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Vitamin D Supplementation Ameliorates Severity of Major Depressive Disorder

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Abstract

Major depressive disorder is a serious neuropsychiatric disease that leads to significant impairment in social functioning and increased morbidity and mortality. Low vitamin D (25-OH D) levels have been hypothesized to contribute to the pathophysiology of MDD. To investigate the therapeutic role of vitamin D in MDD, we recruited 62 male and female patients diagnosed with MDD and randomized them into two groups: the first group (49 patients) received vitamin D supplementation as cholecalciferol vitamin D_3 (50,000 I.U.) for 3 months, in addition to standard of care (SOC) which included pharmacological treatment and psychological support, and the second group (13 patients) received only SOC without vitamin D supplementation for 3 months. The Beck depression inventory (BDI) scale was used to assess the severity of MDD symptoms. Immunoassays were utilized to determine levels of serum vitamin D_3 and serotonin in all patients. The results showed significant gender differences; female patients showed the most improvement in their depressive symptoms after 3-month vitamin D supplementation. Females with moderate, severe, and extreme depression had significantly lower BDI scores after vitamin D treatment ($p < 0.05$). Among males, only those diagnosed with severe depression showed significant improvement in their BDI scores ($p < 0.05$). Serum serotonin levels were significantly increased after vitamin D supplementation compared to baseline in both male and female patients. No significant changes in other biochemical parameters were detected between the two groups. These findings suggest that vitamin D supplementation may ameliorate symptoms of MDD, particularly in females, via a serotonin-dependent mechanism.

Keywords Antidepressant drugs · Beck depression inventory (BDI) · Major depressive disorder (MDD) · Serotonin · Vitamin D

Introduction

Major depressive disorder (MDD) is a common psychiatric disorder that leads to significant impairment in daily functioning and increased medical morbidity and mortality (Spijker et al. 2014; Ustün et al. 2004). MDD symptoms include persistent sadness, anxiety, sleep dysregulation, loss of appetite, poor concentration, and a loss of interest in social activities (Ustün et al. 2004). Imbalances in different neurotransmitters, including serotonin, dopamine, and noradrenaline, have been postulated to contribute to the pathophysiology of MDD (Lopresti et al. 2013; Maletic et al. 2007). Polymorphic genetic variants, dysregulated production of inflammatory biomarkers including cytokines [interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α] and chemokines [CXCL4, CXCL7, and CCL4], and subsequent hyperactivation of the immune system have also been linked to the etiology of MDD (Tamatam et al. 2012; Farooq et al. 2017; Leighton et al. 2018; Zou et al. 2018) and constitute the foundation of the "inflammatory hypothesis of depression" (Gałecki and Talarowska 2018).

Vitamin D, also known as calciferol, is a fat-soluble steroid hormone that is required to absorb calcium from the gut into the bloodstream (Carlberg 2017). It comes in two main forms: vitamin D2 (ergocalciferol), which is largely human-made and added to foods, and vitamin D3 (cholecalciferol), which is

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synthesized in the skin of humans from 7-dehydroxycholesterol (Jones et al. 1998; Bikle 2014). Vitamin D plays an important role on the formation and maintenance of healthy bones. Deficiencies in vitamin D levels have been associated with metabolic diseases including obesity, diabetes mellitus, insulin resistance, and hypertension (Park et al. 2018), as well as with neuropsychiatric diseases such as schizophrenia, Parkinson's disease, Alzheimer's disease, depression, and cognitive impairment (Penckofer et al. 2010; Kesby et al. 2011). A fat-soluble hormone and its metabolites have special mechanisms for their delivery in the aqueous bloodstream. Importantly, a binding protein carries endogenously synthesized forms of vitamin D, whereas dietary forms are carried within lipoprotein particles. This may result in distinct bio-distributions for sunlight-derived, versus endogenously synthesized vitamin D hormones (Demer et al. 2018).

A myriad of genetic, immunological, neuroendocrinological, and hormonal factors may play a role in the pathophysiology of MDD (Bifulco et al. 1998; Bloch et al. 2005; Banks et al. 2006). These factors may alter reactions to stressors and the processing of emotional information. Genetic studies have shown that MDD patients may have a genetic predisposition to the condition (Craddock and Forty 2006). Evidence points to neuroanatomical and neurochemical elements in the pathophysiology of depression, including dysregulation of the biological feedback mechanisms that regulate the release and metabolism of different neurotransmitters (Brigitta 2002; Ménard et al. 2016). Insufficient intake of vitamin D is thought to potentially contribute to these neuropathological mechanisms, and vitamin D supplementation was reported to improve symptoms of depression (Spedding 2014).

