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Bone regeneration based on stem cells derived from bone marrow, iliac crest, or adipose tissue: a scoping review protocol of clinical applications for dental implant site preparation

Regeneración ósea basada en células madre derivadas de médula ósea, cresta ilíaca o tejido adiposo: protocolo de una revisión de alcance de aplicaciones clínicas para la preparación del sitio de implantes dentales

Valentina Veloso-Casado[1], José Tomás Ramos-Rojas[1,*], Francisca Collao-Fierro[1], Karla Ogaz-Muñoz[1], Camilo Montero-Olivares[1]

Abstract

Introduction: Dental implant therapy is widely recognized as the gold standard for tooth replacement; however, bone atrophy frequently necessitates augmentation procedures to ensure implant success. Conventional grafting methods, while effective, are limited by factors such as donor site morbidity, immunogenicity, and inconsistent osteogenic potential. Mesenchymal stem cells (MSCs) have emerged as a promising alternative due to their capacity for osteogenic differentiation and immunomodulation. Despite rapid advancements, clinical translation remains hindered by variability in cell source, processing protocols, and outcome measures. This scoping review aims to systematically map current clinical applications of MSC-based bone regeneration using bone marrow, iliac crest, or adipose tissue specifically for dental implant site preparation. **Methods:** Following the Arksey and O'Malley framework and JBI Manual for Scoping Reviews, this study adheres to PRISMA-ScR guidelines. Eligible studies will include clinical trials and observational studies evaluating stem cell-based augmentation techniques in human patients undergoing maxillary or mandibular bone regeneration for implant placement. A comprehensive literature search across MEDLINE, EBSCO, and CENTRAL will be supplemented by manual reference screening and expert consultation. Two independent reviewers will conduct study selection and data extraction, focusing on patient characteristics, cell source and processing methods, surgical application, outcomes, and safety profiles. **Expected results**: The results will provide a structured synthesis of current evidence, highlight key methodological trends and gaps, and support clinicians and researchers in navigating the complex landscape of regenerative strategies in implant dentistry.

Keywords: maxillary bone atrophy; bone augmentation; dental implants; mesenchymal stem cells; MSCs; scoping reviews.

Resumen

Introducción: La terapia con implantes dentales es ampliamente reconocida como el estándar de oro para el reemplazo dental; sin embargo, la atrofia ósea con frecuencia requiere procedimientos de aumento para asegurar el éxito del implante. Los métodos convencionales de injerto, aunque eficaces, presentan limitaciones como morbilidad en el sitio donante, inmunogenicidad y un potencial osteogénico inconsistente. Las células madre mesenquimales (MSCs) han surgido como una alternativa prometedora debido a su capacidad de diferenciación osteogénica e inmunomodulación. A pesar de los rápidos avances, la traducción clínica sigue viéndose obstaculizada por la variabilidad en la fuente celular, los protocolos de procesamiento y las medidas de resultado. Esta revisión exploratoria tiene como objetivo mapear sistemáticamente las aplicaciones clínicas actuales de la regeneración ósea basada en MSCs obtenidas de médula ósea, cresta ilíaca o tejido adiposo, específicamente para la preparación del sitio de implantes dentales. **Métodos**: Siguiendo el marco metodológico de Arksey y O'Malley y el Manual JBI para revisiones exploratorias, este estudio se adhiere a las directrices PRISMA-ScR. Los estudios elegibles incluirán ensayos clínicos y estudios observacionales que evalúen técnicas de aumento basadas en células madre en pacientes humanos sometidos a regeneración ósea maxilar o mandibular para colocación de implantes. Se realizará una búsqueda exhaustiva de la literatura en MEDLINE, EBSCO y CENTRAL, complementada con una revisión manual de referencias y consulta a expertos. Dos revisores independientes realizarán la selección de estudios y extracción de datos, enfocándose en las características de los pacientes, la fuente y el procesamiento de las células, la aplicación quirúrgica, los resultados y los perfiles de seguridad**. Resultados esperados:** Los resultados proporcionarán una síntesis estructurada de la evidencia actual, destacarán tendencias metodológicas clave y vacíos existentes, y respaldarán a clínicos e investigadores en la navegación del complejo panorama de las estrategias regenerativas en implantología dental.

