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ISSN: 0423-104X

e-ISSN: 2299-8306

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DOI: 10.5603/EP.a2018.0013

Article type: Original papers

Submitted: 2017-09-18

Accepted: 2017-10-21

Published online: 2018-01-18

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Articles in "Endokrynologia Polska" are listed in PubMed.

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The effect of vitamin D supplementation on sexual functioning and depressive symptoms in young women with low vitamin D status

Running title: Vitamin D and sexuality

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Abstract

Background: Hypovitaminosis D is associated with abnormal female sexual functioning. The aim of our study was to assess whether vitamin D supplementation affects sexual functioning and depressive symptoms in young women with low vitamin D status.

Material and methods: The study included 47 women with vitamin D deficiency or insufficiency. All women with vitamin D deficiency were treated with oral vitamin D, while women with vitamin D insufficiency were either treated with vitamin D or left untreated. At the beginning of the study and six months later, all patients completed questionnaires evaluating female sexual function (FSFI) and depressive symptoms (BDI-II).

Results: The total FSFI score and scores in three domains (sexual desire, orgasm, and satisfaction) were lower while the overall BDI-II score was higher in women with vitamin D deficiency than in women with vitamin D insufficiency. Vitamin D improved sexual desire in women with both vitamin D deficiency and vitamin D insufficiency, increased the total FSFI score and scores for orgasm and sexual satisfaction, and decreased the total BDI-II score, in women with vitamin D deficiency.

Conclusions: The obtained results indicate that vitamin D supplementation improves female sexual functioning and mood in women with low vitamin D status.

Key words: *depressive symptoms, 25-hydroxyvitamin D, questionnaires, sexual functioning, vitamin D status*

Introduction

Apart from its role in the regulation of calcium and phosphorus homeostasis, vitamin D is implicated in different physiological processes, including the regulation of cellular growth and differentiation, glucose metabolism, immune function, and placental function [1–3]. These effects are mediated through specific receptors, which are located in almost any cell and tissue, particularly in the brain, the chest, bones, muscles, and the gastrointestinal tract [4]. Observational studies indicate that serum 25-hydroxyvitamin D levels, being the most reliable marker of vitamin D status [5], predict increased morbidity and mortality [6]. Abnormal production and/or metabolism of vitamin D may make individuals particularly susceptible to various cardiometabolic disorders, such as myocardial infarction, stroke, hypertension, and both types of diabetes [7–9] as well as to several autoimmune diseases, particularly to rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus [1, 3, 10]. Low vitamin D status also seems to be associated with an increased risk of the development of various gynaecological and obstetric disorders including infertility, endometriosis, polycystic ovary syndrome, breast and ovarian cancer, as well as gestational diabetes mellitus and preeclampsia [11].

Very little is known about the association between vitamin D and sexual functioning. In men with type 2 diabetes, 25-hydroxyvitamin D levels inversely correlated with the severity of erectile dysfunction assessed by the International Index of Erectile Function-5 questionnaire [12]. A significant proportion of men with erectile dysfunction, particularly of arteriogenic aetiology, had vitamin D deficiency [13], which suggests that low levels of vitamin D may impair erectile function by promoting endothelial dysfunction. Vitamin D preparations improved erectile function in middle-aged men, which was accompanied by an increase in serum testosterone levels and a beneficial effect on the components of the metabolic syndrome [14]. Recently, Krysiak et al. [15] have found that vitamin D deficiency and insufficiency are also associated with impaired female sexual functioning and depressive symptoms. The degree of these disturbances inversely correlates with vitamin D status. [15]. The aim of the present study was to evaluate sexual functioning and depressive symptoms in women who, because of low vitamin D status, have been treated with vitamin D preparations.

Material and methods

Women (20–40 years old) were eligible for the study if they met the criteria of vitamin D deficiency or vitamin D insufficiency. Vitamin D deficiency was defined as plasma 25-hydroxyvitamin D levels less than 20 ng/mL, while vitamin D insufficiency as circulating 25-hydroxyvitamin D levels between 20 and 30 ng/mL. To minimise the impact of seasonal fluctuations in vitamin D status approximately a half of the patients (n = 47) were recruited in January and February (n = 22) and the other half (n = 25)

between July and August. Some patients included in the present study participated also in our previous one. The exclusion criteria were as follows: any acute or chronic disorder, sexual inactivity, pregnancy or lactation, a history of urogynaecological operations that might affect sexual function, any pharmacotherapy, and poor patient compliance. The study protocol was approved by the Bioethical Committee of the Medical University of Silesia, and all subjects included in the study signed informed consent after careful explanation of the study procedures.

