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Title: Atelo-Collagen Type I Bovine Bone Substitute and Membrane in Guided Bone Regeneration: a series of clinical cases and histopathological assessments

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Keywords: atelo-collagen membrane, guided bone regeneration, osseointegration, implant

Running Title: Atelo-Collagen Bone Substitute and Membrane

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Abstract

Absorbable atelo-collagen type 1 represents a new approach for guided bone regeneration with several reported advantages such as: osteoblast attachment, proliferation, mineralization potential, absorption of growth factors and inhibition of bacterial pathogen colonization. The aim of this study was to assess the clinical, radiological (preoperative width, re-entry width, gain), Periotest measurements and histologic benefits of atelo-collagen-derived bovine bone grafts (ImploBone) in combination with an atelo-collagen type I barrier membrane (ImploSorb) for guided bone regeneration (GBR) of atrophic alveolar crest in thirteen patients.

Eleven patients underwent simultaneous GBR with implant insertion, two had initial GBR procedure followed by implant placement after 6 months of healing. Ridge augmentation was performed using an atelo-collagen membrane (ImploSorb, Bioimplon, Germany) and a combination of 50% ABBM (ImploBone, granule size 0.5-1 mm, BioImplon Germany) mixed with 50% autologous bone.

It was found that simultaneous GBR with implant placement resulted in a 45% gain at bone defect level (preoperative width 4.76±1.3 mm, re-entry width 6.91±1.1 mm, gain 2.16±1.9 mm). Implant placement performed in a 2 stage surgery 6 months following GBR was linked with a 55% gain at bone defect level (preoperative width 3.94±1.1 mm, re-entry width 6.12±1.3 mm, gain 2.17±1.5 mm). The total gain in both groups was 49% utilizing these novel biomaterials (preoperative width 4.53±1.3 mm, re-entry width 6.69±1.2 mm, gain 2.16±1.7 mm).

This case series study presents a protocol where GBR can be performed either simultaneously to implant placement or delayed with this innovative biomaterial to favor bone regrowth. Future randomized controlled clinical trials are needed to further validate the bone-promoting potential of atelo-collagen-based biomaterials for bone regeneration.
Introduction

The placement of endosseous dental implants in the atrophic anterior and posterior areas of the jaw is frequently limited by inadequate bone volume (Bettach et al., 2014). A variety of surgical procedures have therefore been proposed to augment alveolar bone height and width, including guided bone regeneration (GBR), alveolar osteo-distraction, autogenous block grafting from intra/extraoral sites, and the use of biomaterial grafts with collagen/titanium barrier membranes (Felice et al., 2014). While autogenous bone is considered the gold standard for bone grafting procedures due to its excellent combination of osteogenic, osteoinductive and osteoconductive properties (Adeyemo et al., 2008), drawbacks including limited supplies, desire to minimize intra/extraoral bone harvesting and morbidity, invasiveness, and technically-demanding protocols including potential surgical complications have necessitated alternative options (Nkenke et al., 2002).

Over the past decade, GBR has become a standard grafting procedure with long-term documented follow-ups demonstrating optimal bone gain and support. The regeneration of bone can either be created utilizing a staged approach or simultaneous approach using various biomaterials as substitutes for alveolar bone regeneration (Hammerle et al., 2008). A number of clinical studies have shown that the combination of bone grafts with barrier membranes demonstrate excellent long-term outcomes for implants placed in regenerated sites (Buser et al., 2014; Nevins et al., 1998; Araujo et al., 2002; Maiorana et al., 2005). Furthermore, GBR procedures performed simultaneously to immediate implant placement into fresh extraction sockets also demonstrates high success rates (Lekholm and Zarb., 1985).

The use of absorbable collagen barrier membranes derived from animal sources represents a standard biomaterial utilized in regenerative dentistry. Typically, membranes are best characterized based on their resorption rates, space-maintaining ability and biocompatibility. Resorption times should last between 3-9 months depending on the surgical procedure performed (Lekholm and Zarb., 1985). Several studies have now reported that early removal of membranes is associated with reduced bone formation and potential for complications (Lekholm and Zarb., 1985; Becker et al., 1992). Autografts are known to induce optimal bone regeneration based on their ability to release osteoinductive growth factors (Miron et al., 2013; Miron et al., 2011), however due to their limited supply alternatives are required.

