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Vitamin D: Between the brightness of the sun and the darkness of depression



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ABSTRACT

Introduction: The scientific literature suggests a relationship between vitamin D (VitD) and the onset, treatment and prognosis of depression. However, this line of research continues to be controversial. The aim of the study was to analyse the relationship between depression and VitD values, controlling for the influence of the season.

Material and methods: Observational and cross-sectional study. The sample was made up of 150 adult female volunteer participants (aged between 28 and 78 years). The sample was stratified into three groups: a) depression without treatment, b) depression under treatment with antidepressants, and c) without depression (control). VitD values (ng/ml) were compared.

Results: Significant differences were found between the three groups surveyed. The group of participants with depression without treatment obtained the lowest VitD values (mean 18.62 ng/ml; SD 8.42), compatible with severe insufficiency. The group of participants with depression in treatment obtained higher values than the previous group, although in an insufficient range (mean 23.80 ng/ml; SD 11.30). The third group (control) obtained the highest values and in accordance with the desirable range (mean 30.19 ng/ml; SD 10.21). There were no age differences between the groups. When controlling for possible effects of the season, the previous differences in VitD between the three groups were maintained, with an evident decrease of all the mean levels in the winter period.

Conclusions: Depression is associated with insufficient VitD values. Treatment with antidepressants improves these values, although they continue to be insufficient. The findings of this study reinforce the evidence for an association between depression and VitD.

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Vitamina D: entre el brillo del sol y la oscuridad de la depresión

R E S U M E N

Palabras clave:

Vitamina D
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Introducción: La literatura científica indica que hay relación entre la vitamina D (VitD) y el inicio, el tratamiento y el pronóstico de la depresión. Sin embargo, esta línea de investigación continúa siendo motivo de controversia. El propósito del trabajo es analizar la relación entre la depresión y los valores de VitD, controlando por la influencia de la estación.

Material y métodos: Estudio observacional y transversal. La muestra quedó conformada por 150 voluntarias adultas (edad, 28-78 años). Se estratificó la muestra en 3 grupos: depresión sin tratamiento, depresión en tratamiento con antidepresivos y sin depresión (control). Se compararon los valores de VitD.

Resultados: Se hallaron diferencias significativas entre los 3 grupos de comparación. El grupo con depresión sin tratamiento obtuvo los valores de VitD más bajos (media, $18,62 \pm 8,42$ ng/ml), compatibles con una insuficiencia grave. El grupo de participantes con depresión en tratamiento obtuvo valores más altos que el grupo anterior, aunque en la franja de insuficiencia ($23,80 \pm 11,30$ ng/ml). El tercer grupo (control) obtuvo los valores más altos y acordes con el intervalo deseable ($30,19 \pm 10,21$ ng/ml). No hubo diferencias de edad entre los grupos. Al controlar por posibles efectos de la estación del año, las diferencias previas de VitD entre los 3 grupos se mantuvieron, con un descenso ostensible de todas las medias en el periodo invernal.

Conclusiones: La depresión se asocia con valores de VitD insuficientes. El tratamiento con antidepresivos mejora esos valores, aunque continúan siendo insuficientes. Los hallazgos de este estudio refuerzan la evidencia de una asociación entre la depresión y la VitD.

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Introduction

In 1975, Haussler¹ reported having isolated the nuclear vitamin D receptor (VDR), enabling detection thereof in multiple body tissues. Based on this, research commenced on non-classic actions of vitamin D (VitD) which was distinct from research on VitD's known actions on phosphorus and calcium metabolism. The VDR is a member of the family of nuclear hormone receptors which includes glucocorticoid and mineralocorticoid as well as sex and thyroid hormone receptors; a single receptor mediates all VitD actions, including genomic and non-genomic actions. Its presence has been demonstrated in different tissues, including the brain; therefore, VitD is considered not only a hormone but also a powerful neurosteroid that mediates processes of neurotransmission, neuroprotection and immunomodulation. Indeed, a few years ago, it was referred to as the neglected neurosteroid.²

