Taiwanese Journal of Obstetrics & Gynecology 59 (2020) 91–98

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Sexual function and depressive symptoms in primary infertile women with vitamin D deficiency undergoing IVF treatment

Zeynep Ozturk Inal [a, *], Hasan Ali Inal [a], Umit Gorkem [b]

[a] Department of Reproductive Endocrinology, Konya Education and Research Hospital, Konya, Turkey
[b] Department of Reproductive Endocrinology, Hitit University Medical Faculty, Corum, Turkey

ARTICLE INFO

Article history:
Accepted 30 May 2019

Keywords:
Depression
In-vitro fertilization
Sexual function
25-Hydroxyvitamin D3

ABSTRACT

Objective: To investigate the prevalence of female sexual dysfunction (FSD) and depression in primary infertile women with 25-Hydroxyvitamin D3 (25-OH VD) deficiency undergoing in-vitro fertilization (IVF)–intracytoplasmic sperm injection (ICSI) treatment.

Materials and methods: A total of 80 women with 25-OH VD3 deficiency (<20 ng/mL = group 1), 80 women with 25-OH VD3 insufficiency (20–29.9 ng/mL = group 2), and 80 women with a normal 25-OH VD3 level (30–60 ng/mL = group 3) were included the study. Female sexual function and depression were measured using the Female Sexual Function Index (FSFI) and Beck Depression Inventory (BDI).

Results: No statistically significant differences were found among the groups in terms of demographic characteristics, baseline and laboratory parameters. Statistically significant differences were observed among the groups with regard to FSD and depression. The FSFI (group 1 = 22.46 ± 2.13, group 2 = 25.82 ± 2.13 and group 3 = 28.66 ± 2.13, respectively) and sexual domain scores were low in women with 25-OH VD deficiency, and the number of women with depression (BDI score ≥ 17) was high ($p < 0.05$). Correlation analysis showed that the sexual domain scores were positively correlated with the 25-OH VD level, and the BDI score showed a significant negative correlation with the total FSFI score and 25-OH VD levels.

Conclusion: The 25-OH VD status was associated with FSD and depression and that the degree of sexual dysfunction could depend on the severity of 25-OH VD levels. Further studies are needed to elucidate this issue.

Introduction

Infertility, which is the inability to become pregnancy despite unprotected regular sexual intercourse for one year, affects about 9.3% and 16.7% of women of reproductive age, and the estimated prevalence in Turkey is around 10% [1–3]. Infertility negatively affects married couples physically, psychologically, and economically [2]. Social and familial pressures also increase this negative effect, and infertile women are especially more prone to depression, anxiety, and stress than men [4].

Sexual function is an important component of quality life, and it is influenced by biological, social, and psychological factors. Sexual dysfunction (SD), which is observed in 20%–60% of the population, is more common in infertile couples, and affects women more than men, is a health problem involving desire, orgasm, lubrication, arousal, satisfaction, and pain [2,4]. The reason for the wide rate of prevalence is that the number of patients who do not receive medical treatment is relatively higher than that of patients who receive medical treatment [5]. Aging, pregnancy, breastfeeding, childbirth, poor educational level and low income, history of pelvic surgery, adrenal disorders, dysfunction of the hypothalamic–pituitary–ovarian axis, metabolic syndrome, diabetes, thyroid diseases, and drug abuse can cause sexual dysfunction [2,4–7].

25-Hydroxyvitamin D3 (25-OH VD) is not only a vitamin that plays a role in calcium homeostasis and bone development but is also a hormone that has pleiotropic effects, such as the regulation of cellular growth, glucose metabolism, and immune function in many tissues and organs, including brain, chest, bones, muscles, and gastrointestinal tract [5,7,8]. A low of 25-OH VD status has been reported to cause insulin resistance and diabetes development, cancer, cardiovascular diseases, autoimmune diseases such as

* Corresponding author. Konya Education and Research Hospital, Meram Yeni Yol Konya, 42090, Turkey. Fax: +90 332 323 67 23.
E-mail address: zeynephafiza@gmail.com (Z.O. Inal).

https://doi.org/10.1016/j.tjog.2019.11.014

rheumatoid arthritis and systemic lupus erythematosus, infectious diseases, chronic pain, and psychological disorders such as depression [2,4–7]. In addition, observational studies have suggested that women with a low 25-OH VD status are predisposed to polycystic ovary syndrome, endometriosis, infertility, and breast and ovarian cancer [9]. The 25-OH VD receptor is found in the most tissues and cells in the body. 25-OH VD is considered to affect reproductive and sexual functions by regulating the aromatase enzyme [10–12]. In case of 25-OH VD deficiency, reproductive physiology and sexual functions are considered to be adversely affected by the effect on the hypothalamic–pituitary–ovarian axis [12,13].

To the best of our knowledge, the number of studies evaluating female sexual dysfunction (FSD) and depression in primary infertile women with 25-OH VD deficiency in the existing literature is limited. In this study, we investigated the prevalence of FSD and depression in primary infertile women with 25-OH VD deficiency undergoing in-vitro fertilization (IVF)–intracytoplasmic sperm injection (ICSI) treatment.

Materials and methods

The study sample consisted of 240 women (23–40 years old) diagnosed with unexplained infertility attending the IVF clinic of Ali Kemal Belviranlı Women's Health and Children's Hospital in Konya between November 2016 and November 2017. The hospital is a tertiary referral center in Konya for patients throughout the country, and it performs an average of 600 IVF–ICSI cycles per year. Institutional review board approval was obtained from by Necmettin Erbakan University Medical Faculty, Division of Ethics Committee (reference number: 2016/1082). The study protocol was explained to the participants, and voluntary participation was asked from them. The informed consent forms were read and signed by all participants. The ethical principles for medical research involving human subjects stipulated in the 18th World Medical Association Declaration of Helsinki were applied.

