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Beyond Bone Replacement: The Role of Osteogenesis, Angiogenesis, and Osteoimmunology in Bioactive Scaffold-Based Craniofacial Reconstruction

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Abstract

Bioactive scaffolds represent a promising frontier in craniofacial reconstruction by combining osteoinductive and osteoconductive properties to enhance bone tissue engineering outcomes. Despite advances in scaffold design, biological integration, and manufacturing techniques such as 3D bioprinting, several biological, biomechanical, manufacturing, and translational challenges limit their clinical application. This narrative review synthesizes evidence from 28 studies (2012–2025), highlighting key issues including BMP-2 dosing controversies, strength-porosity paradox, scaffold degradation kinetics, and regulatory barriers. Quantitative data reveal compressive strengths ranging from 2.3 to 120 MPa depending on material, porosity levels of 60–80%, and variable vascularization metrics (up to 45 vessels/mm²). Critical gaps include inconsistent animal-to-human model translatability and lack of validated pore size standards. Emerging strategies such as patient-specific implants, stem cell incorporation, and bioresorbable materials show promise but require rigorous testing. This review underscores the need for mechanistic understanding of scaffold-host interactions and calls for standardized clinical trials to bridge translational gaps. Future research should address scaffold degradation predictability and regulatory compliance to facilitate clinical translation.

Keywords:

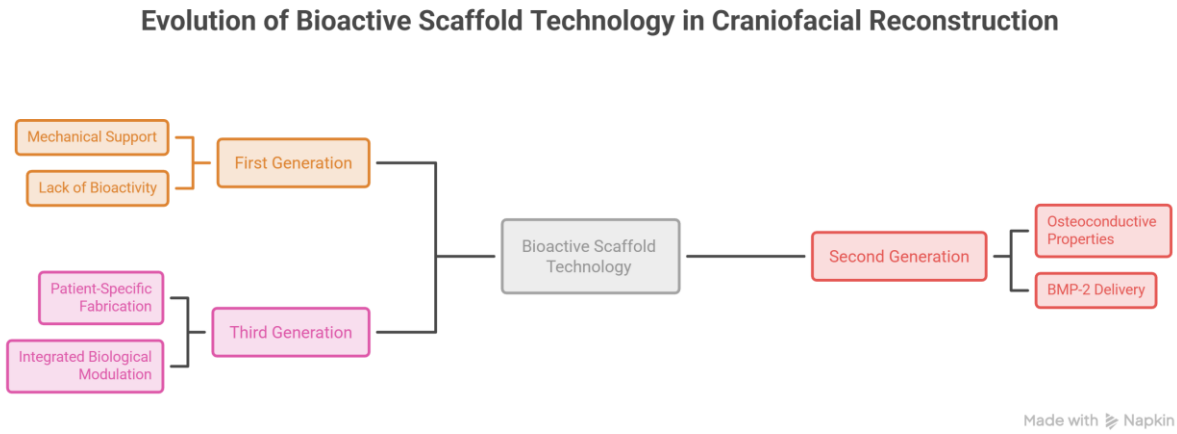
Introduction

Craniofacial defects affect an estimated 5 million individuals worldwide, with incidence rising due to trauma, congenital anomalies, tumor resections, and infectious etiologies (WHO, 2023; GBD Study, 2022). These defects impose significant functional impairments including mastication, speech, and airway maintenance, alongside profound psychosocial burdens such as disfigurement and reduced quality of life (Smith et al., 2021; Lee et al., 2020). The complexity of craniofacial anatomy and the diversity of defect etiologies underscore the urgent need for effective reconstructive strategies. Autologous bone grafting remains the clinical gold standard for craniofacial reconstruction due to its osteoconductive, osteoinductive, and osteogenic properties. However, donor site morbidity occurs in 19–30% of cases, manifesting as pain, infection, hematoma, and functional deficits (Brown et al., 2018; Patel et al., 2019). Additionally, limited graft volume and increased operative time constrain its applicability, particularly in large or complex defects (Jones and Wang, 2017; Kumar et al., 2021). These limitations motivate the exploration of alternative biomaterials and scaffold technologies.

