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ORIGINAL ARTICLE

Effect of vitamin D supplementation on metabolic syndrome and atherosclerosis biomarkers in epilepsy: a randomized controlled trial

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ABSTRACT

Aim To analyze the effect of vitamin D administration on serum 25-hydroxyvitamin D (25[OH]D) level and biomarkers of metabolic syndrome and atherosclerosis: homeostatic model assessment of insulin resistance (HOMA-IR), adiponectin, homocysteine, and high sensitivity C-reactive protein (hs-CRP) in epilepsy patients receiving enzymatic antiseizure medications (ASMs).

Methods This double-blind, randomized, placebo-controlled trial included 40 adult epilepsy patients treated with enzymatic ASMs to receive vitamin D3 (2,000 IU/day) or placebo for 12 weeks. The primary outcome was a change in serum 25(OH)D level. Secondary outcome included changes in HOMA-IR, adiponectin, homocysteine, and hs-CRP. Data were analysed using a per-protocol approach.

Results Thirty-four patients completed the study. Vitamin D supplementation yielded a significantly greater increase in serum 25(OH)D (10.67±8.16 vs. –1.29±3.96 ng/mL; p<0.001) and adiponectin (1.38±3.05 vs. 0.34±1.89 µg/mL; p=0.045), as well as a significantly greater reduction in hs-CRP (–6.74±14.65 vs. 1.81±7.75 mg/L; p=0.041) compared with placebo. Conversely, no significant differences were observed between groups regarding the changes in HOMA-IR (–0.24±3.71 vs. –0.14±3.38; p=0.940) or homocysteine (7.90±1.79 vs. 8.15±2.70 µmol/L; p=0.290).

Conclusion Vitamin D supplementation (2,000 IU/day) effectively restores 25(OH)D level and improves adiponectin and hs-CRP in epilepsy patients on enzymatic ASMs, suggesting a potential benefit for cardiovascular risk reduction. However, vitamin D alone did not prevent the rise in homocysteine, likely due to the concurrent cessation of B-vitamin supplementation.

Keywords: anticonvulsants, cholecalciferol, C-reactive protein, insulin resistance

INTRODUCTION

Epilepsy is one of the oldest neurological diseases associated with a certain stigma in society, psychiatric comorbidity, and high economic costs (1) with prevalence and treatment availability varying across countries. Stigma associated with epilepsy significantly impacts the quality of life (QoL). In 2021, there were approximately 51.7 million people with active epilepsy, with the bulk of the burden (83.7%%) residing in low-income to middle-income countries (2). In addition, idiopathic epilepsy and epilepsy due to other causes, altogether, resulted in 16.2 million, (95% uncertainty interval [UI] 10.5–22.7) global years lived with disability (YLDs) in 2021 and were responsible for 1.8% (1.3–2.4) of total global YLDs (3). Approximately 30% of these patients progress to drug-resistant epilepsy, necessitating lifelong treatment with antiseizure medications (ASMs) (4). However, the long-term use of enzymatic ASMs (such as phenytoin, carbamazepine, and phenobarbital) induces hepatic cytochrome P450 (CYP-450) enzymes, leading to the accelerated catabolism of vitamin D and subsequent deficiency (5–7). This deficiency is critical because vitamin D plays a vital role in immune and metabolic regulation, not just bone health. Consequently, patients on enzymatic ASMs face a dual pathology. The medication-induced depletion of vitamin D exacerbates their susceptibility

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to metabolic syndrome, the prevalence of which ranges from 23.5% to 52.6% in this population (8,9). This unique metabolic vulnerability significantly increases the risk of coronary heart disease and cerebrovascular disease, leading to accelerated atherosclerosis (10). Given this heightened cardiovascular risk, early detection using specific biomarkers is essential to improve patient prognosis (11). Several biomarkers are established indicators of metabolic syndrome and atherosclerosis, including homeostasis model assessment of insulin resistance (HOMA-IR) (12), adiponectin (13), homocysteine (14), and high sensitivity C-reactive protein (hs-CRP) (15). While these biomarkers are widely used in general internal medicine, their specific utility in monitoring ASM-induced metabolic changes remains underutilized.

