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Deproteinized bovine bone in periodontal and implant surgery

N. Baldini, M. De Sanctis, M. Ferrari*

Department of Periodontics and Fixed Prostheses, Faculty of Odontology, University of Siena, Italy

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ABSTRACT

Objectives. To review the histological and clinical outcomes of deproteinized bovine bone in different procedures: periodontal regeneration, socket preservation, peri-implant reconstruction and alveolar bone augmentation.

Methods. Histological animal studies and clinical trials on humans regarding the performances of a bone substitute of natural origin, deproteinized bovine bone, have been evaluated. Different procedures have been examined separately.

Results. Osteoconductive properties of the material are accepted by the majority of authors. In periodontal regeneration deproteinized bovine bone seems to be effective with or without barrier membranes in favorable containing defects, resulting in histological evidence of periodontal regeneration, with a prevalence of bone repair.

Although some reports describe a lower reduction in socket height and width with various techniques and the grafting of deproteinized bovine bone, there is no evidence to recommend socket filling or manipulation to preserve its dimensions.

Peri-implant reconstruction and alveolar ridge augmentation utilizing deproteinized bovine bone are supported by favorable reports but these procedures are affected by a significant amount of adverse events that may jeopardize the success of the treatment.

Significance. Deproteinized bovine bone possesses osteoconductive properties that may improve bone regeneration of favorable containing periodontal defects. No evidence supports socket filling and peri-implant reconstruction.

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1. Introduction

In recent years periodontal regeneration and alveolar bone regeneration have been widely investigated, changing the paradigms of surgical procedures and clinician's treatment planning.

The possibility of reconstructing an infrabony periodontal defect or a resorbed edentulous ridge or to prevent the resorption of the extraction socket represents a significant improvement in the treatment in a number of clinical conditions.

In this regard the use of bone grafts aims to facilitate bone healing and to enhance bone regeneration after a surgical procedure. Bone graft is advocated to act as a sustain for coagulum stabilization and to reduce the risk of soft tissue collapse into the bone defects. The biological rationale in the utilization of bone graft is based on three different healing mechanisms: osteogenesis that is the capacity of the graft to bring into the defect new bone forming vital cells, osteo-

* *Corresponding author at*: Dipartimento di Scienze Odontostomatologiche dell'Università degli Studi di Siena Policlinico Le Scotte, Viale Bracci, Siena, Italy.
E-mail address: baldini.nicola@gmail.com (N. Baldini).

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conduction, the capacity of the graft to serve "passively" as a scaffold for bone formation, osteoinduction, the presence into the graft of bone-inducing substances that may induce an osteoblastic differentiation into host's not-differentiated cells [1]. Probably the best grafting material would be patient's own bone due to its osteogenetic, osteoinductive and osteoconductive properties. Autogenous bone grafts have been recommended by many authors for both periodontal and alveolar bone reconstruction procedures [2–6]. Nevertheless, the withdrawall of autologous bone is an invasive procedure, often requiring a second surgical access for the donor site. Bone substitutes represent a possible alternative to autogenous bone in many situations. Ideally a bone substitute should posses characteristics of biocompatibility, absence of antigenic effects, possibility of sterilization associated with mechanical properties as space maintenance capacity and easy to manipulate during surgical phases. They essentially have an osteoconductive function, since they guarantee a biomechanical support that gives stabilization to the coagulum in the first healing phases and a scaffold for new bone repairing in the later phases [7]. There is a great number of bone substitutes available for clinical use, both of natural and synthetic origin. Demineralized freeze-dried human bone, xenogenic bone substitutes like natural and synthetic hydroxyapatite, deproteinized bovine bone and calcium phosphate compounds are the most investigated and commonly used. In the group of natural ones, deproteinized bovine bone (Bio-Oss®) is widely supported by scientific literature; it has been tested extensively in vitro and in vivo, in a number of researches from animal preclinical studies to human randomized clinical trials.

Bio-Oss® is a bovine bone derivate that undergoes a low heat (300 °C) chemical extraction process by which all organic components are removed, but maintains the natural architecture of bone [8].

Animal studies on rabbit's skulls [9,10] have demonstrated the biocompatibility of this material, by placing deproteinized bovine bone into surgically created calvarial defects; Klinge et al. [11] implanted natural bone mineral (Bio-Oss®) in experimental defects in rabbits and reported that this material, containing in its morphology, inner macropores similar in size to natural cancellous bone, provided an ideal scaffold for new bone formation.