Palabras clave: atrofia ósea maxilar; aumento óseo; implantes dentales; células madre mesenquimales; MSCs; revisión exploratoria.

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(1) Escuela de Odontología. Facultad de Medicina. Clínica Alemana. Universidad del Desarrollo. Santiago. Chile.
**Autor de correspondencia: jose.ramos@udd.cl*

Introduction

Dental implant therapy has significantly improved the rehabilitation of edentulous patients, emerging as the gold standard for tooth replacement with documented long-term success rates exceeding 95% (Jung *et al*., 2012). Despite these impressive outcomes, progressive maxillary and mandibular atrophy, characterized by diminished alveolar bone volume and density, frequently compromises implant therapy. Clinical evidence indicates that approximately 50% of planned implant sites present with inadequate bone dimensions, necessitating adjunctive procedures such as sinus floor elevation or particulate/onlay grafting to establish a biomechanically sound foundation (Hämmerle *et al*., 2012). Such bone insufficiency stems from multiple etiologies including post-extraction resorption, periodontal disease, trauma, or congenital deficiency, underscoring the magnitude of this challenge in contemporary implantology.

Conventional bone augmentation approaches, including autogenous grafts, allografts, and xenografts, have demonstrated predictable outcomes but harbor significant limitations. Autogenous grafts, while considered the gold standard due to their osteogenic, osteoinductive, and osteoconductive properties, are associated with donor site morbidity and limited availability (Urban *et al*., 2019). Allografts and xenografts offer greater accessibility but lack the osteogenic potential of autogenous bone and raise concerns regarding disease transmission and immunogenicity. These constraints have catalyzed exploration of alternative regenerative strategies, particularly in the rapidly evolving domain of cell-based therapies (Al-Moraissi *et al*., 2020, Asahina *et al*., 2021).

Mesenchymal stem cells (MSCs) have emerged as key players in regenerative medicine since their original isolation from bone marrow by Friedenstein in 1968 and subsequent characterization by Pittenger *et al*. (1999) Click or tap here to enter text., who demonstrated their capacity to differentiate into adipocytes, chondrocytes, and osteocytes. The International Society for Cell & Gene Therapy (ISCT) established standardized criteria for MSCs in 2006, including plastic adherence, expression profile (≥95% expression of CD105, CD73, and CD90; absence of CD45, CD34, CD14/CD11b, CD79α/CD19, and HLA-DR), and trilineage differentiation capacity (Torrents *et al*., 2023). These multipotent cells can now be isolated from diverse sources including bone marrow, iliac crest, adipose tissue, and periosteum (Pittenger *et al*., 2019).

Stem cell-based regenerative approaches represent a paradigm shift in bone augmentation strategies. These advanced biological techniques harness the intrinsic regenerative capacity of MSCs through dual mechanisms: direct differentiation into osteoblasts and indirect paracrine effects via secretion of growth factors and cytokines that stimulate angiogenesis and modulate local immune responses. Their immunomodulatory properties further enhance healing outcomes by creating a favorable microenvironment for tissue regeneration (Pittenger *et al*., 2019).

The therapeutic application of stem cells in dental implantology has evolved considerably, encompassing various methodologies ranging from minimally manipulated tissue concentrates to extensively expanded cell populations, frequently combined with scaffolds and growth factors. Yet significant challenges persist in clinical translation, notably pronounced heterogeneity between donors, tissues, and culture conditions, which substantially impacts surface phenotype, proliferation capacity, lineage commitment, and immunomodulatory function. These variables necessitate rigorous source selection, standardized expansion protocols, and comprehensive safety validation (Torrents *et al*., 2023, Li *et al*., 2024, Peng *et al*., 2024) .