VitD is primarily produced in the skin through a photosynthesis process, which acts on a cholesterol derivative (7-dehydrocholesterol) to generate preVitD,³ which later is isomerised to VitD.³ VitD in itself is biologically inactive, and must be metabolised to its active form; once in circulation, it is transported to the liver, where it is hydroxylated to form 25-hydroxyvitamin D, its main circulating form. VitD requires a second hydroxylation to be converted to its active form, 1,25-hydroxyvitamin D (calcitriol); this action is mediated by the enzyme 1- α -hydroxylase, which has been found in many tissues, such as prostate, breast, colon, lung, pancreatic, immune-cell and brain tissue. The presence of 25-

hydroxylase, which biologically activates VitD, in neurons and glial cells backs the notion that it can be synthesised directly in the brain. The VDR has been reported to be present in high concentrations in many areas of the brain, such as the hippocampus, cingulate cortex, sensory cortices, substantia nigra and cerebellum. It can cross the blood-brain barrier, play a role in brain development, exert neuroprotective and neuroplastic effects, and regulate neurotrophic factors.³

Based on these neurobiological findings, researchers thought that there might be mechanisms by which VitD influences mood and other neural functions and that, therefore, it could be a factor for prevention, characterisation and treatment of depressive disorders, which are among the most prevalent mental disorders (affecting approximately one in five adults), and other neuropsychiatric disorders. In this regard, Stumpf et al.⁴ found that, given their link to sunlight, VitD abnormalities might contribute to the prevalence of seasonal affective disorder (SAD). However, the results of trials with VitD supplements in SAD have been inconclusive.⁵

Subsequently, although numerous studies of all kinds indicating a relationship between low VitD levels and an increase in the incidence and severity of mood disorders have been published, the topic remains a matter of significant debate. A review by Berridge⁶ clearly postulated that there is evidence of an association between hypovitaminosis D and depression, finding in numerous studies that people with normal VitD levels not only had a lower likelihood of experiencing depression and/or symptoms of depression but also that people with normal VitD concentrations were at decreased risk

of depression.⁷ In addition, a link has been found in youths between depression and hypovitaminosis D,^{8,9} which is also a risk factor for depression in adulthood.¹⁰ In a recent review, Menon et al.¹¹ found VitD levels to be inversely correlated with clinical depression, but concluded that the evidence was not strong enough to recommend universal supplementation in depression.

Eyles et al.,¹² for their part, maintained that, although several cross-sectional studies have reported an association between VitD deficiency and depression, these findings are difficult to interpret, since they may simply reflect behavioural abnormalities in individuals with depression (less exposure to sunlight, less time outdoors, less physical activity and dietary abnormalities that reduce VitD, and this could constitute a case of inverse causality: limited VitD would not cause depression; rather, depression would cause reduced VitD). They reported that prospective studies would have a lower likelihood of this phenomenon. In this regard, Milaneschi et al.¹³ conducted a prospective study in 954 adults over and under 65 years of age, and found that those with low baseline VitD levels had significantly higher scores for depression after three and six years.

In another prospective study in a cohort of approximately 2700 children in the United Kingdom, Tolppanen et al.¹⁴ found a significant association between low VitD levels after nine years and higher scores for symptoms of depression after 11 and 14 years, with this association persisting after controlling for a number of possible confounding factors.

Considering the above, VitD has been proposed in the treatment of patients with depression; it has been used as a preventive treatment, as a sole treatment, as a co-adjuvant to conventional treatment and to treat treatment-resistant depression and depression that does not improve with conventional treatment. Bertone-Johnson et al.¹⁵ examined, in a large sample ($n=81,189$), dietary VitD supplementation at the start of treatment, and found that patients with higher intake had fewer symptoms of depression after three years of follow-up.

Many patients with depression do not achieve remission after several consecutive treatments; the role of VitD as a therapeutic agent in these patients is promising, but debate persists. A systematic review and meta-analysis found a statistically significant inverse relationship between VitD levels and risk of depression upon analysing observational data,¹⁶ although Aucoin et al.¹⁷ found that, due to various methodological inconsistencies across the studies analysed, conclusions could not be drawn on the role of VitD in treatment-resistant depression.

In a more recent meta-analysis, Vellekkatt et al.¹⁸ concluded that, while VitD supplementation has a favourable impact on rates of major depression, though with a moderate effect size, their results should be considered provisional due to the limited number of high-quality trials available.

In sum, the scientific literature offers evidence that patients with depression have hypovitaminosis D,¹⁹ that normal baseline VitD levels and dietary VitD supplementation prevent the onset of depression and that in patients with depression, resistant or not, VitD supplementation added to conventional treatment improves signs and symptoms.¹⁷

Objective

The purpose of this study was to analyse the relationship between depression and VitD levels, controlling for the influence of seasonality.

