International Journal Multidisciplinary

Volume 1 Nomor 2 May 2024
E-ISSN: 3031-9870
https://journal.antispublisher.com/index.php/ijmi

REVIEW: THE ROLE OF VITAMIN D SUPPLEMENTATION IN REDUCING THE RISK OF ALZHEIMER'S IN ELDERLY PATIENTS

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Abstract

Tantangan global semakin meningkat seiring dengan meningkatnya prevalensi demensia. Demensia dianggap sebagai penyakit multifaktorial. Demensia adalah istilah umum yang digunakan untuk menggambarkan berbagai gejala yang memengaruhi daya ingat, pemikiran, dan kemampuan untuk melakukan aktivitas sehari-hari. Alzheimer adalah salah satu jenis demensia yang paling umum, menyumbang 75% dari semua kasus demensia. Metode yang digunakan dalam review artikel ini adalah metode kontras. Metode kontras adalah metode review jurnal/artikel dengan cara mencari perbedaan antara beberapa jurnal penelitian dan kemudian menarik kesimpulan. Hasil penelitian menunjukkan bahwa alzheimer adalah masalah kesehatan yang terus berkembang di seluruh dunia. Penyakit ini membebani individu dan juga keluarga pasien, yang berdampak negatif pada kualitas hidup yang berkaitan dengan memori dan fungsi kognitif. Penurunan daya ingat atau demensia paling sering terjadi pada orang tua, yang disebabkan oleh penyakit Alzheimer. Kesimpulan penelitian menunjukkan bahwa Suplementasi vitamin D memiliki potensi untuk mengurangi risiko Alzheimer pada pasien usia lanjut. Vitamin D diketahui berperan penting dalam perkembangan dan fungsi otak, serta kognisi. Beberapa penelitian menunjukkan bahwa kekurangan vitamin D dapat meningkatkan risiko gangguan kognitif dan Alzheimer, sedangkan suplementasi vitamin D dapat meningkatkan fungsi kognitif dan mengurangi akumulasi beta-amiloid di otak. Namun, hasilnya masih beragam dan masih terdapat keterbatasan, sehingga penelitian lebih lanjut dengan desain yang lebih baik dan sampel yang lebih besar diperlukan untuk mengonfirmasi temuan ini dan memahami mekanisme biologis yang mendasarinya.

Keywords : *Demensia, Alzheimer*

Global challenges are increasing as the prevalence of dementia increases. Dementia is considered a multifactorial disease. Dementia is a general term used to describe a range of symptoms that affect memory, thinking and the ability to perform daily activities. Alzheimer's is one of the most common types of dementia, accounting for 75% of all dementia cases. The method used in this article review is the contrast method. The contrast method is a journal/article review method by looking for differences between several research journals and then drawing conclusions. The results showed that alzheimer's is a growing health problem worldwide. The disease burdens the individual as well as the patient's family, which negatively affects the quality of life related to memory and cognitive function. Memory decline or dementia is most common in older people, caused by Alzheimer's disease. . The study concluded that vitamin D supplementation has the potential to reduce the risk of Alzheimer's in elderly patients. Vitamin D is known to play an important role in brain

development and function, as well as cognition. Several studies have shown that vitamin D deficiency may increase the risk of cognitive impairment and Alzheimer's, while vitamin D supplementation may improve cognitive function and reduce beta-amyloid accumulation in the brain. However, the results are mixed and limitations remain, so further studies with better designs and larger samples are needed to confirm these findings and understand the underlying biological mechanisms.
Keywords: Dementia, Alzheimer's

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Introduction

Global challenges are increasing as the prevalence of dementia increases. Dementia occurs mainly in people over the age of 65 [1]. In addition, dementia is common in low- and middle-income countries due to the increase in the ageing population. As in other countries, Indonesia is expected to experience a significant increase in the number of people living with dementia from 1.2 million in 2015 to 1.9 million in 2030, and 3.9 million in 2050, an almost threefold increase [2]; [3]. Dementia is considered a multifactorial disease [4]. Dementia is a general term used to describe a range of symptoms that affect memory, thinking, and the ability to perform daily activities [5]; [6] Alzheimer's is one of the most common types of dementia, accounting for 75% of all dementia cases.

