Periodontal and Endodontic Regeneration

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Abstract
Guided tissue regeneration (GTR) is effective in halting tissue and bone destruction and promoting new tissue and bone formation. Although the goal of complete and predictable regeneration still remains elusive, many techniques and materials have been developed that show good clinical and histologic outcomes. The most commonly used materials in GTR include bone replacement grafts from numerous sources, nonresorbable and bioabsorbable membranes, and recently growth hormones/cytokines and other host modulating factors. This article reviews the biologic rationale behind current techniques used for tissue/bone regeneration, reviews the most common materials and techniques, and attempts to explain the factors that influence the outcomes of these therapies. *(J Endod 2009;35:321–328)*

Key Words
Endodontic, GTR, guided tissue regeneration, periodontal, regeneration

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Traditional approaches to treat periodontal and endodontic defects include nonsurgical debridement of root surfaces or root canals, as well as surgical approaches that provide better access to clean the root surfaces and apical lesions and to reshape the surrounding bone/root apex. Although these therapies can be effective, bone is sometimes removed for access or to create better physiologic contours, and healing is almost always by repair. Repair is defined as the healing of a wound by tissue that does not fully restore the architecture or the function of the part (1). Because this is not ideal, newer approaches such as regenerative procedures that aim to restore lost tissue (periodontal ligament, bone, cementum, and connective tissue) have been introduced. This has an advantage over traditional approaches in that after healing, the tissues surrounding the teeth are restored to their original state. Clearly, regeneration is the most desirable outcome for any therapy. However, this is also the most difficult result to achieve. Consequently, a wide variety of treatment modalities have been developed, all with the goal of attaining tissue/bone regeneration. Regenerative procedures frequently include the use of barrier membranes and bone grafting materials to encourage the growth of key surrounding tissues, while excluding unwanted cell types such as epithelial cells (2). Although regenerative therapies have great potential, they remain unpredictable in their ability to consistently produce acceptable outcomes in all situations. To help promote tissue/bone regeneration and healing, the local application of growth factors/cytokines and host modulating agents are being used to maximize the body's healing potential. Growth factors and hormones including platelet-rich plasma (PRP), bone morphogenic proteins (BMPs), platelet-derived growth factor (PDGF), parathyroid hormone (PTH), and enamel matrix proteins (EMD) have shown promise in enhancing regeneration, although their long-term predictability remains questionable, and their anticipated benefits are moderate (3–6). This article reviews the biologic rationale behind tissue/bone regeneration; describes the most common methods used to obtain regeneration, ie, bone replacement grafts, barrier membranes, and host modulating agents; and discusses the factors that influence regenerative success as well as challenges that still need to be overcome.

Biologic Rationale

The type of healing that occurs after conventional endodontic and periodontal therapy, either repair or regeneration, is critically dependent on the cell type that repopulates the wound first. Typically, the cells with the fastest migration rate tend to dominate the initial healing phase. A classic review by Melcher (2) introduced the idea of compartmentalization, which described 4 cell populations in the periodontium: lamina propria of the gingiva, periodontal ligament (PDL), alveolar bone, and cementum. PDL cells, alveolar bone cells, and possibly cementoblasts are all capable of periodontal regeneration, whereas epithelial cells typically produce repair and/or long junctional epithelium formation. Epithelial cells migrate approximately 10 times faster than other periodontal cells types, which is why periodontal therapy typically results in the formation of long junctional epithelium (7). If the epithelial cells could be excluded from the wound long enough for other cell types with regenerative potential to become established, epithelial downgrowth could be prevented (8–10). This is often referred to as guided tissue regeneration (GTR). The same principle also applies to endodontic defects (eg, root end surgery), except the effect of epithelial cells in this clinical situation has been either eliminated or minimized. Another important difference between endodontic and periodontal therapy is that the periodontium is usually healthy in endodontic treatment situations, and tissue removal is only for access, whereas periodontal treatment is initiated in diseased tissues. Furthermore, the periodontal defect is mostly an open wound, whereas the endodontic lesion is primarily a closed environment wound. This has resulted in a more favorable regeneration outcome for the endodontic related defects. Occlusive membrane barriers composed of expanded polytetrafluoroethylene (ePTFE) or collagen have been used successfully to exclude the epithelium and allow connective tissue and bone cells to repopulate the area first, resulting in periodontal regeneration (2). Britain et al (11) compared 3 treatment approaches to chronic periodontal-endodontic lesions—open flap debridement, resorbable collagen membrane, and a resorbable collagen membrane combined with anorganic bovine bone matrix—and found that a resorbable collagen membrane with or without a bone graft resulted in superior periodontal regeneration compared with the open flap debridement group. Bone grafting materials have been used to maintain the space for cell repopulation and to act as osteoinductive or osteoconductive materials for the formation of host bone (12–14). An in-depth review of the available bone replacement grafts and occlusive barrier membranes follows.

