REVIEW ARTICLE

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Vitamin D – the sunshine vitamin – could be correlated with both depression and anxiety

Witamina D – witamina słońca – może być powiązana zarówno z depresją, jak i stanami lękowymi

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Abstract

Introduction and Objective. Sun-derived Vitamin D is vital for diverse physiological functions. Nevertheless, vitamin D deficiency is common and can have serious consequences for mental health. Ongoing research explores the connections between vitamin D deficiency and depression and anxiety disorders, its role in their development and potential therapeutic uses. The aim of the study is to investigate the role of vitamin D in depression and anxiety disorders, and review clinical studies on its potential therapeutic use in treating these conditions.

Brief description of the state of knowledge. The review concludes that vitamin D may influence the occurrence and course of depression and anxiety disorders in various ways, and may find application in their treatment. As evidence of this, several clinical studies have confirmed both the association of vitamin D with symptoms of depression and anxiety and its effectiveness in treating these diseases, especially when combined with other medications. However, there is a lack of complete consistency in the clinical results obtained, which may be attributed to the presence of confounding factors and the complex etiology of mental illnesses.

Summary. Additional research is required to comprehend the causes of depression and anxiety, explore vitamin D›s potential, and conduct thorough investigations into its therapeutic role as an adjunct in treating these disorders. This research should consider the complexities of psychiatric disorder origins, symptom severity, and the impact of environmental and genetic factors, including individual responses to vitamin D treatment.

Key words

vitamin D, anxiety disorders, anxiety, depression

Streszczenie

Wprowadzenie i cel pracy. Witamina D, pochodząca ze słońca, jest niezbędna dla zachowania wielu funkcji fizjologicznych organizmu człowieka. Niemniej jednak niedobór witaminy D jest zjawiskiem powszechnym i może mieć poważne konsekwencje dla zdrowia psychicznego. Coraz więcej badań poświęcono istniejącym powiązaniom między witaminą D a depresją i zaburzeniami lękowymi oraz ocenie znaczenia tej witaminy w etiologii tych zaburzeń, a także potencjalnych możliwości wykorzystania witaminy D w ich leczeniu. Celem pracy jest usystematyzowanie wiedzy na temat związku witaminy D z depresją i zaburzeniami lękowymi oraz przegląd badań klinicznych oceniających możliwości wykorzystania witaminy D w leczeniu wspomnianych zaburzeń.

Opis stanu wiedzy. Z przeglądu wynika, że witamina D może w różny sposób wpływać na występowanie i przebieg zaburzeń depresyjnych i lękowych oraz może znaleźć zastosowanie w ich leczeniu. Na dowód tego przywołano kilka badań klinicznych, które potwierdziły zarówno związek witaminy D z objawami depresji i lęku, jak i jej skuteczność w leczeniu tych chorób, szczególnie w połączeniu z innymi lekami. Uzyskane wyniki kliniczne nie są jednak w pełni spójne, co można wiązać z występowaniem czynników zakłócających oraz złożoną etiologią chorób psychicznych.

Podsumowanie. Konieczne są dodatkowe badania w celu pełnego zrozumienia przyczyn depresji i lęku, zbadania potencjału witaminy D i oceny jej terapeutycznej roli we wspomaganiu leczenia wspomnianych zaburzeń. Badania te powinny uwzględniać złożoność etiologii zaburzeń psychicznych, nasilenie objawów oraz wpływ czynników środowiskowych i genetycznych, w tym indywidualne reakcje na leczenie witaminą D.

Słowa kluczowe

witamina D, zaburzenia lękowe, lęk, depresja

INTRODUCTION

Depression and anxiety disorders affect millions of people worldwide and are among the most common mental

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disorders. The intricacies of their etiology, coupled with their frequent co-occurrence and overlapping symptoms, create challenges in both diagnosis and treatment. Motivated by these complexities, the review comprises a comprehensive examination of existing information and clinical studies concerning the correlation between vitamin D and the aforementioned mental disorders. The focus extended to exploring the potential therapeutic utility of this substance in addressing depression and anxiety disorders.

Vitamin D is known as cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). These compounds, particularly ergocalciferol, are acquired through dietary sources, while the primary origin of cholecalciferol lies in the skin's endogenous synthesis stimulated by sunlight, specifically ultraviolet B radiation with a wavelength ranging from 260–320 nm [1].

