNF-α, IL-6, and BDNF at the end of the study. Within-group comparisons revealed significant increases in serum 25(OH)-D and magnesium levels in the co-supplementation and respective single-supplementation groups, while reductions were observed in the control group. Furthermore, significant reductions in IL-6 and hs-CRP levels were observed in the intervention groups, whereas an increase was noted in the control group. SIRT1 and BDNF levels significantly increased in the intervention groups compared to baseline values. [8]

Regarding mood outcomes, all participants had BDI-II scores ≥ 10 at baseline and after eight weeks of intervention. Significant reductions in depression scores were observed in all intervention groups, as well as in the control group. However, no significant differences in BDI-II scores were found among the four groups post-intervention. Nevertheless, significant differences in the mean changes of BDI-II scores were observed among the groups, with pairwise comparisons indicating significant differences between the control group and the co-supplementation, magnesium, and vitamin D groups. [8]

This study by Mousa et al in 2018 aimed to fill gaps in knowledge by investigating whether 25(OH)D concentrations correlate with depression symptoms, as measured by the Beck Depression Inventory (BDI), in vitamin D-deficient, overweight, or obese yet otherwise healthy adults. Additionally, it explored whether BDI scores could be enhanced by vitamin D supplementation, administered at an adequate dose and duration, without other interventions, to a subgroup of this population. Our hypothesis was that lower 25(OH)D concentrations would be linked to higher BDI scores, and that vitamin D supplementation would lead to a reduction in BDI scores compared to a placebo.[9]

Initially, 65 participants were randomized into either the vitamin D group (n=33) or the placebo group (n=32). Of these, 63 participants had complete baseline BDI data for the cross-sectional analysis phase. By the trial's end, 48 participants had complete data and were analyzed in the intervention study, with 9 dropping out and 2 being excluded due to protocol violations or adverse events. Baseline characteristics, showed a mean age of 31.3 ± 8.5 years, with 39 males and 24 females, and 54% classified as obese. Serum 25(OH)D concentrations ranged from 9 to 50 nmol/l, with 43% having concentrations <30 nmol/l. Univariable analyses revealed no significant associations between BDI scores and demographic, anthropometric, or vitamin D-related factors. [9]

Multivariable analyses adjusting for various factors consistently showed no significant associations between 25(OH)D concentrations and BDI scores. Exploratory analyses among subgroups with different baseline 25(OH)D concentrations or obesity statuses yielded similar results. In the intervention study, data from 48 participants were analyzed, with significant increases in serum 25(OH)D concentrations observed in the vitamin D group post-intervention. However, changes in BDI scores did not significantly differ between the vitamin D and placebo groups. Further exploratory analyses among subgroups with varying 25(OH)D concentrations or obesity statuses also showed no significant differences in BDI scores between vitamin D and placebo groups. [9]

Mina et al., investigated the effects of high-dose vitamin D supplementation on depression, neurotransmitters, and the HPA axis.The primary objective was to observe a significant increase in serum 25(OH)D concentration from baseline to the end of the intervention. Vitamin D status was classified based on circulating 25(OH)D concentrations as deficient (<50 nmol/L), insufficient (50-75 nmol/L), and normal (>75 nmol/L) (Rosen, Abrams et al., 2012). Secondary outcomes included significant alterations in neurotransmitters, serum oxytocin, platelet serotonin, serum intact parathyroid hormone (iPTH), and depression severity (BDI-II score) from baseline to the end of the eight-week intervention.[10]

Out of the initial 69 participants, 56 were new cases, and 13 were recurrent cases (6 in the intervention group, 7 in the control group). However, 13 subjects were excluded due to either unwillingness to continue the study or failure to adhere to the intervention program. Ultimately, 56 subjects (28 in the intervention group, 28 in the control group), comprising 50 women (89.29%) and 6 men (10.71%) with an average age of 43.0±1.15 years, completed the study. Estimated adherence was approximately 100%, as all participants followed the study protocol and completed the entire eight-week intervention period. No statistically significant differences were noted between the baseline characteristics and other study parameters across the groups. Post-intervention, vitamin D status significantly improved only in the intervention group, with a markedly higher final 25(OH)D concentration compared to the control group (+40.83±28.57 vs. +5.14±23.44 nmol/L, P<0.001). None of the participants reported adverse drug reactions, and there were no incidents of suicide attempts. [10]

Following the intervention, a significant reduction in BDI scores was observed in the intervention group compared to baseline (-11.75±6.40, P<0.001) and the control group (-11.75±6.40 vs. -3.61±10.40, P=0.003). However, the control group's BDI score showed no significant changes at the end of the intervention. [10]

