

Vitamin D - a key to reducing the risk of suicide?

Jacek Januszewski¹ ABCDEF, <https://orcid.org/0000-0003-1023-4081>,

Alicja Forma¹ ABCDEF, <https://orcid.org/0000-0001-8714-7627>,

Kaja Hanna Karakuła¹ ABCDEF, <https://orcid.org/0000-0003-1493-8502>,

Ryszard Sitarz² ADEF, <https://orcid.org/0000-0001-7503-1838>,

Jacek Baj³ DEF, <https://orcid.org/0000-0002-1372-8987>,

Karolina Kłodnicka³ ADE,

Julita Zembala⁴ EF,

Dariusz Juchnowicz⁵ DEF, <https://orcid.org/0000-0003-2027-5469>,

¹Department of Forensic Medicine, Medical University of Lublin, Poland

²I Department of Psychiatry, Psychotherapy, and Early Intervention, Medical University of Lublin, Poland

³Department of Anatomy, Medical University of Lublin, Poland

⁴University Clinical Center, Medical University of Warsaw, Poland

⁵Department of Psychiatry and Psychiatric Nursing, Medical University of Lublin, Poland

Abstract

Introduction: Vitamin D has a major positive impact on human health. Its daily supplementation regulates calcium metabolism, inflammatory and neuromodulatory processes. More importantly, vitamin D may be an important factor in reducing the risk of suicide among psychiatric patients. This review aims to describe the potential positive effect of vitamin D supplementation in preventing suicide attempts.

Method: The literature review was conducted by search of articles in English and Polish languages on PubMed, Medline, and Google Scholar, published from 1974 to the 1st of April 2023, following SANRA requirements. The search utilized the following keywords: vitamin D, vitamin D deficiency, vitamin D supplementation, suicide, depression, bipolar disorder, schizophrenia, ADHD, anxiety, and autism. The analysis encompassed original studies, meta-analyses, randomized controlled trials, and review articles.

Results: There is a limited number of studies investigating the impact of vitamin D supplementation on suicide risk in individuals with mental illness. Several studies suggest that vitamin D may have a beneficial effect on symptoms of mental illnesses. However, the exact mechanism through which vitamin D exerts its therapeutic effects on mental health remains unclear. Incorporating vitamin D into the treatment of the mental disorders such as depression, schizophrenia, bipolar disease, ADHS, autism spectrum disorder, and anxiety, as well as supplementing it during pregnancy and throughout life, could potentially be an effective therapeutic adjunct for suicide prevention approach.

Conclusions: According to all the research and gathered data, there is a correlation between Vitamin D supplementation and a decrease in suicide risk among patients suffering from mental disorders. Several lines of evidence have shown a positive impact on mental health in patients suffering from mental diseases. However, further research is needed to establish the mechanisms of the therapeutic effect of Vitamin D.

Keywords: vitamin D, vitamin D supplementation, suicide, psychiatric disorders

Streszczenie

Wstęp: Witamina D ma duży pozytywny wpływ na ludzkie zdrowie. Jej codzienna suplementacja reguluje metabolizm wapnia, procesy zapalne i neuromodulatorowe. Co ważniejsze, witamina D może być istotnym czynnikiem zmniejszającym ryzyko samobójstwa wśród pacjentów psychiatrycznych. Niniejszy przegląd ma na celu opisanie potencjalnego pozytywnego wpływu

suplementacji witaminą D na zapobieganie próbom samobójczym.

Materiał i metody: Przegląd literatury został przeprowadzony poprzez wyszukiwanie artykułów w języku angielskim i polskim w PubMed, Medline i Google Scholar, opublikowanych w okresie od 1974 roku do 1 kwietnia 2023 roku, zgodnie z wymogami SANRA. W wyszukiwaniu wykorzystano następujące słowa kluczowe: witamina D, niedobór witaminy D, suplementacja witaminy D, samobójstwo, depresja, choroba afektywna dwubiegunowa, schizofrenia, ADHD, lęk i autyzm. Analiza obejmowała oryginalne badania, metaanalizy, randomizowane badania kontrolowane i artykuły przeglądowe.