In Saudi Arabia, studies have shown an increasing incidence of MDD, with a higher prevalence in females than males (Al-Khathami and Ogbeide 2002; Al-Modayfer and Alatiq 2015). Studies have also shown that there is a high prevalence of vitamin D deficiency among the general population in Saudi Arabia in spite of the sunny and hot weather many months of the year (Elsammak et al. 2011; Al-Alyani et al. 2018). Cultural apparel traditions, metabolic deficits including diabetes mellitus and obesity, as well ethnic differences in the absorption of calcium and vitamin D gut from the gut may have contributed to these deficiencies (Elsammak et al. 2011; Memish et al. 2014). Accordingly, it is highly possible that vitamin D deficiency may have contributed to the increased diagnosis of MDD patients in this population. The aim of this study was to examine the effect of vitamin D supplementation on depressive symptoms among Saudi MDD patients using the Beck depression inventory (BDI; Beck et al. 1961). We also investigated the biochemical effects of vitamin D supplementation on levels of vitamin D and serum serotonin to examine the potential role of serotonin in mediating the actions of vitamin D.

Materials and Methods

Study Design

This study was approved by the Unit of Biomedical Ethics at the Faculty of Medicine at King Abdulaziz University in Jeddah, Saudi Arabia. All participants signed a form indicating their informed consent. We recruited 62 patients from the psychiatry clinic at the King Abdulaziz University Hospital. The study included adults (18–65 years old) who have been diagnosed with MDD according to criteria from the *5th version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Patients with abnormal PTH levels and renal or hepatic impairment were excluded from the study. All patients received standard of care (SOC), which included treatment with selective serotonin reuptake inhibitors (SSRIs) and psychotherapy during the trial. Participants were randomized into two groups. The first group ($n = 49$) received weekly oral tablets of 50,000 IU of vitamin D (Calciferol) in addition to SOC for the 3-month duration of the study. The second group ($n = 13$) received SOC without vitamin D supplementation for 3 months.

Study Procedures

Gender, age, marital status, level of education, smoking status, and BMI were recorded for all participants. All participants filled the Beck depression inventory (BDI). The BDI is a self-report questionnaire containing 21 questions about participant depression symptoms. It has a score range of 0–63 points. The BDI scores are typically used to determine the severity of depressive symptoms from mild to moderate to severe to extreme as shown in Table 1.

Biochemical Parameters

Serum vitamin D and serotonin levels were measured at the time of recruitment to establish baseline for every patient and then repeated after 3 months. Blood samples from all patients

Table 1 Relative scores of Beck depression inventory (BDI) to symptoms of depression

Total score	Levels of depression
1–10	Considered normal
11–17	Mild mood disturbance
17–21	Borderline clinical depression
21–31	Moderate depression
31–40	Severe depression
Over 40	Extreme depression

BDI questionnaire derived from (Jorde et al. 2008) and (Kjærgaard et al. 2012)

were centrifuged at 2000 g for 10 min, and the sera were collected and aliquoted in Eppendorf tubes then stored at −80 °C until analysis, all within 2 h of the blood draw. Serum 25-hydroxyvitamin D (the most reliable indicator of vitamin D levels) was measured with automated chemiluminescent immunoassay technology. The results were determined via a calibration curve, and the coefficient of variations (CV) for inter-assay analyses was 5.8% at a 25-hydroxyvitamin D level of 39.5 nmol/l and 3.1% at 121.25 nmol/l. Serum calcium, magnesium, and phosphate were determined by a full automated system (Dimension Vista® System) using the required kit for each parameter. Serum serotonin was measured in duplicate with a commercial enzyme immunoassay technique (Abcam's serotonin in vitro competitive ELISA Kit) (Cat. No. ab 133,053 Abcam, Cambridge, UK).

Statistical Analysis

Data were presented as mean ± standard error of mean (SEM) and graphed using GraphPad (version 6.0, Prism, CA, US). We used the t-test and one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test to compare the means of the study parameters for the two independent groups.

Results

The demographics of the participants are presented in Table 2. Vitamin D levels did not change from baseline at 3 months in the group that did receive vitamin D supplementation (Baseline, 53 ± 7.0; 3 months later, 50 ± 11). In the group treated with vitamin D, the levels rose significantly at 3 months in male and female subjects in comparison to the baseline levels [Fig. 1].

