

## Rassegne

# The relationship between Vitamin D and depressive disorders

## *La relazione tra vitamina D e disturbi depressivi*

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**SUMMARY.** Studies have suggested a relationship between low circulating levels of Vitamin D and depression. Vitamin D deficiency may be a consequence of depression-related factors, such as reduced sun exposure, decreased outdoor activity, and dietary changes, but it can also play a role in the pathophysiology of depressive conditions through a range of molecular mechanisms. In the present manuscript, findings related to prospective longitudinal studies on the relationship between Vitamin D levels and depressive symptoms and to randomized controlled trials on Vitamin D supplementation for depressive disorders are reviewed.

**KEY WORDS:** Vitamin D, depressive disorders, pseudo-depression, nutritional psychiatry.

**RIASSUNTO.** È stata suggerita da diversi studi una relazione tra i livelli di vitamina D circolante e la depressione. Il deficit di vitamina D può rappresentare una conseguenza di elementi collegati alla depressione, quali ridotta esposizione alla luce del sole, diminuita attività fisica all'aperto, e cambiamenti nelle abitudini alimentari, ma può anche avere un ruolo nella fisiopatologia dei disturbi depressivi attraverso molteplici meccanismi molecolari. Nella presente rassegna narrativa vengono discussi i risultati inerenti agli studi prospettici longitudinali incentrati sul rapporto tra vitamina D e depressione e agli studi incentrati sulla supplementazione di vitamina D come trattamento di disturbi depressivi.

**PAROLE CHIAVE:** Vitamina D, disturbi depressivi, pseudo-depressione, psichiatria nutrizionale.

## INTRODUCTION

Depressive disorders represent a leading cause of disability worldwide. As mounting evidence suggests a bidirectional relationship between certain dietary patterns and psychological aspects such as cognition, behavior and emotions (i.e. the so-called "nutritional neuroscience")<sup>1</sup>, several macro and micronutrients (such as omega-3 polyunsaturated fatty acids, vitamins, and minerals) have gained attention in the attempt to investigate the neurobiology of depressive disorders<sup>2-6</sup>.

Studies have suggested a relationship between circulating levels of Vitamin D and depression. The sources of Vitamin D include (i) animal-based food (in particular fatty fish), dairy products, and fortified foods (in form of Cholecalciferol, also known as Vitamin D3), (ii) plant-based food (in form of Ergocalciferol, also known as Vitamin D2), and (iii) dietary supplements. Furthermore, another major source of Vitamin D3 is that synthesized in the skin from the precursor steroid 7-dehydrocholesterol by sunlight exposure<sup>7</sup>. However, in order to be biologically active, Vitamin D3 must be hydroxylated in the liver resulting in the formation of 25-hydroxyvitamin (25(OH)D); circulating levels of this form reflect the Vitamin D status<sup>8</sup>. In the kidney the 25(OH)D is further hydroxylated resulting in the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)2D), which is responsible of its biological actions<sup>8</sup>.

Vitamin D was originally studied in relation to bone me-

tabolism, calcium and phosphorus homeostasis. However, the discovery of the nuclear Vitamin D Receptor (VDR) in most tissues throughout the body and of the Vitamin D Response Elements (VDRE) in the promoter regions of targeted genes, opened new frontiers on a more widespread functions of this micronutrient<sup>7,9</sup>.

At the preclinical level, the link between Vitamin D and depression has been suggested by biological research showing the distribution of VDR throughout the adult brain and in the nuclei of neurons in several regions involved in mood and cognition<sup>10,11</sup>. Further, Vitamin D has preliminarily been shown to regulate expression of neurotransmitters and neurotrophic factors in the adult brain<sup>11</sup>, and to have a cross-talk with glucocorticoids in hippocampal cells<sup>12</sup>.

At the clinical level, a cross-sectional association between low levels of Vitamin D and depressive symptoms has been reported extensively (for reviews see<sup>3,4,11,13</sup>). Among the epidemiological studies based on large community groups, several have observed such relationship<sup>14-21</sup> while some failed to replicate the finding<sup>22-25</sup>; differences in outcomes may be related to different age ranges of the included cohort of subjects (with some studies focusing on elderly subjects and some on young or middle-aged subjects), different assessment measures, different clinical severity of the enrolled individuals (with some studies involving patients with Major Depressive Disorders [MDD] and some focusing on depres-

sive symptoms in healthy people), and different potential confounders taken into considerations.

Despite the large quantity of data, the causal relationship between Vitamin D levels and depression is still unclear: Vitamin D deficiency in fact may be a consequence of depression-related factors, such as reduced sun exposure, decreased outdoor activity, and dietary changes, but it has also been suggested to play a role in the pathophysiology of depressive conditions through a range of molecular mechanisms<sup>10,11</sup>.

