

Vitamin D and depression in women: a mini-review

Mohamed Said Boulkrane¹, Julia Fedotova^{1,2*}, Valentina Kolodyaznaya¹, Vincenzo Micale³, Filippo Drago³,
Annemieke Johanna Maria van den Tol⁴, Denis Baranenko¹

¹International Research Centre "Biotechnologies of the Third Millennium", ITMO University, , 9 Lomonosova Str.
St. Petersburg 191002, Russia,

²Laboratory of Neuroendocrinology, I.P. Pavlov Institute of Physiology RASci., 6 Emb. Makarova, St. Petersburg
199034, Russia,

³Department of Biomedical and Biotechnological Sciences, Biological Tower, School of Medicine, University of
Catania, Via S. Sofia 97, Catania 95123, Italy,

⁴University of Lincoln, School of Psychology Sarah, Swift Building 3201, Brayford Pool, Lincoln, LN5 7AY, UK.

* Corresponding author:

Professor Julia Fedotova, Ph.D. habil., Laboratory of Neuroendocrinology, I.P. Pavlov Institute of Physiology,
Russian Academy of Sciences, 6 Emb. Makarova, St. Petersburg 199034, Russia, E-mail: julia.fedotova@mail.ru,
Tel: +7 911 287 92 73, Fax: +7 812 328 05 01.

Running title: **VD for depressed women**

Abstract

Affective-related disorders, including depression are constantly rising, complicating people's personal life style increasing disqualification and hospital care. Because of the high intensity of urbanization, our lifestyle and food altered dramatically in the last twenty years. These food modifications have been associated to scores of depression and other affective-related disorders in urbanized countries with high economic levels. Nutrients imbalance is considered as one of the critical causes enabling to the pathophysiological mechanisms for the development of psychiatric disorders. Application of additional nutritional interventions for treatment of mood deteriorations can be beneficial for both the prophylaxis and therapy of affective-related disorders. This paper will review recent research on the relation of Vitamin D levels and the epidemiology of depression in women.

In this paper we will provide an overview of the results of a variety of different studies taking on board research which both suggests and refutes an association. Based on these findings we will propose important directions for future research in relation to this topic.

Keywords: Vitamin D, brain, depression, mood, affective-related disorders, aging, women

1. Introduction

The ever-popular Vitamin D (VD) is commonly known as the «sunshine vitamin» [1] and (like sunshine) is implicated to positively alter mood. VD itself is known as a secosteroid hormone, recognized as a neuroprotective factor which plays a role in brain development [2,3]. VD is involved in a range of important physiological processes, such as in promoting cell growth and differentiation, facilitating immunomodulation regulation, and being involved in neurotransmission, and anti-inflammatory effects. On the other hand, low concentrations or deficiency of VD have been associated with various mental and neuropsychiatric disorders, consisting of psychotic and mood disorders, autism, and cognitive decline [2,3]. No doubt, depression plays a very important role in women's disease-related disabilities. The current paper will review and summarize recent research on the relation of VD levels and the epidemiology of depression in women. In this paper, we will outline relevant studies about the relationship between VD and depression in women in an attempt to provide useful recommendations in terms of future scientific questions that need to be addressed in this research area.

2. Vitamin D and lifestyle

Vegetables, herbs and fruits can contribute to a person's health in terms of the levels of VD₂, while meat and fish (especially fatty fish) can contribute to VD₃. This means that VD levels are influenced by environment and lifestyle. However, except for fatty fish, relatively few foods naturally contain large amounts of VD [4]. A recent meta-analysis of 31 studies (with 79366 individuals) showed that some genetic factors might also modulate VD levels [5]. The findings of this meta-analysis were also suggestive of a relatively small heritability rate for VD levels, but overall indicated that modifiable environmental factors are the main determinants of VD levels.

Ultraviolet sunlight synthesis of VD depends on the season, latitude, and amount of skin exposure [6]. Levels of VD vary seasonally, with deficiency more common in winter and at higher latitudes, reflecting ambient levels of sunlight [6], as well as in urban settings, owing to lifestyle choice and lower sunlight exposure [7]. Due to difficulties of darker skin to absorb sunlight, Black and Asian populations are more likely to be affected by lower levels of VD and related negative consequences on health [8]. In most parts of the world, during sunny months optimal levels of VD (approximately 1.000 IU per day) can be achieved by minimal (5 to 15 minutes depending on the level of sun) sun exposure of face, arms, and hands without sunscreen [13].

