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MODERN METHODOLOGY FOR IMPROVING BONE TISSUE REGENERATION IN DENTISTRY

Dzupa P. , Stoj O. , Chelpanova I.V. ✉ Modern methodology for improving bone tissue regeneration in dentistry.
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ABSTRACT. The aim of this study is to investigate modern techniques for improving bone tissue regeneration. To achieve this goal, we reviewed sources from domestic and international scientific medical literature. **Results**. Maxillary bone loss can result from chronic dental diseases, trauma, or tumor resection. Bone resorption, most often caused by infection or inflammation, can lead to discomfort, deformity, and complications during dental implant placement. While implants can restore oral function, many patients lack sufficient bone volume for their placement. Therefore, several techniques are used to address this problem. Guided bone regeneration promotes the growth of new bone in damaged areas of the jaw. Despite its effectiveness, this method can be time-consuming to achieve sufficient bone volume. The PASS principle (Primary closure, Angiogenesis, Space maintenance, and Stability) is considered fundamental for successful guided bone regeneration. Guided tissue regeneration utilizes two main types of barrier membranes: resorbable and non-resorbable membranes. Recent advancements in titanium mesh technology include individually pre-bent meshes tailored to specific defect geometries. Distraction osteogenesis offers significant advantages over traditional bone grafting techniques, eliminating the need for donor bone and avoiding complications associated with donor site morbidity. Despite its advantages, distraction osteogenesis is associated with certain challenges. Platelet-rich plasma (PRP) is gaining popularity in dentistry due to its ability to accelerate healing and promote tissue regeneration. PRP's capacity to release high concentrations of growth factors makes it an effective tool in stimulating stem cell activity, promoting tissue healing, and enhancing bone and soft tissue regeneration. Stem cell therapy holds significant promise for the regeneration of teeth, bone tissue, and periodontal structures, making it a key area in modern dental tissue engineering. **Conclusion.** A review of the scientific literature reveals some inconsistencies regarding the effectiveness of the aforementioned guided bone regeneration techniques and an understanding of the situational variations in bone tissue reconstruction across different clinical scenarios. Modern techniques for improving bone tissue regeneration aim to create optimal conditions for natural bone regeneration through the use of biocompatible materials, guided surgical techniques, biologically active factors, and individualized approaches based on a deep understanding of bone tissue histoarchitecture. A significant number of scientific works, both experimental and clinical, are dedicated to the study of osteoregeneration; however, under current conditions, a correct understanding of the sequence and timeframes of osteogenic regenerative processes is of particular importance. Therefore, the pursuit of further research into modern techniques and their associated dynamics of histoarchitectural remodeling during bone defect healing is justified. This will allow for the development of personalized osteoregeneration strategies tailored to the needs of the individual patient.

Key words: bone tissue, osteoregeneration, remodeling.

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Jawbone loss can be a result of chronic dental diseases, as well as a result of trauma or tumor resection. Bone resorption, which in most cases is caused by infection or inflammation, can lead to discomfort, deformity and complications when placing dental implants. Although the latter can restore oral function, many patients lack sufficient CT volume for their placement. Therefore, a number of methods are used to solve this problem [1].

Guided bone regeneration promotes the growth of new bone in damaged areas of the jaw. This technique is primarily aimed at the regeneration of bone defects around dental implants and is used together with bone grafts. It consists in creating a space devoid of cells of epithelial and connective tissue. At the same time, the cells of the periodontal ligament gradually populate the surface of the root, and the CT cells begin to sprout into the damaged area [2]. Despite its effectiveness, this method can take a long time to achieve a sufficient volume of bone tissue.

The need for controlled bone regeneration is largely determined by the size of the bone defect. If all the bone walls are intact after the implant is placed, this technique may not be necessary, as the natural healing of the bone is efficient. However, as the degree of CT loss increases, so does the need for regeneration. In particular, large defects or significant bone wall loss are clear indications for the procedure [3].