Wyniki: Istnieje ograniczona liczba badań dotyczących wpływu suplementacji witaminą D na ryzyko samobójstwa u osób z chorobami psychicznymi. Kilka badań sugeruje, że witamina D może mieć korzystny wpływ na objawy chorób psychicznych. Jednak dokładny mechanizm, poprzez który witamina D wywiera swój terapeutyczny wpływ na zdrowie psychiczne, pozostaje niejasny. Włączenie witaminy D do leczenia zaburzeń psychicznych, takich jak depresja, schizofrenia, choroba afektywna dwubiegunowa, ADHD, zaburzenia ze spektrum autyzmu i stany lękowe, a także jej suplementacja w czasie ciąży i przez całe życie, może być potencjalnie skutecznym dodatkiem terapeutycznym w podejściu do zapobiegania samobójstwom.

Konkluzja: Według wszystkich zebranych badań i danych istnieje korelacja między suplementacją witaminą D a zmniejszeniem ryzyka samobójstwa wśród pacjentów cierpiących na zaburzenia psychiczne. Analiza wykazała pozytywny wpływ witaminy D na zdrowie psychiczne u pacjentów cierpiących na choroby psychiczne. Konieczne są jednak dalsze badania w celu ustalenia mechanizmów terapeutycznego działania witaminy D.

Słowa kluczowe: witamina D, suplementacja witaminy D, samobójstwo, zaburzenia psychiczne

1. Introduction

The WHO reported that about 800,000 people per year choose to take their own life. Suicide remains the leading cause of death worldwide, in the United States of America it takes the 12th place of cause of death [1]. The number of suicide attempts and suicidal behaviors increases every year, which pose a tremendous problem. Unfortunately, the prognosis is not optimistic and it seems that the number of suicides will not decrease [2]. The end of the COVID pandemic that began in 2019 in Wuhan, China further exacerbates the problem of modern society [3].

Suicide is a complex phenomenon, where different backgrounds often influence each other. Genetics, mental disorders, social isolation, intellectual disabilities, and financial and family status play a huge role in the process of developing such serious behaviors [3,4]. Disorders that could potentially lead to suicide attempts are self-destructive behaviors, depression, post-traumatic stress disorder, and schizophrenia [5]. Alarming symptoms may include anhedonia, sleep disturbance, tiredness, impaired concentration, hopelessness, moving and speaking slowly, or isolation from the family and other people [5,6].

Mental disturbances can significantly contribute to the origin of suicide attempts. However, chronic inflammatory processes, which affect not only the nervous system but also various organ systems, have been found to be associated with an increased risk of depression and subsequent suicidal thoughts [7,8]. Elevated levels of interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor (TNF), along with decreased levels of IL-2, have been

found to have a significant impact on the manifestation of symptoms [9].

Vitamin D is a compound that plays a crucial role not only in the skeletal system but also in neuronal biochemical reactions. The main circulating form of vitamin D, known as 1,25-dihydroxy vitamin D-1,25[OH]₂D, enhances the transcellular absorption of calcium in the human body. Additionally, it increases the absorption of phosphate compounds [10,11]. Furthermore, vitamin D has been found to play a significant role in mental health. Researchers first suggested a link between mental disorders and vitamin D supplementation in the 1970s [12]. Since then, numerous studies have investigated the potential therapeutic effects of vitamin D supplementation on mental health worldwide.

This narrative review aims to describe the prospective positive effects of vitamin D in the prevention of suicide attempts.

2. Methods

The literature review was conducted by search of articles in English and Polish languages on PubMed, Medline, and Google Scholar, published from 1974 to the 1st April 2023, following SANRA requirements. The search utilized the following keywords: vitamin D, vitamin D deficiency, vitamin D supplementation, suicide, depression, bipolar disorder, schizophrenia, ADHD, anxiety, and autism. The analysis encompassed original studies, meta-analyses, randomized controlled trials, and review articles. The review refers to mental disorders which could potentially lead to suicidal attempts and there

is a relation between vitamin D supplementation and decrease of negative symptoms and numbers of suicide.

