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Review Article

Regenerative dentistry across specialties: current evidence, clinical relevance, and translational limitations

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ABSTRACT

Regenerative dentistry covers a range of biologically based approaches rather than a single treatment model. This comprehensive review examined the main regenerative domains in contemporary dentistry, including periodontal regeneration, alveolar bone regeneration, pulp–dentin regeneration and regenerative endodontics, pediatric applications, orthodontic relevance, prosthodontic site development, and the role of biomaterials and tissue-engineering strategies. Literature from PubMed, Scopus, and Web of Science was reviewed and interpreted comparatively according to target tissue, biologic aim, representative interventions, outcome measures, and degree of clinical support. The evidence showed clear variation across domains. Periodontal regeneration had the strongest clinical support, particularly in well-selected intrabony defects. Regenerative endodontic procedures offered important advantages in immature teeth, especially with respect to continued root development, although uncertainty remained regarding the exact nature of the tissue formed. Alveolar bone procedures were clinically useful for ridge preservation and site development, but volumetric improvement could not be assumed to represent true regeneration. In pediatric dentistry, regenerative strategies appeared especially relevant because of the healing potential of developing tissues. By contrast, orthodontic and prosthodontic applications were better understood as adjunctive uses of regenerative principles that support periodontal stability, tissue contour, and restorative planning. Overall, regenerative dentistry is best viewed as a field of uneven but meaningful clinical progress, with its strongest support in selected periodontal and endodontic applications.

Keywords: Regenerative dentistry, Tissue engineering, Alveolar bone regeneration, Biomaterials, Scaffolds

INTRODUCTION

Oral diseases remain among the most common health conditions worldwide and continue to impose a substantial burden through pain, functional limitation, tooth loss, and reduced quality of life.[1] Against this background, regenerative dentistry has emerged from the broader movement toward biologically based treatment, aiming not only to control disease or replace missing tissues, but also to restore oral structure and function more meaningfully than conventional reparative approaches permit. Shah et al described regenerative dentistry as a field centered on enhancing the structure and function of oral tissues, while also emphasizing the growing role of mesenchymal stem cells in pulp–dentin, alveolar bone, and periodontal applications.[2] This shift has been driven by advances in tissue engineering, biomaterials, and cell-based strategies. Inchingolo et al summarized regenerative dentistry as an

interdisciplinary field built around stem cells, biocompatible scaffolds, and bioactive molecules, with the aim of repairing or regenerating damaged oral tissues.[3] Ivanovski et al further noted that dental mesenchymal stem cells and their secretome have shown promise in bone, periodontal, and endodontic regeneration, but also stressed that widespread clinical translation remains limited by difficulties in standardization, manufacturing, cost, and regulatory compliance.[4] In parallel, Li et al highlighted that regenerative endodontic therapy is intended to induce new functional pulp tissue through revascularization or tissue-engineering approaches, while also acknowledging that important limitations still constrain translation toward predictable clinical use.[5] Despite this progress, regenerative dentistry is still marked by uneven clinical maturity across tissues and indications. Some applications have moved closer to routine practice, whereas others remain biologically promising but methodologically and translationally unsettled. Shah et al emphasized that the field spans multiple tissues and therapeutic strategies rather than a single uniform intervention, and et al similarly pointed to the continuing gap between experimental promise and clinically standardized use.[2,4] Accordingly, the aim of the present comprehensive review is to provide a structured overview of regenerative dentistry across its principal domains, with emphasis on biologic principles, clinically relevant applications, and the interpretive boundaries between regeneration, repair, and reconstruction.

METHODS

Review framework and scope

This article was prepared as a structured narrative review of regenerative dentistry, with emphasis on the biologic principles, clinical applications, and translational limitations of regenerative strategies across key dental domains. The purpose of this review was to synthesize the literature across major regenerative targets and to examine how regenerative aims differ according to tissue type, clinical indication, and level of evidence. The review was therefore organized around the principal domains addressed in the manuscript: conceptual foundations of regeneration, periodontal regeneration, pulp–dentin regeneration and regenerative endodontics, alveolar bone regeneration, regenerative applications in pediatric dentistry, regenerative relevance in orthodontics, regenerative relevance in prosthodontic/restorative treatment planning, biomaterials and tissue-engineering strategies, and the determinants of success and sources of heterogeneity across the field.

Information sources and search strategy

A targeted literature search was undertaken in major biomedical databases, including PubMed/MEDLINE, Scopus, and Web of Science, with supplementary hand-searching of the reference lists of relevant reviews, consensus papers, and key primary studies. The search strategy was designed to capture literature on both the biologic foundations and the specialty-specific applications of regenerative dentistry. Search terms combined broad regeneration-related concepts with tissue-specific and clinically oriented terminology. Representative terms included regenerative dentistry, tissue engineering, periodontal regeneration, guided tissue regeneration, enamel matrix derivative, regenerative endodontics, pulp–dentin complex, revitalization, alveolar bone regeneration, ridge preservation, guided bone regeneration, pediatric dental regeneration, orthodontic periodontal phenotype, alveolar augmentation, pontic site development, soft-tissue grafting, biomaterials, scaffolds, growth factors, platelet concentrates, stem cells, exosomes, and 3D printing. The purpose of the search was to capture literature describing biologic constraints, variability in outcomes, limited histologic confirmation, and barriers to clinical translation.