Xenografts are largely utilized in Europe where the use of allografts is restricted. The main disadvantage of this class of regenerative graft lies in their limited osteoconductive potential. Typically, all collagen/growth factors are removed during the processing of xenografts (commonly referred to as deproteinized). Recently the development of a natural bone mineral containing atelo-collagen type I has been developed utilizing atelo-peptidation and lyophilization technologies (Miron et al., 2013; Miron et al., 2011). This processing technique modifies the collagen components within the bone structure to non-immunogenic atelo-collagen making it possible to further improve the biocompatibility of grafting materials. (Fujioa-Kobayashi et al. 2017.) These xenografts have also been shown to preserve lyophilized collagen with lower humidity making the bone matrix more hydrophilic. Following sterilization, they contain roughly 2% moisture, 65-75% hydroxyapatite, 25-35% atelo-collagen content and up to 0.1% non-collagenous proteins.

Most of the research to date on atelo-collagen derived bone grafts and membranes have been performed in pre-clinical models demonstrating improved biocompatibility when compared to standard deproteinized xenografts. The aim of this study was to assess clinically, radiologically and histologically the benefits of this new generation of atelo-collagenized bovine bone mineral (ABBM) bone grafts with integrated Atelo-Collagen Type I in combination with an atelo-collagen type I barrier membrane for GBR procedures of atrophic alveolar crests. The ability of this new class of biomaterials to support tissue ingrowth and provide long-term stability of bone following GBR augmentation was evaluated.
Materials and methods

Patients

This study was approved by the local ethical committee (protocol no. 746/24.10.2016). Before all procedures, written informed consent was obtained from each patient. A number of 13 patients (4 males, 9 female), were enrolled in this study between June 2016 and June 2018, in a dental clinic in Cluj-Napoca, Romania. Criteria for inclusion were age ≥18 years, requirement for a bone augmentation procedure with implant placement and systemic health. Heavy smokers (e.g. ≥2 packs of cigarettes/day), drug users, alcohol consumption, systemic disease (diabetes mellitus, hyperparathyroidism, osteoporosis, liver dysfunction, cancer, immunosuppressive agents, corticosteroids) or pregnancy were excluded.

Pre-surgical evaluation

Pre-operative evaluation included a complete medical history, extra/intraoral examination and radiographic analysis of the edentulous area with orthopantomography (OPG) or Cone-Beam Computed Tomography (CBCT) (Figure 1). The edentulous alveolar ridge was measured on CBCT images to determine the buccal-lingual dimensions. In cases with an absence of two or more teeth, the coronal margin of the alveolar crest was measured at 5, 12 and 18 mm from the mesial tooth. In cases with one absent tooth, the alveolar crest was measured in the middle of the mesio-distal distance. Immediate implant placement with GBR was performed in cases where the width of the alveolar crest was above 3.5 mm (Figure 2. A). Cases with insufficient bone (the width of the alveolar crest was below 3.5 mm or post-extraction sockets), a GBR procedure was initially performed followed by implant placement after 6 months of healing (Figure 3. A). All cases included in this research presented an alveolar height proper for implant insertion.

Surgical protocol for GBR with simultaneous implant placement

Patients presenting an alveolar crest width ≥3.5 mm were treated with a ridge augmentation using an atelo-collagen membrane (ImploSorb, Bioimplon, Germany) and a combination of 50% ABBM (ImploBone, granule size 0.5-1mm, BioImplon Germany) mixed with 50% autologous bone and simultaneous implant placement.

After local anesthesia, the flap design was chosen to ensure primary tension-free closure after the bone grafting procedure despite a planned dimensional increase of the ridge. A full-thickness, mid-crestal incision into the keratinized gingiva was performed with a 15c surgical blade. The two divergent vertical incisions were placed one tooth away from the surgical site. In the terminally edentulous areas, the vertical incisions were placed at least 5 mm away from the augmentation site. The reflection of the full-thickness flap was made using periosteal elevators (Urban et al., 2011; Urban et al., 2014).

The edentulous alveolar ridge was then measured using a periodontal probe to determine the buccal-lingual dimensions. A periosteal releasing incision connecting the two vertical incisions was performed to achieve elasticity of the flap. Implant insertion was then performed. Drilling of the bone recipient site was performed with adequate irrigation in order not to overheat the bone, force and torque were adapted to different mandibular or maxillary regions. The recipient site was widened according to the manufacturer’s recommendations. Implant placement was made using the phisiodyspenser by adapting force and torque to maxillary or mandibular region.