Bone Replacement Grafts

Perhaps the most commonly used technique for regeneration is the use of bone replacement grafts. Bone replacement grafts can promote tissue/bone regeneration through a variety of mechanisms. Some grafts actually contain cells that lay down bone matrix, ultimately resulting in new bone formation. These grafts are referred to as having osteogenic properties (1). Other grafts release growth factors and other mediators that signal the host to produce native bone. These grafts are considered osteoinductive (1). Furthermore, other graft materials might simply act as a scaffold on which host bone might grow. This property is referred to as osteoconductive (1). There are many different sources of bone replacement grafts, each with different advantages, disadvantages, and success rates. In general, grafts can be categorized into autogenous, allograft, alloplast, and xenograft sources (Table 1).

Autogenous Grafts

Autogenous grafts are those obtained from a remote location within the same host and are considered the gold standard bone replacement graft (1). Typically, these grafts are obtained intraorally from the extraction sockets, edentulous ridges, ramus, symphysis, tuberosity, or the surrounding buccal plate. Alternatively, larger grafts can be obtained extraorally from areas such as the iliac crest or tibia. Advantages to using autogenous grafts are that these grafts are osteogenic, prevent disease transmission, and are low cost. However, they do require a second surgical site at the donor site.

Schallhorn (15) used iliac crest grafts in the treatment of infrabony defects and reported up to a 4-mm gain in bone height. However, reports of root resorption made this treatment option less favorable (16). The realization that intraoral autogenous grafts resulted in similar outcomes to bone obtained from extraoral sources made this a more favorable approach for small defects (17). Vertical bone gains in infrabony defects average 3.5 mm for autogenous grafting materials, and several groups have shown that this approach results in true periodontal regeneration with new cementum formation (18–20).

Allografts

A bone allograft refers to a graft between genetically dissimilar members of the same species. The grafts are often obtained from tissue banks that process the donor tissues. Depending on the manner in which these tissues are processed, allografts might be osteoconductive or osteoinductive. These grafting materials have relatively high success rates and have an additional advantage in that no additional surgical procedure is required to procure bone from a donor site. Disadvantages potentially include a foreign body immune response, cost, and contamination of the graft during processing. The most commonly used forms of allografts are freeze-dried bone allografts (FDBA) and decalcified freeze-dried bone allografts (DFDBA). In addition, these bone replacement grafts might be further separated into cortical or cancellous components. Decalcifying the bone allograft exposes BMPs, which have osteoinductive properties (21). However, decalcifying the bone graft also causes this type of graft to resorb much faster and act as a less effective scaffold than its counterpart, FDBA.

Studies evaluating the clinical success of FDBA report bone fill between 1.3–2.6 mm in periodontal defects (22–24). Mellonig (25) found at least 50% bone fill in 67% of periodontal defects if FDBA was used, and this percentage increased to 78% if FDBA was combined with autogenous bone. Studies evaluating DFDBA report similar bone fill compared with FDBA, with an average range of 1.7–2.9 mm (26, 27). Conversely, in a systematic review, fresh-frozen and DFDBA allografts were associated with significant improvements in bone level compared with open flap debridement, although this did not hold true for FDBA (28). When used in periapical defects after root end surgery, one endodontic study demonstrated that FDBA results in histologic periodontal regeneration with no adverse tissue response (29). Similarly, several case reports have demonstrated healing with mature bone and hemopoietic marrow in periapical areas by using DFBA with or without a membrane (30–32).