Eligibility and source selection

Articles were considered eligible when they addressed a clearly defined regenerative concept, biologic mechanism, material platform, or clinical regenerative application relevant to dental tissues. Studies were retained when they contributed meaningfully to one or more domains covered in the review and reported outcomes related to tissue healing, regeneration, structural preservation, clinical performance, or translational relevance. Eligible sources included randomized or non-randomized clinical studies, observational clinical reports, animal studies, systematic reviews, and mechanistic in vitro investigations, provided they offered interpretable evidence relevant to the review's scope. Preference was given to higher-level and clinically oriented evidence when available, while preclinical studies were used primarily to clarify mechanisms and emerging technologies. Articles were excluded if they focused exclusively on non-dental biomedical regeneration, discussed regeneration only in broad conceptual terms without relevance to dental tissues, or were limited to material synthesis and physicochemical characterization without meaningful biologic or clinical interpretation. Editorials, opinion papers, conference abstracts, and reports lacking sufficient methodological or outcome detail were also excluded.

Data interpretation and synthesis

The final synthesis was narrative and domain-based. Within each domain, the literature was interpreted comparatively in relation to biologic objective, target tissue, representative interventions, main outcome measures, and major sources of uncertainty. Particular attention was given to distinctions between true regeneration, repair, and reconstruction, as well as to the difference between histologic confirmation, radiographic improvement, and clinically favorable outcomes. The review also aimed to identify areas of agreement and disagreement across studies, to explain likely reasons for conflicting findings, and to distinguish relatively

established clinical applications from emerging or still investigational approaches.

REVIEW

Conceptual foundations and biologic principles of regenerative dentistry

Li et al positioned regenerative dentistry as a biologically driven field that aimed to restore oral tissues such as alveolar bone, periodontium, dental pulp, and gingiva within the uniquely demanding oral environment.[6] Bădărău-Șuster et al, however, made an important conceptual distinction in periodontology by separating repair, which restored function without fully rebuilding the original attachment apparatus, from regeneration, which required reconstitution of cementum, periodontal ligament, and alveolar bone.[7] Taken together, these views support using regenerative dentistry as an umbrella term, while reserving true regeneration for outcomes that plausibly restore native tissue identity and function rather than merely improve defect morphology or clinical manageability. Fischer et al stressed that regeneration of the periodontal complex involved multiple tissues and interfaces and therefore demanded more than a simple scaffold-based approach.[8] The broader implication is that the classical triad of cells, scaffolds, and signaling cues remains central, but its clinical translation is tissue-specific rather than uniform across dentistry. Dissanayaka et al identified vascular ingrowth as a central bottleneck in pulp regeneration, because newly forming tissue within the canal space depended on rapid vascular support for survival and functionalization.[9] Dolińska et al, in contrast, showed that periodontal regeneration was especially dependent on primary wound closure, clot stabilization, and maintenance of a protected regenerative space.[10] This comparison is biologically useful: pulp regeneration is constrained primarily by vascular access, whereas periodontal regeneration is constrained more heavily by wound stability and organized multi-tissue healing. Jia et al argued that peri-implant tissues had limited regenerative capacity because implants lacked the periodontal ligament and its associated stem-cell contribution, which made peri-implant reconstruction biologically different from regeneration around natural teeth.[11] Meng et al reinforced another key principle by evaluating socket preservation through separate histological and radiological outcomes, implicitly showing that tissue composition and image-based improvement were not interchangeable endpoints.[12] Conceptually, therefore, regenerative claims become strongest when biologic identity, structural improvement, and clinical function converge rather than when only one of these dimensions improves (Figure 1).

