Psychiatr. Pol. 2017; 51(3): 437–454
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/66809

The effect of vitamin D3 deficiency on the severity of depressive symptoms. Overview of current research

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Summary

Traditional methods of depression treatment with the use of pharmacotherapy with antidepressants have limited effectiveness. Biological, psychological and environmental causes of depressive disorders are known, but pathophysiology of depression has not been fully explained. Many factors and mechanisms play role in the pathophysiology of depression, one of which may be vitamin D3 deficiency. Deficiency or border level of vitamin D3 is fairly common in the general population and may occur even in one billion people globally. Epidemiological studies show that vitamin D3 or its metabolites do not reach an optimal level in most adults. Even lower than the optimal level may cause clinical symptoms and be one of the risk factors for depression. In the population of patients suffering from depressive disorders deficiency or insufficiency of vitamin D3 occur more frequently than in the general population. The use of vitamin D3in patients with depression may have antidepressant effect. Continuous supplementation may also reduce the risk of recurrence. This article is a review of literature on the possible impact of vitamin D3 deficiency on the prevalence of depression and antidepressant effect of the supplementation. Selection of articles was made by searching the Medline and PubMed databases using specific keywords: depression, vitamin D3 deficiency.

Previous studies on the use of vitamin D3 and its role in prevention and treatment of depressive disorders included too small number of people to clearly assess the effectiveness and safety of supplementation used as adjunctive therapy to antidepressants, as well as and dose range which should be used.

Key words: depression, vitamin D3, depression treatment

Introduction

Depressive disorders are the leading cause of disability [1] and affect overall health, to a similar extent or even sometimes more than other chronic diseases [2]. Traditional methods of depression treatment with the use of antidepressants are of limited effectiveness [3]. In the pathogenesis of depression many factors and mechanisms play role, with

one of them could possibly be deficiency of vitamin D3 [4]. Receptors for calcitriol (active form of vitamin D3) are found in almost all cells. Although the importance of this relationship is not entirely clear, there is no doubt that vitamin D3 has regulatory function in many organs and tissues, and is essential for the proper functioning of calcium-phosphate metabolism, endocrine glands, immune system and nervous system.

The active form of vitamin D3, calcitriol (1,25 (OH) 2) has a structure of a steroid and has endocrine, paracrine and autocrine effect. The impact of vitamin D3 deficiency on the pathogenesis of various diseases, e.g., autoimmune diseases, cardiovascular diseases, infections, osteoporosis, obesity, diabetes, and certain types of cancers has been proven [5, 6]. In recent years, a correlation between very low vitamin D3 levels and neuropsychiatric diseases such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, and also between an impact of vitamin D3 level and cognitive functioning profile has been observed [7–9].

In 1982 the presence of vitamin D3 receptors in the CNS [10], in the brain structures that are involved in processes of emotion and mood regulation (cingulate cortex, hippocampus, thalamus, hypothalamus) was discovered [11]. It has been shown that vitamin D3 significantly affects the functioning of the CNS, taking part in the processes of neuromodulation, regulating the secretion of brain neurotrophic factors, processes of neuroprotection and neuroplasticity [12]. Calcitriol activates the expression of tyrosine hydroxylase, which is involved in the synthesis of catecholamines, increasing the production of dopamine, noradrenaline and adrenaline [13]. It can also enhance cholinergic neurotransmission by activating acetylcholine transferase, an enzyme involved in the synthesis of acetylcholine [14].

Vitamin D3 also affects the increase in the level of neurotrophic growth factors, i.e., NGF and GDNF, NT-3 [15–17]. Recent studies have shown that the dysfunction of NGF, NT-3 and GDNF could be important in the pathogenesis of depressive disorders and schizophrenia [18–23]. Vitamin D3 increases the synthesis of gamma-glutamyltranspeptidase – the enzyme which participates in the synthesis of glutathione and has the function of antioxidant in the brain [24]. Vitamin D3 has therefore, in the central nervous system, protective role against free radicals.

The main source of vitamin D in humans (80 to 90% of vitamin D) is de novo synthesis from 7-dehydrosterol which takes place in the skin under the exposure to ultraviolet UVB with a wavelength of 290 nm to 315 nm. The remaining part of vitamin D is supplied with food. The relationship between the occurrence of mood disorders and insufficient exposure to sunlight is well known and was first observed probably already 2000 years ago [25]. The deficiency or lower than optimal level of vitamin D3 occur in the general population quite commonly. It corresponds to the level of insolation, the climate zone, but also with individual characteristics and may occur even in one billion people on a global scale [26]. The high prevalence of vitamin D3 deficiency was found among the people in the USA and Europe. In the USA, the prevalence of vitamin D3 deficiency is estimated at the level of 25–50% among adults, there is also no direct correlation between the level of vitamin D3 and the level of insolation in the

area of residence [27, 28]. In Europe, the prevalence of deficiency or a border level of vitamin D3 in the general population may be slightly higher and affect even 28–87% of the adult population [29–31].