All patients with vitamin D deficiency ($n = 16$) were then treated with oral vitamin D preparations (4000 IU daily) for six months. In turn, the participants with vitamin D insufficiency ($n = 31$) on the basis of patient preference were allocated to one of two groups treated with oral vitamin D preparations (2000 IU daily; $n = 17$) for six months or not receiving vitamin D therapy ($n = 14$). The investigation of possible drug-induced side effects was performed fortnightly.

Venous blood samples for laboratory assays were collected from the antecubital vein after an overnight 12-h fasting at 8 a.m. Serum levels of 25-hydroxyvitamin D were measured by enzyme immunoassay using reagents obtained from ALPCO Diagnostics (Windham, NH, USA).

Immediately after blood collection, all participants were asked to fill in a questionnaire assessing their demographic characteristics, marital status, education, general health, medical and sexual history, and physical activity, as well as to complete questionnaires investigating their sexual function (Female Sexual Function Index — FSFI) and depressive symptoms (Beck Depression Inventory-Second Edition — BDI-II). At this stage of the study, neither the women nor the investigators were aware of the vitamin D status of the patient.

FSFI is a standardised questionnaire used worldwide to assess sexual function within the last four weeks and to evaluate the treatment outcome in clinical trials. This survey consists of 19 questions, divided into six domains: desire (items 1 and 2), arousal (items 3–6), lubrication (items 7–10), orgasm (items 11–13), satisfaction (items 14–16), and pain (items 17–19) [16, 17]. Each answer is rated from 0 to 5 or 1 to 5. The total FSFI score is obtained from the sum of the items in each domain multiplied by the domain factor (0.6 for desire, 0.3 for arousal and lubrication, and 0.4 for orgasm, satisfaction, and pain). Higher scores for each domain and higher total scores indicate better sexual function. The total FSFI cutoff score for the diagnosis of dysfunction is less than 26.55 [16, 17].

BDI-II is a valid and reliable indicator of the presence and severity of depressive symptoms, corresponding well to a clinical diagnosis of depressive disorders described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [18, 19]. BDI-II contains 21 items, each with a four-point scale ranging from 0 to 3; total scores range from 0 to 63 (higher scores representing greater severity of depression). In accordance with manual guidelines, the BDI-II was interpreted as follows: minimal range = 0–13, mild depression = 14–19, moderate depression = 20–28, and severe depression = 29–63 [18, 19].

Although all participants underwent laboratory tests and filled in the questionnaires, only the data of individuals with normal vitamin D status (defined as circulating 25-hydroxyvitamin D levels between 30 and 75 ng/mL) at the end of the treatment and data of all vitamin D-naïve women with vitamin D insufficiency were included in the final analyses. The normality of distribution was determined using the Kolmogorov-Smirnov test. Natural log transformation was then applied to variables not meeting normality. Comparisons between the groups were made using analysis of covariance followed by Bonferroni *post-hoc* tests after consideration of age, smoking, body mass index, blood pressure, marital status, education, occupational activity, type of work, profession, physical activity, and stress exposure as potential confounders. Student's paired *t*-test was applied to compare pre- and post-therapy data within the same treatment group. Qualitative variables were compared using the χ^2 test. Associations were calculated using Pearson's correlation coefficient (*r*). Differences were considered statistically significant at $p < 0.05$.

Results

General characteristics of the study groups

At baseline, women with vitamin D deficiency and both groups of women with vitamin D insufficiency were similar in regard to age, body mass index, weight, waist circumference, physical activity, education, occupational activity, type of work, stress exposure, the number and duration of marriages, the number of deliveries, the number of sexual partners, and blood pressure (Table I).

Vitamin D treatment was well tolerated, and all patients receiving vitamin D preparations completed the study period. Two women with vitamin D deficiency, as well as two women with vitamin D insufficiency failed to achieve normal vitamin D status and therefore only data of 14 vitamin D-treated women with vitamin D deficiency, 15 vitamin D-treated women with vitamin D insufficiency, and all 14 vitamin D-naïve women with vitamin D insufficiency were included in statistical analyses.