Periodontal/endodontic regeneration has been demonstrated with both FDBA and DFDBA, although one report from Dragoo and Kaldahl showed FBDA healing by repair (33–35). In an animal study, FDBA or DFDBA was placed into surgically created infrabony defects and evaluated histologically (36). Three months postoperatively, the FDBA group showed earlier, more rapid, and more substantial new bone formation than DFDBA.

Xenografts

A xenograft refers to tissue taken from one species and placed into another species. For intraoral bone replacement grafts, the most common animal sources are bovine and porcine. Because antigenicity is a concern with this type of graft, the tissues are processed to remove all organic constituents, leaving only an inorganic matrix. Thus, xenografts are osteoconductive by nature. Typically, these grafting materials resorb very slowly and might sequester or undergo fibrous encapsulation (37).

Positive clinical results have been reported for xenografts in the treatment of infrabony, furcation, and endodontic-related surgical defects (38–40). However, tissue/bone regeneration with xenografts might be unpredictable. In a study of 8 infrabony defects treated

TABLE 1. Available Bone Graft Materials and Their Sources

	Autogenous	Allograft	Alloplast	Xenograft
Source	Host	Different individuals	Synthetic	Different species
Properties	Osteogenic Osteoinductive Osteoconductive	Osteoinductive Osteoconductive	Osteoconductive	Some osteoinductive? Osteoconductive

with anorganic bovine bone, 7 defects showed some evidence of regeneration, whereas 1 defect healed completely by repair (38). One group evaluated the use of GTR by using anorganic bovine bone and a resorbable collagen membrane in periapical defects after surgical endodontics (41). At 1 year, 78% of defects healed successfully, although there were no differences in outcomes between GTR and no treatment of the residual periapical lesion. In contrast, one group used anorganic bovine bone in combination with a bioabsorbable collagen membrane to treat through-and-through endodontic lesions during root end surgery (42). This group reported a success rate of 88% in the treatment group compared with 57% in the control group (no bone graft or membrane). Consequently, it might be concluded that GTR might be beneficial in more difficult or compromised situations, but it is unnecessary for simple endodontic surgery where sufficient bone remains around the defect to regenerate on its own.

Alloplasts

An alloplast is a synthetic or inert foreign body that is implanted into host tissue. They are osteoconductive only and can be further categorized as hydroxyapatite, beta-tricalcium phosphate, non-ceramic, polymer, or bioactive glass (Table 2). Alloplasts serve primarily to maintain space, and consequently they are not ideal for promoting periodontal regeneration. Hydroxyapatite grafts can achieve attachment gains of around 1–1.5 mm, and polymer grafts can average 2 mm of bone fill. However, tissue/bone regeneration is highly unpredictable in these cases (43, 44). One study with bioactive glass only reported regeneration in 1 of 5 cases (45).

Alloplast materials are perhaps the most commonly investigated grafting materials for periapical defects. Positive results with respect to periodontal regeneration in periapical defects have been reported by using calcium sulfate, ceramic hydroxyapatite, and polylactide/polyglycolide copolymers (46–49).

Membranes

Occlusive barrier membranes are used to exclude epithelial cells and connective tissue fibroblasts from a periodontal wound. This allows other regenerative cells (eg, bone, periodontal ligament, cementoblast) to repopulate the area and promote periodontal regeneration in the area. Barrier membranes can be divided into nonresorbable and bioabsorbable categories (Table 3).

TABLE 2. Commercially Available Alloplast Grafting Materials that Have Been Tested for GTR Applications in Periodontal Defects

Material	Commercial name
β-TCP*	Cerasorb (Curasan, Research Triangle Park, NC)
Bioactive glass*	Biogran (Biomet 3i, Palm Beach Gardens, FL) Perioglas (Novabone, Jacksonville, FL)
Calcium carbonate	BioCoral (Wilmington, DE) C-Graft (ScionX LLC, Denver, CO)
Polymethylmethacrylate (PMMA)/HEMA polymers*	Bioplant (Kerr, Orange, CA)
Porous/nonporous hydroxyapatite (HA)*	Osteograf D (DENTSPLY Friadent, York, PA) Ostogen (Impladent, Holliswood, NY)

*Studies testing these products for endodontic applications.

