

The effect of pulse steroid therapy on bone density and turnover: A systematic review and meta-analysis

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ABSTRACT

Introduction: Chronic exposure to glucocorticoids (GC) is a leading cause of secondary osteoporosis and fractures. While the skeletal effects of long-term oral GC are well-established, the bone effects of intermittent high-dose intravenous pulse methylprednisolone therapy remain less clearly defined. This study aimed to evaluate its impact on skeletal health in adults not receiving anti-osteoporosis treatment.

Methods: This meta-analysis was conducted according to PRISMA guidelines and prospectively registered. PubMed, Scopus, Embase, and Google Scholar were searched up to September 2025. Studies included longitudinal cohort and case-control studies with appropriate comparators and randomised controlled trials reporting pre- and post-intravenous methylprednisolone bone outcomes.

Results: Eight studies (n=192, 72% females) were included. Pulse intravenous methylprednisolone did not significantly reduce bone mineral density (BMD) at the lumbar spine (mean difference [MD] 0.01 g/cm²; 95% confidence interval [CI] -0.02 to 0.03), femoral neck (MD -0.01 g/cm²; 95% CI -0.03 to 0.01), or total hip (MD -0.03 g/cm²; 95% CI -0.06 to 0.01) over a mean follow-up period of 5.5 months. Trabecular bone score showed no significant pooled change (MD -0.01 g/cm²). In contrast, procollagen type-1 N-terminal propeptide (MD -36.95 ng/mL; 95% CI -56.86 to -17.03) and C-terminal telopeptide (MD -0.19 ng/dL; 95% CI -0.32 to -0.07) significantly decreased. Serum 25-hydroxyvitamin D increased modestly, while serum calcium and parathyroid hormone remained unchanged.

Conclusion: Pulse intravenous methylprednisolone does not cause short-term BMD loss, though it is associated with measurable suppression of bone turnover markers. Larger controlled studies with standardised sampling, peripheral site assessment, and fracture outcomes are needed to determine long-term skeletal risk from pulse regimens.

Keywords: endocrinology, neurology, osteoporosis, pulse methylprednisolone, rheumatology

CLINICAL IMPACT

What is New

- Pulse intravenous methylprednisolone was not associated with short-term loss of lumbar spine or hip bone mineral density (BMD).
- Bone turnover markers were suppressed, indicating early effects on bone remodelling that are not captured by BMD alone.
- Limited fracture reporting precludes firm conclusions regarding fracture risk.

Clinical Implications

- Stable short-term BMD should not be equated with skeletal safety during pulse intravenous methylprednisolone therapy.
- Patients at high fracture risk or receiving repeated/ high cumulative doses may still warrant careful skeletal risk assessment and preventive management.

INTRODUCTION

Glucocorticoids (GC) are potent anti-inflammatory agents used for the treatment of various acute autoimmune and inflammatory disorders. Current studies estimate that the prevalence of GC use among countries varies between 0.5 and 21%.¹⁻⁴ Although they are highly effective, GCs are known to have negative impacts on skeletal health, particularly when administered at high doses and/or for a prolonged period.⁵⁻⁷ Among individuals receiving long-term GC therapy, the estimated prevalence of osteoporosis or fractures is up to 50%, rendering GCs the most common form of secondary (iatrogenic) osteoporosis.^{8,9} Thus, it is recommended to carry out a fracture risk assessment at GC initiation and to start

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bone-protective strategies in patients at moderate to high risk of fracture, particularly for those receiving the equivalent of ≥ 2.5 to 5 mg prednisolone daily for ≥ 3 months.¹⁰

GC-induced skeletal harm is most pronounced in the trabecular-rich regions, such as the vertebrae and proximal femur.¹¹ GC therapy increases the risk of hip and vertebral fractures by at least two- and threefold, respectively, compared with individuals without GC exposure.¹¹ Bone loss occurs most rapidly after GC initiation, with the most rapid decline occurring within the first year of GC therapy at a bone loss rate of 6 to 12%. This later slows to a rate of approximately 3% per year subsequently.¹² Consistent with this early bone loss rate, fracture risk is highest within the first 3 to 6 months after GC initiation, reflecting early osteoclast activation, increased osteoblast apoptosis, and reduced osteoblast proliferation.¹³ In individuals initially commenced on GC, fracture incidence was 5.1% (95% confidence interval [CI] 2.8–8.2%) for vertebral fractures and 2.5% (95% CI 1.2–4.2%) for non-vertebral fractures. For chronic GC users (>6 months), the corresponding incidences were 3.2% (95% CI 1.8–5.0%) and 3.0% (95% CI 0.8–5.9%), respectively.¹⁴ More importantly, fracture risk is influenced by current GC dose and cumulative GC exposure.¹⁰ Even low doses of GC ≤ 2.5 mg per day have been associated with increased risk of vertebral fractures,⁹ and doses above the 2.5 mg per day threshold have been shown to increase the risk of spine and hip fractures.^{10,15} Cumulative GC exposure is similarly important: higher doses of GCs ≥ 30 mg per day increase the risk of fragility fractures, with peak fracture incidence at 12 months. Indeed, fracture rate rises with cumulative GC exposure from an average 4.6 per 1000 person-years (95% CI 3.8–5.4) at <0.675 g of cumulative GC to a nearly threefold rate of 13.4 per 1000 person-years (95% CI 10.7–16.7) at a cumulative GC dose of ≥ 5.4 g.¹⁶