Autogenous bone was harvested using an Auto-Max drill (MegaGen) from the retromolar regions. Autologous bone was then mixed with ABBM bone in a 50-50% ratio. The bone defect was reconstructed with this combination bone graft and covered with an ImploSorb barrier membrane (Figure 2. C, D).

A periosteal releasing incision connecting the two vertical incisions was performed to achieve elasticity of the flap. Once the membrane was completely secured, the flap was mobilized to permit tension free closure. Then, the flap was sutured in two layers. First, horizontal mattress sutures were placed 4 mm from the incision line, then single interrupted sutures were placed to close the edges of the flap. The single interrupted sutures were removed after 10-14 days’ post-surgery, and mattress sutures were removed after 2-3 weeks.

Post-operative instructions and medications (1g of amoxicillin-clavulanic acid, every 12h was prescribed, for 5 days post-surgery) were administered to the patient. The patient was evaluated postoperatively every 3 weeks after suture removal and complications were recorded if any of the following occurred: soft tissue dehiscence; membrane exposure; implant exposure; implant failure; abscess.

After 4 months, CBCT assessment of the GBR procedure was performed (Figure 2. B). Postoperatively, the measurements were performed applying the same protocol as in the presurgical stage.
A partial thickness flap was then raised, the implants were uncovered (Figure 2. E, F, G), and a biopsy from the newly formed bone was taken. Implants with the healing cap were periotested. Implants were loaded 4 months after GBR. A final restoration was then screwed into place (Figure 2. H) and final X-rays were taken one month later.

**Surgical protocol for GBR with implant placement after 6 months**

Patients presenting with an alveolar crest width of $\leq 3.50$ mm were treated by a first ridge augmentation procedure using an atelo-collagen membrane (ImploSorb, Bioimplon, Germany) and a combination of 50% ABBM (ImploBone, granule size 0.5-1mm, BioImplon Germany) mixed with 50% autologous bone. Implant placement was planned after 6 months. The GBR protocol was performed as described in the previous section. Prior to implant insertion, bone formation obtained through GBR was assessed using CBCT and OPG (Figure 3. B, C).

Implant placement was carried out 6 months later. The measurements of the bony ridge width was then taken (Figure 3. D). Implants were placed by raising a full-thickness mucoperiosteal flap following the protocol described for GBR with simultaneous implant placement (Figure 3. E). Implants were loaded 12 weeks post-insertion (Figure 3. F, G).

**Clinical Follow-up**

Follow-up visits were performed every 6 months after implant loading, with the last visit performed 24 months after implant loading. Follow-up visits were planned and performed every 6 months following prosthetic rehabilitation. Implant failure was assessed based on clinical signs – pain, presence/absence of pus and radiologically - bone loss surrounding the implant and appearance of a radio transparency surrounding the implant surface. No implant failure was recorded.

**Periotest evaluation**

After healing cap insertion, periotest measurements were taken using Periotest M. The Periotest M was positioned at a distance of 0.6-2.0 mm between the tip of the measurement probe and the healing cap in a perpendicular position to the vertical axis of the healing cap, a low pitched tone indicated that the position was correct. The measuring procedure took four seconds. The tapping head has a pressure sensitive tip which records the duration of contact with the implant. The looser the implant, the longer the contact time and the higher the Periotest value. Conversely, stable implants give short contact times, which means low Periotest value.

**Histological evaluation**

At the time of implant uncovering, tissue was harvested from the reconstructed site from three patients. Biopsy specimens were taken using a bone scrapper from the vestibular wall of the reconstructed site and from the alveolar crest. Dimension of the harvested bone was 2 mm width and 4 mm length. Harvested tissues were fixed in 10% formaldehyde for 24 hours, embedded in paraffin wax, sectioned at 3 micrometres, stained in Hematoxylin-Eosin (HE) and Tricrom Masson and then processed for histological analysis. Descriptive histology was then performed.

**Statistical analysis**

For each patient, the following data was recorded: age, gender, pre-operative alveolar crest dimension, post-GBR dimension of the alveolar crest, number of implants inserted, dimension and diameter of each implant, Periotest value at implant uncovering. All data were analyzed for means, standard deviations, percentages, correlations and Student test using GraphPad Prism 6 statistical software and Microsoft Excel. Normal distribution was verified using Saphiro-Wilk test. Two-tailed student test for unequal variances was used and p-values of less than 0.05 were considered statistically significant.