Nonresorbable Membranes

Many materials have been used as nonresorbable barriers for GTR including bacterial (Millipore, Billerica, MA) filters and a rubber dam, but the most commonly used material is the ePTFE membrane. The first case report evaluating GTR as a therapy used a Millipore filter as a barrier membrane to regenerate the periodontium in a 9-mm defect on a hopeless tooth (8). Three months after surgery, the tooth was extracted, and subsequent histology revealed 5 mm of connective tissue attachment coronal to the base of the defect. Similarly, Gottlow et al (50) took block sections of 12 hopeless teeth treated with ePTFE membranes and found new bone growth to be an average of 5.1 mm and an average clinical attachment level (CAL) gain of 5.6 mm. Recent studies showed that intrabony defects treated with ePTFE membranes can be expected to undergo between 3.0–5.0 mm of bone fill with 4.0–7.0 mm CAL gain, regardless of whether a bone replacement graft is placed concomitantly (51–54). One study compared the use of ePTFE membranes versus no membranes in the treatment of periapical lesions after apical surgery (55). Radiographic analysis of the defects showed that defects treated with an ePTFE membrane healed faster and with greater quality and quantity of regenerated bone compared with controls, especially in through-and-through lesions.

Nonresorbable membranes have been used to treat furcation involvement as well, although with more variable success. Studies have shown that for class II furcations, up to 36.7% horizontal bone fill and 2.0 mm horizontal and vertical CAL gain can be achieved (56–59). However, one study showed that in some patients the initially positive outcomes might not be sustainable over the long term (5 years), with one furcation even converting to a class III (58). Although most nonresorbable membranes are biocompatible and highly effective at maintaining space, they require a second surgery to facilitate their removal. Consequently, other materials were introduced to eliminate these drawbacks.

Bioabsorbable Membranes

Bioabsorbable membranes are composed of a wide variety of materials including collagen, polylactic acid, polyurethane, polyglactin-910, acellular dermal matrix, dura mater, chitosan, periosteum, and calcium sulfate. The most common material is collagen, which can be modified through various collagen cross-linking processing techniques to vary the resorption rate (60).

Numerous studies have shown bioabsorbable membranes to be effective at promoting regeneration in both endodontic and periodontal defects (11, 41, 61–63). Because alveolar bone and the periodontal ligament contain collagen, using a collagen membrane might impart some additional advantages for GTR purposes by augmenting its native properties. Collagen facilitates hemostasis and therefore wound stability by promoting platelet aggregation in addition to promoting fibroblast migration, which could accelerate wound closure (64).

Histologic studies of bioabsorbable membranes indicate that regeneration can occur after healing, although repair was seen in a minority of instances (38, 65, 66). Bioabsorbable membranes also appear to achieve better regenerative outcomes in infrabony defects as compared with furcation defects (67). Britain et al (11) evaluated the effects of open flap debridement, GTR with a bioabsorbable collagen membrane, and GTR with a membrane plus anorganic bovine bone matrix on surgically created endodontic-periodontal defects in foxhounds (11). After 6 months, the membrane plus graft group experienced 3.45 mm bone gain compared with 3.24 mm in the membrane group and 2.16 mm in the control group. In addition, evidence of new cementum was found in both GTR groups.

TABLE 3. Commercially Available Absorbable and Bioabsorbable Membranes that Have Been Tested for GTR Applications in Periodontal Defects