Mechanistically, GCs increase skeletal fragility through direct and indirect pathways. GCs directly suppress bone formation by inhibiting osteoblast differentiation, promoting osteoclast apoptosis while reducing osteocyte viability, leading to deterioration of bone microarchitecture and overall quality, ultimately increasing bone fragility. GCs also influence bone remodelling indirectly through suppression of anabolic pathways, including the growth hormone axis, while promoting insulin resistance and muscle catabolism, further compounding skeletal fragility. While the association between chronic GC exposure and adverse skeletal outcomes (including bone loss and fragility fractures) is well established, the impact of intermittent high-dose intravenous pulse methylprednisolone therapy remains less clearly defined.^{10,17} To date, relatively few studies have directly

assessed bone outcomes associated with intermittent pulse methylprednisolone use, and no clear quantitative synthesis of these skeletal effects is available. The authors therefore conducted this systematic review and meta-analysis to clarify the current evidence base. The authors hypothesised that intermittent pulse intravenous methylprednisolone may exert adverse skeletal effects that are detectable in short-term bone turnover markers, even if changes in bone mineral density (BMD) are less readily apparent over short follow-up periods. Accordingly, the authors evaluated the effects of intermittent pulse intravenous methylprednisolone therapy on skeletal health by investigating changes in BMD, bone turnover markers, fracture rate, and bone biochemistry in adults who did not receive osteoporosis therapy.

METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁸ As only published data were used, Institutional Review Board approval was not required. The study protocol was prospectively registered in the International Database of Registered Systematic Reviews (<https://doi.org/10.17605/OSF.IO/VFMJR>).

Selection criteria

Eligible studies were identified through comprehensive searches of PubMed, Scopus, Embase, and Google Scholar, including all publications up to September 2025. Studies were included if they met the following criteria: (1) case-control study, cohort study, longitudinal study or randomised controlled trial; (2) reported at least 1 outcome of interest; (3) conducted in humans; (4) available in full text; and (5) English-language published studies. The authors excluded: (1) duplicate or overlapping cohorts; (2) case-control or cross-sectional studies without control groups; (3) case reports, case series, editorials, protocols, opinion pieces, commentaries, abstracts, and review articles; or (4) grey literature, including conference abstracts and unpublished reports (these sources lacked sufficient methodological detail and complete outcome data for reliable extraction and quality assessment).

Search strategy

The search strategy was developed using the Population, Intervention, Comparison, Outcome (also known as PICO) framework.¹⁹ The population group consisted of patients receiving pulse intravenous methylprednisolone, with or without maintenance GC therapy. The intervention was exposure to pulse intravenous methylprednisolone, and the comparator group was baseline (pre-exposure) measurements

obtained prior to treatment initiation. Outcomes of interest included BMD, bone turnover markers, fracture incidence, and use of osteoporosis treatment. The full search terms are provided in Supplementary Table S1.

Data extraction

Data extraction was performed independently by 4 investigators using a 3-stage process. In the first stage, titles and abstracts were screened, with full texts retrieved when necessary. In the second stage, full-text articles and their reference lists were reviewed for eligibility. In the third stage, study objectives, methods, and suitability for inclusion were critically appraised. Discrepancies were resolved by consensus, with adjudication by third and fourth reviewers. When essential data were unavailable, corresponding study authors were contacted for clarification or provision of unpublished data.

Extracted data included study characteristics and reported outcomes: patient age; underlying disease conditions resulting in GC therapy; pulse intravenous methylprednisolone regimens; radiological measures (BMD, trabecular bone score [TBS]); bone turnover markers, e.g. procollagen type 1 N-terminal propeptide (P1NP), C-terminal telopeptide (CTX), osteocalcin, hydroxyproline, bone-specific alkaline phosphatase (bsALP); bone biochemistry (serum calcium, 25-hydroxyvitamin D, intact parathyroid hormone; and urine calcium/creatinine ratio); and fracture rate. All included full-text articles were reviewed and approved by all authors prior to final data extraction.

Data synthesis and analysis

Meta-analysis was performed when at least 2 or more studies reported the same outcome in a numerical outcome (e.g. BMD, bone turnover markers, fracture rates). Small study effects and publication bias were assessed using funnel plots (log odds against inverse standard error).

Risk-of-bias assessment

Risk of Bias was evaluated using the Risk of Bias In Non-randomized Studies—of Exposures (ROBINS-E) tool (Supplementary Table S2).²⁰ ROBINS-E evaluates the quality of the study based on 7 domains, including exposure classification, deviations from intended exposures, missing data, outcome measurement, and selective reporting. Each domain was rated as low risk, some concerns, high risk, or very high risk of bias. Four reviewers independently performed assessments for risk of bias, with disagreements resolved through discussion.

Statistical analysis

All analyses were performed using RevMan version 5.3 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) using random-effects models. When standard deviations (SDs) were not reported, they were estimated from *P* values or imputed using pooled SDs from comparable studies: $\sqrt{(\sum(N \times SD^2) / \sum N)}$.