Pre-clinical studies on animal models further tested the healing pattern around material's particles and their behavior in a short-time period when applied in a clinical environment reproducing an human's bone defect: in histological sections Bio-Oss® particles were well detectable, usually surrounded by a varying amount of newly formed bone, osteoid tissue and marrow including blood vessels [12,13].

Human biopsies detected a bone blend, a mix of biomaterial and bone tissue: new bone formation has been described as predominantly thin trabeculae in continuity with resident bone often contacting, occasionally immersing, the particulate bovine bone biomaterial. The bone substitute occupies a major portion of the defect sites, in sections distant from resident bone. In the more coronal aspects of the sites, the bone particles largely appear embedded in fibrovascular connective tissue. Nevertheless the new bone formation does not always parallel a new cementum deposition and the regenerated periodontal ligament often appears irregular in shape and width without distinct periodontal fiber bundles connecting the newly formed cementum and bone [14–17].

Deproteinized bovine bone has been suggested to have also an osteocoductive function [12]; despite the absence of organic materials, since Bio-Oss® possesses authentic hydroxyapatite crystals, and therefore may permit the prompt attachment of osteoblasts and subsequent deposition of new bone matrices [18].

Deproteinized bovine bone resorption is a controversial issue: osteoclastic activity on biomaterial's particles, scalloped-edged resorption pits and the presence of giant multi-nucleated cells have been documented [18]; reports with short healing intervals suggest that the bovine bone biomaterial undergoes osteoclastic resorption [12,19], implying that the material would eventually be cleared from the defect site. Nevertheless deproteinized bovine bone seems to be inert and stable over time and to remain sequestered in bone, marrow, and fibrovascular tissue (up to 10 years) [20,21]. Other studies failed to demonstrate the presence of an osteoclastic activity around biomaterial's particles [22].

The aim of this study is to produce a review on the clinical performance of deproteinized bovine bone in three different conditions: regeneration of periodontal defects, manteinence of post extractive sockets, lateral and vertical augmentation of alveolar bone.

2. Bone substitutes in periodontal regeneration

Periodontal regeneration is defined as regeneration of the tooth-supporting tissues including cementum, periodontal ligament and alveolar bone [23].

Although periodontal regeneration is a possible objective of several periodontal therapeutic modalities, outcomes of such modalities are not always predictable. Clinical outcomes do not necessarily reflect true regeneration. In particular with mineralized grafting materials the interpretation of radiographic and probing evidence is difficult.

The regenerative potential of periodontal tissue is an accepted issue. Melcher's studies [24] clarified the healing pattern of the periodontal wound. The type of cells that first colonizes the wounded area characterizes the type of healing. The apical downgrowth of junctional epithelium is the more frequent event in the healing process. If it is not impeded, the downgrowth of the gingival epithelium may mediate the relationship between the root surface and the maturing coagulum, thus creating a long junctional epithelium [25].

Although in some cases a conventional periodontal therapy may result in bone repair, histological studies have demonstrated that an epithelial lining is often interposed between the root surface and the newly formed bone [26]. Histological findings from a series of animal experiments have demonstrated that periodontal ligament cells play an important role in determining the formation of a new connective tissue attachment [27–29].

Animal researches has confirmed that periodontal surgical wounds undergo the same sequence of healing events as all incisional wounds, with the formation of a fibrin clot between

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the flap margin and the root surface, followed by the replacement of this fibrin clot by a connective tissue matrix attached to the root surface [30]. Data also suggest that when this "fibrin linkage" is maintained, a new connective tissue attachment to the root surface develops while the fibrin linkage is disrupted, a long junctional epithelium results [31].

Actually osseous grafting and guided tissue regeneration (GTR) are the two techniques with the best histological evidences of periodontal regeneration [32].

Bone grafts have been claimed as useful adjunctive to gain blood clot stability into the periodontal defect: significantly greater loss of alveolar crest height was demonstrated in nongrafted than grafted defects; regeneration of new attachment apparatus, showing new bone, and new cementum occurred more frequently in grafted when compared to nongrafted defects [33]. Autografts, allografts, xenografts, and alloplasts, with or without the use of barrier membrane, remain among the most widely used therapeutic strategies for the correction of periodontal osseous defects [34].

Pre-clinical animal studies evaluated the influence of bone grafts and membranes in different types of surgically created periodontal defects: supra alveolar defects, furcation defects, intra-bony defects and fenestration defects have been tested: independent of defect type and animal model, regenerative periodontal surgery using combinations of barrier membranes and grafting materials may result in periodontal regeneration to a varying extent [35].

