



Original article

Association between mental disorders, cognitive disturbances and vitamin D serum level: Current state

Paul P. Lerner^a, Laura Sharony^{a, b}, Chanoch Miodownik^{c, *}^a Mental Health Center Geha, Petakh Tikva, Israel^b Mazor Mental Health Center, Acre, Israel^c Be'er Sheva Mental Health Center, Faculty of Health Sciences Ben-Gurion University of the Negev, Be'er Sheva, Israel

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SUMMARY

Background & aims: Vitamin D deficiency has been identified as a global problem. Approximately 14% of the world population has inadequate vitamin D levels. This vitamin has been usually associated with bone disorders such as rickets, osteomalacia, and osteoporosis. However, these disorders present only a small part of all the disturbances which can be induced by its deficiency. Low serum vitamin D is associated with development of cardiovascular diseases, hypertension, neurodegenerative diseases, diabetes mellitus, metabolic syndrome and even cancer. This vitamin may be an important factor in the development of psychiatric illnesses, therefore clinicians should not leave this serious issue unresolved. The aim of this review is to describe the current data concerning the association between vitamin D serum levels, cognition and mental disorders.

Methods: We conducted a systematic bibliographical research, of PubMed, MedLine literature and Cochrane database without language restriction to identify all publications concerning this issue from 1995 to the first quarter of 2017.

Results: We found 48,937 articles concerning vitamin D, published during the last 22 years and 3 months (1995–2017). We selected only those publications focused on the association between vitamin D serum deficiency and mental disturbances (depression, schizophrenia, cognitive disturbances, attention deficit disorder, and autism). One hundred and sixty-seven papers were found suitable to our selection criteria. Careful evaluation of the relevant literature demonstrates that addition of vitamin D to conventional antidepressive agents can improve antidepressive effect in contrast to placebo. Regarding other mental conditions there are no clear-cut conclusions.

Conclusions: An association between low vitamin D serum levels and different mental disorders was found. Yet, nonetheless there is no clear consensus that addition of vitamin D improves or is related to a beneficial effect on mental health. More randomized clinical control trials should be performed in order to reach evidence based conclusions.

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1. Introduction

Since the discovery of vitamin D in 1922 by an American researcher Elmer McCollum, its role in calcium homeostasis and bone health was well established. Vitamin D is a secosteroid, fat-soluble vitamin as well as a hormone precursor that plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties. It exists in two

forms: ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃) [1]. Vitamin D₂ is synthesized by plants. Vitamin D₃ is synthesized by humans in the skin when it is exposed to ultraviolet-B (UVB) rays from sunlight. Vitamin D from sun exposure, food, and supplements is not biologically active. To become biologically active, this vitamin must undergo two hydroxylation steps: first-in the liver, cholecalciferol (vitamin D₃) is converted to calcidiol (25-hydroxyvitamin D₃). Next, part of the calcidiol is converted by the kidneys to calcitriol, the biologically active form of vitamin D [1,2].

Vitamin D deficiency has been identified as a global problem with an estimated one billion people worldwide suffering from

* Corresponding author. Be'er Sheva Mental Health Center, PO Box 4600, Be'er-Sheva, 8417000, Israel. Fax: +972 8 6401733.

E-mail address: miodownik.ch@gmail.com (C. Miodownik).

vitamin D deficiency or insufficiency [3]. According to Dickens et al., about 14% of the world population has inadequate vitamin D low levels [4]. Among different researchers there is no consensus concerning the optimal serum levels of 25-hydroxyvitamin D. Nevertheless vitamin D deficiency is defined by most experts as lower than 20 ng/mL [4–9]. Studies performed in different countries found that 30%–50% of children and adults have low levels of vitamin D (<20 ng/mL) [6]. Other studies demonstrate that 40%–100% of U.S. and European elderly men and women who live in the community (not nursing homes), have vitamin D deficiency [10].

Vitamin D is highly active in regulating cell differentiation, proliferation, and peroxidation in a variety of structures. Receptors for vitamin D are present in most cells of the body including the brain [11–14]. This means that vitamin D deficiency is not only associated with bone disease, but also may play a role in other body systems as well, including cardiovascular diseases, several autoimmune diseases, cancer, infections, and diabetes [15–17].

Since the discovery of vitamin D, its role in calcium homeostasis and bone health was well established. Inadequate levels of vitamin D have been usually associated with bone disorders such as rickets, osteomalacia, and osteoporosis [18]. However, these disorders can be considered as “the tip of vitamin D deficiency iceberg” [6].

During the last years the number of publications about this topic has significantly increased. A little over half of all articles regarding vitamin D since its discovery in 1922 were published only in the last 10 years (34,679 of 68,473 articles). A preliminary search of literature shows that only during the 2016, there already were 4239 publications. These researches show a growing body of knowledge regarding vitamin D and also highlight its role in brain development and function, as well as stir interest in the investigation of its role in the pathogenesis of mental disorders. For example, some studies demonstrated a connection between the lack of vitamin D supplementation in the first year of life and increased risk of schizophrenia in males [19], while another study found a nonlinear increase in the risk of schizophrenia in patients with low levels of the vitamin [20]. Furthermore, several studies demonstrated a link between vitamin D and depression [21–23].

