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Review Article

Impact of vitamin D supplementation on post-stroke rehabilitation outcomes: A systematic review and meta-analysis

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Abstract

Each year, there are approximately 12.2 million new stroke cases and 6.5 million stroke-related deaths, with low- and middle-income countries shouldering a disproportionately high financial burden. Studies have associated vitamin D deficiency with arteriosclerosis, left ventricular hypertrophy, and vascular dysfunction, contributing to an elevated risk of stroke. The aim of this study was to evaluate how vitamin D supplementation affects post-stroke outcomes. A comprehensive literature search was performed across PubMed, Scopus, the Cochrane Library, ScienceDirect, Springer Link, ProQuest, and Epistemonikos from April to May 2024. This study focused on comparing the efficacy of vitamin D supplementation versus no supplementation in stroke patients of all ages. Outcome measures included the Functional Ambulation Classification (FAC), Brunnstrom Recovery Stage (BRS), Modified Rankin Scale (mRS), and National Institutes of Health Stroke Scale (NIHSS). Case reports, reviews, and research on other cardiovascular or metabolic issues were excluded. Five authors extracted data and analyzed bias separately using the Risk of Bias Version 2 (RoB V2) algorithms. The results of continuous variables were pooled into the mean difference (MD) along with 95% confidence intervals (CI) using random-effect models. Review Manager 5.4 was used to evaluate the data. Out of the 1,152,449 papers evaluated, six met the inclusion criteria, with a sample size ranging from 42 to 123 patients. Vitamin D supplementation was found to yield better outcomes after stroke. BRS in lower extremities showed better results (MD: 0.59 (95%CI: 0.27–0.91)) and NIHSS improved with an MD of -1.47 (95%CI: -2.03–(-0.90)). Furthermore, there was also an improvement in mRS, with an MD of -0.91 (95%CI: -1.25–(-0.56)). In conclusion, vitamin D improved post-stroke outcomes, which supported its supplementation as a part of stroke rehabilitation.

Keywords: Vitamin D supplementation, stroke outcome, stroke management, functional recovery, meta-analysis

Introduction

Stroke remains a major challenge to emergency care worldwide, negatively affecting the quality of life of survivors and raising the chance of death [1]. Stroke is the world's second leading cause of death and disability [2]. The treatment of this disease places a significant financial burden on low- and middle-income countries, where survivors also require prolonged care, adding to the

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strain on already scarce healthcare resources. According to a 2019 WHO report, stroke leads to approximately 6.5 million deaths annually and results in 12.2 million new cases worldwide, equating to a crude rate of 157.99 per 100,000 people. These concerning figures underscore the urgent need for innovative strategies to decrease stroke incidence and enhance treatment outcomes [3].

Stroke survivors face a significant risk of recurrence: 1.2% in the first 30 days, 3.4% in 90 days, 7.4% in a year, and 19.4% in five years [4]. Long-term problems affecting mental, emotional, and cognitive abilities are frequently brought on by recurrent strokes. Children are also at risk, where a study involving 355 cases of arterial ischemic stroke (AIS) revealed that more than 10% of the cases had recurred within a year. This finding has driven many researchers to investigate strategies to improve stroke management outcomes and prevent recurrence, including vitamin D supplementation [5].

Vitamin D is essential to prevent strokes and can be found naturally as well as in commercial forms, such as supplements and fortified meals. When exposed to UV radiation, the skin produces vitamin D by converting ergosterol and 7-dehydrocholesterol into active vitamin D [6]. For the majority of people ages 1 to 70, the recommended daily intake is 600 IU [1]. Recent research has revealed that vitamin D has the potential to prevent stroke by promoting vasodilation, lowering inflammation, and controlling blood pressure [7-9]. Due to its neuroprotective properties, vitamin D supplementation may be a useful adjunct to stroke prevention techniques. These properties include minimizing oxidative stress, improving synaptic plasticity, and mitigating brain damage during ischemia or neurodegenerative circumstances [10,11].

Vitamin D deficiency is known to increase the risk of stroke [12]. Research has linked vitamin D deficiency to arteriosclerosis, left ventricular hypertrophy, and vascular dysfunction, all of which are associated with an increased risk of stroke. A study of 138 acute stroke patients in Egypt found that 82% had vitamin D insufficiency, which was associated with a 1.8-fold increase in poor functional outcomes and a 2.3-fold higher mortality rate compared to patients with sufficient vitamin D levels [13,14]. However, despite the limited reliable data on the effectiveness of vitamin D supplementation in reducing stroke incidence, especially among survivors, it remains an area of interest [15]. Therefore, the aim of this study was to assess the impact of vitamin D supplementation on clinical decision-making and its role in enhancing post-stroke recovery outcomes.

Methods

Study design

The aim of this review was to investigate the efficacy of Vitamin D supplementation on post-stroke recovery outcomes. The research question guiding this study was: "Does Vitamin D supplementation improve functional recovery in stroke patients compared to no supplementation?" The primary parameters analyzed in this review included post-stroke recovery measures such as Functional Ambulation Categories (FAC), Modified Rankin Scale (mRS), Brunnstrom Recovery Stages (BRS), and National Institutes of Health Stroke Scale (NIHSS). Additionally, secondary parameters included study design, mean age of participants, population characteristics, time to follow-up, participant type, and Vitamin D supplementation dosage.