The liver transports consumed VD₂ and VD₃ with the use of chylomicrons. Plasma which then binds to proteins in turn carries the VD₃ which originates from sunlight exposure [9]. VD is synthesized predominantly endogenously (approx. to 90% of the total VD in human body). In the skin, the ultraviolet light transforms 7-dehydroxycholesterol (provitamin D) to pre-vitamin D, which under the influence of body temperature spontaneously isomerizes to cholecalciferol (VD₃). Approximately 10% of total body VD is taken orally (ergocalciferol and cholecalciferol). VD is transported via VD-binding protein to the liver, where it is hydroxylated to 25-hydroxyVD [9,10]. The next step in VD activation is hydroxylation of 25VD by the enzyme 1 α – hydroxylase (CYP27B1) to 1,25-dihydroxyvitamin D (1,25VD), which is the active VD metabolite. This process occurs predominantly in the renal tubules. In addition,

non-renal CYP27B1 was detected in skin (basal keratinocytes, hair follicles), lymph nodes (granulomata), colon (epithelial cells and parasympathetic ganglia), pancreas (islets), adrenal medulla, brain (cerebellum and cerebral cortex), prostate epithelial cells and placenta (decidual and trophoblastic cells), indicating the wider significance of the VD metabolites [10]. Finally, 1,25VD is inactivated by the enzyme 24-hydroxylase.

1,25VD exerts its effect via the VD receptor (VDR), which is detected in all human organs [10-12]. 1,25VD binds to VDR, the complex forms a heterodimer with the receptor for retinoid X (RXR) within the nucleus. The 1,25VD-VDR-RXR complex binds to VD reacting elements, modulating gene expression [10,11].

Dietary intake of VD rich foods is also important for maintaining healthy 25(OH)VD levels, especially when direct sun-exposure is low. VD status is being evaluated via the serum level of 25(OH)VD – the metabolite formed in the first hydroxylation in the liver, due to its longer half-life (approximately 3 weeks), compared to the active metabolite 1,25(OH)VD (4 – 6 hours) [15]. There is a consensus among experts that we should revise the recommendations for VD intake of 200-600 IU per day which is currently in place, as these cannot adequately prevent VD insufficiency [14, 15]. A healthier recommendation for VD related food intake for individuals with low levels of sunlight exposure would range from 800 to 1000 IU per day. This would subsequently also affect 25(OH) VD levels to be more in the preferred range (30–40 ng/ml) and affect VD related health consequences [15].

3. Women and depression: pathophysiology and epidemiology descriptive

Depression is a condition characterized by at least a 2 weeks period of a variety of symptoms, which include; low and depressed moods, feeling of worthlessness and/or hopelessness, loss of pleasure and/or interest in daily activities, decreased energy levels, loss of appetite, disturbance of sleep, and changes in psychomotor function, and suicidal ideation and/or action [16,17]. Nowadays, approximately 840 million people worldwide are affected by depression with females being affected more commonly than males (at a ratio of roughly 2:1) [16].

3.1. The pathophysiology of depression

Genetic and epigenetic factors have commonly been named as playing a potential role in depression. Belmaker and Agam [17], however, also argued for two other predominantly pathophysiological contributors of depression, which we will outline below. First, according to the «monoamine deficiency hypothesis», with respect to the brain depression can be related to the functioning and amount of monoamine neurotransmitters. Traditionally, selective serotonin reuptake inhibitors (SSRIs)/selective norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, and tricyclic antidepressants are commonly prescribed for treatment of affective-related disorders. It is generally accepted that these psychotropic drugs can reduce levels of biogenic monoamines in the structures of the brain that are closely involved in the pathophysiology of mood disorders [17]. While some research has found that levels of serotonin and norepinephrine are reduced among those people suffering from depression, research does also suggest that impairments in the functioning of monoamine plays a role in depression [17]. It has for example been demonstrated that depression can be produced in individuals with a history of the disorder when levels of neurotransmitter substrates

are intentionally depleted [18] yet, the depletion of these neurotransmitter has not been found to effect healthy individuals. This can be interpreted as monoamine malfunctioning playing an important role in people's predisposition to depression.

