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The influence of vitamin D_3 level and supplementation on the severity of symptoms and quality of life of female patients with depression

Abstract

Introduction. Vitamin D_3 has many functions in the human body. The impact of vitamin D_3 on mental health is seen in various neurological and psychiatric disorders. In this study, we are assessing its impact on the symptoms and the quality of life of female patients with depressive episodes.

Aim. The study aimed to determine whether higher levels of serum 25(OH)D correlate with milder symptoms of depression and better quality of life among female patients with depressive episodes as well as to establish whether vitamin D_3 supplementation reduces the symptoms of depression and increases the quality of life in the population above.

Material and methods. Patients (n=33) were divided into a study group (supplementing 2000 IU vitamin D_3 daily for 2 months) and a control group. In both groups, the serum 25(OH)D was measured at the study's beginning and end. The symptoms of depression and the quality of life were assessed using BDI-II, HDRS, and SF-36 questionnaires, which the patients answered at baseline and after two months. The trial was completed by 12 patients in the study group and 10 in the control group.

Results and conclusion. No association between the serum 25(OH)D level, symptoms of depression severity, and life quality was shown in patients (n=33) who completed the initial bloodwork. No statistically significant difference was found in changes in depression scores and life quality between the study and control group. No correlation was found between the changes in the scores of depression and life quality and the changes in serum 25(OH)D levels. A statistically significant difference was found in the serum 25(OH)D levels (p=0.0004), with no such difference in the control group (p=0.06). A statistically significant difference was also found in the BDI-II depression scores both in the study and in the control group (p=0.02 and p=0.04). No such difference was found in the study or control in the HDRS depression score or SF-36 life quality score. Therefore, the study does not show the benefit of vitamin D_3 supplementation in the reduction of depression symptoms or life quality in female patients with depressive episodes.

Keywords: vitamin D3, depressive disorders, mood disorders, life quality.

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INTRODUCTION

Vitamin D_3 has many functions in the human body. The best known ones are the regulation of calcium metabolism and developing or maintaining the normal bone structure. However, the importance of vitamin D_3 is broader. Receptors for an active form of vitamin D_3 can be found in almost all cells of the human body. The main source of vitamin D in humans (80 to 90% of vitamin D) is de novo synthesis which takes place in the skin under exposure to ultraviolet radiation (UVB). The remaining part is supplied exogenously, e.g. by consuming oily fish, yolk eggs, or cheese [1]. The deficiency or lower than optimal level of vitamin D_3 is very common in the general population. A high prevalence of vitamin D_3 deficiency was found among people in the USA and Europe. In the USA, the prevalence of vitamin D_3 deficiency is estimated at the level of 25-50% among adults, there is also no direct correlation between the level of vitamin D_3 and the level of insolation in the area of residence [2,3]. In Europe, the prevalence of deficiency or a border level of vitamin D_3 in the general population may be slightly higher and affect even 28-87% of the adult population [4-6].

Among others, it is proven or postulated that vitamin D_3 prevents muscle diseases, cancer, obesity, and cardiovascular or immunological diseases. In recent years, the interest in a correlation between very low vitamin D_3 levels and neurological and psychiatric disorders (including depressive disorders) can be observed [1]. Multiple sclerosis, Alzheimer's disease or Parkinson's disease, and cognitive functioning profiles within these disorders have been associated with low vitamin D_3 levels [7-9].

In 1982 the presence of vitamin D_3 receptors in the brain structures that are responsible for emotion and mood regulation (cingulate cortex, hippocampus, thalamus, hypothalamus) was discovered [10,11]. It has been observed that vitamin D_3 significantly affects the functioning of the brain, taking part in the processes of neuroprotection, neuroplasticity, and neuromodulation [12]. Vitamin D_3 activates the expression of tyrosine

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hydroxylase, which is involved in the synthesis of catecholamines, increasing the production of dopamine, noradrenaline, and adrenaline [13]. It can also activate acetylcholine transferase, an enzyme involved in the synthesis of acetylcholine thus enhancing cholinergic neurotransmission [14].

Vitamin D_3 also affects the regulation of the secretion of brain neurotrophic growth factors, i.e., NGF and GDNF, NT-3 [15-17]. Recent studies have shown that the dysfunction of these factors could be important in the pathogenesis of depressive disorders and schizophrenia [18-22]. Moreover, the metabolic function of Vitamin D_3 within the central nervous system plays a protective role against free radicals [23].