This review was conducted following the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. The protocol of the systematic review and meta-analysis was registered on the Open Science Framework (OSF) as of August 3, 2024 (accessed at https://doi.org/10.17605/OSF.IO/FVCN4).

Eligibility criteria

This review follows the guidelines outlined in the Cochrane Handbook and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The studies that comprised this review met specified requirements. Firstly, to be included, the studies should examine patients of all ages diagnosed with stroke, including hemorrhagic, ischemic, cerebrovascular, and cerebral stroke. Secondly, the studies should compare the efficacy of

Vitamin D supplementation (cholecalciferol) versus no Vitamin D (supplementation versus Control). Lastly, the studies should report primary post-stroke outcomes, including the FAC, mRS, BRS, and NIHSS. Studies that included persons taking medicine for the remainder of their lives, included patients with additional cardiovascular or metabolic issues or were presented as observational studies were excluded.

Literature search and study selection

Five independent writers were involved in a complete search of the English-language literature, which was performed from April 28 to May 4, 2024. Seven databases were used: PubMed, Scopus, the Cochrane Library, ScienceDirect, Springer Link, ProQuest, and Epistemonikos. To find all potentially pertinent papers, the search technique combined the keywords " ("Vitamin D"[MeSH] OR "Cholecalciferol"[MeSH]) AND ("Dietary Supplements"[MeSH] OR "Supplementation" OR "Vitamin D Supplementation") AND ("Stroke"[MeSH] OR "Cerebrovascular Disorders"[MeSH] OR "Brain Ischemia"[MeSH])". After removing duplicate papers with the Mendeley Web Importer tool, the remaining articles were screened by their abstracts and titles to ensure they met the inclusion and exclusion criteria. Those who qualified moved on to the next stage, where we carefully examined the full-text publications. Research that satisfied the inclusion and exclusion criteria moved on to a second stage, when full-text publications were examined. The authors who searched were also in charge of choosing the articles. When an agreement could not be reached, discrepancies were addressed through discussion, and another review author (DP) made the final decision on study conclusions and eligibility.

Data extraction

Data extracted from the included literature were divided into primary and secondary. The primary data included the post-stroke recovery parameters such as the FAC, mRS, BRS, and NIHSS. As for the secondary extracted data included study design, participant characteristics, sample size, mean age, time to follow-up, and the dose of vitamin D supplementation. Five separate authors retrieved and arranged these data using Microsoft Excel 2019. Data presented as medians were extracted with their lowest and maximum values or interquartile ranges (IQR). Meanwhile, the averaged values were extracted with their standard deviation.

Risk of bias assessment

We had five different authors assess the risk of bias independently using established instruments. For randomized controlled trials (RCTs) in the review, we used to the Cochrane Collaboration's Rob 2 tool, which assesses five domains: (1) the randomization process, (2) deviations from the intended interventions, (3) outcome data missingness, (4) outcome measurement, and (5) selection of the results presented. For cohort studies, we used the ROBINS-I tool, which assesses bias in seven domains: (1) bias due to confounding, (2) bias in participant selection, (3) bias in intervention classification, (4) bias due to deviations from the intended interventions, (5) bias due to missing data, (6) bias in outcome measurement, and (7) bias in the selection of the results presented. The ratings were categorized into three levels: "low risk," "high risk," or "some concerns" for the possibility of bias."

Statistical analysis

We used the inverse variance algorithm to analyze continuous variables, reporting results as mean differences (MD) with 95% confidence intervals (CI). Since demographic differences and varying follow-up durations could lead to high variability, we applied a random-effects model. To measure heterogeneity among studies, we used the *I*-squared (I^2) statistics, considering values above 50% as significant heterogeneity. A publication bias analysis was carried out when each outcome of interest was the subject of more than ten research. Funnel plot asymmetry was evaluated using Egger's test. We determined statistical significance using a *p*-value threshold of 0.05. All statistical analyses were conducted using Cochrane Collaboration's software package, Review Manager 5.4.

Results

Study selection and characteristics

A comprehensive search of seven global databases yielded a total of 1,152,449 studies. After removing duplicates and filtering by year and study design, 14,815 studies remained under consideration. This number was further narrowed down to 25 studies through title and abstract screening. Nineteen of these 25 papers were eliminated based on full-text assessments for various reasons. Nineteen studies included patients who were not diagnosed with a stroke; four had no control group; six did not provide data on the outcome of interest; four were review articles; and five did not employ vitamin D supplements in the treatment of stroke. As a result, only six studies [16-21] were included in the final analysis (**Figure 1**).

