

## Concluzii

1. La instalarea într-o ședință chirurgicală, fără lambou a implanturilor dentare de stadiul doi fenotipul gingival subțire conduce la o resorbție periimplantară mai elevată comparativ cu fenotipul gingival gros sau cu cele instalate în două ședințe chirurgicale
2. În cazul instalării într-o ședință, poziționarea supracorticală a implanturilor conduce la o resorbție semnificativ mai mică decât cea juxta-sau subcorticală.
3. Rezultatele obținute demonstrează și rolul microspațiului în resorbția corticală periimplantară.
4. Metoda de instalare a implanturilor și fenotipul gingival nu influențează stabilitatea lor.
5. Prezența unui spațiu biologic matur la sfârșitul perioadei de vindecare și lipsa diferențelor statistice între celelalte subgrupuri demonstrează eficiența metodei miniinvazive descrise.

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Recenzent: Natalia Rusu

## BIOMATERIALS AND TISSUE ENGINEERING TECHNIQUES IN ORAL IMPLANTOLOGY

**Victor Pălărie,**  
DMD

**Dumitru Sarbu,**  
DMD, PhD, ass.  
professor

**Valentin Topalo,**  
DMD, PhD, Dr. Hab.  
Med., university  
professor

*Department of oral and  
maxillofacial surgery  
and oral implantology  
„Arsenie Guțan“  
State Medical and  
Pharmaceutical  
University „Nicolae  
Testemitanu“*

### Summary

Currently, diverse biomaterials are approved for complex regeneration as a bone-filling material. Although the biomaterial needs to be used with a biological scaffold as a carrier, there has been considerable clinical interest in combining biological factors with different bone grafts. This article reports a review regarding using biomaterial bone substitutes for implant site development. After careful evaluation of the literature data of current and emerging evidence, the use of biomaterials in combination with diverse biological factors was determined in the following reports to be consistent for the good clinical practice regarding bone augmentation.

**Key words:** biomaterial, augmentation, bone graft, dental implantation.

### Rezumat

#### BIOMATERIALE SI TEHNICI DE INGINERIE TISULARA IN IMPLANTOLOGIA ORALA

În prezent, diverse biomateriale sunt aprobate pentru regenerarea complexa osoasa. Deși, classic un biomaterial este utilizat numai ca un suport biologic, a existat un interes clinic considerabil în combinarea factorilor biologici cu diverse grefe osoase. Acest articol reprezinta un reviu în ceea ce privește utilizarea diverselor biomateriale in implantologia orala. După o evaluare a datelor din literatură, utilizarea științifică a biomaterialilor in combinatie cu tehnicile de inginerie tisulara relatează indicații favorabile pentru utilizarea clinică în augmentarea osoasă.

**Cuvinte cheie:** biomateriale, augmentare, grefa osoasa, implanturi dentare.

## Search strategy

The Cochrane Oral Health Group's Trials Register, CENTRAL, MEDLINE and EMBASE were searched. Hand searching included several dental journals.

**Data collection and analysis.** Data were extracted, in duplicate, by the present authors.

## Introduction

The resorption of the alveolar ridges of the superior and inferior maxillary bones following tooth extraction, periodontal aggression and trauma is a physiologically undesirable and probably avoidable phenomenon [1]. The reconstruction of the vertical and horizontal defects and atrophies in human and animal trials has been studied extensively by evaluating healing events via histological, radiological and clinical methods [2]. But in fact of these studies the vertical and horizontal regeneration of severe localized edentulous atrophic ridges remains a challenging procedure [3]. The available modalities for the bone reconstruction started to be compromised by different intraoperative and postoperative discomforts. With the exception of selected autogenous bone grafts and demineralized bone matrix, most bone replacement grafts are generally considered passive scaffolds providing a framework for cellular migration and tissue formation [4]. Several types of filling biomaterials have been evaluated for bone regeneration and the choice of the biomaterial mostly depends on its features and application site. The grafts could be classified as autologous, homologous, heterologous and synthetic materials.

### Autologous grafts

The „gold standard“, the autogenous graft, requires invasive techniques for harvesting of bone from intra oral and extra oral regions. And, also in front of the well-known advantages of autografts, like its capacity for osteoconduction as well as induction and restricted immune reaction, there are also significant drawbacks, like induction of a secondary defect at the donor site, followed by possible infection and donor-site-morbidity. The resorption of such grafts could grow up till 50% of the total volume of reconstructed site [5].