	Commercial name(s)	Source	Components
Nonresorbable	Gore-Tex (W.L. Gore and Associates, Inc, Newark, DE*	Synthetic	e-PTFE
Bioabsorbable	Atrisorb/Atrisorb Free Flow (Citagenix, Quebec, Canada)	Synthetic	Lactic acid, poly (D,L-lactide) dissolved in N-methyl-2-pyrrolidone (NMP)
	Atrisorb-D (Citagenix, Quebec, Canada)	Synthetic	Lactic acid, poly (D,L-lactide) dissolved in N-methyl-2-pyrrolidone (NMP)
	Alloderm or Puros Dermis (LifeCell, Branchburg, NJ; Zimmer Dental, Carlsbad, CA)	Human dermis	Dermis
	BioBar (Colbar Research & Dev Ltd, Ramat-Hasharon, Israel)	Bovine tendon	Collagen type I
	Biofix (Bioscience, Tampere, Finland)	Synthetic	Polyglycolic acid
	BioGide (Geistlich, Wolhusen, Switzerland)*	Porcine dermis	Collagen type I and III
	Biomend/Biomend XT (Sulzer Calcitek, Carlsbad, CA)*	Bovine tendon	Collagen type I
	Biostite (Coletica, Lyon, France)	Calfskin	Collagen and hydroxyapatite
	Epi-Gide (Curasan, Research Triangle Park, NC)	Synthetic	Polylactic acid
	Ossix Plus (OraPharma Inc., Warminster, PA)	Bovine	Collagen type I
	NeoMem(Citagenix, Quebec, Canada)	Bovine	Collagen type I
	Paroguide (Coletica, Lyon, France)	Calfskin	Collagen type I and chondroitin 4 sulfate
	Periogen (Collagen Inc, Palo Alto, CA)	Bovine dermis	Collagen type I and III
	Puros Pericardium (Zimmer Dental, Carlsbad, CA)	Human pericardium	Human pericardium
	Resolut XT/Resolut Adapt (W.L. Gore and Associates, Inc, Newark, DE)	Synthetic	Glycolide and trimethylene carbonate copolymer fiber with glycolide and lactide copolymer membrane
	Tissue guide (Koken Co, Tokyo, Japan)	Bovine dermis	Atelocollagen and tendon collagen
	Vicryl (Ethicon, East Brunswick, NJ)	synthetic	Polyglactin 910 mesh (copolymer of glycolide and lactide)

e-PTFE, expanded polytetrafluoroethylene

*Those tested in endodontic defects.

The necessity of using a membrane to enhance GTR for endodontic applications is controversial. One study found that bioabsorbable membranes could be used to successfully enhance periodontal regeneration of buccal dehiscences after periapical surgery (63). In this animal study, the use of a bioabsorbable membrane significantly increased bone and connective tissue formation while decreasing the length of long junctional epithelium formation compared with controls. In contrast, another study compared the rate of healing of periapical defects by using a bioabsorbable membrane compared with no membrane and found no difference between groups (68). Similarly, periosteal sliding grafts were compared with bioabsorbable membrane grafts in periapical defects after endodontic surgery (69). No significant differences were found between treatment groups, although both groups resulted in successful periapical healing. These studies suggest that if complete closure of the endodontic wound can be achieved, a membrane might be unnecessary. However, in more challenging situations such as where a buccal dehiscence exists, a membrane might enhance treatment outcomes.

Growth Factors/Cytokines/Host Modulating Agents

The application of local growth factors (Table 4) has been studied to enhance the healing and regeneration potential of periodontal/endodontic surgery. PRP, growth factors including BMPs, PDGF, and EMD are the most commonly used agents (3–6). Other promising therapeutics include collagen fragments bound to bone grafts, PTH, and transforming growth factor beta 3 (TGF-b3) (70).

PRP is a highly concentrated suspension of autologous platelets, which secrete bioactive growth factors on activation. Because these growth factors are present at increased concentrations in PRP, they help to enhance key stages of wound healing and regenerative processes including chemotaxis, proliferation, differentiation, and angiogenesis (71). Similarly, autologous platelet concentrate (APC) contains PDGFs that promote regeneration. One study comparing APC with a bioabsorbable membrane in infrabony defects found similar results between the 2 groups, suggesting that APC could be used in lieu of a membrane for periodontal GTR applications (72).

BMPs have an anabolic effect on periodontal tissues through stimulation of osteoblastic differentiation in human periodontal ligament cells (73). An animal study showed new bone formation and connective tissue attachment with cementum regeneration occurred around circumferential periodontal defects in dogs treated with rhBMP-2 compared with controls (74). Still, there is some hesitation to use BMPs in humans because ankylosis has been a reported finding in animal studies (75). To date, sufficient human studies with BMPs in periodontal defects are lacking. In the endodontic literature, one animal study showed no benefit to using BMP-2 to enhance regeneration after surgical root resection (76).