For continuous variables, mean difference (MD) was used given its clinical interpretability. Analyses were repeated using standardised mean difference to assess robustness across heterogeneous measurement approaches (e.g. different densitometry platforms and laboratory assays). Apart from statistical significance ($P < 0.05$), a 4% change in BMD was prespecified as the least significant change (LSC).^{21,22}

Statistical heterogeneity was assessed using the I^2 statistic, with $P < 0.10$ considered as statistically significant, and $I^2 \geq 50\%$ indicating substantial heterogeneity. Potential sources of heterogeneity were explored through sensitivity analyses after exclusion of outlier studies (defined a priori as those with opposing effect directions, disproportionately large effect sizes, or high risk of bias), followed by recalculation of pooled effect estimates.

Quality of evidence was assessed by the Grading of Recommendations, Assessment, Development, and Evaluations (also known as GRADE) approach.²³

RESULTS

The initial database search identified 4195 records. After removing 461 duplicates, 3734 articles were available for screening. Of these, 3655 articles were excluded based on the predefined eligibility criteria; 79 articles underwent full-text review, of which 69 were excluded, leaving 10 publications (8 studies) in the final review. The 8 included studies comprised 6 cohort studies, 1 retrospective study, and 1 randomised trial. Of the 8 studies, 4 studies recruited patients with Graves' disease, 2 studies included patients with multiple sclerosis, and 2 studies recruited individuals with mixed rheumatological conditions (Fig. 1). Table 1 summarises the study characteristics and sample sizes ranging from 10 to 45 participants, yielding a total sample of 192 patients (72% female). Means (SDs) of age and body mass index were 49.4 (18.13) years and 25.2 (8.56) kg/m², respectively.

Bone mineral density

Eight studies (10 publications)^{24–33} reported BMD outcomes before and after pulse methylprednisolone. One study³⁴ reported T-scores and Z-scores only, which could not be reliably converted to BMD values;

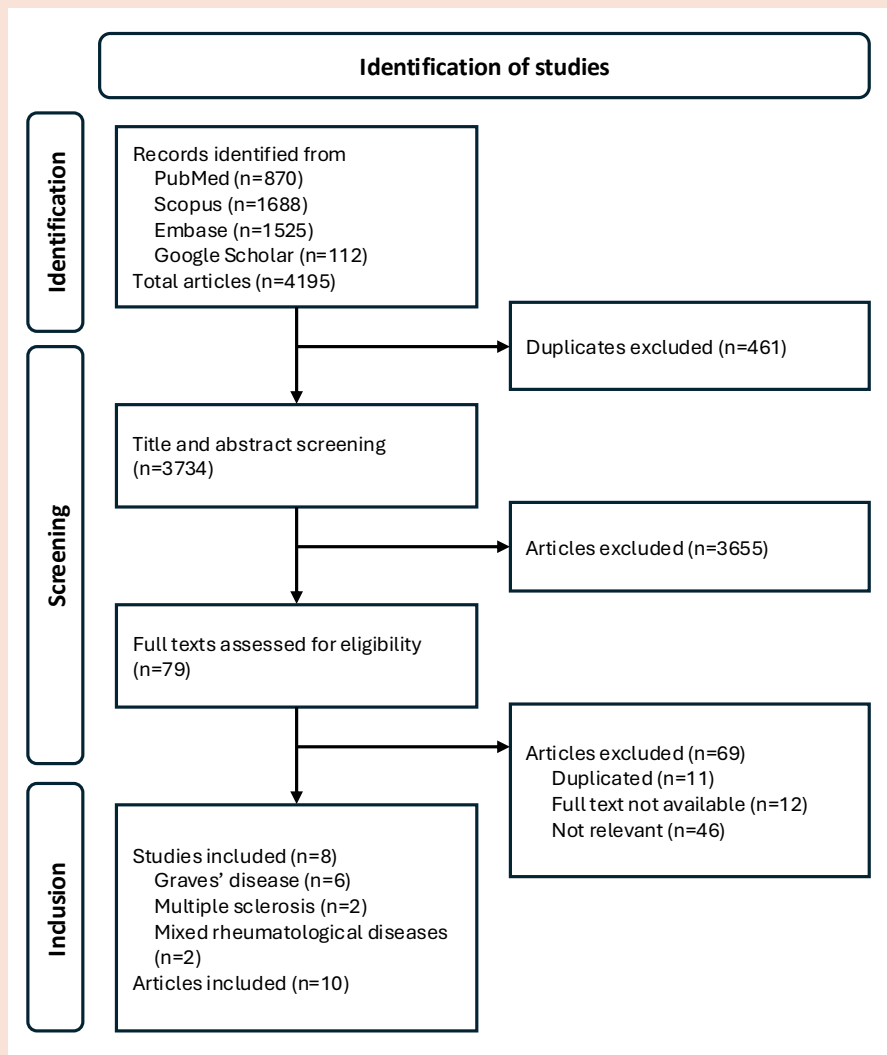
Table 1. Summary of included studies.