There are two main sources of vitamin D3 supply: exogenously taken with food and endogenously produced in the body. Vitamin D3 can be supplied with plant products, as ergocalciferol (D2) and with animal products as the active form cholecalcitriol. The rich source of this vitamin are oily fish (salmon, mackerel, tuna, sardines, herring). Endogenous synthesis of vitamin D3occurs in the epidermis and dermis, where the 7-dehydrocholesterol is converted to vitamin D3 under the exposition to ultraviolet B. Vitamin D2 and D3 derived from food is transported to the liver with the use of chylomicrons, while D3 derived from the production in the skin is transported by the blood. In the liver, both forms are hydroxylated to 25-hydroxyvitamin D(25)(OH)D. 25 (OH)D is hydroxylated to 1,25(OH)2 D by 1-alpha-hydroxylase in the nephrons in the kidneys. Receptors for vitamin D3 VDRs can be found in various tissues and organs of the body. VDRs receptor activation by vitamin D3 activates the transcription of genes. 1,25(OH)2D also binds with VDRs receptors located in cell membranes mediating various processes in the body.

The absolute vitamin D deficiency can be recognized when level of 25(OH)D is lower than 10 ng/dl (25 nmol/l). Cases when the level is in the range of 10–30 ng/dl (25–75 nmol/l) can be defined as a relative deficiency of the vitamin. In accordance with the recommendations of the International Panel of Experts (*Wytyczne suplementacji witaminy D dla Europy Środkowej* (Guidelines of vitamin D Supplementation for Central Europe), Endokrynologia Polska 2013) [32] in order to maintain the recommended levels (≥ 30 ng/ml) a supplementation of 2,000 IU of vitamin D/day should be administered to adult patients. In patients with the deficiency of D3, the supplementation of 7,000–10,000 IU/day should be implemented until reaching the normal values of D3, then it is recommended to continue the treatment with a typical maintenance dose.

Methodology

Selection of articles have been made searching the Medline and Pubmed databases for publications using keywords: depression, deficiency of vitamin D3, with the overall result of the search of 653 publications. Inclusion criteria for the analysis were the publication year from 2009 to 2015. For the present article population studies evaluating the effect of vitamin D3 on the incidence of depressive disorders and studies evaluating the impact of supplementation with vitamin D3 on the reduction of depressive symptoms were taken into account. Summary of the results regarding the articles meeting the inclusion criteria are shown in Diagram 1.

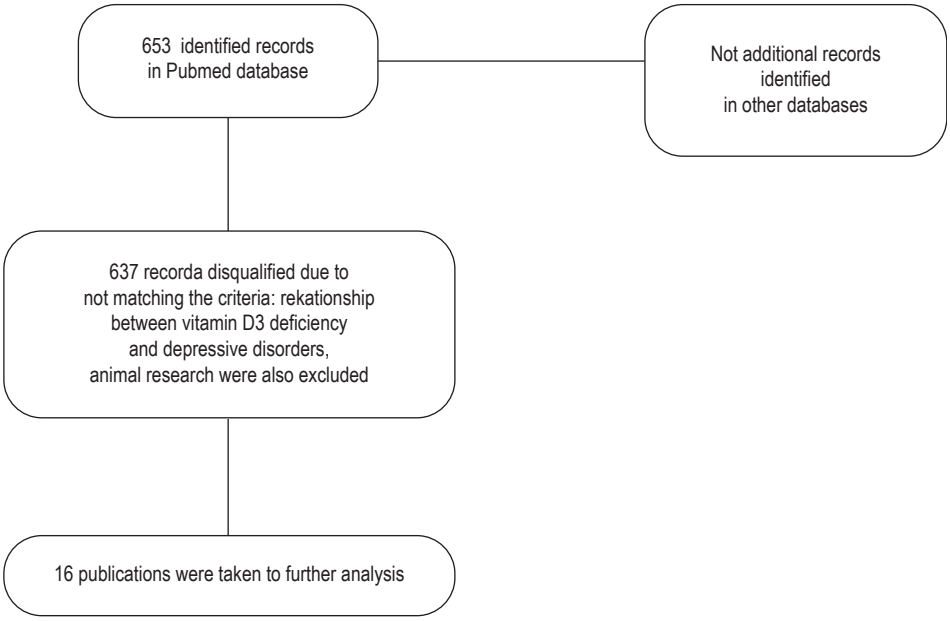

Diagram 1.

Aims

The aim of this work was to review the results of the recent studies investigating the effect of vitamin D3 deficiency on the incidence and severity of depressive symptoms and the possibility of using supplementation as an additional method of antidepressant treatment. In the first part the results of epidemiological studies regarding vitamin D3 deficiency and the prevalence of depressive disorders will be presented. In the remaining part of this article presents a review of studies evaluating the effects of supplementation with vitamin D3 on the reduction of depressive symptoms.

