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Vitamin D and Traumatic Brain Injury: A Systematic Review of Preclinical Evidence

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Abstract

Traumatic Brain Injury (TBI) triggers multiple secondary injury processes, such as inflammation, oxidative stress, apoptosis, BBB disruption, and impaired autophagy. These mechanisms contribute to progressive neuronal damage and functional decline. Vitamin D has emerged as a potential multi-target neuroprotective agent due to its regulatory roles in immune signaling, oxidative balance, neuronal survival, and autophagy pathways. This systematic review synthesized preclinical evidence evaluating the effects of Vitamin D supplementation in animal models of TBI. A comprehensive search of PubMed, OVID, and ProQuest identified six eligible studies. Across diverse dosing regimens and formulations, Vitamin D consistently improved key TBI outcomes. Reported benefits included reduced apoptosis, decreased neuroinflammation, attenuation of oxidative stress, preservation of BBB integrity, restoration of autophagy flux, and enhanced cognitive performance. Mechanistically, Vitamin D influenced several pathways, including Nrf2 activation, TLR4/MyD88/NF-κB suppression, mTOR and TRPM2 normalization, and improved microglial polarization. Although methodological quality varied, most studies demonstrated moderate rigor and supported the neuroprotective actions of Vitamin D. Heterogeneity in injury models, dosing strategies, and outcome measures limits direct comparison and highlights the need for standardized experimental approaches. Overall, current preclinical evidence indicates that Vitamin D confers robust neuroprotection following TBI. Further studies examining its mechanistic pathways, optimal therapeutic windows, and translational potential are warranted to inform future clinical applications.

Keywords: traumatic brain injury, Vitamin D, neuroinflammation, oxidative stress, neuroprotection, animal models

Abstrak

Cedera Otak Traumatis (TBI) memicu berbagai proses cedera sekunder, seperti peradangan, stres oksidatif, apoptosis, gangguan sawar darah otak (BBB), dan gangguan autofagi. Mekanisme ini berkontribusi pada kerusakan neuron progresif dan penurunan fungsi. Vitamin D telah muncul sebagai agen neuroprotektif multi-target potensial karena peran pengaturannya dalam pensinyalan imun, keseimbangan oksidatif, kelangsungan hidup neuron, dan jalur autofagi. Tinjauan sistematis ini mensintesis bukti praklinis yang mengevaluasi efek suplementasi Vitamin D pada model hewan TBI. Pencarian komprehensif di PubMed, OVID, dan ProQuest mengidentifikasi enam studi yang memenuhi syarat. Di berbagai rejimen dosis dan formulasi, Vitamin D secara konsisten meningkatkan hasil utama TBI. Manfaat yang dilaporkan termasuk pengurangan apoptosis, penurunan neuroinflamasi, pengurangan stres oksidatif, pelestarian integritas BBB, pemulihan aliran autofagi, dan peningkatan kinerja kognitif. Secara mekanistik, Vitamin D memengaruhi beberapa jalur, termasuk aktivasi Nrf2, penekanan TLR4/MyD88/NF-κB, normalisasi mTOR dan TRPM2, serta peningkatan polarisasi mikroglia.

Meskipun kualitas metodologis bervariasi, sebagian besar studi menunjukkan ketelitian yang moderat dan mendukung tindakan neuroprotektif Vitamin D. Heterogenitas dalam model cedera, strategi dosis, dan ukuran hasil membatasi perbandingan langsung dan menyoroti perlunya pendekatan eksperimental yang terstandarisasi. Secara keseluruhan, bukti praklinis saat ini menunjukkan bahwa Vitamin D memberikan neuroproteksi yang kuat setelah cedera otak traumatis (TBI). Studi lebih lanjut yang meneliti jalur mekanistiknya, jendela terapeutik optimal, dan potensi translasionalnya diperlukan untuk memberikan informasi bagi aplikasi klinis di masa mendatang.