A work of Sonis in 1985 [36] documented histologically the sequence of healing following implantation of bovine demineralized bone powder into severe, spontaneous periodontal defects in beagle dogs. No differences were found in the progression of periodontitis between sites treated with xenograft and control sites treated with conventional flap surgery. Nevertheless authors underlined the capacity of new bone substitute to successfully induce bone formation.

Yamada et al. [37] evaluated the differences in the histological healing of surgically created periodontal defects in dogs between a guided tissue regeneration performed with a collagen membrane (Bio-Gide®) and with or without the adjunction of deproteinized bovine bone (Bio-Oss®). New cementum with inserting collagen fibers was observed on the exposed surfaces in both groups. The amount of new bone was significantly greater in the group treated by means of bone graft and barrier membrane than in the control group. Authors concluded that the use of the collagen barrier membrane in combination with the porous bone graft material may enhance new bone and cementum formation.

Sculean et al. [35], in a recent review on preclinical animal studies, stated that data from controlled clinical studies do not seem to clearly indicate improved clinical outcomes in terms of probing depth reduction, clinical attachment level (CAL) gain and defect fill when the combination of grafting materials and GTR is compared with GTR alone or grafting materials alone [38].

Sculean's review [35] concludes that: no additional benefits of combination treatments were detected in models of three wall intrabony, Class II furcation or fenestration defects, while in supra-alveolar and two wall intrabony (missing buccal wall) defect models of periodontal regeneration, the additional use of a grafting material gave superior histological results as far as bone repair when compared to barrier membrane alone.

In a study using a supra-alveolar model, combined graft and barrier membrane gave a superior result to graft alone [39].

Data from systematic reviews suggest that the implantation of grafting materials may indeed result in superior clinical outcomes in terms of probing depth reduction and clinical attachment gain compared with open flap debridement [34,40].

In a recent literature review [40] concluded that the use of specific biomaterials is more effective than open flap debridement in improving attachment levels in intraosseous defects. Differences in CAL gain vary greatly with respect to different biomaterial agents. General conclusions about the expected clinical benefit of grafts need to be interpreted with caution, due to significative heterogeneity of results among the studies in most treatment groups.

Bone substitutes provide better clinical outcome in the treatment of periodontal bone defects than surgical debridement alone. With respect to the treatment of intrabony defects, the results of metaanalysis support the following conclusion: bone grafts increase bone level, reduce crestal bone loss, increase clinical attachment level, and reduce probing pocket depths when compared to open flap debridement procedures.

Deproteinized bovine bone has been tested in several human clinical studies in periodontal defect alone or in association to autogenous bone, collagen membranes, enamel matrix derivate, or collagen matrix [41–45].

Mellonig demonstrated in a human histologic study new bone, new cementum, and new periodontal ligament in 3 of the 4 specimens of the study utilizing in periodontal defects bovine-derived xenograft and covered with a bioresorbable barrier [15].

In an human histological study, Camelo observed that autogenous bone in combination with porous bone mineral matrix, as well as the Bio-Gide collagen membrane, have the capacity to stimulate substantial new bone and cementum formation with Sharpey's fiber attachment [46].

Lekovic et al. [47] showed that deproteinized bovine bone has the ability to augment the effects of enamel matrix protein in reducing probing pocket depth, improving clinical attachment levels, and promoting defect fill when compared to presurgical levels.

Richardson et al. [48] compared the bovine derived xenograft (BDX) Bio-Oss to demineralized freeze dried bone allograft (DFDBA) in a randomized clinical trial examining 30 human intrabony defects. Each material was used alone, without membranes, root conditioners, and antibiotics. The results demonstrated that when compared to baseline a significant improvement in defect parameters was seen in both groups, but there was no statistical difference between the materials when compared to one another.

Scabbia and Trombelli [49] evaluated the clinical outcome of deep intra-osseous defects following reconstructive surgery with the use of a synthetic hydroxyapatite/equine Type I collagen/chondroitin sulfate biomaterial (Biostite), as compared to a bovine-derived hydroxyapatite xenograft (Bio-Oss). The results of the study indicated that both Biostite and Bio-Oss

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produce a statistically significant improvement in terms of CAL gain, PPD reduction and radiographic DEPTH gain when used in the treatment of deep intra-osseous defects.