Cholecalciferol, derived through isomerization from previtamin D3 produced in the skin, is initially biologically inactive. Following conversion in the liver, it assumes the form of 25(OH)D, commonly known as calcidiol – the primary metabolite discerned in serum. Further hydroxylation in the kidneys leads to the active form, 1,25-dihydroxyvitamin (abbreviated to 1,25(OH)D), referred to as calcitriol [2].

The magnitude of endogenous synthesis and the ultimate attainment of serum 25(OH)D levels are subject to numerous factors, including latitude, skin colour, body weight, age, diet, and initial vitamin D levels [3]. Furthermore, studies involving twins propose that serum vitamin D levels may exhibit a genetic heritability ranging from 23% – 80%. Additionally, alterations in genes that impact transport, metabolism, and binding to vitamin D receptors can play a pivotal role in determining the levels of serum vitamin D [4]. The collective influence of these factors contributes to vitamin D deficiency becoming a prevalent global issue with potentially significant ramifications, including those impacting mental health.

OBJECTIVE

The aim of this study was to systematically consolidate information regarding the significance of vitamin D concerning specific mental disorders, namely depression and anxiety. Additionally, the study aimed to comprehensively review clinical studies assessing the potential utility of vitamin D in treating these disorders.

MATERIALS AND METHOD

A comprehensive literature search was carried out utilizing the databases PubMed and Google Scholar. The search incorporated specific key words: 'vitamin D', 'depression', 'anxiety', and 'anxiety disorders', entered in English with appropriate configurations. The analysis encompassed data from 55 scientific articles published between 1994–2021.

RESULTS

Key localization of VDR receptors. The identification of the nuclear vitamin D receptor (VDR) dispersed across various tissues in our body has unveiled valuable insights into the pleiotropic significance of vitamin D. It is now recognized that the functionality of vitamin D is shaped by polymorphisms in regions of the gene encoding the VDR receptor [5]. As a result, vitamin D plays a multifaceted role in the body, potentially impacting the onset of diseases such as depression and anxiety disorders.

The potential involvement of vitamin D in conditions like depression and anxiety disorders is indicated by the identification of vitamin D receptors (VDRs) and enzymes related to vitamin D metabolism on neurons and glial cells within the hippocampus and prefrontal cortex [6]. Additionally, the presence of VDRs on various cells of the immune system further underscores the potential role of vitamin D in these health conditions [7].

Genetic studies. In 2021, a study utilizing the UK Biobank was published which was aimed at exploring genetic connections between depression, anxiety disorders, and vitamin D. The study involved the creation of a polygenic risk score (PRS) for vitamin D through a genome-wide association study (GWAS). Additionally, to evaluate the impact of the interaction between vitamin D and genes on anxiety disorders and depression, a genome-wide environmental interaction study (GWEIS) was conducted. The findings of the study affirmed a genetic link between vitamin D and the occurrence of depression and anxiety disorders.

Through GWEIS, numerous vitamin D-responsive genes were identified which played pivotal roles in regulating the central and peripheral nervous systems. Specifically, genes such as GNB5 and DPP6 were associated with anxiety disorders, while LRRTM4 was linked to depression. GNB5 encodes a GTP-binding protein primarily responsible for regulating neurotransmitter signal transduction in the brain by forming a complex with G protein [8].

Another study substantiated that vitamin D deficiency leads to a decrease in GNB5 gene expression [9]. Consequently, vitamin D's influence on the GNB5 gene suggests a potential role in regulating signaling within the brain, particularly through the G protein pathway. PP6, a protein found in hippocampal neurons, among other locations [10], plays a key role in regulating neuronal excitability. It is also involved in neurogenesis, influences intelligence levels, and has been associated with certain neurodevelopmental disorders [11]. In contrast, LRRTM4 encodes a transmembrane protein crucial for the formation of glutamate synapses, playing a significant role in nervous system development by affecting axon growth [12].

It is noteworthy that despite data indicating the heritability of anxiety symptoms at approximately 31% [13] and the heritability of major depression estimated to be around 38% [14], a comparison of genetic loci associated with anxiety disorders and depression has revealed no overlapping loci [8]. This observation may suggest different mechanisms of vitamin D effects in these two diseases.

