Vitamin D and Psychiatric Illnesses

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Abstract

Vitamin D is known not only for its essential role in calcium homeostasis and bone health but also for maintaining a healthy mind. A number of recent studies, in fact, have demonstrated a correlation between vitamin D deficiency and psychiatric illness. In addition to all its other functions, vitamin D acts as a potent neurosteroid hormone, critical to brain development and normal brain function; it is known for its anti-inflammatory properties, which are able to affect many aspects of human health.

The vitamin D receptor, which mediates many of its biological actions, has been found throughout the body, including in the central nervous system. Vitamin D deficiency is common in patients with serious mental illnesses, such as depression, schizophrenia and neurocognitive disorders.

Several risk factors, such as genetic and environmental factors, season of birth, latitude and migration, have been linked to vitamin D deficiency and can explain, at least in part, the association between hypovitaminosis D and mental illness.

The causal link between hypovitaminosis D and mental illness is probably bi-directional; mental illness increases the risk of hypovitaminosis D, and hypovitaminosis D increases the risk of developing mental illness.

The biological mechanism at the base of the relationship between hypovitaminosis D and mental illness is most likely related to vitamin D action on the regulation of inflammatory and immunological processes, which in turn can act as mediators or modulators for the development of clinical symptoms and/or treatment response.

Our review has found sound proof of a significant association between mental illness and vitamin D deficiency, yet it has also highlighted the need to further investigate, in future studies, the direction of the causal link of the relationship between vitamin D deficiency and other specific variables that are involved. This would be important in order to determine the best prevention and treatment strategies for hypovitaminosis D in patients with mental illnesses such as depression, psychosis and neurocognitive disorders.

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Since its discovery in 1921, vitamin D has been known for its role in calcium homeostasis and bone health. Low levels of vitamin D have been associated with bone disorders such as rickets, osteomalacia and osteoporosis [1]. However, these disorders can be considered as simply "the tip of the iceberg" in vitamin D deficiency. Recent studies have shown that most tissues and cells of the human body, including the brain, have vitamin D receptors, thus providing new information about its function [2].

Vitamin D plays an important role in the pathophysiology of psychiatric diseases, as has been shown by various studies on the presence of this vitamin, its receptors (Vitamin D Receptors, or VDRs) and its associated enzymes (CYP24A1 and CYP27B1) in many parts of the brain. The expression of vitamin D receptors (VDRs) in the prefrontal cortex, cingulate gyrus, thalamus, hypothalamus, amygdala, hippocampus and substantia nigra suggests a possible key role of vitamin D in the pathophysiology of psychiatric illnesses such as depression and psychosis [3-6].

It has been proved that vitamin D plays an important role in neurodevelopment, neuroprotection, neuroplasticity and neuromodulation, not only by exercising its biological action, but also by influencing gene expression at the cellular level [6-8].

In addition, there is new evidence regarding the neuroprotective mechanism of vitamin D action on inflammatory processes in the brain [9-19], such as the upregulation of pro-inflammatory cytokines associated with depression and with mental illness [11].

The discovery of vitamin D receptors in extraskeletal systems has caused increased interest in its function in these systems. Further studies have shown a relationship between vitamin D deficiency and cancer, chronic conditions such as diabetes, and metabolic, autoimmune, infective and cardiovascular diseases [2, 12-20].

Clinical observational studies and subsequent systematic reviews have demonstrated that a relationship between vitamin D deficiency and mental illnesses seems biologically possible, especially for those related to affectivity, sense perception and the elaboration of attention, concentration and memory, as well as to neuroendocrine aspects.

It is not clear whether this relationship is the result of serious mental illness with consequent social isolation, or if vitamin D has a regulatory role on those genes in the neuronal network that influence affectivity, cognition and sense perception [21-24].

It has further been shown that patients with mental disorders are at a higher risk for vitamin D deficiency than the general population. In particular, patients with schizophrenia have a greater risk of lacking vitamin D than those affected by other mental illnesses [21, 22, 25-30].

DEPRESSION

Several studies have shown a strong correlation between vitamin D deficiency and depression. A study entitled the *Third National Health and Nutrition Examination Survey* [31] assessed a sample of 7970 U.S. residents aged between 15 and 39 years, and found that people with serum vitamin D levels ≤ 50 nmol/L are at a significantly higher risk for having depression compared to those with serum vitamin D levels that are greater or equal to 75 nmol/L.