Epidemiological studies regarding a correlation between vitamin D3 deficiency and the prevalence of depressive disorders

Database analysis indicates that all over the world many studies confirming a link between vitamin D3 deficiency and the prevalence of mood disorders had been conducted. The population study conducted in Norway between 2007 and 2008 including 10,086 patients showed that the low level of vitamin D3 is a predictor of depressive disorders. To evaluate the mental state SCL-10 was used (Hopkins Symptoms Check List 10). The SCL-10 score ≥ 1.85 was considered as a criterion of depression. The correlation between low levels of vitamin D3 and the prevalence of depressive disorders was statistically significant, even after taking into account such factors as gender,

physical activity, economic status, chronic illness, season, age, BMI [33]. The correlation between low levels of vitamin D3 and severity of depressive symptoms was higher among women.

The results of the analysis conducted by Swedish researchers seem interesting, as they have compared the levels of vitamin D3 in the serum in the population of patients taking psychotropic medications who have a suicide attempt, in the population with a diagnosis of depression and healthy control group [34]. The study involved 59 patients who received psychiatric treatment and had a history of suicide attempt, 17 depressed patients without a history of suicide attempts and 14 healthy subjects in the control group. In the group of patients who had a suicide attempt, the average level of vitamin D3 was significantly lower than in patients with depression without a history of suicide attempts and in the control group. The deficiency of vitamin D3 (defined as the concentration of vitamin D3 in serum < 20 ng/ml) was found in 58% of patients with a history of suicide attempt. In contrast, in the group of patients suffering from depression who have never tried to commit suicide, vitamin D3 deficiency was found in 29% of patients. A correlation between low levels of vitamin D3 and an increase in the concentration of pro-inflammatory cytokines IL-6 and IL-1 beta in the blood has also been demonstrated in this study. Researchers indicate that there is the relationship between dysregulated immune system and the increased risk of suicide in the population of psychiatric patients. In the group of patients after a suicide attempt low levels of vitamin D3 and increased levels of IL-1beta in serum were found. In patients suffering from depression without the history of suicide attempt, a correlation between levels of vitamin D3 and the level of IL-6 was found.

Other studies also indicate a possible immunomodulatory effect of vitamin D3, which may explain the impact of this vitamin supplementation on the presence of depressive disorders. Immunomodulatory effect of D3 is probably related to the increase of anti-inflammatory cytokines, i.e., IL-10, IL-4, IL-5 and reduction of proinflammatory cytokines, i.e., IL-1beta, IL-2, IL-6, IFN-gama, TNF-alpha, secretion [35, 36]. The authors of these reports suggest that assessing the level of vitamin D3 and, in case of deficiency, introduction of the supplementation can be beneficial for the treatment of depressive disorders.

The results of studies conducted in the Netherlands within the program Netherlands Study of Depression and Anxiety-NESDA confirmed the correlation between low levels of vitamin D3 in the serum and the prevalence of depressive disorders [37]. The study involved 1,102 patients with diagnosed depressive episode, 790 persons who were in remission and 494 healthy subjects in the control group. In the group of depressed patients and in patients successfully treated for depression who were in remission, the vitamin D3 level was significantly lower than in the control group. In subjects with more severe vitamin D3 deficiency, more symptoms of depression were reported. During the two-year follow-up, increase of the risk of depression recurrence was found in the population of patients with vitamin D3 deficiency. Higher levels of vitamin D3 correlated with a shorter duration of a depressive episode.

The link between vitamin D3 deficiency and the presence of depressive symptoms was also confirmed by researchers in the USA [38]. 185 female psychology students

were included to this study. Inclusion criteria were as follows: female, age 18–25, weight at least 49 kg. Researchers excluded pregnant women. During a four-week follow-up, level of vitamin D3 was measured at weekly intervals. At the same time the mental state of the participants was evaluated. To evaluate the mental state the CES-D scale was used (Center for Epidemiologic Studies Depression). A cut-off point of 16 points was considered to confirm the occurrence of depressive symptoms. Vitamin D3 insufficiency, which was defined as < 30 ng/ml, was found in 42% of the participants in the first week and 46% after four weeks of observation. The study showed that in the group of patients with vitamin D3 insufficiency at baseline depressive symptoms occurred more frequently during the next four weeks of observation in comparison to the population with normal vitamin D3 level. This correlation was statistically significant even after taking into account such variables as season, body mass index (BMI), ethnicity, diet, physical activity, time outside. Depressive symptoms was found at baseline in 26% of patients with normal levels of vitamin D3. In contrast, in the population of patients with vitamin D3 insufficiency depressive symptoms occurred in 45%of participants.