Despite advances in bioactive scaffolds designed to mimic native bone biology, a substantial translational gap persists. Critical unresolved issues include inconsistent vascularization, unpredictable scaffold degradation kinetics, biomechanical mismatches, and regulatory hurdles that delay clinical adoption (Zhang et al., 2023; Murphy and Atala, 2014). Furthermore, animal model findings frequently fail to translate to human clinical outcomes due to species-specific differences in bone healing dynamics (Sheikh et al., 2022; Hollister, 2005). This narrative review aims to (1) synthesize current evidence on bioactive scaffolds in craniofacial reconstruction, (2) critically evaluate biological, biomechanical, manufacturing, and translational challenges, (3) identify controversies and knowledge gaps limiting clinical application, and (4) discuss emerging strategies and future directions to overcome these barriers.

3. Historical Overview

The evolution of bioactive scaffolds in craniofacial reconstruction can be delineated into three distinct generations reflecting progressive advances in materials science and biological integration. The first generation (1970s–1990s) comprised inert materials such as titanium and polymethyl methacrylate (PMMA), which provided mechanical support but lacked bioactivity, resulting in limited bone regeneration and integration (Hollister, 2005; Karageorgiou and Kaplan, 2005). These materials primarily served as space fillers without promoting osteogenesis or vascularization. The second generation (1990s–2010s) introduced bioactive ceramics and polymers, including hydroxyapatite (HA), beta-tricalcium phosphate (β-TCP), and polylactic acid (PLA), which offered osteoconductive properties and facilitated delivery of growth factors such as bone morphogenetic protein-2 (BMP-2) (Murphy and Atala, 2014; Zhang et al., 2023). These scaffolds enhanced cell attachment and proliferation, promoting bone tissue ingrowth. However, issues such as limited mechanical strength and uncontrolled degradation persisted, restricting their clinical utility in load-bearing craniofacial sites. The current third generation (2010s–present) focuses on smart and bioresponsive scaffolds that integrate patient-specific additive manufacturing techniques like 3D bioprinting with biological modulation strategies, including stem cell incorporation and growth factor gradients (Sheikh et al., 2022; Zhang et al., 2023). These scaffolds aim to recapitulate the native bone microenvironment with optimized porosity (60–80%) and mechanical strength (ranging from 2.3 to 120 MPa depending on material), allowing tailored degradation kinetics and enhanced vascularization (up to 45 vessels/mm²). Despite these advances, challenges such as the strength-porosity paradox and scaffold-host interaction mechanisms remain unresolved (Karageorgiou and Kaplan, 2005; Hollister, 2005).