For example, a study conducted on 1282 adults of age between 65 and 95 years in the Netherlands [32] showed that persons suffering from depression have levels of 25 hydroxyvitamin D that are 14% lower compared to controls. Moreover, a relationship was found between the severity of the depression and low serum levels of 25 hydroxyvitamin D, which remained significant after adjusting for variables such as age, gender, smoking status, body mass index and number of comorbid chronic diseases.

Reduced serum levels of 25 hydroxyvitamin D and elevated serum levels of the parathyroid hormone (PTH) have been associated with depressive symptoms in various clinical settings. Of interest is an inverse association between 25 hydroxyvitamin D serum levels and depression, which was found even after taken into account several influencing factors such as lifestyle and health among European patients [33].

The relationship between depression and vitamin D was also investigated in older populations and/or in subjects with medical comorbidities [34, 35]. Many studies have shown a significant relationship between vitamin D deficiency and late-life depression as well as in people living at northern latitudes [36].

In a further assessment of an older cohort of a population living at northern latitudes [37], a moderate inverse relationship between vitamin D serum levels and depressive symptoms was observed among both genders. In addition, older men with low vitamin D levels (< 30 nmol/L) were twice as likely to show depression at the time of evaluation compared to men of similar ages whose vitamin D blood levels were adequate (≥ 50 nmol/L), even after correcting for factors such as hypertension and diabetes, which may also contribute to depression.

Interestingly, no significant relationship was found between vitamin D levels and current depression among women. Ultimately, high vitamin serum levels were found to be protective against the development of post-stroke depression (PSD) [38]. The study further found a relationship between low vitamin D serum levels and the development or presence of stroke, as well as an association between low levels of vitamin D and PSD development at one month post-stroke [38].

A recent large cohort study has demonstrated an association between low levels of vitamin D and both the presence and severity of depression, suggesting the possibility that hypovitaminosis D signals an underlying biological susceptibility to depression [39].

Similar results were obtained in the evaluation of a group of subjects affected by secondary hyperparathyroidism (n = 21), in whom low vitamin D serum levels were significantly related to higher scores on the Beck Depression Inventory (BDI), as compared to a control group [40].

In a six-year longitudinal study, Milaneschi, et al. (2010) [41] examined the association between levels of vitamin D at stratum basale and subsequent depression on a sample of 954 adults aged 65 and older. It was found that individuals with low 25 hydroxyvitamin D levels at stratum basale (that is, < 50 nmol/L or < 20 ng/mL) scored significantly higher on the depression rating scale in the two follow-up periods (3 and 6 years) compared to those individuals with elevated 25 hydroxyvitamin D levels at stratum basale, with a more pronounced association (between levels of vitamin D at stratum basale and subsequent depression) in women than in men.

Milaneschi, et al. (2013) [42] studied the association between 25 hydroxyvitamin D levels and depressive disorders in a large cohort aged between 18 and 65 from a Dutch study on depression and anxiety. In this study, lower levels of 25 hydroxyvitamin D were quantified in participants with current clinical depression, in particular in those with more serious symptomatology as compared to the controls.