Kata kunci: *cedera otak traumatis, Vitamin D, neuroinflamasi, stres oksidatif, neuroproteksi, model hewan*

I. INTRODUCTION

Traumatic brain injury (TBI) remains a major global health burden and is associated with substantial long-term neurological and cognitive impairments.[1] While the primary mechanical insult occurs at the moment of impact, much of the subsequent damage arises from secondary injury processes that evolve over hours to days. These processes include neuroinflammation, oxidative stress, apoptosis, cerebral edema, blood–brain barrier (BBB) disruption, and impairment of cellular homeostatic pathways such as autophagy. Together, these mechanisms contribute to progressive neuronal loss and persistent functional deficits.[2] Given the complexity of these interacting pathways, therapies that modulate multiple biological targets may offer greater therapeutic potential than single-pathway interventions.

Vitamin D has emerged as a promising candidate in this context. Beyond its classical role in calcium metabolism, Vitamin D influences immune regulation, neuronal survival, oxidative balance, and inflammatory signaling.[3] The presence of Vitamin D receptors in neurons and glial cells indicates that Vitamin D can modulate key molecular pathways implicated in TBI pathophysiology, including Nrf2 signaling, TLR4/MyD88/NF-κB activation, mTOR regulation, and autophagy function.[4] These pleiotropic actions provide a strong rationale for examining its neuroprotective potential.

However, findings across studies remain inconsistent. For example, clinical research in chronic kidney disease demonstrated vascular protective effects of Vitamin D through receptor activation and reduced inflammation, supporting its mechanistic role in tissue remodeling.[5] In contrast, large-scale analyses across diverse populations reported variable associations between Vitamin D status and inflammatory biomarkers or clinical outcomes, suggesting possible influences of genetic factors, baseline levels, or methodological differences.[6] This discrepancy highlights the need for systematic synthesis of preclinical evidence to determine whether the observed effects are consistent across experimental conditions.

This gap highlights the importance of synthesizing animal studies that evaluate Vitamin D in TBI. Differences in study design and outcome measures must be carefully considered to determine whether Vitamin D provides reliable benefits in secondary brain injury. The present review, therefore aims to bring together existing preclinical evidence on the effects of Vitamin D on inflammation, oxidative stress, neurological function, and other key outcomes following TBI in animal models. The central question is how Vitamin D supplementation influences these mechanisms in experimental TBI.

II. METHODS

This systematic literature review followed established standards for preclinical evidence synthesis and adhered to the PICO framework[7], which guided the selection of the population, intervention, and comparison groups. A comprehensive search was conducted in PubMed, OVID, and ProQuest using combinations of keywords related to TBI, animal experimentation, and Vitamin D supplementation based on the Prisma Guideline.[8] This search, completed on November 25, 2025, included articles without time restrictions.

Inclusion and exclusion criteria were defined before the screening process. Eligible studies involved rodent models with experimentally induced TBI through methods such as controlled cortical impact, weight-drop injury, or closed-skull impact. Only studies administering Vitamin D supplementation as the sole intervention and comparing it with placebo, vehicle, or untreated TBI groups were included. Relevant outcomes had to address aspects of TBI pathology, including structural brain damage, cognitive performance,

inflammatory responses, oxidative stress, or indicators of tissue repair. Studies involving humans, combination therapies, missing control groups, or unrelated outcomes were excluded, along with reviews, conference abstracts, and non-experimental reports.

Study selection was conducted by two independent reviewers who screened titles and abstracts, followed by full-text evaluation of potentially eligible articles. Disagreements were resolved through discussion or consultation with an expert. A standardized data extraction form ensured consistency in capturing information on study characteristics and reported outcomes. Additional methodological information, such as randomization, blinding, and sample-size justification, was recorded when available. Data concerning the accuracy, sensitivity, and detection thresholds of laboratory assays, including ELISA, TUNEL staining, and Western blotting, were documented to support the appraisal of methodological quality. Only studies using vertebrate animal models were included. Although this review did not involve direct animal experimentation, all included studies were required to report approval from Institutional Animal Care and Use Committees, Institutional Review Boards, or equivalent ethics committees.