PDGF is a growth factor involved in wound healing that stimulates the regenerative potential of periodontal tissues including bone,

TABLE 4. Growth Factors/Cytokines/Host Modulating Agents Used to Promote Periodontal Regeneration and, If Available, Their Commercial Product Names, that Have Been Tested for GTR Applications in Periodontal Defects

Commercial name	Components
Gem-21* (Osteohealth, Shirley, NY)	PDGF-BB in β-TCP
Emdogain* (Straumann, Andover, MA)	Amelogenin and other EMD
INFUSE bone graft* (Medtronic, Minneapolis, MN)	BMP-2
PepGen-P15*(*in vitro*) (DENTSPLY Friadent, Mannheim, Germany)	15 amino acid sequence from collagen bound to inorganic bovine matrix

*Those tested in endodontic defects.

cementum, and periodontal ligament (77). PDGF-BB is one form of PDGF, and it has shown the most promise as a regenerative agent. A large multicenter randomized controlled trial was conducted to assess the effects of PDGF-BB on intrabony defects in 180 patients (4). At 6 months, PDGF-BB treatment resulted in 2.6 mm linear bone gain, 57% defect fill, and an accelerated CAL gain of 3.8 mm by 3 months. One endodontic study evaluated the healing of the periradicular tissues when exogenous growth factors were delivered to the resected root end (78). The results of this study showed that using insulin-like growth factor (IGF) in combination with PDGF or fibroblast growth factor alone did not significantly enhance regeneration in the apical defect. PDGF has also been studied to enhance implant site development (79). In one case report, a tooth was extracted as a result of failed endodontic therapy, and the buccal plate was absent. The site was grafted with human bone allograft and PDGF. At 7 months, histology was done, and successful bone regeneration was achieved, suggesting PDGF has potential for implant site development applications.

EMD are deposited onto the dentin root surface and provide the initial step in the formation of acellular cementum (80). Autoradiographic and scanning electron microscopy studies have provided additional evidence that EMD are responsible for both initiation and modulation of cementogenesis (81, 82). Consequently, they have been incorporated into GTR attempts to promote cementogenesis and, thus, periodontal regeneration. A systematic review by Giannobile and Somerman (3) suggested that EMD and growth factors are promising in terms of their ability to promote tissue/bone regeneration, but that long-term data and sufficient evidence were still lacking. In a case report, EMD was used successfully to treat a large periradicular lesion involving an adjacent implant (83). An apicoectomy of the involved tooth was performed in addition to EMD application. At 18 months, there was radiographic evidence of bone fill, and no symptoms were reported by the patient. Thus, EMD might be a promising treatment for both endodontic and implant applications.

Another approach to regeneration is to rely on collagen to promote the binding of fibroblasts and osteoblasts in the tissue matrix (84). A15 amino acid sequence from collagen has been incorporated into an inorganic bovine matrix for this purpose and marketed as ABM/P-15. Twenty-five patients with infrabony defects were treated with this material and followed for 36 months (85). The long-term results were positive, with an average CAL gain of 1.6 mm and 2.4 mm probing depth reduction. No adverse outcomes such as ankylosis or root resorption were noted. Unfortunately, as of the time of this writing no studies evaluating the ability of ABM/P-15 to promote periodontal regeneration in periapical defects are available.

PTH is an endogenous hormone with anabolic actions in bone if used at low intermittent doses. Preliminary animal studies have shown that this might be a promising technique for regenerating bone in the periodontium. Miller et al (86) administered intermittent PTH to the mandibles of aged ovariectomized rats and found that PTH stimulated bone formation in this area. Similarly, another group found that PTH protects against periodontitis-associated bone loss (87). Recently, Jung et al (88, 89) developed an arginine-glycine-aspartic acid (RGD) modified polyethylene glycol–based matrix (PEG) containing covalently bound peptides of the parathyroid hormone (PTH(1-34)) to promote bone regeneration around dental implants. In their studies, they found this technique enhanced bone regeneration in a similar magnitude as autogenous bone grafting in both rabbit and foxhound models.