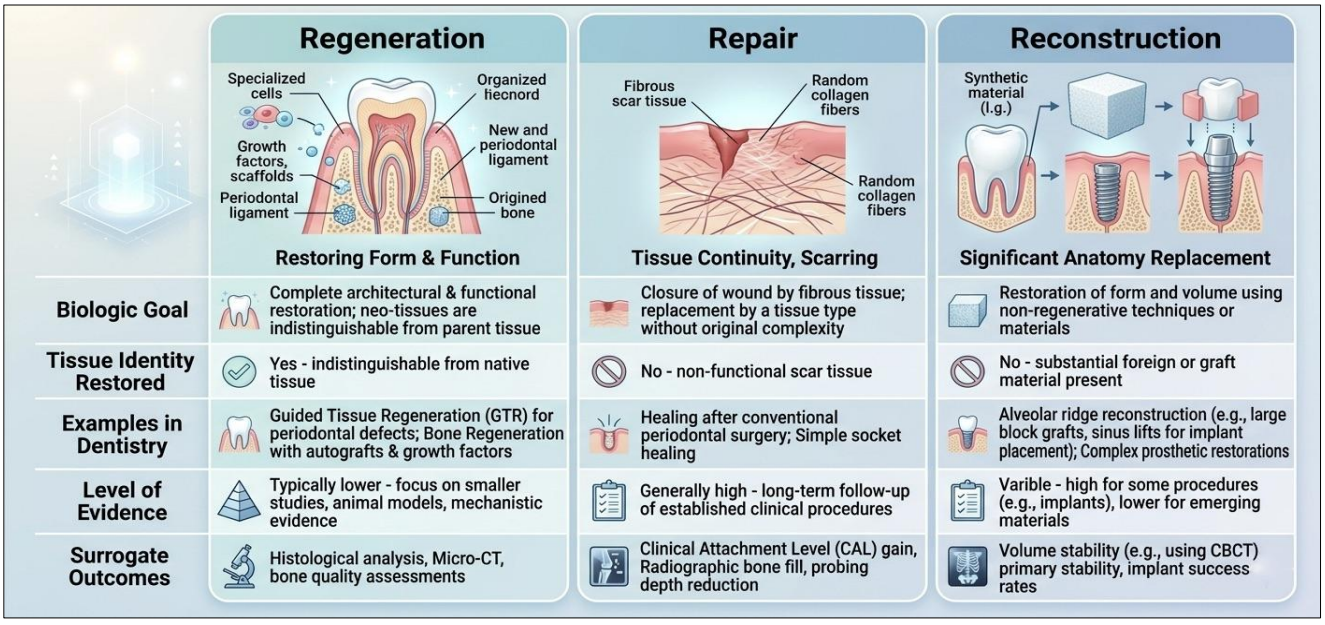

Figure 1: Conceptual distinctions between regeneration, repair, and reconstruction in dentistry.

Periodontal regeneration

Nibali et al reported that regenerative surgery for intrabony periodontal defects produced greater clinical attachment gain than access flap surgery, supporting the view that periodontal regeneration can improve not only defect morphology but also clinically relevant healing outcomes.[13] Nibali et al also showed, in a separate systematic review, that deeper defects, narrower defect angles, and a greater number of residual walls were associated with greater clinical attachment gain and radiographic bone gain after regenerative surgery.[14] Figure 1 illustrates the conceptual distinction between true regeneration, repair, and reconstruction in dentistry, which is important when interpreting periodontal outcomes that may show clinical improvement without necessarily proving full reconstitution of the native attachment apparatus. This suggests that periodontal regeneration is

not uniformly predictable across all defects, but is most convincing when the defect anatomy is inherently favorable. Valente et al found that adding graft materials to biologic agents produced only modest additional benefit in probing-depth reduction and radiographic bone level gain, while clinical attachment gain was not significantly improved.[15] Menhadji et al further suggested that the apparent benefit of biomaterials is influenced by flap design, with clearer gains in traditional access and papilla-preservation approaches than in single-flap variants.[16] Taken together, these comparisons argue against routine material escalation and instead favor a more selective approach in which biomaterial choice is matched to the surgical design and defect environment. Kaddas et al reviewed minimally invasive surgical techniques for intrabony defects and concluded that less invasive approaches were associated with more uneventful postoperative healing and reduced patient morbidity.[17] Jepsen et al, however, argued that failures and complications in regenerative periodontal surgery often reflect plaque-infected dentitions, poor case selection, or technical and wound-management errors rather than failure of the regenerative concept itself.[18] This comparison is important because it shifts the discussion from whether regeneration works in principle to the conditions under which it is executed well enough to work predictably. Wang et al reported that regenerative procedures maintained significant probing-depth reduction and clinical attachment gain at follow-up of at least 5 years, although the certainty of evidence remained low and long-term superiority over access flap surgery was not definitively established.[19] Chen et al reported that regenerative therapy remained economically favorable compared with extraction and replacement or open flap debridement alone, even though membrane-based approaches were associated with longer chair time and more complications than flap surgery with biologic agents or access flap alone.[20] Overall, the evidence supports periodontal regeneration as a clinically established therapy, but one whose predictability still depends heavily on anatomy, technique, wound stability, and case selection.

