ORIGINAL ARTICLE

A REVIEW ON ALVEOLAR RIDGE PRESERVATION FOLLOWING TOOTH EXTRACTION

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ABSTRACT

Context The question that clinicians face is whether the use of bone replacement grafts and/or barrier membranes enhance their ability to provide for the future placement of a dental implant or to maximize ridge dimensions following the extraction of a tooth versus no additional treatments.

Evidence Acquisition The evidence was obtained by search of Entrez PubMed and manual search of *The International Journal of Oral and Maxillofacial Implants, The International Journal of Periodontics & Restorative Dentistry, Clinical Oral Implant Research, The Journal of Periodontology, The Journal of Clinical Periodontology,* and *The Compendium of Continuing Education in Dentistry*. Key search words included Guided Bone Regeneration, Dental Extraction, Tooth Extraction, Bone Replacement Graft, Alveolar Ridge. The years of search included from January 2011 through February 2012.

Evidence Synthesis The recurring theme was that there was considerable heterogeneity to study designs, time periods, and methods of evaluation. This created great difficulty in trying to answer with good high-quality evidence questions about the techniques and materials to be used for maximizing regeneration at the time of tooth extraction or in which situations this ought to be used.

Conclusions There appears to be consensus from the reviewed literature supporting ridge preservation techniques as a whole. Multiple studies demonstrated less ridge resorption occurring when alveolar ridge preservation procedures were used versus the placement of no graft material in fresh alveolar sockets. The analysis did not show any grafting materials demonstrating a clear benefit over any others or that a barrier membrane is necessary. The evidence is also too premature about whether socket preservation efforts require primary closure. In the emerging area of growth factors, there is no high-quality evidence to either support or refute their use.

Background Tooth extraction is one of the most widely performed procedures in dentistry today and it has been historically well documented that this procedure may induce significant dimensional changes of the alveolar ridge. The dilemma that clinicians face is how to manage tooth extractions to provide for the future placement of a dental implant or to maximize ridge dimensions for the fabrication of a fixed or removable prosthesis. If performed inadequately, the resulting deformity can be a considerable obstacle to the esthetic, phonetic, and functional results that both our patients and we clinicians expect at this current time.

Keywords:

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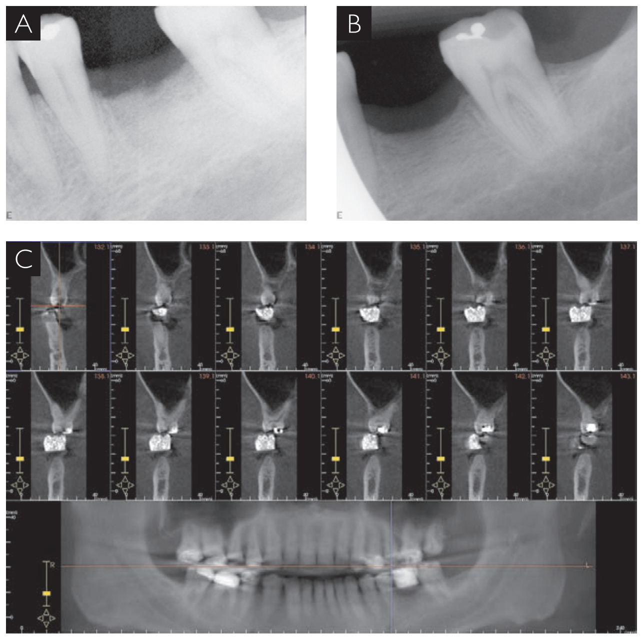
Figure 1. Site collapse after traumatic injury as seen clinically demonstrating bone and gingival loss.

Figure 2. Diagnostic cast showing ideal gingival location of restoration for anterior maxillary teeth.

The key processes of tissue modeling and remodeling after tooth extraction have been well documented in both animals[1] and humans.[2,3] Horizontal buccal bone resorption has been shown to reach as much as 56% **(Fig. 1)**, lingual bone resorption has been reported to be up to 30%,[4] and the overall reduction in width of the horizontal ridge has been reported to reach up to 50%.[5] With this horizontal ridge resorption, the alveolar housing assumes a more lingual/palatal position, with possible negative effects on esthetics, phonetics, and function **(Fig. 2)**. Although the bone resorption continues over time, the most statistically significant loss of tissue contour occurs during the first month after tooth extraction and can average up to 3 to 5 mm in width by 6 months.[6]

A systematic review of the existing literature was recently performed by Tan et al[7] to assess the magnitude of dimensional changes of both the hard and soft tissues of the alveolar ridge up to 12 months after tooth extraction in humans. A total of 20 studies were included that reported on undisturbed postextraction dimensional changes relative to a fixed reference point over a clearly stated time period having searched and reviewed 3954 titles and 238 abstracts. The authors concluded that human reentry studies showed horizontal bone loss of 29% to 63% and vertical bone loss

Figure 3. Clinical view after removal of failed right posterior mandibular fixed restoration showing soft tissue collapse, altered mucogingival junction. AQ9



of 11% to 22% after 6 months following tooth extraction. These studies demonstrated rapid reductions in the first 3 to 6 months that was followed by gradual reductions in dimensions thereafter.

