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Morphological Assessment of Dental Implantation Outcomes

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ABSTRACT

Numerous publications have addressed gingival and bone augmentation involving both the alveolar processes of the jaws and the floor of the maxillary sinuses. In some cases, patients require not only dental restoration but also complex reconstruction of facial skeletal regions damaged by trauma, radiation exposure, cancer surgery, and other factors. Dental implantation is an essential component in the correction of extensive defects not only of the jaws but also of the paranasal sinuses. Additionally, various techniques have been described for covering the outer part of dental implants immediately after insertion to enhance integration. At the same time, certain disagreements remain regarding gingival manipulation during dental implantation and preparatory procedures. Some sources recommend covering implants with a flap of autologous soft tissue, whereas others support flapless approaches. Reports also differ on the source of soft tissue used for coverage: ranging from autologous grafts to allogeneic transplants, such as porcine-derived monolayer collagen matrices. There is no consensus on the optimal bone augmentation method for implant placement. Morphological data on the processes of lysis, replacement, or consolidation of autologous bone fragments that are placed into or left within tissues damaged during preparation and implantation are clearly insufficient, and existing publications lack detailed descriptions of these processes. All of this indicates that none of the challenges in dental implantation have been definitively resolved, including the need for a step-by-step understanding of the pathomorphological processes involved in bone graft consolidation or resorption.

Keywords: dental implantation; bone grafting; gingival tissue augmentation; maxillary sinus floor augmentation; jawbone augmentation.

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Морфологическая оценка результатов дентальной имплантации

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АННОТАЦИЯ

Имеется множество публикаций об аугментации (пластике) десны и костных тканей как альвеолярных отростков челюстей, так и дна верхнечелюстных пазух. В некоторых случаях пациенты нуждаются не только в восстановлении зубных рядов. Существует проблема комплексной реконструкции отдельных частей лицевого скелета, повреждённых при травмах, лучевых воздействиях, операциях при онкопатологии и т. п. Дентальная имплантация является необходимым компонентом при коррекции значительных дефектов не только челюстей, но и придаточных пазух. Кроме того, есть описание различных способов закрытия наружной части дентальных имплантатов для улучшения интеграции непосредственно после их внедрения в кость. Вместе с этим имеются определённые разногласия относительно манипуляций с десной при дентальной имплантации и подготовительных процедурах. Приводятся как рекомендации закрывать внедрённые изделия лоскутом собственных мягких тканей, так и мнение, что имплантация может быть осуществлена без лоскута. Также разнородны сообщения об источнике мягких тканей для закрытия имплантата: от аутологичных тканей до аллогенной трансплантации, например, использование монослойного коллагенового матрикса свиньи. Нет единого мнения о самом оптимальном методе наращивания костных тканей для установки имплантатов. Явно недостаточны морфологические сведения о процессах лизиса, замещения или консолидации фрагментов аутогенной кости при помещении их или оставлении в тканях, повреждённых при подготовке и в ходе самой процедуры имплантации, статьи не содержат подробного описания этого процесса. Всё вышеизложенное свидетельствует, что ни одна проблема дентальной имплантации окончательно не решена, в том числе нет пошагового представления патоморфологических процессов консолидации или лизиса костных трансплантатов.

Ключевые слова: дентальная имплантация; трансплантация кости; аугментация десны; пластика дна верхнечелюстных пазух; аугментация челюсти.

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BACKGROUND

The use of dental implants has grown significantly in contemporary dentistry. Implants are employed in treating both completely and partially edentulous patients. Key factors influencing the success of implantation include anatomical conditions, the patient's overall health, the clinician's expertise, and the chosen surgical technique. Achieving optimal outcomes requires effective interdisciplinary collaboration, involving periodontists, prosthodontists, and maxillofacial surgeons [1].

Replacing missing teeth presents ongoing challenges for implant surgeons due to factors such as bone volume and quality, the anatomy of the posterior maxillary sinus, and limited surgical access. Frequently, the available hard and soft tissue at the beginning of treatment is inadequate. A range of implantation techniques is now available, each with distinct advantages and limitations. A clear understanding of these methods, along with thorough diagnosis and careful case selection, is essential to ensure appropriate treatment for each patient. Several surgical approaches, such as bone augmentation and sinus floor elevation, are commonly used in patients with hard and soft tissue deficiencies [2]. Additionally, selecting the appropriate implant material is crucial, particularly when using prosthetic bars, and must be guided by a careful assessment of relevant indications and contraindications [3–5].