Mildly depressed male participants showed no significant changes in their BDI scores after vitamin D supplementation. However, males with moderate, severe, and extreme depression showed significant decreases in their BDI scores after vitamin D supplementation ($p < 0.05$). Female subjects diagnosed with mild depression also displayed no significant differences in their BDI scores after vitamin D supplementation. Females with moderate, severe, and extreme depression had significantly ($p < 0.05$) lower BDI scores after vitamin D supplementation, respectively. For female patients with moderate depression, BDI scores changed from 28 ± 1.2 to 23 ± 1.4 ($p < 0.05$). For severe depression, BDI scores improved from 36 ± 0.9 to 27 ± 3.6 ($p < 0.05$), and for female patients with extreme depression, BDI scores improved from 44 ± 1.5 to 34 ± 2.5 ($p < 0.05$) [Fig. 2].

Serum serotonin levels significantly increased after (A) vitamin D supplementation when compared to serum levels at the baseline before (B) for both male (B, 330 ± 68 vs. A, 534 ± 25 ng/ml, $p < 0.05$) and female patients (B, 278 ± 34 vs. A, 483 ± 14 ng/ml, $p < 0.0001$). Patients who did not receive vitamin D supplementation did not display any changes in their serum serotonin levels after 3 months when compared to their baseline (B, 396 ± 54 vs. A, 486 ± 51 ng/ml) [Fig. 3].

Table 2 Demographics of the study population

Parameter	Mean ± SEM
Age (years)	41.5 ± 1.8
Body mass index (BMI)	32.6 ± 2.9
Marital status	Single 18%
	Married 78%
	Divorced 4%

Discussion

Depression is a global mental health problem (Lopez-de-Andrés et al. 2015). The currently approved pharmacotherapies for MDD are not always effective in achieving complete remission of symptoms or preventing relapse and may be associated with undesirable side effects (Shinohara et al. 2019). There is a continued need for new interventions or novel pharmacotherapies to augment and improve the therapeutic benefits of standard antidepressant treatments. Interestingly, over 1 billion people worldwide have vitamin D deficiency or insufficiency (Holick 2007). Vitamin D receptors and 1-α-hydroxylase enzymes are widely expressed in the central nervous system, including the limbic system (Eyles et al. 2005; Lewis-Fernandez et al. 2005). It has been hypothesized that low serum vitamin D levels may contribute to the severity of MDD symptoms and vitamin D supplementation would improve these symptoms (Penckofer et al. 2010). In this study, we provided an evidence to support this hypothesis, as our data indicated that vitamin D supplementation improved depression scores in the MDD patients enrolled in the clinical trial.

Low levels of vitamin D have been identified in patients with MDD and other mood disorders. However, studies examining vitamin D supplementation to normalize vitamin D levels and subsequently improve symptoms of MDD and mood disorders produced inconsistent results (Haines and Park 2012). To date, no reliable data are available on the therapeutic benefits of vitamin D in MDD patients as well as in subjects with seasonal affective disorder or healthy subjects with seasonal mood changes (Harris and Dawson-Hughes 1993; Oren et al. 1994). For example, a clinical trial showed significant evidence of modest improvement in BDI scores after 1 year of vitamin D supplementation (Bertone-Johnson 2009). Another study found that weekly administration of 50,000 IU D2 in women who had significant depressive