Placing a graft material into a socket has been one proposed method of preserving the natural tissue contours at extraction sites for possible reconstruction with an implant-supported prosthesis.[8] As implants serve as an aid for prosthetic devices, they need to be placed in a 3-dimensionally perfect location to achieve the appropriate esthetic, phonetic, and functional demands of the patient. This is particularly important in the esthetic zone where the gracile natural contours of the periodontium are quite evident and their absence can be devastating.[9] To optimize implant positioning, placement of grafting materials has been advocated as either a combined

9 **Figure 4. Osseous view from occlusal of same area after extraction of tooth #29. Significant bone loss is seen in the area of the first molar requiring bone augmentation before implant placement.**

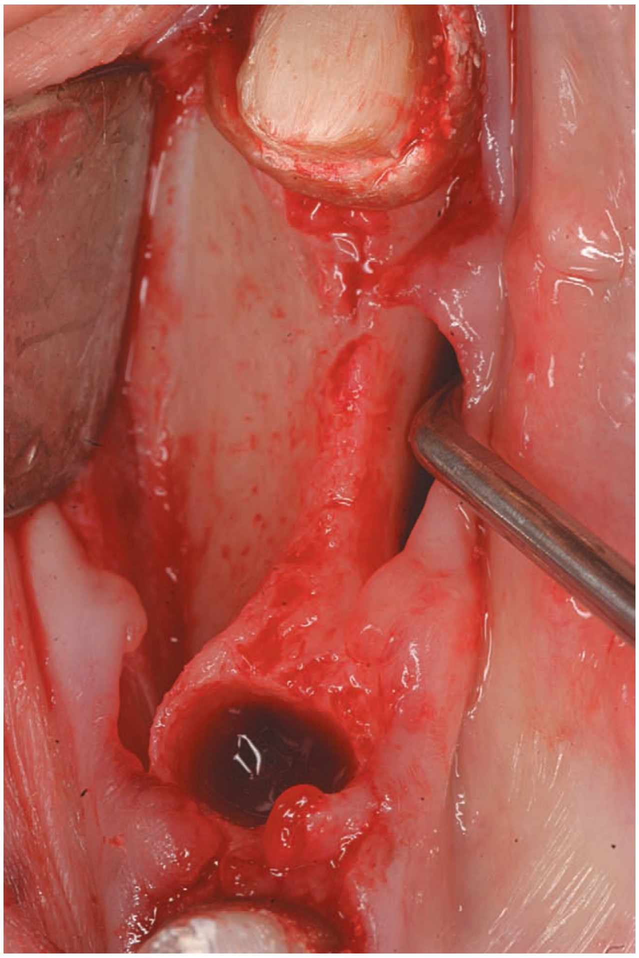
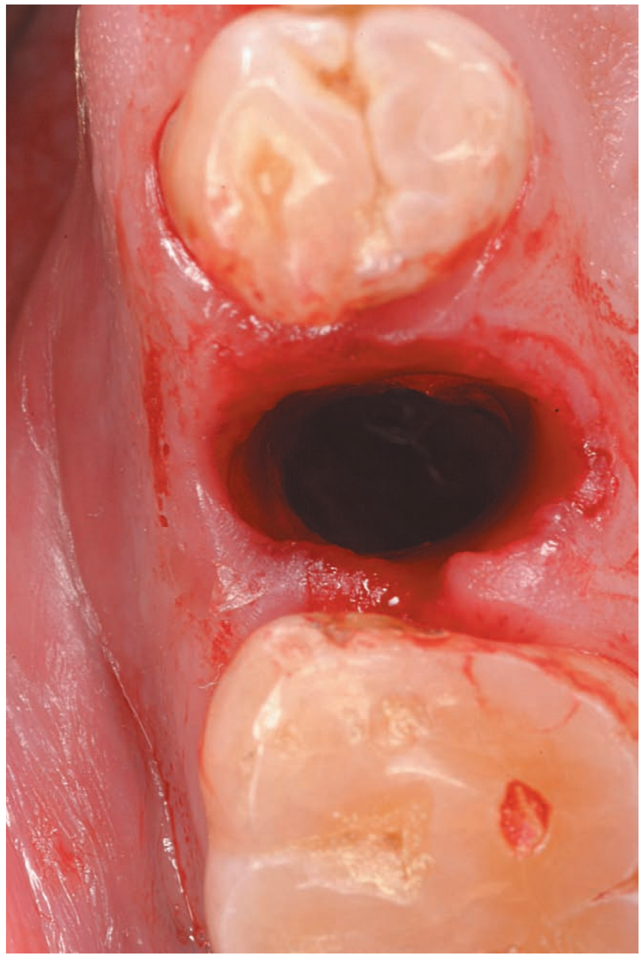


Figure 5. Maxillary right second premolar socket after flapless, atraumatic extraction.



procedure with a barrier membrane or in some instances with a barrier membrane alone to help to stabilize the blood clot.[10,11] The use of graft materials has met with rather contradictory results, however.[12,13] Issues have been reported in the literature related to the use of slowly or nonresorbing bone graft materials with regard to the maintenance of alveolar ridge volume, the presence of residual graft material, and its potential interference with osseointegration **(Fig. 3, A)**. As the case in Fig. 3, *A*, documents, in the absence of "stimulation" of the alveolar bone by the placement and function of a dental implant, the increased bone volume may disappear over time **(Fig. 3, B and C)**.

