

Xenografts and Periodontal Regeneration

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Abstract

Title: Xenografts and Periodontal Regeneration. **Background:** The goal of periodontal therapy is to regenerate a functional attachment apparatus. However, the extent of regeneration is variable, and depends on a variety of biologic and procedural factors. In this review, we summarize the current literature describing the use of xenografts for periodontal regeneration. **Methods:** An electronic search using the PubMed database of the U.S. National Library of Medicine, National Institutes of Health was performed in April 2015. In addition, a manual search of the Journal of Periodontology, Journal of Clinical Periodontology, and the International Journal of Periodontics and Restorative Dentistry also was conducted, as well as additional papers derived from the initial search. **Key search words** included grafting, xenografts, regeneration, guided tissue regeneration, and immunogenicity. All available publication years were searched, although papers published in the last 10 years were given greater consideration. **Conclusions:** The literature supports the use of xenografts as an effective alternative in periodontal regeneration. Xenograft materials generally are biocompatible and widely accepted. When compared to open flap debridement, treatment of intrabony or furcation defects using bovine-derived bone generally results in enhanced clinical outcomes similar to other grafting materials used in periodontal therapy.

Key Words: Xenograft; regeneration; guided tissue regeneration; immunogenicity.

Abbreviations: GTR: Guided tissue regeneration, ABM: Anorganic bovine-derived hydroxyapatite matrix, ABB: Anorganic bovine bone.

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Biology of Periodontal Regeneration

The formation of new bone and cementum with supportive periodontal ligament is referred to as periodontal regeneration [1,2]. The ultimate goal of periodontal therapy is to regenerate the functional attachment apparatus that has been destroyed by inflammatory periodontal disease [3]. Unfortunately, periodontal regeneration is not uniformly predictable, and complete regeneration may be difficult to achieve in many situations due to the complex biological events, factors, mediators, and cells involved in periodontal regeneration [2]. Histological studies have shown different patterns of healing associated with various periodontal procedures. Those outcomes include the formation of long junctional epithelium, connective tissue attachment, or periodontal regeneration [4-7].

Guided tissue regeneration (GTR) describes procedures attempting to regenerate lost periodontal structures through differential tissue responses. It typically refers to regeneration of periodontal attachment [1]. GTR is based on the concept of

selective repopulation; the type of cells that first repopulate the wound influence and dictate the type of attachment that will form on the root surface [3]. Four different types of cells might be available at the healing sites, including epithelial cells, cells derived from the gingival connective tissue, cells derived from the bone, and cells originating from the periodontal ligament [3].

GTR can be achieved through utilization of barrier techniques using a variety of materials, such as expanded polytetrafluoroethylene, polyglactin, polylactic acid, calcium sulfate, and collagen. Those barriers are employed to exclude epithelium and the gingival corium from the root surface that might interfere with osseous regeneration [1]. The process of epithelial exclusion leads to selective cellular repopulation at the root surface [8,9]. Additionally, barrier membranes also assist the regenerative process by providing clot stabilization and space maintenance [8,10,11].

During periodontal therapy, the use of grafting material within periodontal defects when indicated is commonly used and well

documented [12]. The addition of such material for treatment of periodontal defects has the potential to provide improved clinical outcomes as measured by pocket depth reduction and clinical attachment gain, when compared to open flap debridement alone [13,14]. Those materials may facilitate formation of alveolar bone, periodontal ligament and root cementum through localization of bone-forming cells (osteoneogenesis), providing a scaffold for bone formation (osteoconduction), and by containment of bone-inducing substances (osteinduction) [12].

The clinical restoration of bone tissue (bone fill) that has been lost in the process of periodontal disease is a desired clinical outcome. However, clinical or radiographic demonstration of bone fill does not address the presence or absence of histological evidence of new connective tissue attachment, nor the formation of new periodontal ligament [1].

Preclinical animal studies have showed that space provision is the main mechanism by which some grafting materials support periodontal and bone regeneration when used in combination with GTR [15]. It has been shown that bone graft material maintains that space by overcoming the problems related to barrier membrane collapse [14].

In general, using bone grafts in combination with GTR will result in more gain in clinical attachment level, and more significant reduction in probing depth, compared to using grafts alone [13].

Definition and Properties

Four different bone replacement graft materials are widely accepted and commonly used in periodontal therapy. Those include autografts, allografts, alloplasts, and xenografts [2,13,14]. A xenograft (heterograft) is a graft obtained from another species such as bovine, equine, or coral [1,16]. Bovine-derived bone, such as anorganic bovine bone, [14] and anorganic bovine-derived hydroxyapatite matrix (ABM) with a synthetic cell-binding peptide (PepGen (P-15), Dentsply Friadent, Germany) are among the most commonly used xenografts in periodontal therapy [16-19]. The processing of such materials is reported to remove cells, organic, and proteinaceous materials, leaving inert absorbable bone scaffolding that assists in revascularization, osteoblast migration, and new bone formation [17,20]. The crystal size of a commercially available anorganic bovine bone (ABB) (Bio-Oss, E. Geistlich, Ltd., Switzerland) is approximately 10 nm, 21 which is similar to human cancellous bone structure [18]. Additionally, the physical properties of xenogenic bone are comparable to human cancellous bone [22-24].

Bovine derived bone is available in different particle sizes, ranging from 240 to 2,000 μm . A relatively small particle size, 240 to 1000 μm , provides a correspondingly larger surface area, which will enhance angiogenesis and osteoconduction, serving as a scaffold for the formation of new bone [17,25-27]. Human and animal studies also have shown that ABB is osteoconductive and facilitates new bone formation [28-34]. ABB contains growth factors that might facilitate the induction of new bone [32]. On the other hand, a variety of animal and human studies have suggested that the resorption of ABB and its replacement with new bone appears to be a relatively slow compared to allografts [27-29].