Alzeimer's is a multifactorial disorder resulting from a combination of age-related brain changes and major genetic, environmental, lifestyle, vascular, and dietary risk factors [7]. Alzheimer's disease is a chronic neurodegenerative disorder pathologically defined as the accumulation of extracellular amyloid-beta (Aβ) and neocortical neurofibrillary tangles and amyloid plaques characterized by deterioration of memory and cognition [8]; [9]. Aβ plaques are formed and deposited in different regions of the brain. These plaques are recognized as foreign bodies by the brain which initiates an inflammatory and immune response by activating microglia and cytokine release, ultimately leading to cell death and neurodegeneration [10]. Amyloid-beta (Aβ) is involved in the initiation of pathophysiological changes that lead to cognitive impairment and neurodegeneration through disruption of axonal transport, neurotrophic factor synthesis, and neural signaling pathways [11]. Management of alzeimer's is largely symptomatic, and there is no curative or preventive treatment [7]. Interventions based on modifiable things such as risk factors for dementia have been explored as a potential way to slow disease progression. Vitamin D deficiency may be a modifiable risk factor [2].

Vitamin D has been widely recognized for its effect on calcium and bone metabolism, but its effect on chronic diseases involving neurocognitive decline has only recently been recognized [7]. Vitamin D deficiency is associated with cognitive impairment. Current evidence suggests that vitamin D is also involved in the development of dementia and Alzheimer's disease [12]. Low serum 25-hydroxyvitamin D (25(OH)D) concentrations are associated with an increased risk of incident dementia

[13] and Alzheimer's disease [14]. Both 1,25dihydroxyvitamin receptor and 1a-hydroxylase are enzymes responsible for synthesizing the bioactive form of vitamin D, found throughout the human brain [14]. 1,25-Dihydroxyvitamin D [1,25(OH)2D] plays an important role in neuronal differentiation and maturation through the control of synthesis of neurotrophic agents such as nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF), neurotrophin 3, and low-affinity synthesis of p75 NTR receptor [15]. In addition, vitamin D is known to participate in the clearance of amyloid beta (Aβ) aggregates which is one of the hallmarks of alzheimer's disease, and may provide neuroprotection against Aβ-induced tau hyperphosphorylation [2].

Vitamin D works through the vitamin D receptor (VDR), a nuclear hormone receptor, which is present on nerve and glial cells in almost all brain regions of the central nervous system (CNS). Areas important for cognition are primarily expressed in the hippocampus, amygdala, hypothalamus, cortex, and subcortex. Vitamin D helps in neuroprotection by regulating nerve growth and neurotrophic factors such as nerve growth factor, decreasing the expression of L-type calcium channels, and regulating the toxicity of reactive oxygen species and nitric oxide synthase. In addition, vitamin D shows a role in lowering the accumulation of Aβ 42 by increasing its phagocytosis and strengthening the transport of beta amyloid removal from the brain to the blood at the blood-brain barrier (BBB), causing fewer amyloid plaques. Several studies have shown an association between D receptor (VDR) gene polymorphisms and alzeimer's cognitive decline. Vitamin D deficiency is more common with age due to decreased skin synthesis and decreased absorption of vitamin D. It is apparent that low vitamin D concentrations in older adults have shown an association with decreased cognitive performance and are more common in those with alzeimer [7].

With the increasing number of elderly population in Indonesia and worldwide, it is important to identify strategies that can help reduce the burden of Alzheimer's disease. Vitamin D supplementation may be one intervention worth considering, given its potential benefits in bone health as well as cognitive function.

This review article aims to evaluate and analyze the efficacy of vitamin D supplementation in reducing the risk of Alzheimer's disease progression and delaying cognitive function decline in elderly patients. Through a review of the current literature, this article seeks to assess the scientific evidence on whether vitamin D supplementation can slow the decline of cognitive function and the progression of Alzheimer's disease. As well as assess whether vitamin D could be an effective prevention strategy for Alzheimer's in the elderly. By achieving these objectives, this article is expected to provide insight for researchers, healthcare practitioners, and policy makers in developing more effective Alzheimer's prevention and management strategies based on vitamin D supplementation. This article is expected to make a meaningful contribution to Alzheimer's prevention and management through an evidence-based approach.

Methods

The research method used PubMed, Science Direct, Mendeley and Google Scholar are some of the sources of articles used in the search for information on the effect of vitamin D supplementation in elderly patients on reducing the risk of Alzheimer's

progression or delaying cognitive function decline. The majority of articles used were recent articles written within the last 10 years, from 2014-2024. The keywords used in searching the journals were “Vitamin D”, “Alzheimer”, “Cognitive”, “Geriatric”. The number of initial articles found was 199 articles, Pubmed as many as 27 articles, Mendeley as many as 21 articles, Science Direct as many as 83 articles, Google Scholar as many as 68 articles. The article was then removed based on the abstract alone as many as 184 articles, filtered based on full text articles resulting in 15 articles, and in accordance with the formulation of the problem and research objectives as many as 7 articles that provide information about the effect of Vitamin D on the risk of Alzheimer's development. The selection of these articles is based on internationally published journals and indexed by Scopus.