In the past decade, the use of materials and techniques for alveolar ridge preservation has received considerable attention. The question continues to be whether there is any benefit
AQ1 to grafting or GBR efforts to manage the extraction socket. Moreover, does placing a graft and/or membrane postextraction improve the site dimensionally, radiographically, and/or histologically? Recently, there have been 3 systematic reviews that have examined the issue of ridge preservation following tooth extraction. In 2011, Ten Heggeler et al[14] performed a systematic review on the effect of socket preservation therapies following tooth extraction in nonmolar regions in humans. A total of 163 Cochrane papers led to 9 of these publications meeting the eligibility criteria for evaluation.[11,15-22] The findings of this review indicated that with natural healing af- AQ2
ter extraction, a reduction in width ranging between 2.6 and 4.6 mm and in height between 0.4 and 3.9 mm was observed **(Fig. 4)**. With respect to socket preservation, the freeze-dried bone allograft group performed best with a gain in height and concurrent loss in width of 1.2 mm. The authors felt that although socket preservation showed some evidence of reducing bone dimensional changes following tooth extraction, scarce data concerning socket preservation therapies in humans precluded firm conclusions regarding this procedure. Moreover, Vignoletti et al[23] looked at surgical protocols for ridge preservation after tooth extraction **(Fig. 5)**. Their search strategy resulted in 296 potential articles, of which 14 were identified as having met inclusion criteria **(Table 1)**.[11,15-20,22-26] AQ3

AQ11

Figure 6. Clinical view of socket grafted with synthetic hydroxyapatite hydrated in PRF mixed in a 1:1 ratio with biphasic CS.

Nine of these articles qualified for placement into a meta-analysis that looked at changes in bone width[11,15,16,18,19,27,29] and height.[11,15-20,27] The conclusion of this article suggested the potential benefit of socket preservation therapies was demonstrated, as these procedures resulted in significantly less vertical and horizontal contraction of the alveolar bone crest **(Figs. 6-8)**; however, the scientific evidence did not provide clear guidelines with regard to the type of biomaterial or surgical procedure to best achieve ridge preservation. Finally, there were no data available to draw conclusions on the consequences of ridge preservation benefits as they relate to the long-term outcomes for implant therapy **(Fig. 9)**.

Hammerle et al[30] summarized the evidence-based knowledge on the biology and treatment of extraction sockets based on the reviews performed for the Sixth Expert Meeting: Evidence-Based Knowledge on Biology and Treatment of Extraction Sockets Including the Placement of Dental Implants. Their review of the meta-analyses that were performed in preparation for this conference indicated the

Figure 7. Six layers of PRF fibrin clot sutured over graft material in socket.

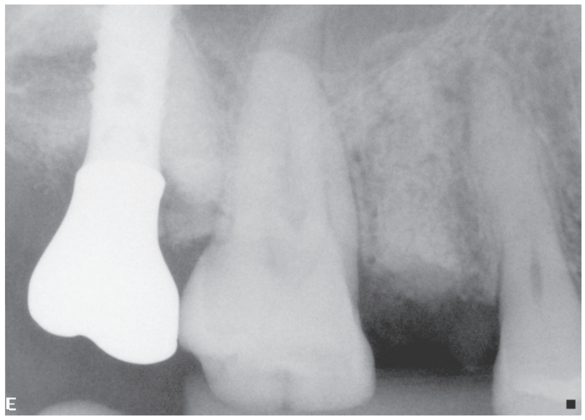


Figure 8. Reentry view of socket healed at 2 months after extraction showing ridge preservation.

alveolar ridge undergoes a mean horizontal reduction in width of 3.80 mm and a mean vertical reduction in height of 1.24 mm within 6 months after tooth extraction without ridge preservation therapies. Regarding the various materials applied to retain alveolar ridge width evaluated in the clinical

Figure 9. A sectional view of the CBCT of tooth #4 before extraction.

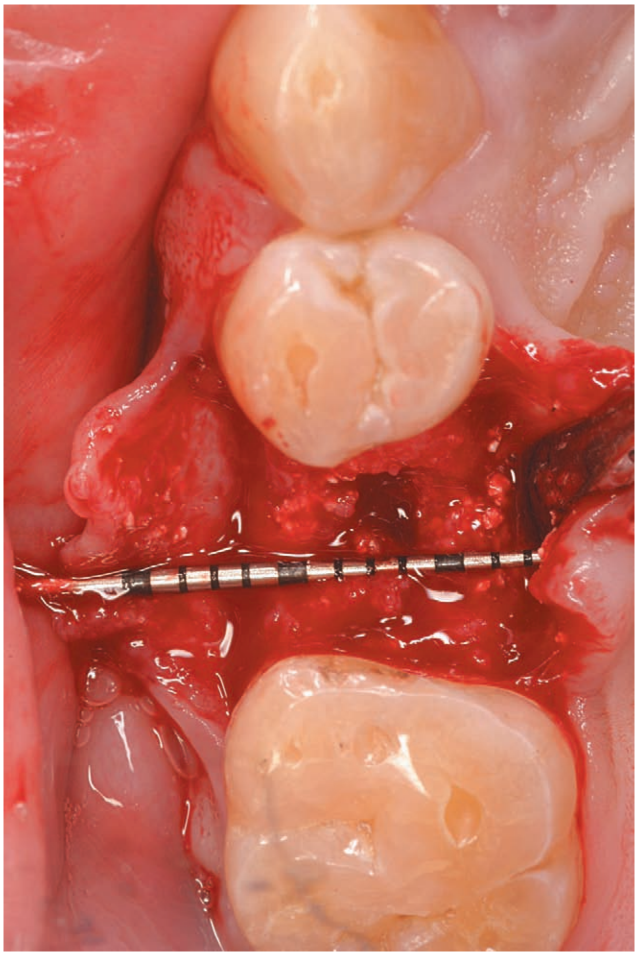


Figure 10. The same view of the CBCT of tooth #4 at the time of implant placement, 2 months after extraction.