The prospective study conducted by Hoang et al. [39] was based on the data collected within Cooper Center Longitudinal Study (CCLS). The cross-sectional study conducted at the Cooper Clinic in the period from November 2006 to October 2010 included a total of 12,594 patients. 11,031 patients had no depressive episodes in the past, and 1,563 of subjects previously suffered from depression. The level of vitamin D3 in serum of each of the subjects was measured. Depression was assessed with the use of the Center for Epidemiologic Studies Depression Scale (CES-D). Depressive episode was diagnosed in patients who obtained at least 10 points in the CES-D. In addition, participants of the study filled out a questionnaire about the occurrence of depressive episodes in the past. Questionnaire data were further verified during an interview conducted by a doctor.

Deficiency of vitamin D3 was found in 50.7% of the participants (25(OH) D < 20 ng/ml). In the study there was no difference in the average level of vitamin D3 between people with or without medical history of depression. It was found, however, that in the population of patients who had previously suffered from depression there is a correlation between the occurrence of depressive symptoms in the present study and reduced levels of vitamin D3. This correlation was not observed in patients who had not suffered from depressive disorders. It was also found that in all of the surveyed populations the higher levels of vitamin D3 were associated with a reduced risk of depressive episode in the period studied by the authors.

The results of the meta-analysis conducted by Ju et al. [40] were crucial for further work regarding the role of vitamin D3 in the development of depressive disorders. The authors summarized the results of 11 cross-sectional studies enclosing a total of 43,137 participants and 5 cohort studies enclosing 12,648 participants. A statistically significant relationship between the prevalence of depression and the level of 25(OH)D were found in 5 out of 11 cross-sectional studies, and in 2 out of 5 cohort studies. The authors demonstrated that increase in the level of vitamin D3 by 10 ng/

ml is associated with risk of depression reduction of about 8% in the cohort studies and about 4% in epidemiological studies. The authors believe that the administration of vitamin D3may play important protective role. It should be noted that 30 ng/ml is generally considered as the lowest safe level, but vitamin D3 deficiency is diagnosed only if the level is below 20 ng/ml. It can be assumed that those whose level of vitamin D3 is between these two values, do not have absolute vitamin D3 deficiency but are in the group of higher risk.

Preventative daily dose of vitamin D3 of at least 1,000 IU is, in the author's opinion, sufficient to cause increase in the level of the vitamin of about 10 ng/ml. It is also sufficient to exceed the level of 30 ng/ml in more than half of the study population, which should significantly reduce the risk of depressive disorders. The correlation between the occurrence of depression and insufficient levels of vitamin D3 was more explicitly marked in the elderly (than in younger patients) and in Western Europeans.

Elderly patients are at risk of vitamin D3 deficiency due to decreased vitamin D3 skin synthesis, lower exposure to sunlight, less time outdoors and reduced ability to produce sufficient amounts of calcitriol due to renal hydroxylation of vitamin D decrease with age. All these factors cause an increased risk of vitamin D insufficiency in this population, and thus may affect the possible increased risk of depression if the importance of this vitamin deficiency for the risk of depression was finally confirmed.

A limitation of the study conducted by Ju et al. [40] was the inclusion to the analysis both studies in which the diagnosis of depression was based on the structured clinical interview or clinical diagnosis based on the DSM criteria as well as the studies, which used solely self-assessment questionnaires. This last approach poses a risk of including to the study patients with subclinical symptoms and patients who do not meet the clinical criteria of the diagnosis of depression as depressed patients. According to the authors of this study, including only studies which used the structured clinical interview or the DSM or ICD criteria to diagnose depression would result in the omission of significant parts of the data, on the other hand, the analyzed population would then undoubtedly be more homogenous.

Anglin et al. [41] conducted a meta-analysis including 10 cross-sectional studies, 3 cohort studies, one placebo-controlled study (a total of 31,424 participants). In the population of patients suffering from depression the mean level of vitamin D3 was lower in comparison to the control group (SMD = 0.60, 95% CI 0.23–0.97). The results of the cross-sectional studies demonstrated an increased risk of depression in patients with the lowest levels of vitamin D3 in comparison to the group with the highest levels (OR = 1.31, 95% CI 1.0–1.71). The results of cohort studies showed an increase of the risk of depression in the group with the lowest levels of vitamin D3 as compared to the group with the highest level (HR = 2.21, 95% CI 1.40–3.49).

Due to the fact that diseases of the cardiovascular system are a major public health problem and the leading cause of death both among women and men, researchers from the USA decided to investigate the relationship between levels of vitamin D3 and the risk of depression in patients with diseases of the cardiovascular system [42]. 7,358 patients with the history of cardiovascular disease (coronary heart disease, myocardial

infarction, congestive heart failure, stroke, transient ischemic stroke, atrial fibrillation or peripheral vascular disease) who had never suffered from depression were enrolled in the study. A prospective analysis of American databases including cardiac patients was carried out. The serum levels of vitamin D3 and parathyroid hormone (PTH) were assessed in individuals participating in the study. Mean follow-up was 1.07±1.13 years. The patients were divided into 4 groups according to the level of vitamin D3: optimal (> 50 ng/ml, $n = 367$), normal (31–50 ng/ml, $n = 2{,}264$), low (16–30 ng/ml, $n = 3{,}402$), and very low (≤ 15 ng/ml, $n = 1{,}325$). Two-thirds of the patients (64.2%) had vitamin D insufficiency. Most cases of depression were reported in patients with very low levels of vitamin D3. The risk of depression was greater in patients with vitamin D3 insufficiency, three times higher in patients with very low levels of vitamin D3, and twice as high in patients with low vitamin D3 levels compared to patients with normal level of the vitamin. It was also found that the level of vitamin D3 is a predictive factor of depressive disorders regardless of the level of PTH.

