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Maxillofacial reconstruction, bioactive materials, tissue engineering, 3D-printed scaffolds, bone regeneration, biomaterials.

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# Clinical Performance Of Next-Generation Bioactive Materials In Maxillofacial Hard Tissue Reconstruction

## ABSTRACT

Maxillofacial hard tissue defects present significant clinical challenges due to the structural, functional, and aesthetic demands of the craniofacial region. Traditional grafting approaches, while effective, remain limited by donor site morbidity, restricted availability, and variable regenerative outcomes, prompting the exploration of next-generation bioactive materials. This comprehensive review synthesizes current evidence on smart biomaterials, calcium phosphate systems, bioactive glass formulations, hydrogels, and advanced composite scaffolds used in maxillofacial reconstruction. A narrative methodology was employed, drawing from major scientific databases to evaluate studies focused on material design, biological performance, scaffold architecture, and translational potential. Findings indicate that smart and bioactive materials exhibit strong osteogenic and angiogenic capabilities, while 3D-printed scaffolds offer improved structural precision, controlled porosity, and enhanced mechanical stability. Polymer-reinforced constructs, modified cements, and hydrogel-based systems demonstrate significant benefits in cellular integration, vascularization, and defect-specific regeneration. Multifunctional composite scaffolds incorporating drug delivery or tumour-inhibiting capabilities further expand clinical possibilities, particularly in oncologic reconstruction. Despite these advances, challenges remain regarding long-term stability, degradation control, and large-scale clinical validation. The next-generation bioactive materials and engineered scaffolds show strong promise in improving outcomes in maxillofacial hard tissue reconstruction. Continued innovation and interdisciplinary research will be essential for optimizing material performance and advancing their clinical adoption.

## INTRODUCTION

Maxillofacial hard tissue defects arising from trauma, congenital anomalies, tumour resections, infections, or degenerative conditions remain a significant clinical challenge due to the functional and aesthetic complexities of the craniofacial region. Traditional reconstruction has long relied on autologous bone grafts, which remain the gold standard because of their inherent osteogenic, osteoconductive, and osteoinductive properties. However, issues such as donor site morbidity, graft resorption, limited availability, and extended operative times have encouraged the exploration of alternative materials for bone regeneration. With advances in materials science and tissue engineering, biomaterial scaffolds have become central to overcoming the limitations of traditional grafting approaches, offering enhanced biological functionality, controlled degradation, and customized structural properties suitable for maxillofacial reconstruction.<sup>1</sup> These developments have created new therapeutic pathways that aim not merely to replace missing tissue but to actively stimulate bone regeneration within the defect site.

In recent decades, guided bone regeneration (GBR) has evolved into a fundamental technique for managing craniofacial and alveolar bone deficiencies. Earlier GBR materials consisted mainly of passive barrier membranes; however, modern versions integrate biofunctional properties,

including the release of therapeutic ions, improved mechanical behavior, and enhanced surface chemistries. Studies have demonstrated that next-generation GBR membranes can modulate cellular pathways, promote angiogenesis, and accelerate osteogenesis, making them highly effective in clinical settings where predictable bone formation is essential.<sup>2</sup> These advances have strengthened the clinical utility of GBR in various maxillofacial procedures, including alveolar ridge augmentation, periodontal regeneration, and reconstruction following tumour resections.