The method used in this article review is the contrast method. The contrast method is a method of reviewing journals/articles by finding differences between several research journals and then drawing conclusions. Then the method that is widely used in the articles to be reviewed is the Retrospective Intervention Study which aims to assess the impact of vitamin D supplementation in elderly patients on the risk of Alzheimer's disease progression. The data extraction process involved measuring plasma Vitamin D levels, measuring plasma Aβ40 and Aβ42, measuring cognitive function in both the control and test groups. This assessment was conducted using HPLC-MS instrumentation for plasma Vitamin D measurement, using ELISA for plasma Aβ40 and Aβ42 measurement, and MMSE questionnaire for cognitive function measurement. The scores obtained from the questionnaires were then statistically analyzed to evaluate the impact of plasma Vitamin D levels, plasma Aβ40 and Aβ42 levels, Vitamin D supplementation and cognitive abilities of patients. Inclusion and exclusion criteria were determined to minimize bias and ensure the relevance and quality of the study, the following inclusion and exclusion criteria were applied in the selection of articles:

Inclusion Criteria:

1. Articles published in English or Indonesian.
2. Articles published within the last 10 years (2014-2024).
3. Articles that are available in full text.
4. Studies involving elderly patients (≥ 65 years old).
5. Studies that evaluate the effect of vitamin D supplementation on the risk of Alzheimer's progression or delayed decline in cognitive function.
6. Studies that use valid measurement methods for plasma Vitamin D, Aβ40 and Aβ42 levels, and cognitive function.
7. Studies published in Scopus indexed journals.

Exclusion Criteria:

1. Articles that are only available in abstract form or not available in full text.
2. Articles published before 2014.
3. Studies that did not include elderly patients or the general population.
4. Studies that did not evaluate the effect of vitamin D supplementation on Alzheimer's or cognitive function decline.
5. Studies that used measurement methods that were invalid or not described in detail.

6. Review articles, editorials, or commentaries that did not present original research data.

By using these inclusion and exclusion criteria, it is expected that relevant and high-quality articles will be analyzed in this review, so that the results can provide a clearer understanding of the effect of vitamin D supplementation on the risk of developing Alzheimer's in elderly patients.