Reference	Study type	Population	Intervention	No.		Gender Male/ Female	Age Mean (SD)	BMI
				Intervention	Control			
Hu, 2020 ³²	Retrospective cohort	Moderate-to-severe active Graves' disease ophthalmopathy	Intravenous MP 0.5 g once per week x 6 weeks, then intravenous MP 0.25 g per week for 6 weeks	16 with 2 courses	-	19/26	42.5 (13.24)	-
				45 with 1 course	-			
Harsløf, 2023 ²⁵	Prospective cohort	Active Graves' disease orbitopathy with clinical activity score 3 or more		32	-	11/21	52.9 (10.2)	25.45
Rymuza, ^a 2022 ²⁷	Prospective cohort	Moderate-to-severe active Graves' disease orbitopathy, euthyroid		23	-	3/20	54 (12)	26.5
Censi, 2018 ²⁴	Prospective cohort	Active Graves' disease orbitopathy		11	-	1/10	56 (47–71)	24.5
Rymuza, ^a 2019 ²⁹	Prospective cohort	Moderate-to-severe active Graves' disease orbitopathy, euthyroid		35	-	6/29	47 (22–66)	27
Rymuza, ^a 2022 ²⁸	Prospective cohort	Moderate-to-severe active Graves' disease orbitopathy, euthyroid		15	-	2/13	53.6 (40–74)	28
Simeakis, 2023 ³⁰	Prospective cohort	Newly diagnosed multiple sclerosis	Intravenous MP 1g x 5 days followed by PO prednisolone tapering over 21 days	25	-	15/10	-	26.72
Zorzon, 2004 ³¹	Prospective randomised trial	Multiple sclerosis	Regular pulses of MP (1 g/day for 5 days, every 4 months for 3 years, then every 6 months for 2 years) + pulses of MP for relapses	25	61	7/18	-	-
			Pulses of MP for relapses only	18		7/11		
Frediani, 2004 ³³	Prospective randomised trial	Active rheumatoid arthritis	Intervention: intravenous MP 1 g for 3 alternate days, repeated monthly if disease still active Control: oral MP 16 mg/day for at least 1 month, tapered to minimum 4 mg/day	31	31	5/12	-	-
Haugeberg, 2004 ²⁶	Prospective cohort	Various rheumatic disorders requiring intravenous MP pulse treatment	Intravenous MP pulses (dose and schedule varied based on disease and patient's response), with or without concomitant oral prednisolone	38 including 14 without oral prednisolone	-	8/30	48.4 (16.3)	24.9

BMI: body mass index; MP: methylprednisolone; PO: per os/by mouth; SD: standard deviation

^a Recognised as the same study in 3 publications.

Fig. 1. PRISMA flow chart.



hence, it was excluded from the analysis. No significant changes were observed in BMD at femoral neck (MD -0.01 g/cm²; 95% CI -0.03 to 0.01; quality of evidence: low ⊕⊕○○), the lumbar spine (MD 0.01 g/cm²; 95% CI -0.02 to 0.03; quality of evidence: low ⊕⊕○○), or total hip (MD -0.03 g/cm²; 95% CI -0.06 to 0.01; quality of evidence: low ⊕⊕○○) following pulse methylprednisolone therapy (all $I^2 = 0\%$; fixed-effect models applied) that was administered over a weighted mean of 5.5 months (range 3 to 12 months). The lower limit of 95% CI for the BMD changes at femoral neck and lumbar spine did not exceed the prespecified LSC. Of the 2 studies^{24,28} that reported TBS, no significant difference was detected (MD -0.02; 95% CI -0.10 to 0.07; $I^2 = 0\%$; fixed-effect; quality of evidence: very low ⊕○○○) (Fig. 2).

Bone turnover markers

Five studies^{24,25,27,30,32} reported bone turnover markers. Both P1NP (MD -36.95 ng/mL; 95% CI -56.86 to -17.03;

quality of evidence: low ⊕⊕○○) and CTx (MD -0.19 ng/dL; 95% CI -0.32 to -0.07; quality of evidence: low ⊕⊕○○) showed significant reductions following pulse methylprednisolone treatment ($I^2 \geq 50\%$; random-effects models applied) (Fig. 3).