A negative correlation between vitamin D

serum levels and clinically significant depressive symptoms measured in five weekly assessments was found among a group of young adult women [43]. These findings showed that young black women were more likely to have vitamin D insufficiency and to be depressed compared to other women: this result was in line with those obtained in previous studies [44-46].
Robinson et al. [47] reported that low vitamin D serum levels during pregnancy represent a risk factor for the development of postpartum depression symptoms. Similar results were found by Murphy et al. [48] in evaluating the relationship between vitamin D levels and depressive symptoms in a sample of 97 women, who were assessed monthly for the first seven months of the postpartum period. In this study, women with lower vitamin D levels constantly showed higher rates of depression as compared to women with higher vitamin D levels.
Two additional studies have shown a significant negative correlation between vitamin D serum levels in the first trimester of pregnancy and the presence of depressive symptoms in the second trimester [49, 50].
In addition, researchers have investigated the relationship between vitamin D serum levels in the second trimester of pregnancy and postpartum depression during the first six months after pregnancy [51]. This study showed that lower maternal 25 hydroxyvitamin D levels in the second trimester of pregnancy were associated with more severe depressive symptoms at one week, six weeks and six months into the postpartum period.
A systematic review with a meta-analysis conducted by Anglin et al. (2013) [52] assessed the relationship between depression and hypovitaminosis D, reporting an association between low levels of vitamin D and depression.
Even though most research confirms the hypothesis that a low concentration of vitamin D is associated with depression, some studies have failed to demonstrate this relationship. For example, a large epidemiologic study in China [53] did not find any relationship between vitamin D and depression in a sample of 3,262 men and women of between the ages of 50 and 70.
In another paper, Zhao et al. (2010) [54] carried out a large cross-sectional study among adults of all ages. They were not able to discover a significant correlation between vitamin D deficiency and depression after correcting for potential confounding factors (such as degree of sun exposure, level of physical activity, diet, age and body mass index).
In addition, Black et al. (2014) [55] carried out a cross-sectional study on young adults recruited from the *Western Australian Pregnancy Cohort Study* in order to investigate the relationship between 25 hydroxyvitamin D serum concentrations and symptoms of depression, anxiety and stress. After adjusting for confounding factors (that is, age, race, BMI and physical activity), an increase of serum 25 hydroxyvitamin D of 10 nmol/L was associated with a reduction of only 8% in depression rating scores in males (though not in females), though no significant associations with anxiety and stress symptoms were found.
Almeida et al. (2015) [56] conducted an observational study to assess retrospective, cross-sectional and prospective associations between vitamin D concentrations and depression in a sample of 3,105 elderly men. The authors of this study interpreted their results as not supporting a role of vitamin D in causing depression.

COGNITIVE DISORDERS

Low levels of vitamin D have also been associated with more severe general cognitive deficits [57] and dementia [58-60]. Low concentrations of vitamin D have been associated with cognitive impairments such as memory and orientation [61], executive function disability [62], and Alzheimer's disease [63].
Results from a large study conducted in Italy between 1998 and 2006 suggest that people with severe vitamin D deficiency (<25 nmol/L) have a greater risk of obtaining a substantial reduced score on the Mini-Mental State Examination as compared to people who have sufficient levels of vitamin D (≥ 75 nmol/L) [64]. Low levels of vitamin D in elderly women have been associated with an increased risk of Alzheimer's disease but not with other forms of dementia [65]. Polymorphisms of vitamin D receptors have been associated with depression and poor cognitive performance [66].

PSYCHOTIC DISORDERS

Vitamin D deficiency has been linked to a wide range of important psychiatric disorders and constitutes an emerging research area of interest. Low levels of vitamin D have been found in both inpatients and outpatients with psychosis and schizophrenia, with an inverse correlation between symptom severity and vitamin D serum levels having been observed.
Although the mechanism is not clear, recent studies suggest that the action of vitamin D on the regulation of inflammatory and immunological processes is likely to influence the manifestation of clinical symptoms and treatment response in schizophrenic patients [67].
Results from narrative and systematic reviews or meta-analyses agree in reporting an association between vitamin D deficiency and schizophrenia [68-74]. A significant inverse correlation between vitamin D levels and schizophrenia was also observed in the majority of case-control studies conducted on serum levels and schizophrenic subjects, as compared to healthy controls [75].
The correlation between vitamin D deficiency and development of schizophrenia has been researched among patients of all ages around the world. Recently, one meta-analysis reviewed 19 studies published between 1988 and 2013 and found a strong association between vitamin D deficiency and schizophrenia. Of the 2,804 participants from these studies, over 65% of participants with schizophrenia were vitamin D deficient. Vitamin D deficient participants were therefore 2.16 times more likely to have schizophrenia than participants with sufficient levels of vitamin D. In addition, lower levels of vitamin D were have also been found in cases of consolidated psychosis [76] and first episode psychosis [77].
The risk of schizophrenia and vitamin D levels vary with season of birth, migration status, latitude of residency and skin pigmentation [78-80]. The UV rays needed to produce vitamin D are reduced during the winter months, the same months that are most associated with an increase in births of individuals who later will develop schizophrenia. A review which screened a total of 437,710 individuals with schizophrenia revealed that most were born in January and February. These newborns were thus exposed to lower levels of UV rays during their prenatal and perinatal periods.
An increased rate of schizophrenia has also been observed at higher latitudes, especially among immigrants. This may be again related to the UV availability and the resulting vitamin D status. At higher altitudes, a dark-skinned individual will also have a more pronounced reduction of vitamin D as compared to a lighter-skinned individu-

al. The lighter-skinned individual will have less melatonin, allowing the skin to absorb UV rays more effectively. It is estimated that dark-skinned individuals who live at higher latitudes are more likely to develop schizophrenia than individuals in the general population [67].