### Homologous grafts (Allografts)

Vital bone tissue is obtained from donors and it is stocked in bone banks. The use of homologous grafts is limited, due to the risk of infection, in particular the risk of contracting HIV is estimated to be 1:1.6 million, compared with 1:450000 in blood transfusions. The bone should be lyophilized and demineralized (DFDB — Demineralized Freeze-Dried Bone) or only lyophilized (FDB — Freeze-Dried Bone). The histomorphometric analysis has shown 29% of neo-synthesized bone, 37% of medullary spaces, while 34% of DFDB residual particles; moreover, the replacement of homologous bone is slow and it causes the formation of connective areas and where graft integration is reduced there is a visible inflammatory infiltrate [4,5].

## Heterologous grafts (Xenografts)

Heterologous materials are obtained from bones of different animal species; bovine bone being the most common source. Xenografts have different properties depending on their origin, constitution and processing.

**Bovine grafts.** Bovine bone xenografts have been used in several types of bone defects with satisfactory results. These biomaterials are made of apatite crystals in a reticular form, with an inside surface of about 70 m<sup>2</sup>/g which induces coagulum synthesis and stability. The demineralized bone matrix, which is represented on the market by the deprotenized bovine bone (DBB) showed a resistance to resorption following placement into bony defects or as an onlay graft. It has been shown to induce periodontal and periimplant bone regeneration. But these applications are recognized to assist in regeneration of the small amount of lost bone [6].

### Alloplastic grafts

Alloplastic grafts are synthetic bone substitutes that are available in different sizes, forms and textures. The structural characteristics of the alloplastic grafts are similar to bone tissue.

**Hydroxyapatite allografts.** Hydroxyapatite is a natural component of hard tissue (65% in bone tissue, 98% in enamel). Synthetic hydroxyapatite is available in different forms: porous, non-porous, ceramic and non-ceramic. Hydroxyapatite is bioinert and biocompatible, but it does not induce significant bone regeneration. Histomorphometric analysis resulted in a percentage of 41% of neo-synthesized bone, 30% of medullary spaces and 31% of residual hydroxyapatite graft [5], so it is poorly reabsorbed.

**Tricalcic phosphate grafts.** Tricalcic phosphate grafts (Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>) is treated with naphthalene and then is compacted at 1100–1300°C to obtain a diameter porosity of 100-300 mm. The review of Ciapasco [5] had shown an increase of bone regeneration after 12 weeks from surgery placement. Moreover, during reabsorption, it provides ion calcium and magnesium to bone tissue and so creates a correct ionic environment, which induces alkaline phosphatase activation, fundamental for bone synthesis [4,5].

**Bioglass grafts.** Synthetic glass ceramics are made of silicon dioxide (45%), sodium oxide (24.5%) and phosphorus pentoxide. The bioglass is used mainly in maxillary sinus lifts and is characterized by particles with a diameter of 300-335 mm. Histomorphometric analysis has given a percentage of 40% of new bone, 43% of medullary spaces and 17% of bioglass particles surrounded by neo-synthesized bone. Bioglass has osteoconductive properties and their solubility is directly dependent on sodium oxide [5].

**Coralline hydroxyapatite grafts.** Coralline hydroxyapatite is composed of calcium carbonate (87-98%), strontium, fluoride, magnesium, sodium and potassium (2-13%). It has a porous structure (over 45%) and pores have a diameter of 150-500 mm. The coralline hydroxyapatite also has osteoconductive

properties and the reabsorption of the coralline skeleton is due to the action of the carbonic anhydrase of osteoblasts [6].

The bone splinting and horizontal alveolar distraction are an alternative technique to harvesting operations [7,8,9]. But this technique has limitations due to non-tolerance of the devices and a small amount of bone especially when the vertical augmentation is indicated. At the moment the most common methods of ridge reconstructions include grafting procedures, with or without coverage by a barrier membrane, the guided bone regeneration (GBR). Bone replacement grafts and GBR membranes appear to function primarily through the preservation of space critical for clot development and tissue maturation. There are different types of membranes commercially available today: membranes that create a correct biological space (semi-hard synthetic membranes), membranes with restricted ability to create it (synthetic membranes) or membranes that do not maintain the biological space (collagen membranes). However, the barrier function and the membrane longevity may differ considerably, thereby limiting their function to a few weeks [3]. Also, the membrane placement is often associated with flap dehiscence due to compromised vascularity, which can adversely impact the regenerative outcome [10,11,12,13].