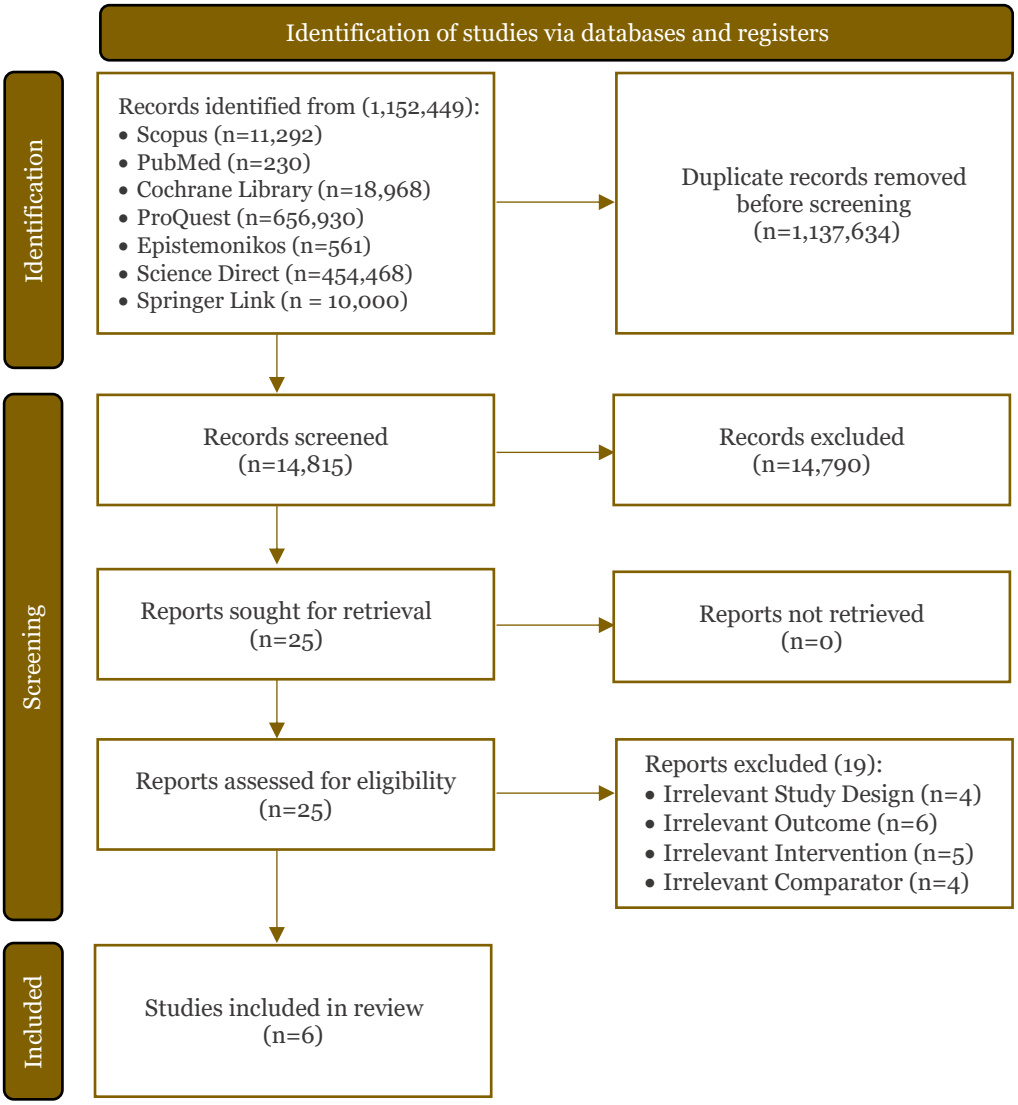

Figure 1. PRISMA diagram depicting the comprehensive process of selecting papers for inclusion in the systematic review and meta-analysis.

The characteristics of the included studies are presented in **Table 1**. The six included studies consisted of two retrospective cohort studies and four prospective RCTs. These trials included between 42 and 123 participants, with doses ranging from 54,000 to 600,000 IU, and supplementation periods lasting three months. **Table 1** summarizes the baseline characteristics of the studies included.

The trials in this review included patients with hemiplegia or acute ischemic stroke. The RCTs were conducted in Turkey [17], Iran [18,19], and Indonesia [20]. Interestingly, in most of the research, the average age of the patients in the supplemented groups was higher than in the control groups [17-22].

Table 1. Characteristics of studies reporting vitamin D (cholecalciferol) supplementation during post-stroke rehabilitation

Studies	Country	Design	Supplementation dose per treatment (IU)	Total supplementation dose (IU)	Patients	Supplement/ control	Follow-up (months)	Mean age (years)		Type of participants
								Supplement	Control	
Sari *et al.*, 2018 [17]	Turkey	RCT	300,000 single-dose intramuscular	300,000	64	33/34	3	69.84±10.09	66.93±10.05	Patients with hemiplegia resulting from ischemic stroke and insufficient vitamin D levels
Kouchek *et al.*, 2023 [18]	Iran	RCT	300,000 single-dose intramuscular	300,000	42	23/19	3	61.47±4.54	61.42±5.10	Patients with mild severity of stroke based on their NIHSS scores and low vitamin D levels
Rezaei *et al.*, 2021 [19]	Iran	RCT	300,000 single-dose intramuscular	300,000	59	29/30	3	62.07±12.08	62.60±10.71	Patients with first-time acute ischemic stroke and insufficient vitamin D levels
Kadri *et al.*, 2020 [20]	Indonesia	RCT	50,000 weekly oral	600,000	60	30/30	3	62.65±5.66	66.35±5.30	Patients with ischemic stroke who were admitted to the hospital within three days after the stroke beginning
Karasu *et al.*, 2021 [21]	Turkey	Cohort	50,000 weekly oral	600,000	76	39/37	3	61.96±13.51	58.21±17.64	Patients with stroke for the first time without chronic kidney, lung, or liver disease and having pre rehabilitation vitamin D level measurement
Wang *et al.*, 2021 [22]	China	Cohort	600 daily oral	54,000	123	72/51	3	62.0±8.2	64.4±8.6	Patients with first-ever acute ischemic stroke and did not have any exclusionary pre-existing medical disorders