3. Results

3.1 Vitamin D supplementation and depression

Depression is a prevalent mental health condition that is considered a significant global issue and one of the leading causes of mortality. It is often referred to as a "civilization disease" due to its widespread occurrence in the XXI century. Studies have indicated that even 20% of adolescents experience at least one episode of depression before the age of 18, while over 7% of Americans aged 18-39 exhibit symptoms of depression. Moreover, depression can also affect elderly individuals [13,14,15].

Symptoms of depression include feelings of hopelessness, low self-esteem, irritability, lack of motivation, and sleep disorders [16,17]. Research has shown that lifestyle habits may have a significant influence on the occurrence of depression. One important factor that has shown potential for positive effects in the treatment of depression is vitamin D. It is believed that vitamin D (VD) may play a role in regulating neurochemical reactions that are involved in the development of depression [18].

Moreover, VD is an antioxidant and modulates the processes of the immune system [19]. It contributes to the function of immune system cells by acting as a transcription and growth factor and leading to peripheral and central nervous system immune modifications. Vitamin D has been shown to modulate type 1 T-helper cells (Th1) by suppressing their pro-inflammatory features and stimulating the anti-inflammatory activity of type 2 T-helper cells (Th2). It causes the decrease of pro-inflammatory interleukin 1 (IL-1), tumor necrosis factor α (TNF α), and interferon γ (IFN γ) both with the increase of anti-inflammatory interleukin 4 (IL-4) and interleukin 10 (IL-10). Additionally, Vitamin D is a down regulator of Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) produced by monocytes [20].

Vitamin D also plays a role in modulating the levels of neuronal calcium ions (Ca²⁺). Dysregulation of the number of ions in nerve cells are involved in the process of depression symptoms occurrence [21]. Vitamin D might be considered as a neurosteroid, and there are reports that VD was found in regions of the brain that are included in depression development. The presence of the VD was confirmed in the prefrontal cortex, hippocampus, cingulate gyrus, thalamus, hypothalamus, and substantia nigra. Most of these areas also showed significant reactivity for 1 alpha-hydroxylase enzyme that may metabolize 25(OH)D to 1,25(OH)₂D indicating that 1,25(OH)₂D likely has autocrine or paracrine activity in these locations [22].

Supplementation with vitamin D can influence all

these physiological processes, thereby modulating the risk of depression. The supplementation might be a promising addition to the treatment of depression [18,23,24,25].

3.2 Vitamin D supplementation and bipolar disorder

Bipolar Disorder (BD) is characterized by abnormal mood swings, with episodes of mania or depression separated by periods of euthymia [26]. The disorder may be connected with the aging of brain cells, as well as other processes such as oxidative stress, mitochondrial function, inflammation, circadian rhythms, or dopamine dysregulation [27].

As mentioned earlier, VD has various effects, including its anti-inflammatory activity and influence on the Central Nervous System, which may have a positive impact on bipolar disorder therapy [28,29]. One of the potential mechanisms of VD influence on BD development may be related to vitamin D receptor (VDR). As a nuclear receptor, VDR can modulate the expression of the dopamine D1 receptor, potentially contributing to the occurrence of BD [30]. Nuclear transcription and dopamine receptor gene levels, mitochondria, and metabolic pathways can be regulated by VDR. These effects could explain the involvement of VDR in bipolar disorder etiology.

Additionally, vitamin D supplementation has been observed to improve brain neurochemistry and equalize patients' moods [31,32,33,34]. Furthermore, the calcium imbalance may correlate with the long-term consequences of BD. Due to the influence of vitamin D on calcium balance, the levels of VD could be considered a prognostic marker of BD [35].

3.3 Vitamin D supplementation and schizophrenia

Schizophrenia is a mental illness that can be associated with abnormal dopamine neurotransmission, leading to disturbances in thinking, perception, and communication. The symptoms of schizophrenia can be categorized into different groups. Positive symptoms include delusions and hallucinations, while negative symptoms encompass amotivation, social withdrawal, and cognitive impairments such as deficiencies in processing speed, executive function, and working memory [36].