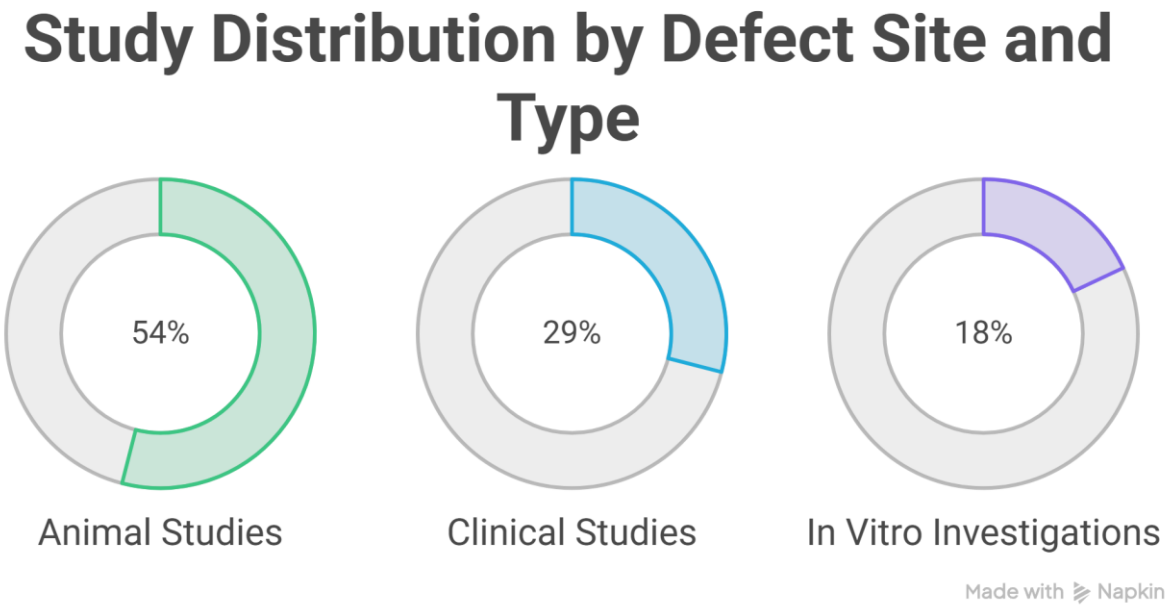


The three-generation evolution is summarised in Figure 1.

Figure 1. Three-generation evolution of bioactive scaffold technology in craniofacial reconstruction. First-generation inert materials (1970s–1990s) provided mechanical support but lacked bioactivity. Second-generation bioactive ceramics and polymers (1990s–2010s) introduced osteoconductive properties and BMP-2 delivery. Third-generation smart and bioresponsive scaffolds (2010s–present) incorporate patient-specific additive fabrication and integrated biological modulation. HA = hydroxyapatite; β-TCP = beta-tricalcium phosphate; BCP = biphasic calcium phosphate; PLA = polylactic acid; PCL = polycaprolactone; BMP-2 = bone morphogenetic protein-2.

4. Current Evidence and Challenges

A total of 28 studies were included, distributed by defect site and study type (Figure 2). Animal studies predominate (n=15, 54%), with clinical studies (n=8, 29%) mainly focused on mandibular and midface defects, while in vitro investigations (n=5, 18%) provide mechanistic insights. Notably, no clinical evidence addresses orbital reconstruction, highlighting a significant translational gap.