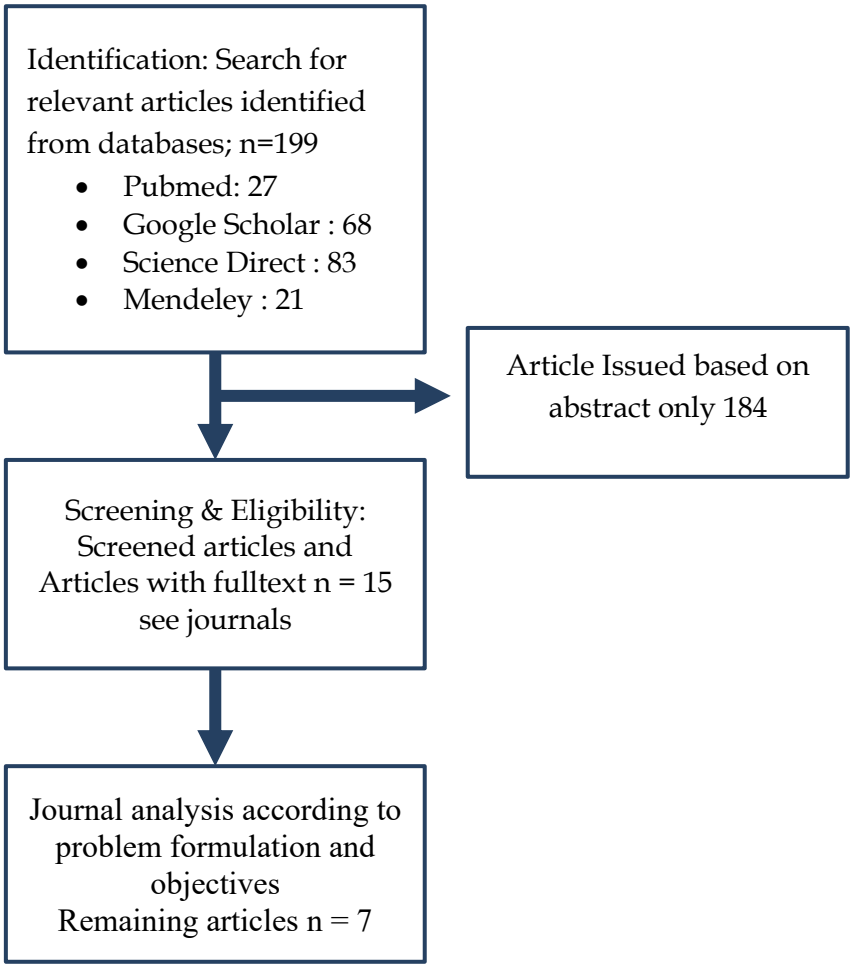

Figure 1. Article Search

Results and Discussion

Table 1. Role of Vitamin D in Elderly Alzheimer's Patients

Journal Citation	Research Methods	Intervention	Research Results
(Miller, et al., 2016)	The study was a parallel approach, double-blind, randomized control trial design. Volunteers were recruited in Phoenix through electronic advertising and word of mouth, and screened for a Mini Mental State Examination (MMSE) score greater than 26, 50+ years of age, serum total 25OHD less than 30 ng/mL, and absence of diabetes, kidney, liver disease, statin use, or blood disorders. Participants provided written informed consent, knowing that a placebo and not vitamin D would be received. After being randomized into groups, participants consumed 50,000 IU cholecalciferol or similar flour capsules once a week for eight weeks. Follow-up visits were	Serum total 25OHD, plasma A40, vitamin D intake (IU-d), and physical activity (METS/week) data were collected before and after eight weeks of the experiment. Total serum 25OHD was quantified using liquid chromatography liquid tandem mass spectrometry. Plasma Aβ40 was detected using a commercially available ELISA. All participants reported fasting and had blood samples drawn into a serum separator or sodium heparin vacutainer. After centrifugation, serum samples were transferred into transport tubes, and protease inhibitor (Pefabloc) was immediately added to the plasma samples, which were stored at -80◦C and thawed once. Vitamin D intake was measured using the Vitamin D Brief Questionnaire, and physical activity was measured using the Community Health Activities Model Program for the Elderly Community Health Activities Model	Vitamin D-deficient adults (6/18 L/P; 64.3 ± 10.9 years) were randomized to placebo or vitamin treatment (50,000 IU/week). The vitamin group experienced greater changes in plasma Aβ40 than controls, +14.9 ± 12.0 and +12.8 ± 12.8 pg/mL (p = 0.045; effect size, 0.228). Changes in Aβ40 for older participants (≥60 years) were +18.3 ± 33.6 and -3.2 ± 44.5 pg/mL for the vitamin (n = 4) and placebo (n = 4) groups, respectively (effect size, 0.295). Thus, vitamin D may increase plasma Aβ, especially in older adults, suggesting a decrease in brain Aβ.

Journal Citation	Research Methods	Intervention	Research Results
	conducted within a week after the eighth supplement was consumed.	Questionnaire, both of which had been previously validated.	
(Jia et al., 2019a)	The study used a randomized double-blind, placebo-controlled trial. 210 Alzheimer's patients were randomly divided into intervention and control groups. Participants received 800 IU/day of vitamin D for 12 months or granulated starch as a placebo. Cognitive performance tests and β-related biomarkers were measured at baseline, 6 months and 12 months.	Repeated measures analysis of variance showed significant improvements in plasma aβ42, app, Bace1, appmRNa, Bace1mRNa ($p<0.001$) levels and information, arithmetic, digit span, vocabulary, block design and picture organization scores ($p<0.05$) in the intervention group compared to the control group. According to mixed model analysis, the vitamin D group had a significant improvement in full-scale IQ during follow-up ($p<0.001$)	Daily oral vitamin D supplementation (800 IU/day) for 12 months can improve cognitive function and reduce β-related biomarkers in elderly people with Alzheimer's disease. Larger-scale, long-term randomized trials on vitamin D are needed.
(Ghahremani, et al., 2023)	Early exposure to vitamin D was considered D+; no exposure before the onset of dementia was considered D-. Kaplan-Meier curves compared dementia-free survival between groups. Cox models assessed dementia incidence rates across groups, adjusted for age, sex, education, race, cognitive diagnosis, depression, and apolipoprotein E (APOE) ε4. Sensitivity analysis examined incidence rates for each vitamin D formulation. Potential	Across all formulations, vitamin D exposure was significantly associated with longer dementia-free survival and lower dementia incidence rates than without exposure (hazard ratio = 0.60, 95% confidence interval: 0.55-0.65). The effect of vitamin D on event rates differed significantly across layers of sex, cognitive status, and APOE ε4 status.	In a prospective cohort study, we assessed the effect of Vitamin D on the incidence of dementia in 12,388 participants from the National Alzheimer's Coordinating Center. Vitamin D exposure was associated with a 40% lower incidence of dementia compared to non-exposure. The effect of vitamin D was significantly greater in women than men. Women also had normal cognitive function, compared to men who had mild cognitive impairment. The effect of vitamin D

