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The Effect of Bone Marrow Mesenchymal Stem Cell-Derived Extracellular Vesicles on Bone Mineral Density and Microstructure in Osteoporosis: A Systematic Review and Meta-Analysis of Preclinical Studies

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ADMINISTRATIVE INFORMATION

Support - Not application.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202540080

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 April 2025 and was last updated on 23 April 2025.

INTRODUCTION

Review question / Objective This study aims to evaluate the effects of BMSC-EVs on bone density, trabecular microstructure, and biomechanical properties in osteoporotic animal models, providing evidence to support clinical translation and mechanism exploration.

Condition being studied Osteoporosis is a common metabolic bone disease characterized by decreased bone mineral density (BMD) and disrupted bone microstructure, leading to increased bone fragility and elevated fracture risk. In postmenopausal women, its incidence has significantly increased with the aging global population. Due to the high prevalence of osteoporosis and its associated health burden, which affects over 200 million people worldwide, it has become a global public health issue. Osteoporotic fractures, particularly hip and vertebral fractures, are linked to increased mortality and medical costs. It has been reported that osteoporosis leads to more than 8.9 million fractures annually worldwide.

METHODS

Participant or population Osteoporosis animal models of any species, such as rats, mice, etc., with model induction methods including but not limited to ovariectomy (OVX), glucocorticoids (e.g., dexamethasone), and age-related osteoporosis models.

Intervention The intervention group must use BMSC-EVs, with no restrictions on the administration route.

Comparator 1) Preclinical animal studies, which must include control groups (e.g., blank control, placebo control).

Study designs to be included Preclinical animal studies, which must include both intervention and control groups (e.g., blank control, placebo control).

Eligibility criteria
Exclusion criteria:
1) In vitro cell studies, human clinical trials, case reports, reviews, conference abstracts;
2) Studies using non-BMSC-EVs (e.g., EVs derived from adipose stem cells, umbilical stem cells) or EVs combined with other bioactive substances (e.g., BMP-2, VEGF);
3) Non-osteoporosis-related bone disease models (e.g., fracture healing models, bone tumor models);
4) Studies without a control group or using other active drugs as controls;
5) Studies where the full text cannot be accessed or data presentation is incomplete.

Information sources Two independent authors conducted a comprehensive search of relevant literature through four public databases (PubMed, Cochrane Library, Embase, and Web of Science). The search strategy was constructed using both Medical Subject Headings (MeSH) and free-text terms (Emtree Terms), incorporating AND/OR combinations for database querying. A manual review of the reference lists from included studies was also performed to identify potentially relevant research. Discrepancies between the findings of two authors were discussed and resolved with input from a third author.

Main outcome(s) Primary outcomes included BMD, BV/TV, Tb.Th, Tb.N, and Tb.Sp, which reflect bone density and bone strength indicators.

Quality assessment / Risk of bias analysis Two authors will independently assess the quality of the studies using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool, which will evaluate four areas: randomization, allocation concealment, blinding, and outcome reporting. Discrepancies in the results will be resolved through discussions with a third author. For each study, the risk of bias for specific criteria will be recorded as “low”, “unclear” or “high”, and the results will be visualized using Review Manager (RevMan) 5.4.

Strategy of data synthesis A random-effects model will be applied to calculate the standardized mean differences (SMDs) with 95% confidence intervals for all outcomes. Heterogeneity will be quantified using the I^2 statistic and χ^2 test. According to the Cochrane Handbook, the levels of heterogeneity will be classified as follows: 0%–40% considered low, 30%–60% moderate, 50%–90% substantial, and 75%–100% considerable heterogeneity.

Subgroup analysis Pre-specified subgroup analyses (species, engineering methods/targets, administration frequency, and duration) will be performed when $I^2 \geq 50\%$.

Sensitivity analysis Sensitivity analysis will be conducted to assess the stability of the results.

Language restriction Not application.

Country(ies) involved China.

Keywords Extracellular vesicle; Osteoporosis; Bone marrow mesenchymal stem cell; Bone mineral density; Animal models; Meta-analysis.

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