Unique properties of vitamin D. Signs of atrophy and a decrease in the number of normal neurons, potentially indicative of nervous system inflammation, have been observed in individuals with both depression and anxiety disorders [15]. The underlying cause of nervous system inflammation in both conditions may be attributed to prolonged exposure to chronic stress.

At this juncture, it is noteworthy to highlight the properties of vitamin D, including its recognized anti-inflammatory,

neuromodulatory, and proneurogenic effects. These features may hold crucial protective significance in the context of depression and anxiety disorders. Vitamin D plays a role in the regulation of both innate and acquired immunity [7]. There is speculation that calcitriol, a form of vitamin D, may contribute to the immune response in the central nervous system by engaging in the immune activation of microglia [6]. Calcitriol serves a crucial function in modulating antioxidant enzymes, influencing redox homeostasis and thereby diminishing the intensity of the neuroinflammatory process [16, 17]. The proneurogenic attributes of vitamin D stem from its impact on the synthesis of various neurotrophins, such as neurotrophin-3 (NT-3), responsible for neuronal growth, survival, and differentiation [18], brain-derived neurotrophic factor (BDNF) [19], glial cell lineage-derived neurotrophic factor (GDNF) [20], and nerve growth factor (NGF) [21].

Regulation of neurotransmission. Vitamin D plays a vital role in the regulation of neurotransmission, both directly and indirectly. Directly, it enhances the synthesis of serotonin, dopamine, and norepinephrine by inducing the expression of enzymes, such as tryptophan hydroxylase and tyrosine hydroxylase, crucial in the production of these monoamines [22]. Indirectly, it influences neurotransmission through its anti-inflammatory properties and its impact on the proper functioning of the intestinal microflora [23], considering that the majority of serotonin is produced in the gut. Furthermore, clinical studies have demonstrated that administering vitamin D can elevate serotonin levels in individuals with depression [24].

It's worth noting that the same neurotransmitters implicated in the etiology of depression, namely serotonin, norepinephrine, and dopamine, likely play a role in the occurrence of anxiety disorders. This connection is evident in the fact that certain antidepressants have been incorporated into the pharmacotherapy of anxiety disorders. These medications include selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants.

Clinical studies on the association of vitamin D with depression and anxiety conditions. Among the clinical studies examining the relationship between vitamin D deficiency and the prevalence of anxiety disorders and depression, a noteworthy example is a 2015 study conducted in Prague. This study assessed calcidiol levels in three distinct groups of patients: one group with anxiety disorders (20 men and 20 women), another with depression (20 men and 20 women), and a control group consisting of healthy individuals (24 women and 12 age-matched men). To minimize the impact of seasonality, patients were recruited throughout the year. Significantly lower calcidiol levels were noted in patients with anxiety disorders (men averaged 19.9ng/ml and women 20.2 ng/ml) and in patients with depression (men averaged 16.0 ng/ml, women averaged 20.9 ng/ml), compared to a control group of healthy subjects whose 25(OH)D results were within the normal range of 30–40 ng/ml [25]. The study therefore supported the claim that both depression and anxiety disorders are associated with vitamin D deficiency in both genders. Numerous studies have consistently demonstrated a correlation between vitamin D deficiency and the presence of depressive symptoms [26–35] or anxiety disorders [31, 36, 37].

However, it is important to acknowledge that some studies contradict this thesis concerning anxiety [38–40], as well as depression [38, 39, 41, 42, 43, 44], failing to establish significant associations of these diseases with 25(OH)D levels.