To avoid these problems, new techniques were initiated which include combination of the GBR and tissue engineering. Tissue engineering is broadly defined as the application of engineering and life science principles to develop biological substitutes that improve or reconstitute organs, tissues, and tissue function [14]. Early efforts to engineer periodontal and alveolar bone regeneration relied largely on matrices or scaffolds, including bone grafts and synthetic bone substitutes, or cell-exclusive materials that compartmentalize the regenerative site, as in GBR.

The regenerative process of the skeletal system is characterized by the remodeling cycle, in which cell populations are recruited and differentiated for the purposes of bone resorption or bone formation. These activities are coordinated and regulated by an elaborate system of growth factors and cytokines, several of which are either now available or in promising stages of development for clinical application through recombinant technology.

Recent attention has focused on the potential for biological mediators to improve wound healing and enhance the clinical benefits of bone replacement grafts [15]. The introduction of recombinant growth factors for osteogenic enhancement has potentiated the possibilities of bone augmentation of edentulous deformities for the purpose of implant placement. This process is dependent on the presence of 3 critical ingredients: molecular signals, responding cells with associated receptors and assembly of the extracellular matrix [16]. One of the crucial biological factors responsible for reparative osseous activity is platelet-derived growth factor (PDGF). PDGF was discovered

as a major mitogenic factor present in serum but absent from plasma. It is secreted from the  $\alpha$ -granules of platelets activated during the coagulation of blood to form serum. PDGF works by binding to cell-surface receptors on most cells of mesenchyme origin, and it stimulates the reparative processes in multiple tissue types. The potent stimulatory effects of PDGF as a chemo attractant and a mitogen, along with its ability to promote angiogenesis, complementing the actions of vascular endothelial growth factor (VEGF) in vessel formation, position it as a key mediator in tissue repair [17,18]. Subsequent studies have demonstrated that PDGF is not one molecule but three, each a dimeric combination of two distinct but structurally related peptide chains designated A and B. The group PDGF polypeptide growth factors include PDGF-A, B, C, and D, encoded by four genes located on different chromosomes.

Following injury and hemorrhage, bone repair is characterized by activation of the coagulation cascade and formation of a blood clot at the site of trauma (Fig. 1). Platelets aggregate and release their cytokine-laden granules, including varying amounts of PDGF-AA, PDGF-BB, and PDGF-CC, into the developing blood clot.

As a consequence of injury, alpha granules containing PDGF are jettisoned by platelets for the purpose of angiogenesis, chemotaxis, and mitogenesis. Transforming growth factor-beta (TGF- $\beta$ ) also appears to play a role in chemotaxis and cell proliferation during wound healing. The attraction of osteoprogenitor cells (chemotaxis) and their increase in number (mitogenesis) provide a pool of osteo-regenerative cells that will respond to the bone morphogenetic proteins (BMP) [19].

PDGF-BB has been shown to enhance the chemotactic and mitogenic activity of periodontal ligament cells at concentrations as low as 1 ng/mL [20,21]. PDGF-BB delivered in a methylcellulose gel was reported to have a half-life of 4.2 hours, with greater than 96% clearance of the radio labeled growth factor by 96 hours, when applied for the treatment of naturally occurring periodontal disease in beagle dogs [22]. Accordingly, following clinical application, the potent actions of this growth factor must occur early, triggering a cascade of biologic and cellular events at the surgical wound. These effects are characterized by the recruitment and differentiation of mesenchymal cell populations, as well as new vessel formation, ultimately supporting wound healing and regeneration [17]. Cooke et al [23] examined the effects of PDGF-BB on levels of VEGF and bone turnover in periodontal wound fluid in 16 patients who were randomized to receive treatment of intra-bony defects with either  $\beta$ -TCP carrier alone,  $\beta$ -TCP plus 0.3 mg/mL rhPDGF-BB, or  $\beta$ -TCP plus 1.0 mg/mL rhPDGF-BB. These patients had participated in a large clinical trial evaluating the efficacy and safety of PDGF-BB in the treatment of intraosseous periodontal defects. Pyridinolone cross-linked carboxy-

terminaltelopeptide of Type I collagen (ICTP) is an indicator of osseous metabolic activity and provided a marker of bone turnover. Low-dose rhPDGF-BB application was found to elicit increasing in ICTP at 3 to 5 days in the wound healing process, with the 1-mg/mL rhPDGF-BB group showing the most pronounced difference in VEGF at 3 weeks. Thus, a single dose of rhPDGF-BB exhibited demonstrable, sustained metabolic actions at the clinical site of application [24]. In a parallel study, the release of the ICTP into the periodontal wound fluid was monitored longitudinally in 47 patients for 24 weeks following regenerative surgical treatment with PDGF-BB. The 0.3 and 1 mg/mL PDGF-BB treatment groups exhibited increases in levels of ICTP for as much as 6 weeks. ICTP levels were significantly higher in defects treated with PDGF-BB and  $\beta$ -TCP compared with sites grafted with  $\beta$ -TCP alone at the 6-weeks point. Given the rapid biologic clearance of the growth factor, these results provide further evidence that a single administration of PDGF-BB exerts a sustained effect on periodontal bone metabolism and helps clarify the sequence and timing of signal cascades involved in periodontal wound healing [24].