This paper presents a review of studies focused on the morphological assessment of bone graft consolidation and resorption in the context of dental implantation. A search of the *PubMed* database was conducted using the keyword combinations *dental + implant + own + bone*, *dental + implantation + bone + fragments*, and *lysis + bone + fragments*, covering the period from 2015 to 2024. A total of 129 publications were identified during this time frame. Studies that addressed the mechanisms of bone fragment degradation or integration into surrounding tissues were selected for inclusion. In addition, foundational earlier works were consulted, resulting in a total of 35 studies being included in the review.

SOFT TISSUE AUGMENTATION DURING DENTAL IMPLANTATION

There are two commonly used techniques for placing dental implants. The conventional method involves elevating a mucoperiosteal flap, while the alternative, flapless approach does not include flap elevation. Each technique has specific advantages and disadvantages [6].

Kumar et al. [6] investigated tissue changes surrounding endosseous implants placed using either the flap or flapless method. After 12 months, the average peri-implant probing depth was lower in the flapless group compared to the flap group. Both techniques showed a significant reduction in bone height around the implants during the follow-up period; however, the decrease was less marked in the flapless group. The study concluded that flapless implant placement resulted in a significantly lower peri-implant probing depth and bone loss than flap surgery. Nonetheless, the clinical relevance of these differences remains unclear.

Zafiropoulos and John [7] assessed the effectiveness of using a monolayer porcine collagen matrix as an alternative to autologous connective tissue for soft tissue augmentation in conjunction with immediate implant placement. A total of 27 implants were placed immediately in 27 patients, with soft tissue augmentation performed simultaneously using the porcine collagen matrix. The patients were randomly assigned to two groups. In group 1, an envelope flap was created, leaving the coronal portion of the matrix exposed. In group 2, a coronal flap was raised, fully covering the matrix with mucosa. After 6 months, both groups, as well as the overall patient group, showed significant soft tissue hypertrophy. The reduction in the volume of the grafted matrix was also similar in both groups. The use of a monolayer porcine collagen matrix increases soft tissue thickness around implants regardless of the flap design and may be considered a substitute for autologous grafts. In a study involving 12 adult beagle dogs, implants were placed immediately after tooth extraction along with guided bone regeneration. After 25–45 weeks, the animals were randomly assigned to receive soft tissue augmentation using either a stable-volume collagen matrix or a subepithelial connective tissue autograft. A control group consisted of sham-operated animals. Impressions were taken before and after augmentation, as well as at 4, 8, and 24 weeks postoperatively. Both the collagen matrix and the connective tissue autografts resulted in an increase in alveolar tissue volume following surgery. However, by the end of the observation period, bone volume had returned to near-baseline levels across all three groups. In both treatment groups, the increase in tissue volume at the apex of the alveolar ridge was inconsistent during follow-up.

There is still a lack of consensus regarding gingival handling during dental implantation and related preparatory procedures. Some studies recommend covering implants with an autologous soft tissue flap, while others favor flapless techniques. There is also variation in the reported sources of soft tissue used for coverage, ranging from autologous grafts to allogeneic materials such as monolayer porcine collagen matrices.

BONE AUGMENTATION GRAFTING

During the healing process following bone grafting, grafted bone fragments are partially resorbed and replaced by autologous tissue [9]. Although autografts (autologous bone) possess strong osteogenic, osteoinductive, and osteoconductive properties, their clinical use is limited by the potential for perioperative and postoperative complications, including pathological conditions at the donor site and the restricted availability of graft material. Allogeneic bone, used as an alternative, has shown good effectiveness in promoting healing without the risk of donor site complications. Demineralized bone matrix has proven to be a useful supplement to bone

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healing, either as an extender or enhancer when used with allografts. The choice of bone grafting technique may depend on the extent of pathological condition, the clinical experience and preferences of the orthopedic surgeon, and the severity of donor site involvement [10].

Li et al. [11] and Um et al. [12] explored the development and clinical application of demineralized dentin matrix scaffolds derived from patients' extracted teeth for use in dental implantation. This autologous demineralized dentin matrix exhibits both osteoinductive and osteoconductive properties, along with favorable safety and efficacy, making it a viable alternative to conventional bone grafts.