Recent studies demonstrated that periodontal reconstruction obtained with a GTR therapy, with or without the adjunction of deproteinized bovine bone, seems to remain stable over time [50,51].

It may be concluded that demineralized bovine bone, as other bone grafts, in periodontal regenerative procedures seems to be effective with or without barrier membranes in favorable containing defects, resulting in histological evidence of periodontal regeneration, with a prevalence of bone repair. There is limited evidence supporting the potential of combined therapy of barrier membranes and grafting materials in non-containing defects. Further studies on appropriate animal models, creating supra-alveolar not-containing defects, are needed to produce evidences on these aspects of periodontal regenerative procedures [52].

3. Bone substitutes in socket preservation

Tooth extraction is followed by dimensional changes of the alveolar ridge contour: marked alterations of the height and width of the alveolar ridge will occur following single or multiple tooth extractions. The healing process following tooth removal apparently results in more pronounced resorption on the buccal than on the lingual/palatal aspects of the ridge.

Araùjo and Lindhe [53] clarified that the resorption of the buccal/lingual walls of the extraction site occurred in two overlapping phases. During a first phase, the bundle bone was resorbed and replaced with woven bone. Since the crest of the buccal bone wall was comprised solely of bundle bone this modeling resulted in substantial vertical reduction of the buccal crest. The reduction of the height of the walls was more pronounced at the buccal than at the lingual aspect of the extraction socket. Following the removal of a tooth, the bundle bone at the site will lose its function and disappear. In a second phase, resorption occurred from the outer surfaces of both bone walls: at eight weeks, histological samples showed numerous osteoclasts both on the outer surface of the crestal and on a more apical region of the buccal bone, while scattered osteoclasts were found in the corresponding locations of the lingual bone wall.

Socket preservation at time of tooth extraction has been advocated to minimize horizontal ridge resorption and facilitate ideal implant placement and thus an aesthetic site reconstruction.

Different approaches have been developed to preserve or improve the ridge contour following tooth extraction: the use of immediate implants, occlusive membranes with or without graft materials, grafting with different bone substitutes.

Araùjo et al. [54] evaluated the dimensional alterations of the alveolar ridge that occurred following implant placement in fresh extraction sockets.

The placement of an implant in a fresh extraction site failed to prevent the re-modeling that occurred in the bone walls of the socket. The resulting height of the buccal and lingual walls at 3 months was similar at implants and edentulous sites and vertical bone loss was more pronounced at the buccal than at the lingual aspect of the ridge. Results from this study indicate that the placement of an implant in the fresh extraction site failed to prevent the re-modeling that occurred in the walls of the socket. Also it was suggested that the resorption of the socket walls that occurs following tooth removal must be considered in conjunction with implant placement in fresh extraction sockets.

Araujo et al. in a following study [55] indicate that the remodeling process of the alveolar bone continues even after the process of osteointegration has occurred in fact, part of the bone that was “integrated” on the implant surface was lost at 8 weeks healing on the buccal surface.

Botticelli et al. [56] assessed the dimensional alterations that occurred in the alveolar ridge during a 4-month period following implant placement in fresh extraction sockets. The distance between the implant surface and the buccal and lingual/palatal bone walls was measured at baseline and at re-entry after 4 months. The authors concluded that during the 4-month interval following tooth extraction the buccal bone dimension had undergone horizontal resorption that amounted to about 56%. The corresponding reduction of the lingual/palatal bone wall was 30%.

Similar findings were evidenced by Araújo et al. [55] evaluating implants inserted in different bone morphologies. By placing implants in the premolar and molar region, they evidenced that buccal bone resorption occurred irrespectively from the thickness of the bony wall, in fact molar area with thicker buccal bone wall showed the highest degree of reduction in bone volume.

de Sanctis et al. [57] have investigated on the influence of implant morphology and shape on bone remodeling. They evidenced, utilizing 4 different implant systems that the same buccal resorption occurred irrespectively of the implant morphology.

Other studies reported a significantly reduction of bone resorption both in vertical and horizontal direction in sites where the socket was covered with a membrane when compared to control sites where only extraction was performed [58,59].

Bone graft has been proposed as a method for maintaining alveolar ridge dimensions after tooth extraction [60–62].