Journal Citation	Research Methods	Intervention	Research Results
	interactions between exposure and model covariates were explored.		was significantly greater in apolipoprotein E ε4 non-carriers than carriers. Vitamin D has potential for dementia prevention, especially in high-risk groups.
(Kalra et al., 2020b)	This study used a systematic review and meta-analysis with PubMed and Scopus electronic bibliographic databases. Test method Prospective cohort study, with community-dwelling elderly as the study sample. Data extraction and analysis were performed based on the following criteria: (a) community-based, (b) free of dementia or Alzheimer's or vascular dementia at baseline, (c) measured serum vitamin D as an exposure variable, (d) information on incident dementia (all causes) and/or Alzheimer's and/or vascular dementia as an outcome measure, (e) risk measure information 95% CI for risk of dementia (all causes) and/or AD and/or vascular dementia and, (f) age greater than 50 years at baseline assessment of participants.	Serum vitamin D concentrations were categorized in three groups: normal levels (>50 nmol/L), insufficient levels (25 - 49.9 nmol/L), and deficient levels (<25 nmol/L). We conducted a meta-analysis using the generalized method to calculate the pooled risk of Alzheimer's and all-cause dementia according to vitamin D levels. Randomeffects or fixed-effects models were used to calculate the pooled risk based on heterogeneity analysis	Five studies were included in the meta-analysis. The combined risk of all-cause dementia and Alzheimer's was significantly higher in those with deficient serum vitamin D levels compared to those with normal levels (1.33, CI95% [1.15, 1.54], and 1.87, CI95% [1.03, 3.41], respectively). Those with insufficient levels also had a higher combined risk of all-cause dementia and Alzheimer's, but the strength of the association was less strong (1.14 CI95% [1.02, 1.27] and 1.25, CI95% [1.04 - 1.51], respectively).

Journal Citation	Research Methods	Intervention	Research Results
(Kang et al., 2022b)	The 5xFAD mice were randomly assigned into eight groups (n=6/group) which included: (1) Early Control Group (2) Early Deficiency Group (3) Late Control Group (4) Late Deficiency Group. (5) Intermediate Vitamin Group (6) Intermediate Animal Group (7) Late Vitamin D supplementation group (8) Late Animal Group. Then brain tissue testing was conducted, and tested using the ELISA method (to examine the influential genes), behavioral habit testing was also conducted on rats, as well as analysis and quantification testing.	The study was conducted by inducing vitamin D deficiency in 5xFAD mice by administering a vitamin-D deficient diet and observing its changes in the mRNA levels of genes associated with Aβ processing, which resulted in increased Aβ load in the brain. The vitamin D-deficient diet also suppressed the expression of genes for microglial Aβ phagocytosis. Interestingly, vitamin D deficiency in the early stages of Alzheimer's results in earlier memory impairment. In addition, we administered vitamin D intraperitoneally to 5xFAD mice on a normal diet and found lower Aβ levels with suppressed gene expression for Aβ generation and observed improved memory function, which may be potentially related to reduced MAO-B expression.	Vitamin D supplementation improves memory function by ameliorating amyloidopathy and gliopathy in a mouse model with Alzheimer's. By understanding these mechanisms, especially with regard to nutritional factors affecting Alzheimer's, we propose further research investigating the role of vitamin D as a potential therapeutic treatment for Alzheimer's patients.
(Chakkera, et al., 2022)	This study was a systematic review using five databases such as PubMed, PubMed Central (PMC), Medical Literature Medical Literature Analysis and Retrieval System Online (MEDLINE), ScienceDirect, and Google Scholar searched for articles relevant to the research question with filters such as English language and human studies	Most RCTs did not show significant improvement on vitamin D supplementation except for one study, which reported significant improvement in cognition when taking vitamin D in Alzheimer's disease but not much consideration as it had a small sample size (n=210) and was of shorter duration. Another study proved significant improvement in Mini-Mental State Examination (MMSE) scores when memantine and vitamin D were taken together	Studies have shown that vitamin D deficiency is associated with an increased risk of developing cognitive impairment. But there is insufficient evidence to suggest that vitamin D supplementation can improve cognitive function in Alzheimer's disease.