The importance of maintaining the proper level of vitamin D3 as a factor essential for maintaining a balanced mental state was also confirmed by the study conducted by Gur et al. [43]. The authors assessed the impact of vitamin D3 deficiency during pregnancy on the incidence of postpartum depression. The study included women in the second trimesters of pregnancy (24–28 weeks). 179 women completed the study. The study excluded women with the risk factors of postpartum depression and women who experienced complications during labor or health complications in a child. All participants had vitamin D3 levels determined in the second trimester of pregnancy, 1 and 6 weeks after labor and 6 months after labor. The mental state was assessed in the same time intervals. To assess the prevalence of postpartum depression the Edinburgh Postnatal Depression Scale (EPDS) was used. The higher incidence of postpartum depression has been demonstrated in all three assessments after labor among women with vitamin D3 deficiency during pregnancy. The relationship between levels of vitamin D3 and severity of postpartum depression symptoms were statistically significant for all measurements ($p = 0.003$, $p = 0.004$ and $p < 0.001$).

To summarize this part of the review: the majority of studies (some of them with a large sample size) found a significant correlation between the prevalence of depression and vitamin D3 deficiency. The occurrence of depression was associated not only with an absolute deficiency – it seems that also the levels of vitamin lower than optimal increase the risk of depressive disorders.

The short review of the results of the studies discussed above is included in Table 1.

Table 1. **Epidemiological studies assessing the correlation between the deficiency of vitamin D3 and the occurrence of depressive disorders**

Name of research	Scale used to measure the severity of depressive symptoms	What was assessed	Size of the group	Conclusions	Comments
May et al. [42] 2010		The impact of vitamin D3 level on the occurrence of depressive disorders	7,358 participants	Greater risk of depressive episode among patients with vitamin D3 deficiency compared to groups with normal level	Prospective study
Honag et al. [39] 2012	CES-D	Assessment of the impact of vitamin D3 level on the occurrence of depressive disorders	12,594 participants	Reduction of the risk of depressive episode in patients with higher level of vitamin D3	Prospective study
Kjærgaard et al. [33] 2011	SCL-10	Relationship between occurrence of depressive disorders and the serum level of vitamin D3	10,086 patients	Low level of vitamin D3 was a predictor of depressive disorders	Population study
Ju et al. [40] 2013		Assessment of the impact of vitamin D3 level on the risk of occurrence of depressive disorders	11 population studies (43,137 participants) 5 cohort studies (12,648 participants)	Reduction of the risk of depression with the increase of vitamin D3 level	Meta-analysis of epidemiological and cohort studies
Anglin et al. [41] 2013		The assessment of the relationship between the level of vitamin D3 and the occurrence of depressive disorders	31,424 participants	The increase of the risk of depression with the decrease in the level of vitamin D3	Meta-analysis of 10 cross-sectional studies, 3 cohort studies, 1 study with case-control group
Milaneschi et al. [37] 2014		Comparison of the level of vitamin D3 during the episode of depression with a population in remission and healthy control group	1,102 patients diagnosed with depression episode, 790 patients in remission, 494 participants in control group	Lower level of vitamin D3 in the group of patients with depression and patients in remission compared to the control group	Greater severity of depressive symptoms in patients with severe vitamin D3 deficiency. Increase of risk of depressive episode in patients with D3 deficiency

table continued on the next page

Grudet et al. [34] 2014		The assessment of vitamin D3 levels in patients with a history of suicide attempt, depressed patients without a history of suicide attempts and healthy subjects in the control group	Suicide attempters (n = 59), non suicidal depressed patients (n= 17), healthy controls (n = 14)	Suicide attempters had significantly lower mean vitamin D levels than non-suicidal depressed patients and healthy controls	Correlations between low vitamin D3 level and increase of the inflammatory cytokine concentration (IL6,IL1-beta) has been shown
Gur et al. [43] 2014	7.6% of women were supplemented regularly with vitamin D3 at the dose of 1,200 IU/d (at least 3 days a week); 84.6% were supplemented with vitamin D3 at the dose of 400 IU/d; 7.6% did not receive vitamin D3	The impact of vitamin D3 deficiency on the occurrence of postpartum depression	179 participants	More frequent occurrence of postpartum depression among women, who had vitamin D3 deficiency during pregnancy	The survey excluded women with risk factors for postpartum depression
Kerr et al. [38] 2015		Comparison of the occurrence of depressive disorders in the group of people with normal level of vitamin D3 to the group with D3 deficiency	185 women	More frequent occurrence of depressive disorders in the group with vitamin D3 deficiency compared to groups with normal level. Lower level of vitamin D3 at baseline was a predictor of depressive disorders during 4 weeks of observation	Less severe depressive symptoms in patients studied in the autumn compared to subjects studied in the winter and spring