Alveolar bone regeneration and craniofacial hard-tissue reconstruction

Benekou et al reported that new bone formation in alveolar ridge preservation groups ranged from 23.9% to 62.04%, whereas the corresponding range in spontaneous-healing groups was 5.98% to 39.69%, indicating that post-extraction intervention can improve histologic bone formation but not with uniform magnitude across protocols.[21] Alavi et al concluded that regenerative materials were beneficial for radiographic preservation of alveolar width and height after extraction, although the relative advantage differed across materials, with rhBMP-2 performing better for width preservation and L-PRF remaining an attractive autologous alternative.[22] These findings suggest that alveolar ridge preservation is supported more consistently as a dimensional-preservation strategy than as a universally superior route to rapid histologic maturation. Mahardawi et al found that, in the posterior maxilla, alveolar ridge preservation reduced sinus pneumatization and the need for sinus floor augmentation at implant placement, while significantly improving ridge height but not demonstrating a statistically significant advantage for ridge width.[23] Sologova et al likewise concluded that socket augmentation with osteoplastic materials was effective in preserving ridge dimensions and preparing sites for later implant placement, but they also emphasized that differences in clinical performance across materials still required careful material selection.[24] Taken together, these comparisons show that the clinical value of alveolar regeneration is often site-specific and rehabilitation-driven, with posterior maxillary preservation serving not only to limit resorption but also to reduce the need for more invasive secondary augmentation. Frantzopoulos et al reported that both guided bone regeneration (GBR) and the shell technique achieved clinically meaningful vertical ridge augmentation, with no clearly dominant approach emerging across the included studies.[25] Alotaibi et al, however, found in a network meta-analysis that GBR procedures using non-resorbable membranes yielded the most favorable results for vertical bone gain and complications, suggesting that barrier characteristics may influence performance at least as much as graft selection.[26] Garcia et al further reported that membrane exposure had a significant detrimental influence on the outcome of bone augmentation, underscoring how easily technical success can be undermined by soft-tissue failure.[27] This pattern suggests that in vertical and horizontal augmentation, space maintenance and wound protection are often more decisive than the nominal choice of regenerative technique alone. Marian et al reviewed both conventional methods, such as GBR and bone grafting, and newer approaches including stem cell therapy, gene therapy, and 3D bioprinting, but they emphasized that complex defects still make predictable alveolar regeneration difficult.[28] Elboraey et al similarly highlighted inconsistencies across studies and proposed a clinical decision tree to guide selection of ridge-augmentation techniques and biomaterials according to defect scenario.[29] Overall, the literature supports alveolar bone procedures as clinically useful for site development and reconstruction, but it also suggests that the label true regeneration should be used cautiously because histologic quality, volumetric preservation, and implant-oriented clinical success do not always move in parallel.

Pulp–dentin complex regeneration and regenerative endodontics

Theekakul et al reported a 97.5% functional retention rate and an 80% healed rate after regenerative endodontic procedures (REPs) in immature permanent teeth with a mean recall of 41.7 months, supporting the clinical viability of this approach in carefully selected cases.[30] Anas et al found in their systematic review of randomized trials that REPs produced greater root lengthening and dentinal wall thickening than apexification, while

achieving comparable or superior apical closure.[31] Tewari et al, however, concluded that RET and apexification showed comparable success rates above 85% across most domains, which suggests that the distinctive advantage of regenerative endodontics lies less in short-term disease control and more in its potential to promote continued root maturation.[32] Sabeti et al ranked platelet-rich plasma (PRP) highest for root lengthening at 6–12 months in their network meta-analysis, although they also judged the certainty of that evidence to be very low.[33] Huang et al likewise reported that PRP and PRF improved root length and root thickness compared with blood-clot scaffolds, with PRP showing a modest advantage in clinical success over blood clot.[34] Rahul et al, in contrast, found no statistically significant scaffold-related differences in clinical success, root maturation, apical closure, or pulpal sensibility among PRP, PRF, and blood clot, indicating that scaffold superiority remains uncertain and may depend on whether the chosen endpoint is structural, sensibility-based, or purely clinical.[35] Vitali et al reported that pooled clinical and radiographic healing exceeded 81% across pre-operative factors, but they also showed that root development remained sensitive to baseline conditions, indicating that prognosis cannot be reduced to a single success percentage.[36] Song et al similarly reported complete periapical healing in 91.2% of teeth and root lengthening in 86%, yet they also documented increasing intracanal calcification over time, which highlights that biologic success may be accompanied by structural trade-offs rather than ideal tissue restoration.[37] Digka et al concluded from the available human histologic evidence that tissues formed after REPs in immature teeth reflected repair or a combination of repair and regeneration, rather than consistent recreation of a native pulp–dentin complex.[38] Fouad et al similarly noted that clinically feasible cell-homing protocols still fell short of providing histologic proof of true regeneration.[39] Meschi et al added a further caution by finding no robust evidence that revitalization is effective specifically for treating apical periodontitis in immature permanent teeth.[40]