Materials and methods

A cross-sectional observational design was used. The study was conducted in two cities in Argentina with similar latitudes, 236 km apart: the Autonomous City of Buenos Aires (latitude: 34°36'47"S) and Junín (latitude: 34°35'1.8"S). First, informed consent was requested; then, VitD was dosed in 150 women 28–78 years of age. Later, the women were divided into three groups:

- Group 1: 50 women from the Autonomous City of Buenos Aires, diagnosed with major depressive disorder by an experienced psychiatrist according to the DSM-V criteria, at that time not on antidepressant treatment (ADT).
- Group 2: 50 women who visited the centre with a diagnosis of depression and had already been on treatment for at least six months; this group visited the endocrinology centre in Junín for endocrinology-related reasons, not for depression.
- Group 3, considered a control group: 50 women who visited the endocrinology centre for endocrinology-related reasons without any psychiatric disease, medication or history thereof.

The following were considered exclusion criteria for all groups: patients with diseases of phosphorus or calcium metabolism and patients taking any medication that might alter said metabolism.

Being aware of seasonal differences in VitD levels, the three groups were subdivided and studied in terms of the variables of wintertime ($n=25$), from 21 March to 21 September, and summertime ($n=25$), from 21 September to 21 March.

VitD was dosed by different laboratories with conventional methods from routine clinical practice. VitD levels were considered desirable (>30 ng/ml), insufficient ($20–30$ ng/ml), severely insufficient ($20–10$ ng/ml) or deficient (<10 ng/ml).

Data analysis

Using a statistics software program, first, VitD levels corresponding to the different comparison groups (subjects with depression not on ADT, subjects with depression on ADT and subjects without depression) were obtained (Table 1).

Next, quantitative variable distribution normality was analysed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Once normality was verified, analysis of variance (ANOVA) parametric tests were applied, then subgroups were compared using Tukey's honestly significant difference (HSD) test (Table 2) and Student's t-test (Table 5). A p value <0.05 was accepted as a threshold for statistical significance.

Table 1 – Vitamin D levels in the three comparison groups (n = 150).

	Depression not on ADT (n = 50)	Depression on ADT (n = 50)	Controls without depression not on treatment (n = 50)
Vitamin D (ng/ml)	18.62 ± 8.42	23.80 ± 11.30	30.19 ± 10.21
Age (years)	52.29	52	50.12
Normal VitD levels: desirable (>30 ng/ml), insufficient (20–30 ng/ml), severely insufficient (20–10 ng/ml) and deficient (<10 ng/ml).			

Table 2 – Mean comparison (ANOVA) between the three groups with Tukey's HSD correction. Dependent variable: vitamin D.

(I) Groups:	(J) Groups:	Mean difference (I-J)	Standard error	Sig.	95% confidence interval	
		Lower limit	Upper limit	Lower limit		
ADT	Not on ADT	5.18340(*)	2.01031	0.029	0.4236	9.9432
ADT	Without depression	-6.39100(*)	2.01031	0.005	-11.1508	-1.6312
Not on ADT	Without depression	-11.57440(*)	2.01031	<0.001	-16.3342	-6.8146

Not on ADT: with depression not on antidepressant treatment; ADT: with depression on antidepressant treatment.

The mean difference was significant with $p < 0.05$.

Considering possible effects of seasonal variation over the course of the year in VitD levels, supplementary descriptive statistics are presented for cases evaluated in the summertime (Table 3) and in the wintertime (Table 4).

Results

As Tables 1 and 2 show, there were statistically significant differences between the three comparison groups. The group of participants with depression (not on treatment) showed the lowest VitD levels, consistent with severe insufficiency. The group of participants with depression (on treatment) showed higher levels than the previous group, though in the range of insufficiency, while the third group (control group, without depression) showed the highest VitD levels, which were found to be desirable.

Discussion

This study had the objective of disclosing and comparing VitD levels in a group of adult women with depression not on ADT, a group with depression on ADT and a group without depression (control group). Possible confounding variables, such as age and season of the year, were taken into account.

The first finding to consider was the confirmation that the patients with depression on or not on ADT had low plasma VitD levels, which were maintained in spite of age and season of the year in which they were measured. Women with depression (not on treatment) had severe VitD insufficiency. For their part, the group with depression (on ADT) showed higher VitD levels, though in the range of insufficiency. Only the control group (without depression) showed VitD levels in the normal range. It is important to stress that all the differences indicated were statistically significant. It should also be considered that these differences were independent of age, a possible confounding variable.