The correlation between vitamin D_3 serum level (or/and its supplementation) and depressive symptoms is not very well-known and doing research in this area is complicated. Even fundamental issues such as setting the optimal level of serum 25(OH)D (range of norms), methods of supplementation, and general clinical indications cause controversy [24]. The American NIH proposes a wide range of standards from 20ng/ml to 50ng/ml [25], although there are also those who support the recognition of other ranges, e.g. 60ng/ml as the optimal level [26]. The issue of quality of life has been tackled in some research on vitamin D_3, e.g. PolSenior [27]; however, it has not been a primary goal. The matter is complicated by additional variables, such as seasonality – exposure to light, age, gender, and the association of different therapy methods with vitamin D_3 supplementation. Several studies state there is a positive correlation between vitamin D_3 supplementation and the alleviation of symptoms of depressive episodes [28-30]. Several factors related to lifestyle may predispose to the emergence of vitamin D_3 deficiency in patients suffering from depression. They do not often provide the appropriate amount of vitamin D_3 with food by eating less diverse foods. They have low physical activity, spend more time indoors than the healthy subjects, and thus have less exposure to UV radiation. All these factors may promote the emergence of vitamin D_3 deficiency, which may predispose to the exacerbation of depressive symptoms [31]. There are also papers published that do not indicate any link between the occurrence or exacerbation of the symptoms of depressive episodes and vitamin D_3 deficiency [32,33].

AIM

The aim of the study is to determine whether higher levels of serum 25(OH)D correlate with milder depression symptoms and higher life quality among female patients with depressive episodes (F32 according to ICD-10). The secondary aim was to determine whether the supplementation of vitamin D_3 can reduce symptoms and increase the quality of life of females with depressive episodes.

MATERIAL AND METHODS

Measures

The severity of depression and the quality of life were quantitatively measured with the following questionnaires:

1. Beck Depression Inventory-II (BDI-II) – a scale that serves as a quantitative assessment of the severity of depression during the psychiatric diagnosis. It is a tool that allows measurement of the progress in therapy [34]. The scale is composed of 21 questions that relate to symptoms of depression (both somatic and psychic). Each question is valued 0-3, which results in a maximum score of 63. The higher the score, the more severe the depression: 0-13: minimal depression, 14-19: mild depression, 20-28: moderate depression, 29-63: severe depression [35].
2. Hamilton Depression Rating Scale (HDRS) – used to assess the severity of depression by analyzing mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and also somatic symptoms. The HDRS questionnaire contains 21 items. The first 17 items measure the severity of depressive symptoms and for instance, the interviewer can rate the level of agitation noted during the interview or how the mood is impacting the patient's work or other activities. The extra four items on the extended 21-point scale measure factors that can be associated with depression, but are not thought to be measures of severity, such as paranoia or obsessional and compulsive symptoms. Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine are scored from 0 to 2. Scoring is based on the 17-item scale and results of 0-7 are considered as being normal, 8-16 suggest mild depression, 17-23 points to moderate depression, and scores over 24 are indicative of severe depression [36,37].
3. Quality of life SF-36 questionnaire(SF-36) – the Polish version is a 36 questions self-reporting survey on the patient's general health that reflects their quality of life. According to the Polish version of the questionnaire, the highest score (100) means the lowest level in the assessment of the quality of life, while the lowest score (0) means the highest level of quality of life [38-40].

Participants

The participants of the study were women, aged 18-50, with a diagnosis of a depressive episode (F32 according to research criteria of the International Classification of Diseases (ICD-10)).

The inclusion criteria were the following: females, age 18-50, diagnosis of depressive episodes (ICD-10; F32), BMI 18-35.

The exclusion criteria were the following: any active somatic disease currently requiring treatment, and the need to change the pattern of pharmacological or psychotherapeutic treatment of depressive episodes during the procedure.

Procedure

The patients reported their willingness to participate in the study by completing the online survey containing the information about the research and questions associated with their physical and mental health, chronic diseases, and the type of treatment they were receiving in order to verify if the candidates for the study met the inclusion criteria.