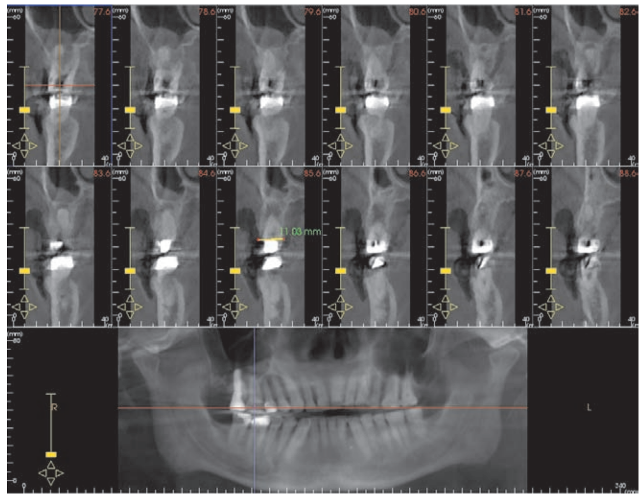
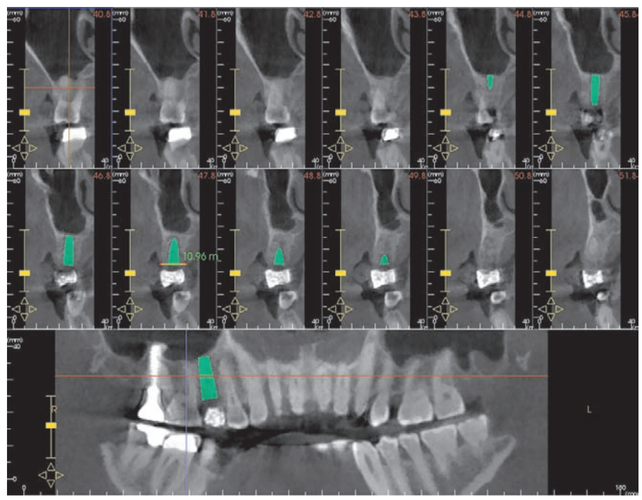


Figure 11. Screw-retained transitional prosthesis to sculpt soft tissues.



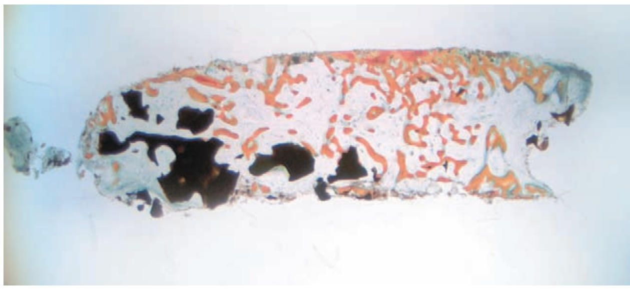
studies, the systematic reviews did not show significant differences except for the collagen plug alone, which revealed negative results. Moreover, the group advocated that to maximize maintaining ridge volume following tooth extraction, one should consider raising a flap, placing a biomaterial with a low resorption/replacement rate, and trying to obtain primary closure if possible.

The third systematic review by Morjaria et al[31] screened 2861 articles of which 9 met inclusion criteria **(Table 3)**.[15,16,18,19,25,27,32-34] Owing to the paucity of studies and their relative heterogeneity, these authors were unable to perform a meta-analysis. They did, however, conclude there were limited data regarding the effectiveness of alveolar ridge preservation therapies when compared with controls. Overall, socket intervention therapies did reduce alveolar ridge dimensional changes postextraction, but were unable to completely prevent such changes **(Figs. 10, 11)**. Moreover, histology demonstrated a large proportion of residual graft material that may account for some of the differences in alveolar ridge dimensions at follow-up evaluations

When looking at these 3 systematic reviews, there were 4 articles that commonly met the evaluation criteria.[15,16,18,19] None of these studies had a common material evaluated, as Iasella et al[15] looked at freeze-dried bone allograft plus a collagen membrane, Fiorellini et al[18] looked at recombinant BMP-2, Barone et al[19] evaluated corticocancellous porcine bone + collagen membrane, and Lekovic et al[16] examined expanded polytetrafluoroethylene barrier alone. All of these treatments diminished the amount of postsurgical ridge resorption, but did not completely eliminate the occurrence of this phenomenon.

The scientific evidence from all of these systematic reviews seems to suggest that socket preservation techniques are of some benefit with regard to reducing horizontal loss of the alveolar ridge. Whether this is consequential for the placement of a dental implant using a delayed approach, whether

Figure 12. Clinical view after insertion of the transitional prosthesis.



the results to such care hold up long term, whether this becomes more critical as the buccal plate becomes thinner, and which technique and/or material might provide the best results are still questions that require clarification. Clearly, if bone width is of importance, then grafting the socket at the time of extraction may be important.

The purpose of this article was to address the most recent literature pertaining to alveolar ridge preservation. Of these articles, 2 look at a test material versus control of an untreated extraction socket, whereas the others are comparative between materials.