The primary outcome was the prevalence of FSD. The sample size calculation was performed by the DSS Research Sample Size Calculation Program Statistical package. A minimum of 80 participants was required for each group to demonstrate the difference at $\alpha = 0.05$ and $\beta = 0.20$ [14]. Patients who consecutively underwent the first IVF cycle for unexplained infertility were included in this study and 25-OH VD levels were routinely evaluated during the study period in unexplained infertile patients. According to serum 25-OH VD levels defined by The Endocrine Society clinical practice guideline [15], the participants were divided into three groups. 25-OH VD deficiency was diagnosed in 80 women with serum 25-OH VD levels of below 20 ng/mL (group 1), and 25-OH VD insufficiency was diagnosed in 80 women with serum 25-OH VD levels of 12–29.9 ng/mL (group 2). The control group included 80 age- and body mass index (BMI) - matched healthy women with a normal 25-OH VD status (group 3) defined as serum 25-OH VD levels of 30–60 ng/mL. Infertility was described as the failure to conceive in one year with regular sexual activity. The inclusion criteria were participants who had a male partner and who were sexually active in the last four weeks. The exclusion criteria were male infertility, premature ovarian failure, polycystic ovary syndrome, genital prolapse, history of pelvic surgery, drugs possibly affecting 25-OH VD levels (glucocorticoids and anticonvulsants), psychiatric disorders, acute or chronic systemic disorders (e.g., diabetes, hypertension, cardiovascular disease, neurological disease, thyroid disease, pituitary disease, endometriosis, histories of sexual assault and cancer), use of medication, ongoing treatment for mood disorder and sexually inactive women. Detailed medical histories and patient information, such as age, partner's age, BMI, duration of infertility, educational level, economic status, residence, smoking status, fast food consumption, and cell phone usage, were obtained from all participants. Venous blood samples were collected from the antecubital veins of all subjects from 8 a.m. on cycle day three of the menstrual cycle in the IVF–ICSI cycle after a night of fasting. Thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), prolactin (PRL), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), free testosterone, total testosterone, dehydroepiandrosterone sulfate (DHEA-S), and 25-OH VD levels were measured on the day of sampling.

Serum TSH, fT3, fT4, PRL, FSH, LH, testosterone, and E_2 levels were measured by Advia Centaur XP systems (Siemens Healthcare Diagnostics, Germany). Serum free testosterone was measured by the radioimmunoassay method (LB 2111 Multi Crystal Gamma Counter- Berthold, Germany). Serum DHEA-S levels (NR: 6–27 mIU/ml) was measured by Immulite 2000 through the chemiluminescent immunometric method (Siemens Healthcare Diagnostics). Serum 25-OH VD levels were measured by liquid chromatography–tandem mass spectroscopy.

As asking about sexual activities is embarrassing in our conservative community, a separate comfortable place in the IVF unit was provided for the participants to fill in questionnaires. Complete privacy was assured. Researchers did not know the 25-OH VD status of the participants.

The Turkish version of the Female Sexual Function Index (FSFI), a questionnaire including 19 items divided into six domains (desire, orgasm, lubrication, arousal, pain, and satisfaction), was used to evaluate sexual function in the last four weeks (Table 1). Sexual desire was assessed as frequency and desire level with 2 questions (score 0 or 1 to 5 for each question). Arousal was assessed as frequency, level, confidence and satisfaction with 4 questions. Lubrication was assessed as frequency, difficulty, frequency of maintaining and difficulty in maintaining with 4 questions. Orgasm was assessed as frequency, difficulty and satisfaction with 3 questions. Satisfaction was assessed as the amount of closeness with partner, sexual relationship and overall sex life with 3 questions. Pain was assessed as pain frequency during vaginal penetration and pain frequency following vaginal penetration with 3 questions. It provides a total score and six different domain scores. The total FSFI score ranges at 2–36, with a score <26.55 suggestive of sexual dysfunction [16].

Part III of the questionnaire consisted of the Beck Depression Inventory (BDI), which is a self-reported measure of mood disturbances and systemic disorders, consisting of 21 questions focusing on particular aspects of depression related symptoms (e.g., mood, sense of failure, appetite, and sleeping). In this inventory (Table 2), each item is related to a four-point scale (0–3), and the total score ranges at 0–63. A total score $\geq$17 was considered depression [17,18].

The statistical analyses were performed using SPSS 15.0 for Windows (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was used for examining the continuous variables with normal and abnormal distributions, while the one-way analysis of variance (ANOVA) was used for the normally distributed continuous variables. The Kruskal-Wallis test was used for the abnormally distributed continuous variables. When the Kruskal-Wallis test indicated statistically significant differences, the causes of those differences were determined using a Bonferroni-adjusted Mann-Whitney U test. The nominal variables were analyzed using the Pearson's chi-square or Fisher's exact test, when applicable. The continuous variables were presented as the mean ± standard deviation, and the categorical variables were presented as the number of cases and percentage. For all possible multiple comparisons, the Bonferroni-adjustment was performed to control the

Table 1
Female sexual function index (FSFI).