## PROSPECTIVE LONGITUDINAL STUDIES ON THE RELATIONSHIP BETWEEN VITAMIN D LEVELS AND DEPRESSIVE SYMPTOMS

Despite the abundance of cross-sectional data, relatively few longitudinal studies on the relationship between Vitamin D and depressive symptoms have been conducted. Among these, the majority are on elderly individuals (i.e. age  $\geq 65$ )<sup>19-21,26,27</sup>. May et al.<sup>26</sup> examined the association over a follow-up period of  $1.07 \pm 1.13$  years between levels of Vitamin D and the risk of developing clinical depression (diagnosed using the International Classification of Diseases, Ninth Edition) in a cohort of 7,358 patients with previous cardiovascular and cerebrovascular diseases (age of  $73.1 \pm 10.2$  years); they found that, when compared to optimal levels of 25(OH)D ( $>50$  ng/mL), very low ( $\leq 15$  ng/mL), low (16-30 ng/mL), and normal (31-50 ng/mL) levels of 25(OH)D were significantly associated with depression, and that the risk of incident depression was almost 3-fold for individuals with very low vitamin D levels and approximately 2-fold for individuals with low and normal Vitamin D levels. Milaneschi et al.<sup>27</sup> investigated the relationship between baseline serum levels of 25(OH)D and the development of depressive symptoms (assessed using the Center for Epidemiological Studies Depression Scale - CES-D) over a 6-years follow-up in a sample of 954 older adults (age  $\geq 65$ ) as a part of the Invecchiare in Chianti (InCHIANTI) Study; they found in parallel models that men and women with less than 50 nmol/liter of 25(OH)D compared with those with higher levels showed a significant increases in CES-D scores over time, with such prospective association being stronger in women than in men. Chan et al.<sup>20</sup> prospectively evaluated a sample of 629 community-dwelling men aged  $>65$ , among which the majority had moderately high baseline levels of 25(OH)D; their results did not show significant associations of baseline 25(OH)D with incident depression (assessed using the Geriatric Depression Scale) at follow-up. Almeida et al.<sup>21</sup> found that among 2740 subjects (aged 71-88 years) with no past or current history of depression, 81 developed clinically significant symptoms (established by the Patient Health Questionnaire 9 or by administrative health data) during 6-years follow up, with the adjusted hazard ratio of incident depression for men with plasma 25(OH)D  $<50$  nmol/L being 1.03; the authors concluded that the findings did not support a role for vitamin D in causing depression. Jovanova et al.<sup>19</sup> prospectively followed a sample of 3251 participants (mean age was  $71.6 \pm 6.6$ ) from the Rotterdam Study for  $10 \pm 3.5$  years for the occurrence of depression, finding that baseline low 25(OH)D serum levels were not prospectively associated with change of depressive symptoms (assessed using the CES-D) or incident MDD (according to the Diagnostic and

Statistical Manual of Mental Disorders Fourth Edition - DSM-IV - criteria).

Among the studies on adult individuals (i.e. age between 18 and 65), Milaneschi et al.<sup>18</sup> examined whether serum 25(OH)D predicted depression course at 2-year follow-up in 902 subjects from the Netherlands Study of Depression and Anxiety with current depressive disorders defined according to DSM-IV; they observed that increased 25(OH)D concentration was associated with decreased risk of having a depressive disorder at follow-up, and that higher circulating levels of 25(OH)D were associated with lower duration of depressive symptoms at follow-up. Kerr et al.<sup>42</sup> explored the associations between Vitamin D3 serum levels and depressive symptoms (assessed with the CES-D) in 185 healthy young adult women (age 19-25 years) over five weeks, and found that lower vitamin D3 at week 1 predicted clinically significant depressive symptoms at follow-up. Briggs et al.<sup>28</sup> prospectively followed a sample of 3965 community-dwelling adults older than 50 years from the Irish Longitudinal Study on Aging, examining the relationship between vitamin D levels at baseline and incident depression (evaluated with the CES-D) over 4 years; their results suggested that participants with vitamin D deficiency ( $<30$  nmol/L) had a significantly higher likelihood of incident depression.

One prospective longitudinal study on the relationship between Vitamin D levels and depressive symptoms was performed in children: Tolppanen et al.<sup>29</sup> found in a sample of over 2700 children with  $9.8 \pm 0.74$  years that higher concentrations of 25(OH)D were associated with lower levels of depressive symptoms (assessed with the Mood and Feelings Questionnaire) at age 13.8 years.

## RANDOMIZED CONTROLLED TRIALS ON VITAMIN D SUPPLEMENTATION FOR DEPRESSIVE DISORDERS

While prospective longitudinal studies on the relationship between Vitamin D and depressive symptoms are relatively few, several studies evaluated the impact of Vitamin D supplementation, mainly in the form of cholecalciferol (Vitamin D3), for the treatment of depressive symptoms alone or in combination with antidepressant medications<sup>4,30-35</sup>.

Systematic reviews and meta-analyses on such randomized controlled trials (RCTs) have showed controversial results. For instance, four meta-analyses of RCTs published in 2014 and 2015 led to different findings: Li et al.<sup>30</sup>, Shaffer et al.<sup>32</sup>, and Gowda et al.<sup>34</sup> found that Vitamin D supplementation had no overall effect on the improvement of depressive symptoms, while Spedding found, among studies in which Vitamin D was deficient at baseline and in which patients received a large enough dose of Vitamin D supplements to achieve Vitamin D sufficiency during the trial, a statistically significant improvement in depression with Vitamin D supplements<sup>31</sup>.

