The association of serum 25-hydroxyvitamin D and Alzheimer’s Disease: A meta-analysis

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ABSTRACT

Serum 25-hydroxyvitamin D deficiency has been suggested as a promising prognostic factor for dementia. Meta-analysis published revealed statistically significant differences of 25-hydroxyvitamin D levels in patients with Alzheimer’s disease (AD) but other studies have been published since then. The purpose of present study was to quantify the association of serum 25-hydroxyvitamin D and AD. Literature search was performed from inception up to November 22 using Pubmed database. Based on the pooled analysis, patients with Alzheimer’s disease tend to have a vitamin D deficiency relative to patients with normal cognitive function. These results strongly support the involvement of vitamin D as a critical disease-modifying variable in the reduction of AD symptoms.

INTRODUCTION

Alzheimer’s disease (AD) is an age-related neurodegenerative disease that is the leading cause of dementia (Cortes-Canteli & Iadecola, 2020). Dementia is a type of brain diseases in which the deterioration of brain cells effects in memory, thought, analysis, language, and other nerve activity malfunction (Pentkowski, Rogge-Obando, Donaldson, Bouquin, & Clark, 2021) (Pentkowski et al., 2021) (Long & Holtzman, 2019). This dysfunction can alter a behavior and personality (Archer et al., 2007) (Pentkowski et al., 2021). There are currently more than 55 million incidences of dementia globally, with the prevalence of the disease reaching to 10 million new cases year (World Health Organization, n.d.). The onset and progression of AD are influenced by genetic and environmental factors (Dunn, O’Connell, & Kaczorowski, 2019). Vitamin D deficiency has been suggested as a promising prognostic factor for dementia, along with other possibly risk factors for AD including a family history of Alzheimer’s, being an APOE-e4 gene carrier, depression, hypertension, and diabetes (Pogge, 2015). In determining dietary vitamin D requirements, circulating 25-hydroxyvitamin D is an effective marker of vitamin D state, especially for assessing vitamin D deficiency or insufficiency (Trimboli et al., 2021). Since vitamin D is involved in neural transmission, neuroprotection, and neural plasticity, it has...
been investigated that low concentration of vitamin D may assist in the progression of AD (Mayne & Burne, 2019).

Meta-analysis published in 2013, revealed statistically significant differences between patients with AD patients and control for serum 25-hydroxyvitamin D levels (Annweiler, Llewellyn, & Beauchet, 2013; Zhao, Sun, Ji, & Shen, 2013). However, 33% (Zhao et al., 2013) and 57% (Annweiler et al., 2013) of studies that were included in an earlier meta-analysis failed to fulfill the criteria for inclusion in the present meta-analysis. Meanwhile, since then, other studies have been published (Wintzell V, Svanström H, 2022). This study specifically uses normal cognitive patients as a comparator which is a great potential method for reducing bias. The aim with this meta-analysis is to investigate quantitatively the association of serum 25-hydroxyvitamin D and Alzheimer’s disease, which could get clarify the association, potential effects on the therapy and prevention of the diseases. Additionally, meta-regression was also performed to investigate the source of heterogeneity that was not addressed statistically by previous meta-analysis.

METHODS

This review is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021).

Eligibility criteria

The studies must fulfill these criteria in order to be considered for inclusion: (1) Target population was patients with Alzheimer’s Disease; and (2) Patients with normal cognitive function was used as comparator; (3) Studies that reported 25-hydroxyvitamin D level in mean ± standard deviation values; (4) Observational studies.

Information source

Pubmed database was used to perform the literature search from inception up to November 2022.

Searching strategies

The following search term was used to find relevant articles: “Alzheimer” AND “Vitamin D” OR “25-hydroxyvitamin D” OR “25(OH)D”.

Study selection

The article titles and abstracts were assessed in accordance with the inclusion criteria. A consensus must be reached during the full-text selection stage to determine which studies need to be included or excluded. Disagreements in the findings of the selected studies were resolved by discussion.

Data extraction

From eligible studies, the following information were extracted using pre-designed form: (1) Publication year; (2) Name of first author; (3) Country; (4) The number of participant; and (4) Gender; (5) The mean and standard deviation values of age; (6) The value of mean and standard deviation of 25(OH)D. The outcomes from studies which provided data in ng/dl were converted to nmol/L (the value in ng/ml was multiplied by 2.5). Additionally, WebPlotDigitizer was also used to obtain numeric data from eligible studies that present outcome in graphs.