Regenerative relevance in pediatric dentistry

In pediatric dentistry, the regenerative dimension extends beyond necrotic teeth because preserving pulpal vitality in young permanent teeth directly supports apexogenesis, continued root development, and strengthening of dentinal walls that would otherwise remain vulnerable to fracture.[41] This already sets pediatric care apart from a purely restorative model: in primary teeth, treatment is often directed toward maintaining function until exfoliation, whereas in immature permanent teeth the biologic objective is to preserve or recover developmental potential whenever feasible. That is why contemporary pediatric regenerative care should not be reduced to regenerative endodontic procedures alone. Coll et al, in the AAPD permanent-tooth guideline, recommended partial or full pulpotomy over direct pulp capping for traumatic pulp exposures in vital permanent teeth and also favored calcium silicate cements over calcium hydroxide for direct pulp capping, which places vitality-preserving, biologically based treatment at the center of care for many children and adolescents.[41] Lu et al likewise found that Biodentine achieved clinical and radiographic success comparable to other bioceramics in vital pulp therapy for young permanent teeth, while reducing discoloration, suggesting that material choice in pediatric cases also has esthetic implications that matter clinically.[42] When the pulp has already become necrotic, the pediatric advantage shifts from vitality preservation to the possibility of continued root maturation. Kahler et al reported that regenerative endodontic treatment in traumatized immature teeth showed high survival and success, but they also found that root maturation tended to be lower in traumatized teeth and that high-level comparative evidence against apexification remained limited.[43] Cheng et al similarly reported satisfactory outcomes for regenerative procedures in traumatized immature necrotic permanent teeth, yet they cautioned that severe injuries, especially avulsion, required careful case selection and that gains in root length were limited.[44] These comparisons suggest that pediatric patients offer real biologic opportunity, but trauma severity can narrow the regenerative payoff even when tooth retention and periapical healing are achieved. The limits of that opportunity become even clearer in avulsion-related cases. Koum et al found that regenerative treatment of avulsed immature permanent teeth achieved an overall success rate of only 44% across the studies they reviewed, which contrasts sharply with the more favorable results often reported for non-avulsion immature teeth.[45] Sheng et al reported reliable periapical healing in delayed replanted immature permanent teeth with apical periodontitis, but continued root development occurred in only 41.2% of cases, even though teeth that continued to develop showed better functional healing.[46] Overall, pediatric dentistry provides one of the strongest biologic justifications for regenerative care, but its greatest advantages appear in carefully selected young permanent teeth rather than uniformly across all traumatic scenarios.

Regenerative relevance in orthodontics

Kwon et al reviewed the literature and reported that orthodontic treatment may increase the risk of periodontal disease or conditions, which is why periodontal evaluation is needed before, during, and after treatment.[47] Fleming et al further argued that a thin periodontal phenotype is associated with a greater risk of gingival recession during orthodontic treatment, but they also emphasized that orthodontic tooth movement can help prevent or manage recession when roots are repositioned more favorably within the alveolar housing.[48] This suggests that orthodontics becomes regeneratively relevant mainly when it is used to respect or restore the periodontal envelope rather than simply to align teeth. Kadkhodazadeh et al assessed periodontal phenotype modification in orthodontic patients using combined bone and soft-tissue grafting and concluded that this approach was feasible and could reduce adverse consequences while improving esthetic outcomes.[49] Tironi et al similarly reported that

surgically facilitated orthodontic treatment was proposed not only to accelerate movement, but also to modify the periodontal phenotype, particularly in thin tissues where orthodontic movement may otherwise create recession or dehiscence.[50] Taken together, these reports indicate that regenerative or augmentative procedures in orthodontics are used mainly to widen the biologic safety margin for tooth movement, not to replace orthodontic mechanics themselves.

Zhou et al found that corticotomy- and PAOO-based approaches reduced treatment duration without significantly increasing root resorption, which supports their use as selective adjuncts in cases where treatment efficiency and alveolar remodeling are both concerns.[51] Kuc et al, however, concluded that the validity of corticotomy-assisted orthodontic therapy and PAOO remained controversial, and they noted that better periodontal results were obtained when these approaches were combined with tissue augmentation or gingival phenotype thickening rather than used as stand-alone procedures.[52] This comparison suggests that the regenerative value of facilitated orthodontics lies less in acceleration alone and more in whether it is paired with phenotype-supportive tissue management. Wang et al reviewed animal studies on orthodontic tooth movement in augmented bone and concluded that movement during the woven-bone stage was feasible, although grafting generally impeded tooth movement and the overall quality of evidence was suboptimal.[53] Papageorgiou et al emphasized that in stage IV periodontitis, orthodontic treatment should be undertaken only after periodontal stability has been achieved and must be adjusted to the specific limitations of a severely reduced periodontium.[54] Marya et al likewise concluded that interdisciplinary orthodontic treatment in reduced periodontal support can be effective, but that the evidence base remains limited and still needs stronger prospective confirmation.[55] Overall, orthodontics is best viewed as an adjunctive domain of regenerative dentistry: it can benefit from regenerative or phenotype-modifying strategies, but it is not itself a primary regenerative therapy.