Vitamin D deficiency is a very common disturbance but often clinically invisible, therefore the clinicians may be unaware to it. It may be an important point in psychiatric illnesses development [24–26], and according to the Bradford Hill criteria [27], clinicians should not leave this serious issue without an attention.

The aim of this literature review is to describe the current knowledge about the association between vitamin D deficiency, cognition, and mental disorders. The authors summarized all relevant publications during the last 22 years and 3 months (1995–2017). We believe that a better understanding of this issue can help clinicians' efforts to correctly diagnose and treat these disturbances.

2. Methods

We conducted a bibliographical research of various medical databases such as PubMed, MedLine literature and Cochrane database without language restriction to identify all studies concerning the association (or absence of such association) between vitamin D deficiency and mental disorders. Additional publications were hand searched from the reference lists of every primary study.

Two independent researchers (PL and CM) investigated the library databases in order to reduce errors/bias in accessing evidence. Relevant publications were identified from the title, abstract and study descriptions by one researcher; the decision to include was independently validated by a second and disagreements were referred to a third researcher for an independent ruling. We included only publications which specifically investigated the association between mental disturbances and vitamin D deficiency.

Since the association between vitamin D and psychiatric phenomena, is a relatively new researchable issue, the current review is integrative and includes clinical as well as animal trials. In this review the following Medical Subject Heading (MeSH) terms using both common and chemical names for vitamin D, such as 'Vitamin D' OR 'ergocalciferol' OR 'vitamin D₂' OR 'cholecalciferol' OR 'vitamin D₃' OR 'calcitriol' OR 'vitamin 1,25 D₃' OR 'vitamin 25 D' OR 'hydroxy vitamin D' OR '25-OHD' AND 'Alzheimer's disease', 'Attention deficit hyperactivity disorder', 'ADHD', 'autism', 'autism spectrum disorder', 'ASD', 'Asperger', 'bipolar disorder', 'bipolar affective disorder', 'cognition' 'cognitive impairment', 'cognitive decline', 'delusional disorder', 'depression', 'dementia', 'depressive disorder', 'depressive mood disorder', 'memory', 'psychosis', 'seasonal affective disorder', 'schizoaffective disorder', 'schizophrenia' were used.

Case reports and open treatment studies were not included in this review. Additionally, the initial search of publications with the mentioned above keywords yielded a large number of works due to brief mentions of vitamin D in various articles without examination of vitamin D levels and/or its association with the mental disorder/cognitive disturbance. Thus the actual number of relevant articles concerning our specific subject is significantly lower. For example: a preliminary search for “vitamin D deficiency” and “schizophrenia” yielded 91 articles, but only 38 of them were relevant for future review (the other 53 articles were not suitable according to the inclusion criteria).

Electronic databases and bibliographies were searched and identified for articles to be evaluated for this work. In this review, the included studies were grouped according to the association between serum level vitamin D deficiency and specific mental disturbances.

3. Vitamin D and mental disorders

3.1. Vitamin D and depression

The association between the lack of sun exposure and mood changes was first described about two thousand years ago [28]. Some recent reports demonstrate that vitamin D deficiency is associated with an increased risk of depression from 8% to 14% [29,30] and a 30% increased risk of suicide [31].

The idea about the relationship between the deficiency of vitamin D and depression comes from studies dealing with seasonal affective disorder. This phenomenon describes rhythmic decreases of mood during the same season each year. Usually, these mood changes occur during autumn and winter months, when the days are shorter and there is less sunlight.

The researchers assumed that a low exposure to sunlight produces a low formation of vitamin D₃ in winter. One study demonstrated that there are seasonal variations in the plasma levels of precursor 25-hydroxyvitamin D₃ (25(OH)D₃) (the inactive precursor for active vitamin D), with peak values occurring during autumn. At the same time, there was no seasonal change in the serum concentrations of 1,25-(OH)₂D₃ [32]. Low serotonin (5-HT) levels in the brain have been linked to the symptoms of seasonal affective disorder and it has been suggested that vitamin D may play a role in seasonal mood cycles due to dysregulation of 5-HT [33,34]. Vitamin D deficiency or low serum levels of 25(OH)D₃ are associated with low mood and depression in humans and vice versa [35–38]. Supplementation with vitamin D for 5 days during late winter had a significant positive effect on mood in healthy subjects [39] and on the well-being of endocrine outpatients with low serum 25(OH)D₃ levels [40]. In a pilot study, 8 subjects with seasonal depression received 100,000 IU of vitamin D over a month, while 7 others were treated only with phototherapy during the same period. Vitamin D treatment was associated with improved

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