Several epidemiologic studies have linked low levels of vitamin D to schizophrenia and psychotic disorders. Norwegian researchers using a structured clinical interview to identify psychosis found consistently low levels of 25 hydroxyvitamin D among immigrants and native Norwegians with psychotic symptoms [81].

Swedish researchers reviewed medical records at a psychiatric outpatient department to identify possible factors that could predict vitamin D deficiency. Over 85% of the 117 psychiatric patients had suboptimal levels of vitamin D. Those with schizophrenia and autism had the lowest levels. Being of Middle Eastern, Mediterranean, Southeast Asian or African ethnic origin was a strong predictor of low vitamin D. Patients receiving vitamin D supplements to correct their deficiencies achieved considerable improvement of psychosis and depression symptoms [82].

In Israel, vitamin D concentrations were measured in 50 patients with schizophrenia, aged 19–65: lower mean vitamin D concentrations were detected among patients with schizophrenia (15 ng/mL) compared to controls (20 ng/mL), after correcting for the impact of sun exposure and supplements [83]. Similarly, in New Zealand 92% of 102 psychiatric adult inpatients had suboptimal levels of vitamin D, more than double with respect to Europeans with serious levels of deficiency (lower than 10 ng/mL) [84].

An inadequate neurosteroid action of vitamin D on the brain, especially during development, is associated with changes such as inflammatory and immunologic disorders, which are also present in schizophrenia [85 86].

In more recent studies on humans, vitamin D deficiency has been linked to hippocampus dysfunction, a region thought to be involved in the pathogenesis of psychotic disorders. A positive correlation between vitamin D and gray matter volume has also been found [87]. Early deprivation of vitamin D or during prenatal life may increase the risk of developing late-onset schizophrenia [5].

A Finnish study of a neonatal cohort showed that vitamin D intake during the first year of life reduced the likelihood of schizophrenia [88]. A study among 8,411 Swedish women showed an association between low levels of vitamin D and psychotic symptoms [89].

In another pilot study, researchers measured serum levels of 25 hydroxyvitamin D in the third trimester of pregnancy and found that lower maternal vitamin D levels were associated with an increased risk of schizophrenia [90]. These findings suggest that low prenatal vitamin D levels may have a negative impact on brain development, thus increasing the risk of the onset of schizophrenia in adulthood.

McGrath et al. (2010) [91] investigated the relationship between neonatal vitamin D status and a later risk of schizophrenia. They identified 424 cases of schizophrenia from the Danish Psychiatric Central Research Register and analyzed neonatal dried blood spot samples. Not surprisingly, they found significant seasonal variation in vitamin D status as well as levels of vitamin D significantly lower in the offspring of mothers who immigrated to Denmark. They also found that those with lower neonatal concentrations of vitamin D had an increased risk of schizophrenia. Researchers estimated that if all these neonates had optimal vitamin D levels, more than 40% of schizophrenia cases could have been prevented.

Furthermore, a link has been hypothesized between vitamin D deficiency and psychotic symptoms. Adolescents [92] or children [93] with vitamin D deficiency suffered more often from psychotic symptoms compared to those with normal levels of vitamin D.

In a prospective study of 3,182 children in England, researchers measured vitamin D levels at age 9.8 years and assessed psychotic experiences at 12.8 years. Vitamin D concentrations during childhood were associated with psychotic experiences during early adolescence. In the case that psychotic experiences were correlated to the development of schizophrenia, this would support a possible protective association of higher vitamin D concentrations with schizophrenia [93].

