VITAMIN D
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Vitamin D and psychiatric disorders: analysis of possible causal relationships

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INTRODUCTION

According to the World Health Organisation, more than one billion people suffer from a mental or behavioural disorder. It has been estimated that more than 300 million people in the world, i.e., 4.4% of the global population, suffer from depression. Schizophrenia has a prevalence of 4 to 7 per 1000 people, thus affecting about 20 million people. It follows that not only does treating such a large number of people represent a significant economic effort for the entire healthcare system it also constitutes a challenge for the entire medical sector, given the impact of these illnesses on several clinical fields.

Many scientific findings have clearly shown an association between vitamin D deficiency and depression or schizophrenia. Vitamin D, which is found in the human brain, has been identified as one of the key factors in the regulation of many neurotransmission pathways, including those of dopamine, serotonin, noradrenaline and glutamine. Recent studies have shown that vitamin D deficiency is associated with dysfunction of the hippocampus, a region involved in the pathogenesis of mental disorders, whilst it has also been positively correlated with grey matter volume.

Nevertheless, the causal relationship between vitamin D and mental disorders is still unclear. Even though it has been observed [1].

The aim of this study is to summarise the main scientific findings on the association between vitamin D deficiency and mental disorders, in order to increase the level of knowledge available to clinicians in all fields of medicine as well as to stimulate scientific production and experimental observation on this subject. Indeed, the establishment of a causal relationship would make it possible to understand whether and to what extent vitamin D supplementation might prevent the onset of mental disorders or reduce their symptoms.

VITAMIN D: MECHANISM OF ACTION IN MENTAL DISORDERS

Vitamin D is a steroid hormone that plays key roles in the body's mineral balance, in the proper functioning of the immune system and in the pathogenesis of various disorders, such as cancer and autoimmune diseases.

In psychiatric disorders, vitamin D itself is involved in the region-specific expression of vitamin D receptors (VDRs) in areas such as the cingulate cortex, thalamus, cerebellum, substantia nigra, amygdala and the hippocampus [2]. Most of these regions express 1α-hydroxylase enzymes, which are capable of metabolising 25(OH)D in 1,25$(OH)_2$ D_3, which means that vitamin D has both an autocrine and a paracrine function in the human brain.

The presence of vitamin D, VDRs and related enzymes (CYP27B1 and CYP24A1) in different regions of the brain has made it possible to understand vitamin D's fundamental role as a neuroactive neurosteroid hormone in neuro-immunomodulation, neuroprotection, brain development and normal brain function. Vitamin D deficiency in early life negatively affects neuronal differentiation, axonal connectivity and brain structure and function. All these mechanisms explain the association between vitamin D deficiency in infancy and increased risk of schizophrenia [3]. Analogously, alterations in dopamine transporter expression, neonatal catechol-O-methyltransferase expression and dopamine metabolism have also been reported, which are findings that link vitamin D and its deficiency to schizophrenia.

Given vitamin D's involvement in the control of the inflammatory response, it has been hypothesised that, in the case of depression it acts as a modulating mechanism, regulating the overexpression of depression-associated pro-inflammatory cytokines and the same inflammatory response [4]. Vitamin D is also in-

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volved in regulating the activity of enzymes such as tyrosine-hydroxylase and the rate-limiting enzyme for the biosynthesis of dopamine, norepinephrine and epinephrine. Again, all these mechanisms may justify a positive association between vitamin D deficiency and depression.

VITAMIN D AND DEPRESSION

Depression is the most commonly debilitating psychiatric disorder. The etiopathogenetic mechanisms of depression are pathological and related to multiple aspects of neuronal function [1]. Among the elderly, depression mainly affects those with chronic conditions and cognitive impairment, as the processes associated with ageing and chronic illness and associated endocrine and immune inflammatory changes compromise the integrity of frontostriatal, amygdala and hippocampal circuits, thus increasing vulnerability to depression. The association between meagre sun exposure and mood changes has been acknowledged for over 2000 years [5]. Recent studies have shown a correlation between low blood levels of vitamin D and an 8% to 14% increased risk of depression, with a 30% risk of suicide [6-8], with no significant difference between the populations of young adults and the elderly [7].

Comparably, Sherchand et al. (2018), in analysing the relationship between low vitamin D levels and the risk of depression, showed that individuals with vitamin D deficiency have a 3.8-fold increased likelihood of developing depression compared to those with normal vitamin D levels [9]. The Third National Health and Nutrition Examination Survey, studying a sample of 7,970 individuals aged 15-39, identified a higher risk of developing depression in patients with vitamin D levels < 50 nmol/L compared to those with vitamin D levels > 75 nmol/L [6].

Furthermore, hypovitaminosis D appears to be linked to the development of postpartum depression [10,11]. Recent studies have shown a negative correlation between low vitamin D levels during the first trimester of pregnancy and the development of symptoms of depression during the second trimester [12,13]. Similarly, a correlation has been shown between hypovitaminosis D in the second trimester and a higher risk of developing symptoms of depression six months postpartum [14].

Another important observation concerns the association between vitamin D deficiency and the development of depression in later life and in northern populations [15]. One study of 1,282 Dutch patients (aged 65 to 95 years) observed vitamin D deficiency in 14% of depressed patients. Significantly lower rates of vitamin D deficiency were found in the control group [7].

