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The synergistic role of combined Guided Bone Regeneration (GBR) and secretome in facilitating the reparative mechanisms of bone defect healing

Moza Zikra Loveisca [1], Putri Calista Jeconia Rahardjo [1], Aqsa Sjuhada Oki [2] and Pratiwi Soesilawati [2,*]

[1] *Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Department of Oral Biology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.*

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Abstract

Background: Bone defects are the main cause of aesthetic and functional impairments that negatively impact patient's quality of life. Guided Bone Regeneration (GBR) is a bone grafting procedure that utilizes a covering membrane to block soft tissue invasion. In bone healing, Mesenchymal Stem Cells (MSCs) stimulate endogenous cells to increase by releasing various growth factors and cytokines, collectively known as the secretome. The secretome consists of bioactive factors produced by MSCs during the culture process. The combination of GBR with the secretome is expected to function not only as a biomaterial for bone defect healing but also as a growth factor that accelerates stem cell differentiation.

Objectives: This study aims to explore the benefits of combining GBR with the secretome for bone defect healing based on findings from previous research, providing a foundation for further studies in the future.

Methods and Result: This research was carried out by searching for several kind of literature relevant to the topic discussed as references. This type of research is a literature review design. After doing some research, GBR combined with secretome has been proven to have benefits in the bone regeneration process in both in vitro and in vivo studies. Research shows that secretome effectively supports bioactivity in bone regeneration. There are studies in which secretome combined with biomaterials has been identified to produce hundreds of proteins. The secretome was found to contain factors related to angiogenesis and osteogenesis, contributing to enhanced bone healing.

Conclusion: This study reveals that the combination of GBR with secretome has been shown to effectively support bone regeneration, as demonstrated in both in vitro and in vivo studies.

Keywords: Bone Defect; Guided Bone Regeneration; Biomaterials; Secretome; Dentistry

1. Introduction

Bone tissue regeneration or bone regeneration is a challenge in medicine and dentistry. Bone defects are the main cause of aesthetic and functional impairments that negatively impact a patient's quality of life [1]. Craniofacial bone defects occur due to several causes, such as trauma, infections, congenital malformations, and tumor resection [2]. The goal of bone repair is to restore the affected area to its original cellular composition, structure, and function. Bone healing in cases of comorbidities carries a higher risk of failure. In certain conditions, significant bone loss can obstruct the healing process [3].

Guided Bone Regeneration (GBR) is a bone grafting procedure that utilizes a covering membrane to block soft tissue invasion [4]. GBR can also lead to an increase in alveolar bone with stable and predictable outcomes. The basic guideline

* Corresponding author: Pratiwi Soesilawati

of GBR includes using a mechanical boundary to disconnect the surgical location from epithelial and connective tissue cells, permitting the expansion of osteogenic cells and bone formation [5].

In the bone healing process, Mesenchymal Stem Cells (MSCs) stimulate endogenous cells to increase by releasing various growth factors and cytokines, collectively known as the secretome. The secretome consists of bioactive factors produced by MSCs during the culture process. It offers several advantages over MSCs. The secretome has better immune compatibility and carries a lower risk of tumorigenicity, embolism formation, or infection transmission. Studies have demonstrated that the secretome can accelerate and enhance bone healing, even in large bone defects, as evidenced by trials conducted on rats [6].

The combination of GBR with the secretome is expected to function not only as a biomaterial for bone defect healing but also as a growth factor that accelerates stem cell differentiation. This study aims to explore the benefits of combining GBR with the secretome for bone defect healing based on findings from previous research, providing a foundation for further studies in the future.

2. Material and methods

This research was carried out by searching for several kind of literature relevant to the topic discussed as references. This type of research is a literature review design. The research was done in October 2024.

2.1. Research Strategy

Literature and data were sourced from journals or articles by utilizing keywords and Boolean Operators (AND, OR, AND NOT). The search was restricted to articles published within the past five years, specifically between 2019 and 2024. The keywords used in this literature review are “bone defect”, “guided bone regeneration”, “biomaterials”, “secretome”, “dentistry” which aims to specify the search and make it easier to determine the literature used.

2.2. Inclusion and Exclusion Criteria

In this study, the inclusion criteria consist of literature that available in full text, open access, published in English, and based on original research designs within the past five years. The exclusion criteria involve literature in languages other than English, literature reviews or systematic reviews, sources that are not available in full text or open access, and articles published more than five years ago.

2.3. Synthetic Data

The literature was collected through full-text review and extraction, including details such as the research title, author, year of publication, objectives, methods, and conclusions. The data were then analyzed to draw conclusions and recommendations that address the research questions and objectives. Literature was selected through keyword searches and filtered based on the title and abstract. The full text of each source was reviewed to assess its relevance according to the inclusion and exclusion criteria set for this study.

3. Results and discussion

GBR combined with secretome has been proven to have benefits in the bone regeneration or bone healing process in both in vitro and in vivo studies. Research shows that secretome effectively supports bioactivity in bone regeneration [7]. The combined secretome can be directly applied to the defect area, promoting cell adhesion, proliferation, differentiation, ECM formation, and the diffusion of biomolecules that aid tissue recovery. Biomaterials combined with secretomes can also recruit endogenous stem cells and endothelial cells. Additionally, the combination of biomaterials with secretome has been found to reduce inflammation [8].