Sexual function (Table II)

At baseline, the mean total FSFI score was insignificantly lower in women with vitamin D deficiency than in women with vitamin D insufficiency ($p = 0.058$). Sexual dysfunction was observed in six subjects (43%) with vitamin D deficiency and six subjects (21%) with vitamin D insufficiency. Women with vitamin D deficiency obtained lower scores in three domains (sexual desire, orgasm, and sexual satisfaction) than women with vitamin D insufficiency.

Vitamin D administered to women with vitamin D deficiency improved sexual desire, orgasm, and sexual satisfaction and increased the FSFI score, while if administered to women with vitamin D insufficiency, it improved only desire. The mean FSFI score and all domain scores did not change throughout the study in vitamin D-naïve women with vitamin D insufficiency. The percentage of

patients with sexual dysfunction decreased to 14% in vitamin D-treated patients with vitamin D deficiency and did not change in the remaining two groups. The effect of vitamin D on the mean FSFI score, desire, orgasm, and satisfaction was stronger in women with vitamin D deficiency than vitamin D insufficiency.

At the end of the study, the mean FSFI score as well as all domain scores were similar in both vitamin D-treated groups. The domain score for desire was lower in women with untreated vitamin D deficiency than in the remaining groups of women.

Depressive symptoms (Table III)

Compared to women with vitamin D insufficiency, women with vitamin D deficiency had insignificantly higher values of the BDI-II score ($p = 0.062$), and were characterised by a more frequent occurrence of total and mild depressive symptoms.

In women with vitamin D deficiency, vitamin D reduced the overall BDI-II score, and decreased the percentage of women with total and mild depressive symptoms. In women with vitamin D insufficiency the drug tended to reduce BDI-II score ($p = 0.075$), and the percentage of patients with total ($p = 0.065$) and mild ($p = 0.065$) depressive symptoms, but it did not affect the percentage of women with moderate or severe depressive symptoms. No changes in the overall BDI-II score, as well as the percentage of patients with total, mild, moderate, and severe depressive symptoms was observed in vitamin D-naïve women with vitamin D insufficiency. The effect of vitamin D on the overall BDI-II score was stronger in women with vitamin D deficiency than vitamin D insufficiency. At the end of the study, the overall BDI-II score, as well as the percentage of patients with total, mild, moderate, and severe depressive symptoms did not differ between the study groups.

Correlations

In all study groups, the mean total FSFI score inversely correlated with the total BDI-II score, as well as with the percentage of women with total and mild depressive symptoms (vitamin D deficiency: r values between -0.30 [$p < 0.05$] and -0.46 [$p < 0.001$]; vitamin D insufficiency: r values between -0.25 [$p < 0.05$] and -0.43 [$p < 0.001$]), while the BDI-II score positively correlated with body mass index (vitamin D deficiency: $r = 0.40$ [$p < 0.001$]; vitamin D insufficiency: $r = 0.47$ [$p < 0.001$]). In women with vitamin D deficiency, 25-hydroxyvitamin D levels positively correlated with sexual desire ($r = 0.47$ [$p < 0.001$]), orgasm ($r = 0.35$ [$p < 0.01$]), and sexual satisfaction ($r = 0.24$ [$p < 0.05$]), while in women with vitamin D insufficiency, 25-hydroxyvitamin D positively correlated with desire ($r = 0.34$ [$p < 0.05$]).

The effect of the treatment on the total FSFI score inversely correlated with baseline vitamin D levels (vitamin D deficiency: $r = 0.36$ [$p < 0.01$]; vitamin D insufficiency: $r = 0.31$ [$p < 0.05$]), and negatively correlated with the baseline total BDI-II score (vitamin D deficiency: $r = 0.29$ [$p < 0.05$];