To date, no studies have specifically explored whether correcting vitamin D deficiency can reversibly improve these specific biomarkers of metabolic syndrome and atherosclerosis in the epilepsy population. Existing literature discusses the relationship between vitamin D and metabolic health in the general population, but fails to account for the unique metabolic disruption caused by enzymatic ASMs in epilepsy patients.

The aim of this study was to analyse the effect of vitamin D administration on biomarkers of metabolic syndrome and atherosclerosis in epilepsy patients receiving enzymatic ASMs.

PATIENTS AND METHODS

Patients and study design

This study encompassed a randomized, double-blinded, parallel controlled trial design on adult patients with epilepsy. The patients were enrolled either in the group that received vitamin D supplementation at a dose of 2,000 IU or the placebo group. This study was conducted from October 2024 to May 2025 at the Department of Neurology, Mohammad Hoesin Hospital, Palembang, Indonesia.

The study was registered in the Indonesia Clinical Research Registry (INA-CRR) on 17 February 2025 (registration number: INA-13022025BB3713B).

This clinical trial also has met the ethical eligibility of the Ethics Institute of Mohammad Hoesin Hospital Palembang (Ethics approval number: DP.04.03/D.XVIII.06.08/ETIK/280/2024).

Methods

Patients diagnosed with epilepsy who were ≥18 years old, received enzymatic ASMs therapy for at least 6 months, and were willing to participate in the study and signed an informed consent form were included in this study. Exclusion criteria were as follows: patients who had a history of chronic kidney disease, chronic liver disease; patients who routinely received vitamin D supplementation every day for the past 2 weeks; hypercalcemia (serum calcium level >10.5 mg/dL); vitamin D level above normal range (>100 ng/mL); patients suffering from acute infections in the past 2 weeks; serious physical injury or trauma in the past month; history of active non-metabolic autoimmune or inflammatory disease; active cancer patients in the last 6 months; being on immunosuppressant treatment; history of acute heart disease in the last 3 months; and history of motor seizures in the last week. Patients were dropped from the study if they did not adhere to the intervention for two consecutive weeks, decided to quit the study, or experienced moderate or severe side effects from the intervention.

The sample size calculation was based on the study's primary outcome, serum 25(OH)D level. We determined the minimum sample size required to detect a large standardized effect size (Cohen's d=1.0) between the Vitamin D and placebo groups. The calculation utilized the formula for the difference between two independent means, assuming a two-tailed significance level (α) of 0.05 ($Z_{\alpha/2}$=1.96) and a power (1−β) of 80% (Z_{β} =0.84). Based on a standardized variance (S^2) of 1.0 and a detectable mean difference (Δ) of 1.0, the calculation indicated a minimum of 16 patients per group. To account for a potential dropout rate of 20%, a total of 20 patients were enrolled in each group.

After recruitment of study participants, randomization was conducted to determine whether the study participants belonged to the group that received vitamin D supplementation or a placebo. Research participants were numbered 1 to 40 based on the order of arrival (*consecutive*) and were asked to choose one envelope to determine whether they were in group A (vitamin D) or in group B (placebo). Previously, 20 envelopes containing the letter A and 20 envelopes containing the letter B were prepared and placed in one selection box. The study participants were chosen manually in front of a third party (outpatient pharmacists at Mohammad Hoesin Hospital, Palembang). The pharmacists provided intervention according to the selected envelope. The intervention was in the form of vitamin D3 administration at a dose of 2,000 IU or placebo containing sucrose per day for 12 weeks. The researchers and the study participants were blinded.