Statistical analysis

In present meta-analysis, the continuous outcome from eligible studies were used to assess the 25-hydroxyvitamin D levels in AD patients versus normal cognitive patients. In terms of missing data, imputation was not performed. The WMD was determined with a 95% confidence interval (CI) using a random-effect model. Statistically significant difference was evaluated using a p-value ≤ 0.05 and the I² was used to represent statistical heterogeneity. A random-effects meta-regression was also conducted using the mean age of the participants to identify the potential source of heterogeneity. All statistical analysis was conducted using the Stata 16.0.

RESULTS

Study selection process

There were 510 potential identified articles in our database search. After removing duplicates (n = 1) and retracted articles (n = 9), 500 articles were screened manually based on title and abstract. Twenty-three were classified as relevant articles. Then, a full-text assessment was carried out for those articles resulting in 6 articles to be considered for inclusion. The selection of the studies was summarized in Fig. 1.

Study characteristics

The studies included were published between 1990 and 2021. In addition to two studies in the United State of America (Wintzell V, Svanström H, 2022) (Page et al., 2021), studies were also carried out in England (Ferrier et al., 1990), Germany (Luckhaus et al., 2009), Greece (Mavraki et al., 2020), and Turkey (Ertilav, Barcin, & Ozdem, 2021). The number of patients were range from 15 (Ferrier et al., 1990) to 138 (Mavraki et al., 2020) and all of the studies focused on elderly people (Wintzell V, Svanström H, 2022) (Page et al., 2021) (Evatt, DeLong, et al., 2008) (Buell et al., 2010) (Ferrier et al., 1990) (Luckhaus et al., 2009). Concisely, table 1 presents the baseline characteristics of the six included studies.

Serum 25-hydroxyvitamin D in AD patients

The overall analysis revealed a significant difference of 25-hydroxyvitamin D between AD and normal cognitive patients (WMD = -9.82, 95% CI = -15.09, -4.55, p = 0.00. Fig. 2). Moreover, it also indicated that levels of 25-hydroxyvitamin D in AD patients were lower compared to normal cognitive patients.
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**Fig. 1. PRISMA selection flow.**

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>First Author</th>
<th>Country</th>
<th>N</th>
<th>Gender (% male)</th>
<th>Age (years)</th>
<th>25-hydroxyvitamin D levels (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Ferrier (Ferrier et al., 1990)</td>
<td>England</td>
<td>15</td>
<td>15</td>
<td>76.00 ± 7.00</td>
<td>40.00 ± 25.00</td>
</tr>
<tr>
<td>2008</td>
<td>Evatt (Evatt, Delong, et al., 2008)</td>
<td>USA</td>
<td>97</td>
<td>97</td>
<td>66.4 (47-88)</td>
<td>36.43 ± 36.19</td>
</tr>
<tr>
<td>2009</td>
<td>Luckhaus (Luckhaus et al., 2009)</td>
<td>Germany</td>
<td>20</td>
<td>60</td>
<td>70.35 ± 8.23</td>
<td>35.94 ± 12.97</td>
</tr>
<tr>
<td>2010</td>
<td>Buell (Buell et al., 2010)</td>
<td>USA</td>
<td>41</td>
<td>60</td>
<td>80.40 ± 8.00</td>
<td>49.92 ± 20.46</td>
</tr>
<tr>
<td>2020</td>
<td>Mavraki (Mavraki et al., 2020)</td>
<td>Greece</td>
<td>138</td>
<td>61</td>
<td>75.51 ± 6.72</td>
<td>47.34 ± 20.81</td>
</tr>
<tr>
<td>2021</td>
<td>Ertilav (Ertilav et al., 2021)</td>
<td>Turkey</td>
<td>85</td>
<td>41.2</td>
<td>75.54 (60-99)</td>
<td>31.69</td>
</tr>
</tbody>
</table>

**Fig. 2. Forest plot of serum 25-hydroxyvitamin D in AD**

**Study**

- Ferrier et al. 1990: WMD = -8.00 [ -21.45, 5.45]; Weight (%) = 10.46
- Evatt et al. 2008: WMD = -5.49 [ -15.95, 4.97]; Weight (%) = 14.31
- Luckhaus et al. 2009: WMD = 3.49 [ -10.50, 17.48]; Weight (%) = 9.90
- Buell et al. 2010: WMD = -7.74 [ -13.29, -2.19]; Weight (%) = 24.05
- Mavraki et al. 2020: WMD = -15.20 [ -20.34, -10.06]; Weight (%) = 25.00

Overall: WMD = -9.82 [ -15.09, -4.55]; Weight (%) = 55.84%

Random-effects REML model
Meta-regression

In previous studies it was stated that differences in the mean age of patients could be the source of heterogeneity although no meta-regression analysis was performed (Zhao et al., 2013). In present meta-analysis, meta-regression was carried out to confirmed the previous statement. The study’s findings revealed mean age was not the potential source of heterogeneity (coefficient = -0.55, 95 % CI = -2.23, 1.11, \( p = 0.513 \)). Regarding the heterogeneity among studies (\( I^2 = 55.84\% \)), it might be due to the differences in genetic factors, ethnicities, variation of sunshine exposure and vitamin D supplementation of the patients [24–26].