Materials derived from calcifying corals containing calcium carbonate [16] also can serve as xenografts. Although bone has been shown to form at experimental defects using such coral-derived grafts, it generally has resulted in less bone formation when compared to autogenous bone or other synthetic graft materials [35].

Immunogenicity

Histologic studies performed in animals have shown that xenografts such as ABB are biocompatible materials that evoke minimal inflammation, without the induction of foreign body reactions, and their use generally results in normal uneventful healing [36-38]. We have described the distribution and phenotypic characterization of mononuclear phagocytes in connective tissue following subcutaneous implantation of ABB, and composite ABB/collagen grafts in a rodent model system. Our findings revealed no systemic or local immune responses eight weeks post-implantation [39, 40]. Similarly, human clinical trials and case reports have demonstrated uneventful healing and a limited inflammatory response following the implantation of bovine derived bone [27, 41-51].

Histological Evidence of Periodontal Regeneration

Periodontal regeneration and new bone formation have been demonstrated in human histological studies after grafting periodontal osseous defects with xenografts such as ABB or ABM and a synthetic cell-binding peptide [41-43,52-54]. Recently, a three-dimensional micro-computed tomographic [20] evaluation in humans has confirmed those histological findings, and also has demonstrated absence of ankylosis or root resorption after grafting with xenogenic bone [55]. Nevertheless, periodontal regeneration is not an inevitable outcome after grafting with bovine derived bone, and other human studies have reported healing by formation of a long junctional epithelium or connective tissue attachment instead of periodontal regeneration [42,53,54].

Application of Xenograft Bone Material in Periodontal defects:

Intrabony and furcation defects are the primary periodontal defects amenable for periodontal regeneration [2].

Intrabony defects

Dog model systems have demonstrated that grafting of experimental intrabony defects with ABB leads to significant bone formation [50,56]. Similarly, numerous human clinical trials have been performed. When compared to open flap debridement alone, grafting of intrabony defects using ABM/P-15, ABB alone, or ABB with GTR have resulted in significant pocket depth reduction, clinical attachment gain, and bone fill [44,45,48,57-61]. Several human clinical trials have demonstrated bone fill and defect resolution through reentry surgery and direct clinical measurement after 6 months [19,62-66]. Those clinical findings are consistent with radiographic assessment 6 months or more after grafting intrabony defects with bovine derived bone, with

or without GTR [57,60,67,68]. Pocket depth reduction, clinical attachment gain, and bone fill have been shown to be stable over five years [59,68].

Paolantonio has reported better clinical outcomes, with regard to clinical attachment gain and less gingival recession, using a bioabsorbable collagen membrane in combination with ABB, compared to ABB alone [69]. However, others have reported similar outcomes after using ABB alone or in combination with a bioabsorbable membrane [57,58,62,68]. It should be noted that a variety of membranes were utilized in those studies. This, along with variations between clinicians, patients, and defect morphology, might have led to some degree of inconsistency among the reported outcomes. Addition of antibiotics to ABB such as gentamicin, platelet rich plasma, or synthetic peptides, with or without GTR, did not appear to significantly improve clinical outcomes [19,57,70,71]. When compared to demineralized freeze-dried bone allograft, ABB has resulted in comparable clinical outcomes as measured by pocket depth reduction and clinical attachment gain [65].

More recently, a meta-analysis was performed to evaluate the efficacy of coral calcium carbonate in the treatment of intrabony defects. This study found that significant gain in clinical attachment level could be obtained after grafting intrabony defects using coral xenografts compared to open flap debridement alone [14].

Furcation defects:

Human clinical studies have shown that grafting mandibular class II furcations generally result in better clinical outcomes as measured by pocket depth reduction, attachment gain, and vertical and horizontal defect depth reduction, compared to open flap debridement alone [63,72,73]. Those studies have reported complete or partial resolution of furcation defects. For example, upon reentry 6 months after grafting class III or class II defects, Houser et al. found evidence of bone fill and defect resolution. They also have found some of the deep class II or class III furcation areas converted to class I or class II, respectively [73]. The combination of GTR using bioabsorbable collagen membrane and

ABB/collagen resulted in improved resolution of furcation defects [74]. However, a more recent study has found no difference in the clinical outcomes when using ABB alone, or with GTR using bioabsorbable collagen membrane [75].

Application of ABB with or without GTR in the treatment of class III furcation defects has resulted in comparable clinical outcomes as measured by pocket depth reduction, clinical attachment gain, and change in gingival margin position [76]. The efficacy of ABB or any other xenografts in the treatment of maxillary furcations in humans has not been extensively reported in the literature. Generally, regenerative therapies of class III and maxillary class II furcations are less favorable, compared to mandibular or maxillary buccal class II furcations [77].

Conclusion

Xenografts are considered to be regenerative and serve as a biocompatible grafting material. Use of these materials in periodontal regeneration is widely accepted and well documented in the literature. When compared to open flap debridement, treatment of intrabony or furcation defects using bovine-derived bone alone or in combination with GTR generally results in significantly better short and long term clinical outcomes, with results similar to other bone substitutes that are used in periodontal therapy. Although bovine derived xenografts have been shown to support periodontal regeneration, the extent of periodontal regeneration using xenogenic bone is not always predictable.

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Competing and Conflicting Interests

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