Another observation, which was to be expected, was that VitD levels for all groups were lower during the wintertime compared to the summertime. Even the subjects in the control group showed levels corresponding to mild insufficiency in the wintertime evaluation. In any case, those differences were only statistically significant in the group without depression. Interestingly, even with changing seasons, the structure in which the most obvious insufficiency in the group not on treatment and milder insufficiency in the group on treatment were observed was maintained.

Clearly, these observations are in line with the current evidence from the international literature on the relationship between VitD, the brain and depression. One of the mechanisms considered is that VitD might affect brain function and mood through its effects on different neurotransmitters,^{2,3,20,21} such as serotonin (5-HT), a neurotransmitter that has been the subject of extensive study due to its involvement in both the pathophysiology and treatment of depression. VitD would appear to play an important role in managing synthesis and maintenance of normal levels of 5-HT through 5-HT tryptophan hydroxylase 2 promoter activation, while repressing 5-HT tryptophan hydroxylase 1 expression; this would indicate that VitD insufficiency would alter 5-HT production, with the resulting alteration in mood.^{12,22,23} There is also preclinical and clinical evidence of VitD's capacity to increase brain levels of DA and NA; hence, it is considered a potential neuroprotector. It would seem that it also exerts its effects by activating tyrosine hydroxylase, an enzyme with a DA synthesis-limiting function.^{12,24} Furthermore, VitD supplementation — either dietary supplementation or direct addition — is known to increase DA and NA levels in different areas and circuits linked to mood.

In addition, by controlling expression of responsible genes, VitD participates in maintaining the homeostasis of Ca^{2+} and oxidative stress (reactive oxygen species [ROS]), an essential balance for maintaining healthy, functional neurons. While hypovitaminosis D increases Ca^{2+} and ROS by altering neural function, normal VitD levels, as Ca^{2+} reduces, may be

Table 3 – Vitamin D levels and age in the cases evaluated in the summertime (n = 76).

	Depression not on ADT (n = 25)	Depression on ADT (n = 26)	Controls without depression not on ADT (n = 25)
Vitamin D (ng/ml)	20.78 ± 9.02	26.61 ± 10.64	33.81 ± 8.75
Age (years)	50.64	51.62	51.72

ADT: antidepressant treatment.
Normal vitamin D levels: desirable (>30 ng/ml), insufficient (20–30 ng/ml), severely insufficient (20–10 ng/ml) and deficient (<10 ng/ml).

Table 4 – Vitamin D levels and age in the cases evaluated in the summertime (n = 74).

	Depression not on ADT (n = 25)	Depression on ADT (n = 24)	Controls without depression not on treatment (n = 25)
Vitamin D (ng/ml)	16.46 ± 7.32	20.76 ± 11.43	26.58 ± 10.43
Age (years)	53.38	52.57	48.52

ADT: antidepressant treatment.
Normal vitamin D levels: desirable (>30 ng/ml), insufficient (20–30 ng/ml), severely insufficient (20–10 ng/ml) and deficient (<10 ng/ml).

another plausible mechanism for preventing or improving depression.⁶

Lately, there has been a great deal of emphasis on research on the inflammatory component of depression, based on the finding of an increase in the cytokines interleukin (IL)-1, IL-6, C-reactive protein (CRP) and tumour necrosis factor (TNF), indicators of a low-grade pro-inflammatory state in these patients. There is evidence of VitD exerting significant immunomodulatory — in particular, anti-inflammatory — effects by activating the Th2 anti-inflammatory branch and decreasing pro-inflammatory Th1 cytokines. Through this pathway, VitD might decrease the associated pro-inflammatory state in some patients with depression.²⁵

As can be seen, this evidence supports the notion that hypovitaminosis D would alter 5-HT, DA and NA function; Ca and ROS equilibrium; and neuroinflammation. That is, it backs the notion that VitD insufficiency would interfere with the function of neurons and neural circuits linked to depression. It indicates plausible pathways for understanding that hypovitaminosis D alters brain function and, on a secondary basis, causes depression. It also explains plausible mechanisms for the preventive effects of prior suitable levels, and the clinical improvement brought by adding VitD to conventional treatment for depression.