Becker et al. [63] tested different materials in post-extraction sockets: deproteinized bovine bone, demineralized freeze-dried bone, autogenous bone and human bone morphogenetic proteins in an osteocalcein/osteonectin carrier. The results of this study indicated that bovine bone, DFDBA, and intraoral autologous bone do not promote healing in extraction sites. Authors also stated that intraoral autologous bone, xenogenic bone, and DFDBA appear to interfere with the normal healing processes in extraction sites.

Carmagnola et al. [64] in an human study divided 31 post-extractive sockets into 3 groups: in group A sockets were covered with a collagen membrane, in group B sockets were filled with deproteinized bovine bone (Bio-Oss®) and group C served as control without further treatments. Authors reported that samples from group A showed large amounts of lamellar bone and bone marrow and small proportions of woven bone. Sites grafted with Bio-Oss® (group B) were comprised of connective tissue and small amounts of newly formed bone surrounding the graft particles. Only

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40% of the circumference of the Bio-Oss® particles was in contact with woven bone. Sites from group C were characterized by the presence of mineralized bone and bone marrow.

Araújo et al. [65], in an animal study on dog models utilizing deproteinized bovine bone and collagen matrix Bio-Oss Collagen®, reported that the presence of Bio-Oss Collagen® failed to inhibit the processes of modeling and remodeling that took place in the socket walls following tooth extraction. However, it apparently promoted de novo hard tissue formation, particularly in the cortical region of the extraction site. Thus, the dimension of the hard tissue was maintained and the profile of the ridge was better preserved. Authors concluded that the placement of a biomaterial in an extraction socket may promote bone modeling and compensate, at least temporarily, for marginal ridge contraction.

The same group in another study [66] evaluated the long-term effect on the hard tissue formation and the amount of ridge augmentation that can occur by the placement of a xenogeneic graft in extraction sockets of dogs.

The placement of Bio-Oss® collagen in the fresh extraction socket served as a scaffold for tissue modeling but did not enhance new bone formation. In fact, when compared with the non-grafted sites, the dimension of the alveolar process as well as the profile of the ridge was better preserved in Bio-Oss®-grafted sites. The authors concluded that the placement of a biomaterial in an extraction socket may modify modeling and counteract marginal ridge contraction that occurs following tooth removal.

A recent work of Araújo et al. [67] clarified the mechanisms of incorporation of Bio-Oss Collagen® in the host tissue: they described different phases. The biomaterial is first trapped in the fibrin network of the coagulum. Neutrophilic leukocytes (PMN cells) migrate to the surface of the foreign particles. In a second phase the PMN cells are replaced by multinuclear osteoclasts. The osteoclasts apparently remove material from the surface of the xenogeneic graft. 1–2 weeks later, osteoclasts disappeared from the Bio-Oss® granules: they were followed by osteoblasts that laid down bone mineral in the collagen bundles of the provisional matrix. In this third phase the Bio-Oss® particles became osseointegrated.

Fickl et al. [68] showed that the placement of DBBM into extraction sockets is a suitable technique for socket augmentation which has the potential to maintain the ridge dimension to a certain amount, although the preservation of the buccal bone plate and complete ridge stabilization could not be shown.

A recent histological study performed by the same group [69] on dogs histometrically assessed alterations of the ridge following socket preservation alone and socket preservation with additional buccal overbuilding. Four different techniques of socket preservation were tested. In group 1 the socket was filled with Bio-Oss Collagen® and covered with a free gingival graft derived from the palate. In group 2 the buccal bone plate was augmented using the GBR-technique, the socket was filled with Bio-Oss Collagen® and covered with a free gingival graft. In group 3 the buccal bone plate was forced into a buccal direction using a manual bone spreader. The socket was filled with Bio-Oss Collagen® and covered with a free gingival graft from the palate. In group 4 the socket was filled with Bio-Oss Collagen® and a combined free gingival/ connective tissue graft was used to cover the socket and for buccal tissue augmentation. Authors reported that all treatment groups showed horizontal and vertical bone loss. The mean vertical bone loss of the buccal bone plate was significantly lower in group 4 than in the other groups, while no statistical significant differences could be detected among the groups in the horizontal dimension.

They concluded that overbuilding the buccal aspect in combination with socket preservation does not seem to be a suitable technique to compensate for the alterations that follow tooth extraction.

In Fickl's study [69] authors underlined that the effect of invasive over-augmentation procedures was nullified by an additional resorption of the buccal bone plate induced by the supplementary trauma applied to the buccal tissue during the extra intervention.