Monitoring of the intervention was carried out every month by means of routine control of research subjects at the Neurology Clinic of Mohammad Hoesin Hospital. During the visit, the patients brought all the intervention drugs given, and the researchers would count the remaining amount of drugs available to assess the patients' compliance. During the intervention, other vitamins and supplements were discontinued. The primary outcome was the change in serum 25-hydroxyvitamin D (25[OH]D) level from baseline to 12 weeks. Secondary outcome included changes in biomarkers of metabolic syndrome and atherosclerosis, including HOMA-IR (calculated by multiplying fasting glucose [in mg/dL] by fasting insulin [in μU/mL], divided by 22.5), adiponectin, homocysteine, and hs-CRP.

Blood samples were collected in the morning after a 10-12 hour fasting period to measure the levels of 25(OH)D, fasting glucose, insulin, adiponectin, homocysteine, and hs-CRP, both before and 12 weeks after the intervention.

Blood samples were then analyzed in the laboratory of Mohammad Hoesin Hospital, Palembang. Especially for adiponectin and homocysteine, blood samples were centrifuged, and the plasma was collected, centrifuged, and preserved at -20°C. Serum adiponectin and homocysteine levels were quantified using commercial ELISA kits according to the manufacturers' protocols. Adiponectin was measured using a sandwich ELISA (EUROIMMUN EQ 6446-9601, Germany; LOD 0.064 ng/mL; intra/inter-assay CV: 4.6–7.5%/6.6–8.4%; 1:1000 dilution). Homocysteine was quantified by a competitive inhibition ELISA (CED984Ge, Cloud-Clone Corp., China; range 98.77–8000 ng/mL; sensitivity <40.22 ng/mL; intra/inter-assay CV <10%/<12%).

Statistical analysis

Normality of numerical variables was assessed using the Shapiro–Wilk test. Normally distributed data were analysed using parametric tests, including the independent samples t-test for comparisons between the groups and the paired t-test for within-group changes. For non-normally distributed data, non-parametric tests (Mann–Whitney U test for between-group comparisons and Wilcoxon signed-rank test for within-group changes) were applied.

The analysis followed a per-protocol approach, and participants who did not complete the intervention were excluded from the final analysis. Missing data due to drop-out or non-adherence were not imputed. Results are presented as mean ± standard deviation (SD) or median (minimum–maximum), and 95% confidence intervals were reported where applicable. A $p<0.05$ was used to determine statistical significance for all analyses, and no adjustment for multiple comparisons was applied.

RESULTS

At the beginning of the study, a total of 40 patients were included and put into two main groups, the group that received vitamin D and placebo with equal distribution (n=20). A total of 34 patients completed the study, with similar distribution between the groups (n=17), thus meeting the minimum sample size (Figure 1).

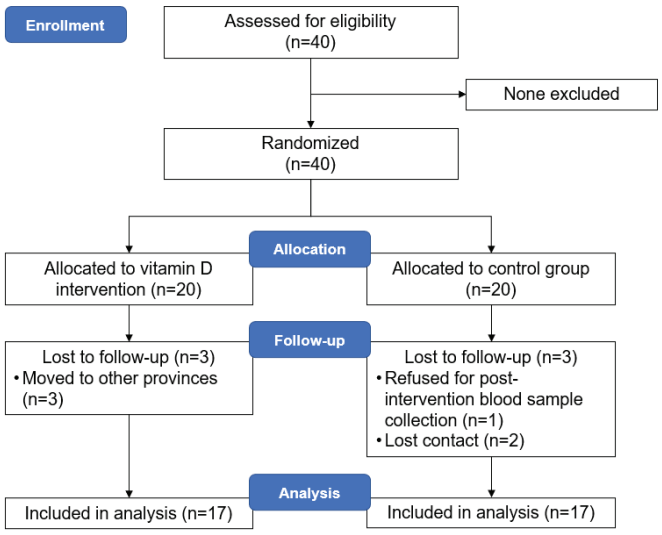

Figure 1. Flowchart of patient selection

The study population was predominantly young adults (18–45 years; 88.2%) with a balanced sex distribution, where slightly more than half were male (52.9%). Baseline age showed a normal distribution, with the vitamin D and placebo groups having mean ages of 28.53 ±5.94 and 36.59±14.12 years, respectively. Most patients had received ASMs for more than two years (73.5%), with therapy duration showing a non-normal distribution and median values of 6 years (range: 1–30) in the vitamin D group and 5 years (0.66–20) in the placebo group. Enzyme-inducing ASMs were most frequently used (55.9%), followed by enzyme inhibitor (17.6%) and combined regimens (26.5%), with comparable distributions across the two groups (Table 1).