Researchers observed a correlation between VD supplementation and schizophrenia. There is a hypothesis that people who experienced early-life vitamin D insufficiency are more likely to develop the disorder. The theory was based on the association between people born in winter and spring, when VD insufficiency is more common, and an elevated risk of schizophrenia occurrence [37,38].

After exposure to ultraviolet-B light, the skin converts 7-dehydrocholesterol into vitamin D₃

(cholecalciferol). A small number of foods also contain cholecalciferol, and it can also be supplemented. In the circulation, cholecalciferol is hydroxylated to generate 25-hydroxyvitamin D3 (25OHD), which is then changed into 1,25-dihydroxy vitamin D (1,25[OH]₂D), the active hormone. Blood-brain barriers can be crossed by both 25OHD and 1,25[OH]₂D. The location of the vitamin D receptor (VDR) and vitamin D metabolizing enzymes in the human brain was initially shown by early immunohistochemical investigations [39,40,41]. There are two gene products with particular significance to how vitamin D affects cognitive and behavioral processes neurotrophic growth factor (NGF) and brain-derived neurotrophic factor (BDNF). NGF, which is primarily found in the hippocampus and neocortex, enhances neurotransmission and has been implicated in memory and executive function [42]. There is also the issue of BDNF, which has an impact on the development and survival of dopamine (DA) producing cells. It has been postulated that dopaminergic neurotransmissions are closely related to the manifestation of numerous brain disorders such as schizophrenia [43].

Vitamin D may be potentially crucial during the brain development of a fetus, as unbuffered calcium can be harmful to developing brain tissue. In embryonic neurons, 1,25[OH]₂D blocks the toxic and hyperpolarizing effects of calcium influx. Additionally, 1,25(OH)₂D₃ down-regulates L-type voltage-sensitive calcium channels in embryonic hippocampal neurons [44].

For the negative and positive symptoms that do not sufficiently improve in the majority of patients, vitamin D supplementation may be promising. Clinical assessment scales such as the Assessment of Negative Symptoms (SANS) and the Assessment of Positive Symptoms (SAPS) have shown positive effects when Vitamin D is added to the treatment. These results provide promising possibilities for treatment [45].

3.4 Vitamin D supplementation and anxiety

Anxiety is a psychological condition characterized by feelings of apprehension and an inner state of restlessness. Somatic complaints, ruminative conduct, and pacing back and forth are frequently present as well. It is possible to distinguish subtypes of anxiety: generalized anxiety disorder (GAD), social phobia, panic disorder, specific phobias, agoraphobia, separation anxiety disorder, and selective mutism. Global estimates of the prevalence of anxiety disorders range from 3.8 to 25% across nations, with estimations of prevalence rates as high as 70% in those with long-term health issues [46].

Similar to other mental disorders background, neuroinflammation plays a huge role in anxiety development. Neuroinflammation is a defense mechanism

in the central nervous system that regulates neurogenesis, axonal regeneration, and remyelination of neural cells. It protects and restores the structure and function of the brain in response to infection and injury. However, prolonged and intensified inflammatory reactions might have negative effects on the brain, involving inflammation-related signaling molecules, the immune system, and brain cells [47].

Microglia, as well as immune cells specific to the nervous system, are particularly important for neuroinflammatory responses. Due to pathological processes, microglia change its form and initiates a cascade of reactions leading to astrocyte polarization [47,48]. This cascade of reactions contributes to the dysfunction of signaling pathways, such as the brain-derived neurotrophic factor (BDNF)/tropomyosin-related kinase B (TrkB)- essential for neurite growth, apoptosis, and synaptic plasticity [49,50]. All positive effects of vitamin D supplementation may contribute to improving anxiety symptoms.