Vitamin D deficiency was found in approximately 58% of the sample in a cross-sectional study of 80 elderly patients (aged 60-92 years), including 40 with Alzheimer's disease and 40 without any form of dementia (Wilkins, 2006).

Finally, patients with chronic diseases such as fibromyalgia or those affected by comorbid depression have a higher incidence of vitamin D deficiency or insufficiency (Hospital and Anxiety Depression Scale = 31) [16].

VITAMIN D AND SCHIZOPHRENIA

Schizophrenia is a chronic mental disorder, characterised by the affected individual presenting abnormal social behaviour and severely impaired thought content and conduct. Schizophrenia has an acknowledged multifactorial pathogenesis. The significant risk factors include genetic vulnerability, neurodevelopmental disorders, viral infections, smoking, IQ, cannabis use and childhood trauma. According to a recent meta-analysis, the risk of developing schizophrenia is 2.14 times higher in individuals with vitamin D deficiency compared to individuals with normal blood levels [17]. Environmental risk factors such as the season of birth, place of birth, latitude and migration have been acknowledged as linking vitamin D deficiency to schizophrenia [3,18].

Specifically, according to a review of 86 studies involving a total of 437,710 individuals, there was a 5-8% higher risk of schizophrenia in individuals born between December and May, with a peak of increased vulnerability in those born between January and February, due to the lower presence of UVB rays capable of stimulating vitamin D production [19].

In a study of 424 schizophrenia patients and an equal number of controls selected by age, gender and date of birth, the patients were divided into quintiles according to their vitamin D levels measured within one year of birth. Those who were in the lowest two quintiles and the highest quintile were found to be at twice the risk of developing schizophrenia compared to individuals in the other quintiles [3]. Correspondingly, a study conducted on a cohort of 12,058 Finnish children showed that vitamin D supplementation during the first year of life was associated with a significant reduction in the risk of developing schizophrenia in adulthood, especially among the males [20].

To support these hypotheses, in a recent study by Okasha et al. (2020) on 20 schizophrenic patients and 20 control patients, vitamin D levels were observed to be statistically lower in patients with schizophrenia (55%) than in non-schizophrenia patients [21].

Moreover, vitamin D deficiency appears to be correlated with a higher risk of isolated psychotic symptoms. In a Swedish study conducted on 33,623 women, a significant association was found between low levels of vitamin D and the development of isolated psychotic symptoms, which suggests that hypovitaminosis D is a possible risk factor for the development of psychosis in adulthood [22].

VITAMIN D SUPPLEMENTATION

Vitamin D supplementation may be a valid approach to improving symptoms of depression and psychosis. In a randomised, double-blind clinical trial of 441 subjects (aged 21-70 years) divided into three groups and treated for one year with 20,000 IU (first group) and 40,000 IU (second group) of vitamin D or with placebo (third group), an improvement in the subjects' Back Depression Inventory Scale (BDI) values was observed after one year of treatment [23]. In an 8-week randomised clinical trial of 42 patients with major depressive disorder, the concomitant use of fluoxetine (20 mg) and vitamin D (1500 IU) led to a significant improvement in symptoms of depression compared with the fluoxetine-placebo group, after just four weeks of treatment [24].

However, there are still conflicting results on the efficacy of supplementation. According to the meta-analyses conducted by Gowda et al. (2015) and Shaffer (2014), vitamin D supplementation was shown to not generally produce any improvement of depression symptoms, except for a moderate effect in patients with clinically significant symptoms of depression [25,26].

In the case of schizophrenia, a randomised open-label clinical trial conducted by Sheikhmoonesi (2016) in a sample of schizophrenic patients treated with vitamin D supplements in addition to standard basic therapy showed no change in symptoms [27].

CONCLUSIONS

This brief narrative review provides numerous insights. Although many studies have highlighted the relationship between hypovitaminosis D during embryonic development and childhood and the onset of schizophrenia in adulthood, this correlation has not yet been accepted definitively. The relationship to depression, which is multifactorial, is still unclear. In addition to the mechanisms of action linking vitamin D deficiency to the biological mechanisms typical of depression, other behavioural factors make understanding the relationship even more complex. On the one hand, depression is associated with reduced outdoor physical activity, with a resulting reduction in the absorption of sunlight. On the other hand, the symptoms of vitamin D deficiency, such as feelings of fatigue and pain, are in and of themselves capable of generating lower mood and thus a state of depression.

Further research is needed to establish appropriate protocols for vitamin D testing and supplementation in clinical practice and to determine whether, when and to what extent vitamin D supplementation may improve the course of depression or reduce the incidence of schizophrenia. It is advisable that clinicians include a vitamin D level assessment in their diagnostic decision-making process. By analysing these levels, the possible psychophysical consequences related to low vitamin D levels can be predicted with a good margin of probability and thus prevented.

Healthy lifestyles that include eating foods high in vitamin D, taking food supplements to reduce vitamin D deficiency or insufficiency, and increasing exposure to sunlight are essential indications for improving mental wellbeing, which should be part of every patient's routine education, regardless of the specific pathological condition.

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