REVIEW OF RECENT RIDGE PRESERVATION LITERATURE

The human, randomized controlled trial of Toloue et al[35] evaluated ridge preservation with calcium sulfate (CS) alone compared with sites preserved with freeze-dried bone allograft (FDBA). The sites included in the study had teeth that were extracted atraumatically. If the buccal plate had fractured or it was determined that a large dehiscence or fenestration of 3 mm or larger was detected, the site was eliminated from the study. There was no information provided regarding instrumentation used for tooth extraction, such as high-speed hand pieces, piezosurgery, or other devices and their potential effect on the healing process.[36] Additionally, variability in flap elevation between the surgeries could have affected the healing process. Although the inter-examiner calibration was very good, one could argue that providing participants may not be impartial observers with regard to materials used for site preservation. Another concern with the study is that many study participants did not follow through with the entire protocol, as one-third of the patients dropped out of the study before completion, yielding a small sample size. This study did demonstrate preservation of horizontal ridge width, but could not completely eliminate the resorptive process. Histologic analysis provided the most significant findings, as the 2 graft materials studied were found to be eliminated by the body in very different methods. As a salt, the CS dissolves, leading to much resorption. This yielded 2.54% residual CS on average as compared with 21.37% remaining FDBA. Additionally, there was higher conversion to vital bone (32%) in the CS cases compared with only 17% in the FDBA cases **(Fig. 12)**. An interesting side note of the study was that CS was placed as a thin barrier over the FDBA-grafted sockets. There was no mention of this CS layer being a standardized thickness nor was it mentioned how long the barrier lasted in situ. Dislodging of the barrier will eliminate the guided bone regenerative effects of the material and can lead to inferior histologic results. Finally, the bone volume was only somewhat preserved at 3 months. There was slight loss of alveolar height in both groups and 15% to almost 20% of facial collapse in the 2 groups. There is no indication of how long the process of resorption of bone height and width would continue, which could be 6 to 12 months, according to other authors.[5] A higher percentage of vital bone in the socket could be advantageous in the placement of early delayed implants, as long as there is not continued loss of facial or vertical bone volume after the implant is placed or prosthetically loaded.

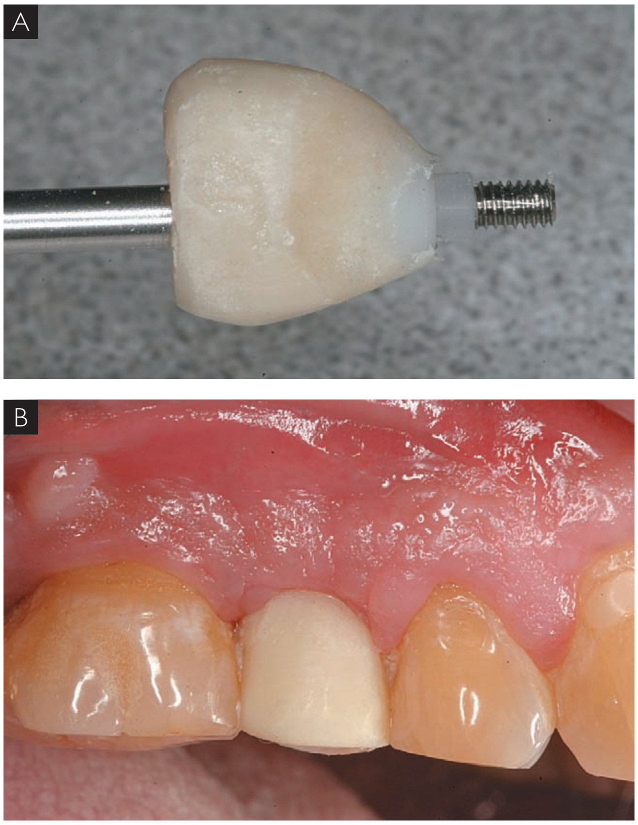
Gholami and coworkers[37] studied human extraction sockets grafted with either a synthetic or bovine form of hydroxyapatite. In their study of 12 patients, nonmolar teeth were extracted and studied in a split-mouth design. There were no control sites that were treated without graft and barrier protection. Additionally, all sites were protected with both a resorbable barrier and primary closure. As has been previously stated, elevating flaps at the time of extraction could have led to some portion of the 14% site collapse that was found on average at the 6- to 8-month reentry time point. Full-thickness flaps were elevated at the reentry, which could lead to further bone loss around the newly placed dental implants.[38] Numerous cases had barrier exposure documented during early healing phases, which may have led to decreased bone formation, but was not quantified in the results. Numerous histologic samples demonstrated significant components of inflammation, even in the absence of clinical infections. Although the amount did not reach statistical significance, it was evident clinically as well in the NCHA AQ4 groups, which could be of concern to surgeons using that type of material. Processing of the specimens was done in a decalcified manner in this study, which may not yield as much information on the stages of healing and mineralization of the grafted site compared with nondemineralized processing with histomorphometric analysis.[39] Unlike other studies with xenograft materials used for bone preservation and/or formation, there were some osteoclasts demonstrated histologically. Only a few were shown, and it was not made clear if these would cause any substantial loss of the grafted particles over time. Other studies with similar materials have shown that they were relatively inert and did not appreciably resorb in the time frame studied between extraction and implant placement, even if delayed out to 9 months or more.[40] Bet- AQ5 ter results in both volume preservation and healing (bone formation and decreased inflammation) may have been obtained if flaps had not been elevated and a different barrier membrane used over the extraction sockets.[41]