Regenerative relevance in prosthodontics and restorative treatment planning

Gomez-Meda et al described pontic-site management from a perio-prosthodontic perspective and emphasized that pontic design must be matched to defect complexity, while interim soft-tissue conditioning and clear communication with the laboratory remain critical to a successful outcome.[56] This frames regenerative procedures in prosthodontics as site-development tools that make a ridge more compatible with esthetic, cleansable, and biologically acceptable restoration rather than as isolated surgical goals. Strauss et al found that soft-tissue grafting at pontic sites tended to limit contour changes and maintain esthetic outcomes over time, whereas the absence of grafting still produced stable clinical outcomes but was associated with a gradual decline in esthetics.[57] Bienz et al reported, however, that over a 10-year follow-up, pontic sites with and without previous subepithelial connective tissue grafting both showed only minimal linear and volumetric changes, with no significant intergroup differences.[58] Taken together, these findings suggest that soft-tissue augmentation may be most valuable when the initial ridge contour is insufficient for the desired prosthetic emergence profile, whereas long-term stability may still be acceptable without grafting when the baseline topography is already favorable.

Du Toit et al concluded that root submergence is an established technique for ridge preservation, although root exposure remains its most common complication.[59] Ogawa et al reviewed partial extraction therapy and explained that socket-shield and related approaches aim to preserve the buccal root fragment and thereby reduce postextraction ridge collapse, but they also noted complications such as infection, shield exposure, and migration, all of which can compromise the restorative plan.[60] This comparison is clinically important because prosthodontic benefit depends not only on preserving ridge contour, but also on choosing techniques whose complication profile does not undermine the planned definitive restoration. Roper et al stated that pontic site augmentation and pontic site development play key roles in creating a natural emergence profile and good cleansability, and they noted that final reconstruction may be considered from about 3 months after augmentation in selected cases.[61] The same review also emphasized that soft-tissue grafting alone may be insufficient in more severe defects, where hard-tissue reconstruction may still be required before definitive prosthodontic treatment. Overall, regenerative procedures influence prosthodontic planning by altering not only ridge form, but also the timing, design options, esthetic ceiling, and maintenance burden of the final restoration. Figure 2 summarizes the principal biologic and clinical bottlenecks that shape regenerative outcomes in each domain.

Biomaterials, scaffolds, biologics, and tissue-engineering strategies

Thalakiriyawa et al reported that contemporary regenerative dentistry is moving beyond conventional surgical and nonsurgical approaches toward modified strategies that incorporate guided tissue regeneration, computer-aided design, and 3-dimensional bioprinting.[62] Umapathy et al likewise argued that stem cell–based tissue repair and biomaterial-assisted regeneration already show substantial promise, but they also emphasized persistent biological, technical, regulatory, ethical, and economic barriers.[63] Taken together, these reviews suggest that the regenerative toolbox is becoming more biologically instructive and technologically sophisticated, yet still falls short of routine, predictable clinical translation across all dental tissues. Miron traced the evolution of autologous platelet concentrates from platelet-rich plasma to platelet-rich fibrin and highlighted their broad clinical use as biologically active adjuncts rather than stand-alone regenerative solutions.[64] Blanco et al similarly reviewed

autologous platelet concentrates in alveolar bone augmentation and framed their role as potentially beneficial, but not uniformly decisive, across horizontal and vertical augmentation settings.[65] Arora et al added that platelet-rich fibrin appeared to accelerate wound healing and reduce postoperative discomfort in alveolar ridge reconstruction and guided bone regeneration, whereas its effect on actual bone gain remained less clear.[66] This pattern suggests that platelet concentrates are best interpreted as healing modifiers and biologic enhancers, not as universal substitutes for sound scaffold design, defect management, or surgical technique. Taymour et al described hydrogels as biomimetic platforms that support oral stem-cell functionalization and noted that 3D printing now allows the fabrication of cell-laden hydrogel scaffolds with diverse biohybrid functions.[67] Li et al reviewed native and engineered exosome-based approaches and concluded that exosomes show substantial promise as cell-free regenerative therapies across multiple oral and maxillofacial tissues, while also requiring rational solutions to overcome translational barriers.[6,8] Kannan et al further emphasized the synergistic role of stem cells, scaffolds, and signaling molecules in oral and maxillofacial regeneration, but they also noted that future progress depends on stronger clinical translation, large-scale trials, and cost-effectiveness data.[69] Collectively, these approaches indicate that the field is shifting from passive scaffolds toward bioactive and even acellular signaling systems, although the strongest evidence still remains preclinical or early translational rather than definitively clinical Zhao et al reported that 3D-printed scaffolds offer high fidelity, customized topographies, and superior production efficiency, and they reviewed their application to dental pulp, dentin, periodontal ligament, and alveolar bone regeneration.[70] Dixit et al extended that discussion into clinical translation and argued that 3D bioprinting enables patient-specific, functional constructs, but they also concluded that clinical adoption of viable cell-laden constructs remains limited by vascularization, neural integration, biomaterial standardization, and regulatory challenges.[71] Overall, biomaterials and tissue-engineering strategies now offer unprecedented control over scaffold architecture, biologic signaling, and patient-specific design, but their clinical value still depends on whether they can achieve durable integration and reproducible outcomes rather than merely technical sophistication.