Only a small proportion of participants had adequate vitamin D status at baseline, with most exhibiting deficient levels (50.0%). Following supplementation, the vitamin D group showed a marked shift toward normal 25(OH)D levels, with no remaining cases of deficiency. In contrast, the placebo group continued to show persistent insufficiency and deficiency. The distribution of HOMA-IR, hs-CRP, and adiponectin categories remained comparable between the groups, both before and after the intervention, suggesting no major baseline or placebo-driven changes in insulin resistance, inflammatory status, or adiponectin levels. Homocysteine showed a different pattern, where a majority of participants initially had abnormally low levels (47.1% in vitamin D; 41.2% in placebo), but post-intervention most patients in both groups shifted into the normal range (5–15 µmol/L) (Table 2).

Table 1. Baseline characteristics of antiseizure medication (ASM)-treated patients receiving vitamin D or placebo

Characteristic	Vitamin D	Placebo	Total
Age (mean±SD)	28.53±5.94*	36.59±14.12*	
	No (%) of patients		
Age group (years)			
18–45	17 (50.0)	13 (38.2)	30 (88.2)
46–65	0 (0)	4 (11.8)	4 (11.8)
Sex			
Male	9 (26.5)	9 (26.5)	18 (52.9)
Female	8 (23.5)	8 (23.5)	16 (47.1)
Type of ASMs			
Enzyme induction	8 (23.5)	11 (32.4)	19 (55.9)
Enzyme inhibition	3 (8.8)	3 (8.8)	6 (17.6)
Combination	6 (17.6)	3 (8.8)	9 (26.5)
Duration of therapy			
6 months–2 years	4 (11.8)	5 (14.7)	9 (26.5)
>2 years	13 (38.2)	12 (35.3)	25 (73.5)
Duration of therapy (median, min-max)	6 (1–30) †	5 (0.66–20)†	

Shapiro-Wilk normality test: *normally distributed data, †non-normally distributed data
ASMs, antiseizure medications;

Serum 25(OH)D increased significantly in the vitamin D group after 12 weeks (19.14±7.62 to 29.81±6.44 ng/mL; $p<0.001$), with no significant change in the placebo group (22.60±9.18 to 21.31±7.96 ng/mL; p=0.198). HOMA-IR slightly decreased in both groups but without statistical significance. Adiponectin increased modestly following vitamin D supplementation (6.98±7.33 to 7.45±5.52 µg/mL; p=0.039), p=0.039, whereas no meaningful change was observed in the placebo group (8.18±9.05 to 8.51±9.99 µg/mL; p=0.449). Homocysteine levels rose markedly in both groups. hs-CRP decreased significantly after vitamin D supplementation (8.54±15.37 to 1.75±1.10 mg/L; p=0.012), while no significant change occurred in the placebo group (2.76±2.70 to 4.56±7.98 mg/L; p = 0.638) (Table 3).

Vitamin D supplementation yielded a significantly greater increase in serum 25(OH)D (10.67±8.16 vs. –1.29±3.96 ng/mL; $p<0.001$), and adiponectin (1.38±3.05 vs. 0.34±1.89 µg/mL; p=0.045), as well as a significantly greater reduction in hs-CRP (–6.74±14.65 vs. 1.81±7.75 mg/L; p=0.041), compared with placebo. Conversely, no significant differences were observed between the groups regarding the changes in HOMA-IR (–0.24±3.71 vs. –0.14±3.38; p=0.940), or homocysteine (7.90±1.79 vs. 8.15±2.70 µmol/L; p=0.290), (Table 4).