The 2012 study by Mealey and Wood[42] compared 2 different types of allograft putty. Teeth were extracted in a manner that used either no elevation of the flap or full-thickness exposure of up to 2 mm of the alveolar crest. If there was a dehiscence of less than one-half of the length of the socket, the periosteum was elevated and a slowly resorbing collagen barrier was placed over the defect. If the dehiscence was longer, the site was excluded from the study. The graft material was inserted to a level up to or slightly over the alveolar crest after measurements were taken and then covered with a collagen barrier. No soft tissue closure was made over the occlusal barrier. A cone-beam tomographic (CBCT) study was performed 3 months after treatment and implants placed 6 to 8 weeks later with minimal flap elevation. Measurements and a trephine core were taken at the time of implant placement with histologic specimens processed in a demineralized manner. Three of the 33 sites were infected 1 week postoperative and none of the grafted sites lost material. On average, the sites lost 1 mm of height and 2 mm of width with the results similar between the 2 materials. Histologic analysis revealed approximately 50% connective tissue in the 2 groups. There were significant differences in vital bone formed and residual
AQ6 graft material. The DFDBA grafted sites had 38% vital bone compared with less than 25% vital bone in the FDBA grafted sites. Of the mineralized component, the FDBA grafted sites had 49% residual graft compared with only 18% in the DFDBA sites. Of the total bone area in the 2 groups, new bone accounted for 81% of the total bone in the DFDBA site and only 50% in the FDBA sites. The results for site preservation compare favorably with other studies where grafts and barrier membranes are placed. By eliminating or reducing the amount of flap elevation, there is less trauma near the bundle bone; however, the physiology of healing of the grafts may have been improved further with the addition of CS. By in-
4 corporating this material into the graft at a 4 parts graft to 1 part CS mixture and potentially covering the graft with a CS barrier, it is possible to get even better results.[43] If the goals of socket preservation include not only maintaining the volume of the site, but true biologic regeneration, this is a simple way to attain those goals. With no control patients in this study, it is unknown how just a resorbable barrier would have aided in socket preservation and bone formation compared with placement of a biomaterial in and over the socket.

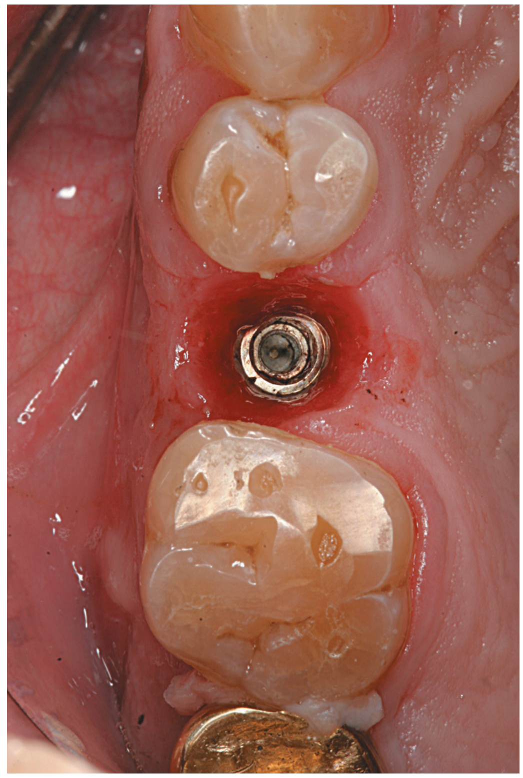
Festa and coworkers[44] performed a randomized, bilateral controlled study to compare the placement of a xenograft with a laminar membrane with no treatment at the time of extraction. Full-thickness flaps were elevated and primary
5 closure obtained over the socket at the time of extraction. There are a few differences between this study and others discussed in this literature review. Despite other articles documenting increased bone loss with flap elevation, the soft tissues were mobilized fully in this study. This significant flap mobilization could have contributed to the significant amount of bone loss in the control teeth. Additionally, the extent of surgery was probably responsible for the pain and swelling noted by the patients and authors. The amount of buccolingual site collapse in control sites was 3.7 mm or 37.4% of the initial width. The graft and barrier–treated sites exhibited only 18.4% loss of ridge width on average. The increased bone loss in the treated sockets compared with other studies could have been a result of either the specific graft and barrier combination or the fact that a flapped, surgical approach was used. There are a few omissions from this article that are of interest to surgeons. There is no histologic evaluation of either graft loss or vital bone formation, which has been well documented in other articles.[39,41] Also important at the time of implant placement is the firmness of the graft and how stable the inserted implants are when placed in the grafted site.[45] A lower value of stability when the implant is placed may result in a statistically significant decreased survival rate in unloaded implants and might have a similar effect on immediately loaded implants as well.

In a Cochrane review from 2010,[46] the authors looked at the difference between clinical and esthetic results when implants were placed in an immediate, immediate-delayed, or delayed manner. Although the studies included in this review did not go into detail on what extraction therapies were performed in the delayed implant placement groups, some interesting conclusions were reached. Most important, the reviewers of the articles believed that many of the authors' conclusions could not be completely validated owing to possible bias in interpretation of the results. There were many differences in timing of "immediate-delayed" implants and various graft and/or barrier combinations that prevented accurate comparison between articles included in this analysis. There were trends noted (without statistical significance) toward higher failure rates in the immediate socket implants. There were some indications of higher esthetic satisfaction at early time points with the immediate or immediate-delayed implants compared with those placed at more "conventional" times after extraction **(Figs. 13 and 14)**. In one of the articles, those perceived advantages of the earlier placement of implants had disappeared by the 5-year postoperative evaluation.[5] This article strengthens the conclusion that the ideal way to significantly reduce bone loss at the time of extraction is the bone regenerative approach. Dr Sanz and coworkers, in their systematic review,[47] could not add much clarification to that issue. Of the articles they reviewed, only 8 studies met their inclusion criteria. Of those, only 2 could be included in their meta-analysis. They stated that there may be an advantage for bone and gingival preservation with early versus delayed placement of dental implants; however, there was a tremendous variation in the number, quality, and results of the

AQ12 **Figure 13. One month after insertion of transitional, the soft tissues have been sculpted to ideal shape for support of the final prosthesis.**



AQ13 **Figure 14. BruxZir milled zirconia crown with a titanium insert for a screw-retained final crown. Note ideal, computer-designed emergence profile to maintain soft tissue shape.**



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studies investigated, which limits the strength of any conclusions on this approach **(Figs. 15 and 16)**.