**Results**

Out of the 13 patients enrolled in our clinical study, two had a 2 stage GBR procedure followed by implant placement 6 months later. The other 11 patients had simultaneous GBR and implant placement. 18 guided bone regeneration procedures were performed in 11 patients, and a total of 25 implants were inserted (Table 1). Bone regeneration was then assessed clinically and radiologically at implant uncovering. All treated sites exhibited excellent bone formation. During the entire healing period, healing was uneventful in all cases with no reported
soft tissue dehiscence, membrane exposure, implant exposure, implant failure, or abscess reported. Table 1 indicates patient number and surgical site in the first column, columns 2,3,4 indicate age, sex and reconstructed arch. Preoperative bone defect width, re-entry bone defect width, gain in bone defect width are recorded in columns 5,6,7. Implant length and diameter (mm), Simultaneous Guided Bone Regeneration (GBR), Histology and Periotest value are recorded in columns 8,9,10,11.

No statistically significant differences in terms of bone defect or Periotest values between simultaneous GBR vs. post GBR implantation, maxilla vs. mandible, male vs. female was reported (Table 2). Simultaneous GBR and implantation resulted in a 35% gain in the ridge width following GBR procedure (preoperative width=5.03±1.25, re-entry width=6.81±0.98, gain=1.78±1.71). In the delayed approach, a 63.9% bone gain was noted (preoperative width=3.79±1.10, re-entry width=6.22±1.41, gain=2.43±1.43). The total combined bone gain in both groups was 41.9% (preoperative width=4.68±1.32, re-entry width=6.65±1.12, gain=1.96±1.64).

The histological evaluation from case 1 demonstrated that xenograft particles were partially resorbed and surrounded by newly formed bone, supporting the effectiveness of this material in promoting bone regeneration (Figure 4.A). Formation of viable bone, without multi-nucleated giant cells or any other indication of host-tissue inflammation or material rejection was noted. New blood vessel ingrowth was further evident suggesting that the material also supported new vascularization into the host tissues without inducing an immune response (Figure 4.B).

The histological evaluation from case 2 demonstrated that atelo-collagen membrane and a combination of 50% anorganic bovine bone matrix (ABBM) mixed with 50% autologous bone induced non-mineralized osteoid formation covered by a mineralized bone layer. Xenograft particles were fully resorbed and no longer identified (Figure 5). The presence of granulation tissue indicates an inflammatory response of the host to this material as part of the neoosteogenesis process. In all biopsies assessed the bone mix graft was connected with a dense network of newly formed bone of various degrees of maturation. There was no histologic evidence of the GBR membrane. Clinical and radiological follow-up of all patients included in this study indicated no implant failure.

(Tables 1,2) (Figure 4,5)

Discussion

While the role of bone grafting materials was initially described as a passive support for tissue ingrowth, more recently the aim has gradually evolved towards one that is able to actively support tissue regeneration (Miron et al., 2011; Miron et al., 2013). ABBM scaffolds containing atelo-collagen type I are processed utilizing atelopeptidation and lyophilisation technologies modifying the collagen components within the bone structure to non-immunogenic atelo-collagen (ImploBone, BioImplon, Germany). This processing technique does not use heat (thermal) processing which has been shown to negatively impact the natural crystalline micro-structure of hydroxyapatite, causing ceramization and destroying collagen components. In comparison with ABBM deproteinized bovine bone mineral (DBBM) is a defatted and deproteinized xenograft reduced to porous grains of different dimensions (0.25–2 mm), deprived of all its organic components through high-temperature processing in order to minimize an immune response (Gross, 1997).

The use of this new generation of atelopeptidized bovine bone mineral (ABBM) xenografts impacts the first two stages of bone regeneration by stimulating osteoblast attachment, proliferation, and increasing their mineralization potential (Figure 6). The use of collagen type 1 contained within bone grafts and barrier membranes plays an important role in inhibiting bacterial pathogens (Figure 7). Atelo-collagen-based grafts may also further provide protection against the early degradation of scaffolds induced by synovial fluids that contain various matrix metallopeptidases and plasmin proteins (Palmer et al., 2011; Elnayar et al., 2018).