Table 2. Characteristics of 25(OH)D, homeostatic model assessment of insulin resistance (HOMA-IR), adiponectin, homocysteine, and high sensitivity C-reactive protein (hs-CRP) levels before and after the intervention

Biomarkers (reference value)	No (%) of patients					
	Before intervention		Total	After intervention		Total
	Vitamin D	Placebo		Vitamin D	Placebo	
25(OH)D (ng/mL)						
Normal (≥30)	1 (2.9)	1 (2.9)	2 (5.9)	9 (26.5)	2 (5.9)	11 (32.4)
Insufficient (21–29)	7 (20.6)	8 (23.5)	15 (44.1)	8 (23.5)	8 (23.5)	16 (47.1)
Deficient (≤20)	9 (26.5)	8 (23.5)	17 (50.0)	0 (0)	7 (20.6)	7 (20.6)
HOMA-IR						
Normal (<2.5)	8 (23.5)	10 (29.4)	18 (52.9)	7 (20.6)	10 (29.4)	17 (50.0)
Insulin resistance (≥2.5)	9 (26.5)	7 (20.6)	16 (47.1)	10 (29.4)	7 (20.6)	17 (50.0)
Hs-CRP (mg/L)						
Low-moderate risk (≤3)	12 (35.3)	10 (29.4)	22 (64.7)	12 (35.3)	13 (38.2)	25 (73.5)
High risk (>3)	5 (14.7)	7 (20.6)	12 (35.3)	5 (14.7)	4 (11.8)	9 (26.5)
Adiponectin (μg/mL)						
Normal (≥5)	9 (26.5)	11 (32.4)	20 (58.8)	10 (29.4)	10 (29.4)	20 (58.8)
Low (<5)	8 (23.5)	6 (17.6)	14 (41.2)	7 (20.6)	7 (20.6)	14 (41.2)
Homocysteine (μmol/L)						
Normal (5–15)	1 (2.9)	3 (8.8)	4 (11.8)	16 (47.1)	13 (38.2)	29 (85.3)
Low (<5)	16 (47.1)	14 (41.2)	30 (88.2)	0 (0)	1 (2.9)	1 (2.9)
High (>15)	0 (0)	0 (0)	0 (0)	1 (2.9)	3 (8.8)	4 (11.8)

Table 3. Comparison of 25(OH)D levels and biomarkers of metabolic syndrome and atherosclerosis in the vitamin D supplementation and placebo groups before (Pre) and after (Post) the intervention

Biomarker	Treatment group					
	Vitamin D			Placebo		
	Pre'	Post	p	Pre	Post	p
25(OH)D (ng/mL)	19.14±7.62*	29.81±6.44*	0.000†	22.60±9.18*	21.31±7.96*	0.198†
HOMA-IR	3.79±3.32	3.56±2.73	0.758c‡	3.11±3.04	2.97±2.89	0.795‡
Adiponectin (μg/mL)	6.98±7.33	7.45±5.52	0.039c	8.18±9.05	8.51±9.99	0.449‡
Homocysteine (μmol/L)	3.55±1.10	11.45±2.13	0.000c‡	4.17±2.58	12.32±3.33	0.000‡
Hs-CRP (mg/L)	8.54±15.37	1.75±1.10	0.012c‡	2.76±2.70	4.56 ± 7.98	0..638‡

Normality test of data distribution with Shapiro-Wilk normality test: *normally distributed data, †Paired t-test, ‡Wilcoxon signed Ranks Test, α=0.05, significant if p<0.05
HOMA-IR, homeostatic model assessment of insulin resistance; Hs-CRP, high sensitivity C-reactive protein;

DISCUSSION

This study demonstrated that high-dose vitamin D supplementation (2,000 IU/day) significantly improved serum 25(OH)D levels and positively modulated key biomarkers of metabolic syndrome and atherosclerosis, specifically adiponectin and hs-CRP, in patients with epilepsy receiving enzymatic ASMs.