At the endpoint, serum oxytocin levels were significantly reduced in the control group compared to baseline (-6.49±13.69 ng/mL, P=0.01); however, this reduction did not reach statistical significance compared to the intervention group. No significant differences were found within or between groups in platelet serotonin concentrations after the intervention. Nevertheless, the control group exhibited a greater increase in platelet serotonin concentration compared to the intervention group post-intervention (+0.86 ±10.82 vs. +0.26 ±9.38 ng/mL, P=0.83). Final iPTH concentrations did not significantly differ between the study groups. However, after the intervention, iPTH concentrations significantly increased in the control group compared to baseline (+5.10±6.002 pg/mL, P<0.001). [10]

DISCUSSION

In Al-Ramadhan et al. study the impact of intraperitoneal (IP) doses of vitamin D3 (VD3), fluoxetine, and a combination of VD3 + fluoxetine on behavioral tests and serum corticosterone levels in a chronic unpredictable mild stress (CUMS) rat model was investigated. Over three weeks, we induced stress and depressive symptoms in rats using CUMS procedures. Results revealed that both the VD3 + CUMS group and the VD3 + fluoxetine + CUMS group exhibited antidepressant effects from VD3 treatments, as indicated by three behavioral tests (forced swimming test [FST], open field test [OFT], and sucrose preference test [SPT]), along with a decrease in corticosterone hormone levels. Interestingly, the combination of VD3 and fluoxetine showed superior antidepressant effects compared to individual VD3 or fluoxetine treatments, as per the behavioral test results. Moreover, a negative correlation between sucrose preference test and 25-OH-VD levels was observed in the VD3 + fluoxetine + CUMS group. Compared to the CUMS group, all treated groups showed significant reductions in corticosterone levels, suggesting a mechanism for alleviating depressive behaviors through corticosterone modulation. [6]

Furthermore, the findings align with previous studies indicating the efficacy of combining antidepressants with VD3. Notably, the current study differs in dose, route of administration, duration, and subject sex compared to previous research. Additionally, the study underscores the potential of VD3 to prevent the rise in corticosterone levels associated with stress, similar to fluoxetine's effect. Moreover, VD3 may affect depressive symptoms through its impact on microglial activation and neuroprotective pathways. [6]

Vitamin D, a steroid hormone crucial for various bodily functions including mental health, is often insufficiently obtained in regions like Pakistan due to inadequate sunlight exposure and limited awareness about its importance in daily diet. [11] Apart from its role in bone health, vitamin D deficiency can lead to conditions like rickets, osteomalacia, osteoporosis, cancer, diabetes, and even depression. Addressing such deficiencies often requires vitamin D supplements, with recommended dietary intake ranging from 600 to 800 International Units depending on age. [12]

Research suggests that vitamin D might play a role in brain function, as it can pass through the blood-brain barrier and its receptors are found in different brain regions. Low vitamin D levels have been associated with conditions like depression, possibly due to their impact on parathyroid hormone levels. Studies have noted vitamin D deficiency in various countries, including the US, Europe, Australia, and Pakistan, with significant implications for mental health. [14]

Depression and mood disorders pose significant global health concerns, impacting quality of life and contributing to disability. Vitamin D deficiency has been linked to mood disorders, and while supplementation may play a role in treatment, low vitamin D levels can also exacerbate mood and behavior issues, affecting cognitive function and overall well-being. In the US, depression ranks as a leading cause of disability among young people. [8]

Previous research suggests that vitamin D and magnesium may offer a promising complementary treatment for complications in obese individuals by modulating inflammation, BDNF, and SIRT1. However, it's uncertain whether co-supplementation of these nutrients would be beneficial for obese women. Abiri et al's study, the first of its kind, investigated the effects of vitamin D or magnesium supplementation, as well as their combination, versus placebo over an 8-week period on mood, inflammation, serum BDNF, and SIRT1 in obese women with mild to moderate depressive symptoms. Researcher found that vitamin D (50,000 IU weekly) and magnesium (250 mg daily) supplementation had positive effects on inflammatory status and mood in these individuals. Obesity and depression often coexist, with shared underlying mechanisms such as

inflammation, oxidative stress, and endocrine dysfunction. Both vitamin D and magnesium deficiencies have been implicated in the pathogenesis of these disorders. [9]

Magnesium plays a crucial role in CNS function, and some studies suggest its supplementation can alleviate depressive symptoms. Similarly, vitamin D deficiency has been linked to depression, likely due to its role in serotonin synthesis. However, findings from clinical trials on vitamin D supplementation for depression have been inconsistent. Vitamin D deficiency is common in obese individuals and is associated with increased inflammation and metabolic dysfunction. On the other hand, magnesium deficiency can exacerbate inflammation and metabolic disorders, particularly in obese individuals. The present study observed significant reductions in inflammatory markers and improvements in mood with vitamin D and magnesium supplementation, possibly due to their synergistic effects. This intervention could be a beneficial strategy for improving systemic inflammation, mood, and quality of life in obese and/or depressed women.