vitamin D insufficiency: $r = 0.26$ [$p < 0.51$]), vitamin D-induced changes in 25-hydroxyvitamin D levels (vitamin D deficiency: $r = 0.43$ [$p < 0.001$]; vitamin D insufficiency: $r = 0.38$ [$p < 0.001$]), and vitamin D-induced changes in the total BDI-II score (vitamin D deficiency: $r = 0.35$ [$p < 0.01$]; vitamin D insufficiency: $r = 0.32$ [$p < 0.05$]). The changes in the total BDI-II score positively correlated with the changes in 25-hydroxyvitamin D levels (vitamin D deficiency: $r = 0.34$ [$p < 0.01$]; vitamin D insufficiency: $r = 0.28$ [$p < 0.05$]). In women with vitamin D deficiency, there were positive correlations between baseline 25-hydroxyvitamin levels and vitamin D-induced changes in sexual desire ($r = 0.42$ [$p < 0.001$]), orgasm ($r = 0.31$ [$p < 0.05$]), and sexual satisfaction ($r = 0.32$ [$p < 0.05$]), as well as between treatment-induced changes in 25-hydroxyvitamin D levels and the changes in in sexual desire ($r = 0.46$ [$p < 0.001$]), orgasm ($r = 0.28$ [$p < 0.05$]), and sexual satisfaction ($r = 0.24$ [$p < 0.05$]). In women with vitamin D insufficiency, vitamin D-induced changes in desire inversely correlated with baseline 25-hydroxyvitamin levels ($r = -0.29$ [$p < 0.05$]) and positively with treatment-induced changes in 25-hydroxyvitamin levels ($r = 0.30$ [$p < 0.05$]).

Discussion

In agreement with the recent study by Krysiak et al. [15], women with vitamin D deficiency had impaired sexual functioning in comparison to women with vitamin D insufficiency. This observation as well as the presence of correlations between the total FSFI score and 25-hydroxyvitamin D levels support our previous observations suggesting that a degree of sexual dysfunction depends on the severity of vitamin D deficiency. The study protocol does not allow us to answer the question whether impaired sexual functioning contributes to different intensity of depressive symptoms in both populations of women and/or is rather its consequence.

However, the most important finding of our study was that vitamin D supplementation improved sexual dysfunction, which was accompanied by an improvement in mood. Interestingly, vitamin D affected functioning in exactly the same domains of FSFI in which patients presented worse scores in comparison with healthy women, namely in sexual desire, orgasm, and sexual satisfaction in subjects with 25-hydroxyvitamin D levels below 20 ng/mL, as well as in sexual desire in women with 25-hydroxyvitamin D levels between 20 and 30 ng/mL. Although the number of domain scores affected by the treatment was higher and the strength of vitamin D action was greater in subjects with vitamin D deficiency than insufficiency, this discrepancy probably reflects differences in baseline sexual functioning of both groups. In line with this hypothesis, the impact on FSFI score and domain scores correlated with baseline- and treatment-induced changes in 25-hydroxyvitamin D levels. It seems reasonable to assume that post-treatment sexual functioning does not differ between individuals effectively treated with vitamin D and healthy women included in the previous study [15] (women with normal vitamin D status were not participants of the present study). In this study, we took into consideration only results of women in whom vitamin D normalised 25-hydroxyvitamin D levels,

eliminating these subjects in whom the supplementary treatment did not fully restore normal vitamin D status. This allows us to conclude that sexual dysfunction in women with vitamin D deficiency is fully reversible provided they are effectively treated with exogenous vitamin D.

Vitamin D was found to increase endothelial nitric oxide production [20], which was observed to be impaired in the case of hypovitaminosis D [21, 22]. Moreover, low vitamin D levels are associated with an increased risk of atherosclerosis, coronary artery disease, stroke, hypertension, heart failure, dyslipidaemia and atrial fibrillation [8, 9, 23, 24], low serum levels of testosterone, and low free androgen index [25], as well as with an increased risk of both autonomic and peripheral neuropathy [26, 27]. These findings taken together indicate that the effects on the cardiovascular system, androgen production, and the nervous system may mediate the impact of this vitamin on female sexual functioning. It is possible that genital blood flow, as well as hormonal and neural regulations of sexual function are disturbed in women with hypovitaminosis D and correlate with its severity, while a normalisation of vitamin D status by normalising these disturbances may restore normal sexual functioning. Although post-treatment sexual functioning did not differ from that observed in healthy subjects, we cannot exclude that at least some disturbances mentioned above, if lasting for a long time, may be, at least in part, irreversible.