Studies evaluating the effect of vitamin D3 supplementation on the reduction of depressive symptoms

Since it have been proved that a specific factor (vitamin D3) deficiency increases the risk of depression, further research aimed to verify that supplementing this factor has a therapeutic effect. Although the existence of such a relationship seems to be logical, it does not necessarily have to be confirmed in reality. As an example, the relationship between reduced levels of estrogen in women and risk of depression has been confirmed, in spite of this estrogen has no significant antidepressant activity. Therefore, the finding of a relationship between deficiency and the prevalence of the illness is not sufficient to confirm the therapeutic effect of a supplementation.

Gowda et al. [44] conducted a meta-analysis of the studies evaluating the antidepressant efficacy of vitamin D3 preparations. The analysis included 9 randomized placebo-controlled trials with a total of 4,923 participants. The analysis included studies with vitamin D3 supplementation used as monotherapy or in combination with antidepressants. The analysis included adult patients with depression diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or with the use of scales assessing the prevalence of mood disorders. The patients with a diagnosis of bipolar disorder and schizoaffective disorders were excluded from the study. This analysis did not confirm the effectiveness of vitamin D3 supplementation in reducing the symptoms of depression. It should be, however, emphasized that most of the participants of the study had normal levels of vitamin D3 in the serum, which could weaken the supposed antidepressant effect of vitamin D3 supplementation. In addition, most of the participants had mild depressive disorders. The authors suggest that patients with more severe depressive symptoms and a greater vitamin D3 deficiency, can obtain more benefits from vitamin D3 supplementation. It should also be noted that the studies differed in terms of dose and time of calcitriol supplementation, which could have an impact on weaker antidepressant effect of vitamin D3 preparations.

The results of another study conducted in the USA by Shipowick et al. [45] confirmed the antidepressant effect of vitamin D3. Nine female patients with a deficient or insufficient levels of vitamin D3 (< 40 ng/ml), with concomitant depression were classified to participate in this study. Before entering the study the levels of vitamin D3 in the serum were determined and the symptoms of depression were assessed using the BDI-II. Mean scores in the BDI-II was 31.8±4.79. All patients received the supplementation of vitamin D3at a dose of 5,000 IU per day during 8-weeks period. After 8 weeks, the level of vitamin D3 in the serum was measured and the mental state of participants was assessed. Six patients completed the study. In all subjects the severity of depressive symptoms was reduced, the mean scores in the BDI-II endpoint was 21.2±11.7. Supplementation of vitamin D3 resulted in the increase of this vitamin levels by 27 ng/ml on average and a reduction in the BDI-II score by 10 points on average.

Högberq et al. [46] confirmed impact of vitamin D3 supplementation on the severity of depressive symptoms in a population of teens. The study included 54 adolescents suffering from depression. 48 patients were deficient in vitamin D3 (defined as a level <

60 nmol/l) and qualified for supplementation for 3 months. For the first month 4,000 IU of vitamin D3 per day and 2,000 IU for another 2 months were administered orally to the participants. To assess the mental state the following scales were used: WHO-5 Well-being Scale (WHO-5), MFQ-Mood and Feelings Questionnaire and the scale of vitamin D3 deficiency before and after 3 months of supplementation. All patients also received psychotherapy. Among the participants of the study, two patients with concomitant ADHD also received methylphenidate. Antidepressants were used in four subjects (three patients received fluoxetine and one patient duloxetine). The improvement of the mental state in the WHO-5 and MFQ-S scales and improvement in eight of the nine points in vitamin D3 deficiency scale were found in the study. The mean vitamin D3 level was 41 at baseline and 91 nmol/l ($p < 0.001$) after 3 months of supplementation. The improvement in well-being ($p < 0.001$) and improvement in such parameters as depressive feelings, irritability, fatigue, mood swings, sleep disturbances, feeling of weakness, the ability to concentrate attention and perception of pain, were statistically significant ($p < 0.05$ or $p < 0.01$), as well as the improvement on the MFQ-S found after three months.

