Vitamin D in schizophrenia: a clinical review

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ABSTRACT

Vitamin D (vitD) is known for its essential role in calcium homeostasis and bone health. VitD is made endogenously in the skin from UVB radiation from sunlight. VitD is now considered as a potent neurosteroid hormone, critical to brain development and normal brain function, and is known for its anti-inflammatory property affecting various aspects of human health. VitD ligand-receptor, a receptor that mediates much of vitD's biological actions, has been found throughout the body including the central nervous system. VitD deficiency is common in patients with severe mental illness such as schizophrenia. Schizophrenia is a debilitating chronic mental illness characterised by positive symptoms, such as hallucinations and delusions, and negative symptoms including flat affect and lack of motivation. Several environmental risk factors for schizophrenia, such as season of birth, latitude and migration, have been linked to vitD deficiency. Recent studies have suggested a potential role of vitD in the development of schizophrenia. For example, neonatal vitD status is associated with the risk of developing schizophrenia in later life obesity, insulin resistance, diabetes, hyperlipidaemia and cardiovascular disease, which are commonly seen in patients with schizophrenia. It has been well established that vitD deficiency is related to these metabolic problems. The biological mechanism is most likely related to vitD's action on the regulation of inflammatory and immunological processes, consequently affecting the manifestation of clinical symptoms and treatment response of schizophrenia. Potential benefits of vitD supplementation to improve schizophrenia symptoms as well as physical health in patients with schizophrenia should be further explored in future studies.

INTRODUCTION

Vitamin D (vitD), the 'sunshine' vitamin, is widely known for its essential role in calcium absorption and bone health.[1] VitD is created in mammals after the epidermis comes into contact with UVB light. UVB radiation catalyses the conversion of 7-dehydrocholesterol to previtamin D_3 in the skin, which is then quickly converted into vitamin D_3 (cholecalciferol) by the body. 25-hydroxyvitamin D [25(OH)D], the main circulating form of vitD, is used by clinicians to measure vitD levels in the body.[1] VitD is also obtained through dietary sources. Fatty fish, fungus and eggs naturally contain high levels of vitD. In many countries, cereal, milk and other everyday foods are fortified with vitD. VitD is also readily available as a dietary pill. However, since most individuals lack the necessary amount of exposure to UVB light and do not consume enough dietary vitD, vitD deficiency has become a global pandemic.[1 2]While vitD has long been associated with bone health and related diseases, research in the past decade has uncovered its widespread effects on other aspects of the human body. Studies have identified links between vitD and a multitude of conditions including various cancers, autoimmune diseases, cardiovascular diseases, infectious diseases and mental disorders.[3–6]

Studies have unveiled the presence of vitD, vitD receptors (VDR) and related enzymes (CYP 27B1, CYP 24A1) in various regions of the brain,[7] leading researchers to establish vitD as a neuroactive/neurosteroid hormone critical to brain development and normal brain function.[8] Furthermore, VitD's possible role in depression has led researchers to explore its potential benefits in other mental illnesses.[9 10]

Schizophrenia is a severe and debilitating mental illness characterised by chronic positive (hallucinations, delusions) and negative symptoms (lack of motivation, speech issues).[11 12] Schizophrenia occurs in ~1% of the population, affecting male and female populations equally. Although symptoms of schizophrenia typically appear around the ages of 16–30, they can develop earlier in life. Men typically develop schizophrenia about 5 years earlier than women.[11 12] It has been shown that patients with psychiatric illness are much more likely to be vitD deficient than the general population; [13 14] patients with schizophrenia in particular are more likely to be deficient than individuals with other psychiatric disorders.[10 15] Additionally, several well-established risk factors for the development of schizophrenia such as birth month, migration status and/or latitude of residency might all be related to vitD deficiency.[16–18] A 2010 study in a cohort of 33 000 women from the general population in Sweden demonstrated that vitD intake was associated with a significantly decreased relative risk of psychotic-like symptoms.[19] These results suggest that patients with schizophrenia or other psychotic disorders could potentially benefit from vitD supplementation. Our review seeks to discuss the findings from previous studies on vitD deficiency and schizophrenia, the possible underlying mechanism, and the potential benefits of vitD supplementation to prevent or improve schizophrenia symptoms in this patient population. We search MEDLINE using the following words: 'vitamin D and schizophrenia,' 'vitamin D and inflammation' and 'schizophrenia and inflammation'; the search was carried out in May 2015 and retrieved 85 articles ranging from 1997 to 2015.