Some clinical studies conducted so far have shown that low circulating levels of 25-hydroxyvitamin D are associated with poor mood and that vitamin D supplementation improves depressive symptoms [28, 29]. In line with these results, mild depressive symptoms occurred more frequently in women with vitamin D deficiency than vitamin D insufficiency, and supplementary treatment reduced BDI-II and the percentage of patients with total and mild depressive symptoms in both groups of women with low vitamin D status, as well as that this effect was significant only in the first group of patients. This action may result from stimulation of specific receptors expressed in the hypothalamus, thalamus, prefrontal cortex, and hippocampus [30], which are brain regions involved in mood regulation. Through affecting these receptors, vitamin D may modulate central dopaminergic and/or serotonergic neurotransmission and/or affect hypothalamic-pituitary-adrenal axis response to stress. The presence of correlations both at entry and during treatment clearly suggests that sexual dysfunction and depressive symptoms are reciprocally interrelated. Because these correlations are weak, we may assume that sexual dysfunction is important but is not the only factor playing a role in the development of depressive symptoms. Another factor that seems to contribute to depressive symptoms is excessive weight in many participants, because the body mass index correlated with BDI-II score both at baseline and after treatment.

Our study has some limitations that must be considered. Its main limitation is the small number of participants, which means that larger studies are required to confirm our results. FSFI and BDI-II scoring systems, like other self-report inventories, are subjective in nature. It cannot be totally excluded that seasonal variation in 25-hydroxyvitamin D concentrations, observed at high latitudes

[31], may have an impact on the obtained results. Finally, the effect of vitamin D supplementation may be different (probably less pronounced) in women suffering from concomitant disorders and/or taking other drugs.

Summing up, the total FSFI score and scores in three domains (sexual desire, orgasm, and satisfaction) were lower while the overall BDI-II score was higher in women with vitamin D deficiency than in subjects with vitamin D insufficiency. Exogenous vitamin D improved desire and depressive symptoms in both treated groups, and increased scores for orgasm and sexual satisfaction in individuals with vitamin D deficiency. The results of the study suggest that vitamin D produces a beneficial effect on female sexual functioning and mood in women with low vitamin D status.

Disclosure of interest

The authors report no conflicts of interest.

Source of funding

This study did not receive any specific funding.

Institutional approval

The study was approved by the local Bioethical Committee.

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Table I. Baseline characteristics of the study population

	Vitamin D-treated women with vitamin D deficiency	Vitamin D-treated women with vitamin D insufficiency	Vitamin D-naïve women with vitamin D insufficiency
Number of patients	14	15	14
Age [years; mean (SD)]	30 (6)	31 (5)	30 (5)
Body mass index [kg/m ² ; mean (SD)]	28.0 (3.5)	27.5 (3.1)	27.3 (4.0)
Smokers (%) / Number of cigarettes a day [n; mean (SD)] / Duration of smoking [months, mean (SD)]	29/11 (4)/88 (29)	27/11 (5)/90 (32)	29/12 (5)/80 (24)
Physical activity: total/once a week/several times a week/once a month (%)	71/29/21/21	73/27/27/20	79/29/29/21
Primary or vocational/secondary/university education (%)	36/36/28	40/40/20	36/36/28
Occupational activity/Blue-collar/white-collar/pink-collar workers (%)	93/36/36/12	87/27/40/21	86/29/29/29
Number of sexual partners [n; mean (SD)]	2.0 (0.6)	1.9 (0.8)	1.8 (0.7)
Number of marriages [n; mean (SD)] / duration of marriages [months; mean (SD)]	1.1(0.7)/48 (22)	1.2 (0.6)/53 (29)	1.1 (0.6)
Number of deliveries [n; mean (SD)] / Number of abortions [n; mean (SD)]	1.3 (0.6)/ 0.6 (0.7)	1.5 (0.6)/0.5 (0.6)	1.4 (0.6)/0.7 (0.7)
Stress exposure (%)	79	79	71
Systolic blood pressure [mmHg; mean (SD)]	123 (12)	124 (11)	123 (14)

Diastolic blood pressure [mmHg; mean (SD)]	76 (8)	77 (6)	75 (9)
25-hydroxyvitamin D levels [ng/dL; mean (SD)]	11 (4) ^{a,b}	24 (3)	24 (4)

SD — standard deviation

^a $p < 0.001$ vs. vitamin D-treated women with vitamin D insufficiency; ^b $p < 0.001$ vs. vitamin D-naive women with vitamin D insufficiency