A narrative synthesis was conducted due to substantial methodological and clinical heterogeneity across studies. Differences in TBI models, Vitamin D formulations and dosing regimens, timing of administration, outcome domains, made statistical pooling inappropriate. These variations precluded meaningful meta-analytic comparison, and therefore findings were summarized descriptively and presented in tables.

III. RESULT

A total of 170 records were identified across all databases, and after duplicate removal and screening, six studies met all eligibility criteria and were included in the final synthesis. The study selection process is presented in Figure 1, which outlines the number of records identified, screened, excluded, and retained for qualitative analysis.

To contextualize the interventions examined in the included studies, it is important to note that Vitamin D supplementation can be administered in several biochemical forms. Calcitriol ($1,25(OH)_2D_3$) represents the active hormonal metabolite that directly binds to the Vitamin D Receptor (VDR), while Cholecalciferol (Vitamin D_3) acts as a precursor that requires hepatic and renal hydroxylation to become biologically active. Some studies administered Vitamin D in an unspecified form, without detailed identification of the biochemical type used. These distinctions are relevant because different formulations may exert variable pharmacokinetic and biological effects following TBI.

Vitamin D metabolism involves multiple forms with distinct physiological roles. Vitamin D_3 (cholecalciferol) is the primary source for humans and animals, synthesized in the skin through sunlight exposure and obtained from dietary or supplemental sources. Vitamin D_2 (ergocalciferol) is derived from plant-based foods and certain supplements. After absorption, both forms are converted in the liver to calcidiol (25OHD), the main circulating marker used to assess Vitamin D status. Calcidiol is then transformed in the kidneys into calcitriol ($1,25(OH)_2D_3$), the active hormone responsible for regulating immune, inflammatory, and neuroprotective processes. Inactive metabolites, including $24,25(OH)_2D$ and calcitroic acid, are subsequently produced and excreted.[9] Understanding these metabolic steps provides context for interpreting the diverse Vitamin D formulations administered in TBI studies.

Across the six included studies, controlled cortical impact and weight-drop models were

used in mice and rats to induce TBI. Vitamin D was administered either as calcitriol, cholecalciferol, or unspecified "vitamin D supplementation," using intraperitoneal injections or oral gavage. Despite variations in animal species, injury severity, dose regimens, and timing of treatment, the studies consistently demonstrated beneficial effects of Vitamin D on post-TBI outcomes. The characteristics of all included studies, including species, strain, sample size, injury model, intervention details, comparator groups, and outcome domains, are summarized in the Table 2.

Methodological quality was appraised using the CAMARADES checklist.[10] Reported adherence to randomization, blinding, allocation concealment, compliance with animal welfare regulations, and sample size calculation varied substantially across studies. Studies that provided detailed descriptions of anesthetic procedures, temperature control, and outcome assessor blinding achieved higher quality scores, whereas incomplete reporting of group allocation methods, animal number justification, and missing statements of conflict of interest contributed to lower scores in others. Overall, the included studies demonstrated moderate methodological rigor, with several high-quality studies providing consistent evidence supporting the neuroprotective role of Vitamin D in experimental TBI (Supplementary file).

Across studies, Vitamin D supplementation improved multiple facets of TBI pathology. Several studies showed enhanced neurological function, reduced apoptosis, and restoration of autophagy flux following calcitriol administration.[11–13] Improvements in spatial learning and memory were reported in studies employing Morris Water Maze tasks, particularly when Vitamin D modulated VDR expression, NOX2 activity, or Nrf2 signaling.[11,13,14] Anti-inflammatory effects were observed in studies measuring cytokine levels, where Vitamin D decreased TNF-α, IL-1β, and IL-6 concentrations or increased IL-10 expression.[14–16] Additional protective mechanisms included attenuation of oxidative stress[11,13,16], preservation of BBB integrity[14,16], reduction of brain edema[14], modulation of microglial polarization,[16] and enhancement of neuronal survival[12,13]. Although the magnitude of benefit varied, the direction of effect was uniformly favorable across all studies.