RCT: randomized controlled trial

The population in the study consisted of between 33.9% and 57.1% male subjects. All the trials had a standard three-month follow-up period [17-22]. The subjects in the observational trials, which were conducted in China [22] and Karasu *et al*., 2021 [21], were new patients with strokes with no comorbidities, with their follow-up durations similar to those in the RCTs. The general inclusion criterion in all the research was the deficiency in vitamin D, indicating its probable role in the recovery and rehabilitation of strokes [17-22].

Quality of study assessment

No observational studies [21,22] or RCTs [17-20] showed a "high risk" of bias in any of the five analyzed categories, according to the bias assessment conducted using the RoB v2 tool for RCTs and the ROBINS-I tool for observational studies. Regarding bias, three RCTs were categorized as having "some concerns." In particular, two RCTs [17,18] did not use suitable randomization techniques, which resulted in a bias in the randomization process that lassified the data as "no information." Due to changes made to the intended intervention, one RCT [20] revealed "some concerns" regarding bias in the intervention delivery.

The ROBINS-I assessment for observational studies indicated a low risk of bias across all domains, with no studies classified as having a serious or critical risk of bias. Similarly, the RoB v2 methodology's review found that none of the six assessment categories indicated any "high risk" or "some concerns" of bias in any of the observational or RCT research. The summaries of the risk of bias assessment for RCT and observational studies are presented in **Figures 2** and **Figures 3**, respectively.

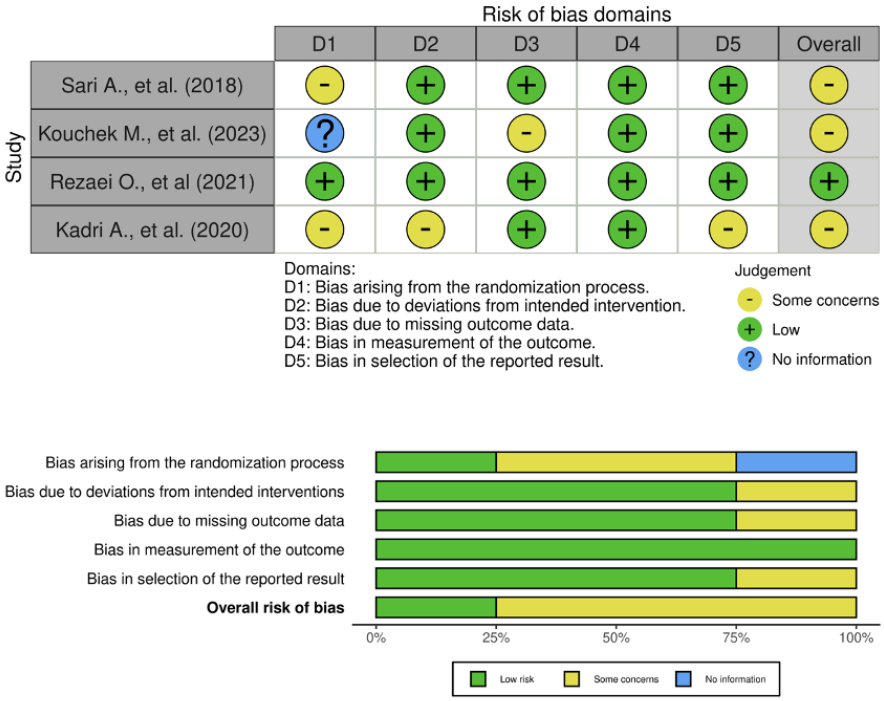

Figure 2. Risk of bias evaluation of the included RCTs using the RoB v2 tool.

Effect of vitamin D supplementation based on NIHSS

Comparisons of NIHSS score outcomes between the vitamin D supplementation group and the control group are presented in **Figure 4**. Comparison of pre- and post-rehabilitation suggested significant improvement in supplementation group (MD=-2.98 (95%CI: -3.60–(-2.36))) and in control group (MD = -2.28 (95%CI: -4.38–(-0.19)). The pooled random-effects analysis revealed a significant improvement in NIHSS scores in the vitamin D group, with a mean difference of -1.47 (95%CI: -2.03–(-0.90)). Heterogeneity is only significant in pre- and post-rehabilitation comparison among control groups (I^2=90%).