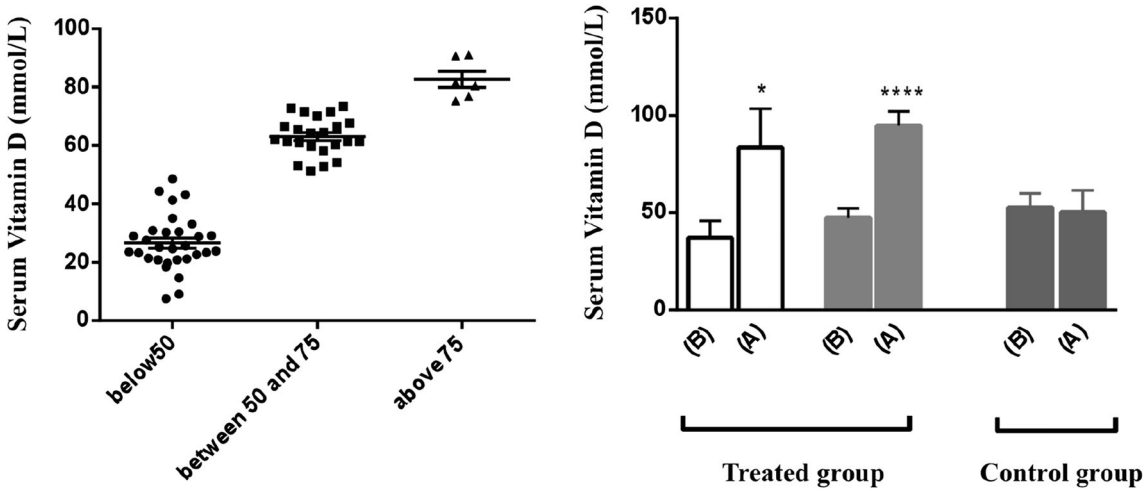

Fig. 1 Serum vitamin D levels in MDD patients
(A) Vitamin D baseline. (B) Comparison between vitamin D levels in male and female before (B; baseline) and after (A) 3 months of vitamin D supplementation in the treated and untreated control groups. The mean values were calculated and plotted, and the error bars represent standard error of the mean (SEM). Data were analyzed by two-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test, and *P* values are shown where the difference between responses of different treatments were determined to be statistically significant. * $P < 0.05$ and **** $P < 0.0001$

symptoms and low 25-(OH) D levels had improved depression, anxiety, and mental health outcomes (Penckofer et al. 2017). In contrast, a study by Kjærgaard and colleagues reported no improvement in depressive symptoms (measured by BDI) in individuals with low serum vitamin D who were randomized to either weekly 40,000 IU D3 or placebo for