VITD DEFICIENCY AND SCHIZOPHRENIA

Several environmental risk factors for schizophrenia, such as season of birth, latitude and migration, have been linked to vitD deficiency.[16 17 20]

Environmental risk factors

Season-of-birth effect

A review of 86 studies, including a total of 437 710 individuals with schizophrenia, reported a consistent 5–8% increase in the birth of individuals who later developed schizophrenia between December and May, with the absolute maximum appearing between January and February. It has been hypothesised that vitD plays a role in the season-of-birth effect as the UVB rays required to make vitD are reduced or not available in the months most associated with an increase in the birth of individuals at risk of schizophrenia.[17]

Latitude

There also seems to be a relationship between the risk of schizophrenia and latitude, with an increased incidence rate of schizophrenia seen at a higher latitude.[17] Miller hypothesises that the observed relationship may be related to UVB availability: individuals at higher latitudes tend to receive substantially less vitD than individuals at lower latitudes; [21] furthermore, at latitudes above 35°, the UVB rays required to make vitD

are not available during the winter months.[1] Interestingly, latitude is linked with the season-of-birth effect as the magnitude of the season-of-birth effect increases at a higher latitude, further suggesting vitD deficiency as a culprit in the development of schizophrenia.[16 22]

Migration

It has been reported that schizophrenia is three times more likely to occur in immigrants than in native born participants.[18] Studies suggest that the increased risk of schizophrenia in immigrants stems from the discriminatory experiences and abuse that migrants often face.[23] However, these experiences can only account for part of the increased risk in immigrant populations. The shorter day lengths and less intense sunlight that individuals receive at higher latitudes decrease an individual's vitD intake. The reduced vitD intake is more pronounced in darker skinned individuals as the lighter skin that individuals at higher latitudes tend to display is a result of their decreased melanin that allows the skin to absorb UVB light more effectively and synthesise vitD.[17] Thus, an individual migrating from a warmer to a colder climate receives less vitD.[1] A Norwegian population study revealed that migrants, regardless of race, tend to be more vitD deficient than the general population. Additionally, the study showed that dark skinned African immigrants had significantly lower levels of vitD than the lighter skinned Asian immigrants, who were more deficient than the light skinned Norwegian natives; individuals with darker skin and/or migrants tend to be more vitD deficient and more likely to develop schizophrenia than the general population.[15] A possible relationship between vitD deficiency and the increased risk of immigrants developing schizophrenia is further supported by the report that the relative risk of developing schizophrenia for a migrant from a predominantly black country versus one from a predominantly white country was almost five times greater.[24]

Neonatal vitD status and schizophrenia

A study on schizophrenia risk and neonatal vitD status revealed that there may exist an optimal level of vitD in neonatal individuals regarding the risk of developing schizophrenia. The study included 424 individuals with schizophrenia and 424 controls matched for gender and date of birth. VitD status was determined by serum 25(OH) vitD$_3$ levels in dried blood spots collected from the participants during their first year of life. The study found that individuals in the lowest two quintiles had a significantly higher risk (twofold increased risk) of developing schizophrenia compared to members of any other quintile. However, individuals in the highest quintile also displayed an increased risk of developing schizophrenia, suggesting that both low and high neonatal levels of vitD are associated with schizophrenia.[25] Another study in the neonatal population examined the effect that vitD supplementation during the first year of life had on the risk of developing schizophrenia later in life. Data were collected from the Finnish 1966 Birth Cohort, which included 12 058 children. A total of 100 cases of schizophrenia were diagnosed by the age of 31(0.091%). In addition, 55 individuals of the cohort had developed non-schizophrenic psychotic disorders. The study found that the use of vitD supplements during the first year of life was associated with a reduced risk of schizophrenia in males but not in females.[26]

Early psychosis and vitD deficiency

A recent case–control study (69 individuals with first episode psychosis and 69 healthy controls matched for age, gender and ethnicity) found severe vitD deficiency in patients with first episode psychosis (23). Another study measuring serum 25(OH) vitD levels in 20 recent onset patients with schizophrenia and 20 matched healthy comparison participants showed that lower vitD levels were correlated with more severe positive, negative and overall symptoms in patients with schizophrenia; lower vitD levels were associated with more severe overall cognitive deficits.[27] Another study assessed the relationship between serum vitD levels and psychotic features in mentally ill adolescents. The study (n=104) found that adolescents (12–18 years) with vitD deficiency (serum 25(OH) <20 ng/mL) were 3½ times more likely to have psychotic features. The study found no difference in mean serum 25(OH) vitD levels between individuals with antipsychotic treatment and those without antipsychotic treatment, suggesting that antipsychotic medications might not be the source of the low levels of vitD.[28]

VitD deficiency and metabolic problems in patients with schizophrenia

Data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) suggested that the metabolic syndrome, which includes a cluster of clinical features such as abdominal adiposity, atherogenic dyslipidaemia, hypertension and impaired fasting glucose or overt diabetes, is highly prevalent in US patients with schizophrenia: 40.9% using the National Cholesterol Education Program (NCEP) criteria and 42.7% using the updated American Heart Association (AHA) criteria that include a lower fasting glucose threshold of 100 mg/dL.[29] In contrast, the age-adjusted prevalence of the metabolic syndrome from the third National Health and Nutrition Examination Survey (NHANES III) is 23.7% using the NCEP criteria.[30] In the general population, vitD deficiency has been associated with an increased risk of various metabolic disorders.[31 32] VitD's role as an anti-inflammatory agent could potentially help reduce insulin resistance and obesity.[33–35] 1,25-dihydroxyvitamin D, the main circulating form of vitD, impacts glucose homeostasis, improves insulin sensitivity, promotes β-cell function, and helps regulate overall metabolic function.[36] Studies in the general population regarding vitD supplementation and metabolic health have produced limited results, reporting mixed results or only slight improvements in metabolic outcome measures.[37 38] An open label, eight-week pilot study examined the short-term effects of vitD supplementation on weight, glucose and lipid metabolism in patients with schizophrenia. A total of 19 schizophrenic or schizoaffective patients (body mass index >27 kg/m^2) taking atypical antipsychotics were recruited and dispensed a 2000 IU daily dose of vitamin D$_3$. There were no statistically significant changes in weight, glucose or lipids measurements. Patients whose vitamin D$_3$ levels at week 8 were 30 ng/mL or more achieved a significantly greater decrease in total cholesterol levels compared with those whose week 8 vitamin D$_3$ levels were less than 30 ng/mL. Randomised trials with a longer follow-up period would be helpful in further evaluating the effect of vitD supplementation on metabolic problems in patients with schizophrenia.[39]