Such inconsistency of the findings may reflect the importance of assessing baseline Vitamin D status and of providing the appropriate dosing of Vitamin D supplementation in the evaluation of the antidepressant properties of Vitamin D. Inconsistency of the results across different studies and meta-analyses can also be related to the considerable heterogeneity of the clinical characteristics of the enrolled samples. In fact, the majority of RCTs on Vitamin D treatment for de-

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pression has been conducted in healthy subjects, community dwelling people, individuals with somatic morbidity, and/or subjects with minimal depressive symptoms, while relatively few RCTs have been performed on individuals with clinically well characterized depressive disorders.

The studies investigating the treatment with Vitamin D, alone or in combination with antidepressant medications, in patients with MDD or with high levels of depressive symptoms mainly suggested a significant impact of Vitamin D supplementation on depression improvement<sup>36-41</sup>. This has been supported by Vellekkatt et al., who recently performed a meta-analysis including exclusively clinical trials of Vitamin D supplementation in patients with clinically diagnosed depression, showing that Vitamin D supplementation had a significant positive impact on depression ratings<sup>35</sup>.

## DISCUSSION

Cross-sectional, longitudinal and interventional studies suggest a meaningful relationship between depressive disorders and Vitamin D, although certain confounding factors (including heterogeneity in age ranges of the cohort of subjects, assessment measures, clinical severity of participants, modalities of vitamin supplementation, and covariates in statistical analyses) need to be addressed before drawing definitive conclusions.

At the preclinical level, several links have been investigated which connect Vitamin D to the pathophysiology of depression. Vitamin D has been shown to be implicated in brain development, neurogenesis, neurotransmission, and modulation of proinflammatory cytokines<sup>10,11</sup>, all molecular pathways which have an established role in depressive disorders; this, plus the fact that some<sup>18,26-29,42</sup>, although not all, longitudinal prospective studies in humans showed significant relationships between low levels of Vitamin D at baseline and depressive symptoms over time, raises the possibility that decreased levels of Vitamin D can have a role as contributing factors in the pathophysiology of such disorders.

At the clinical level, Vitamin D supplementation has been shown to be promising as an antidepressant intervention for individuals with clinically significant depressive symptoms<sup>32,35</sup> and/or with baseline Vitamin D deficiency<sup>31</sup>. This is important as, within people with the same diagnosis (e.g. MDD), diverse subgroups may exist which may respond differently to different interventions based on individual underlying biology (for example, studies have been showing that anti-inflammatory medications can significantly ameliorate depressive symptoms only in the subgroup of patients with elevated inflammatory markers)<sup>43</sup>. However, more precise trials need to be implemented as those performed so far used a variety of approaches (e.g. oral or intramuscular administration, with different dosages, in combination or not with antidepressants) which make difficult to elucidate the potentially appropriate Vitamin D supplementation strategy.

Studies have suggested that low circulating levels of Vitamin D and/or supplementation may have a role in (respectively) pathophysiology and treatment of other psychiatric diseases such as schizophrenia and autism spectrum disorders<sup>44,45</sup>, although the knowledge on this is still limited. Further, hypovitaminosis D has been described as a condition which could be misdiagnosed as depression due to the fact

that certain symptoms primarily related to hypovitaminosis D can resemble those of depression, such as myalgias and generalized weakness<sup>46</sup>; this suggests the potential utility of evaluating vitamin D levels in subjects with pseudo-depressive symptoms.

It is possible that Vitamin D supplementation may represent a useful intervention for depression in specifically at-risk groups such as people with insufficient exposure to sunlight, elderly subjects, and individuals with obesity. In relation to the first group, it is known that light, circadian rhythms and seasonality may influence the onset and course of depressive symptoms<sup>4,47-49</sup>. Psychiatrists previously tended to consider that almost exclusively people in Nordic countries were at risk for reduced sunlight exposure; however, the digital era has markedly changed the lifestyle and has reduced the total daylight time worldwide, especially among young individuals, thus increasing their overall risk of Vitamin D deficiency and related health disturbances. This might be less evident in elderly subjects, who are at increased risk of developing hypovitaminosis D due to several factors including poor skin integrity, reduced time spent outdoor, decreased dietary intake, malabsorption disorders, and impaired renal function, as they often routinely receive Vitamin D supplementation for the prevention and management of age-related osteoporosis<sup>50</sup>. Lastly, as obesity is associated with Vitamin D deficiency (this being mediated by a variety of mechanisms including the sequestration of Vitamin D in the adipose tissue)<sup>51</sup> and with increases in lifetime diagnosis of mood disorders<sup>52,53</sup>, it is possible that individuals with obesity represent a group which could potentially benefit from Vitamin D evaluation and/or supplementation in relation to depressive symptoms.

Overall, although the study of Vitamin D in psychiatry is still at a preliminary stage, there is increasing evidence suggesting a potential role of this nutrient for mental health and in particular for depressive disorders, encouraging further research on the topic.

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