Outcomes

There is some debate as to the best treatment modality for obtaining regeneration. Some advocate the use of bone replacement grafts alone, others suggest that a membrane alone might be sufficient, and still others recommend a combination of both. A systematic review by Reynolds et al (28) demonstrated that in infrabony defects, bone replacement grafts increased bone level, reduced crestal bone loss, increased clinical attachment level, and reduced probing depth compared with open flap debridement. In addition, they found no differences in clinical outcomes when they compared particulate bone allografts with calcium phosphate (hydroxyapatite) ceramic grafts. They also established that using a bone graft in combination with a barrier membrane resulted in increased clinical attachment levels and reduced probing depths compared with a graft alone.

Similarly, one group compared 3 treatment modalities for achieving GTR after endodontic surgery: control group (no bone graft or membrane), nonresorbable membrane, and nonresorbable membrane and hydroxyapatite bone graft (90). The results of this study showed the best result can be obtained by using both a membrane and a bone graft, and the least successful result occurs when no bone graft or membrane is used. Another group compared the histologic outcome of different types of membranes and bone grafts after apicoectomy in beagle dogs: e-PTFE nonresorbable membranes, PLGA bioabsorbable membranes, collagen membranes, calcium sulfate, and control (no membrane or bone graft) (49). The results of this study indicate that a nonresorbable membrane results in the greatest amount of bone regeneration followed by calcium sulfate. One animal study evaluated 3 treatment modalities for regenerating bone in periapical defects (11). In this study, open flap debridement, a bioabsorbable membrane, and a membrane combined with bovine allograft all resulted in similar amounts of epithelial formation. The average connective tissue attachment was 3.79 mm for open flap debridement, 2.63 mm for the membrane group, and 1.75 mm for the membrane/bone graft group. The mean radicular bone height was 2.16 mm, 3.24 mm, and 3.45 mm for each group, respectively. In addition, both treatment groups had significantly more cementum formation than the control group.

Similarly, Laurell et al (91) showed that when bone graft alone was placed in infrabony periodontal defects, limited pocket reduction was achieved, but CAL gain and bone fill were significantly improved, averaging 2.1 mm. When GTR with both bone graft and a membrane was used, GTR resulted in significant pocket reduction, a CAL gain of 4.2 mm, and bone fill averaging 3.2 mm (91). In this same study, open flap debridement surgery resulted in minimal probing depth reduction, an average CAL gain of 1.5 mm, and bone fill of 1.1 mm. However, the predictability of GTR has been questioned. Caton et al (92) conducted a study in monkeys comparing the histologic outcome of 4 treatment modalities: scaling and root planing, modified Widman flap (MWF), MWF with autogenous bone graft, and MWF with beta tricalcium phosphate (b-TCP). All treatments resulted in the formation of a long junctional epithelium without new connective tissue attachment. Eikholz et al (73) treated 50 infrabony defects with GTR. After 5 years, 47 of the defects still showed evidence of vertical attachment gain, but 3 defects had a net loss of up to 2.2 mm. In a systematic review of the literature, Murphy and Gunsolley (93) found some heterogeneity in the outcome of GTR and concluded that it was difficult to assess the efficacy of periodontal treatment by using physical barriers because no studies were performed that measured tooth retention for more than 5 years. Consequently, there is still no definitive agreement on what the preferred treatment is for attaining periodontal regeneration.

A recent Cochran database systematic review compared GTR with membranes alone and GTR and bone grafting with open flap debridement procedures (94). In this comprehensive review, the authors concluded that GTR with or without a bone graft improved CAL gain, reduced pocket depths, prevented gingival recession, and experienced more gain in hard tissue probing at reentry surgery compared with open

TABLE 5. Factors that Influence GTR Outcomes Resulting Primarily from Periodontal Defects

Positive	Negative
Defect/anatomic factors	
Deep (≥4 mm) infrabony defects	Shallow infrabony defects
Narrow defect angle <45 degrees	Wide defect angle >45 degrees
Vertical defects	Horizontal bone loss
3-wall defects*	1- or 2-wall defects*
No or minimal furcation involvement	Deep furcation involvement
Adequate tissue thickness (>1.1 mm)*	
Adequate keratinized gingiva (2 mm)*	
Patient factors	
Systemic health*	Systemic compromised patient*
Stable occlusion*	Occlusal trauma*
Good oral hygiene/compliance*	Poor oral hygiene/compliance*
	Smoking habit*
	Mechanical trauma (eg, aggressive tooth brushing)*
	Inflamed gingival tissues*
Surgery-related factors	
Passive flap tension*	Excessive flap tension*
Stable wound*	Early mechanical disruption*
Sterile surgery*	Contamination during surgery*
Short/minimally traumatic surgery*	Lengthy/traumatic surgery*
Primary wound closure*	Inadequate wound closure*
No membrane exposure*	Membrane exposure*
Proper incision location*	Poorly designed incisions*