Another study of the same group [70] described a major bone resorption when extraction was performed in conjunction with a muco-periosteal flap compared to sites where extraction was performed flapless thus confirming that a more invasive technique determines an increased bone loss.

Jung et al. [71] described in a case series of twenty patients a punch technique for post-extraction tissue management: socket was filled with Bio-Oss® and then covered with a graft of palatal mucosa harvested with a punch technique.

Nevins et al. [72] in a clinical study, demonstrated the advantage of augmenting extraction sockets with deproteinized bovine bone material (DBBM), as compared with untreated controls. However, the authors reported a mean reduction of the buccal bone plate of DBBM-treated extraction sockets of 2.42 mm, resulting in a failure to preserve the alveolar ridge.

Mardas et al. [73] in a randomized, controlled clinical trial evaluated the capacity of a synthetic bone substitute (Straumann Bone Ceramic®) or a bovine-derived xenograft (Bio-Oss®) combined with a collagen membrane to preserve the alveolar ridge dimensions following tooth extraction.

No differences in the width of buccal and palatal bone plate were observed between the two groups.

Both biomaterials partially preserved the width and the interproximal bone height of the alveolar ridge.

From available data it can be concluded that neither grafting the socket with bone substitutes nor augmentation procedures of the buccal bone plate are able to alter the biologic process which takes place in extraction socket with particular respect to the resorption of the buccal bone plate. Although some reports describe a minor reduction in socket height and width with various techniques, evidence is still lacking to recommend socket filling or manipulation to preserve its dimensions. Care must be exercised when inserting implants at fresh extraction sockets.

4. Bone substitutes around implants

The use of titanium dental implants is considered as a successful and predictable treatment for partial and full edentulism [74].

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The presence of a sufficient bone crest, allowing for a correct implant insertion, is a pre-requisite for the treatment.

An alveolar bone crest inadequate, in terms of quantity and quality of the available bone, is a common and well known problem for implant placement. In recent years many surgical techniques have been described to correct and allow for the treatment of these clinical conditions: these surgical approaches may be performed before implant placement, in a separate phase, creating an augmented bone crest before implant insertion; on the other hand, if the available bone allows for primary stabilization of the implant, bone crest may be reconstructed during the implant procedure in a single surgical phase.

Interventions to correct these conditions can be classified in lateral and vertical ridge augmentation as well as sinus floor elevation or distraction osteogenesis.

The use of bone substitutes and in particular of deproteinized bovine bone has been described in bone regenerative procedures.

Animal studies on rabbit sculls tested the biocompatibility of deproteinized bovine bone as a filler during a guided bone regeneration procedure: in combination with a stiff resorbable membrane made of polylactic acid, the deproteinized bovine bone increased the amount of initial soft tissue formation and the rate of mineralized bone formation compared to blood-filled control sites [75,76].

In a series of studies on animals the clinical performances of the material in regenerative procedures of surgically created peri-implant defects have been tested.

Hämmerle et al. [19] used Bio-Oss® in standardized dehiscence defects (2.5 mm in width and 3 mm in height) around implants in monkeys. Four different procedures were compared (2 sites for each procedure): defect covered by an expanded polytetrafluoroethylene (e-PTFE) membrane, defect filled with Bio-Oss®, Bio-Oss® covered by a membrane and a control site without any regenerative treatment. Authors reported a mean vertical bone growth on implant surface exposed of: 100 ± 0% for Bio-Oss® + membrane group, 91 ± 9% for membrane group, 52 ± 24% for Bio-Oss® group and 42 ± 35% for control group. Similar results were reported for horizontal bone growth. They also reported about 80% direct bone-to-graft contact when an expanded polytetrafluoroethylene (e-PTFE) membrane was used and 89% when there was no barrier. However, they did not indicate whether the measured proportions included bone marrow-to-graft contact or solely contact areas adjoining the mineralized bone.

A similar study has been performed by Hockers et al. [77] on dogs to test Bio-Oss® and a collagen membrane (Bio-Gide®). Four different procedures were tested: defect covered by a Bio-Gide® membrane (BG), defect filled with Bio-Oss® covered by a Bio-Gide® membrane (BG + BO), defect filled with autogenous bone covered by a Bio-Gide® membrane (BG + Aut) and a control site without any regenerative treatment (C).