Journal Citation	Research Methods	Intervention	Research Results
	from 2011 to 2022. Two researchers extracted the data and assessed the quality of the studies using predefined criteria. We identified 24 relevant articles after critical screening. There were five randomized controlled trials (RCTs), two observational studies, two systematic reviews and meta-analyses, one pilot study, and 14 review articles.	compared to when memantine and vitamin D were taken independently.	
(Littlejohns, et al.,2014)	In this prospective cohort study, a study sample of 1658 ambulatory elderly free of dementia cardiovascular disease and stroke who participated in the US population-based Cardiovascular Health Study between 1992-1993 and 1999 was included. Serum 25-hydroxyvitamin D (25(OH)D) concentrations were determined by liquid chromatography-tandem mass spectrometry from blood samples collected in 1992-1993. The incidence of all-cause dementia and Alzheimer's disease was assessed during follow-up using National	During a mean follow-up period of 5.6 years, 171 participants developed all-cause dementia, including 102 cases of Alzheimer's disease. Using Cox proportional hazards models, the multivariate-adjusted hazard ratios (95% confidence intervals [CIs]) for incident all-cause dementia in participants with severe 25(OH)D deficiency (,25 nmol/L) and deficiency (>25 to, <50 nmol/L) were 2.25 (95% CI: 1.23-4.13) and 1.53 (95% CI: 1.06-2.21) compared with participants with sufficient concentrations (50 nmol/L). The multivariate-adjusted hazard ratios for incident Alzheimer's Disease in severe 25(OH)D deficient and insufficient participants compared to participants with sufficient concentrations were 2.22 (95% CI: 1.02-4.83) and	Our results confirm that vitamin D deficiency is associated with an increased risk of dementia and Alzheimer's disease. This adds to the ongoing debate about the role of vitamin D in nonskeletal conditions.

Journal Citation	Research Methods	Intervention	Research Results
	Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.	1.69 (95% CI: 1.06-2.69). In multivariate-adjusted spline plots, the risk of all-cause dementia and Alzheimer's disease increased markedly below the 50 nmol/L threshold.	

Alzheimer's is a growing health concern worldwide. The disease burdens the individual as well as the patient's family, negatively affecting quality of life related to memory and cognitive function. Memory decline or dementia is most common in the elderly, caused by Alzheimer's disease. Alzheimer's is a progressive neurodegenerative disorder that causes cognitive impairment and memory loss with cortical atrophy. Approximately 10% of people over the age of 70 experience significant memory loss, with more than 50% attributed to Alzheimer's [16]. Alzheimer's is a multifactorial disorder caused by a combination of age-related, brain changes and genetic, environmental, lifestyle, vascular and dietary risk factors. The pathogenesis of Alzheimer's is thought to be primarily due to the accumulation of amyloid beta (Aβ) 42 and tau protein in the form of neuritic plaques and neurofibrillary tangles. Management of Alzheimer's is largely symptomatic, and there is no curative or preventative treatment.

Vitamin D can be converted into hormones in the body through genomic and non-genomic mechanisms, exerting various physiological effects. Existing evidence suggests that vitamin D can ameliorate neurodegeneration by regulating related signaling molecules and pathways, such as maintaining calcium homeostasis, reducing oxidative stress, inhibiting inflammation, and suppressing the formation and aggregation of pathogenic proteins [17]. Vitamin D can prevent the increased expression of iNOS, NO, as well as other proinflammatory factors such as TNF-α and IL-6 in damaged neurons, microglia, and astrocytes [13].

In addition to the potentially modifiable risk factors of dementia such as obesity, diabetes, hypertension and smoking, a potentially modifiable prognostic role is addressing vitamin D deficiency. Because based on research vitamin D plays a role in brain development, brain function and cognition. It has been reported that vitamin D deficiency may have a contributing role in the development of dementia and its subtypes including Alzheimer's. Several longitudinal studies have revealed that vitamin D deficiency may have a contributing role in the development of dementia. Several longitudinal studies have revealed that vitamin D deficiency may increase the risk of cognitive impairment and memory decline. In accordance with these findings, two large population-based studies showed that lower dietary intake of vitamin D and less sun exposure were associated with a greater risk of cognitive impairment. In an effort to understand the effect of vitamin D supplementation on the risk of Alzheimer's progression and cognitive function decline in the elderly, several studies have been conducted with various methods and study populations.