The second hypothesis suggest that the onset of depression can partly be explained by the pathophysiological impact of stress [17]. It is well-known that stress factors activate the corticotropin-releasing hormone (CRH) release rein the hypothalamus, which produces secretion of the adrenocorticotrophic hormone (ACTH) by the pituitary gland, which than induces cortisol release from the adrenal glands [18,19]. This suggest that reduced functioning of the hypothalamic-pituitary-adrenal (HPA) axis may directly contribute to mood disorders such as depression and anxiety. However, support for this hypothesis is mixed, as clinical studies among individuals with depression have not consistently found that cortisol levels or the function of the HPA axis in depressed individuals are different than in non-depressed counterparts [18,19]. Supporting this hypothesis, it was, however found that some depressed individuals had chronically elevated cortisol levels, increased CRH levels in their cerebrospinal fluid, and impaired negative feedback [19]. Moreover, recent research [20], also found that the hippocampus of depressed individuals was significantly smaller than in non-depressed individuals and found lower levels of neurogenesis in their hippocampus as a result to stress. Moreover, other evidence for this hypothesis comes from studying the working of antidepressants, as these stimulate monoamines which affect stress related activity of the HPA axis [20].

3.2. Epidemiology

The estimated total population prevalence of major depression is ranging between 6% and 17% [26]. However, research on the psychiatric epidemiology of depression has extensively found that women more commonly suffer from depression than men and that women have higher risk to develop depression than men. This trend is already present among teenagers [21-24] and mood disorders in this group are estimated to be one and a half to three times as high among women when compared to men [25]. Mood disorder related sex differences continue during adolescence, with girls experiencing elevated depression scores compared to boys [28-31]. A small numbers of epidemiological studies on minor depression [35] or brief recurrent depression [36] have found more depression prevalence among women than men. Moreover, in survey research among young individuals it was found that this gender divergences starts at the age of 11 to14 years old [37], and that the likelihood of girls to develop depression over boys is clear by the age of 12 years and follows through the lifespan. When studying minor depression and dysthymia many epidemiological studies have also found similar results, with a female to male prevalence ratio around 2 to 1 [27]. Fortunately, depression symptoms are still reduced for early childhood (<1%) and research fails to demonstrate statistically differences for depression development in boys and girls during this stage [32-34].

The above findings may indicate that sex gonadal hormones have a role in the heightened predominance of depression scores among women. These hormones such as progesterone and estrogen have been reported to have a key role in depression among women [38]. Moreover, a nuanced interplay between the HPA axis and sex specific hormones may also play a very significant role in the onset of depression [38]. Clinical studies reported that affective-related disorders in women are more frequently connected with other pathophysiological alterations in their organism, such as

modifications of sex hormones levels for menopause [39], taking birth control, or undergoing hormonal replacement therapy [40].

It is well-known that gonadal steroid receptors are nuclear receptors which act as transcription factors and can thereby induce long-lasting effects on the brain functions modulating gene expression [38]. Moreover, gonadal hormones have both organizational influence on organisms (creating permanent modifications during critical periods of development) and ameliorating influence on organisms (facilitating transient influence on organism). Endocrine imbalance or abnormal functioning of steroids receptors can therefore significantly change monoamines balance in the brain, especially serotonin and noradrenalin levels [41]. Estrogens imbalance significantly contributes to the vulnerability of women to become depressed and may also contribute to physiological alterations in the effectiveness of pharmacological therapy.

It is well-established that gender differences in depression occur for the first time at adolescence with great scores in adulthood [42]. That is why adult women have higher rates of depression compared to other populations [42]. In this age group, depression levels are similar to other stages of life, but the specific mechanism of affective-related disorders is not completely understood [43]. Nevertheless, the evidence clearly indicates that genes interact with the environment [43,44] and a particularly provocative impact of hormonal balance.

Another high-risk period for developing a new depression episode in women is during pregnancy or after birth of a child and this is especially the case for women who have had mental health problems or depressive symptoms before [45]. It has been found that 10 to 16 % of pregnant women will suffer from depression [46-48]. Moreover, women with bipolar disorder during pregnancy are estimated to have moderate rate relapse between 30% and 50% during the postpartum period.