Clinical trials on the potential use of vitamin D in the treatment of depression and anxiety disorders. The D-Vitaal study conducted in the Netherlands from 2013–2016, yielded no significant impact of vitamin D administration at a daily dose of 1,200 IU for 12 months on depressive symptoms, physical functioning, and the incidence of anxiety disorders in an elderly population. The inclusion criteria of the study are worth considering: enrollment of 155 participants aged 60–80 years, with sub-threshold depression assessed by the Centre of Epidemiological Studies-Depression scale (CES-D) – score of ≥16 (participants prohibited from taking any anti-depressants during the study). Additionally, participants had to exhibit ≥1 limitation in physical functioning and have reduced vitamin D levels – (25(OH)D levels of 15–70nmol/L in the months of April – September, or 15–50 nmol/L in the months of October -March). However, upon comparing the severity of depressive symptoms in the intervention group after six months with the results obtained after one year of the study, a noteworthy trend emerged. After six months, individuals supplementing with vitamin D exhibited a notably significant improvement, marked by a reduction in the severity of depressive symptoms, a change not observed in the placebo group (55.6% compared with 44.4%, P in the adjusted model = 0.09). Nevertheless, after one year of the study, this difference became less pronounced (48.8% compared with 51.3%, P in the adjusted model = 0.63) [45]. The variance in these results may suggest a beneficial effect of addressing vitamin D deficiency early in the treatment of depressive disorders, highlighting that vitamin D pharmacotherapy alone may be insufficient and should be complemented with standard depression treatment.

This hypothesis finds support in a 2013 study involving 42 individuals diagnosed with a major depressive disorder. The study revealed that daily oral supplementation of 1,500 IU of vitamin D, in combination with 20 mg of fluoxetine for two months, proved more effective than administering fluoxetine alone. The intervention group showed a significant reduction in depression severity on both the Hamilton Depression Rating Scale (HDRS) and Beck Depression Inventory (BDI), compared to the group taking fluoxetine alone [46].

A clinical trial, published in 2020 and conducted in China by researchers Zhu Dao-min and Peng Zhu, focused on 158 vitamin D deficient patients (25(OH)D > 75nmol) concurrently experiencing depressive and anxiety disorders. The trial aimed to evaluate the effects of oral vitamin D supplementation at a dose of 1,600 IU per day for six months and produced intriguing findings. Although no significant difference was noted between the study group and the control group concerning changes in the severity of depressive symptoms, a noteworthy alleviation of anxiety symptoms was observed in the vitamin D supplementation group compared to the control group during the study period. It is essential to highlight that in this study, the use of any psychiatric medication was considered one of the confounders, not in terms of inclusion in the study, with the majority of patients not utilizing this type of treatment [47]. Another study conducted in Iran, encompassing 56 subjects with recognized mild to moderate depression, revealed that

the administration of vitamin D at a dosage of 50,000 IU every two weeks for two months led to a reduction in the severity of depression. However, this improvement occurred without significant alterations in neurotransmitter levels. It is noteworthy that participants in the study were restricted from using antidepressants [48].

In a 2019 study conducted in Saudi Arabia, involved 62 patients diagnosed with major depressive disorder (MDD). The treatment regimen included cholecalciferol at a dosage of 50,000 IU for a duration of three months, together with standard drug treatment. This approach led to an increase in serum serotonin levels across all patients in the study group. Additionally, a reduction in the severity of depressive symptoms was observed, as assessed by the Beck Depression Inventory (BDI). Notably, the improvement was evident in vitamin D-supplemented women with moderate to extreme depression, while in men, it was observed specifically in those diagnosed with severe depression [24].

A study conducted in Iran between 2011–2012, involving 120 patients with both vitamin D deficiency and depression scoring at least 17 on the BDI II scale, revealed that a single intramuscular injection of 300,000 IU of vitamin D was safer and more effective in reducing the severity of depressive symptoms, compared with a dose of 150,000 IU [49]. Similar conclusions were reached in a study published in 2020, which used a single dose of 300,000 IU vitamin D injection as initial adjunctive treatment in patients with major depression and reduced serum 25(OH)D levels. After 12 weeks, the intervention group exhibited a significant reduction in depression severity and an improvement in the quality of life [50].

In a 2019 study conducted in Saudi Arabia by researchers Alaa Eid and Sawsan Khoja et al., the administration of vitamin D to alleviate symptoms of Generalized Anxiety Disorder (GAD) yielded positive outcomes. The study comprised 30 participants (13 females and 17 males aged 18–65) with GAD and insufficient serum 25(OH)D levels (25–50 nmol/L). Participants were randomly assigned to a control group (receiving standard treatment for GAD) and an intervention group (taking 50,000 IU of calcitriol once a week for three months in addition to GAD medication). Individuals diagnosed with additional diseases, such as depression, were excluded from the study. The changes in serum vitamin D concentrations of GAD patients during the study are depicted in Figure 1.