Our baseline data confirm that vitamin D deficiency is a prevalent comorbidity in this population. Half of the enrolled patients exhibited Vitamin D deficiency prior to intervention, a finding consistent with previous meta-analyses regarding ASM-treated patients (16). This susceptibility is largely attributed to the use of enzymatic ASMs, which induce cytochrome P450 enzymes, thereby accelerating the catabolism of vitamin D and other micronutrients (17) often requiring long-term treatment. Following the 12-week intervention, 100% of the supplementation group achieved non-deficient levels, suggesting that 2,000 IU/day is an effective dosage for correcting deficiency in patients on polytherapy, contrasting with previous studies where lower doses (400–1,000 IU) were insufficient (18).

A key finding of this study was the significant increase in adiponectin level in the vitamin D group compared to placebo. Adiponectin is a cardio-protective adipokine often suppressed in epilepsy patients due to mitochondrial dysfunction and medication side effects (19,20). Biologically, vitamin D likely upregulates adiponectin through the activation of the vitamin D receptor (VDR) on adipocytes, which directly stimulates adiponectin gene transcription. Concurrent with this rise in adiponectin, we observed a significant reduction in hs-CRP levels. vitamin D exerts anti-inflammatory effects by suppressing NF-κB activation and downregulating pro-inflammatory cytokines (21,22). The reduction of hs-CRP combined with elevated adiponectin suggests that vitamin D supplementation may offer a dual protective mechanism against the chronic inflammatory state associated with atherosclerosis in epilepsy.

Despite improvements in inflammatory markers, we did not

Table 4. Comparison of vitamin D levels and biomarkers of metabolic syndrome and atherosclerosis between vitamin D supplementation and placebo groups

Biomarker	Group	Mean±SD	Median	Min.	Max.	95%CI	p
25(OH)D (ng/mL)							
Pre	Vitamin D	19.14±7.62*	30.4	7.9	33.8	–9.36	0.240[§]
	Placebo	22.60±9.18*	20.4	10.4	47.5	–2.43	
Post	Vitamin D	29.81±6.44*	30.4	20.8	45.6	3.46	0.002[§]
	Placebo	21.31±7.96*	20.4	9.5	35.5	–13.54	
Δ	Vitamin D	10.67±8.16*	12.1	–3.7	26.5	7.41	0.000[§]
	Placebo	–1.29±3.96*	-0.6	–12.0	4.0	–16.51	
HOMA-IR							
Pre	Vitamin D	3.79±3.32	2.77[†]	0.4	10.75	0.68	0.683[¶]
	Placebo	3.11±3.04	1.60[†]	0.50	11.30	–0.70[‡]	
Post	Vitamin D	3.56±2.73	3.27[†]	0.58	10.07	0.41	0.413[¶]
	Placebo	2.97±2.89	2.23[†]	0.41	10.47	–0.43[‡]	
Δ	Vitamin D	–0.24±3.71*	–0.67	–6.10	6.59	–2.57	0.940[¶]
	Placebo	–0.14±3.38*	–0.16	–5.64	7.84	–2.39	
Adiponectin (µg/mL)							
Pre	Vitamin D	6.98±7.33	5.12[†]	1.81	29.71	0.44	0.433[¶]
	Placebo	8.18±9.05	5.34[†]	2.44	40.0	–0.46[‡]	
Post	Vitamin D	7.45±5.52	5.89[†]	2.35	20.66	0.87	0.865[¶]
	Placebo	8.51±9.99	5.63[†]	2.62	45.0	0.88[‡]	
Δ	Vitamin D	1.38±3.05	1.91[†]	-8.03	6.22	0.041–	0.045[¶]
	Placebo	0.34±1.89	0.23[†]	-3.79	5.0	0.049[‡]	
Homocysteine (µmol/L)							
Pre	Vitamin D	3.55±1.10	3.10[†]	1.96	5.91	0.83	0.865[¶]
	Placebo	4.17±2.58	3.48[†]	2.24	13.21	–0.85[‡]	
Post	Vitamin D	11.45±2.13	11.46[b]	8.7	17.65	0.13	0.131[¶]
	Placebo	12.32±3.33	12.8[†]	3.37	17.64	–0.15[‡]	
Δ	Vitamin D	7.90±1.79	7.69[†]	5.04	11.74	0.28	0.290[¶]
	Placebo	8.15±2.70	8.90[†]	0.65	11.93	0.30[‡]	
Hs-CRP (mg/L)							
Pre	Vitamin D	8.54±15.37	2.0[†]	1.0	58.0	0.86	0.865[¶]
	Placebo	2.76±2.70	1.6[†]	1.0	12.0	–0.88[‡]	
Post	Vitamin D	1.75±1.10	1.2[†]	1.0	4.0	0.23	0.245[¶]
	Placebo	4.56±7.98	2.8[†]	1.0	34.5	–0.24[‡]	
Δ	Vitamin D	–6.74±14.65	–0.7	–54.9	1.0	0.038–	0.041[¶]
	Placebo	1.81±7.75	0[†]	–5.0	31.2	0.046[‡]	