Markers of AD pathology include beta-amyloid buildup outside of cells to form amyloid plaques and hyperphosphorylation of tau protein in brain cells, which is a multifactorial condition influenced by genetic, aging, environmental, and lifestyle factors, leading to neuronal degeneration. Vitamin D, found as ergocalciferol (vitamin D2) in the diet or synthesized into cholecalciferol (vitamin D3) in the skin, requires two

hydroxylation reactions to become active, with calcitriol (1,25(OH)2D) being regulated by hormonal, blood calcium, and cytokine mechanisms, as well as vitamin D receptor (VDR) expression in the brain. Low levels of vitamin D are associated with an increased risk of point loss on the MMSE over six years in the elderly, and other studies have shown that vitamin D deficiency is associated with risk of dementia and Alzheimer's [7].

The study (Miller et al., 2016) used a parallel approach, double-blind, and randomized control trial design. Volunteers in Phoenix were recruited through electronic advertising and word of mouth, with inclusion criteria involving a Mini Mental State Examination (MMSE) score greater than 26, age over 50 years, serum total 25OHD less than 30 ng/mL, and absence of conditions such as diabetes, kidney or liver disease, statin use, or blood disorders. Participants were randomized to receive 50,000 IU cholecalciferol or placebo weekly for eight weeks. The results showed that the group receiving vitamin D had a significant improvement in plasma Aβ40 levels over the control group, especially in older adults. This suggests the potential of vitamin D in reducing Aβ accumulation in the brain, which is one of the main markers of Alzheimer's. These findings support the hypothesis that vitamin D may influence Aβ metabolism in the body, which has potential implications in the prevention or delay of Alzheimer's progression. Nonetheless, this study also highlights the need for further research to validate these findings in a wider population and to understand the underlying biological mechanisms in greater depth.

This study (Jia et al., 2019) used a double-blind randomized trial with 210 Alzheimer's patients who were randomly divided into intervention and control groups. Participants received 800 IU/day of vitamin D for 12 months or placebo. The results showed that vitamin D supplementation increased plasma aβ42 levels and various other biomarkers, as well as improved cognitive scores on tests such as information, arithmetic, and vocabulary compared to the control group. The findings also showed that vitamin D supplementation positively affected cognitive scores on various tests such as information, arithmetic, and vocabulary. These results support the hypothesis that daily vitamin D supplementation can improve cognitive function and lower Aβ-related biomarkers in Alzheimer's patients. This study corroborates the evidence that vitamin D plays an important role in reducing Aβ accumulation and improving cognitive function in individuals with Alzheimer's. The implication is that vitamin D supplementation can improve cognitive function. The implication is that vitamin D supplementation may be a potential therapeutic strategy for managing Alzheimer's, although further research is needed to validate these findings and understand the underlying mechanisms better.

In a study (Ghahremani et al., 2023a) using a prospective cohort method, the effect of early exposure to vitamin D on dementia incidence was evaluated in 12,388 participants from the National Alzheimer's Coordinating Center. Results showed that vitamin D exposure was significantly associated with longer dementia-free survival and lower dementia incidence rates. The effect of vitamin D was greater in women than men and in apolipoprotein E ε4 non-carriers than carriers. This suggests that vitamin D has potential for dementia prevention, especially in high-risk groups. This study suggests

that vitamin D exposure may play a role in reducing the risk of dementia, especially through managing risk factors such as genetic status and gender. The stronger effect in women may be related to the complex interactions between vitamin D, estrogen, and the aging process that affect vitamin D metabolism and activation. The consistent results of this study confirm the potential of vitamin D as a dementia-preventive agent, independent of the type of formulation used. Nonetheless, this study also identified limitations related to optimal dose, duration of exposure, and factors such as sunlight exposure and socioeconomics that need to be considered for further development of interventions in dementia prevention in the future.

Through a systematic review and meta-analysis, this study evaluated the risk of dementia based on serum vitamin D levels in the elderly. The meta-analysis results showed that the risk of dementia and Alzheimer's was higher in individuals with low vitamin D levels compared to those with normal levels. This confirms that vitamin D deficiency is associated with an increased risk of dementia and Alzheimer's (Kalra et al., 2019). This study makes a significant contribution to our understanding of the role of vitamin D in cognitive health, particularly in the context of dementia and Alzheimer's risk. By pooling evidence from multiple prospective studies and conducting a meta-analysis, this study corroborates the association between vitamin D deficiency and increased risk of both conditions in the elderly population. This finding is important as it highlights the potential of simple interventions such as vitamin D supplementation that may be able to influence the course of these neurodegenerative diseases. Nonetheless, the limitations of observational studies and variations in follow-up periods suggest the need for further research for generalization of these findings and further consideration of preventive interventions.