The PASS principle (P:primary closure, A: angiogenesis, S: space maintenance, S:stability) is considered fundamental for successful guided bone regeneration (GBR) [4]. Ensuring initial wound closure helps prevent complications, such as infection, that could compromise the procedure. Angiogenesis, or the development of a powerful blood supply in the transplant area, promotes bone healing. Maintaining the necessary space for bone regeneration, as well as stabilization of the graft and membrane, are crucial for proper bone growth and integration with the implant.

There is some controversy regarding the necessity and benefit of barrier membranes. While some studies suggest that the use of a membrane has no significant effect on clinical outcomes, others emphasize its advantages in providing minimal soft tissue intervention and preserving space for CT regeneration [5, 6]. The periosteum itself has been proven to act as a functional barrier with osteogenic properties, and some studies support its use as an alternative to synthetic membranes [5].

In controlled cell regeneration, two main types of barrier membranes are used: resorbable membranes and non-resorbable membranes. Resorbable membranes include collagen membranes and synthetic alternatives [7–9]. The advantage of resorbable membranes is a reduced risk of infection after wound healing, but the lower rigidity of such membranes makes them less suitable for vertical bone augmentation. However, they are often used in combination with graft materials to preserve space during bone regeneration. Nonabsorbable membranes such as titanium mesh and polytetrafluoroethylene provide excellent space preservation and predictable bone formation, making them suitable for cases requiring vertical or horizontal bone augmentation [10–12].

Nonabsorbable membranes such as titanium mesh and polytetrafluoroethylene provide excellent space preservation and predictable bone formation, making them suitable for cases requiring vertical or horizontal bone augmentation [10–12]. However, they are more prone to infection if the wound dehiscence occurs. Titanium mesh, in particular, is very effective in stabilizing bone grafts and resisting infection, making it a popular choice for large bone defects [13]. Recent advances in titanium mesh technology include individual pre-bent meshes that correspond to specific defect shapes [10, 14, 15].

Research in the field of controlled cell regeneration is moving towards more complex tissue engineering solutions. Functional barrier membranes including bone substitutes, growth factors, and stem cells are being developed to improve CT regeneration [3]. These innovations promise to create more predictable and effective outcomes in complex implant cases. Guided cellular regeneration is a valuable technique in implantology, especially for the treatment of large bone defects. Its success depends on the adherence to key principles such as the concept of PASS and the selection of an appropriate membrane based on the clinical scenario.

Distraction osteogenesis is a regenerative bone engineering technology used to reconstruct or lengthen bones. It uses the body's innate ability to regenerate bone tissue, which makes it unique, as it provides a shorter operation time, less blood loss, no need for bone grafts, and simultaneous distraction of bone, soft tissues, and nerves [16]. The process of distraction osteogenesis begins with an osteotomy of the area that needs lengthening. After a short latent period, a distractor is applied, which gradually stretches the ends of the bone, stimulating the growth of new bone in the gap. This phase is known as the distraction period, when the bone regenerates through natural processes. After that, during the consolidation period, the newly formed bone is allowed to mature, that is, to mineralize and remodel to achieve stability and strength [17, 18].

Distraction osteogenesis has significant advantages over traditional bone grafting techniques as it eliminates the need for donor bone, preventing complications such as donor site morbidity. This technique is widely used for the treatment of various diseases, ranging from limb lengthening and craniofacial reconstruction to alveolar ridge augmentation in dentistry [18].

Distraction osteogenesis is used in many medical disciplines, including orthopedics, maxillofacial surgery, and plastic surgery. It is often used to treat congenital or acquired diseases of the limbs, bone defects due to tumors, injuries or infections, as well as craniofacial deformities [19–21]. In severe cases of congenital malformations, where a bilateral LV defect contributes to obstructive sleep apnea, distraction osteogenesis can improve airway function, potentially avoiding the need for tracheostomy in infants [22, 23]. This technique showed promise in improving the quality of life of patients with micrognathia (small jaw) by expanding the LV and improving breathing and jaw function [24].