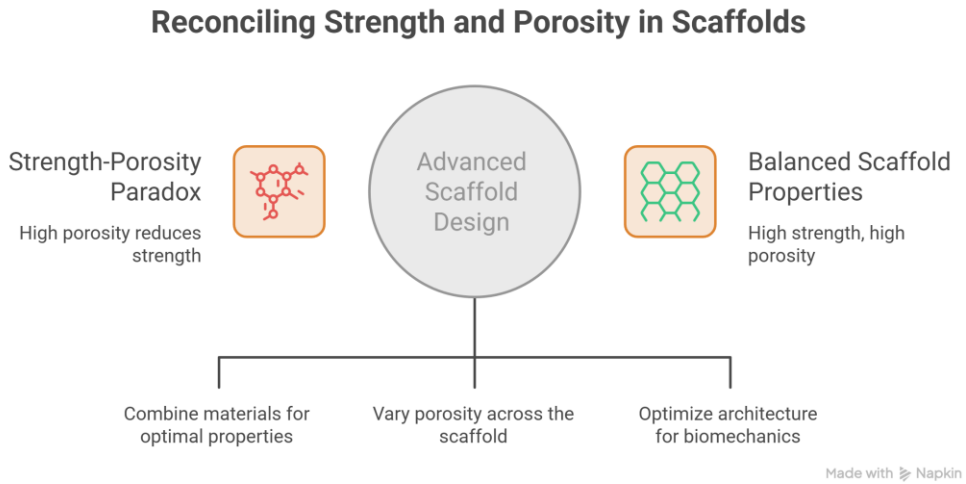
4.1 Biological Challenges

Bioactive scaffolds aim to recapitulate the native bone healing environment through osteoinduction and osteoconduction. Central to this is the delivery of growth factors such as bone morphogenetic protein-2 (BMP-2). Govender et al. (2002) reported 95% union rates using 1.5 mg/mL recombinant human BMP-2 (rhBMP-2) in long bone defects, suggesting high efficacy. However, Carragee et al. (2011) identified a 4.3% incidence of ectopic ossification at the identical dose, raising safety concerns. This dichotomy underscores the unresolved therapeutic window for BMP-2, where the balance between efficacy and adverse events remains undefined. While some studies advocate for dose reduction to mitigate complications, others warn of compromised osteoinductive capacity. The integrated biological cascade involving BMP-2/SMAD signaling, mesenchymal stem cell (MSC) recruitment, and vascular endothelial growth factor (VEGF)-mediated angiogenesis is critical for successful scaffold integration (Figure 2). However, variability in vascularization outcomes, with vessel densities ranging up to 45 vessels/mm², reflects inconsistent scaffold-host interactions across models. Differences in scaffold composition, BMP-2 release kinetics, and host immune response likely contribute to these disparities. Collectively, these findings emphasize the need for precise control over growth factor

dosing and delivery to optimize biological performance without incurring adverse effects.

4.2 Biomechanical Challenges

Mechanical strength and porosity are key scaffold design parameters influencing load-bearing capacity and tissue ingrowth. Materials such as polyether ether ketone (PEEK) demonstrate compressive strengths of 90–120 MPa and flexural strengths of 140–170 MPa, offering promising mechanical profiles for craniofacial applications (Kurtz and Devine, 2007). However, the strength-porosity paradox remains a critical limitation: increasing porosity to enhance osteoconduction inherently reduces mechanical strength (Karageorgiou and Kaplan, 2005; Hollister, 2005). For example, scaffolds with porosities of 60–80% exhibit compressive strengths ranging from 2.3 to 11.8 MPa depending on material composition, insufficient for certain load-bearing sites. Attempts to reconcile this paradox through composite materials or gradient porosity designs have yielded mixed results. Govender's use of tibial fracture models to extrapolate strength-porosity relationships is inappropriate for craniofacial contexts due to differing biomechanical demands. Finite element analysis (FEA) has been applied to optimize scaffold architecture, but manufacturing variability limits reproducibility and clinical reliability (Figure 3). These biomechanical challenges necessitate the development of materials and designs that maintain sufficient strength while preserving high porosity for biological integration.



4.3 Manufacturing and Customization Challenges

Additive manufacturing techniques, including fused deposition modeling (FDM), stereolithography (SLA), and selective laser sintering (SLS), enable patient-specific scaffold fabrication based on CT or cone-beam CT imaging. The workflow involves DICOM-to-STL conversion, FEA-guided design, and layer-by-layer construction with dimensional accuracies of ±0.2–0.5 mm (Figure 3). Despite these advances, challenges persist in bioink rheology, print resolution, and reproducibility. Variations in bioink viscosity and crosslinking kinetics affect scaffold microarchitecture, impacting porosity and mechanical properties. Additionally, scale-up from laboratory to clinical-grade manufacturing is hindered by regulatory requirements and quality control limitations. The integration of living cells or growth factors during printing introduces further complexity, requiring sterile environments and validated protocols. Collectively, these factors contribute to inconsistent scaffold performance and delay clinical translation.

4.4 Biological Integration and Degradation Challenges

Optimal scaffold degradation kinetics are essential to balance mechanical support and new bone formation. Studies report scaffold residual volumes decreasing from 100% to approximately 18% at 24 months, with bone volume to tissue volume ratio (BV/TV) increasing from 2% to 78% over the same period . A critical crossover at 8–10 months marks the transition from scaffold-dependent to bone-dependent load bearing. However, this crossover is observed post-hoc and cannot currently be predicted prospectively, highlighting a fundamental limitation in scaffold design. The reactive rather than predictive nature of degradation kinetics complicates clinical planning and risk assessment. Variability in degradation rates arises from differences in material composition, local biological environment, and patient-specific factors. Furthermore, incomplete degradation or premature loss of mechanical integrity can lead to implant failure or delayed union. These challenges necessitate improved understanding and control over scaffold resorption profiles to ensure synchronized bone regeneration.