Table II. The effect of vitamin D on sexual functioning in young women with low vitamin D status

Variable	Vitamin D-treated women with vitamin D deficiency	Vitamin D-treated women with vitamin D insufficiency	Vitamin D-naïve women with vitamin D insufficiency
FSFI score [mean (SD)]			
At the beginning of the study	29.60 (2.47)	31.61 (2.29)	31.64 (2.37)
At the end of the study	32.08 (2.25) ^{e, h}	32.54 (2.54)	31.53 (2.05)
FSFI score ≤ 26.55 (%)			
At the beginning of the study	43 ^{a, c}	20	21
At the end of the study	14 ^f	13	21
Sexual desire [mean (SD)]			
At the beginning of the study	4.54 (0.56) ^{a, d}	5.10 (0.42)	5.16 (0.41)
At the end of the study	5.49 (0.40) ^{c, g, h}	5.56 (0.41) ^{c, e}	5.12 (0.42)
Sexual arousal [mean (SD)]			
At the beginning of the study	5.11 (0.45)	5.25 (0.42)	5.34 (0.37)
At the end of the study	5.31 (0.36)	5.38 (0.37)	5.29 (0.42)
Lubrication [mean (SD)]			
At the beginning of the study	5.17 (0.51)	5.28 (0.43)	5.25 (0.44)
At the end of the study	5.34 (0.37)	5.36 (0.42)	5.26 (0.44)
Orgasm [mean (SD)]			
At the beginning of the study	4.86 (0.50) ^{b, c}	5.40 (0.49)	5.42 (0.63)
At the end of the study	5.36 (0.42) ^{e, h}	5.36 (0.43)	5.38 (0.43)

Sexual satisfaction [mean (SD)]

At the beginning of the study 4.80 (0.41)^{b, d} 5.36 (0.44) 5.31 (0.46)

At the end of the study 5.31 (0.40)^{f, h} 5.48 (0.40) 5.27 (0.39)

Dyspareunia [mean (SD)]

At the beginning of the study 5.12 (0.53) 5.22 (0.64) 5.16 (0.68)

At the end of the study 5.27 (0.37) 5.40 (0.34) 5.21 (0.36)

SD — standard deviation

^a $p < 0.05$, ^b $p < 0.01$ vs. vitamin D-treated women with vitamin D insufficiency; ^c $p < 0.05$, ^d $p < 0.01$ vs. vitamin D-naïve women with vitamin D insufficiency;

^e $p < 0.05$, ^f $p < 0.01$, ^g $p < 0.001$ vs. baseline value; ^h $p < 0.05$ — the effect stronger than in vitamin D-treated women with vitamin D insufficiency

Table III. The effect of vitamin D on depressive symptoms in young women with low vitamin D status

Variable	Vitamin D-treated women with vitamin D deficiency	Vitamin D-treated women with vitamin D insufficiency	Vitamin D-naïve women with vitamin D insufficiency
BDI-II score [mean (SD)]	13.4 (3.8)	10.2 (2.8)	10.1 (3.0)
At the beginning of the study	9.1 (3.6) ^{d, e}	8.1 (3.0)	9.8 (3.2)
At the end of the study			
depressive symptoms [n (%)]			
At the beginning of the study	6 (43) ^{a, b}	3 (20)	3 (21)
At the end of the study	3 (21) ^c	1 (7)	3 (21)
mild symptoms [n (%)]			
At the beginning of the study	6 (43) ^{a, b}	3 (20)	3 (21)
At the end of the study	3 (21) ^c	1 (7)	3 (21)
moderate symptoms [n (%)]			
At the beginning of the study	0 (0)	0 (0)	0 (0)
At the end of the study	0 (0)	0 (0)	0 (0)
severe symptoms [n (%)]			
At the beginning of the study	0 (0)	0 (0)	0 (0)
At the end of the study	0 (0)	0 (0)	0 (0)

SD — standard deviation

^a $p < 0.05$ vs. vitamin D-treated women with vitamin D insufficiency; ^b $p < 0.05$ vs. vitamin D-naïve women with vitamin D insufficiency; ^c $p < 0.05$, ^d $p < 0.01$ vs. baseline value; ^e $p < 0.05$ — the effect stronger than in vitamin D-treated women with vitamin D insufficiency