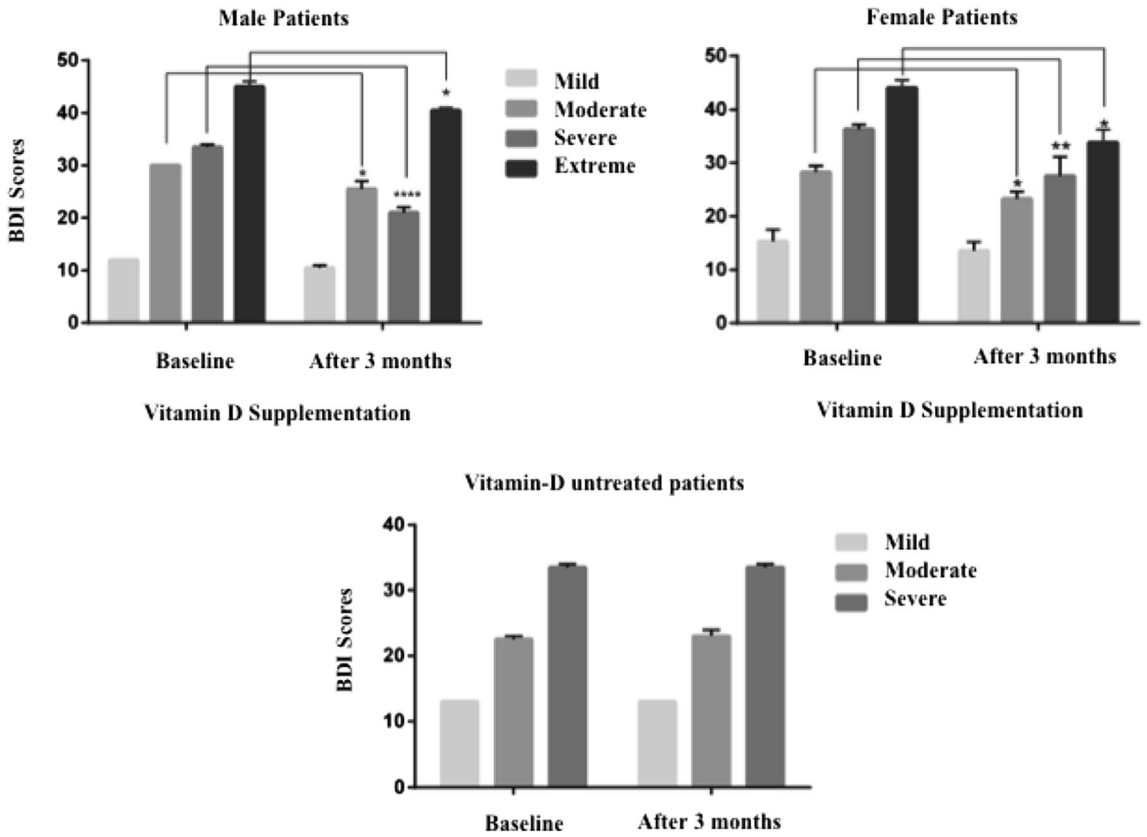

Fig. 2 Beck's depression inventory (BDI) score. BDI scores values were compared between male and female patients supplemented with vitamin D for 3 months or patients who did not receive vitamin D (control group). The mean values were calculated and plotted, and the error bars represent standard error of means (SEM). Data were analyzed bytwo-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test, and *P* values are shown where the difference between responses of different treatments was determined to be statistically significant. * $P < 0.05$ and **** $P < 0.0001$

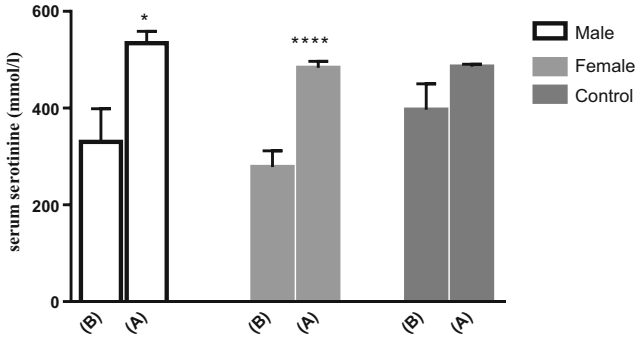

Fig. 3 Serum serotonin levels after vitamin D supplementation
Serum serotonin values in male (M) and female (F) patients before (B) and after (A) vitamin D supplementation. Non-treated control group (P) was included for comparison. Mean value ± standard error of means (SEM) were calculated and plotted. Data were analyzed by two-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test, and *P* values are shown where the difference between responses of different treatments was determined to be statistically significant. $*P < 0.05$, $****P < 0.0001$

6 months. In their post hoc analyses, however, they reported that participants with high BDI scores were significantly less depressed after vitamin D supplementation when compared to placebo-treated patients (Kjærgaard et al. 2012).

It is not clear whether vitamin D deficiency is a contributor to or a consequence to the manifestations of symptoms of depression. MDD patients may be more likely to develop low vitamin D because of lower outdoor activity levels, minimal sun exposure, or reduced intake of nutrients rich with vitamin D (Cuomo et al. 2017). In the present study, serum serotonin was significantly increased in MDD patients after vitamin D supplementation. Brain serotonin is synthesized from tryptophan by tryptophan hydroxylase 2 (Patrick and Ames 2014), which is transcriptionally activated by vitamin D. Accordingly, we provide evidence that optimal levels of vitamin D can promote extracellular serotonin levels and consequently improve symptoms of MDD. This is in agreement with other studies, which reported that vitamin D controls serotonin synthesis (Patrick and Ames 2014, and that vitamin D-induced stimulation of serotonin release mimics the therapeutic actions of SSRIs and other antidepressants drugs, but with lower incidence of side effects (Sabir et al. 2018). Moreover, vitamin D enhances the gene expression of tyrosine hydroxylase, an essential enzyme involved in the synthesis of norepinephrine and dopamine, neurotransmitters that are involved in mood regulation and depression * = (Newmark and Newmark 2007) Taken together, these results suggest that dietary intervention with vitamin D may boost brain serotonin concentrations and ameliorate some of the symptoms associated with MDD without triggering undesirable side effects.

This study has limitations as it lacks placebo-treated patients. However, improved BDI scores coupled with increased serotonin levels in MDD patients suggest that the therapeutic benefits of vitamin D are genuine rather than typical variation among patients. A randomized, double-blind, placebo-controlled trial would provide a definitive evidence for the potential therapeutic benefits of vitamin D in treatment of MDD.

In conclusion, the present study adds additional support to prior data suggesting a relationship between mood regulation, depressive symptoms, and vitamin D level. We report that vitamin D supplementation has therapeutic benefits in moderate and severely depressed patients, particularly in females and overweight participants. This improvement appears to occur by promoting serotonin release and function, and normalizing deficits in serotonergic neurotransmission postulated to occur in MDD patients (Meltzer 1989). Further clinical trials with larger number of participants are still needed to confirm our findings and to validate the adoption of vitamin D as an effective supplement to augment the therapeutic benefits of antidepressant drugs and improve treatment of MDD patients.

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Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

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