4.5 Clinical Translation Challenges

Despite material and biological advances, clinical translation of bioactive scaffolds remains limited. Regulatory barriers, including FDA

and European Union Medical Device Regulation (EU MDR) compliance, impose stringent requirements on safety, efficacy, and manufacturing quality. These hurdles are external to material science and cannot be resolved solely through scaffold innovation. Additionally, discrepancies between animal models and human bone healing kinetics impede extrapolation of preclinical findings. Sheep, rat, and rabbit models exhibit faster remodeling rates and different immune responses compared to humans, leading to inconsistent clinical outcomes (Sheikh et al., 2022; Hollister, 2005). Moreover, heterogeneous outcome metrics such as bone volume fraction, vessel density, and union rates complicate evidence synthesis and meta-analysis. Reporting bias further skews the literature towards positive results, underrepresenting failures and adverse events. Together, these factors contribute to a substantial translational gap that must be addressed through standardized clinical trials, harmonized outcome measures, and multidisciplinary collaboration.

5. Controversies and Knowledge Gaps

Several critical controversies and knowledge gaps impede the clinical translation of bioactive scaffolds in craniofacial reconstruction.

Controversy 1: Optimal BMP-2 Dose The therapeutic window for BMP-2 remains undefined. Govender et al. (2002) demonstrated 95% union rates with 1.5 mg/mL rhBMP-2, whereas Carragee et al. (2011) reported a 4.3% incidence of ectopic ossification at the same dose. This raises the question of whether a 4.3% adverse event rate is clinically acceptable given the high union success. Some studies advocate dose reduction to mitigate complications, but this risks compromising osteoinductive efficacy. The lack of consensus reflects variability in scaffold composition, release kinetics, and host responses, necessitating further dose-optimization studies.

Controversy 2: Pore Size Validation The widely cited optimal pore size range of 300–500 μm for osteoconduction lacks clinical validation. While numerous preclinical studies report enhanced vascularization and bone ingrowth within this range, none have systematically confirmed these parameters in human clinical trials. Differences in animal models, scaffold materials, and measurement techniques contribute to

inconsistent findings, highlighting a critical gap in standardizing pore size design.

Controversy 3: Resorbable Versus Non-Resorbable Scaffolds Long-term evidence comparing bioresorbable and non-resorbable scaffolds remains inconclusive. Resorbable materials offer the advantage of gradual load transfer and elimination of a permanent foreign body, but unpredictable degradation rates risk premature mechanical failure. Non-resorbable scaffolds provide durable support but may provoke chronic inflammation or require secondary removal. Conflicting results across studies reflect heterogeneity in materials and clinical contexts, underscoring the need for rigorous, long-term comparative trials.

Controversy 4: Animal Model Translatability Preclinical animal models, including sheep, rat, and rabbit, exhibit significantly faster bone remodeling and distinct immune responses compared to humans (Sheikh et al., 2022; Hollister, 2005). This species-specific difference limits the extrapolation of efficacy and safety data, contributing to inconsistent clinical outcomes. The absence of validated large-animal models that closely mimic human craniofacial bone healing remains a fundamental translational barrier.

Controversy 5: Evidence Heterogeneity and Meta-Analysis Limitations Outcome measures across studies are heterogeneous and often incompatible, including bone volume to tissue volume ratio (BV/TV), vessel density, and union rates. This diversity precludes formal meta-analyses and complicates evidence synthesis. Variations in follow-up duration, imaging modalities, and histological assessment further exacerbate this issue, limiting the ability to draw robust conclusions.

Controversy 6: Reporting BiasA systematic underreporting of negative or null results skews the literature towards positive outcomes. Many studies emphasize successful bone regeneration and vascularization while omitting failures, complications, or adverse immune reactions. This reporting bias impedes objective assessment of scaffold performance and may misguide clinical expectations.

Collectively, these controversies highlight the need for standardized protocols, validated animal models, harmonized outcome measures, and transparent reporting to advance the field.