Question	Response Options
Q1: Over the past 4 weeks, how often did you feel sexual desire or interest?	5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q2: Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?	5 = Very high 4 = High 3 = Moderate 2 = Low 1 = Very low or none at all
Q3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?	0 = No sexual activity 5 = Very high 4 = High 3 = Moderate 2 = Low 1 = Very low or none at all
Q5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?	0 = No sexual activity 5 = Very high confidence 4 = High confidence 3 = Moderate confidence 2 = Low confidence 1 = Very low or no confidence
Q6. Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q7: Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q8. Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse?	0 = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q9: Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q10: Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	0 = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q12: Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?	0 = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q13: Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?	0 = No sexual activity 5 = Very satisfied 4 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
Q14: Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?	0 = No sexual activity 5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
Q15: Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?	5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
Q16: Over the past 4 weeks, how satisfied have you been with your overall sexual life?	5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
Q17: Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?	0 = Did not attempt intercourse I = Almost always or always 2 = Most times (more than half the time) 3 = Sometimes (about half the time) 4 = A few times (less than half the time) 5 = Almost never or never
Q18: Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration?	0 = Did not attempt intercourse 1 = Almost always or always 2 = Most times (more than half the time) 3 = Sometimes (about half the time) 4 = A few times (less than half the time) 5 = Almost never or never
Q19. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or following vaginal penetration?	0 = Did not attempt intercourse 1 = Very high 2 = High 3 = Moderate 4 = Low 5 = Very low or none at all

type I errors. The Spearman correlation analysis was used to study the correlations between measurements. Statistical significance was considered at $p < 0.05$.

Results

From the 261 participants, 21 (8.04%) dropped out. Thus, 240 women were included in the study: 80 with 25-OH VD deficiency, 80 with 25-OH VD insufficiency, and 80 with a normal 25-OH VD status (Fig. 1).

Table 3 describes the demographic characteristics of the study participants. The study groups were comparable in age, partner age, BMI, duration of infertility, educational level, economic status, residence, smoking status, fast food consumption, and cell phone usage ($p > 0.05$).

The baseline and laboratory parameters of the groups are compared in Table 4. No significant differences were found among the groups in terms of baseline FSH, LH, E_2, AFC, TSH, fT3, fT4, PRL,

Table 2
Beck's depression inventory.

	Score	Response
1. Sadness	0	I do not feel sad
	1	I feel sad
	2	I am sad all the time and I can't snap out of it
	3	I am so sad and unhappy that I can't stand it
2. Pessimism	0	I am not particularly discouraged about the future
	1	I feel discouraged about the future
	2	I feel I have nothing to look forward to
	3	I feel the future is hopeless and that things cannot improve
3. Past Failure	0	I do not feel like a failure
	1	I feel I have failed more than the average person
	2	As I look back on my life, all I can see is a lot of failures
	3	I feel I am a complete failure as a person
4. Loss of Pleasure	0	I get as much satisfaction out of things as I used to
	1	I don't enjoy things the way I used to
	2	I don't get real satisfaction out of anything anymore
	3	I am dissatisfied or bored with everything
5. Guilty Feelings	0	I don't feel particularly guilty
	1	I feel guilty a good part of the time
	2	I feel quite guilty most of the time
	3	I feel guilty all of the time
6. Punishment Feelings	0	I don't feel I am being punished
	1	I feel I may be punished
	2	I expect to be punished
	3	I feel I am being punished
7. Self-Dislike	0	I don't feel disappointed in myself
	1	I am disappointed in myself
	2	I am disgusted with myself
	3	I hate myself
8. Self-Criticalness	0	I don't feel I am any worse than anybody else
	1	I am critical of myself for my weaknesses or mistakes
	2	I blame myself all the time for my faults
	3	I blame myself for everything bad that happens
9. Suicidal Thoughts or Wishes	0	I don't have any thoughts of killing myself
	1	I have thoughts of killing myself, but I would not carry them out
	2	I would like to kill myself
	3	I would kill myself if I had the chance
10. Crying	0	I don't cry any more than usual
	1	I cry more now than I used to
	2	I cry all the time now
	3	I used to be able to cry, but now I can't cry even though I want to
11. Agitation	0	I am no more irritated by things than I ever was
	1	I am slightly more irritated now than usual
	2	I am quite annoyed or irritated a good deal of the time
	3	I feel irritated all the time
12. Loss of Interest	0	I have not lost interest in other people
	1	I am less interested in other people than I used to be
	2	I have lost most of my interest in other people
	3	I have lost all of my interest in other people
13. Indecisiveness	0	I make decisions about as well as I ever could
	1	I put off making decisions more than I used to
	2	I have greater difficulty in making decisions more than I used to
	3	I can't make decisions at all anymore
14. Worthlessness	0	I don't feel that I look any worse than I used to
	1	I am worried that I am looking old or unattractive
	2	I feel there are permanent changes in my appearance that make me look unattractive
	3	I believe that I look ugly
15. Loss of Energy	0	I can work about as well as before
	1	It takes an extra effort to get started at doing something
	2	I have to push myself very hard to do anything
	3	I can't do any work at all
16. Changes in Sleeping Pattern	0	I can sleep as well as usual
	1	I don't sleep as well as I used to
	2	I wake up 1–2 h earlier than usual and find it hard to get back to sleep
	3	I wake up several hours earlier than I used to and cannot get back to sleep.
17. Irritability	0	I am not more irritable than usual.
	1	I am more irritable than usual.
	2	I am much more irritable than usual.
	3	I am irritable all the time.
18. Changes in Appetite	0	My appetite is no worse than usual
	1	My appetite is not as good as it used to be
	2	My appetite is much worse now
	3	I have no appetite at all anymore
19. Concentration Difficulty	0	I can concentrate as well as ever.
	1	I can't concentrate as well as usual.
	2	It's hard to keep my mind on anything for very long.
	3	I find I can't concentrate on anything.
20. Tiredness or Fatigue	0	I don't get more tired than usual
	1	I get tired more easily than I used to
	2	I get tired from doing almost anything
	3	I am too tired to do anything
21. Loss of Interest in Sex	0	I have not noticed any recent change in my interest in sex
	1	I am less interested in sex than I used to be
	2	I have almost no interest in sex
	3	I have lost interest in sex completely
Total Score		