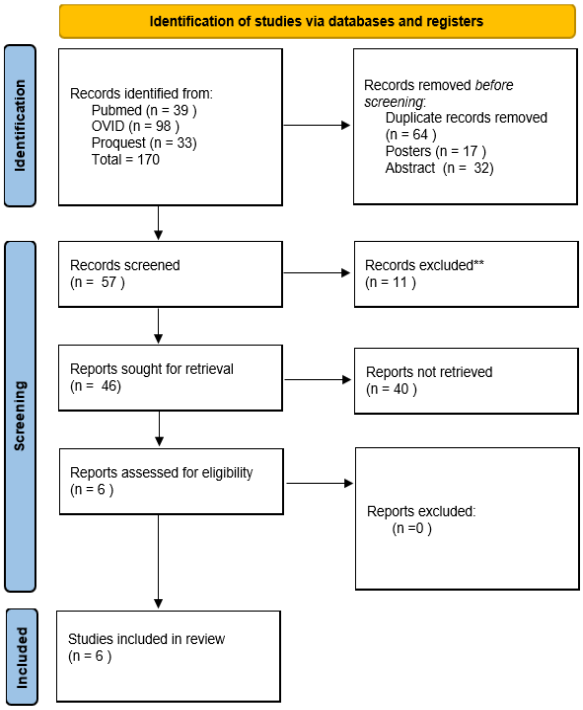

FIGURE 1 PRISMA

IV. DISCUSSION

This systematic review demonstrates that Vitamin D supplementation improves multiple outcomes in animal models of traumatic brain injury and provides a clear answer to the research question posed in the introduction. Across the included studies, Vitamin D consistently produced neuroprotective effects through the modulation of apoptosis, inflammation, oxidative stress, autophagy, and neurobehavioral performance. Studies in other neurological conditions have similarly shown that Vitamin D attenuates microglial activation and enhances neuronal survival.[17] This reinforces the biological plausibility of

its role in mitigating secondary injury after traumatic brain injury.

The findings of this review are consistent with those reported in individual experimental studies. Activation of Nrf2 signaling, restoration of autophagy flux, reduction in NADPH oxidase activity, preservation of blood-brain barrier integrity, and suppression of TLR4 and NF kappa B pathways were documented across the evidence base. Nevertheless, between-study differences must be considered. Variability in animal species, age, traumatic brain injury models, Vitamin D formulations, doses, and timing of administration produced heterogeneous outcomes. Some studies used pre-injury supplementation, whereas others relied on early post-injury dosing, which may account for differences in behavioral recovery or inflammatory marker profiles. Variation in outcomes measured, such as the focus on oxidative stress markers in some studies and behavioral or histological assessments in others, also limits direct comparability.

In addition to these sources of heterogeneity, several methodological limitations warrant careful consideration when interpreting the findings. Dosing variability was substantial across studies, with Vitamin D administered as calcitriol, cholecalciferol, or unspecified formulations at markedly different dose ranges and schedules, making it difficult to define an optimal therapeutic window. Importantly, none of the studies reported serum 25OHD or $1,25(OH)_2D_3$ measurements, leaving uncertainty regarding whether treatment normalized deficiency, induced supraphysiological levels, or produced pharmacologic rather than physiological effects.

Furthermore, several studies provided incomplete reporting of key methodological practices. While some described randomization or blinded outcome assessment, others lacked sufficient detail, raising concerns about inadequate randomization, limited allocation concealment, and absence of blinding, all of which increase the risk of selection and detection bias. The CAMARADES assessment reflected this inconsistency, with studies showing variable adherence to core quality criteria. Finally, all included studies reported beneficial effects of Vitamin D, suggesting the possibility of publication bias, a known issue in preclinical research that may exaggerate the perceived magnitude or consistency of treatment benefits.