DISCUSSIONS

The present meta-analysis aimed to evaluate the association of 25-hydroxyvitamin D levels and Alzheimer’s Disease. The findings found a lower levels of 25-hydroxyvitamin D in AD than in normal cognitive patients. The underlying mechanisms of vitamin D levels implications on the onset and progression of AD have not been fully established in current studies, but several possible mechanisms have been proposed. First, preclinical studies have demonstrated that low levels of vitamin D play an important role in the brain. Vitamin D deficiency can modulate \( A_\beta \) clearance from the brain (Luckhaus et al., 2009). While studies on humans has also revealed diminished of \( A_\beta \) in the brain modulated by vitamin D (Soares et al., 2021). Second, vitamin D has been confirmed to maintain calcium homeostasis of nerve impacted by peptide \( A_\beta \) by modulating voltage-gated calcium channels, which are the target of peptide \( A_\beta \) (Dursun, Gezen-Ak, & Yilmazer, 2011). Third, by promoting vitamin D receptor expression and performing as an antioxidant, vitamin D can defend against glutamate neurotoxicity (Patel & Shah, 2017).

There are several factors that affect vitamin D levels in AD patients, including genetic and environmental factors (Farag, Jomaa, El-Wahed, & El-Seedi, 2020). In genetic factor, it has been proposed that there is a significant relationship between APOE 4 allele and AD (Belloy, Napoliioni, & Greicius, 2019). Although it is not entirely specific or sensitive, APOE 4 is the only biological predisposition for AD that has been firmly established (Soares et al., 2021). The APOE 4 allele may contribute to the development of AD patients who initiate show symptoms of cognitive deterioration (Bialecka-Debek, Granda, Szmidt, & Zieleńska, 2021).

Age is a factor that has an important effect on the levels of vitamin D (Zhao et al., 2013). Calcium malabsorption commonly occurs in individuals older than 70 years (Shilsky et al., 2022). Age-related changes in calcium absorption have been linked to abnormalities in transport proteins that act via vitamin D receptors (Aydemir, Erdogan, & Türkeli, 2021). Furthermore, lower levels of 7-dehydrocholesterol in the epidermis (Anderson et al., 2020) and a reduced response to UV are more common in the older age, thus there is a 50% decrease in the formation of previtamin D3 (Wei, Zhu, & Ji, 2019).

Ethnicity is another factor that plays a role in influencing vitamin D concentration. Vitamin D deficiency is more common among African Americans (blacks) than other Americans (Sutherland et al., 2021). Whereas risk factors for dementia, such as hypertension and diabetes, are more frequent in black and other ethnic minorities (Clark et al., 2018). Numerous studies show that people from black ethnic groups have a higher incidence of AD than people from Asian ethnic groups (Mayeda, Glymour, Quesenberry, & Whitmer, 2016).

An external factor that is commonly known to affect vitamin D levels is the duration a person is exposed to the sunlight (Elseesy et al., 2020). Since AD is a degenerative condition that leads to disabilities and functional decline, patients have trouble getting adequate sunlight exposure to generate enough vitamin D (Bivona et al., 2019). Furthermore, it could be challenging for some patients to get enough foods that are rich in vitamin D, though some patients take vitamin D supplements to reach their body’s needs (Bivona et al., 2019). Moreover, dementia may lead to decreased vitamin D intake and less time spent outside activity with decreased exposure to sunlight, both of which can limit the substrate source to 25-hydroxyvitamin D (Bivona et al., 2019). This substrate deficiencies are important to identified because they can be prevented and treated (Bikle, 2014). By controlling these factors, some of the studies included strengthen the findings’ reliability.

Present meta-analysis has some limitations. First, this study does not explicitly describe the duration of AD patients are exposed to sunlight per day. Second, there is no extraction of data related to the source of vitamin D derived from diet or supplementation. Third, the historical medication of AD patients is also not described.

CONCLUSIONS

This study showed that patients with AD had lower levels of 25-hydroxyvitamin D than patients with normal cognitive function. These findings suggest a potential role of vitamin D which could have effects on the prevention and therapy of AD. Further research are needed to explore and elucidate potential neuroprotective effects of vitamin D in AD.

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Consent for publication

Not applicable.

Conflicting interests

The authors declare that no commercial or financial relationships existed that could be construed as a potential conflict of interest during the research.

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Annweiler, C., Llewellyn, D. J., & Beaufret, O. (2013). Low serum vitamin D concentrations in Alzheimer’s disease: A