total testosterone, free testosterone, and DHEA-S ($p > 0.05$). The mean 25-OH VD levels for women with 25-OH VD deficiency, 25-OH VD insufficiency, and normal 25-OH VD status were 8.14 ± 3.41, 25.26 ± 2.70, and 40.60 ± 7.54, respectively ($p < 0.001$).

The comparison of the different sexual domain scores and prevalence of female sexual dysfunction and depression is summarized in Table 5. Statistically significant differences were observed in the FSFI and sexual domain scores. The mean total FSFI scores ($p < 0.001$) and all sexual domain scores were lower in women with 25-OH VD deficiency than in other groups. The mean total FSFI score was 22.46 ± 2.13 in the 25-OH VD deficiency group, 25.82 ± 2.13 in the 25-OH VD insufficiency group, and 28.66 ± 2.13 in the normal 25-OH VD status group (Fig. 2). In the evaluation of the sexual function domain scores in the groups, all domain scores were found to be significantly lower in the 25-OH VD deficiency group than in other groups ($p < 0.05$ for each parameter). The distributions of FSFI score and BDI score according to 25-OH VD level are demonstrated in Fig. 3. Sexual dysfunction was observed in 58 (72%) women in the 25-OH VD deficiency group, 38 (48%) in the 25-OH VD insufficiency group, and 21 (26%) in the normal 25-OH VD status group (group 1 vs group 2, $p = 0.024$; group 1 vs group 3, $p < 0.001$ and group 2 vs group 3, $p = 0.038$, respectively).

BDI scores and the number of women with depression was statistically different among the groups: 46 (56%) in the 25-OH VD deficiency group, 28 (34%) in the 25-OH VD insufficiency group, and 11 (14%) in the normal 25-OH VD status group (group 1 vs group 2, $p = 0.044$; group 1 vs group 3, $p < 0.001$ and group 2 vs group 3, $p = 0.034$, respectively). Correlation analysis showed that the desire ($r = 0.469$, $p < 0.001$), arousal ($r = 0.386$, $p < 0.001$), lubrication ($r = 0.469$, $p < 0.001$), orgasm ($r = 0.380$, $p < 0.001$), satisfaction ($r = 0.371$, $p < 0.001$), pain ($r = 0.609$, $p < 0.001$) domain scores, and BDI score ($r = -0.565$, $p < 0.001$) were correlated with the levels of 25-OH VD. The BDI score showed a