Effect of vitamin D3 supplementation on the incidence of mood disorders has also been confirmed in the Norwegian cross-sectional double-blind, placebo-controlled study conducted by Jorde et al. [47] in a population of 441 overweight or obese people. 334 people completed the study. Before the inclusion to the study the level of vitamin D3 in serum was measured and mental state was assessed with the use of the 21-point scale BDI-II. The patients taking antidepressants were excluded. Subjects were randomly assigned to three groups, the first group of patients received 2 pills of vitamin D3 (40,000 IU per week), the second group received 1 pill of vitamin D3 (20,000 IU per week) and one placebo pill per week, while the third group of patients received only two placebo pills. The study lasted 12 months. Patients in whom the level of vitamin D3 in serum did not exceed 40 nmol/l had higher mean scores in BDI-II in comparison to the population with the level of vitamin D3 $\geq$ 40 nmol/l (6.0 points vs. 4.5 points in BDI-II on average). After one year in both groups treated with vitamin D3 a statistically significant improvement in the mental state was also demonstrated compared to the placebo group. The reduction in parathyroid hormone levels and an increase of calcium concentration in serum in the groups receiving supplementation of vitamin D3 was also observed, which is the obvious consequence of vitamin D3 supplementation, indicating, however, that vitamin D3 deficiency had an impact on physiological functions.

Stokes et al. [48] demonstrated a beneficial effect of vitamin D3 supplementation on the reduction of depressive symptoms in the population of patients with chronic liver disease. Vitamin D3 deficiency coexisting with depressive disorders can be found in patients with chronic liver disease more frequently than in the general population. 111 patients were included in the study. To assess the prevalence of depression the Beck Depression Inventory II (BDI-II) was used. 77 patients (81%) had insufficient level of vitamin D3 (< 30 ng/ml) while depression was diagnosed in 31% of participants (number of points in the BDI-II $\geq$ 14). Patients with vitamin D3 deficiency were en-

rolled to vitamin D3 supplementation at a dose of 20,000 IU per week for 6 months. In patients diagnosed with depression, an inverse correlation between levels of vitamin D3 and the intensity of depressive symptoms have been demonstrated. In the population receiving vitamin D3 supplementation, the severity of depressive symptoms after 3 and 6 months was significantly reduced.

It should be noted that antidepressant effect of vitamin D3 was greater in patients not treated with antidepressants. Presumably patients already treated with antidepressants could have consequently less severe depression, the effect of supplementation of vitamin D3 on the reduction of depressive symptoms in that group could therefore be less visible. 6 months after the end of supplementation, the mental state and the level of vitamin D3 were re-evaluated. In both groups of patients a decrease in the level of vitamin D3 was found 6 months after the end of supplementation. In patients with a diagnosis of depression, decreased levels of vitamin D3 were associated with a relapse manifested in an increase in the BDI-II scores.

Shaffer et al. [49] conducted a meta-analysis of randomized controlled trials evaluating the effects of vitamin D3 supplementation in the population of patients with depression and the group of healthy participants. This study revealed that in the population of patients diagnosed with depression, supplementation of vitamin D3 has a moderate, but statistically significant effect on the reduction of depressive symptoms (2 studies: SMD – standardized mean difference, -0.60; 95 CI, -1.19 to -0.01; $p = 0.046$). In contrast, in the group of patients without depression no benefits from the administration of the preparations of vitamin D3 have been found (5 studies: SMD, -0.04; CI, -0.20 to 0.12; $p = 0.61$).

The effect of vitamin D3 supplementation on the mental state in patients with depressive disorders was also assessed in the meta-analysis published by Spedding et al. [50]. This study introduces the concept of the so-called biological flaws, such as: incorrect intervention consisting of the absence of supplementation with vitamin D3; intervention, which does not increase levels of vitamin D3; lack of the initial measurement of vitamin D3 level; inclusion of patients with normal levels of vitamin D3, which is the reason why the antidepressant effect of the supplementation may be less apparent. The authors of the study assessed separately studies with "biological flaws" and studies that did not contain such irregularities. The meta-analysis enrolled a total of 15 randomized controlled trials.

In the meta-analysis with no errors in the biological treatment (7 studies) an increase in the level of vitamin D3 was associated with reduction of depressive symptoms (+0.78 CI +0.24, +1.27). In contrast, the meta-analysis of studies with errors in biological treatment (8 studies) showed that vitamin D3 administration may have unfavorable effect, causing deterioration in the mental state (-1.1 CI -0.7, -1.5). The authors suggest that the studies with biological flaws should be excluded from further analysis of the effectiveness of vitamin D3 supplementation in the treatment of depression. It is worth noting that the efficacy of vitamin D3 supplementation in the reduction of depressive symptoms, confirmed in this study, is comparable to the effectiveness of antidepressants.

A short review of the results of the studies discussed above is included in Table 2.