These findings are in line with general reports that the risk of the development of mood disorders is enhanced with a past medical report of affective-related disorders [49-50]. It has however also been found that a third of depressed pregnant women have never had major depression before [51]. Other risk factors for antenatal depression include; marital issues, a lack of or inadequate social support, recent negative life events, low socio-economic status, and unplanned pregnancies [50,52].

Adolescence, pregnancy, parturition, and reproductive senescence are all well-established states in women which are characterized by a profound hormonal shift. The earlier studies postulated that depression which is associated with estrogen deficiency in menopause related to a number of physiological factors, among which loss of fertility [53,54]. These factors can be the biological drivers that increase susceptibility for depressive disorders. Perimenopause is also characterized by estrogen deficits and is accompanied by affective-related disorders [42,55]. It was found that women without clinical manifestations of depressive episodes before the menopause, but with medical report of early life adversity, have a higher risk for the development of depressive-like disorders during the menopause in contrast to women without such a history earlier in life [56]. The main predictors for depression in the menopausal period in women are; postpartum depression, miscarriages, or no live births [53]. Moreover, there are some association between vaginal dryness and/or hot flashes and the symptoms of perimenopausal depression in women [57,58]. Furthermore, appearance of depression in menopausal women can be more declared than earlier in life [59]. These results indicate that deteriorations of the normal cyclicity of female hormones may intensify the risk for development of depression

in women at the menopausal transition. These findings are consistent with the hypothesis that female hormones imbalance can drive postpartum depression [60- 61]. Interestingly, a history of major depressive episodes in women is very often linked to an earlier lack in functioning of the ovaries [62], indicating that the relationship between female steroids and mood disorders may be synchronous. The depressive symptoms levels at post-menopause state are much more comparable to those of men [63], indicating that the negative effects of female gonadal hormones have weakened. Neuroactive steroids, nevertheless, keep their biological activity in the central nervous system even after the menopause. Additionally, the general organizational effects of female hormones in the brain are presented during all life in women. Thus, the total endocrine medical record of a woman, especially following menopause, may provide her more or less vulnerable to arising episodes of depression [64].

4. Vitamin D and women depression: is there a relationship?

Only few studies or reviews demonstrated that VD insufficiency is corresponded to mood disorders in young females with good health, even despite women's high rates of mood disorders and increasing evidence to show that VD deficiency is associated with depression [65]. Moreover, a long-term clinical work recently showed that the cumulative rate of depression was 63.4% for women vs. 34.7% for men [66]. So, depression puts a huge health burden on women in specific. Moreover, even without a VD deficiency, it has been documented in many studies that individuals with a normal to high levels of VD develop depression [67-77].

There is a growing scientific opinion that links VD deficiency to the pathophysiology of depression [78-81]. Four lines of evidence proposed that the biological mechanisms play an important role in this: first – there are receptors of VD distributed in various areas of the brain (limbic system, cerebellum, and cortex) which control behaviors and are involved in emotional processing and affective-related disorders [82-85], second – there are lower levels of VD in depressed people compared to controls [67,78,80,86], third - VD regulates the synthesis of serotonin via the modulation of the tryptophan hydroxylase 2 gene expression [87], fourth – there is an important modulatory role for VD in the regulation of immuno-inflammatory pathways that has proven to be relevant to the pathophysiology of depression by activating the stress response [88-94].

The above-mentioned evidence has spawned a series of trials (with mixed results) that have tried to answer the question whether VD supplementation among depressed patients might improve their depression scores. Thus far, a few meta-analyses have included studies assessing the effect of VD on depressive symptom scores in individuals without a clinical diagnosis of major depression [95-99]. Further, as the authors of these studies point out, many of the included patients had very low depression scores to begin with, which may be the reason for the marginal effects noted. However, the observational nature of the included studies don't give any clear conclusion on a typical link between VD and depression. Therefore, there is little longitudinal data on the relationship between VD and depression. Thus far, meta-analyses indicate that VD treatment failed to markedly reduce manifestation of depression [98,100]. Recently, a large-scale population-based study, included 3.251 adults of over 55 years old, examining long-term associations between serum VD levels and depression identified a cross-association between low VD and depression, but did not reveal any evidence of a longitudinal relationship [101]. However, if VD is a risk factor for depression,

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we would expect VD concentrations to have a longitudinal association with depression and depressive symptoms, which was not found in this study [101]. Although this is in contradiction with the findings of two other longitudinal studies [102,103] and with studies of Vellekatt [103], which revealed a relationship between suboptimal VD concentrations and the presumed appearance of mood disorders.