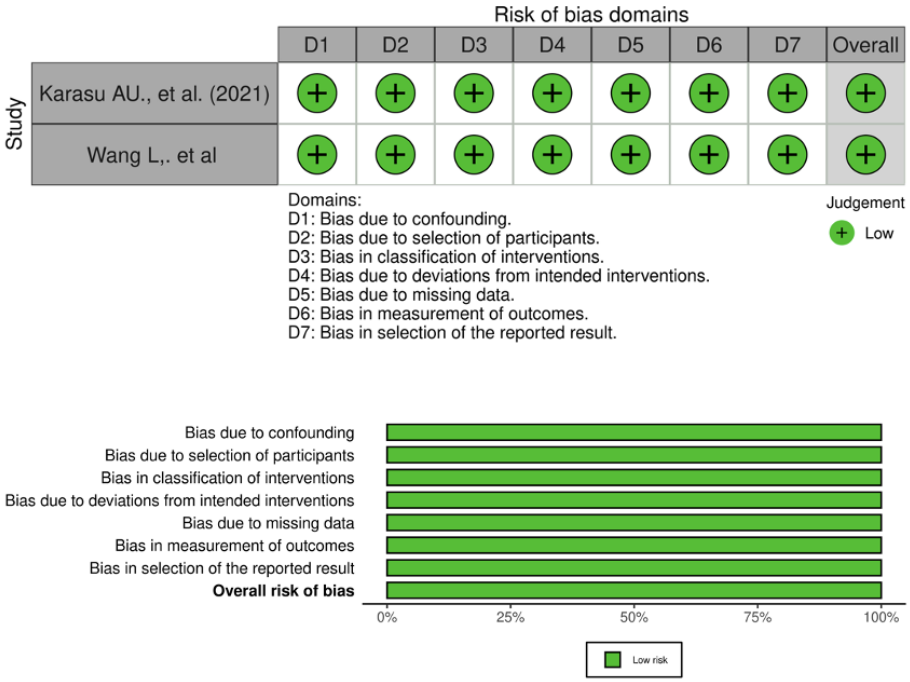

Figure 3. Risk of bias assessment of the included observational studies using ROBINS-I tool.

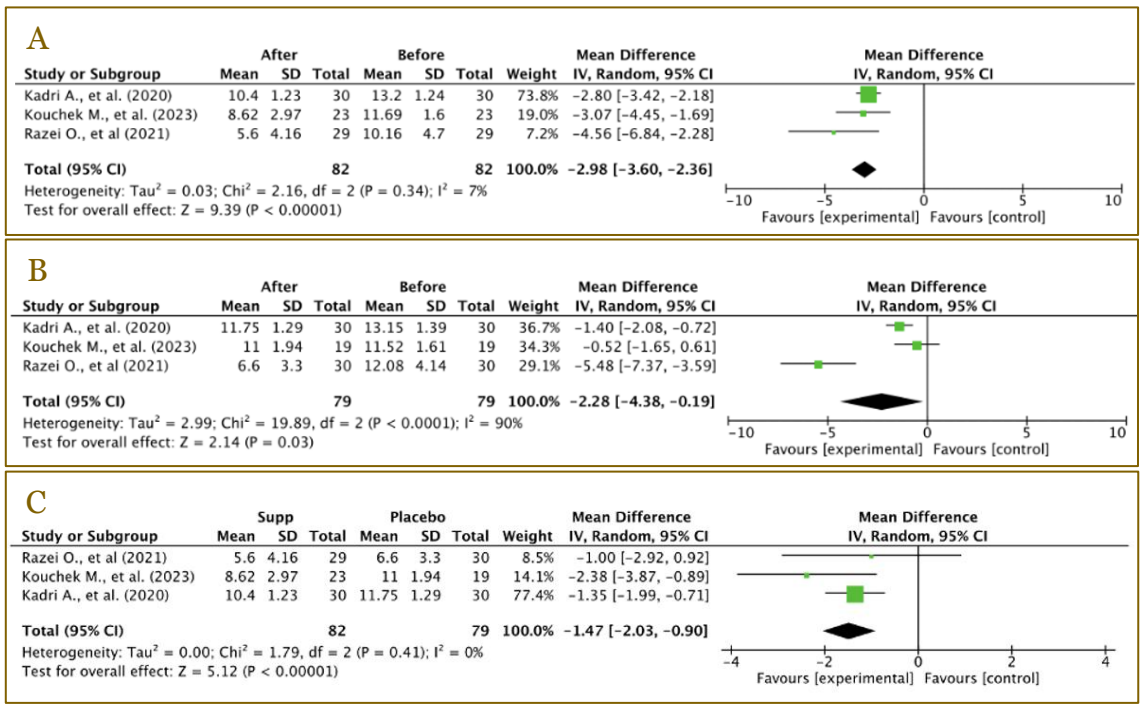

Figure 4. Forest plots comparing NIHSS pre- versus post-rehabilitation in vitamin D supplementation group (A) and control group (B). Forest plot comparing NIHSS of vitamin D supplementation versus control group after rehabilitation (C). The effect of each study is expressed as mean±SD, with 95% confidence intervals shown as horizontal lines.