The meta-analysis by Morjaria et al[31] and other articles reviewed by the authors of this current article come to similar conclusions. Although there are numerous strategies to reduce the amount of bone resorption, there is a "cost" associated with all of them. The use of a graft and barrier will limit the amount of facial and occlusal collapse in the treated area; however, no clear conclusions can be drawn from the numerous studies in the literature. When a graft material is inserted into the socket, it may have any of a number of effects. As a scaffold, it may enable osteoid deposition. If it is not resorbable in the time frame studied, there will be a limit on the amount of vital bone formed and available for osseointegration. Many of the grafted sites evaluated in the articles referenced in this review had remnants of the graft materials in histologic samples. If the grafting material resorbs and is converted to vital bone too quickly, the site may exhibit increased vertical and/or horizontal collapse of the alveolar socket. If the grafting material resorbs too slowly, the site may exhibit reduced amounts of vital bone formation. The surgeon who is performing extraction therapy must be aware of the physical and physiologic interactions of the host environment with any graft and/or barrier inserted at the time of extraction. A cost/benefit analysis has to be determined to enable ideal regeneration and bone volume preservation synergistically. Continued research in this field will lead to improved biomaterials to act as bone replacement grafts and/or barriers. As more are developed and different techniques are studied, the process will be made simpler and more predictable from both biologic and physiologic viewpoints **(Fig. 17)**.

CONCLUSION

In making final conclusions regarding the viability of alveolar ridge preservation as a treatment option, the recent addition of the studies examined in this article should be considered. Fundamental questions to ponder when making these conclusions are as follows:

Question 1: Is there a benefit to alveolar ridge preservation? Yes. Multiple studies have consistently demonstrated that less ridge resorption occurs when alveolar ridge preservation procedures are used versus the placement of no graft material in fresh alveolar sockets. Trends indicate that with alveolar ridge preservation procedures, horizontal resorption of just over 1 mm will still occur with relative preservation of

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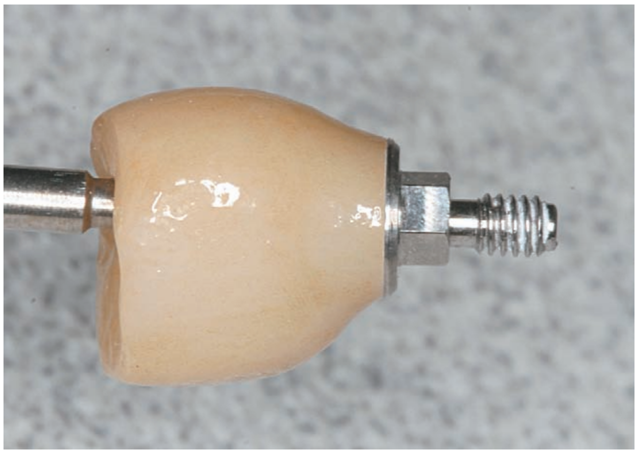
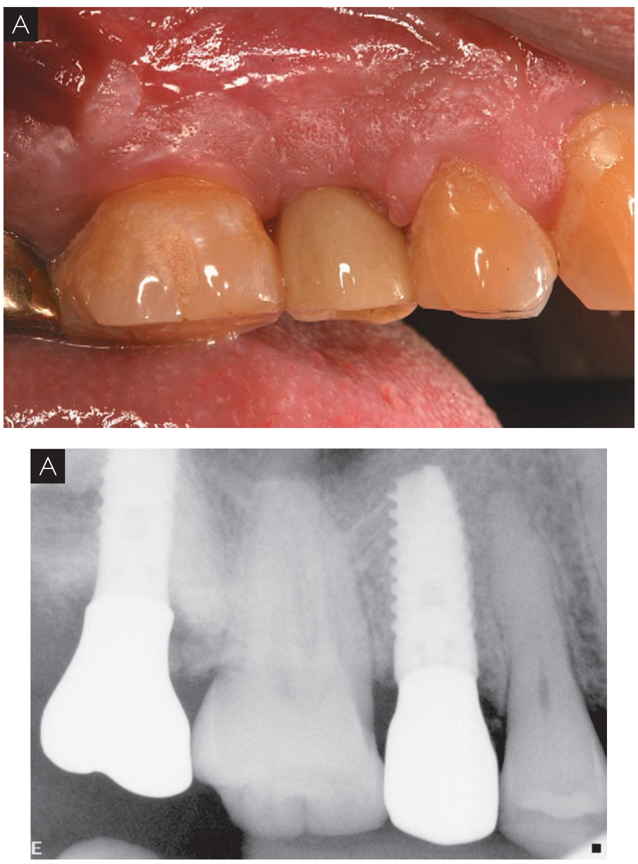
Figure 15. Final restoration on tooth 4 showing preservation of aesthetics.