There are studies in which secretome combined with biomaterials has been identified to produce hundreds of proteins. The secretome was found to contain variables related to angiogenesis and osteogenesis, contributing to enhanced bone healing. In spite of the fact that information on the biological effects of the secretome from osteogenically initiated populaces in vivo is still limited, researchers have verified increased expression of biomolecules that promote osteogenesis, such as collagen alpha-1(I) chain, AE binding protein 1, and stanniocalcin-1, as well as molecules related to bone resorption, like fibrillin-2 and cathepsin K [9]. The secretome contains various growth factors and inflammatory agents like TGF-β, IGF-1, VEGF, and HGF, which effectively work in the bone healing process. Secretome offers a better alternative to BMP-2 for supporting bone healing without severe inflammatory side effects [10]. Moreover, the secretome is wealthy in different proteins that invigorate safe framework particles, such as prosaposin, annexin A1,

alpha-2-macroglobulin, plasminogen activator inhibitor 2, and others. The proteins within the PMSC secretome contribute to natural forms related to osteogenesis, cell-ECM interaction, chondrogenesis, cytoskeleton, separation, ECM arrangement, safe reaction, digestion system, movement, neurogenesis, signaling, transport, wound recuperating, and angiogenesis [11].

Table 1 Summary of study results

No.	Author Name, Year	Objective	Research Result
1.	Shanbhag *et al*., 2023	The main objective of this study is to compare the efficacy of the conditioned media from mesenchymal stem cell secretome (MSC-CM) with leukocyte- and platelet-rich fibrin (PRF-CM) in enhancing GBR when used in conjunction with a collagen barrier membrane. This study aims to evaluate the potential of MSC-CM as a new strategy for delivering growth factors in tissue regeneration, particularly in critical-sized calvarial defects in rats.	This study found that both of MSC-CM and PRF-CM contain several bone-related proteins. MSC-CM, in conjunction with a collagen membrane, could be a promising approach to enhance outcomes GBR procedures.
2.	Gugliandolo *et al*., 2021	The main goal of this review is to assess the potential application of mesenchymal stem cell (MSC) secretome combined with various biomaterials for bone regeneration, particularly in the field of dentistry. This approach aims to harness the beneficial factors released by MSCs without the need for the incorporation of live cells.	Exploration of the MSC secretome has revealed promising results in experimental models for bone tissue regeneration. This suggests that the secretome can serve as a viable alternative to direct MSC application, potentially simplifying treatment protocols while achieving effective regeneration. This review also notes that various types of biomaterials, including natural and synthetic polymers, can be used in combination with MSCs or their secretome to optimize the bone regenerative process.
3.	Pranskunas *et al*., 2021	The main objective of this research is to assess the function of the secretome from mesenchymal stem cells (MSCs) derived from the periosteum, both in basal and osteogenically induced conditions, in enhancing bone healing in a critical-size calvarial defect model in rabbits. This study aims to analyze the biological response to the combination of xenograft secretome and bioceramics through clinical, histological, histomorphometric, and microtomographic analyses.	The results indicate that when bioceramic xenografts combined with secretome, its significantly enhance the process of new bone formation, with osteogenically induced secretome (OsteoSec) showing the highest level of bone tissue formation compared to the control conditions. The osteogenically induced secretome demonstrated an increased diversity of proteins associated with osteogenesis, which may contribute to its enhanced functionality in promoting bone healing.
4.	Dilogo *et al*., 2021	This study investigates the effectiveness of secretome, particularly when combined with biomaterials, in treating critical-sized bone defects (CSD) in rat models. The key findings and implications regarding the use of secretomes in combination with biomaterials are as follows.	The application of secretome showed a significant improvement in bone healing compared to traditional methods. The secretome group demonstrated superior results in all measured parameters, highlighting its potential as a powerful agent for bone regeneration. The combination of secretome with biomaterials showed promising results in enhancing bone healing in critical-sized defects.

5.	Pranskunas *et al*., 2021	This study aims to conduct a detailed proteomic analysis of the secretome of mesenchymal stem cells (PMSC) derived from the periosteum to identify the protein composition and potential biological functions that may aid bone regeneration. Additionally, it seeks to explore the synergistic effects of combining PMSC secretome with biomaterials, to enhance the overall effectiveness of bone regeneration strategies.	The analysis reveals that bioactive molecules in the PMSC secretome can stimulate osteogenic differentiation and promote angiogenesis, both of which are crucial for effective bone healing and regeneration. The findings also suggest that combining the PMSC secretome with biomaterials could provide a new strategy for regenerative treatment, particularly in addressing bone defects and injuries.

4. Conclusion

The combination of GBR with secretome has been shown to effectively support bone regeneration, as demonstrated in both in vitro and in vivo studies. Secretome aids in cell attachment, proliferation, differentiation, and ECM formation, while also recruiting endogenous stem cells and endothelial cells. Additionally, secretome helps reduce inflammation. Studies indicate that secretomes contain factors that support osteogenesis and angiogenesis, as well as molecules that stimulate the immune system. In conclusion, the combination of GBR with secretomes holds great potential as a therapy for bone healing.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest declared by authors in this study.

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