The vertical bone growth amounted to 45% (SD ± 13%) of the defect height in the BG group, to 78% (SD ± 29%) in the BG + BO group, to 69% (SD ± 9%) in the BG + Aut group, and to 22% (SD ± 10%) in C group. The horizontal bone growth measured 78% (SD ± 16%) in the BG group, 81% (SD ± 21%) in the BG + BO group, 82% (SD ± 12%) in the BG + Aut group, and 46% (SD ± 21%) in the C group. The vertical height of bone growth in contact with the implant measured 17% (SD ± 12%) in the BG group, 20% (SD ± 12%) in the BG + BO group, 17% (SD ± 7%) in the BG + Aut group, and 12% (SD ± 8%) in the C group. Authors remarked that deproteinized bovine bone and autogenic bone grafts appeared to be equally well integrated into regenerating bone and no additional effects in the bone growth were observed with the autogenous bone.

Carmagnola et al. [78] in a study on dogs placed implants in artificially bone defects previously filled with Bio-Oss®. Implant were inserted after 5 months from the first surgery. Authors observed that osseointegration failed to occur to implant surfaces within the alveolar ridge portion previously augmented with Bio-Oss®. In the augmented portion of the crest, the graft particles were separated from the host tissue as well as from the implant by a well-defined connective tissue capsule. Although the lingual aspect of all fixtures (test and control) was in contact with hard tissue at the time of installation, after 4 months of function, a deep vertical bone defect frequently had formed at the lingual surface of the implants. Authors concluded that Bio-Oss® failed to integrate with the host bone tissue and no osseo-integration occurred to the implants within the augmented portion of the crest.

Araùjo et al. [79] utilized a block of Bio-Oss® for lateral ridge augmentation on dogs. After tooth extraction artificial defects were created: a block of Bio-Oss® of cylindrical shape was fixed to the buccal surface of the defect and compared to an autogenous block of the same dimension. Both implant materials were covered by a resorbable barrier membrane.

In the Bio-Oss® site the outer portion of the graft was separated from the mucosa by dense layers of connective tissue that occasionally also contained remnants of the membrane placed during surgery to protect the graft. Close to the interface between the graft and the host bone, a varying amount of newly formed bone had established contact with the biomaterial.

In more peripheral areas of the graft, however, small amounts ('spots') of new bone could also be detected. Such foci of de novo bone formation were found to be in direct contact with trabeculae of deproteinized bovine bone. In such peripheral areas of new bone formation, osteoclast-like cells could be observed on the surface of the Bio-Oss® material. Authors speculated that this finding demonstrates that 6 months after the grafting procedure there was some bone forming activity in the central and more peripheral areas of the graft. They suggested that it may be hypothesized therefore that with longer periods of healing a more comprehensive bone formation could have occurred within the graft.

In sites augmented with autologous bone the transplanted block during healing had undergone marked surface resorption. Only at the base of the experimental site newly formed bone was found to have replaced the grafted bone tissue.

Authors concluded that grafts of autologous cortical bone, placed on the surface of a one-wall defect, may undergo marked resorption during healing. A similar graft of Bio-Oss® may retain its dimension, however only limited amounts of new bone will form within the biomaterial.

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In a recent study on dogs [80], Bio-Oss block was compared to a similar block of equine derived hydroxyapatite, linked with a collagen matrix. The materials utilized yelded similar histological results.

Deproteinized bovine bone has been also utilized as a carrier for growth factors. Boyne tested deproteinized bovine bone as a carrier for delivering growth factors and bone morphogenetic proteins into bone defects [81].

Jung et al. [82], in a clinical trial on 11 patients and 34 implants, reported that the combination of the xenogenic bone substitute with rhBMP-2 can enhance the maturation process of bone regeneration and can increase the graft to bone contact in humans. According to the author, rhBMP-2 has the potential to predictably improve and accelerate guided bone regeneration therapy.

In a human study, Zitzmann et al. [83] tested the histological outcomes of a guided bone regeneration procedure utilizing only deproteinized bovine bone (Bio-Oss®) and a collagen membrane (Bio-Gide®). Histological samples were taken after 6 months, at the moment of implant insertion.

Authors reported that a mean of 37% of the Bio-Oss® surface was detected to be in contact with mineralized bone. The rest of the particle surface was found to be close to bone marrow or connective tissue compartments. They also described resorption lacunae found along the regenerated bone and adjoining graft particles, both facing marrow compartments.

It was concluded that the xenograft Bio-Oss® may certainly be used for the staged approach to localized ridge augmentation in humans, underlining the osteoconductive properties of the material and the possibility of its slow resorption.