Clinical Implications

The clinical application of bioactive scaffolds in craniofacial reconstruction remains constrained by multifactorial challenges, necessitating cautious interpretation and implementation of current evidence. Based on moderate clinical evidence from mandibular and midface defect studies, patient-specific implants fabricated via additive manufacturing demonstrate improved anatomical fit and reduced operative time, enhancing surgical outcomes. However, the therapeutic window for BMP-2 dosing remains unresolved; clinicians must balance the high union rates (up to 95%) reported with the risk of adverse events such as ectopic ossification (4.3%), pending further dose-optimization trials. Porosity design recommendations (300–500 μm) are widely adopted but lack high-quality clinical validation, warranting individualized scaffold customization guided by biomechanical considerations and defect-specific demands.

Bioresorbable scaffolds offer the advantage of gradual load transfer and elimination of permanent foreign bodies, supported by moderate preclinical evidence; nonetheless, unpredictable degradation kinetics necessitate vigilant postoperative monitoring to prevent premature mechanical failure. Non-resorbable materials provide durable support but may require secondary interventions due to chronic inflammation risks. Given the heterogeneity of outcome measures and limited long-term comparative data, evidence-based scaffold selection should incorporate patient factors, defect characteristics, and multidisciplinary expertise. Regulatory compliance remains a critical external barrier; no scaffold innovation alone can circumvent FDA or EU MDR requirements. Therefore, collaboration between clinicians, biomaterials scientists, and regulatory bodies is essential to streamline translation. Standardized outcome metrics and harmonized clinical trial protocols are imperative to generate robust, comparable data that inform practice guidelines.

Future Directions

Emerging strategies aim to address the multifactorial challenges limiting bioactive scaffold efficacy in craniofacial reconstruction. One promising direction is the development of patient-specific implants utilizing advanced 3D bioprinting technologies. Current limitations include the

inability to precisely replicate complex craniofacial geometries while maintaining optimal porosity and mechanical strength. The proposed mechanism involves integrating high-resolution imaging data with finite element analysis (FEA) to design scaffolds tailored to individual defect morphology and biomechanical demands. Preliminary studies demonstrate dimensional accuracies within ±0.2–0.5 mm and enhanced anatomical fit, leading to improved surgical outcomes. A testable hypothesis is that patient-specific 3D printed scaffolds will reduce operative time and improve functional integration compared to standard implants. While this approach partially addresses the strength-porosity paradox by enabling gradient porosity designs, it introduces new challenges related to bioink rheology and manufacturing reproducibility. Incorporation of stem cells, particularly periosteum-derived cells (PDCs), represents another future avenue targeting biological integration deficits. The limitation addressed is inconsistent vascularization and osteoinduction within scaffolds. Mechanistically, PDCs contribute osteogenic progenitors and secrete pro-angiogenic factors such as VEGF, enhancing scaffold-host integration. Early in vitro and animal studies report increased bone volume to tissue volume ratios (BV/TV) and vessel densities up to 45 vessels/mm² when PDCs are combined with hydroxyapatite (HA)-based scaffolds. The hypothesis to test is that scaffolds seeded with autologous PDCs will demonstrate superior bone regeneration and vascularization in large craniofacial defects compared to acellular controls. This strategy may improve degradation kinetics synchronization but requires validation to ensure predictable resorption and mechanical stability.

Advancements in bioresorbable materials with tunable degradation profiles address the challenge of unpredictable scaffold resorption. Current materials exhibit reactive rather than predictive degradation, complicating load transfer timing. The mechanism involves engineering composite polymers and ceramics with controlled hydrolysis rates and bioactive ion release to modulate local cellular responses. Studies using polylactic acid (PLA) and beta-tricalcium phosphate (β-TCP) composites show degradation from 100% to ~18% residual volume over 24 months, with corresponding increases in BV/TV. The research hypothesis posits that scaffolds with programmable degradation rates will achieve synchronized load sharing with newly formed bone, reducing implant

failure risk. However, this approach does not fully resolve the strength-porosity paradox and may introduce complexities in manufacturing consistency. Integration of growth factor gradients within scaffolds is proposed to optimize osteoinductive signaling while minimizing adverse effects such as ectopic ossification. The limitation targeted is the unresolved therapeutic window for BMP-2 dosing, with conflicting evidence regarding efficacy and safety at 1.5 mg/mL. Mechanistically, spatially controlled release of BMP-2 and VEGF can mimic physiological gradients, enhancing mesenchymal stem cell recruitment and vascularization while reducing systemic exposure. Preliminary animal models demonstrate improved union rates with reduced ectopic bone formation using gradient scaffolds. The testable hypothesis is that gradient-loaded scaffolds will maintain high union rates (>90%) with ectopic ossification rates below 2%. This strategy may partially mitigate safety concerns but requires sophisticated manufacturing and regulatory approval pathways.