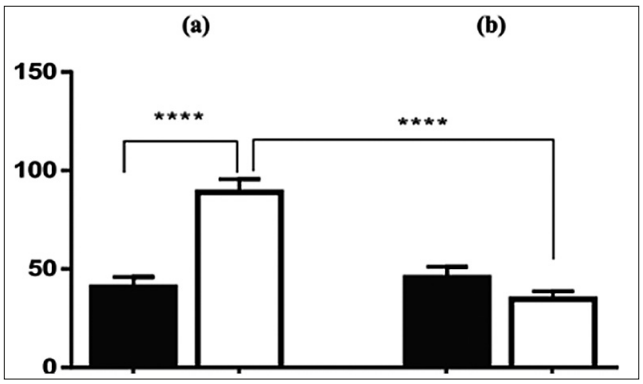

Figure 1. Vitamin D levels (in nmol/L) in GAD patients: (a) treated with standard medications in combination with vitamin D, (b) treated with standard medications alone.
Baseline 25(OH)D levels, shown by black bars, were comparable in both groups: 41.7 nmol/L in the study group (a) and 43.5 nmol/L in the control group (b). White bars represent vitamin D levels after 3 months of follow-up: 90.1 nmol/L in the study group (a), and 36.54 nmol/L in the control group (b), **** $p < 0.0001$

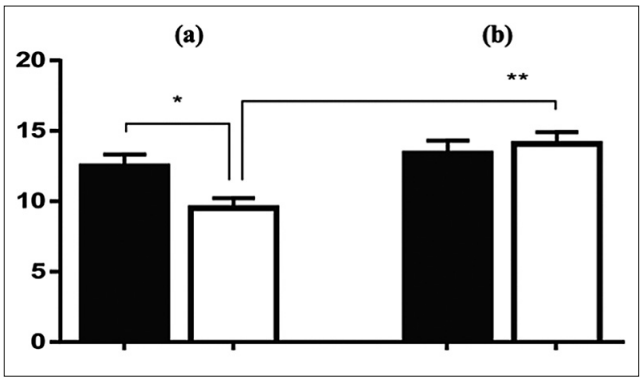

Figure 2. displays the changes in Generalized Anxiety Disorder-7 scale (GAD-7) scores among patients with anxiety disorders.
GAD-7 scores in patients with Generalized Anxiety Disorder (mean ± SEM): (a) treated with standard medications in combination with vitamin D, (b) treated with standard medications alone. Baseline GAD-7 scores, depicted by black bars, were as follows: mean 13.6 in the study group (a) and mean 13.8 in the control group (b). White bars represent mean GAD-7 scores after 3 months of follow-up: 9.5 points in the study group (a) and 14.1 in the control group (b), respectively. *$p < 0.05$, **$p < 0.01$

In the vitamin D supplement group, a notable reduction in the severity of anxiety symptoms was observed after three months (an average decrease of 9.5 points on the GAD-7 scale, compared to the baseline 13.6 points; $p < 0.0001$). Conversely, no significant difference was noted in the control group on the GAD-7 scale. The study also evaluated changes in serum concentrations of selected neurotransmitters and inflammatory factors. Figure 3 specifically illustrates alterations in serum serotonin concentrations among patients with Generalized Anxiety Disorder (GAD).

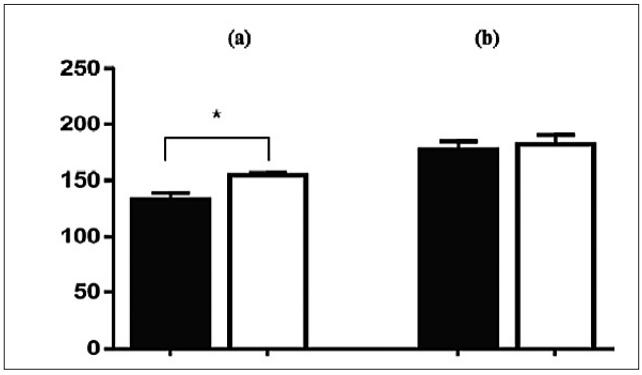

Figure 3. Serum serotonin concentrations in patients with Generalized Anxiety Disorder (GAD) in nmol/L (mean ± SEM): (a) treated with standard drugs in combination with vitamin D, (b) treated with standard drugs alone
Baseline serotonin concentrations, depicted by black bars, were 135 nmol/L in the study group (a) and 182.1 nmol/L in the control group (b), respectively. White bars represent serum serotonin concentrations after 3 months of follow-up: averaging 155 nmol/L in the study group (a) and 176.6 nmol/L in the control group (b). ****$p < 0.0001$.

