**INTRODUCTION**

**Review question / Objective:** The objective of this review is to estimate the efficacy and safety of bisphosphonates analogues, as compared to placebo, usual care, or calcium, in patients with osteoporosis after spinal cord injury.

**Condition being studied:** With the expansion of human activities, the incidence of spinal cord injury has gradually increased, which brings severe physical, psychological, socioeconomic burdens on persons and their families. Osteoporosis is a common complication after spinal cord injury. Osteoclasts become overactive after spinal cord injury, resulting in rapid bone resorption and reduced bone density. Bisphosphonate, an antiresorptive agent, can inhibit osteoclast-mediated bone resorption by binding to the bone surface. Therefore, the effectiveness and safety of bisphosphonates analogs for osteoporosis in spinal cord disease worth being discussed and analyzed.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 July 2020 and was last updated on 03 July 2020 (registration number INPLASY202070013).
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METHODS

Participant or population: Participants were adults and had osteoporosis acquired after spinal cord injury. Animal studies and participants with other systemic diseases were excluded in the review.

Intervention: Participants are treated with bisphosphonate analogs. Studies with a range of doses, route (oral and intravenous) and timing of administration were included.

Comparator: A control group (placebo, usual care, or calcium) was required.

Study designs to be included: Randomized controlled trials with no limits on language, date or form of publication.

Eligibility criteria: 1) Types of participants: study participants were adults and had osteoporosis acquired after SCI. 2) Types of intervention: study treatment with bisphosphonate analogs. 3) Types of comparison: the included studies contained at least two groups, bisphosphonate groups and control groups. The control interventions comprised placebo, usual care, or calcium. 4) Types of outcome evaluated: the study must have reported a measure of BMD by dual-energy X-ray absorptiometry (DEXA). 5) Types of study design: RCTs were regarded as eligible for evaluation of bisphosphonate analogs in osteoporosis individuals with SCI.

Information sources: We searched four databases through PubMed, EMBASE, Cochrane Library and Web of Science from its inception up to 30 April 2020. References and abstracts of previous systematic reviews or meta-analysis were screened for related studies. There were no restrictions on language, publication date, or publication status. We used the following search terms to search all databases: “spinal cord injury,” “paraplegia,” “tetraplegia,” “diphosphonate,” “pamidronate,” “alendronate,” “zoledronate,” “bisphosphonate,” “etidronate,” “osteoporosis,” “bone loss,” “BMD,” “randomized controlled trial,” “placebo,” “controlled clinical trial” and all of its synonyms.

Main outcome(s): 1) The percentage of BMD change at different sites (total hip, distal femur, and lumbar spine) in 12 months from baseline: weighted mean difference for BMD with corresponding 95% confidence interval; 2) Adverse events, including flu-like syndrome (fever), urinary tract infection, and constipation: risk ratio for adverse events.

Additional outcome(s): The secondary outcomes were biochemical markers of bone turnover, such as type 1 procollagen N-terminal peptide (P1NP) and C-terminal telopeptide (CTX). The effect measure was weighted mean difference for P1NP and CTX with corresponding 95% confidence interval.

Quality assessment / Risk of bias analysis: The methodological quality of the RCTs was assessed by Cochrane's Collaboration tool. For each trial, bias was estimated qualitatively as low risk, unclear, or high risk by independent reviewers. The quality indicators included adequacy of random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

Strategy of data synthesis: The primary outcome was the percentage of BMD
change from baseline and standard deviation as measured by DEXA. When it was not available, BMD was calculated between baseline and 12 months divided by BMD at baseline. The SD was estimated from the square root \( [(SD \text{ of mean BMD at baseline})^2 + (SD \text{ of BMD in 12 months})^2 - (SD \text{ of BMD at baseline}) \times (SD \text{ of BMD during in 12 months})] \) divided by BMD at baseline. For studies that reported inter-quartile ranges, we divided it by 1.35 to obtain the SD. Statistical analyses will be conducted using the program Review Manager 5.3 software. We will test for heterogeneity using the statistical tests the Cochran Q and the \( I^2 \). The \( I^2 \) statistic measures the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. Results will be combined in a meta-analysis using the random-effects model as it provides a more conservative effect estimate. The effect measures of choice were risk ratio for dichotomous variables and weighted mean difference for continuous parameters with corresponding 95% confidence interval.

**Subgroup analysis:** Subgroup analyses, specified a priori, will be performed for outcomes if significant heterogeneity is found, in order to explore potential sources of heterogeneity regarding the primary outcome and the consistency of our results. The subgroup analyses are considered the effects of zoledronate on BMD in different sites.

**Sensibility analysis:** Sensitivity analyses were conducted to investigate the robustness of our results to assess whether any of the included studies had a considerable influence on the results. Subgroup analyses, specified a priori, will be performed for outcomes if significant heterogeneity is found, in order to explore potential sources of heterogeneity regarding the primary outcome and the consistency of our results. Sensitivity analyses are prespecified. If there is considerable unexplained heterogeneity for an outcome that couldn't be explained by a subgroup analysis, the studies with the highest risk of bias will be excluded and the analysis repeated to determine if heterogeneity can be reduced. In addition, sensitivity analysis will also be performed to estimate the effect on outcome, from excluding studies that did not report mean, standard deviation or both.

**Country(ies) involved:** China.

**Keywords:** bisphosphonates; osteoporosis; spinal cord injury; BMD.

**Contributions of each author:**
Author 1 - Yao Wu - Author 1 was responsible for designing the review protocol, conducting the search, screening potentially eligible studies, extracting and analyzing data, interpreting results, and writing the report.
Author 2 - Fangyong Wang - The author contributed to the design of the review protocol and provided feedback on the report.
Author 3 - Zhenrong Zhang - The author contributed to screening potentially eligible studies, extracting, and analyzing data.