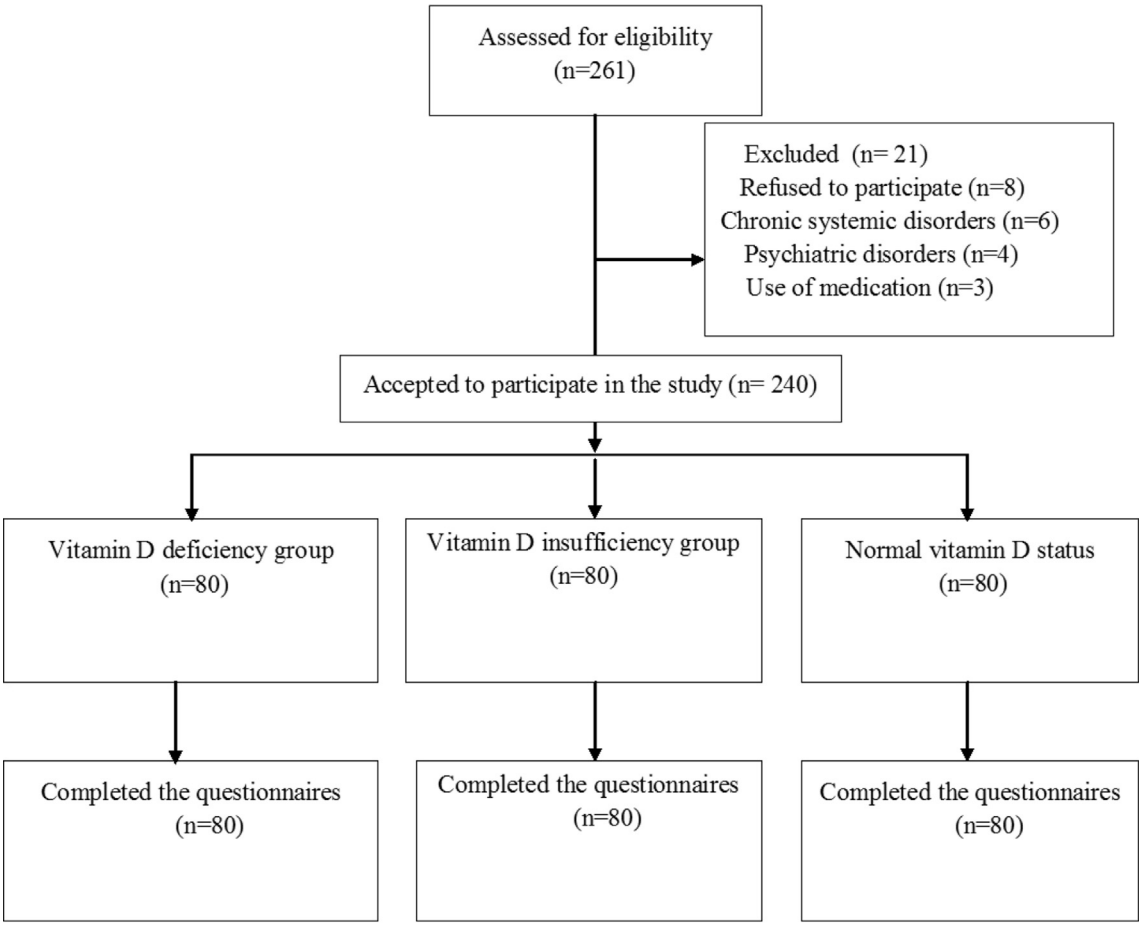

Fig. 1. Enrollment and follow-up of the study subjects.

Table 3
Demographic characteristics of the study participants.

Features (n = 240)	Group 1 Vitamin D Deficiency (n = 80)	Group 2 Vitamin D Insufficiency (n = 80)	Group 3 Normal Vitamin D levels (n = 80)	p value
Age (years)	29.80 ± 3.55	29.12 ± 3.39	28.36 ± 3.64	0.129
Partner age (years)	33.40 ± 4.88	32.52 ± 4.12	32.26 ± 4.30	0.408
BMI (kg/m^2)	26.18 ± 3.82	25.58 ± 3.74	24.62 ± 3.61	0.112
Duration of infertility (years)	5 (2.75–8.00)	4 (3.00–8.00)	5 (2.75–9.00)	0.464
Education level (%)				
Primary or secondary school	35 (44%)	26 (32%)	18 (22%)	0.065
High school	24 (30%)	36 (44%)	27 (34%)	
University	21 (26%)	18 (24%)	35 (44%)	
Economic status (%)				
Lower level (**< 5.000 dollars/year**)	38 (48%)	27 (34%)	22 (28%)	0.130
Intermediate level (**5.000–10.000 dollars/year**)	29 (36%)	34 (42%)	29 (36%)	
High level (**>10.000 dollars/year**)	13 (16%)	19 (24%)	29 (36%)	
Residence the partner lives (%)				
Rural	54 (68%)	51 (64%)	42 (52%)	0.234
Urban	26 (32%)	29 (36%)	38 (48%)	
Smoking status (%)	22 (28%)	14 (18%)	27 (14%)	0.203
Fast-food consumption (%)	22 (28%)	26 (32%)	27 (34%)	0.804
Cell phone usage (%)	53 (66%)	61 (76%)	66 (82%)	0.179

BMI: body mass index.
p<0.05 is statistically significant.

significant negative correlation with total FSFI score (r = −0.332, p < 0.001), desire (r = −0.236, p = 0.004), arousal (r = −0.244, p = 0.002), lubrication (r = −0.199, p = 0.015), orgasm (r = −0.188, p = 0.021), satisfaction (r = −0.258, p = 0.002), and pain (r = −0.262, p < 0.001) (Table 6).

Discussion

In this study, we assess FSD and depression in primary infertile women with 25-OH VD deficiency undergoing IVF treatment. We found that the 25-OH VD status was associated with FSD and

Table 4
Baseline and laboratory parameters of all groups.

Features (n = 240)	Group 1 Vitamin D Deficiency (n = 80)	Group 2 Vitamin D Insufficiency (n = 80)	Group 3 Normal Vitamin D levels (n = 80)	p value		
				1 versus 2	1 versus 3	2 versus 3
FSH (IU/L)	7.24 ± 1.38	7.07 ± 1.17	6.85 ± 1.48	0.365		
LH (IU/L)	5.81 ± 1.37	6.43 ± 1.45	6.26 ± 1.69	0.113		
Estradiol (pg/mL)	49.50 ± 10.01	51.11 ± 8.66	53.87 ± 11.77	0.105		
Antral Follicle Count	8.26 ± 2.33	8.46 ± 2.28	8.98 ± 2.47	0.285		
TSH (μIU/mL)	1.57 ± 0.99	1.72 ± 1.05	1.98 ± 1.18	0.162		
Free T_4 (ng/dL)	1.31 ± 0.45	1.28 ± 0.34	1.18 ± 0.19	0.166		
Free T_3 (pg/dL)	3.20 ± 0.51	3.24 ± 0.51	3.37 ± 0.27	0.145		
Prolactin (ng/mL)	11.93 ± 7.57	14.39 ± 7.98	14.52 ± 7.32	0.164		
Total testosterone (ng/ml)	0.36 ± 0.13	0.37 ± 0.12	0.40 ± 0.11	0.155		
Free testosterone (pg/dl)	1.26 ± 0.46	1.31 ± 0.52	1.41 ± 0.46	0.296		
DHEA-S (μg/dl)	183.47 ± 78.14	187.04 ± 72.58	213.46 ± 88.48	0.127		
25-Hydroxyvitamin D levels (ng/mL)	8.14 ± 3.41	25.26 ± 2.70	40.60 ± 7.54	<0.001[a]	<0.001[a]	<0.001[a]

FSH:follicle-stimulating hormone, LH: luteinizing hormone, TSH: thyroid stimulating hormone, E_2: estradiol, DHEA-S: dehydroepiandrosterone sulfate, fT4: Free thyroxine, fT3: Free triiodothyronine.
[a] Statistically significant.

Table 5
Comparison of the different sexual domain scores, prevalence of female sexual dysfunction, and depression.