Distraction devices can be both internal and external, and each of them has its own advantages and disadvantages [25]. Internal distraction devices are more predictable, accurate and comfortable for patients. They are invisible from the outside and allow full use of the jaw during treatment, minimizing the risk of damage to the device. External distraction devices are more bulky and can cause discomfort, especially in young patients. They are easily damaged, which can interrupt the treatment. In addition, these devices often leave visible scars on the patient's cheek. Other advances include intraoral curvilinear distraction devices that allow more precise control of the direction of bone regeneration, making them potentially better for treatment [26].

Distraction osteogenesis is also used in dentistry to reconstruct the alveolar ridge. After all, injuries, periodontal disease or removal of large jaw cysts or tumors can cause CT deficiency. Alveolar ridge defects prevent proper placement of dental implants, requiring CT augmentation for successful implantation. Alveolar distraction osteogenesis not only increases the height of the bone, but also contributes to the simultaneous expansion of the surrounding soft tissues, ensuring better integration of the newly formed bone. This technique has a lower risk of resorption and recurrence, contributing to a more stable long-term result compared to autogenous bone plastic [27, 28]

Despite its advantages, the technique of distraction osteogenesis is associated with certain problems. The long period of consolidation required for bone maturation increases the risk of complications such as infection, nonunion, and patient discomfort [17]. These complications, along with psychological and economic ones, are a burden for long-term treatment and limit the wide application of distraction osteogenesis [29]. To partially minimize these problems, it is possible to combine distraction osteogenesis with bone tissue engineering technologies such as exogenous scaffolds, stem cells, and growth factors. The role of immune regulation in CT regeneration is also being studied in order to develop auxiliary treatment methods that could optimize the process of distraction osteogenesis and shorten the treatment time [18].

Platelet-enriched plasma is often used to accelerate healing and regeneration of tissues, especially in procedures such as regeneration of the lower and upper jaws, treatment of periodontal defects, installation of implants and other surgical interventions in the oral cavity [30]. It is obtained from the patient's own blood, which is processed to concentrate platelets and other biologically active substances that contribute to tissue regeneration. Plasma can be used both alone and in combination with autogenous bone, inorganic bone minerals and bone substitutes [31] It is believed that growth factors, in particular, transforming growth factor beta, platelet-derived growth factor, platelet-derived epidermal growth factor, platelet-derived angiogenesis factor, insulin-like growth factor, and others, which are present in platelet-rich plasma, promote bone healing [32, 33]. In addition, blood proteins such as fibrin, fibronectin, and vitronectin improve osteoconduction and facilitate bone formation in various ways [34, 35].

Platelet-rich plasma is becoming increasingly popular in dentistry due to its ability to accelerate healing and promote tissue regeneration. This method was used in regenerative endodontics, periodontology and maxillofacial surgery [36, 37]. The ability of platelet-rich plasma to release a high concentration of growth factors makes it an effective tool in stimulating stem cell activity, promoting tissue healing, and enhancing bone and soft tissue regeneration [38, 39].

In endodontics, platelet-rich plasma has shown itself as a promising tool for the regeneration of damaged or necrotic tissues of the pulp-dentin complex, such as dentin, pulp, and root structures [39]. After proper disinfection, platelet-rich plasma creates a favorable environment that stimulates the development and differentiation of dental stem cells, which leads to tissue regeneration. It serves as an environment to support the growth of stem cells in the root canal [40]. This is a key factor in the treatment of immature teeth with compromised structural integrity, such as necrotic immature teeth, because it promotes further root development [41, 42]. Platelet-enriched plasma has been shown to be a viable framework for endodontic regeneration, although the results of treatment do not differ significantly from traditional methods of creating a framework from blood clots [43, 44]. Despite the promising results, the lack of a standardized treatment protocol using platelet-rich plasma and the need for long-term clinical studies remain relevant in regenerative endodontics [45].