Effect of vitamin D supplementation based on BRS

Impact of vitamin D supplementation on lower limb motor recovery, as measured by the Balance Recovery Score (BRS), is presented in **Figure 5**. In the supplementation group, the results significantly favored the post-rehabilitation outcome with MD of 0.63 (95%CI: 0.29–0.97). In control group, however, the impact of vitamin D supplementation was not significant (MD=0.93 (95%CI: -0.89–2.75). The improvement in lower limb motor recovery was significantly higher in supplementation group as opposed to control group (MD=0.59 (95%CI: 0.27–0.91)). Significant heterogeneity was observed only in the pooled estimates of control groups (I^2=74%).

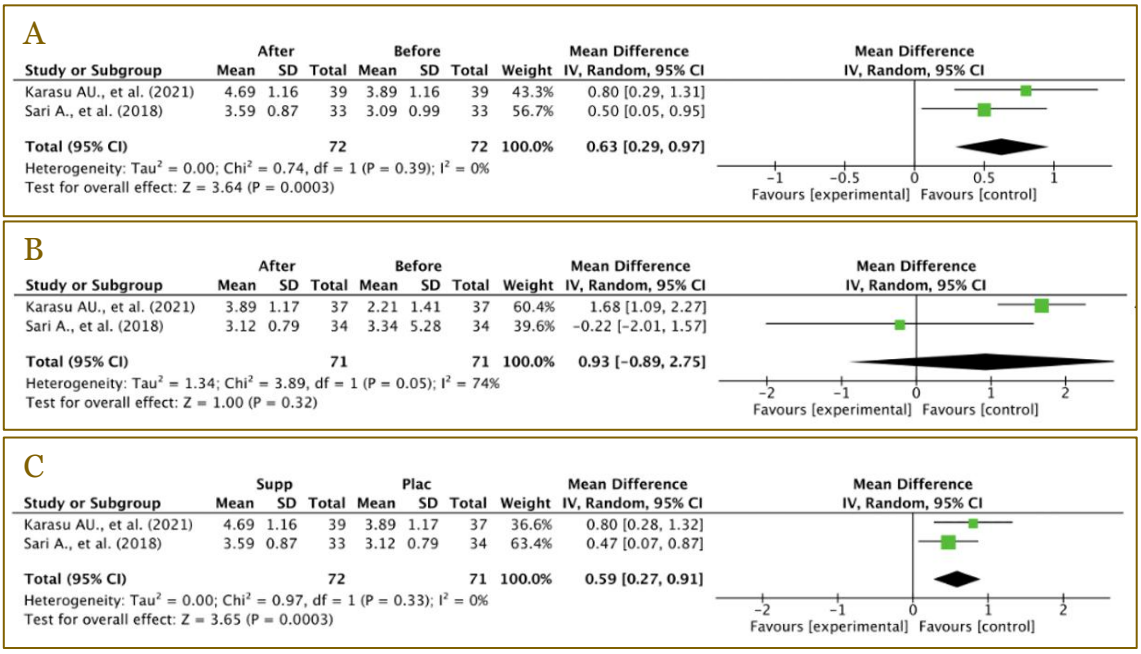

Figure 5. Forest plots comparing BRS pre- versus post-rehabilitation in vitamin D supplementation group (A) and control group (B). Forest plot comparing BRS of vitamin D supplementation versus control group after rehabilitation (C). The effect of each study is expressed as mean±SD, with 95% confidence intervals shown as horizontal lines.

Effect of vitamin D supplementation based on FAC

The effect of vitamin D supplementation on walking ability as measured by the Functional Ambulation Category (FAC) is presented in **Figure 6**. No significant change was observed for FAC after the rehabilitation in supplementation group (MD=1.09 (95%CI: 0.63–1.55)) and control group (MD=0.29 (95%CI: -0.50–1.07)). Comparison between the two groups using the post-rehabilitation results also suggested the non-significant effect (MD=0.36 (95%CI: -0.37–1.08)).