Commonly-used xenografts are devoid of proteins and growth factors and have limited osteoconductive properties. The main concern related to ABBM-use was associated with its potential immune response induced by collagen. In vivo and in vitro studies have demonstrated the absence of pro-immune responses to ABBM grafts and for these reasons, the present case series sought to investigate clinically, histologically and radiologically the effects of ABBM in a human clinical study.

The presented case series demonstrated by clinical, radiological and histological means that bone regeneration following GBR with atelo-collagen based bone grafts and barrier membranes resulted in optimal bone without signs of inflammatory changes, rejections or allergic reactions in response to implantation of either of these biomaterials during the regenerative process. Our data provides evidence from human patients that directly supports previous studies (Miron et al., 2013; Miron et al., 2011). Our case series indicated that atelo-collagen based grafts are safe and effective in promoting bone regeneration of deficient ridges in the maxilla or mandible, in female and male patients. Healing in all the presented cases was uneventful. No complications including abscess, wound dehiscence, or membrane exposure occurred.
Based on the meta-analysis of Elnayef Bet et al, the GBR procedure was performed by overcorrection of the bone defects in order to compensate for the resorption of the grafting materials (Elnayef et al., 2018). Simultaneous GBR and implantation resulted in a 35% gain in ridge width at the bone defect level (preoperative width=5.03±1.25, re-entry width=6.81±0.98, gain=1.78±1.71). Postoperatively out of all cases with GBR simultaneous with implant insertion bone loss was recorded in three situations (7(1), 7(2), 10(3)). Although bone loss was recorded implant surface was not exposed and implants were osseointegrated, as indicated by the Periotest values recorded. The highest bone gain was recorded for the case 7(3), bone gain was associated with a good bone implant interface, as indicated by the Periotest values (-8).

Implantation six months after GBR was linked with a 63.9% bone gain (preoperative width=3.79±1.10, re-entry width=6.22±1.41, gain=2.43±1.43). The total bone gain in both groups resulted in a 41.9% increase in bone ridge width (preoperative width=4.68±1.32, re-entry width=6.65±1.12, gain=1.96±1.64). Prior to implant loading, the Periotest values also indicated good bone quality at the bone-to-implant interface. Periotest values were not statistically significantly different between groups or correlated with age, sex, or the re-entry width of the bone defect. The best Periotest values were recorded for implant inserted in the maxilla (1(3), 4(1),7(3), 8(1), 9(1), 9(2)) as indicated in Table 1. This indicates that although the maxilla is characterized by a low density, proper vascularization can induce a good bone implant interface. Only one implant inserted in the mandibula recorded -8.2 Periotest values.

In this case series treated with the mixture of atelo-collagenized bovine bone mineral and autogenous bone showed good incorporation with the newly formed ridge. This finding is supported by histology of the augmentation area showing that the bone mix graft was connected by a dense network of newly formed bone. Clinical and CBCT assessment indicated sufficient quantity of bone for implant insertion.

The benefits of this new generation of atelo-collagenized bovine bone mineral (ABBM) bone grafts with integrated Atelo-Collagen Type I (ImploBone, BioImplon) in combination with an atelo-collagen type I barrier membrane (ImploSorb, BioImplon) for GBR procedures of atrophic alveolar crests, can offer less morbidity and therefore increased patient comfort and quality of life. Other techniques used to improve the bone offer in atrophic alveolar crest are bone blocks. This technique is associated with varying morbidity depending on the harvest site (Nkenke et al., 2001; Nkenke et al., 2004; Raghoebar et al., 2001) and early resorption (von Arx and Buser., 2006). In light of that guided bone regeneration techniques have been recommended as an alternative for improving bone offer in ridge atrophy (Chiapasco et al., 2006). Von Arx and Buser (von Arx and Buser., 2006) reported a combination of bone blocks and GBR, by covering bone blocks with particulated xenografts and resorbable membranes. At re-entry, the xenograft particles showed fibrous encapsulation only and no osseous integration. This finding supports the use of particulated autogenous bone mixed with xenograft rather than xenograft layered onto autogenous bone blocks (Urban et al., 2011). In the same study, the authors found no differences between the sites augmented with particulated autogenous bone only and those augmented with a mixture of particulated autogenous bone and xenograft. Combining particulated xenografts and autograft reduces patients discomfort during surgery, reduces surgery time and reduces postoperative recovery by minimal invasive approach. GBR techniques induce bone formation that can sustain implants with a good survival rate (Hämmerle et al., 2002).