Single-cell sequencing (SCS) has emerged as a transformative analytical tool in this context. By enabling high-resolution profiling of individual MSCs, SCS reveals intra-population heterogeneity, refines phenotypic markers, and maps osteogenic and immunoregulatory pathways relevant to bone regeneration (Torrents *et al*., 2023, Daneshian *et al*., 2024). Collectively, advances in MSC biology, stem cell-based augmentation strategies, and SCS analytics form a synergistic framework poised to overcome current limitations in oral bone regeneration and optimize clinical outcomes in implant dentistry (Pittenger *et al*., 2019, Shanbhag *et al*., 2019, Torrents *et al*., 2023, Daneshian *et al*., 2024, Li *et al*., 2024, Peng *et al*., 2024).

While previous systematic reviews (Shanbhag *et al*., 2019, Al-Moraissi *et al*., 2020) have addressed specific aspects of stem cell therapy in oral bone regeneration (Shanbhag *et al*., 2019), their scope and approaches differ from the present protocol. Shanbhag *et al*. (2019) evaluated a wide range of clinical indicators (sinus lift, ridge augmentation, alveolar preservation, cleft repair, among others) and cell sources from minimally manipulated tissue fraction to expanded mesenchymal stem cell and committed bone cells, finding potential benefits of cell therapy compared to graft with biomaterials or autogenous bone, but with heterogeneous evidence and limited methodological standardization. Al-Moraissi *et al*. (2020) restricted their analysis to randomized clinical trials comparing MSC graft versus conventional graft in atrophic maxilla regeneration, concluding that, although bone formation at 6 months was significantly greater with MSCs, there were no consistent differences in other histomorphometric or clinical outcomes. The breadth and heterogeneity of available evidence suggests the need for a more comprehensive analytical approach. A scoping review methodology is particularly appropriate given the emerging nature of this field, the diversity of intervention types and outcome measures, and the critical need to map the

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current landscape of clinical applications to identify knowledge gaps and guide future research directions.

Objective

Previous literature shows that, although stem cell-based therapies show significant potential for orofacial bone regeneration, significant gaps remain: heterogeneity in cell sources and processing methods, lack of standardization in clinical protocols, diversity of indications and defect treated and limited long term follow up. This scoping review aims to systematically map and analyze the current landscape of stem cell-based bone regeneration techniques using bone marrow, iliac crest, or adipose tissue for dental implant site preparation. Specifically, we seek to:

1. Identify and categorize the various protocols and methodologies employed in clinical applications
2. Examine reported outcomes and success parameters across different techniques
3. Evaluate safety considerations and complications associated with different cell sources
4. Highlight gaps in current knowledge and potential directions for future research

Through this comprehensive analysis, we aim to provide clinicians and researchers with an evidence-based framework to guide decision-making and future investigations in this rapidly evolving field.

Methods

This scoping review will adhere to the methodological framework proposed by Arksey and O'Malley and further refined in the JBI Manual for Scoping Reviews (Arksey *et al*., 2005, Peters *et al*., 2020). The manuscript will comply with the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews (PRISMA-ScR) to ensure transparent and comprehensive reporting (Tricco *et al*., 2018). This protocol was registred and is available in OSF Registries (Ramos-rojas *et al*., 2025), and any methodological deviations during the review process will be explicitly documented in the final publication.

Eligibility Criteria

Population

The review will include studies assessing individuals undergoing maxillary or mandibular surgery requiring bone regeneration prior to dental implant placement. We will include patients regardless of age, gender, or underlying systemic conditions that might affect bone metabolism or healing (including diabetes mellitus, osteopenia, osteoporosis, history of bisphosphonate therapy, and tobacco use). This inclusive approach will enable a comprehensive understanding of stem cell applications across diverse patient populations with varying regenerative challenges.