Li et al. [11] assessed the clinical efficacy of autologous demineralized dentin matrix compared to *Bio-Oss granules* in the periodontal region after tooth extraction, in the context of guided bone regeneration combined with immediate implant placement. The study involved 40 patients (45 implants), randomly assigned to receive either the autologous dentin matrix from extracted teeth or *Bio-Oss granules*, both with immediate implant placement. After 1 year of implant loading, there were no significant differences between the groups in terms of implant stability quotient or marginal bone resorption. Autologous dentin matrix granules represent an effective and readily available alternative to bone grafts in guided bone regeneration, including for patients with advanced periodontal disease. Other studies have also confirmed the strong regenerative potential of tooth-derived materials [13].

Sapoznikov et al. [14] compared the clinical efficacy of *Ivory Dentin Graft*™, composed of porcine dentin particles, with that of commercially available porcine bone grafts for bone regeneration following tooth extraction, with alveolar ridge preservation and titanium implant placement after 4 months. The dentin graft led to a significant increase in the volume of newly formed bone, improved integration of the graft material, and higher average bone density at the surgical site. Titanium implants were successfully placed in 95% of patients in the dentin graft group, compared to 81.25% in the bone graft group. Both graft materials showed similar clinical safety and tolerability, based on the incidence of side effects and local reactions. Dentin-based materials of animal origin may serve as a broader substitute for autologous dentin in clinical practice.

The predictability of procedures to correct remodeling and bone resorption in extraction sockets with severely resorbed edges due to periodontal disease is currently unclear. In a patient with severe periodontal disease, the maxillary right lateral and central incisors were extracted. The area around the central incisor showed complete buccal bone loss and a 9-mm vertical bone deficiency from the palatal side. The extraction sockets were filled with a collagen sponge and covered with a nonresorbable high-density polytetrafluoroethylene membrane. While primary closure was not achieved, no rigid scaffolding material was used. Twelve months later, cone beam computed tomography showed sufficient bone volume for the placement of two standard dental implants along with horizontal bone augmentation [15].

Jones [2] used a palatine bone plate to reconstruct a deficient alveolar ridge (lack of the buccal wall) in the maxillary central incisor area after the extraction of an ankylosed tooth. An implant was placed 3 months later, along with soft tissue augmentation using a connective tissue graft. The dental restoration was successful, with a satisfactory esthetic outcome. The short healing time and excellent tissue quality were particularly notable.

Preoperative physical, clinical, and imaging assessments of a 23-year-old patient revealed slight mobility of the maxillary central incisor (tooth No. 8) due to severe cervical resorption. The treatment included atraumatic tooth extraction, followed by immediate implant placement and temporization. Due to a very thin maxillary bone plate caused by a thin gingival biotype, two grafts (bovine bone and connective tissue) were used. The extracted crown was utilized for immediate implant placement, resulting in a favorable long-term esthetic outcome. Anterior tooth extractions typically require the creation of monolithic dentures made from synthetic materials, which may not always achieve the expected esthetic or functional results [16].

Covering the implant surface with a full-thickness flap in patients with peri-implant defects or fenestration was found to be significantly less effective than using a combination of resorbable membranes and bone grafts. Treatment using both graft and membrane/periosteum showed slightly better results compared to graft or membrane treatment alone. Allogeneic grafts proved to be more effective than autologous bone tissue. A combination of nonresorbable membrane and autologous periosteum resulted in a greater increase in buccal bone thickness than a combination of resorbable material and bone graft.

Osteotensors® bone matrix activates autologous multipotent stromal cells (MSCs) through targeted flapless bone distraction before implant placement and/or bone grafting, stimulating new bone formation. Maxillary and mandibular bones were activated for 21 days (type I bone) to 45 days (type IV bone) before implant placement and/or bone grafting. After new bone formation, tapered and disk implants were placed. Three years later, all implants showed successful clinical and radiological osseointegration, with excellent functional and esthetic outcomes. Flapless distraction osteogenesis with Osteotensors, performed for several weeks before surgery, enhances the quality and volume of the implant bed [18].