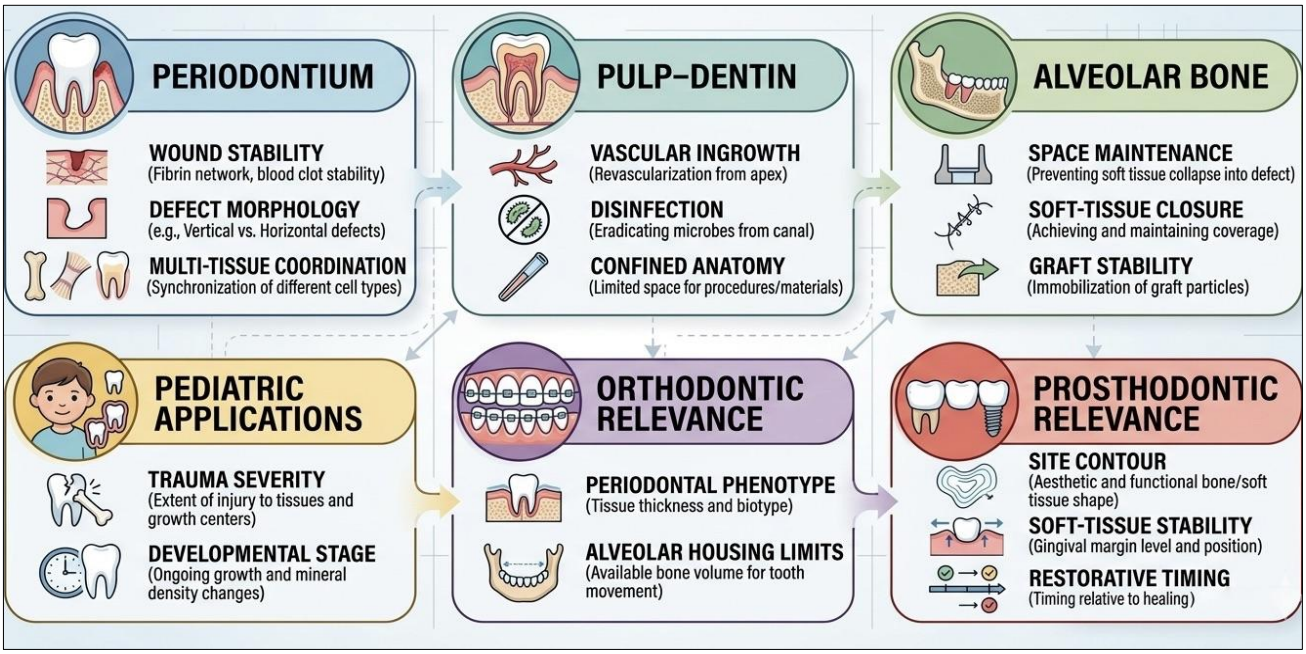

Figure 2: Main biologic constraints in regenerative dentistry.

Determinants of regenerative success and sources of heterogeneity

Levine et al proposed a periodontal regeneration risk assessment specifically because regenerative outcomes are influenced by multiple interacting variables rather than by the biomaterial alone, including factors related to wound-healing potential, regenerative-space maintenance, and operator contribution.[72] Elboraey et al similarly concluded that, in alveolar bone augmentation, defect-specific technique selection is crucial and should be matched to the anticipated resorption pattern and clinical scenario rather than applied uniformly across cases.[29] Taken together, these reports indicate that regenerative success is strongly anatomy-dependent and indication-dependent, which helps explain why techniques that perform well in one defect configuration may show more modest or inconsistent results in another. Baseline patient and tooth characteristics also appear to shape outcomes before treatment even begins. Theekakul et al reported that, after regenerative endodontic procedures, patients younger than 12 years showed higher healed rates and greater continued root development, while teeth affected by caries or developmental anomalies showed more favorable root