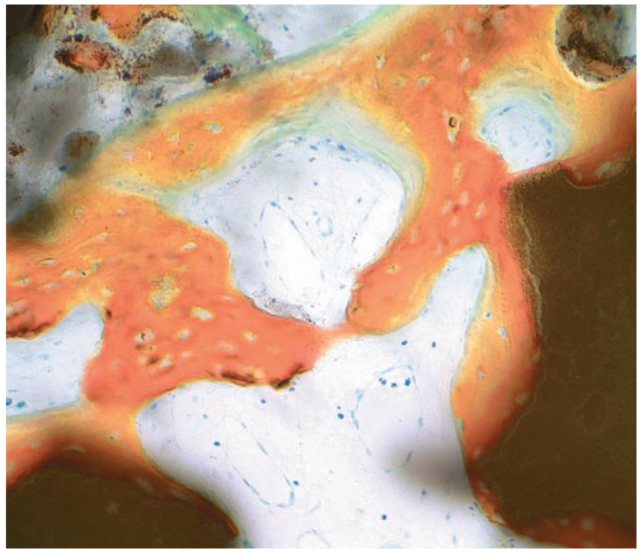
AQ14 **Figure 16. Radiographic view of final restoration demonstrating bone preservation around MIS 7 implant and ideal trabecular nature of regenerated bone.**



vertical height, whereas a lack of alveolar ridge preservation will generally result in more than 3 mm of horizontal loss and at least 1 mm or more of vertical loss.

• Question 2: Do any alveolar ridge grafting materials demonstrate a clear benefit over any others? Inconclusive.

Figure 17. Nondemineralized histologic evaluation of site. Regenerated bone in site #4 reveals 17% vital bone. There is a small portion of residual HA (25%), which is to be expected at this early stage of healing. There is no CS remaining. AQ15



Although all alveolar ridge preservation studies demonstrated beneficial results, no one particular grafting material has proven superior to others. Alveolar ridge preservation materials demonstrated relative consistency regarding dimensional ridge changes following healing. One trend, however, that shows possible signs of difference concerns mineralized versus nonmineralized grafting materials. Whereas multiple studies using mineralized ridge preservation grafting materials demonstrated biopsy core samples of approximately 17% to 27% vital bone following 3- to 6-month healing periods, nonmineralized products tend to demonstrate vital bone findings of approximately 28% to 53%. Additional studies are needed to confirm these results, and if they hold any importance with regard to dental implant success.

• Question 3: Is a barrier necessary for alveolar ridge preservation? Inconclusive at this time. Heterogeneity existed among the studies regarding barrier use for alveolar ridge preservation procedures. Although results among the studies were relatively similar, no clear benefit was demonstrated with or without a barrier in the context of the studies examined. Use of a barrier may prove beneficial in cases where extraction socket walls are either partially or completely missing. Additional controlled and comparative studies are needed to confirm or refute this finding.

• Question 4: Is primary closure necessary? Too premature to make any conclusions regarding this question at this time. The benefits of not obtaining primary closure are a stable mucogingival junction and increased zone of keratinized gingiva compared with cases where primary closure is obtained for site preservation. Although a small number of studies suggest that ridge preservation dimensions and vital bone formation are not affected by a lack of primary closure, definitive conclusions about this technique cannot be made at this time. Studies evaluating alveolar ridge preservation without primary closure used barriers in their protocols. Accordingly, early indications suggest that in an absence of primary closure for alveolar ridge preservation, use of a barrier may be beneficial. Questions remain, however, regarding which barriers are best suited for exposure to the oral cavity and the type of gingival tissue that forms as these products are bioabsorbed.

• **Question 5:** Does the addition of biologic growth factors provide a benefit for alveolar ridge preservation procedures? Premature to make any conclusions regarding this question at this time. Although a small number of studies have evaluated the use of biologic growth factors for alveolar ridge preservation following tooth removal, there was significant heterogeneity in the condition of the host extraction socket and bone at the time of graft placement. Use of such growth factors may provide benefits in cases of extreme alveolar defects following tooth removal, but additional controlled and comparative studies are needed to confirm these findings. Additionally, the cost/benefit ratio of these products must be considered, as certain biologic growth factors can add significant expense to alveolar ridge preservation procedures.

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AQ1 - Please spell out GBR.

AQ2 - Original ref 16 was a duplicate of ref 11 and original ref 38 was a duplicate of ref 5. Original refs 16 and 38 were deleted, in-text citations to res 16 and 38 were changed to 11 and 5, respectively, and all references from 17 to 49 were renumbered. Please check carefully to ensure all changes are correct.

AQ3 - Tables 1 and 3 are cited in the text but no tables were included with the document. There was no citation for a table 2. Please provide tables or delete the citations.

AQ4 - Please spell out NCHA.

AQ5 - Originally, ref 41 was cited before 40, so refs 41 was renumbered 40 and ref 40 was renumbered 41.

AQ6 - Please define DFDBA.

AQ7 - Please update ref 31.

AQ8 - Please update ref 37.

AQ9 - Please update ref 44.

AQ10 - Fig 3: Please provide captions for A-C.

AQ11 - Fig 6: Please define PRF.

AQ12 - Fig 13: Please provide captions for A and B.

AQ13 - Please provide the name and location of BruxZir in the Fig 14 caption.

AQ14 - Fig 16: B is a radiographic view. Please provide a caption for A.

AQ15 - Fig 17 caption: Please spell out HA.