Features (n = 240)	Group 1 Vitamin D Deficiency (n = 80) (%)	Group 2 Vitamin D Insufficiency (n = 80) (%)	Group 3 Normal Vitamin D levels (n = 80) (%)	p value		
				1 versus 2	1 versus 3	2 versus 3
Desire score	3.94 ± 0.83	4.56 ± 0.89	4.98 ± 0.70	<0.001[a]	<0.001[a]	0.029[a]
Arousal score	3.54 ± 0.94	4.10 ± 1.03	4.62 ± 0.91	0.012[a]	<0.001[a]	0.022[a]
Lubrication score	3.94 ± 0.83	4.34 ± 0.65	4.74 ± 0.91	0.027[a]	<0.001[a]	0.040[a]
Orgasm score	3.56 ± 0.84	4.04 ± 0.90	4.58 ± 0.75	0.013[a]	<0.001[a]	0.040[a]
Satisfaction score	3.72 ± 0.76	4.18 ± 0.99	4.68 ± 0.80	0.033[a]	<0.001[a]	0.004[a]
Pain score	3.76 ± 0.80	4.60 ± 0.64	5.06 ± 0.50	<0.001[a]	<0.001[a]	0.021[a]
Total score	22.46 ± 2.13	25.82 ± 2.13	28.66 ± 2.13	<0.001[a]	<0.001[a]	<0.001[a]
FSFI score ≤ 26.55 (%)	58 (72%)	38 (48%)	21 (26%)	0.024[a]	<0.001[a]	0.038[a]
BDI score	20.02 ± 7.40	16.04 ± 6.32	13.02 ± 4.23	0.014[a]	<0.001[a]	0.018[a]
BDI score ≥ 17 (%)	46 (56%)	28 (34%)	11 (14%)	0.044[a]	<0.001[a]	0.034[a]

FSFI: Female Sexual Function Index, BDI: Back Depression Inventory.
[a] Statistically significant.

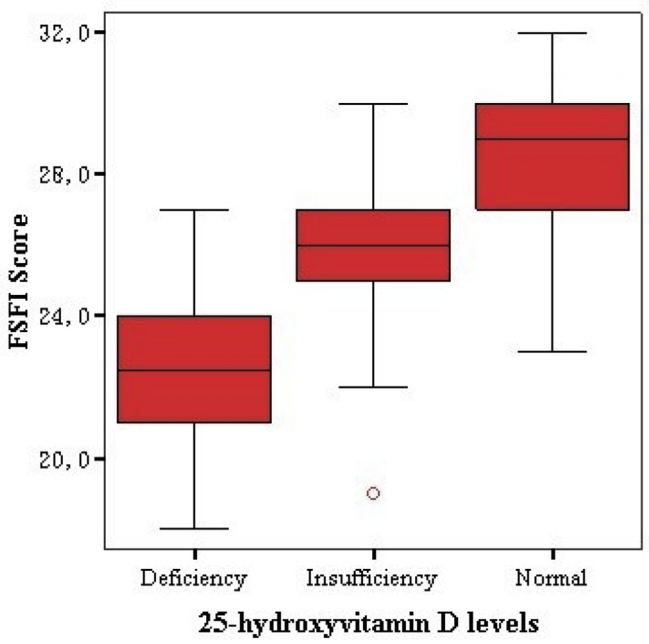

Fig. 2. Whisker plot of FSFI score.

depression and that the degree of sexual dysfunction could depend on the severity of 25-OH VD levels. Moreover, all sexual domains were affected more severely in case of a low 25-OH VD status.

Although research examining the effect of infertility on sexual dysfunction is sufficient, the number of studies investigating the effect of 25-OH VD on sexual dysfunctions is limited. To the best of our knowledge, this study is the first to evaluate the association between FSD and 25-OH VD levels in infertile women undergoing IVF–ICSI treatment. SD is known to be more common in infertile women than in fertile women, varying from 17% to 75% [6,19]. This high incidence is due to psychological pressure, a forced timing of coitus and trying many procedures to become pregnant, and anxiety [6,20]. In the literature, this rate ranges at 40%–60% in Turkey [2,4,21]. However, whether infertile women received any treatment (expectant management, intrauterine insemination, or IVF–ICSI treatment) is not known in these studies. In the present research, all infertile women were treated with IVF–ICSI as fertility therapy, and the prevalence of FSD was observed at 48.66% according to the FSFI score using a 26.55 cutoff value. Several mechanisms, such as age, partner age, BMI, duration of infertility, educational level, economic status, and residence, influence the prevalence of SD in infertile women [22,23]. As our primary aim was to identify the prevalence of FSD in infertile women with 25-OH VD deficiency undergoing IVF–ICSI treatment, we found no difference among the groups in terms of the demographic characteristics of the study participants that could affect the FSD prevalence noted above. In addition, no correlation was observed between FSD and the demographic characteristics of the study participants.