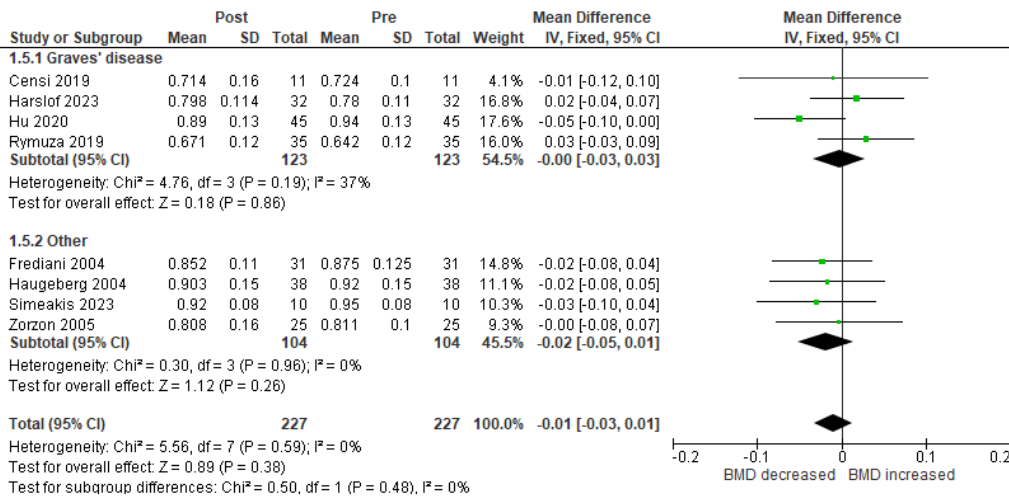
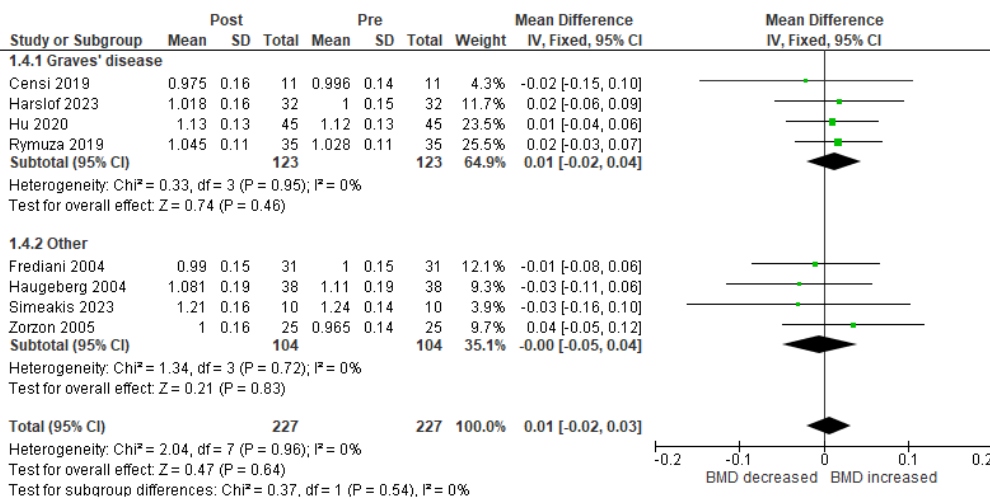
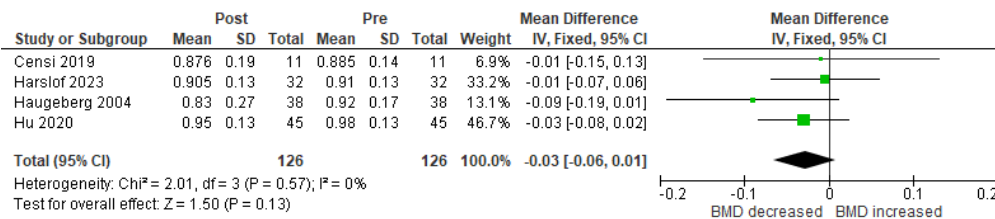
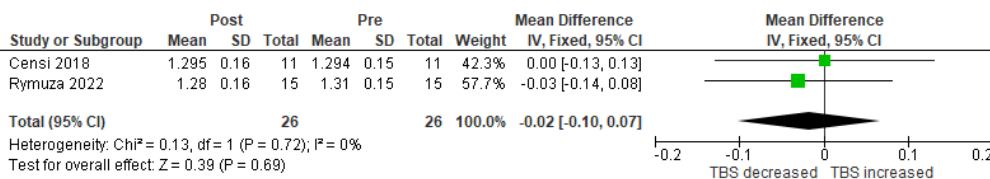
Biochemistry

Serum 25-hydroxyvitamin D levels significantly increased after treatment (MD 1.03 ng/mL; 95% CI 0.24 to 1.83; $I^2 = 0\%$; fixed-effect; quality of evidence: low ⊕⊕○○).^{24,27,29,30,32} No significant changes were observed in serum calcium^{29,30,32} or intact parathyroid hormone^{24,27,29,30,32} concentrations (Fig. 4).

Subgroup analysis

A subgroup analysis comparing Graves' disease^{24,25,27-29,32} with other conditions (multiple sclerosis^{30,31} and rheumatological diseases) revealed no significant changes in BMD within either subgroup. Both P1NP and CTx significantly decreased in the Graves' disease

Fig. 2. Forest plots of bone mineral density and trabecular bone scores.

A: Bone mineral density of femoral neck**B: Bone mineral density of lumbar spine****C: Bone mineral density of total hip****D: Trabecular bone score**

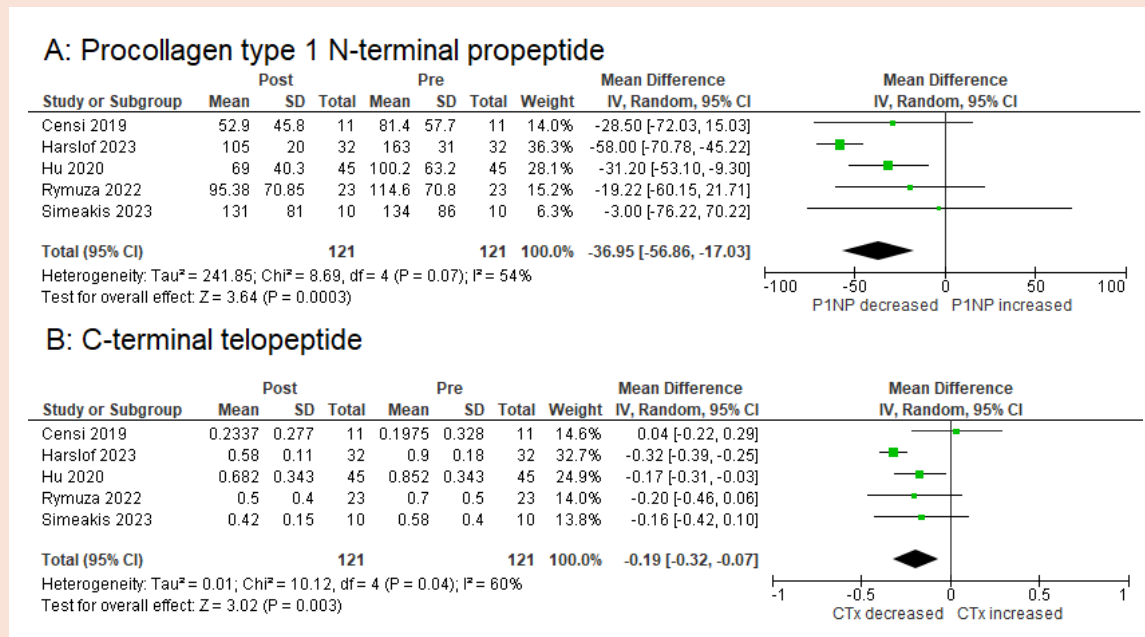
BMD: bone mineral density; CI: confidence interval; df: degrees of freedom; IV: inverse variance; SD: standard deviation; TBS: trabecular bone score