This review has several strengths, including the use of predefined eligibility criteria, systematic searching, and structured quality assessment using the CAMARADES checklist. The inclusion of diverse outcome domains allowed a comprehensive evaluation of Vitamin D's therapeutic potential. However, important limitations should be acknowledged. Heterogeneity across studies prevented quantitative synthesis. Several studies lacked explicit reporting on randomization, blinding, and sample size justification, which increases the risk of bias. Variation in Vitamin D formulations and insufficient reporting of serum Vitamin D levels impede the establishment of standardized therapeutic windows. The exclusive use of rodent models limits translational applicability to human populations, particularly because rodent physiology cannot fully recapitulate the complexity of human neuroinflammatory and neurovascular responses.

TABLE 3.STUDY CHARACTERISTICS

Author	Year	Strain	TBI Method	Form of Vitamin D	Dose	Duration & Frequency	Timing	Brain Damage	Cognitive	Inflammation	Oxidative Stress	Tissue Repair	Main Finding
Cui	2021	CD1	CCI	Calcitriol	0.5–3 μg/kg Oral	Daily, 14 days	Post-TBI	Yes	Yes	No	Yes	No	↓ apoptosis; ↑ autophagy flux; ↑ Nrf2 activation
Kim	2023	C57BL/6	Weight-drop	Cholecalciferol	5 mg/kg I.p	Single dose	1 hour post-TBI	Yes	No	Yes	No	No	↑ IL-10; ↓ inflammation
Cui	2017	Not reported	CCI	Calcitriol	1 μg/kg I.p	3 doses	30 min–48h post	Yes	Yes	No	No	Yes	↓ apoptosis; ↑ neurological score
Jiang	2022	Sprague-Dawley	CCI	Calcitriol	1 μg/kg I.p	3 doses	Post-TBI	Yes	Yes	Yes	Yes	Yes	↑ cognitive performance; ↑ BBB integrity; ↓ oxidative stress; ↓ inflammation
Cui	2017	Sprague-Dawley	CCI	Calcitriol	2 μg/kg I.p	3 doses	30 min–48h post	Yes	Yes	Yes	Yes	Yes	↓ brain edema; ↑ cognitive performance; ↓ apoptosis
Yang	2021	Sprague-Dawley	CCI	Cholecalciferol	1–5 μg/kg/day I.p	Daily, 1 w pre + 3 w post	Pre/Post	No	Yes	Yes	No	Yes	↓ brain edema; ↑ cognitive performance; ↑ BBB integrity

CCI = Controlled Cortical Impact; BBB = Blood–Brain Barrier; IL = Interleukin; Nrf2 = Nuclear Factor Erythroid 2–Related Factor 2; mTOR = Mechanistic Target of Rapamycin; TRPM2 = Transient Receptor Potential Melastatin 2. I.p=Intraperitonea; NR = Not reported in the original publication

V. CONCLUSIONS

Current evidence indicates that Vitamin D supplementation provides benefits in animal models of traumatic brain injury. These effects include improvement in inflammation, oxidative stress, apoptosis, autophagy, and functional recovery. However, the strength of this evidence is limited by variation in study methods, inconsistent dosing, and incomplete reporting of quality measures such as randomization, blinding, and serum Vitamin D levels. These limitations reduce the certainty of the findings and make translation to human populations challenging. Further research is needed to clarify optimal dosing, timing, and biochemical forms of Vitamin D as well as its specific effects on synaptic plasticity, mitochondrial function, neurovascular responses, and long term cognitive outcomes.

Clinical translation will require a structured and stepwise approach. Early clinical studies should determine baseline Vitamin D status in patients with traumatic brain injury and assess whether correcting deficiency improves recovery. Pilot trials should test safe and effective doses supported by pharmacokinetic data. Studies that measure biomarkers of inflammation, oxidative stress, and brain integrity can help identify early signals of benefit. These initial steps will support the development of well designed clinical trials that can evaluate the therapeutic potential of Vitamin D in diverse traumatic brain injury populations.

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