(Figure 6, 7)

Conclusions

In vitro and vivo studies assessing the potential of ABBM bone grafts for bone regeneration have demonstrated an advantage for the processing of xenografts utilizing these technologies. This case series presents a protocol where GBR using these innovative bone biomaterial favors bone regrowth. Future large randomized controlled clinical trials including a larger number of patients are now needed to further evaluate the use of atelo-collagen-based biomaterials for bone regeneration.
FIGURE LEGENDS

Figure 1. Patients pre-surgical assessment protocol

Figure 2 - Case 1 Alveolar crest above 3.5 mm. A: CBCT showing an angulated mandible with indication for GBR + simultaneous implant placement; B: After 4 months, CBCT demonstrated adequate bone formation (red arrow) in the horizontal direction; C, D: Implant placement in sites 3.4 and 3.6, followed by GBR. Horizontal augmentation filled with a mixture of 50% autogenous bone harvested with an Auto-Max drill (MegaGen) and 50% atelo-collagen derived xenograft (ImploBone, granule size 0.5-1mm, BioImplon, Germany); E: Implants uncovered and newly formed bone around the implants; F: healing caps in position; G: 4 months post-grafting - clinical aspect of the peri-implant soft tissue; H: The final prosthetic restoration screwed into position.

Figure 3 - Case 2 Alveolar crest below 3.5 mm. A: CBCT showing the width of the alveolar crest <3.5 mm; B: After 6 months post-GBR, CBCT showed adequate bone formation (blue arrow) in the horizontal and vertical direction. Due to lack of sufficient horizontal and vertical bone a Cytoplast membrane and a titanium screw were used to create and support an adequate regenerative space with minimal compression on the reconstructed bone; C: After 6 months of healing, OPG indicated adequate bone formation; D: Newly formed bone 6 months after GBR; E: Implants in position; F, G: The final prosthetic restoration screwed in position.

Figure 4 - Case 1. A: Fragment of viable bone tissue, formed through reactive ossification. In the conjunctive tissue, dead bone tissue fragments are present (blue arrows) which could be the cause of reactive ossification; HE x40 B: Details from the viable bone (osteocytes in the osteoplast) and small fragments of dead bone (blue arrows). HE x100

Figure 5 - Case 2. Viable bone chips, formed 90% of the non-mineralized osteoid coloured red in Tricrom Masson (*) and covered only on the surface by a mineralized bone layer coloured green in Tricrom Masson (+). Bone chips are in granulation tissue. (scale indicated in the figure)

Figure 6. Bone regeneration stages.

Figure 7. ABBM advantages over DBBM.

TABLE LEGENDS

Table 1. Surgical sites treated with GBR using atelo-collagen membrane (ImploSorb, Bioimplon, Germany) and a combination of 50% ABBM (ImploBone, granule size 0.5-1mm, BioImplon Germany) mixed with 50% autologous.

Table 2. Periotest value was correlated with the following parameters: age (weak negative correlation, r=-0.282), re-entry width of bone defect (moderate negative correlation, r=-0.475) and gain of bone defect (weak negative correlation, r=-0.240).
References


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Table 1
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Table 2
Patients n=13

Alveolar crest < 3.5 mm n=2

GBR

Alveolar crest ≥ 3.5 mm n=11

GBR + Implant placement
Bone regeneration
Implant osseointegration

Osteoconductive

Non-collagenic
Bone formation, mineralization

Bone remodelling

Vascular invasion

Citokine release:
PDGF, TGFβ
IL-1, 6
IGF,
FGFR 1, 2
FGF 1, 2
BMP-2,3,4,6,7,8
TNFα
MCBF, VEGF

Cell recruitment:
LYM, PMN, MONO
MSC
Osteoblasts

Differentiation of pre-osteoblasts into osteoblasts which form the osteoid matrix later mineralization to give rise to bone tissue without trabecular architecture (non-functional bone).
ABBM - Advantages

- Improving osteoblasts attachment, proliferation, differentiation. Increase mineralization potential.
- New blood vessels ingrowth
- Inhibit bacterial pathogens
- Minimise an immune response
- Prevents early degradation of the graft