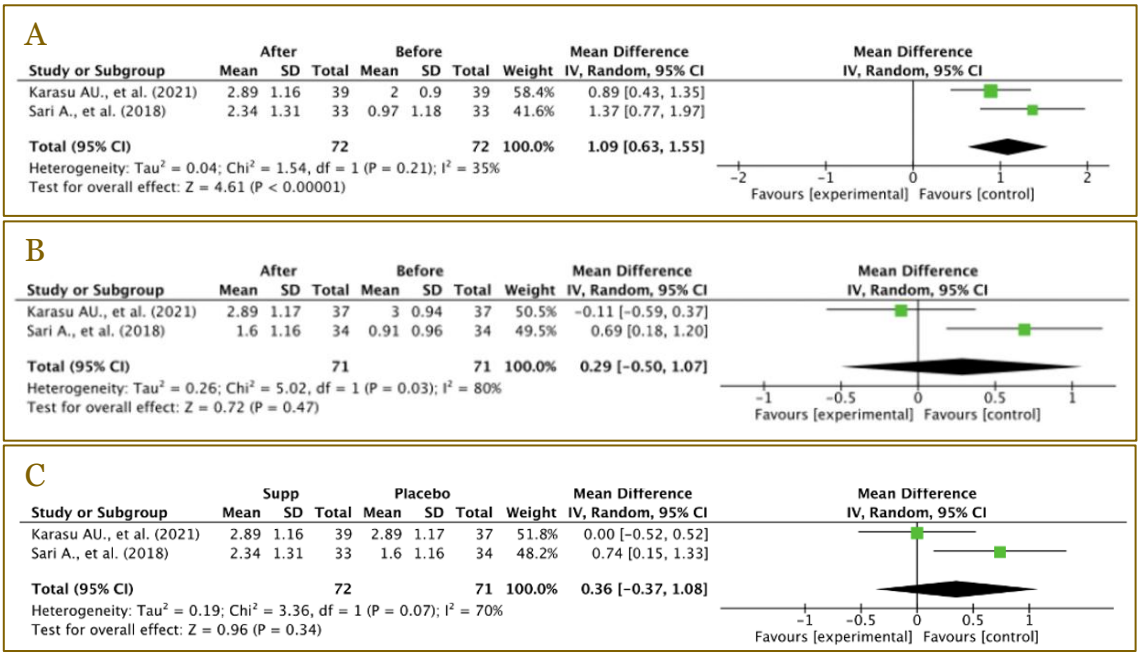

Figure 6. Forest plots comparing FAC pre- versus post-rehabilitation in vitamin D supplementation group (A) and control group (B). Forest plot comparing FAC of vitamin D supplementation versus control group after rehabilitation (C). The effect of each study is expressed as mean±SD, with 95% confidence intervals shown as horizontal lines.

In pooled estimates of pre- and post-rehabilitation data, the I^2 values were 35% (low heterogeneity) and 80% (high heterogeneity) in supplementation and control groups, respectively. Pooled estimates involving the comparison between the two groups yielded I^2=70% (high heterogeneity).

Effect of vitamin D supplementation based on mRS

The impact of vitamin D supplementation on functional recovery as assessed by the modified Rankin Scale (mRS) is presented in **Figure 7**. A significant decrease of mRS was observed following the rehabilitation with vitamin D supplementation (MD=-1.73 (95%CI: -2.22–(-1.24))) or without the supplementation (MD=-1.15 (95%CI -1.64–(-0.66))).

However, the reduction of mRS was more pronounced in supplementation group as compared to control (MD=-0.91 (95%CI: -1.25–(-0.56))). None of the pooled estimates show a significantly high heterogeneity (I^2=0 to 35%).

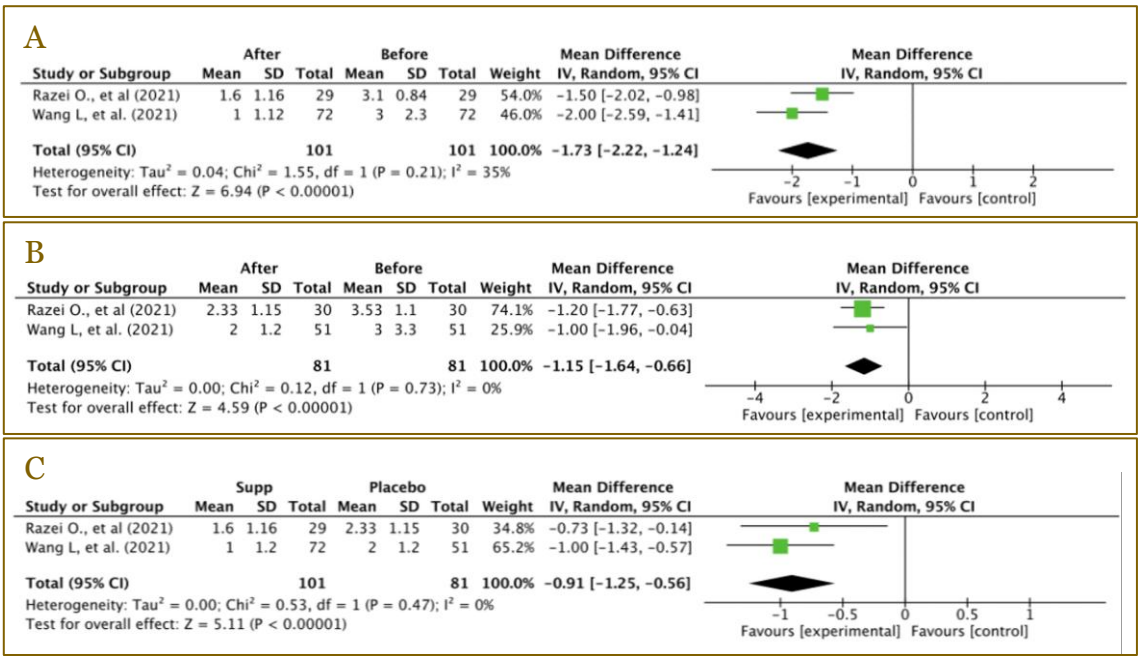

Figure 13. Forest plot comparing mRS pre- versus post-rehabilitation in vitamin D supplementation group (A) and control group (B). Forest plot comparing mRS of vitamin D supplementation versus control group after rehabilitation (C). The effect of each study is expressed as mean±SD, with 95% confidence intervals shown as horizontal lines.