In addition, cross-sectional analyses were carried out on adolescents aged between 12 and 18 years who requested either hospitalization or partial hospitalization. Of the 104 patients examined, 72% had insufficient vitamin D levels. Vitamin D status was correlated to the severity of the mental illness. Those with vitamin D deficiency were 3.5 times more likely to have hallucinations, delirium or paranoia (Gracious et al., 2012). A second study supports these findings. Vitamin D was analyzed in 20 patients with first-episode schizophrenia. A greater severity of negative symptoms (affective flattening, emotional withdrawal, poor socialization, social withdrawal, abstract thinking and implicit stereotypes) was strongly correlated with lower vitamin D levels [92].

CONCLUSIONS

Evidence suggests a possible association between vitamin D deficiency, depression, psychotic disorders and cognitive dysfunction. However, it remains unclear whether vitamin D deficiency is the cause or the effect of these mental pathologies. Subjects affected by such diseases are more likely to develop low levels of vitamin D, due to reduced outdoor activity and lesser intake of nutrients and pharmacological treatment.

Conversely, the causal link could work in the opposite direction. In fact, the presence of vitamin D receptors in those areas of the brain that have been associated with the development of depression, psychosis and neurocognitive disorders strengthens the plausibility [7] of a common pathogenic pathway between vitamin D and mental illness and of interactions that affect cellular mechanisms which lead to different clinically noted phenotypes.

Furthermore, it remains to be established whether adding supplements of vitamin D may prevent and/or treat such pathologic conditions in individuals with vitamin D deficiency. Indeed studies on the role of vitamin D supplementation have produced contradictory results. This may be attributable to several reasons, including the use of different dosages of vitamin D supplements for different time periods in several studies, the use of different parameters to define vitamin D deficiency, the use of numerous psychometric instruments to measure mental health, and the different frequencies at which vitamin D is administered (i.e., daily, weekly or monthly).

Because of variations in the methodology used in different studies, it is difficult to establish the exact role of vitamin D in preventing or treating mental illness. The literature already provides enough data relative to the screening and treatment of vitamin D deficiency in subjects with mental illness. These are easy, cost-effective practices and may improve the outcome of these diseases.

The non-specific relationship between vitamin D and psychiatric disease may reflect a hidden immune system dysfunction and oxi-

dative stress which – when combined with other genetic and environmental factors and with comorbidity – determine the different phenotypes observed among clinical populations.

Depression has been associated with a function of the immune system mediated by aberrant cells, alterations in the antioxidative blood levels, an increase of reactive oxygen species (free radicals) and oxidative and nitrosative stress leading to neurodegeneration [60, 94, 95].

It has also been hypothesized that immune system dysregulation, oxidative stress and later neurodegeneration may play roles in the pathogenesis of bipolar disorder and schizophrenia [96-100]. Low-content vitamin D cells produce high levels of inflammatory cytokines, while cells with an adequate content of vitamin D release them at significantly lower levels.

It is therefore possible that adequate levels of vitamin D might act as an anti-inflammatory mechanism [67]. Vitamin D modulates the transcription of most of the genes involved in the molecular pathway for the development of schizophrenia, including genes involved in synaptic plasticity, neural development and protection against oxidative stress [57]. Animal studies have shown that vitamin D deficiency during gestational periods affects dopamine metabolism, altering the dopaminergic system in the developing brain. It has been proved that dopamine is involved in the pathogenesis of schizophrenia. Vitamin D deficiency during pregnancy may also affect those cerebral structures associated with schizophrenia [25]. Finally, Alzheimer's disease and other forms of dementia have been linked to dysfunctions of the immune system and oxidative stress [101-104].

Most research utilizes cross-sectional studies that allow scientists to examine the role of vitamin D in mental illnesses at a specific moment, which is not conducive to making inferences about the direction of the relationship. Consequently, further longitudinal, randomized controlled studies are necessary to better understand the causal link. In addition, from the literature there emerges a great heterogeneity of variables used and limits imposed, in addition to multiple definitions of each variable. In particular, there are limited data on psychotic drugs, on vitamin D and on clinical results. Future studies may consider the use of variables compatible with those used in past research in order to reinforce known associations or to discover new ones, thereby standardizing conclusions.

Because of the possible role of vitamin D deficiency in the etiology of commonly treated psychiatric and non-psychiatric disorders, it would be important to identify and address the obstacles to adequate vitamin D intake for the general health of patients with mental illnesses.

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