25-OH VD promotes nitric oxide production through endothelial nitric oxide synthase [24,25], cardiovascular diseases, such as hypertension, atherosclerosis, coronary artery disease, stroke, heart failure, dyslipidemia, and atrial fibrillation, have been reported to

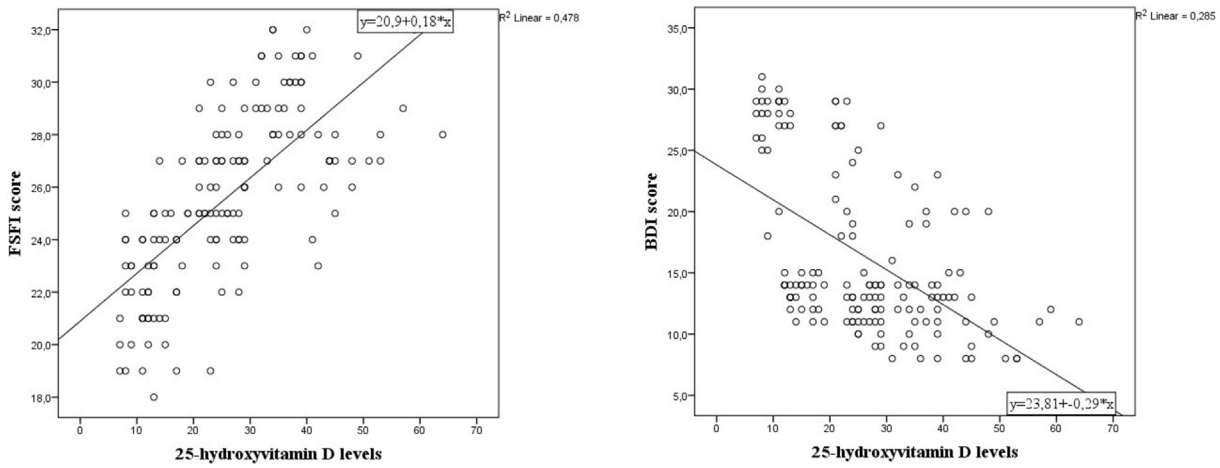

Fig. 3. The distributions of FSFI score and BDI score according to 25-Hydroxyvitamin D3 level.

Table 6
Correlation between domains of the FSFI and 25-Hydroxyvitamin D3, BDI score.

	BDI score		FSFI score		Desire		Arousal		Lubrication		Orgasm		Satisfaction		Pain	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
Vitamin D	−0.565	<0.001	0.736	<0.001	0.469	<0.001	0.386	<0.001	0.385	<0.001	0.380	<0.001	0.371	<0.001	0.609	<0.001
BDI score	–	–	−0.332	<0.001	−0.236	0.004	−0.244	0.002	−0.199	0.015	−0.188	0.021	−0.258	0.002	−0.262	0.001

FSFI: Female Sexual Function Index, BDI: Beck Depression Inventory.
$p < 0.05$ is statistically significant.

be a result of decreased nitric oxide deficiency in 25-OH VD deficiency [2,5–7]. Similarly, sexual functions have been claimed to be affected by decreased blood flow to the pelvic genital organs in women with a low 25-OH VD status [5]. In addition, the production of hormones such as testosterone decreases in infertile women with a low 25-OH VD status, and decreased androgen levels are also associated with hypoactive sexual disorders [5,26]. Exogen androgen and 25-OH VD supplementation has been found to have a positive effect on sexual domains scores [2,5,7]. 25-OH VD plays a regulatory role in reproductive physiology, and in case of its deficiency, female reproductive physiology and sexual functions can be affected unfavorably [12,13]. In our study, total and free testosterone levels did not differ among the groups.

Sexuality in women is complex and managed by the vascular and central nervous system. Therefore, diseases and some drugs affecting the central nervous system can alter sexuality [7]. 25-OH VD receptors are present in the brain, thalamus, hypothalamus, prefrontal cortex, and hippocampus. It regulates the synaptic structure proteins, controls the serotonin synthesis, and affects the production of proinflammatory cytokines in these tissues [7,27,28]. 25-OH VD activates serotonin synthesis through tryptophan hydroxylase activation. Depressive symptoms are common because of decreased synthesis of serotonin in 25-OH VD deficiency [29]. In addition, as 25-OH VD affects the production of proinflammatory cytokines that are active in response to stress, mood changes can also be seen in 25-OH VD deficiency [30]. 25-OH VD replacement therapy may reduce depressive symptoms and has a positive effect on the mood of a person. As FSD is more common in depressed women, 25-OH VD therapy has a positive effect on sexual functions [6,7].

The strengths of the present study include sufficient participants for the groups and the sample being representative of the middle of Turkey. The geographic region where the study participants resided represented typical Anatolia. Therefore, the results of this study could represent Anatolia but could not be generalized to the entire country. Another strength of the study is the addition of a control group.

This study has its limitations. First, in conservative societies, asking questions about sexual functions in the hospital environment could have been embarrassing for the participants, and thus data could have been affected. Second, FSFI and BDI are subjective questionnaires. Third, as the results are single-center results, the findings need to be confirmed with a larger population.

In conclusion, infertile women with low 25-OH VD levels had higher prevalence of FSD and depression than women with a normal 25-OH VD status, and all sexual domains were affected by the low 25-OH VD levels. Therefore, infertility consultants should be aware of FSD and depression because nearly half of women undergoing IVF–ICSI treatment have these problems. Further studies are needed to elucidate this issue.

Funding

None.

Financial support

None.

Presented at a meeting

None.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgements

None.