After submitting the survey, the participants were contacted and invited to a psychiatric appointment in Warsaw, Poland where a thorough anamnesis was conducted. All participants received oral and written information about the study protocol, its anonymity, and the possibility to resign at any time during the study. All the participants gave written consent to participate. After the medical anamnesis, the patient's mental health was assessed with the help of questionnaires: BDI-II, HDRS, and SF-36.

Subsequently, the patients were referred to laboratory testing for serum 25(OH)D (vitamin D_3 level) at SZPZLO Ochota Laboratory in Warsaw, Poland. The patients were informed

about their individual results and randomly assigned to the study and control groups.

A group of 208 patients reported readiness to participate in the study out of whom 58 did not meet the inclusion criteria, and 92 were not present at the initial medical anamnesis. Finally, 58 patients reported to medical anamnesis, out of whom 33 participated in the initial laboratory testing (Figure 1).

The assignment to the study and control groups was randomized and included two sub-populations:

- 17 received standard treatment (SSRI, SNRI or SARI and/or psychotherapy) with vitamin D_3 supplementation;
- 16 received standard treatment (SSRI, SNRI or SARI and/or psychotherapy) without vitamin D_3 supplementation.

The women from the study group, as an addition to standard therapy, supplemented 2000 IU of vitamin D_3 every day for two months. The participants from the control group did not supplement vitamin D_3, but were still treated pharmacologically or/and psychotherapeutically for depression.

After two months of the study, a psychiatrist examined all participants, and their answers to questionnaires and scales were gathered. At that time the serum 25(OH)D was determined again. Some patients resigned from the study before it started or during the procedure. They declared a lack of time, anxiety, reluctance, or personal reasons. Three patients were excluded due to pattern change (e.g. they started to take new medicines during the study). One patient from the control group was excluded as she reported traveling to Spain and extensive sun exposure significantly increased her serum 25(OH)D level. Finally, the study was completed by 12 participants in the study group and 10 participants from the control group (Table 1).

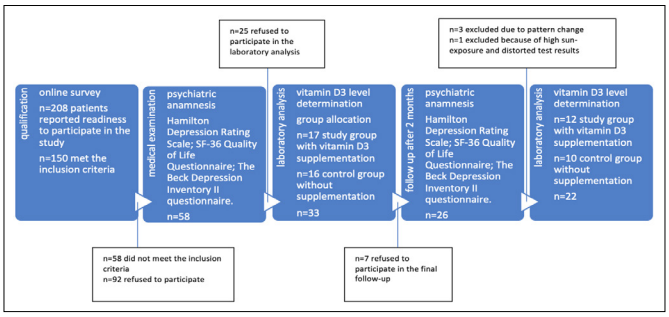

FIGURE 1. The study design.

TABLE 1. The characteristics of patients from the study and control groups who completed the trial.

Variables	Study group (n=12)	Control group (n=10)
Age	M=26.20; SD=7.66	M=27.6; SD=6.69
SSRI (escitaloprame/sertraline/paroxetine/fluoxetine)	n=6	n=5
SNRI (duloxetine/venlafaxine)	n=2	n=3
SARI (trazodone)	n=2	n=0
Psychotherapy	n=5	n=2

Statistical analysis

Initially, the Pearson correlations between the level of 25(OH)D and the initial results of BDI-II, HDRS, and SF-36 were established. Furthermore, changes in BDI-II, HDRS, and SF-36 as well as serum 25(OH)D at the baseline and after the study was measured and compared between the study and control group using the Python programming language and Mann-Whitney U test. Using Wilcoxon statistical test the observations were compared at baseline and after the completion of the study within the study and within the control. Moreover, the Pearson correlations between the mean change of 25(OH)D and changes in questionnaire scores were also established.

RESULTS

Primary results

Thirty-three women with a mean age of 26.46 (SD=6.70) completed the initial laboratory analysis of blood level of 25-hydroxy vitamin D. Pearson correlations were calculated for the level of 25(OH)D and scores of BDI-II, HDRS, and SF-36. Initially, the mean blood level of 25(OH)D was equal to 28.91 (SD 9.45) (Table 1). Among the 33 patients, there was a very weak negative correlation found between the serum 25(OH) D level and the score of BDI-II (r= -0.01), which does not differ from the population, a very weak positive correlation between the level of serum 25(OH)D and the score of HDRS (r=0.11) as well as a weak negative correlation between the serum 25(OH) D level and the SF-36 survey (r= -0.26). The correlations were not significant (Table 1).