Table 2. Quality of evidence and sensitivity analysis.

Variables	No. of studies	Mean difference (confidence interval)	Quality of evidence	Reasons	Sensitivity analysis ^a Mean (confidence interval)
Bone mineral density of femoral neck	8	-0.01 (-0.03 to 0.01) g/cm ²	Low ⊕⊕OO	Observation studies	-0.01 (-0.03 to 0.02) g/cm ²
Bone mineral density of lumbar spine	8	0.01 (-0.02 to 0.03) g/cm ²	Low ⊕⊕OO	Observation studies	0.01 (-0.02 to 0.04) g/cm ²
Bone mineral density of total hip	4	-0.03 (-0.06 to 0.01) g/cm ²	Low ⊕⊕OO	Observation studies	-0.03 (-0.07 to 0.01) g/cm ²
Trabecular bone score	2	-0.02 (-0.10 to 0.07)	Very Low ⊕OOO	Observation studies (small number)	-0.03 (-0.14 to 0.08)
Procollagen type 1 N-terminal propeptide	5	-36.95 (-56.86 to -17.03) ng/mL	Low ⊕⊕OO	Observation studies	-37.47 (-60.55 to 14.38) ng/mL
C-terminal telopeptide	5	-0.19 (-0.32 to -0.07) ng/dL	Low ⊕⊕OO	Observation studies	-0.25 (-0.34 to -0.15) ng/dL
Serum 25-hydroxyvitamin D level	4	1.03 (0.24 to 1.83) ng/mL	Low ⊕⊕OO	Observation studies	1.11 (0.31 to 1.91) ng/mL
Serum calcium level	3	-0.00 (-0.04 to 0.03) mmol/L	Low ⊕⊕OO	Observation studies	-0.00 (-0.04 to 0.03) mmol/L
Intact parathyroid hormone level	4	3.29 (-1.40 to 7.97) pg/mL	Very Low ⊕OOO	Observation studies (inconsistent result)	1.66 (-4.81 to 8.13) pg/mL

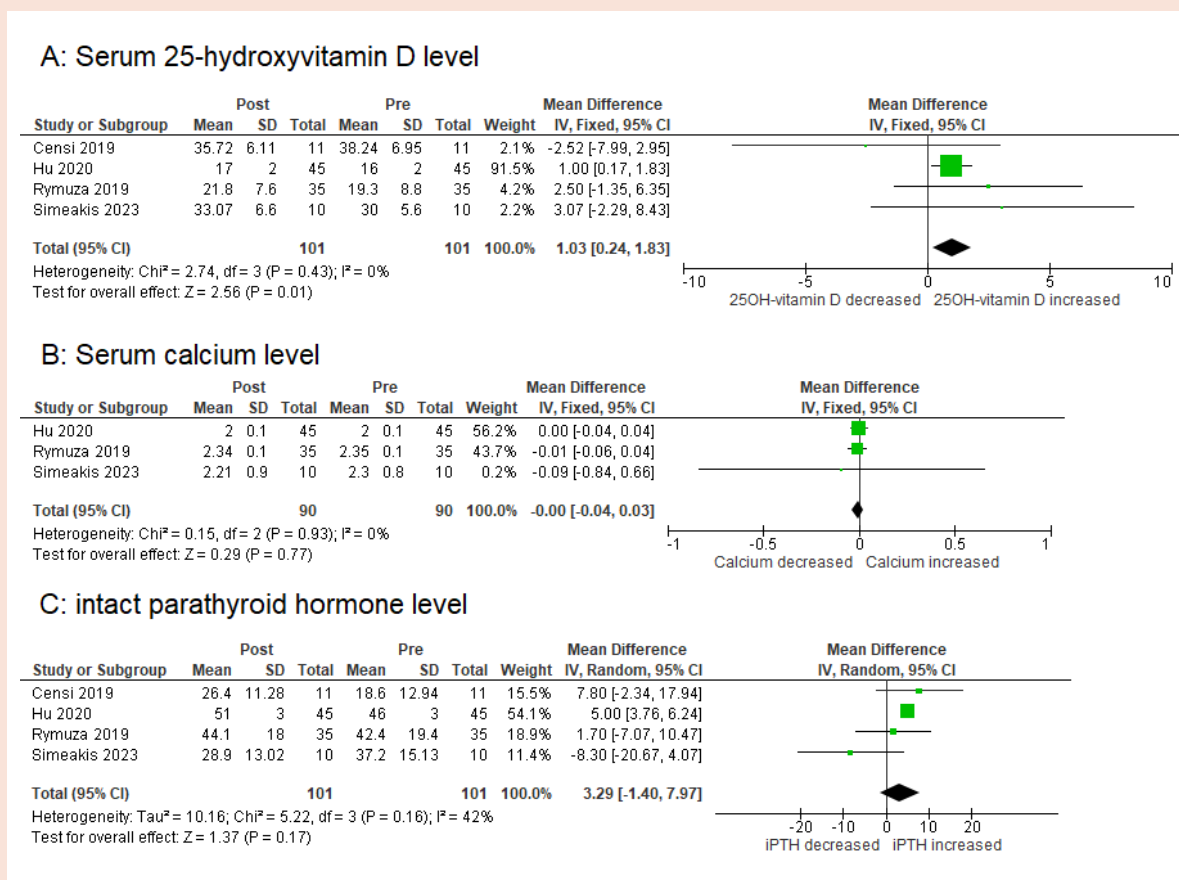
^a Mean difference of meta-analyses excluding Censi (2018),²⁴ Zorzon (2004),³¹ and Frediani (2004)³³ for their overall risk of bias: some concerns.