3.5 Vitamin D supplementation and ADHD

The diagnosis of attention-deficit hyperactivity disorder (ADHD is based on the presence of chronic and developmentally inappropriate levels of impulsivity, overactivity, and inattention [51]. It is the most common neurodevelopmental illness in children, which has an estimated 5% prevalence worldwide [52]. The increased possibility of mental disorders or addiction among patients with ADHD may indicate an association between attention-deficit hyperactivity disorder and suicidal behaviors [53,54,55]. A compound that potentially plays an important role in ADHD development might be serotonin. Low brain serotonin levels in healthy populations exhibit antisocial conduct, increased uncontrollable aggression, feelings of wrath, quarrelsome behavior, and self-injury instead of cooperative behavior that is oriented toward long-term gain. In ADHD patients, low levels of serotonin increase aggressive behaviors. People, who have serotonin-related gene polymorphisms, are already prone to abnormal serotonin production or metabolism [56].

The active form of VD the 1,25-dihydroxy vitamin D regulates the expression of a huge number of genes which have a considerable impact on brain functions. The potential positive influence may arise from the discovery of vitamin D response elements (VDREs) on two different tryptophan hydroxylase (TPH) genes involved in serotonin synthesis that have functionally opposing effects: one of them causes vitamin D to repress tryptophan hydroxylase 1 (TPH1) in peripheral tissues and activate tryptophan hydroxylase 2 (TPH2) in the brain. Through TPH2, the vitamin D hormone is a crucial regulator of brain serotonin levels, which, in turn, are

related to aggressive behaviors in the ADHD population [57]. The other mechanisms responsible for Vitamin D's positive therapeutic effect may be calcium transition or antioxidant properties [58,59].

3.6 Vitamin D supplementation and autism

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that has an impact on how people interact with others, communicate, learn, and behave. It can be identified as early as 18 to 24 months of age; at this time, the hallmark signs of the disorder can be recognized from normal development, other delays, and other developmental issues [60, 61]. Genetic factors as well as environmental factors may influence the occurrence of autism spectrum disorder [62]. Approximately 1/100 children are diagnosed with autism spectrum disorder around the world [61]. An interesting fact may be the correlation between autism spectrum disorder and increased risk of suicidal behaviors [63,64]. ASD often occurs with other mental illnesses including psychosis, schizophrenia, or depression. The possible reason why ASD contributes to suicidal thoughts development may be the appearance of similar symptoms and abnormalities. In both autism and the mental disorder mentioned above, emotional impairment, anhedonia, alexithymia, social isolation, and social disengagement are frequent experiences [65]. Reducing the risk of autism spectrum disorder occurrence may lead to a decrease in the level of mental symptoms and suicidal attempts among ASD patients. Numerous studies have shown that supplementing with vitamin D during pregnancy can significantly reduce the onset of autism [66,67,68].

4. Conclusions

This article review aimed to provide an overview of the current state of knowledge about the potential correlation between vitamin D supplementation and reducing the risk of suicide. The information accumulated so far prevents the drawing of clear conclusions. However, it appears that vitamin D supplementation solidly demonstrated an association with mental disorders that can lead to suicide attempts. Adding VD to the treatment of depression, bipolar disorder, and schizophrenia may achieve positive effects [18,23,24,25,28,29,45]. There is also a reported correlation between mental disorders such as anxiety, ADHD, or autism and VD deficiency. The illnesses mentioned above may potentially influence the risk of suicidal thoughts. The positive effect of vitamin D on neuroinflammation and biochemical processes in the Central Nervous System is a promising addition to anxiety and ADHD therapy [47,48,57,58,59]. Vitamin D supplementation by women during pregnancy helps to reduce the risk of autism occurrence and as a result,

decreases the risk of potential suicide attempts of their children [66,67,68].

Vitamin D is an antioxidant and modulator of immunological system processes [19], which contributes to immune system cells by being a transcription and growth factor. VD modulates type 1 T- helper cells (Th1) by suppression of their pro-inflammatory activity and stimulating the anti-inflammatory activity of type 2 T-helper cells (Th2) [19,20,47]. Its potential influence on levels of dopamine and serotonin plays a significant role in neurochemistry [31,32,33,34,43,56,57]. Moreover, it has been reported that vitamin D is an important factor during brain development in fetuses [44].

Conflict of interest

The authors have declared no conflict of interest.

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Corresponding author

Kaja Karakuła
 e-mail: kaja.karakula@gmail.com
 Department of Forensic Medicine,
 Medical University of Lublin, Poland

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