The rate and extent of dental implant osseointegration were compared between autologous cortico-cancellous bone grafts and freeze-dried cancellous bone grafts. The iliac bone was used as the model site. Forty-five implants were placed in 15 dogs and removed after 1, 2, and 3 months. After 1 month, there was no significant difference in osseointegration between the two bone grafts. After 2 months, autologous cortico-cancellous bone grafts showed significantly better osseointegration compared to freeze-dried grafts. After 3 months, the osseointegration in the two groups was 70% and 33%, respectively [19].

Alveolar ridge reconstruction during dental implant preparation can be done using autologous bone grafts, such as dentin or autologous demineralized dentin matrix from extracted teeth, allogeneic materials like allogeneic dentin, or polymers such as Teflon. Some researchers recommend autografting, while others prefer allogeneic materials or synthetic grafts. There is no consensus on the most effective method for alveolar bone augmentation during implant placement.

Maxillary sinus floor elevation

Sinus issues often arise when placing dental implants in the lateral regions of the maxilla, particularly after early tooth loss. In cases of severe atrophy of the posterior maxilla, vertical sinus floor augmentation may be required for successful implant placement. Grafting techniques aimed at reducing the volume of these pneumatic cavities focus on restoring the necessary viable bone volume at the sinus floor using various bone substitutes. The wide variety of commercially available bone substitute biomaterials reflects significant advancements in this area of implantology. Autologous bone, especially in combination with calcium- and phosphorus-based materials, remains the most effective all-purpose biomaterial. Synthetic biomaterials have specific uses based on their stability (non-resorbable) or resorption (resorbable), as well as their metabolic adsorption rate. Bone materials from tissue banks, treated by different methods, behave similarly to autologous bone, provided they are free from contamination and immunologically compatible [20, 21].

Autologous bone is typically the most reliable material for augmentation and precise implant placement in the atrophic posterior maxilla, despite a 40% resorption rate, due to its high osteoconductivity and reduced risk of endosseous migration along the sinus floor. Incorporating animal-derived minerals into autologous bone can enhance grafting success, as allogeneic materials serve as slowly resorbing fillers. Porous hydroxyapatite can also be combined with autologous bone to improve bone tissue formation and bone-to-implant contact in enlarged sinuses. Morphological assessments suggest that demineralized freeze-dried bone is less effective than other materials. Histological findings indicate that the biomaterial used for augmentation does not impact the early stages of implant osseointegration [22].

A total of 82 maxillary sinus floor elevation procedures were performed in 63 patients. In 39 cases, iliac crest autografts or osteoinductive allogeneic bone powders were used for augmentation, including autolyzed antigen-extracted allogeneic bone, demineralized freeze-dried bone allograft, and/or Grafton (demineralized bone matrix gel) in 43 cases. X-ray examination approximately 4–6 months after implant placement revealed bone formation equivalent to that seen with osteoinductive allogeneic bone grafts. Histological analysis showed that the osteoinductive materials had fully transformed into autologous bone tissue. Both histological and X-ray findings indicated no significant differences in bone quality between the two augmentation materials. Four of 67 implants placed with bone autografts and 2 of 74 dental implants placed with allogeneic materials failed to achieve osseointegration. The average duration of postoperative discomfort was 19±9 days for patients with bone autografts and 3±5 days for those with allogeneic materials. Osteoinductive bone grafts are preferred over iliac crest autografts in maxillary sinus augmentation [23].

Patients with missing posterior teeth and a maxillary sinus floor bone height of 4–10 mm underwent internal sinus floor elevation using autologous bone mixed with β-tricalcium phosphate ceramics, followed by immediate implant placement. Permanent crowns were placed 4–6 months later. A total of 21 implants were placed in 16 patients, with an average bone tissue gain of 4.2 mm (ranging from 2 to 6 mm). All implants were loaded for 32 months, maintaining good stability and osseointegration [24].

Bone tissue quality was assessed during maxillary sinus augmentation using autologous bone alone or combined with platelet-rich plasma (PRP). In group 1, five patients underwent sinus augmentation with autologous bone and implant placement after 6 months. In group 2, 10 patients received sinus augmentation with autologous bone mixed with PRP from autologous blood, with implant placement after either 4 or 6 months (5 patients in each group). Group 1 showed significantly better average bone density at the time of implantation and 3 months later. However, 6 months after implant placement, group 2 exhibited the highest average bone density [25].