Shapiro-Wilk normality test, *normally distributed data: †non-normally distributed data; ‡Monte Carlo simulation, number of samples 10.000; §Independent sample t-test, ¶Mann-Whitney U test; α=0.05, significant p<0.05 HOMA-IR, homeostatic model assessment of insulin resistance; Hs-CRP, high sensitivity C-reactive protein;

observe a significant change in insulin resistance (HOMA-IR). The relationship between vitamin D and insulin sensitivity remains complex; while some studies suggest a benefit, studies which include a meta-analysis have found no significant effect of supplementation on HOMA-IR, particularly in short-term interventions (23,24). It is possible that the 12-week duration was sufficient to alter inflammatory signalling (hs-CRP) but insufficient to effect structural changes in glucose homeostasis, or that HOMA-IR in this population is driven more by ASM-induced hepatic changes than by vitamin D deficiency.

Unexpectedly, homocysteine levels increased significantly in both the vitamin D and placebo groups. This finding contradicts the hypothesis that vitamin D would lower homocysteine via cystathionine beta-synthase (CBS) enzyme upregulation (25). The universal rise in homocysteine in our cohort is most likely explained by the study protocol, which required the cessation of vitamin B supplementation (B6, B12, folate) to isolate the effects of vitamin D. Homocysteine metabolism is fundamentally dependent on these B-vitamin cofactors for remethylation and transsulfuration (26). The withdrawal of these supplements in patients taking enzyme-inducing ASMs who are already prone to folate depletion likely unmasked an underlying deficiency, leading to the observed rise in homocysteine regardless of vitamin D status. This underscores the critical importance of maintaining vitamin B supplementation alongside vitamin D in this patient group.

This study has several limitations. First, variables such as dietary intake, sun exposure, and physical activity were not strictly controlled, potentially introducing confounding factors. Second, baseline levels of vitamin B6, B12, and folate were not measured, preventing a definitive correlation between micronutrient status and the observed rise in homocysteine. Finally, the sample size, while sufficient for the primary outcome, may have been underpowered to detect smaller changes in secondary metabolic parameters like HOMA-IR. Future studies with larger cohorts and comprehensive micronutrient profiling are warranted to validate these findings.

In conclusion, vitamin D administration in epilepsy patients receiving enzymatic ASMs effectively restores vitamin D levels and improves specific biomarkers of metabolic syndrome and atherosclerosis, namely adiponectin and hs-CRP. However, vitamin D alone appears insufficient to control homocysteine levels in the absence of B-vitamin supplementation. These results support the integration of vitamin D into the standard of care for epilepsy to mitigate long-term cardiovascular risk.

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TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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