Table 2. **Studies evaluating the impact of vitamin D3 supplementation on the reduction of depressive symptoms**

Name of research	What was assessed	Size of the group	Conclusions	Comments	Treatment	Dose
Jorde et al. [47] 2008	Assessment of the effectiveness of vitamin D3 supplementation in the reduction of depressive symptoms	441 overweight or obese participants	Reduction of depressive symptoms in the groups treated with vitamin D3 compared to placebo control group	Study with randomization and placebo control	Vitamin D	20,000 or 40,000 IU/ week
Shipowick et al. [45] 2009	Assessment of the impact of the 8 week vitamin D3 supplementation on the reduction of depressive symptoms	9 women	Positive effect of vitamin D3 supplementation on the reduction of depressive symptoms	Study without randomization and placebo control	Vitamin D	5,000 IU/ day
Högberq et al. [46] 2012	Effect of 3-months vitamin D3 supplementation on the reduction of depressive symptoms in the group of teenagers with vitamin D3 deficiency	54 teenagers	Improvement of the mental state as a result of supplementation	Study without randomization and placebo control	Vitamin D	4,000 IU/ day and 2,000 IU/ day
Gowda et al. [44] 2014	Effectiveness of vitamin D3 supplementation in the treatment of depression	4,923 patients	No effect (compared to the placebo)	Meta-analysis of six randomized studies with placebo control	Vitamin D3 monotherapy or adjunctive to antidepressants	400 IU/d –total of 2 million IU
Shaffer et al. [49] 2014	Effect of vitamin D3 supplementation on the reduction of depressive symptoms	3,191 patients	Positive effect of vitamin D3 supplementation on the reduction of depressive symptoms	Meta-analysis of randomized studies	Vitamin D3 monotherapy or adjunctive to antidepressants	600 IU– 300,000 IU/ daily or weekly
Spedding [50] 2014	Effect of vitamin D3 supplementation on the reduction of depressive symptoms	9,658 patients	Positive impact of the supplementation in the meta-analysis of studies without biological flaws	Meta-analysis of 15 studies	Vitamin D	400 IU– 18,400 IU/d
Stokes et al. [48] 2015	Effect of 6-months vitamin D3 supplementation on the reduction of depressive symptoms	111 patients	Positive effect of vitamin D3 supplementation on the reduction of depressive symptoms	Patients with chronic liver disease	Vitamin D	20,000 IU/ week

Recapitulation

It can be concluded with high probability that vitamin D3 affects the functioning of the CNS. Many studies suggest that deficiency of this particular vitamin increases the risk of depressive disorders. The use of vitamin D3 among patients with depressive disorders can have an antidepressant effect and protect against relapses. Many of the studies presented in the article indicate that supplementation of vitamin D3 and conscientious control of the levels in serum, especially in populations which are at risk of depression – such as those with a chronic physical illness, elderly patients, people with a history of depressive episodes, pregnant women – can bring even greater benefits in these groups of patients than in the general population.

The appropriate level of vitamin D3 affects the overall health reducing the risk of cardiovascular disease, osteoporosis, diabetes, and the emergence of some forms of cancer. The limited efficacy of conventional methods of depressive disorders treatment, forced us to look for other potential therapeutic methods. One of such proceedings may be supplementation of vitamin D3. The preparations of vitamin D3 are relatively inexpensive, well tolerated and present a low risk of side effects. The use of daily doses of vitamin D3 up to 10,000 IU/day is considered to be effective and relatively safe.

The latest research indicate that patients suffering from depression are at higher risk of vitamin D3 deficiency. There are several factors related to lifestyle that may predispose to the emergence of vitamin D3 deficiency. People with depression often consume less diverse foods, not providing the right amount of vitamin D3 with food. They are also usually not active, have low physical activity, spend more time indoors, compared to the healthy subjects. All of these factors may promote the emergence of vitamin D3 deficiency, which may in turn predispose to the exacerbation of depressive symptoms. It can be concluded that patients with severe vitamin D3 deficiency may at the same time obtain the greatest benefits in terms of reducing depressive symptoms. Previous studies regarding the use of vitamin D3 in the prevention and treatment of mood disorders had too small sample size to clearly define the effectiveness of vitamin D3 supplementation used in depression treatment as monotherapy and as adjunctive treatment to antidepressant and to assess whether the standard doses of vitamin D3 considered as safe, i.e., 3,000–6,000 IU/d, used in the treatment of mild deficiency, have a significant antidepressant effect.

It is worth noting that the criteria of deficiency and insufficiency of vitamin D3 and the methods of the supplementation differs depending on the country and the study, this is why the authors of this review provided the values that the researchers of the each study considered as threshold values and described how was the supplementation conducted. As indicated by Spedding et al. [50], methodological errors were present in many of the published researches. This is why the results may be questionable and the conclusions may be wrong. Studies with methodological errors, and inappropriate supplementation (intervention which does not bring an increase in the levels of vitamin D3, the wrong dose or duration of supplementation, no baseline measurement of vitamin D3 level) should not be taken into account in the analyzes regarding the effectiveness of vitamin D3 administration. Further, methodologically correct studies with a large sample size are necessary to evaluate the effect of vitamin D3 on the course and treatment of depressive disorders.

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