Discussion

The present study suggested that vitamin D supplementation significantly improved recovery outcomes after ischemic stroke events [23,24]. As demonstrated by a previous study, there is a stronger association between low vitamin D levels and ischemic stroke than hemorrhagic stroke [25]. The hallmarks of ischemia-induced BBB dysfunction include increased nitric oxide levels, disturbed calcium homeostasis, elevated reactive oxygen species (ROS), and increased vascular endothelial growth factor (VEGF) levels [26-29]. Benefits of circulating vitamin D on vascular health via the reduction of inflammatory effects have been reported previously [30,31]. The improvement in mRS and BRS scores in the present study reflects better motor function recovery, which can be attributed to vitamin D's impact on neuromuscular function and neuroplasticity. Vitamin D has been shown to enhance calcium homeostasis in neurons, facilitate neurotransmitter release, and improve muscle strength by modulating VDR expression in both the central and peripheral nervous systems [32].

Herein, vitamin D supplementation had no meaningful effect on walking function, as demonstrated by FAC, because walking is a complex function affected by multiple physiological systems other than neuromuscular function. Vitamin D has been shown to promote neuronal health, alleviate inflammation, and improve muscle strength [33-34]. However, walking is a

function that requires the integration of sensory input and motor output, balance, cardiovascular endurance, and cognitive control [35-36]. Improvements in isolated motor function, as reported in mRS or BRS scores in the present study, may not be sufficient to elicit measurable improvements in walking independence. In addition, walking function is generally subject to interaction with many factors, including baseline mobility, comorbidities, age, motivation, and quality and duration of rehab [37], which may overshadow any specific effects of vitamin D supplementation.

The central nervous system plays a major role in vitamin D metabolism, as there is a presence of the enzyme 1α-hydroxylase and other vitamin D metabolic pathways that have been identified in human brain tissue and cerebrospinal fluid, indicating that the brain is not merely a target for vitamin D action but also participates actively in its conversion and utilization within the body [33-36]. Intriguingly, 1,25-dihydroxyvitamin D can bind to specific brain receptors and penetrate the blood-brain barrier [37-40]. The anti-inflammatory properties of vitamin D stand out in their ability to play a role during stroke recovery, wherein increased inflammation could worsen the ischemic damage and may impede neuronal repair [41-43]. Other studies have recently suggested that vitamin D could also be involved in maintaining white matter integrity and preventing neurodegeneration, which may be relevant in stroke rehabilitation [44-46].

Vitamin D deficiency has been linked to cognitive deficits and depression, as well as other neuropsychiatric conditions, perhaps offering implications for cognitive recovery after stroke [47-51]. Such understanding of these pathways, however, may elucidate how vitamin D in fact supports neurological recovery and pave the way for targeted interventions. However, the question remains unanswered on the doses of vitamin D supplementation in stroke rehabilitation. Studies proposed that vitamin D supplementation at very high doses, for example, by the administration of 300,000 IU across three months, significantly improves neurological recovery and inflammatory markers, especially in terms of reducing IL-1β levels that are associated with post-stroke inflammation [18]. Regardless, the limited and conflicting data on the effectiveness of vitamin D in reducing cardiovascular risk and aiding post-stroke recovery, suggest that vitamin D supplementation should be used cautiously [52,53]. Moreover, excessive doses may pose risks, including hypercalcemia and vascular calcification, particularly in patients with compromised renal function or those receiving calcium supplementation [32].

This meta-analysis has several limitations that affect the interpretation and generalizability of the findings. The included studies were predominantly conducted in Asian populations, limiting applicability to other ethnic groups with different genetic, lifestyle, and environmental factors. Variability in confounding factors, particularly comorbid conditions, and limited exploration of heterogeneity may have influenced the results. While RCTs maintained consistency in follow-up duration, vitamin D formulations, dosages, and frequency, subgroup analyses were constrained by small sample sizes. The absence of patient-specific data prevented stratification by dietary habits, UV exposure, and supplement use. Additionally, the study did not assess the real-world applicability or safety of vitamin D supplementation, warranting further research with diverse populations and more comprehensive analyses.

Conclusion

Vitamin D supplementation contributed to post-stroke neurological recovery as indicated by NIHSS, BRS, and mRS scores. However, the recovery was also recovery observed in control groups. This suggested that vitamin D might support and enhance rehabilitation, but it is not the only factor attributed to the functional improvement. Although the results are promising, the variability in studies highlights the need for more work in the area of vitamin D on post-stroke outcomes. Future work should focus on optimizing supplementation strategies, including dose, duration, timing, and interactions with other therapies, while also measuring any side effects. It is important to conduct better-designed randomized controlled trials with a larger sample, standardized protocols, and a longer follow-up to demonstrate the current findings and understand vitamin D recovery for those who have experienced a stroke.

Ethics approval

Not Required.

Acknowledgments

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Competing interests

The authors state that there are no conflicts of interest.

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Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Declaration of artificial intelligence use

We declare that AI-based language model, ChatGPT, was employed for language refinement, specifically to improve grammar, sentence structure, and readability of the manuscript. We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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