Fig. 3. Forest plots of bone turnover markers.



CI: confidence interval; CTx: C-terminal telopeptide; df: degrees of freedom; IV: inverse variance; P1NP: procollagen type 1 N-terminal propeptide; SD: standard deviation

Fig. 4. Forest plots of bone biochemistry.



CI: confidence interval; df: degrees of freedom; iPTH: intact parathyroid hormone; IV: inverse variance; SD: standard deviation

osteoblast differentiation and activity, in part through inhibition of the Wnt signalling pathway.^{36,37} GCs also increase the expression of Dickkopf-1 and sclerostin, reduce proliferation of osteoprogenitor cells, and promote differentiation of mesenchymal stem cells into adipocytes rather than osteoblasts.³⁶ These effects result in a sustained reduction in osteogenesis. The low P1NP levels observed in this study are consistent with this biology, and suggest that even intermittent high-dose methylprednisolone exposure may lead to prolonged suppression of osteoblast function lasting for months to years.^{35,38} The interpretation of reduced CTx is more complex. GCs have mixed and potentially biphasic effects on bone resorption. Initially, GC use has been associated with early bone resorption driven by increased osteoclast activity and attenuation of osteoblast-lineage suppression.³⁸ Over time, osteoclast activity declines due to reduced receptor activator of nuclear factor kappa-B ligand production from suppressed osteoblasts, leading to variable trajectories in resorption markers.³⁸ Apart from the effect of GCs on osteoclasts, GCs can induce osteocyte apoptosis, leading to variable levels of CTx at different time points.³⁹ In pulse methylprednisolone regimens, the timing of sampling is therefore particularly important: CTx measured during or soon after a pulse may be elevated whereas the CTx measured weeks later may be reduced.⁴⁰ Thus, the concurrent decreases in P1NP and CTx most likely reflect overall suppression of bone remodelling, with a more prominent and sustained inhibitory effect on bone formation. Clinically, this pattern is consistent with a low-turnover skeletal state and may explain the lack of significant BMD changes after a short course of intravenous pulse methylprednisolone therapy. Furthermore, the drug-free intervals in pulse methylprednisolone therapy may allow partial recovery of remodelling signals and normalisation of osteoclast activity.^{41,42} Nevertheless, persistent suppression of bone formation may still have implications for longer-term bone health.

TBS provides a surrogate index of trabecular bone architecture and predicts fracture risk independent of BMD.⁴³ In this analysis, no significant decline in TBS was observed after pulse intravenous methylprednisolone therapy. However, individual studies have reported divergent results. Rymuza et al.²⁸ reported a decline in TBS in individuals with mild to moderate Graves' disease orbitopathy treated with pulse intravenous methylprednisolone, whereas earlier studies by Censi et al.²⁴ observed no demonstrable effect of pulse intravenous methylprednisolone on TBS in individuals with Graves' orbitopathy. Clinically, this suggests that the effect of pulse intravenous methylprednisolone on TBS may be modest and context-specific, and that absence of decline in TBS

does not necessarily exclude deterioration in bone quality in susceptible subgroups.

The results are broadly consistent with comparative studies suggesting less BMD loss with pulse regimens compared with chronic daily GCs. Frediani et al.³³ conducted a randomised trial of 31 women with active rheumatoid arthritis who received either chronic oral methylprednisolone or intermittent methylprednisolone pulse therapy. After 12 months, chronic methylprednisolone therapy led to significant declines in BMD at the total hip, femur, and lumbar spine while no change in BMD was observed in the pulse methylprednisolone group.³³ Handa et al.³⁴ studied 49 patients with dermatological conditions treated with daily prednisolone or intravenous dexamethasone at 4-weekly intervals. The authors found that individuals receiving intermittent intravenous dexamethasone experienced less reduction in lumbar spine T-score than those treated with daily oral prednisolone, consistent with differential effects across trabecular-rich (spine) versus cortical-rich (radius) bone by GC regimen. Among the limited studies reporting fracture outcomes, Zonana-Nacach et al.⁴⁴ found in 539 patients with systemic lupus erythematosus that higher cumulative prednisone exposure was significantly associated with osteoporotic fractures, whereas each additional intravenous methylprednisolone pulse was associated with only a small, non-significant increase in fracture risk (relative risk 1.3, 95% CI 1.0–1.8; $P=0.07$). Similarly, in the retrospective 10-year study by Cheng et al.⁴⁵, no vertebral compression fractures were reported among 46 patients with active systemic sclerosis treated with pulse methylprednisolone therapy, although 21 patients had also received long-term low-dose oral glucocorticoids.