In vitamin D-deficient overweight or obese but otherwise healthy adults, we found no link between 25(OH)D concentrations and depression symptoms, as measured by BDI scores. Even with vitamin D supplementation, which significantly increased 25(OH)D concentrations, there was no effect on depression symptoms. These results remained unchanged after accounting for potential confounders like physical activity, dietary vitamin D intake, and sun exposure. Subgroup analyses for participants with 25(OH)D <30 nmol/l or obesity (BMI ≥30 kg/m2) also yielded non-significant results.[15]

Mousa et al.'s findings align with a recent meta-analysis of 9 cross-sectional studies, which similarly found no significant associations between 25(OH)D concentrations and depression symptoms. Moreover, studies using different assessment tools for depression yielded conflicting results, indicating methodological variability. Previous research primarily focused on older adults, while our study targeted young, healthy individuals, possibly explaining the divergence in findings. [9]

In terms of vitamin D supplementation, Mousa et al. study, along with recent meta-analyses, found no improvement in depression symptoms despite adequate dosages and durations. These results contrast with studies involving older or psychiatric populations, where some observed benefits. However, inconsistencies in study design, participant characteristics, and co-interventions complicate interpretation.[9]

This study conducted the first randomized controlled trial (RCT) to investigate the impact of vitamin D supplementation on platelet serotonin and serum oxytocin levels, neurotransmitters associated with depression, and depression severity in depressed patients. The results revealed that an eight-week supplementation of 50,000 IU/2wks significantly increased serum vitamin D levels, improving the vitamin D status of patients with mild to moderate depression. This was accompanied by a notable reduction in depression severity compared to the control group. However, the supplementation did not significantly affect serum oxytocin or platelet serotonin levels. [10]

While conflicting data exist regarding the sufficiency level of vitamin D, our study dosage (~3571 IU d-1) effectively elevated serum 25(OH) D concentrations without adverse effects, aligning with previous research on mood disorders. Although some studies have suggested that vitamin D supplementation might not improve depression status, particularly in cases of severe deficiency, our findings indicate its potential efficacy, even in individuals with adequate baseline levels. Regarding platelet serotonin, previous studies offer inconsistent results, possibly influenced by factors like genetic polymorphisms and concurrent physical or mental disorders. Similarly, our study did not find significant changes in platelet serotonin levels following vitamin D supplementation. [10]

As for serum oxytocin, this study is the first RCT to investigate its response to vitamin D supplementation in depressed patients. While the control group exhibited a significant reduction in oxytocin levels, the intervention group showed a less pronounced decline, suggesting a potential protective effect of vitamin D. However, further research is needed to clarify the relationship between oxytocin and depression, as current findings are conflicting and influenced by various factors. [10]

CONCLUSION

Findings indicate improvements in behavioral test scores, reductions in corticosterone levels, and prevention of potentially harmful decreases in serum vitamin D. Additionally, the combination of vitamin D and SSRI antidepressants appears to have a synergistic effect in addressing depression and its symptoms. Another study involving supplementation with vitamin D and magnesium in obese women with mild to moderate depressive symptoms showed beneficial influences on mood, serum levels of BDNF, inflammation, and SIRT1. However, no significant associations between baseline 25(OH)D concentrations and depression symptoms, nor did vitamin D supplementation demonstrate a beneficial effect on depression symptoms, despite adequate dosage and duration in vitamin D-deficient but otherwise healthy individuals. These results suggest that using vitamin D supplementation to alleviate depression symptoms in individuals without clinically significant depression may not be justified. Further large-scale studies are necessary, particularly in populations with existing depressive or psychiatric disorders.

Similarly, another study in Peshawar, Pakistan, highlighted a high prevalence of vitamin D deficiency among individuals with depression, particularly among females. While the correlation between vitamin D and depression was explored, the study underscores the need for further investigation into the relationship between vitamin D deficiency and depression in this

population. In summary, our findings underscore the complexity of the relationship between vitamin D and depression. While some studies suggest potential benefits, including improvements in mood and inflammatory markers, others, including ours, fail to demonstrate significant effects on depression symptoms. Further research, particularly in diverse populations with varying degrees of depression severity, is essential to elucidate the role of vitamin D in depression management.

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