Concept

Our primary focus is the application of stem cells harvested from three specific sources:

- Maxillary or mandibular bone marrow
- Iliac crest
- Adipose tissue

We will examine the protocols for cell harvesting, processing, and application, including concentration techniques, expansion methodologies, and combination with various scaffolding materials or growth factors. Studies will be evaluated regarding their reported effectiveness in bone regeneration (both quantitatively and qualitatively), implant integration outcomes, and associated safety profiles.

Studies investigating cells derived from other sources will be excluded, specifically:

- Dental pulp stem cells
- Gingival tissue-derived stem cells
- Periodontal ligament stem cells
- Periosteal stem cells
- Pluripotent cells (e.g., umbilical cord-derived)

Context

The review will encompass clinical applications in surgical settings where maxillofacial procedures are performed for dental implant site preparation. This includes hospital-based surgical facilities, specialized dental clinics, and maxillofacial surgery centers. Both academic and private practice settings will be considered to capture the full spectrum of clinical implementation.

Types of studies

We will include original research publications providing primary clinical data on stem cell-based bone regeneration specifically for dental implant site preparation. Eligible study designs include:

- Randomized controlled trials
- Non-randomized controlled trials
- Comparative observational studies

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Exclusion criteria encompass:

- Preclinical studies (animal or in vitro research)
- Review articles without original data
- Conference abstracts without full-text publication
- Studies focused on applications other than dental implant site preparation

Literature Search Strategy

A comprehensive, systematic search will be conducted to identify all relevant studies without language or date restrictions. The search was performed in September 2024, with additional updates prior to manuscript completion to incorporate newly published literature.

Information Sources

The following electronic databases will be systematically searched:

- MEDLINE (via PubMed)
- Dentistry & oral sciences source (via EBSCO)
- Cochrane Central Register of Controlled Trials (CENTRAL)

Search Strategy

The search strategy was developed through an iterative process involving preliminary literature review and consultation with information specialists and subject matter experts. It combines terms related to "stem cells," "bone regeneration," and "dental implant surgery" using appropriate Boolean operators and database-specific syntax. Controlled vocabulary terms (e.g., MeSH) were not used in this search strategy The comprehensive search strategy for MEDLINE is provided in Table 1 and will be adapted for each database while maintaining conceptual consistency.

Table 1: Line by line search strategy

Term	#	Boolean strategy
Mesenchymal cell	**1**	(MSC OR MSCs OR HMSC* OR BMSC* OR "bone marrow" OR stemstromal* OR stromalstem* OR nestcell* OR ((mesenchymal* OR multipotent*) AND stem* AND cell*))
Maxillary bone	**2**	((dental* OR alveol* OR maxilla* OR jaw OR mandibul*) AND (bone* OR osseous*))
Osseointegration	**3**	(osteogenesis OR regenerat* OR osseointegrat* OR osteosynthesis* OR neoformat* OR "oral implant" OR "oral implants")
Search	**4**	#1 AND #2 AND #3

Note: Controlled vocabulary terms (e.g., MeSH) were not used in this search strategy

Additional literature will be identified through:

- Manual searching of reference lists from included studies
- Consultation with experts in the field

Study selection process

The selection of eligible studies will follow a rigorous, two-stage screening process adhering to established methodological guidelines for evidence synthesis:

1. Initial screening: Two independent reviewers will screen all titles and abstracts identified through the comprehensive search strategy. Each citation will be classified as "include" or "exclude," based on predetermined eligibility criteria.

2. Full-Text Assessment: All studies classified as "include" during initial screening will undergo full-text evaluation. The same two independent reviewers will systematically assess each article against the complete set of eligibility criteria and will document specific reasons for exclusion.

3. Calibration process: prior to formal screening, reviewers will undergo calibration exercises using a random sample of 200 citations to establish consistency in the application of eligibility criteria.

4. Conflict Resolution: Disagreements at any stage will be resolved through consensus discussion between the two reviewers. In cases where consensus cannot be achieved, a third senior reviewer with expertise in regenerative dentistry will adjudicate.

The entire selection process will be documented and reported in a PRISMA flow diagram illustrating the number of studies identified, screened, assessed for eligibility, and included in the final review, with specific reasons for exclusions at the full-text stage.