*Factors that also apply to endodontic defects.

flap debridement. At surgical reentry, sites treated with GTR had an average of 1.39 mm more bone gain than controls, whereas sites treated with GTR and bone substitutes responded even more favorably, with 3.37 mm more bone gain than open flap debridement. The reviewers also stressed that with a wide range of reported outcomes and unknown clinical relevance, these results should be interpreted with caution. No systematic review regarding GTR in endodontic lesions exists, although a recent Cochrane database systematic review was published comparing surgical versus nonsurgical treatment of periapical pathosis (95). This systematic review demonstrated that a surgical approach to re-treating endodontic defects resulted in higher short-term healing rates (risk ratio, 1.13) than a nonsurgical approach, although there were no long-term differences in healing outcomes.

Factors That Affect Success

Case selection is very important to the success of regenerative techniques, which might explain some of the inconsistencies in the literature. Factors that affect success (Table 5) can be divided into patient-specific, defect-specific, and healing categories. Research has elucidated many of the patient factors that might contribute to positive GTR outcomes including good plaque control, compliance, nonsmoking, anti-infective therapy, and systemic health (96–98). Selecting a defect that is amenable to regeneration is also critical for achieving success. This is also true for an endodontic defect. A recent randomized controlled trial compared the use of GTR in 2-walled and 4-walled periapical defects (99). GTR was accomplished by using a bioabsorbable collagen membrane combined with anorganic bovine bone. After 1 year, 81.2% of the 69 treated teeth had healed successfully. According to the authors, GTR improved the outcome of transosseous (2-walled) lesions but was not necessary for 4-walled defects. A prospective study assessed the outcome of periradicular surgery with or without GTR in through-and-through lesions (42). After 1 year, the outcome of the teeth treated with GTR was significantly better than the control group, with success rates of 88% and 57%, respectively. In contrast, another study compared the outcomes of periradicular surgery with or without GTR in large periapical lesions (41). In this study, no significant differences in healing were found between the control group and the group treated with a bioabsorbable collagen membrane and anorganic bovine bone. Three-wall defects with a deep infrabony component of ≥4 mm and a defect angle of less than 45 degrees are associated with the highest success rate (91, 100, 101). Also, adequate tissue thickness and keratinized gingiva support favorable outcomes (102). During the healing phase, membrane exposure can prevent optimal healing (103). Other factors that might also negatively affect the healing process include occlusal trauma, improper surgical technique (such as excessive flap tension), early mechanical disruption, and contamination during surgery. Wang and Boyapati (104) suggested 4 factors, the so-called PASS principle, that are critical for predictable bone regeneration: primary wound closure, angiogenesis as a blood supply and source of undifferentiated mesenchymal cells, space maintenance, and stability of the wound. Space maintenance involves the creation of space for periodontal tissues to grow into. This can involve the use of tenting screws, rigid membranes, or even host bone in the case of 3-wall defects.

Conclusion

Although traditional nonsurgical periodontal therapy and regular endodontic therapy can be predictably used to arrest mild to moderate defects, it might be inadequate for the treatment of disease characterized by deep pockets or wide circumferential apical defects caused by endodontic infection or surgery. Although traditional surgical procedures provide better access in these situations, there is still a disadvantage to both techniques in that tissue repair is the probable outcome. Many techniques and materials are available to promote regeneration, including bone replacement grafts, barrier membranes, and host modulating agents. Currently, regeneration attempts are widely variable in terms of their ability to predictably regenerate the lost tissue/bone in all types of defects or for all situations. Knowledge of the factors that can negatively affect regeneration outcomes and subsequent careful case selection can help to optimize successful regenerative attempts. Moreover, a critical need still exists for a therapy that can enhance the regeneration in a predictable fashion. This article reviewed the currently available techniques and materials for tissue/bone regeneration, as well as their advantages and disadvantages.

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