From a clinical standpoint, these findings suggest that short-term stability in BMD following pulse intravenous methylprednisolone should be interpreted cautiously. Baseline fracture risk assessment remains important, especially in patients with high underlying osteoporosis risk or recurrent pulse methylprednisolone exposure. While BMD is unchanged, changes in bone turnover markers are detectable and early fracture risk in GC exposure can be driven by markers not captured in bone imaging. Notably, the absence of a measurable short-term decline in BMD should not be equated with absence of fracture risk, as GC exposure may impair bone strength through mechanisms not fully captured by areal BMD alone.

Furthermore, early fracture risk associated with chronic oral GC therapy could only be partly explained by BMD loss, as excess GC also impairs bone mineralisation and microarchitecture, and could predispose to falls via muscle myopathy. Thus, clinicians should

avoid over-reliance on BMD alone and consider vertebral fracture assessment, prior fracture history, fall risk, or even consider using TBS where available.^{9,35} Most of the studies in this analysis have focused on assessment of bone density in lumbar spine and hip. Handa et al. reported that patients receiving intermittent intravenous dexamethasone had a significantly greater decline in radial head BMD compared with those on daily oral prednisolone, reinforcing the variable sensitivities of skeletal cells to GC regimens.³⁴ Distal radius BMD may be particularly relevant in younger individuals in predicting upper-limb fracture risk,⁴⁶ and may need to be considered in young individuals receiving intermittent pulse methylprednisolone therapy.^{47,48} Finally, current guidance and risk prediction tools have not addressed the implications of pulse intravenous methylprednisolone therapy. The Fracture Risk Assessment Tool, also known as FRAX (University of Sheffield, Sheffield, UK), treats GC exposure dichotomously with dose adjustments designed for daily regimens, making translation to intermittent high-dose pulses challenging. Until further evidence emerges, patients undergoing pulse intravenous methylprednisolone treatment with a high risk of fractures should be managed in the same way as those on long-term oral glucocorticoids. This includes providing calcium and vitamin D supplementation, along with standard lifestyle measures that align with the principles for preventing glucocorticoid-induced osteoporosis.

This analysis has several strengths, including a well-structured research question defined within a framework, and formal risk-of-bias assessment that improved methodological rigour and transparency. Nonetheless, several limitations should be acknowledged. Only 8 studies involving 192 participants were included, which restricts statistical power and limits robustness and generalisability of the pooled findings. Moreover, the mean follow-up of approximately 5.5 months may be insufficient to detect clinically meaningful changes in BMD and is inadequate for assessing fracture outcomes, which generally require longer observation periods. Additionally, there was substantial clinical heterogeneity across the included studies. The study populations varied widely, including individuals with Graves' disease,^{49,50} multiple sclerosis,^{51,52} and rheumatological or other inflammatory conditions,⁵³⁻⁵⁵ all of which may independently influence bone metabolism through differences in inflammatory burden,⁵⁶ mobility,^{57,58} endocrine status,⁵⁹ nutritional factors,⁶⁰ and concomitant therapies.⁶¹ In addition, pulse intravenous methylprednisolone regimens differed across studies in dose, cumulative exposure, frequency, and duration, which may differentially affect skeletal outcomes. This variability

reflects differences in the design and clinical context of the available primary studies and thus represents an inherent limitation of the current evidence base. Furthermore, inconsistent reporting of incident fractures, limited TBS data, and heterogeneity in bone turnover marker assays and sampling time points further constrained interpretation. Although within-person pre-/post-comparisons may reduce some confounding, the small number of studies precluded meaningful subgroup analyses. Accordingly, the findings should be interpreted cautiously, and larger longitudinal studies with longer follow-up are needed.

CONCLUSION

In conclusion, pulse intravenous methylprednisolone therapy does not significantly alter spine or hip BMD over the short-term, but it suppresses bone formation and resorption markers, indicating early effects on bone remodelling. Although pulse regimens may be less detrimental to BMD than chronic daily GC exposure, current evidence is insufficient to conclude that fracture risk is negligible, particularly among high-risk patients or those receiving repeated or high cumulative doses. From a clinical perspective, preservation of short-term BMD should not be equated with skeletal safety; baseline fracture risk assessment remains important, and clinicians should not rely on BMD alone when evaluating patients receiving pulse intravenous methylprednisolone. Future well-designed controlled studies should directly compare pulse and chronic regimens with standardised timing of turnover marker sampling, incorporate bone quality assessments such as TBS at peripheral skeletal sites such as the radius, and include fracture and fall outcomes.

Ethics statement

Not applicable, as no participants were recruited.

Declaration

The authors declare they have no affiliations with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Supplementary materials

Table S1. Search strategy.

Table S2. Risk of Bias (ROBINS-E).

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