TABLE 2. The means (M) with standard deviation (SD) of initial serum 25(OH)D level, initial questionnaire scores, and Pearson correlations between the serum 25(OH)D and the depression (BDI-II, HDRS) and quality of life (SF-36) questionnaire scores in the patients who completed the initial laboratory analysis.

Variables	Patients n=33
Age (years)	M=26.03; SD=6.33
BDI II (points)	M=21.67; SD=10.18
SF-36 (points)	M=50.76; SD=14.27
HDRS (points)	M=14.21; SD=5.48
25(OH)D (ng/mL)	M=28.91; SD=9.45
Correlation of 25(OH)D with BDI-II	r= -0.01
Correlation of 25(OH)D with SF-36	r= -0.26
Correlation of 25(OH)D with HDRS	r= 0.11

Secondary results

Among the participants who completed the study, changes in the scores of questionnaires and in serum 25(OH)D were compared between the groups using the Mann-Whitney U test. The median change of serum 25(OH)D level in the study group was equal to 5.0; this was the score by which the median level of vitamin D_3 among the study group increased. In the control group, the median change was equal to -8.39. The Mann-Whitney U test showed the difference in changes of serum 25(OH)D between the study and control group was statistically significant (p=0.002), with U-stat equal to 106.5.

Although the median changes in the questionnaire scores (BDI-II, HDRS, and SF-36) before and after the completion of the study were greater in the study group (-7.0; -6.5,

and -12.5 respectively) compared to the control (-3.5, -1.5 and -0.0 respectively) there was no statistical significance found in the difference of the questionnaire score changes between the study and the control groups with p=0.107 and U-stat 35.0 for BDI-II, p=0.254 and U-stat=42.0 for HDRS and p=0.159 and U-stat=38.0 for SF-36 (Table 2.).

TABLE 3. Median changes in depression and life quality questionnaire scores and serum 25(OH)D before and after the intervention of the study, and p-value of differences in the changes between the study and control.

	Median change (post- vs. pre-intervention)			
Variable	**BDI-II**	**HDRS**	**SF-36**	**25(OH)D [ng/ml]**
Study group	-7.0	-6.5	-12.5	5.0
Control group	-3.5	-1.5	-0.0	-9.65
p-value	0.107	0.254	0.159	0.002

No association was found between the changes of 25(OH) D and the changes of the scores of BDI-II, HDRS, and SF-36 (with r equal to -0.03; -0.03; 0.12 respectively) showing a very weak negative correlation for the first two questionnaires scores, and a weak positive in the latter for the participants of both study and control group. The correlations were not significant.

Finally, the questionnaire scores and the serum 25(OH)D values were compared pre- and post-intervention within the study and the control group using the Wilcoxon test. There was a statistical significance found comparing serum 25(OH) D level at baseline and post-intervention in the study group (p=0.0004; test statistic value = 0.0) with no statistical significance in the control (p=0.06; test statistic value = 9.0) Both in the study group and in the control there was a statistically significant change in BDI-II scores (p=0.02 and test statistic value=7.0 in the study group and p=0.04 and test statistic value=7.5 in the control). No statistical significance was established within the HDRS score in the study or control (p=0.07 and test statistic value=12.5 in the study group and p=0.25 test statistic value = 13.0 in the control). Similarly, no statistical significance was established in SF-36 score in the study group or in the control (p=0.9 with test statistic value = 17.5 and 0.63 with test statistic value = 22.5 respectively). (Table 4.)

TABLE 4. The means (M) with standard deviation (SD) and median (Mdn) values of questionnaires and 25(OH)D scores pre- and post-intervention and p-values of comparison of the scores at baseline and post-intervention within the study group and within the control group.

