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Effect of vitamin D supplementation on migraine prophylaxis in adults: a systematic review of randomized clinical trials

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Introduction
Migraine is a prevalent neurological condition with significant impact on quality of life. Its pathophysiology involves trigeminovascular system activation and release of neuropeptides such as Calcitonin Gene-Related Peptide (CGRP), alongside inflammatory processes in chronification. Vitamin D, given its anti-inflammatory properties, has been investigated as an adjuvant.

Objective
To evaluate the effect of vitamin D supplementation, as monotherapy or combined, on frequency, intensity, and duration of migraine attacks in adults, as well as on inflammatory markers.

Methods
A systematic review per PRISMA 2020, based on the PICO strategy. Randomized clinical trials with adults diagnosed with migraine receiving vitamin D at any dose or frequency, with or without other treatments, versus placebo were included. Primary outcomes were attack frequency, intensity, and duration; secondary outcomes were inflammatory markers. The search was performed up to April 2026 in PubMed, SciELO, Virtual Health Library, Web of Science, and Cochrane Library, without language or date restrictions, using descriptors "vitamin D" and "migraine." Study selection and data extraction were done by two independent reviewers. Risk of bias was assessed using the RoB 2.0 tool.

Results
844 records were identified; after screening, 5 publications were included: 4 unique randomized clinical trials (n=194) and one post-hoc analysis. Two studies evaluated vitamin D as monotherapy and two as combination therapy (probiotics or simvastatin). In monotherapy, 4000 IU/day (24 weeks) reduced monthly migraine days versus placebo ($p<0.001$), without altering severity or duration. The 2000 IU/day dose (12 weeks) outperformed placebo ($p<0.05$) in frequency, duration, and severity, besides reducing iNOS ($p=0.001$) and marginally IL-6 ($p=0.055$). Its post-hoc analysis showed lower interictal CGRP in the active group ($p=0.02$). In combination therapy, vitamin D plus probiotics surpassed placebo in frequency ($p=0.031$) and severity ($p=0.017$), with no impact on duration. Vitamin D plus simvastatin (1000 IU twice daily) reduced attack frequency at weeks 1-12 and 13-24 versus placebo ($p<0.001$), without changes in severity or duration. Limitations include dose and treatment duration heterogeneity, with risk of bias in blinding and allocation concealment.

Conclusion
Available evidence signals a trend toward reduced migraine frequency in both monotherapy and combined protocols. Current study designs do not allow inferring superiority of combination over isolated therapy, given the absence of direct comparative arms and marked heterogeneity in doses and intervention times. Intensity and duration outcomes proved heterogeneous, raising the hypothesis of a context-dependent effect. Reduction in inflammatory markers and CGRP in studies assessing these outcomes lends biological plausibility. Future trials with standardized protocols, greater power, and appropriate comparators are needed to confirm this trend and define vitamin D's role in migraine management.

Keywords:
Migraine disorders
Systematic review
Biomarkers
Vitamin D
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