Most publications have indicated that VitD insufficiency could be a cause of depression. The most common causes of hypovitaminosis D include lack of exposure to sunlight, lack of dietary intake, malabsorption syndromes, obesity, liver failure, pregnancy and ageing.¹⁹ However, depression is not usually considered a cause of or factor in hypovitaminosis D. In this regard, due to the (cross-sectional) design of our study, the possibility that depression was a cause of VitD insufficiency in the participants in Group 1 and Group 2 could not be ruled out — since, as proposed by Eyles et al.,¹² behavioural abnormalities would render depressed people more vulnerable to hypovitaminosis D, with subjects with depression altering their health habits, going out less, sleeping more, getting less sun exposure and perhaps following diets with inadequate VitD intake and absorption. Also, as ADT exerts therapeutic effects, sub-

Table 5 – Student's t-test.

	Vitamin D (ng/dl)	p
<i>Depressed not on ADT</i>		0.070
Summertime	20.78 ± 9.02	
Wintertime	16.46 ± 7.32	
<i>Depressed on ADT</i>		0.067
Summertime	26.61 ± 10.64	
Wintertime	20.76 ± 11.43	
<i>Without depression</i>		0.011
Summertime	33.81 ± 8.75	
Wintertime	26.58 ± 10.43	

ADT: antidepressant treatment.

Normal vitamin D levels: desirable (>30 ng/ml), insufficient (20–30 ng/ml), severely insufficient (20–10 ng/ml) and deficient (<10 ng/ml).

jects experience improved mood, go out more, get more sun exposure and follow a better diet with better VitD intake and absorption, which would increase their plasma levels. This could in itself explain why the women in Group 2 had higher VitD levels than in the women in Group 1.

It should be noted that there is no known evidence of biological mechanisms of depression that might interfere with VitD synthesis (due to a change or abnormality in neurohormonal, neurotransmitter or neuroimmune systems). In this regard, Rolf et al.²⁶ showed that hypothalamic neurons with corticotropin-releasing factor (CRF) receptors, central components of the hypothalamic-pituitary-adrenal (HPA) axis, coexist with VitD receptors, and therefore these neurons could respond to VitD and CRF. While it is unknown whether VitD might regulate the HPA axis or vice versa, cross-modulation between CRF and VitD in these neurons could be put forward as one pathway accounting for VitD insufficiency in depression.

We consider it an important finding of this study that women on ADT, such as those in Group 2, had VitD levels above those of the group with depression not on treatment (Group 1). The question of whether this increase was due simply to

changes in behaviour and habits or to a molecular mechanism of ADT remains to be elucidated.

Finally, it must be said that depression is a complex, multicausal disease with a heterogeneous clinical presentation, varied treatments and different pathophysiological mechanisms. These include abnormal HPA axis activity, abnormalities in metabolism and brain levels of 5-HT and NA, abnormal thyroid axis activity, abnormalities in neurotrophic signals such as brain-derived neurotrophic factor (BDNF) affecting neuroplasticity, deficits in dopamine (DA) processing and the brain reward system, an abnormal cognitive style, and a state of neuroinflammation or activation of brain cytokines. The relationship between VitD and depression might be another one of the mechanisms involved, or a different subtype of depression. It would be equally important to clear up the following questions through prospective studies: might a lack of VitD be one of the many causes of depression, or does depression cause VitD insufficiency? Or is there a cross-relationship?

Limitations

This study had significant limitations. First, the sample consisted of subjects from two different urban centres, though they were near each other. Second, blood samples for determining VitD levels were drawn and analysed at different laboratories. Third, the study was conducted in women only, and therefore cannot be generalised to men. Fourth, due to its design (cross-sectional), the study did not allow causal relationships to be established between variables (VitD and depression). Fifth, clinical stage, remission and recovery from depression in Group 2 participants were not considered.

Conclusions and recommendations

Based on the study data, it can be concluded that women with depression had severe VitD insufficiency, while women with depression on treatment had mild VitD insufficiency. VitD insufficiency was heightened in the wintertime in all groups; even in the group of subjects without depression, there were levels corresponding to mild insufficiency, but the structure of the differences between the groups was preserved. There is no evidence of clear biological mechanisms that trigger VitD insufficiency in women with depression; the most plausible mechanism could simply consist of changes in behaviour and habits. The data from this study offer evidence to support the notion that it is essential to determine VitD levels in patients who have symptoms of depression and evaluate the possibility of using it as an addition to conventional treatment, and that suitable levels could play a role in preventing both the onset of depression and relapses of the disease.

Conflicts of interest

The authors have no conflicts of interest to declare.

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