Patients in group A underwent internal sinus floor elevation and implant placement without a bone graft. In group B, conventional internal sinus floor elevation was performed using bovine bone particles, followed by implant placement. Six months after surgery, group A exhibited greater biomechanical stability of the implants compared to group B. However, group B had a significantly higher bone volume. Internal sinus floor elevation without a bone graft encourages bone formation due to the osteogenic potential of the sinus lining. The quality of newly formed bone is crucial for successful implant placement, and the neoformed bone quality was significantly better in group A, where no exogenous bone graft was used [26].

StemVie™ resorbable posts, made of hydroxyapatite and β-tricalcium phosphate, are a modification of the sinus floor elevation technique. This method can increase bone height by 4–10 mm in severely atrophic alveolar ridges, especially when the lateral approach is challenging. The procedure is minimally invasive, simple, and predictable, with less postoperative pain due to a smaller flap and minimal osteotomy. If sufficient alveolar bone volume is present for stabilization, implants can be placed at the same time as sinus floor elevation and grafting. *StemVie posts* are fully resorbed and replaced by autologous bone. Adding bone marrow aspirate and/or peripheral venous blood to the *StemVie posts* can accelerate healing. The graft absorbs blood or bone marrow through its pores. Bone marrow aspirate enhances healing by providing osteoblast precursors, cytokines, and growth

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factors, while peripheral blood mainly offers cytokines and growth factors [27].

Various techniques can be employed to increase the thickness of the sinus floor, often yielding positive results. The quality of newly formed bone is critical for the success of implant placement. In addition to autologous bone grafts, allografts (such as demineralized freeze-dried bone) and osteoinductive materials, which are fully resorbed and replaced by autologous bone, can also be used. Several studies have examined the pros and cons of different methods. Some researchers recommend using osteoinductive materials instead of autologous bone, noting that bone materials obtained from tissue banks and processed in various ways behave similarly to autologous bone. Others contend that demineralized freeze-dried bone is less effective than other materials. Moreover, some studies suggest that sinus floor elevation, which stimulates the osteogenic potential of autologous tissue without using a graft, may be more effective than grafting approaches.

BONE TISSUE LYSIS AND REMODELING DURING DENTAL IMPLANTATION

Screw implants were placed into the proximal condyles of *tibias* in outbred rabbits. Bone damage caused during implant preparation and placement led to *the formation of detritus,* including bone chips, which were pressed into the surrounding bone structures. Three days after implant placement, significant amounts of bone *detritus* (non-viable bone fragments of various sizes and shapes) were observed between the implants and the intact bone. By Day 7, some viable bone fragments had consolidated into bone rods, while necrotic bone fragments were being lysed in other areas. By Day 10, almost all the debris had either been lysed (except for very large bone fragments) or incorporated into the newly forming bone tissue. The prolonged presence of debris at the implant site, causing extended inflammation and delayed tissue regeneration, may negatively affect implant survival [28, 29].

On Day 3 after surgery, non-viable bone fragments and chips resulting from the drilling process for screw implant placement were found in the soft tissues on the surface of the proximal condyle of the *tibia*, adjacent to the metal implant in all animals. Larger bone particles were either surrounded and infiltrated by macrophages at the edges or broken down into smaller fragments by phagocytes. The smaller fragments had already been fully infiltrated and destroyed by multinucleated macrophages through cytoplasmic fusion. After 7 days, necrotic bone fragments of up to 300 μm in diameter, in various stages of destruction, were observed. Some bone particles were surrounded by concentric layers of newly formed connective tissue and infiltrated by leukocytes, while in other areas, bone destruction occurred through the formation of multinucleated macrophages with cytoplasmic fusion. By Day 10, the bone fragments were nearly completely lysed. Thus, bone *detritus* gradually disappears from the surrounding tissues following implant placement [28].

Histological changes in the alveolar bone tissue were observed in all 21 cases of apical infection when the alveolar tissue remained attached to a tooth. The pathomorphological findings included an altered trabecular structure, increased osteoclast activity, and scalloped bone areas within the thickened attached periodontal ligament [30].