A meta-analysis explored randomized controlled trials (RCTs) in which VD supplementation was used as a treatment for depression and identified six RCTs with 1203 participants (72% women), 71 of whom were with current depression (5 trials included patients at risk of depression and 1 trial included patients with depression). There was no significant effect of VD supplementation on depression scores [104,105]. From this systematic review and the aforementioned systematic review of Anglin [70] are corroborated the conclusion of previous narrative reviews, indicating that no clear causal relationship between suboptimal VD levels and depression was identified. Nevertheless, the evidence on the relationship between VD and depression poses the problem that numerous preclinical and clinical studies involve older populations or populations undergoing drug treatments meaning that more research will be needed on this topic [106-108].

5. Application of Vitamin D as preventive and curative agent in women with different health conditions for treatment of depression

Only one small, randomized, double-blind trial of VD₃ augmentation of a specific antidepressant in depressive disorder has occurred. This involved, a clinical study [109], consisting of fifty female participants with type 2 diabetes mellitus (T2DM) and markedly depressive symptoms, all of whom were participating into the “Sunshine Study,” as part of which VD treatment for 7 days (ergocalciferol, 50.000 IU) was applied on a daily basis for a 6 months period. 92% of the women that were examined in this study demonstrated depressive and anxiety symptoms (PHQ-9, State-Trait Anxiety), and worse health parameters (SF-12). A profound reduction of depression (CES-D and PHQ-9) and anxiety scores, as well a high level of mental health status (SF-12) were registered in women treated with VD. The deficit in depressive parameters remained marked (CES-D) when additionally testing for probits (baseline depression (PHQ-9), baseline VD, body mass index, race, and season of enrollment). Moreover, women who did not apply antidepressants/anxiolytics had a more significant therapeutic response to VD treatment. In other words, the conclusion of this randomized trial indicates that VD treatment for correction of physiological and psychological health in T2DM women is beneficial.

Another study reports that 11% of pregnant women showed strong VD deficiency, and 40.3% of them had a moderate VD deficiency. During pregnancy EPDS scores and 25(OH)D₃ levels were found to be inversely correlated with higher depressive symptoms relating to lower 25(OH)D₃ levels. A significant negative correlation was also found for VD levels and depressive symptoms at three postpartum times. Moreover, cross-sectional study showed that elevated VD food intake may be associated with lower levels of depressive symptoms during pregnancy. Moreover, the enhanced serum VD levels were significantly correlated with decreased levels of depressive symptoms during pregnancy [111].

In another study, 47 women with problems with their levels of VD [112] were selected. 16 women with VD deficiency were then submitted to VD treatment (4.000 IU daily, per os) for 6 months. In turn, 31 women with VD insufficiency were equally divided into 2 groups: one group of 17 women who were treated with VD preparations (2.000 IU daily, per os) or another group of 14 women who were not treated with any VD therapy. All women from this study filled in several questionnaires estimating depressive symptoms (BDI-II) and female sexual functioning (FSFI). The total FSFI score and scores on several of the sub-scales (orgasm, sexual desire, and satisfaction) were decreased for the treatment compared to the control group. However, the overall BDI-II score statistically increased in women with VD deficiency compared to women with VD insufficiency. VD enhanced sexual parameters (overall FSFI score, desire, orgasm, and sexual satisfaction) in both groups of patients with VD deficiency and VD insufficiency, and diminished the overall BDI-II score in women with VD deficiency. These findings suggest that VD application contributes to mood and female sexual functioning in women with low VD blood levels.