Platelet-enriched plasma is also used in the treatment of periodontal defects. This allows to reduce bleeding, accelerates healing and improves the results of surgical interventions [46, 47]. In addition, platelet-rich plasma is widely used in maxillofacial surgery for procedures such as tooth extraction, CT surgery, and implant placement. A high concentration of growth factors accelerates the healing of surgical sites, reduces the risk of postoperative complications, and improves CT regeneration around implants [35, 48]. This is particularly useful for reducing healing time and promoting tissue regeneration in areas where bone grafting or other surgical interventions are required [49].

The use of platelet-rich plasma has many advantages in dental procedures. It effectively accelerates the healing of both soft and hard tissues. As an autologous product, it reduces the need for expensive biomaterials, lowering the overall cost of regenerative therapy. Platelet-rich plasma has good anti-inflammatory properties, which helps minimize postoperative complications and pain. In addition, the autologous nature of the material excludes the risk of immune reactions or disease transmission [45]. However, despite its promising field of application, the use of platelet-rich plasma in dentistry faces certain problems, in particular, the lack of standardization of protocols for the preparation and application of the material, which leads to inconsistent clinical results [50].

Stem cell therapy has become a promising direction in dentistry, especially for the regeneration of dental tissues and restoration of structural defects. The regenerative capacity of the dental pulp, due to the presence of stem cells in it, has increased the interest of researchers in studying its therapeutic potential. Stem cells have significant prospects for the regeneration of teeth, CT and periodontal structures, which makes them a key area in modern dental tissue engineering [51].

Mesenchymal stem cells derived from bone marrow are used in clinical trials to effectively treat bone defects. However, bone marrow harvesting is a rather painful and complex procedure for the donor, which can make it difficult for general practitioners to use it. In addition, mesenchymal stem cells are a heterogeneous group of cells, and their ability to proliferate and differentiate depends on factors such as age, gender of the patient, or systemic diseases such as diabetes or hypertension [52]. Therefore, stem cell populations that have been found in various parts of the tooth, including the pulp, periodontal ligament and dental papilla, are quite promising for therapy.

About 20 years ago, stem cells from extracted human milk teeth were described [53]. They are highly efficient and can differentiate into various cell types, including osteoblasts, odontoblasts, adipocytes, and nerve cells. These cells have shown great potential for maxillofacial bone regeneration and can be used in the treatment of neurological and cardiovascular diseases [53, 54].

Stem cells of the apical papilla originate from the surface cells of the dental papilla during the histogenesis of the tooth tissues. These cells have demonstrated the ability to differentiate into odontoblast-like cells, contributing to root formation and dentin regeneration [55, 56].

Stem cells of the periodontal ligament participate in the regeneration of periodontal tissues, which makes them important for the treatment of periodontal defects and improvement of the general health of the oral cavity [57].

Stem cell therapy in dentistry has enormous potential. Current research is aimed at harnessing the regenerative capabilities of dental and non-dental stem cells for a wide range of applications [58]. Dental stem cells can accelerate the healing of soft tissue injuries, shortening the recovery time of patients. Dental pulp stem cells [59] and stem cells from extracted primary teeth [53] have the properties of mesenchymal stem cells, including self-renewal and the ability to differentiate into different cell types. Both populations can generate dental and bone tissue, with stem cells from extracted primary teeth showing a higher proliferation rate and easier accessibility compared to bone marrow-derived mesenchymal stem cells. This makes them a promising option for CT regeneration based on autologous stem cells.

High-frequency accelerations are proposed to be used as a non-invasive and affordable method for preserving and improving the quality of the cellular area of the jaws under both physiological and pathological conditions [60]. This technique contributes to the formation of CT not only in the removal area, but also in the adjacent areas, including areas of bone located at different distances around the neighboring teeth.

Conflict of interest information

There are no potential or apparent conflicts of interest related to this manuscript at the time of publication and are not anticipated.