development than those affected by trauma.[30] Vitali et al further found that immature teeth presenting apical lesions had a 2.55-fold higher relative risk of root-development failure than teeth without apical lesions.[36] These findings suggest that regenerative procedures do not begin from a biologic level playing field: age, etiology, developmental stage, and pre-existing pathosis can materially shift the likelihood of structural recovery even when overall tooth retention remains high. Technique-related and postoperative factors add another major source of variability. Gaudimier et al reported pooled complication rates of 26.44% for guided bone regeneration and 19.61% for onlay grafting, with membrane or graft exposure, wound dehiscence, and infection emerging as the most frequent complications.[73] Sabri et al likewise found that, in titanium-mesh bone augmentation, mesh exposure was the most common complication and graft failure the second most common.[73] This comparison suggests that regenerative failure is often not a failure of biologic intent, but a failure of soft-tissue management, space protection, or complication control, which is why technically sophisticated procedures can still produce inconsistent results in routine practice. A final determinant of apparent success lies in how outcomes are defined and reported. Zanjir et al stated that methodological heterogeneity and reporting bias complicate interpretation of endodontic outcomes, which is why they developed a core outcome set including tooth survival, pain, infection signs, radiographic healing, continued root development, need for further intervention, and adverse events.[74] Ma et al broadened this problem beyond endodontics and argued that the clinical translation of dental materials remains limited by funding uncertainty, gaps in clinical evaluation frameworks, material-performance concerns, and the need for stronger interdisciplinary collaboration and international standards.[75] Therefore, heterogeneity in regenerative dentistry reflects not only biologic diversity across tissues, but also inconsistent endpoints, uneven study design, and incomplete translational infrastructure, all of which make cross-study comparison more difficult than the apparent volume of literature might suggest. As summarized in Table 1, the principal regenerative domains in dentistry differ in their target tissues, biologic aims, typical interventions, and outcome measures, which helps explain why their evidence base and clinical interpretation are not uniform.

Table 1: Summary of regenerative targets across domains.

Domain	Primary target tissue(s)	Main biologic goal	Typical interventions	Main outcome measures	Clinical scope/ interpretive focus
Periodontal regenera-tion	Cementum, periodontal ligament, alveolar bone	Re-establish functional periodontal attachment apparatus	Guided tissue regeneration, enamel matrix derivative, bone grafts/ substitutes, growth factors, biologic combinations	Clinical attachment gain, probing depth reduction, radiographic bone fill, recession changes, tooth prognosis	One of the most clinically established regenerative domains; strongest in carefully selected defect morphologies
Pulp–dentin regenera-tion	Pulp tissue, dentin–pulp complex, immature root structures	Restore vitality-related function and support continued root maturation	Regenerative endodontic procedures, revitalization/revascu larization protocols, scaffold-based approaches, biologically based vital pulp therapy	Tooth survival, periapical healing, apical closure, root lengthening, dentinal wall thickening, sensibility response	Clinically important especially in immature teeth, but distinction between repair and true regeneration remains critical
Alveolar bone regenera-tion	Extraction socket, alveolar ridge, localized craniofacial hard tissue	Preserve or rebuild hard-tissue volume suitable for future function and rehabilitation	Socket/ridge preservation, guided bone regeneration, grafting procedures, membrane-based augmentation, biologic adjuncts	Horizontal/vertical dimensional change, radiographic bone gain, histologic new bone formation, readiness for rehabilitation	Often highly relevant for site development and reconstruction, although histologic regeneration and volumetric success are not always equivalent
Pediatric regenera-tive applications	Immature permanent teeth, vital pulp tissues, developing root structures	Preserve developmental potential and enhance structural maturation of young teeth	Vital pulp therapy, regenerative endodontic treatment, trauma-oriented biologic management	Pulp survival, apexogenesis/apical closure, root maturation, dentinal wall thickening, periapical healing	Biologically favorable field because of developmental potential, but outcomes vary substantially with trauma severity and pulp status

Continued.

Domain	Primary target tissue(s)	Main biologic goal	Typical interventions	Main outcome measures	Clinical scope/ interpretive focus
Orthodontic regenerative relevance	Periodontal phenotype, alveolar housing, supporting periodontal tissues	Protect or enhance the periodontal envelope during or around orthodontic movement	Periodontal phenotype modification, soft/hard-tissue augmentation, surgically facilitated orthodontic procedures, selective alveolar augmentation	Gingival recession changes, alveolar thickness, periodontal stability, treatment feasibility within alveolar boundaries	Best understood as an adjunctive domain in which regenerative strategies support safer tooth movement rather than replace orthodontic mechanics
Prosthodontic/ restorative regenerative relevance	Pontic sites, ridge contour, peri-restorative soft and hard tissues	Improve tissue architecture to support esthetics, cleansability, and restorative design	Pontic-site development, soft-tissue grafting, ridge preservation, ridge augmentation, partial extraction therapy in selected cases	Ridge contour stability, soft-tissue volume, esthetic integration, restorative feasibility, maintenance profile	Regenerative procedures are most valuable when they improve prosthetic site development, timing, and long-term tissue support

CONCLUSION

Regenerative dentistry has clear growing clinical relevance, but it should not be viewed as a uniform therapeutic entity. Current evidence is strongest for periodontal regeneration in appropriately selected intrabony defects and for regenerative endodontic procedures in immature teeth, whereas in other contexts the benefit is more often structural preservation, site development, or treatment support than unequivocal proof of true tissue regeneration. Orthodontic and prosthodontic applications are therefore best viewed mainly as adjunctive uses of regenerative principles rather than primary regenerative endpoints. Overall, cautious terminology and realistic expectations remain essential, and future progress will depend on more consistent outcome definitions, stronger long-term comparative evidence, and sharper distinction between regeneration, repair, and reconstruction.

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