VITD DEFICIENCY AND SCHIZOPHRENIA: POSSIBLE BIOLOGICAL MECHANISMS

The role of immune dysfunction and inflammation has been described in patients with schizophrenia.[40–43] Previous research has tried to identify specific inflammatory markers in relation to schizophrenia. For example, Naudin *et al*[44] and Lin *et al*[45] found that, compared with normal controls, patients with chronic schizophrenia had significantly higher serum levels of tumour necrosis factor α (TNF-α) and interleukin-8 (IL-6). The findings from our group and others support an altered immune function characterised by shifting from a type 1 (cellular) to a type 2 (humoral) immune response.[46 47] Several studies have suggested that the regulation of inflammatory and immunological processes is most likely related to the manifestation of symptoms and treatment response of schizophrenia.[48 49] The reports from our group suggested that elevated blood levels of C reactive protein (CRP) or white cell count are associated with a worse psychopathology profile in patients with schizophrenia.[50 51] Studies have examined the potential benefits of anti-inflammatory agents in treating schizophrenia. Muller *et al*[52] reported that celecoxib, when added to risperidone in patients with an acute exacerbation of schizophrenia, significantly reduced

psychopathology as measured by the PANSS total score. However, in a different sample of symptomatic outpatients with schizophrenia, celecoxib did not improve clinical symptoms or measures of disability.[53] Further, celecoxib and other cyclooxygenase-2 inhibitors are associated with an elevated cardiovascular risk.[54] More recently, Laan *et al*[55] reported that aspirin (1 g/day) as an adjuvant therapy to antipsychotic treatment reduced schizophrenia symptoms as measured by the PANSS total score and the positive symptom subscale. However, it is well known that chronic use of high-dose aspirin is associated with a significant risk of gastrointestinal bleeding.[56] The adverse safety concerns related to celecoxib and aspirin limit their potential clinical therapeutic utility in the schizophrenia population. Second trimester serum levels of IL-8, an inflammatory cytokine, were twice as high in mothers of offspring who would later develop schizophrenia or schizophrenia spectrum disorder compared to mothers of offspring in the general population,[57] and mothers with elevated serum TNF-α levels were eight times more likely to have offspring who would develop a psychosis.[58] Several studies have suggested maternal infection as a potential cause of the elevated blood levels of cytokines and other inflammatory markers in patients with schizophrenia.[34 58 59] A recent study reported that vitD deficient cells in vitro produced high levels of inflammatory cytokines TNF-α and IL-6, while cells in the presence of vitD (30 and 50 ng/mL) released significantly less of these cytokines; the study found that VDR attach to the MKP-1 gene, resulting in increased levels of IL-6 and TNF-α levels in vitD deficient cells.[35] A meta-analysis of 10 trials of patients in the general population (n=924) found that vitD supplementation reduces circulating levels of hs-CRP.[60] VitD does not have the possible concerning side effects of other anti-inflammatory agents (celecoxib and aspirin); therefore vitD supplementation might be a promising treatment strategy for schizophrenia.

LIMITATIONS

This review has several limitations. First of all, it was not possible to perform a quantitative synthesis of the results from different studies. Meta-analysis provides a pooled estimate based on statistical analysis of results from primary studies and meta-analysis of well conducted randomised clinical trials is considered to be a superior level of evidence.[61] Second, potential confounding conditions that might affect vitD levels, such as obesity and diabetes that are commonly seen in patients with schizophrenia, have not been controlled in the included studies. Last but not least, most studies included were cross-sectional or epidemiological studies rather than randomised controlled trials; a causal relationship cannot be drawn from these types of study design, and these studies are likely to have residual confounding.[62]

CONCLUSIONS

VitD seems to play an active role in the normal development and function of multiple body organ systems including the brain. VitD deficiency remains a widespread problem in patients with schizophrenia. Several environmental risk factors for schizophrenia, such as season of birth, latitude and migration, have been linked to vitD deficiency. In addition, obesity, insulin resistance, diabetes, hyperlipidaemia and cardiovascular disease, which are commonly seen in patients with schizophrenia, might be related to vitD deficiency as well. Potential benefits of vitD supplementation to improve schizophrenia symptoms and physical health in patients with schizophrenia should be further explored in future studies.

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