Hammerle and Lang [84] evaluated a guided bone regeneration procedure associated with immediate transmucosal implant insertion. GBR procedures were performed using deproteinized bovine bone mineral (Bio-Oss®) as a membrane-supporting material and a bioresorbable collagen membrane (Bio-Gide®) as a barrier. The membranes and the flaps were adjusted to fit around the necks of the implants, thus leaving the implants extending transmucosally into the oral cavity. Defect resolution, as assessed by the amount of coverage of the initially exposed rough implant surface, reached a mean value of 86% (SD 33%). One hundred percent resolution was accomplished at 8 out of 10 implants, 60% at one and 0% at another implant.

Authors concluded that bioresorbable materials in GBR procedures at transmucosal implants can lead to successful bone regeneration into periimplant defects.

In a recent study of the same group [85] the outcome of lateral ridge augmentation performed with Bio-Oss® and a Bio-Gide® membrane was investigated in 12 patients. No flap dehiscences and no exposures of membranes were observed. An integration of the Bio-Oss® particles into the newly formed bone was consistently observed. Merely on the surface of the new bone, some pieces of the grafting material were found to be only partly integrated into bone; particles were not encapsulated by connective tissue but rather anchored into the newly regenerated bone. In all of the cases, but one, the bone volume following regeneration was adequate to place implants in a prosthetically ideal position and according to the standard protocol with complete bone coverage of the surface intended for osseointegration.

Authors concluded that after a healing period of 9–10 months, the combination of DBBM and a collagen membrane is an effective treatment option for horizontal bone augmentation before implant placement.

Simion et al. [86] described in a case series of 10 patients a vertical ridge augmentation utilizing a mix 1:1 of autogenous bone and deproteinized bovine bone covered by a non resorbable e-PTFE membrane.

Impants were inserted after 6-9,5 months and histological samples of regenerated bone were taken. The histological analysis showed new bone formation and ongoing remodeling of the autogenous bone and the DBBM particles.

Mardas et al. [73] in a randomized, controlled clinical trial, evaluated the potential of a synthetic bone substitute (Straumann Bone Ceramic®) or a bovine-derived xenograft (Bio-Oss®) combined with a collagen membrane to preserve the alveolar ridge dimensions following tooth extraction.

No differences in the width of buccal and palatal bone plate were observed between the two groups.

Both biomaterials partially preserved the width and the interproximal bone height of the alveolar ridge.

Although the use of deproteinized bovine bone seems to yeld good clinical results, nevertheless, the regenerative procedures are affected by a significant amount of adverse events that may jeopardize the success of the treatment.

A recent consensus conference [87] stated that: there is a broad base of evidence supporting the use of lateral bone augmentation and sinus floor augmentation to place dental implant in sites with insufficient bone volumes. Less evidence is available for vertical ridge augmentation.

The consensus highlighted that bone augmentation procedures have significant and sometimes frequent adverse events and can fail to produce adequate bone volumes to allow dental implant positioning. Furthermore, available indications suggest that implants placed in augmented areas do not necessarily enjoy the high long-term survival rates of dental implants placed in pristine sites.

Comparative research is needed to improve evidence on augmentation bone procedures and in particular on clinical outcomes of deproteinized bovine bone in such surgical treatments.

5. Conclusions

Deproteinized bovine bone has been widely documented as a scaffold material in a variety of bone regenerative procedures: in periodontal regenerative procedures, as other biomaterials, it seems to be effective with or without barrier membranes and in favorable containing defects, it has produced histological evidences of periodontal regeneration, with a prevalence of bone repair.

There is limited evidence to support the combined use of barrier membranes and grafting materials in non-containing defects.

None of the procedures present in the literature has demonstrated the ability of preventing the process of bone remodeling at extraction sites. The use of bone substitutes in to the fresh alveoli and the augmentation procedures of the buccal bone plate are effective in reducing the biologic process

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of bone remodeling with particular respect to the resorption of the buccal bone plate.

Nevertheless, in the literature only few evidences suggest that the use of deproteinized bone graft into the fresh extraction socket, may reduce the resorption of the buccal plate and better maintain the bone volume.

Although peri-implant bone reconstruction and alveolar ridge augmentation, by the use of deproteinized bovine bone are supported by favorable reports, nevertheless these procedures are affected by a significant amount of adverse events that may jeopardize the success of the treatment.

Further research is needed to improve evidence on augmentation bone procedures and in particular on clinical outcomes of deproteinized bovine bone in such surgical treatments.

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