The group of patients supplementing with vitamin D exhibited a notable reduction in neopterin, a marker of inflammation (Fig. 4).

The findings from the afore-mentioned study indicate that vitamin D supplementation in individuals deficient in vitamin D and experiencing generalized anxiety disorder, led to a reduction in anxiety severity, potentially attributed, in part, to an elevation in serotonin levels and a decrease in neopterin-an oxidative stress factor [51]. However, a study conducted between 2010 – 2013 assessing the impact of 2,800 IU vitamin D supplementation on individuals with depression

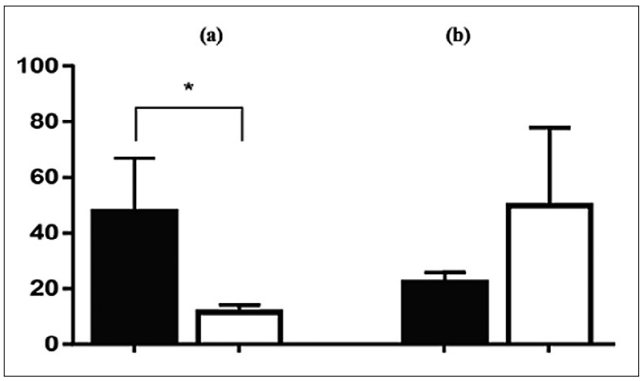

Figure 4. Serum neopterin concentrations in patients with GAD in nmol/L (mean ± SEM): (a) treated with standard drugs in combination with vitamin D, (b) treated with standard drugs alone.
Baseline neopterin concentrations are depicted with black bars, while white bars represent serum neopterin concentrations after 3 months of follow-up. In the study group (a), there was a significant decrease in neopterin concentrations, decreasing from an average of 68 nmol/L at baseline to an average of 12 nmol/L after 3 months of follow-up. * $p < 0.005$

spanning from mild to severe, and with differing baseline serum vitamin D levels, did not demonstrate a significant reduction in symptom severity on the Hamilton scale after 12 weeks of vitamin D supplementation, as compared to the placebo group. The participants in the study were receiving or not receiving standard treatment based on clinical indications [52]. Another study conducted in the USA between 1995–2000 on a large group of 36,282 postmenopausal women, evaluating the effects of daily administration of 400 IU of vitamin D combined with 1,000 mg of calcium over a two-year period, reached similar conclusions. The study found no improvement in terms of reducing the incidence of depressive symptoms as assessed by the Burnam Screen, a short version of the CES-D [53].

CONCLUSIONS

Research on vitamin D metabolism and genetic studies has affirmed connections between this substance and depression and anxiety disorders. The anti-inflammatory and neuroprotective properties of vitamin D may exert a positive influence on nervous system inflammation, a recognized pathophysiological factor in both psychiatric disorders. Clinical studies examining the association of vitamin D with depression and anxiety disorders have produced inconclusive results, potentially influenced by confounding factors, such as gender, age, genetically-determined vitamin D bioavailability, body weight, among others. Conversely, the majority of studies investigating the impact of correcting vitamin D deficiency on reducing the severity of depression and anxiety symptoms have shown promising outcomes, contingent on adequate compensation. Notably, employing vitamin D as an adjunctive treatment alongside standard pharmacological approaches for depression and anxiety disorders, has demonstrated particularly favourable effects.

Further investigation is imperative for a comprehensive understanding of the etiology and pathophysiology of depression and anxiety disorders, as well as to unlock the considerable potential of vitamin D. Moreover, there is a crucial requirement for in-depth research into the therapeutic application of vitamin D as an adjunctive treatment for depression and anxiety disorders. This research should consider the intricate etiology of these psychiatric disorders, the initial severity of symptoms, and the impact of environmental and genetic factors, encompassing the variability in individual responses to vitamin D treatment.

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