	Pre-intervention:		**Post-intervention:**		**P-values for the comparison of the sores at baseline and post-intervention within the respective groups**	
variables	**study group**	**control group**	**study group**	**control group**	**study group**	**control group**
BDI-II	M=18.4, SD=9.1, Mdn=17.5	M=20.40, SD= 12.19, Mdn=15.00	M=10.3 SD=15.8 Mdn=11.0	M=16.60, SD=8.93, Mdn=16.0	0.02	0.04
HDRS	M=13.58, SD=5.38, Mdn=14.0	M=20.40, SD= 12.19, Mdn=13.5	M=9.17, SD= 3.97, Mdn=10.0	M=12.10, SD=5.59, Mdn=11.5	0.07	0.25
SF-36	M=47.58, SD=9.44 Mdn=48.5	M=44.90, SD= 15.95 Mdn=45.0	M=37.17, SD= 15.83 Mdn=36.5	M=43.00, SD=14.78 Mdn=46.5	0.09	0.63
25(OH)	M=27.17 SD=7.25 Mdn=26.5	M=37.19 SD=9.18 Mdn=37.8	M=33.08 SD=8.43 Mdn=34.5	M=28.80 SD=9.67 Mdn=30.5	0.0004	0.06

DISCUSSION

Vitamin D_3 has many functions in our body and its positive impact on human physiology was documented. However, its impact on mental health has not been fully established. Our study did not show an association between the serum level of 25(OH)D and the severity of symptoms of depression and the life quality of female patients with depression in the group of patients who participated in the initial serum analysis. There was no statistically significant difference in changes in scores of depression and life quality between the study and control group. Moreover, no association was found between the changes in the scores of depression and life quality and the changes in serum 25(OH)D levels. These results are consistent with other studies conducted on a larger group of patients [34,42] among whom there was also no reduction in depression symptoms after the supplementation of vitamin D_3.

Similar findings, which included a long-term supplementation in an elderly population also did not prove the benefit of vitamin D_3 in the prevention of depressive symptoms or change in mood scores over a median follow-up of 5.3 years [42]

On the other hand, some authors claim that vitamin D_3 supplementation did alleviate symptoms of depression among the participants of their studies [43]. The studies performed by Amani et al. and Manon et al. prove that supplementation was effective in the case of clinically significant depression [44,45]. Those results were not reflected in our study. The level of serum 25(OH)D changed significantly in the intervention group, with no significant change in the control group. However, both in the intervention group and in the control there was a statistically significant difference in the depression scores (BDI-II) within the study group after supplementing vitamin D_3, and similarly in the control group. On the other hand, there was no statistically significant difference in the depression scores represented by the HDRS questionnaire neither in the study group nor in the control. Therefore, no direct benefit of vitamin D_3 supplementation for mood improvement among the patients with depressive episodes was observed.

There are also studies that suggest the correlation between vitamin D_3 deficiency and symptoms of depression[46,47,49] However, this trend was not observed in our study among thirty-three patients before supplementation or in the final results of the study group. Lack of consistency in this field means that there needs to be more research done. The design of the study differed from the aforementioned studies by focusing solely on female patients. However, the small number of patients participating in the study was a significant limitation.

Therefore although our study shows no evident association between vitamin 25(OH)D level as seen in the initial group, its supplementation, and the improvement of the symptoms and life quality of female patients with depressive episodes, research on a greater number of patients is needed to achieve more reliable results.

CONCLUSION

The study shows no association between the level of serum 25(OH)D and the symptoms of depression and the quality of life as portrayed by the scores of BDI-II, HDRS, and SF-36 among the female patients with depressive episodes as seen at baseline after the initial bloodwork. Moreover, no association was found between the changes in the scores of depression (BDI-II, HDRS) and life quality (SF-36) and the changes in serum 25(OH)D levels.

What is more, the level of serum 25(OH)D changed significantly in the intervention group, with no significant change in the control group. However, both in the intervention group and in the control there was a statistically significant difference in BDI-II depression scores at baseline and post-intervention. On the other hand, there was no statistically significant difference in the depression scores (HDRS) neither in the study group or in the control. Similarly, no statistically significant difference in the quality of life scores (SF-36) was observed at baseline and post-intervention in the study or control group.

Therefore, the study does not show the benefit of vitamin D_3 supplementation in the reduction of depression symptoms, or the increase of life quality of female patients with depressive episodes. No evident association between the higher level of serum 25(OH)D and milder depression symptoms and higher life quality among the female patients with depressive episodes was shown in the study.

All in all, taking into account the small number of patients that took part in the study and the lack of consistency in the results of other studies cited, it should be noted that more research in this area is needed to reach a definitive conclusion on the relationship between serum vitamin D_3 levels (and its supplementation) as well as depression symptoms and life quality of female patients with depressive episodes.

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