This study used the 5xFAD mouse model to examine the effects of vitamin D deficiency and supplementation on Alzheimer's. Results showed that vitamin D deficiency increased Aβ load in the brain and impaired memory in mice, while vitamin D supplementation decreased Aβ levels and improved memory function. This suggests that vitamin D may improve amyloidopathy and gliopathy conditions associated with Alzheimer's [11]. This study provides important insights into the role of vitamin D in Alzheimer's pathogenesis. Using the 5xFAD mouse model which is a model often used to study Alzheimer's, this study successfully demonstrated that vitamin D has a significant effect on decreasing Aβ load in the brain. Aβ, or beta-amyloid, is one of the main characteristics in the development of amyloid plaques in Alzheimer's. The effects of vitamin D deficiency that increase Aβ load and worsen memory function suggest the importance of adequate vitamin D levels in maintaining cognitive health. This is consistent with epidemiological findings showing an association between vitamin D deficiency and increased risk of impaired cognitive progress, including Alzheimer's. Vitamin D supplementation, especially in the advanced stages of Alzheimer's, shows potential to reduce Aβ burden and improve memory function. Although the exact mechanisms are still not fully understood, this study indicates that vitamin D may involve the regulation of enzymes involved in Aβ metabolism, as well as its effects on inflammatory responses and neuroprotection. The results of this study provide a basis for continuing further research, including human clinical trials, to confirm the

effectiveness of vitamin D supplementation in reducing the risk and slowing the progression of Alzheimer's. By better understanding the mechanism of vitamin D in the reduction of Aβ burden and improvement of cognitive function, we can develop more effective prevention and treatment strategies for Alzheimer's in the future.

This study is a systematic review that analyzed several RCTs and observational studies. The majority of RCTs did not show significant improvement in cognitive function with vitamin D supplementation, except for one study with a small sample and short duration that reported significant improvement. These results suggest that the current evidence is not yet strong enough to support vitamin D supplementation as an effective therapy for Alzheimer's [7]. Nevertheless, although the majority of studies in this review did not show a consistent benefit of vitamin D supplementation in improving cognitive function in Alzheimer's patients, it should be noted that several factors may have influenced these results. Variations in dosage, duration of treatment, and characteristics of the study population may be decisive factors affecting the interpretation of these results. In addition, lack of consistency in study design and methodology also adds to the complexity of evaluating the potential effects of vitamin D on Alzheimer's. Therefore, further studies with more rigorous designs and larger sample sizes are needed to provide a more in-depth understanding of the role of vitamin D in Alzheimer's treatment and prevention.

This prospective cohort study included 1658 older adults who were free of dementia at the start of the study. Results showed that vitamin D deficiency was associated with an increased risk of dementia and Alzheimer's disease. The hazard ratio for incident dementia was higher in participants with low vitamin D levels than those with normal levels. This study adds to the evidence that vitamin D deficiency may increase the risk of developing dementia [14].

The study found that additional adjustment for diabetes or hypertension did not change the observed associations with incidence of dementia in general or Alzheimer's disease (AD), suggesting that these conditions are unlikely to mediate the observed associations. Additional adjustment for ethnicity and socioeconomic factors slightly affected the results, while severe vitamin D deficiency was associated with significantly higher odds of dementia and AD at baseline. This study suggests that low vitamin D levels may increase the risk of dementia through neurodegenerative and vascular mechanisms, supported by findings linking vitamin D deficiency to cerebrovascular pathology and increased risk for stroke (llewellyn-et-al-2014-vitamin-d-and-the-risk-of-dementia-and-alzheimer-disease). Overall, the results of these studies suggest that there is evidence to support the role of vitamin D in reducing the risk of developing Alzheimer's and improving cognitive function in the elderly. However, the mixed results and limitations of some studies suggest the need for further research with larger samples and longer duration to confirm these findings.

Conclusion

Vitamin D supplementation has the potential to reduce the risk of Alzheimer's in elderly patients. Vitamin D is known to play an important role in brain development

and function, as well as cognition. Some studies suggest that vitamin D deficiency may increase the risk of cognitive impairment and Alzheimer's, while vitamin D supplementation may improve cognitive function and reduce beta-amyloid accumulation in the brain. However, results are mixed and limitations exist, so further studies with better designs and larger samples are needed to confirm these findings and understand the underlying biological mechanisms.

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