In a clinical double blind, randomized controlled trial by 80 perimenopausal women who had a score ≥ 13 on the Edinburgh Postnatal Depression Scale and ≥ 20 on the Fatigue Identification Form, respectively, were randomly divided to the experimental or control subgroups over a 4 to 10 months after giving birth [113]. One group of women from this study was treated by VD₃ 1000 IU on a daily basis over a period of six months, whereas the women in the control group received a placebo drug for the same period of time. VD treatment reduced depression and fatigue scores in depressed women. Based on these results the authors proposed that VD application should be suggested as a standard treatment for women who have a high trigger factors for depression in the postpartum period after birth.

Other randomized trials [114] have shown benefits with VD supplementation in seasonal affective disorder (100.000 IU daily, per os) patients hospitalized in a general hospital receiving 20.000 IU VD₃ twice a week compared with placebo (participants were neither VD deficient nor clinically depressed) [115]. Nevertheless, a randomized clinical study in which VD₃ (800 IU, per os, daily) was given to women aged 70 or over did not identify any significant improvement in mental health outcomes with supplementation, although the study was limited by a low level of depression in the study sample and the moderately low dose of VD₃ [116].

On the other hand, numerous studies might validate several of the above conclusion. More specific, some of the above studies are limited by being underpowered, due to small sample sizes. In addition, most conclusions have been based on heterogeneous study populations which has resulted in inconsistent results, which at best provide a slight signal of a beneficial effect of VD on mood [116]. In sum findings till data are far from conclusive. The summarized data from several studies is presented in Table 1.

6. Discussion and Conclusion

There appears to be evidence that early-life lack of VD may be as physiological trigger for depression development at a later period in life. It may be that VD at non-optimal levels is no longer neuroprotective, perhaps because of the loss of its antioxidant or anti-inflammatory effects, making it more vulnerable to emerging neuropsychiatric diseases such as affective-related disorders. VD deficiency has been associated with poorer mental health, depression and

psychotic disorders, as well as chronic physical problems. However, the factual basis that VD is a potential cause rather than the consequence of

Table 1

Effects of Vitamin D treatment on affective-related state in women

Women's health status	Dose/duration of VD treatment	Effecacy of VD treatment	Investigation
Adolescents girls	4000 IU, daily for 3 months, than 2000 IU, daily for 2 months	Yes	Högberg et al., 2012
Young pregnant women	228 IU, daily for pregnancy	Yes	Miyake et al., 2017
Young postpartum women	1000 IU, daily for 6 months	Yes	Rouhi et al., 2018
Menopausal women with diabetes type 2	50.000 IU, daily for 6 months	Yes	Penckofer et al., 2017
Menopausal women	40.000 IU, per week for 6 months	No	Kjaergaard et al., 2012
Postmenopausal women	20.000/40.000 IU, per week for 1 year	Yes	Jorde et al., 2008
Postmenopausal women	800 IU, daily for 6 months	No	Dumville et al., 2006
Postmenopausal women	500.000 IU, per year for 3-5 years	Yes	Sanders et al., 2011

depression is lacking, although there is some evidence that VD deficiency in development may be relevant to the risk of psychosis.

In general, several clinical randomized trials are strongly recommended to investigate the interaction between depletion of VD stores and affective-related states, especially, depression. Moreover, these trials should contain healthy and non-healthy women in different life periods and from different race/ethnicity. While impressive gains have been made by researchers to clarify the neurobiology of depression, the contradictory data from clinical and preclinical studies underscore that interpersonal as well as non-personal variables may promote to polymorphism of depressive disorders, which should be considered as the pathophysiological basis for several different forms of treatment . For studying the critical role of VD in depression, research also needs to consider these factors in designing any future research with the aim of treating depression.

LIST OF ABBREVIATIONS

BDI-II = scale of depressive symptoms
CES-D = Center for Epidemiologic Studies Depression
CRH = corticotropin-releasing hormone
CYP2R1 = 25-hydroxylase
EPDS = Edinburgh Postnatal Depression Scale
FSFI = female sexual function
GC = group component
HPA = hypothalamic-pituitary-adrenal
NADSYN1/DHCR7 = 7-dehydrocholesterol reductase
PHQ-9 = Patient Health Questionnaire
SF-12 = Short Form
SNRIs = selective norepinephrine reuptake inhibitors
SSRIs = selective serotonin reuptake inhibitors
T2DM = type 2 diabetes mellitus
VD = Vitamin D

A CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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