References

[1] Khademi A, Alleyassin A, Amini M, Ghaemi M. Evaluation of sexual dysfunction prevalence in infertile couples. J Sex Med 2008;5:1402–10.
[2] Turan V, Kopuz A, Ozcan A, Kocakaya B, Sahin C, Solmaz U. Sexual dysfunction in infertile Turkish females: prevalence and risk factors. Eur J Obstet Gynecol Reprod Biol 2014;182:128–31.
[3] Inal ZO, Inal HA, Aksoy E, Kucukkendirci H. Spermiogram test results of patients presenting to our IVF center due to infertility. J Clin Anal Med 2017;8:365–9.
[4] Keskin U, Coksuer H, Gungor S, Ercan CM, Karasahin KE, Baser I. Differences in prevalence of sexual dysfunction between primary and secondary infertile women. Fertil Steril 2011;96:1213–7. https://doi.org/10.1016/j.fertnstert.2011.08.007.
[5] Krysiak R, Gilowska M, Okopien B. Sexual function and depressive symptoms in young women with low vitamin D status: a pilot study. Eur J Obstet Gynecol Reprod Biol 2016;204:108–12.
[6] Gabr AA, Omran EF, Abdallah AA, Kotb MM, Farid EZ, Dieb AS, et al. Prevalence of sexual dysfunction in infertile versus fertile couples. Eur J Obstet Gynecol Reprod Biol 2017;217:38–43.
[7] Canat M, Canat L, Öztürk FY, Eroğlu H, Atalay HA, Altuntaş Y. Vitamin D3 deficiency is associated with female sexual dysfunction in premenopausal women. Int Urol Nephrol 2016;48:1789–95.
[8] Anderson PH, Lam NN, Turner AG, Davey RA, Kogawa M, Atkins GJ, et al. The pleiotropic effects of vitamin D in bone. J Steroid Biochem Mol Biol 2013;136:190–4.
[9] Colonese F, Laganà AS, Colonese E, Sofo V, Salmeri FM, Granese R, et al. The pleiotropic effects of vitamin D in gynaecological and obstetric diseases: an overview on a hot topic. BioMed Res Int 2015;2015. 986281.
[10] Lerchbaum E, Obermayer-Pietsch B. Vitamin D and fertility: a systematic review. Eur J Endocrinol 2012;166:765–78.
[11] Krishnan AV, Swami S, Peng L, Wang J, Moreno J, Feldman D. Tissue-selective regulation of aromatase expression by calcitriol: implications for breast cancer therapy. Endocrinology 2010;151:32–42.
[12] Kinuta K, Tanaka H, Moriwake T, Aya K, Kato S, Seino Y. Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. Endocrinology 2000;141:1317–24.
[13] Yoshizawa T, Handa Y, Uematsu Y, Takeda S, Sekine K, Yoshihara Y, et al. Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. Nat Genet 1997;16(4):391–6.
[14] DSS Research. Researcher's toolkit. Available at: http://www.dssresearch.com/toolkit/sscalc.
[15] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al., Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911–30.
[16] Derogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. J Sex Med 2008;5:357–64.
[17] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatr 1961;4:561–71.
[18] Yilmaz N, Kahyaoglu İ, İnal HA, Görkem Ü, Devran A, Mollamahmutoglu L. Negative life events have detrimental effects on in-vitro fertilization outcome. Hum Fertil 2015 Sep;18(3):220–4. https://doi.org/10.3109/14647273.2015.1022607.
[19] Iris A, Aydogan Kirmizi D, Taner CE. Effects of infertility and infertility duration on female sexual functions. Arch Gynecol Obstet 2013;287:809–12. https://doi.org/10.1007/s00404-012-2633-7.
[20] Monga M, Alexandrescu B, Katz SE, Stein M, Ganiats T. Impact of infertility on quality of life, marital adjustment, and sexual function. Urology 2004;63:126–30.
[21] Oksuz E, Malhan S. Prevalence and risk factors for fe-male sexual dysfunction in Turkish women. J Urol 2006;175:654–8.
[22] Lenzi A, Lombardo F, Salacone P, Gandini L, Jannini EA. Stress, sexual dysfunctions and male infertility. J Endocrinol Investig 2003;26:72–6.
[23] Hassanin IM, Abd-El-Raheem T, Shahin AY. Primary infertility and health related quality of life in upper Egypt. Int J Gynaecol Obstet 2010;110:118–21.
[24] Martínez-Miguel P, Valdivielso JM, Medrano-Andrés D, Román-García P, Cano-Peñalver JL, Rodríguez-Puyol M, et al. The active form of vitamin D, calcitriol, induces a complex dual upregulation of endothelin and nitric oxide in cultured endothelial cells. Am J Physiol Endocrinol Metab 2014;307:E1085–96. https://doi.org/10.1152/ajpendo.00156.2014.
[25] Andrukhova O, Slavic S, Zeitz U, Riesen SC, Heppelmann MS, Ambrisko TD, et al. Vitamin D is a regulator of endothelial nitric oxide synthase and arterial stiffness in mice. Mol Endocrinol 2014;28:53–6. https://doi.org/10.1210/me.2013-1252.
[26] Shifren JL. The role of androgens in female sexual dysfunction. Mayo Clin Proc 2004;79:19–24.
[27] Annweiler C, Schott AM, Allali G, Bridenbaugh SA, Kressig RW, Allain P, et al. Association of vitamin D deficiency with cognitive impairment in older women: cross-sectional study. Neurology 2010;74:27–32.
[28] Mpandzou G, Aït Ben Haddou E, Regragui W, Benomar A, Yahyaoui M. Vitamin D deficiency and its role in neurological conditions: a review. Rev Neurol (Paris) 2016;172:109–22.
[29] Kerr DC, Zava DT, Piper WT, Saturn SR, Frei B, Gombart AF. Associations between vitamin D levels and depressive symptoms in healthy young adult women. Psychiatry Res 2015;227:46–51.
[30] Berk M, Sanders KM, Pasco JA, Jacka FN, Williams LJ, Hayles AL, et al. Vitamin D deficiency may play a role in depression. Med Hypotheses 2007;69:1316–9.