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Джупа П., Стой О., Челпанова І.В. Сучасна методологія покращення регенерації кісткової тканини в стоматології.

РЕФЕРАТ. Мета – дослідити сучасні методики покращення регенерації кісткової тканини. Для досягнення поставленої мети нами було опрацьовано джерела наукової медичної вітчизняної та світової літератури. **Результати.** Втрата щелепної кістки може бути як наслідком хронічних стоматологічних захворювань, так і наслідком травм чи резекції пухлин. Резорбція кістки, яка у більшості випадків зумовлена інфекціями або запаленням, може призвести до дискомфорту, деформації та ускладнень при встановленні зубних імплантатів. Хоча останні можуть відновити функцію ротової порожнини, багатьом пацієнтам бракує достатнього об'єму КТ для їхнього встановлення. Тому для вирішення цієї проблеми використовують ряд методик. Керована кісткова регенерація сприяє росту нової кістки в пошкоджених ділянках щелепи. Незважаючи на ефективність, даний метод може зайняти багато часу для досягнення достатнього об'єму кісткової тканини. Принцип ПАЗС (Первинне закриття, Ангіогенез, Збереження простору і Стабільність) вважається основним для успішного проведення керованої кісткової регенерації. У керованій клітинній регенерації використовуються два основних типи бар'єрних мембран: мембрани, що розсмоктуються і мембрани, що не розсмоктуються. Останні досягнення в технології титанових сіток включають в себе індивідуальні попередньо зігнуті сітки, які відповідають конкретним формам дефектів. Дистракційний остеогенез має значні переваги над традиційними методами кісткової трансплантації, оскільки усуває потребу в донорській кістці, запобігаючи такому ускладненню, як захворюваність донорської ділянки. Незважаючи на свої переваги, методика дистракційного остеогенезу пов'язана з певними проблемами. Тривалий період консолідації, необхідний для дозрівання кістки, збільшує ризик таких ускладнень, як інфекція, незрощення та дискомфорт для пацієнта. Ці ускладнення, разом із психологічними та економічними є обтяженням для тривалого лікування та обмежують широке застосування дистракційного остеогенезу. Збагачена тромбоцитами плазма стає все більш популярною в стоматології завдяки своїй здатності прискорювати загоєння і сприяти відновленню тканин. Здатність збагаченої тромбоцитами плазми вивільняти високу концентрацію факторів росту робить її ефективним інструментом у стимуляції активності стовбурових клітин, сприянні загоєнню тканин та посиленні регенерації кісток і м'яких тканин. Терапія стовбуровими клітинами має значні перспективи для регенерації зубів, кісткової тканини та структур пародонту, що робить їх ключовим напрямком у сучасній інженерії зубних тканин. **Підсумок.** Підсумовуючи наукову літературу виявлено певні суперечності щодо ефективності вищезгаданих методик керованої кісткової регенерації та розуміння ситуативних варіацій реконструкції кісткової тканини при різних клінічних сценаріях. Сучасні методики покращення регенерації кісткової тканини спрямовані на створення оптимальних умов для природного відновлення кістки шляхом використання біосумісних матеріалів, направлених хірургічних технік, біологічно активних факторів та індивідуалізованих підходів, заснованих на глибокому розумінні гістоархітектури кісткової тканини. Значна кількість наукових праць як експериментальних, так і клінічних присвячена дослідженню остеорегенерації, проте в сучасних умовах особливого значення набувають вірні уявлення про послідовність і часові рамки остеогенетичних регенераторних процесів. Тому виправданим є прагнення до вивчення сучасних методик та пов’язаних з ними динамік гістоархітектурних перебудов, що відбуваються під час загоєння кісткових дефектів, що дозволить розробляти персоналізовані стратегії остеорегенерації, адаптовані до потреб конкретного пацієнта.

Ключові слова: кісткова тканина, остеорегенерація, ремоделювання.