Currently, PDGF-BB is clinical approved for periodontal regeneration together with bone-filling material only [24]. Although the bone-filling material uses  $\beta$ -TCP as the scaffold/carrier, there has been considerable clinical interest in combining this growth factor with other bone replacement grafts, particularly bone allografts. Bone allografts, such as freeze-dried bone allograft and demineralized freeze-dried bone allograft, exhibit highly osteoconductive surfaces and support well-documented clinical improvements in periodontal parameters compared to open flap debridement [25]. These materials have also been shown to possess variable amounts of growth factors, including bone morphogenetic proteins, and the capacity for osteoinduction [26]. Because of the safety and efficacy profile of bone allografts, the potential to serve as carriers for growth factors and other biologic mediators has been extensively explored and documented in cell-culture and preclinical models. Clinical case reports also provide information on the clinical efficacy of PDGF-BB being used with bone allografts. Nevins et al [27] and Camelo et al [28], reported human histological evidence of periodontal regeneration in intra-osseous defects treated employing a combination of rhPDGF-BB and  $\beta$ -TCP. Nevins et al [29] reported a case series describing the clinical and radiographic outcomes following the treatment with rhPDGF-BB and  $\beta$ -TCP of severe periodontal intrabony defects. Clinical reentry and radiographs at one year showed complete bone fill, indicating that rhPDGF combined with  $\beta$ -TCP provides excellent clinical results. Preclinical studies regarding combination of an aloplastic material with a rhPDGF-BB showed the potential to support only initial stages of guided bone regeneration at chronic-type lateral ridge defects [16].

Preclinical studies and case reports provide proof

of principle that rhPDGF-BB, when combined with other graft matrices, can support improved bone formation and wound healing in alveolar ridge reconstruction and implant therapy. Lynch et al [30] found that the direct application of a combination of rhPDGF-BB and IGF-1 around dental implants produced two to three times more new bone at earlier periods in dogs. Becker et al [31] reported an increase in the percentage of implant surface in contact with bone and total length of the implant surface in contact with bone in dehiscence defects treated with expanded-polytetrafluoroethylene membranes (ePTFE) plus PDGF/IGF-I compared with the defects receiving ePTFE membranes alone in dogs. Simion et al. [3] reported a canine study that demonstrated the potential for a deproteinized cancellous bovine block, when infused with rhPDGF-BB, to regenerate significant amounts of new bone in severe mandibular vertical ridge defects without placement of a barrier membrane. The xenogenic block grafts were infused with rhPDGF-BB and stabilized in alveolar defects using two dental implants with or without collagen membranes. The alveolar ridge defects treated with the combination of rhPDGF-BB plus xenograft without a collagen membrane demonstrated the greatest bone formation based on radiographic and histologic outcome measures. The histologic findings revealed robust osteogenesis throughout the block grafts, with significant graft resorption and replacement. In contrast, alveolar ridge defects treated with traditional GBR without the growth factor supported little or no bone formation. Simion et al. [3] reported similar findings using rhPDGF-BB in combination with a novel equine hydroxyapatite and collagen (eHAC) bone block in the canine model. Moreover, recent case reports demonstrate that anorganic bovine bone can serve as effective scaffolds to deliver rhPDGF-BB for lateral ridge augmentation and reconstruction, following extraction for implant placement [27,29]. The scientific base is that during bone regeneration by osteoinduction of the graft (anorganic bovine bone — DBB), pluripotent cells differentiate under influence of humoral and bone morphogenetic proteins into osteoblasts, which can then produce osteocytes [32]. By the other way the DBB regulates micro RNA which represent a class of small, functional, noncoding RNAs of 19 to 23 nucleotides that regulate the transcription of messenger RNAs in proteins [33]. The benefit of this combination is advocated by the presence of the rhPDGF-BB as an interface between graft and anatomical site. In this way the osteoconductive and osteoinductive process could be induced and maintained by rhPDGF-BB.