A randomized, double-blind, placebo-controlled clinical study compared the effects of oral vitamin D3 (5,000 IU) with calcium (600 mg) versus a calcium-containing placebo on bone formation and remodeling following maxillary sinus wall augmentation. Bone samples for histological analysis were collected during implant placement (6–8 months later). Vitamin D3 and calcium significantly increased serum 25-hydroxyvitamin D levels. However, no significant differences were found in bone formation or graft resorption between the groups. The group receiving vitamin D3 showed a significant positive correlation between higher vitamin D3 levels and increased osteoclast counts around the graft particles, suggesting that elevated serum vitamin D3 levels may promote local bone remodeling [9].

Macrophages are among the first immune cells to migrate after dental implant placement, exhibiting various phenotypes, ranging from classically activated (M1) to alternatively activated (M2). Bone remodeling following dental implant placement (as studied in rats) resembles a typical response to tissue damage, such as tooth extraction, but with delayed bone regeneration phases. Macrophage activation in both groups shifted from a predominant M1 phenotype to a predominant M2 phenotype, though M1 macrophages persisted. Further *in vitro* studies showed that M1 macrophages regulated osteoclast activity, acted as their precursors, and recruited bone marrow MSCs. In contrast, M2 macrophages promoted osteogenesis during the later stage due to their ability to produce and release osteogenic proteins. However, osteogenic MSC differentiation was inhibited in high-concentration media after cultivating each macrophage phenotype, suggesting that immune response strategies are regulated to some extent. Bone remodeling requires the coordinated involvement of both M1 and M2 macrophages [31].

POSSIBLE FATAL COMPLICATIONS OF DENTAL IMPLANTATION

Pulmonary embolism, although typically caused by venous thrombosis, has been reported in the context of total joint replacement surgery [32, 33]. There have also been isolated instances of pulmonary embolism caused by bone marrow structures, including both hematopoietic and yellow marrow [34]. A study by Maiborodin et al. [35] investigated the hearts and lungs of rabbits at various time points following titanium dental implant placement into the proximal condyles of the *tibia*. This study found that after implant placement, or any manipulation of bone structures, fibrin, *detritus*, and even red marrow structures could enter the right heart chambers, as evidenced by the presence of blood clots and various blast forms of hematopoietic cells. These thrombi and emboli then travel through the heart and into the lungs, potentially causing arterial occlusion. Moreover, *detritus* transfer from the surgical site may contribute to thrombogenesis in the *right atrium* and *ventricle*, as well as in the pulmonary arteries.

Thus, it is important to implement measures that prevent debris from entering the circulation and the potential development of pulmonary embolism during any bone tissue implantation, including those involving small implants.

CONCLUSION

Dental implantation plays a crucial role in correcting significant defects not only in the jaws but also in the paranasal sinuses. Additionally, various techniques have been proposed for covering the exterior of dental implants immediately after insertion to improve integration. However, the literature on implantology often presents conflicting and contradictory views. There are still disagreements regarding gingival manipulation during dental implantation and preparatory procedures. Some studies suggest covering implants with a flap of autologous soft tissue, while others advocate for flapless techniques. Reports also vary on the source of soft tissue used for coverage, ranging from autologous grafts to allogeneic transplants, such as porcine-derived monolayer collagen matrices. Autologous bone grafts can be utilized for alveolar ridge reconstruction and maxillary sinus floor augmentation when preparing for dental implant placement. In addition to autologous bone grafts, allografts and osteoinductive materials can be used, which behave similarly to autologous tissues. Some sources suggest that sinus floor elevation with stimulation of autologous tissue osteogenic potential, without bone grafting, may be more effective than various grafting methods. Therefore, there is no agreement on the optimal bone augmentation technique for implant placement. Morphological data on the processes of lysis, replacement, or consolidation of autologous bone fragments placed into or left within damaged tissues during preparation and implantation are insufficient. It is important to note that after augmentation using bone grafts, the bone fragments are partially resorbed and replaced with autologous bone, although this process is not discussed in detail in the paper. This highlights that many challenges in dental implantation remain unresolved.

Each method for preparatory procedures and dental implant placement has specific advantages and disadvantages. To achieve the best long-term outcome, the technique should be chosen carefully, considering all indications, contraindications, and the implant surgeon's experience.

ADDITIONAL INFORMATION

Authors' contribution. I.V.M.—conceptualization, analysis, manuscript editing, supervision; B.K.S.—research, draft creation; B.V.S.—manuscript editing, supervision; V.I.M.—research, draft creation, manuscript editing; A.A.S.—conceptualization, manuscript editing. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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