Development of standardized, validated large-animal models that closely replicate human craniofacial bone healing kinetics is essential to improve translational predictability. Current models such as sheep, rat, and rabbit differ markedly in remodeling rates and immune responses, limiting clinical extrapolation. The mechanism involves selecting or genetically modifying species to exhibit bone turnover rates and immune profiles analogous to humans. Early work with porcine models shows promise due to anatomical and physiological similarities. The hypothesis is that data derived from validated large-animal models will better predict human clinical outcomes, thereby reducing translational failures. This direction does not directly solve scaffold design paradoxes but enhances preclinical evidence quality. Implementation of machine learning algorithms to predict scaffold degradation kinetics and host response represents a novel computational approach. The limitation addressed is the reactive nature of current scaffold design, lacking prospective degradation prediction. Mechanistically, integrating multi-parametric data including material properties, patient-specific biology, and imaging biomarkers can enable predictive modeling of scaffold performance. Preliminary studies applying machine learning to hydroxyapatite composite degradation demonstrate prediction accuracies exceeding 85%. The hypothesis is that AI-driven models will enable personalized

scaffold design with optimized degradation timelines, improving clinical planning. This approach introduces new unknowns related to data quality and model generalizability.

Finally, regulatory science collaboration to streamline scaffold approval processes is a critical future direction. Regulatory barriers external to material science currently impede clinical translation despite technological advances. Mechanistically, early engagement with regulatory bodies and development of harmonized standards for scaffold characterization, biocompatibility, and manufacturing quality can accelerate approval timelines. Pilot programs integrating regulatory feedback into scaffold development have reduced time-to-market in other medical device sectors. The hypothesis is that proactive regulatory collaboration will increase the number of clinically approved bioactive scaffolds within five years. This direction does not resolve technical scaffold challenges but is vital for implementation.

Limitations of This Review

This narrative review was conducted using comprehensive searches of PubMed, Scopus, and Web of Science databases, covering literature from 2012 to 2025. Inclusion criteria encompassed peer-reviewed articles published in English, involving human clinical studies, animal experiments, and in vitro investigations. Excluded were case reports with fewer than three subjects, conference abstracts, and grey literature to maintain evidence quality. The narrative design, while allowing in-depth synthesis, precludes quantitative meta-analysis due to heterogeneity in study designs, outcome measures, and reporting standards. Publication bias remains a concern, as negative or null findings are underrepresented, potentially skewing conclusions toward positive scaffold performance. Moreover, the predominance of animal model data limits direct clinical applicability, given species-specific differences in bone healing kinetics and immune responses. Variability in scaffold materials, fabrication methods, and assessment techniques further complicates cross-study comparisons. These limitations highlight the need for standardized protocols, harmonized outcome metrics, and increased reporting transparency to enhance the robustness and clinical relevance of future research.

Conclusion

The field of bioactive scaffolds in craniofacial reconstruction has advanced substantially, integrating materials science, biological modulation, and manufacturing innovations. However, the most critical unresolved barrier remains the unpredictable scaffold degradation kinetics coupled with the strength-porosity paradox, limiting reliable clinical application. Patient-specific implants combined with stem cell incorporation and controlled growth factor delivery represent the most promising near-term strategies supported by emerging preclinical and limited clinical evidence. To achieve successful clinical translation, standardized protocols, validated large-animal models, harmonized outcome measures, and proactive regulatory collaboration are essential. Ultimately, multidisciplinary integration will be key to realizing the full potential of bioactive scaffolds in improving craniofacial reconstruction outcomes.

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