## Results

Biological growth factor technology has increased the options for combinatorial approaches to reconstructive oral surgery. Graft matrices that are space maintaining and osteoconductive support in preventing soft-tissue collapse and provide a scaffold

fold for cellular migration and stabilization of the blood clot. Graft matrices, such as  $\beta$ -TCP and deproteinized cancellous bovine substitutes, can also serve as delivery devices for drugs and biologics, although the release kinetics can differ among scaffolds. The clinical potent effect of rhPDGF-BB on both bone and soft-tissue healing expands the ability to manage cases with bone atrophy and soft tissue dehiscence. For cases in which bone preservation is required, the tissue contours can be maintained with minimally invasive protocols. For sites requiring hard- and soft-tissue augmentation, these procedures can be combined to reduce the number of surgical procedures for patients. Although highly favorable clinical outcomes have been achieved using PDGF-BB in combination with deproteinized cancellous bovine bone grafts, Deproteinized cancellous bovine bone combined with PDGF-BB appear to stimulate more robust bone formation and rapid wound closure, enhancing the development and preservation of bony and gingival contours critical for achieving esthetic implant outcomes. The use of this growth factor in combination with scaffolds for therapeutic indications other than periodontal defects must be based on firm scientific rationale and sound medical evidence.

The clinical goals of growth factor enhanced therapy include less invasive surgical procedures with more robust and predictable treatment outcomes [19,34]. Although autogenous grafts remain widely considered the gold standard for the correction of localized ridge deformities [35], constraints in the volume of available autogenous bone and morbidity associated with graft harvest often limit treatment recommendations and patient acceptance. The ability to achieve optimal and predictable bone and soft tissue for the implant site development without the use of autogenous grafts offers great advantage to the clinician and patient.

The clinical application of bone xenografts for the development of extraction sites, lateral and vertical ridge augmentation is well documented in implant therapy [36,37]. Clinical evidence supports the use of xenogenic grafts for ridge augmentation for dental implant placement [38,39]; however, the extent of bone regeneration appears variable and dependent on factors such as graft form—particulate versus block—and defect location.

The overview presented in this article illustrates the application of bone substitutes and growth-factors enhanced grafts and highlight the favorable clinical results achieved with this therapeutic approach. However, controlled pre clinical experiments are still necessary to establish the relative effectiveness of biomaterials combined with biological factors for early bone formation in case of complex vertical and horizontal augmentation. The secondary studies should be addressed to determine the value of the barrier membranes to improve these procedures.

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Recenzent: Natalia Rusu*

## PARTICULARITĂȚILE REABILITĂRII IMPLANTO-PROTETICE LA PACIENȚII AFLAȚI SUB TRATAMENT ANTICOAGULANT

### Rezumat

Scopul studiului a fost de a determina condițiile optime de reabilitare implant-protetică a pacienților aflați pe fondal de medicație anticoagulantă fără anularea acestor remedii. În studiu au fost incluși 4 pacienți aflați pe fondal de medicație anticoagulantă, cărora au fost efectuate următoarele intervenții: instalarea a 21 implante dentare endosoase de stadiul doi, sinus lift transcrestal, sinus lift lateral bilateral. Medicația anticoagulantă nu a fost suspendată, iar doza acestor remedii a fost modificată în dependență de valorile coeficientului internațional de normalizare (INR). În timpul intervențiilor chirurgicale semne de sângerare sporită nu au fost depistate. În perioada postoperatorie a fost înregistrat un caz de hemoragie tardivă (la a 7-ea zi după inserarea implantelor), cauzată de o supradozare cu anticoagulant (INR=6,2), care a fost de intensitate nesemnificativă și ușor controlată prin aplicații locale de trombină umană și acid aminocaproic de 5%. Prin studiul efectuat a fost demonstrat că instalarea implantelor dentare și alte intervenții de chirurgie orală (sinus lift transcrestal, sinus lift lateral) la pacienții aflați sub medicație anticoagulantă este posibilă fără suspendarea acestor remedii, prioritate fiind acordată metodelor miniinvasive.

**Cuvinte cheie:** *implante dentare, tratament anticoagulant, coeficientul internațional de normalizare, hemoragie, tromboembolie.*

**Oleg Zănoagă,**  
*d. m., asist. universitar*

**Valentin Topalo,**  
*d. hab., prof. univ.*

**Dumitru Sirbu,**  
*d.m., conf.univ.*

**Ghenadie Cucu,**  
*asist. universitar*

**Andrei Mostovei,**  
*doctorand*

*Catedra Chirurgie OMF  
și Implantologie orală  
„Arsenie Guțan”  
USMF „N. Testemițanu”*