Data extraction

Data from included studies will be systematically extracted using a standardized, pre-piloted data collection form developed specifically for this review. Two independent reviewers (GH and IJ) will perform extraction. Disagreements will be resolved through consensus. The data extraction form will capture the following elements:

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Study Characteristics

- Bibliographic information (authors, title, journal, publication year)
- Study design and methodology
- Geographic location and clinical setting
- Eligibility criteria
- Funding source and potential conflicts of interest

Participant Characteristics

- Demographic profile (age, sex, relevant medical history)
- Indication for bone augmentation
- Anatomical site requiring regeneration
- Bone defect classification/dimensions

Intervention Details

- Cell source (maxillary/mandibular bone marrow, iliac crest, or adipose tissue)
- Harvesting protocol (technique, site, anesthesia, volume collected)
- Processing methodology (concentration, isolation, expansion)
- Cell characterization (if performed)
- Cell quantity/concentration applied
- Carrier/scaffold materials used
- Addition of growth factors or other bioactive agents
- Surgical technique for application

Outcome Measures

- Increase in bone height
- Final-to-initial graft volume ratio
- Bone-core volume fraction
- Bone-core mineral density

Data synthesis

A narrative synthesis approach will be employed following established methodological frameworks:

1. **Developing a preliminary synthesis:** the extracted data will be organized into logical categories based on cell source, processing technique, application method, and defect type. Tabular summaries will present key characteristics and findings of included studies, with accompanying text highlighting patterns, similarities, and differences across studies.

2. **Exploring relationships within and between studies:** we will systematically analyze variations in outcomes according to:

- Cell source and processing methodology
- Patient characteristics and defect types
- Surgical techniques and adjunctive interventions
- Study design and methodological quality

3. **Visual representation:** where appropriate, diagrams and graphs will be used to illustrate relationships between study characteristics and outcomes.

Expected contribution to knowledge

This scoping review will provide the first comprehensive mapping of clinical applications utilizing mesenchymal stem cells from bone marrow, iliac crest, and adipose tissue specifically for dental implant site preparation. By systematically synthesizing heterogeneous methodologies, outcomes, and implementation considerations across diverse clinical contexts, this review will address critical knowledge gaps that currently impede evidence-based decision-making in regenerative implantology. For clinicians, this review will offer practical insights into the relative advantages, limitations, and implementation requirements of various stem cell-based approaches, potentially accelerating the translation of these promising technologies into routine clinical practice. Furthermore, the findings could be integrated into standard surgical protocols that optimize the predictability of outcomes and minimize complications, serving as reference in individualized clinical decision making. In the field of research, detailed evidence mapping will allow us to prioritize underexplored areas, such as uniformity in cell procurement and expansion protocols, comparison of long-term results across different sources, and analysis of combinations biomaterials or bioactive molecules. Thus, for example, if it is found that the use of bone marrow concentrates has strong support for horizontal ridge augmentation, but that the use of adipose tissue in sinus

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lifts lacks robust evidence, these data could guide future clinical trials aimed at filling this gap. In this way, the study will not only clarify the current landscape but also facilitate the transfer of stem cell-based strategies toward safer and more predictable protocols, accelerating their integration into evidence-based implantology. Ultimately, this work aims to advance the field toward more predictable, less invasive, and biologically sophisticated solutions for the widespread challenge of inadequate bone volume in implant dentistry.

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Contributions declared by the authors

VVC: conceptualization, methodology, research, drafting of the original manuscript, manuscript review, validation, and supervision.

JRR: conceptualization, methodology, research, drafting of the original manuscript, manuscript review, validation, and supervision.

FCF: conceptualization, research, drafting of the original manuscript, and manuscript review.

KOM: research, drafting of the original manuscript, and manuscript review.

CMO: research, drafting of the original manuscript, and manuscript review.

Conflict of interest declaration

The authors of this work declare no conflict of interest.

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