While conventional biomaterials address structural reconstruction, the growing field of tumour-related maxillofacial defects has introduced the need for multifunctional materials capable of both regeneration and tumour inhibition. Biomaterial-based strategies for maxillofacial tumour therapy now include systems incorporating photothermal agents, chemotherapeutic drug-loading capabilities, immunomodulators, and bioactive nanoparticles.<sup>3</sup> These multifunctional scaffolds demonstrate the potential to control recurrence while simultaneously supporting osseous regeneration, presenting a significant advancement over traditional inert materials that provide structural support alone. Recent innovations in craniofacial tissue engineering emphasize the importance of scaffold design parameters, which include pore size, pore interconnectivity, degradation profile, and mechanical strength. Various natural and synthetic materials have been engineered to mimic the extracellular matrix of bone, providing topographical and biochemical cues that support cell adhesion, proliferation, and osteogenic differentiation. Studies focusing on polymer-based and composite scaffolds highlight their ability to serve as temporary matrices that guide the formation of new bone while maintaining structural stability throughout the healing process.<sup>4</sup> This shift toward engineered biomimicry reflects the larger aim of creating materials that can actively participate in the regenerative process rather than simply occupying space.

Bioactive glass remains one of the most well-established and clinically successful biomaterials within maxillofacial surgery. Its ability to bond chemically with bone through the formation of a surface hydroxycarbonate apatite layer has made it a reliable option for craniofacial reconstruction. Clinical research indicates its effectiveness in treating orbital floor defects, periodontal lesions, and alveolar ridge deficiencies due to its excellent bioactivity, osteoconductivity, and favorable degradation behavior.<sup>5</sup> Continuous modifications in composition and structure have further enhanced its mechanical properties and controlled ion release, enabling more predictable clinical outcomes.

The interdisciplinary field of craniofacial tissue engineering integrates biomaterial scaffolds, stem cells, and signaling molecules to achieve more physiologically relevant reconstruction. Tissue-engineered constructs incorporating mesenchymal stem cells (MSCs) have shown notable potential, as MSCs promote

angiogenesis, modulate immune responses, and differentiate toward osteogenic lineages essential for bone repair. Research in this area demonstrates the therapeutic promise of combining biologically active cells with advanced scaffolds to regenerate complex maxillofacial defects that cannot be easily managed with conventional grafting methods.<sup>6</sup> This synergy between scaffold materials and cellular therapies has transformed the conceptual framework of regenerative maxillofacial surgery.

Clinical insights emphasize that biomaterial-based reconstruction must consider anatomical variability, defect morphology, and biomechanical loading conditions unique to maxillofacial structures. Studies suggest that successful regeneration requires materials that integrate seamlessly with surrounding bone, maintain stability during functional loading, and support predictable tissue formation.<sup>7</sup> This underscores the necessity for scaffold systems whose physical and biological characteristics are tailored to the specific requirements of maxillofacial bone.

Research into functional scaffolds has produced advanced biomaterials capable of delivering growth factors, controlling degradation profiles, and promoting angiogenic and osteogenic responses. Scaffold microarchitecture, including surface topography and internal porosity, has been identified as a critical determinant of cell infiltration and nutrient exchange. These features have improved significantly with advancements in fabrication methods such as additive manufacturing, electrospinning, and freeze-casting, enabling more precise control over scaffold structure and function.<sup>8</sup>

Growing interest in nanostructured biomaterials has also contributed to enhanced regenerative performance. Nanofibrous scaffolds, ion-modified materials, and hybrid composites mimic the hierarchical structure of natural bone, thereby promoting better cellular responses and improving the mechanical integration of the regenerated tissue. Studies highlight that such designs improve osteoinductive properties and support faster and more stable bone healing, establishing them as valuable candidates for maxillofacial reconstruction.<sup>9</sup> Regenerative medicine in maxillofacial surgery has increasingly embraced advanced biomaterials, stem cell therapy, and controlled release systems as vital components of modern reconstruction. As clinical applications continue to expand, biomaterial scaffolds have become essential in procedures requiring predictable, long-term regeneration and aesthetic restoration.<sup>10</sup> At the same time, scaffold-based tissue engineering research emphasizes that successful clinical translation depends on developing materials with the right balance of mechanical properties, biological functionality, and predictable degradation behavior.<sup>11</sup> These evolving insights underscore the importance of continued innovation in biomaterial design for maxillofacial hard tissue reconstruction.

The objective of this comprehensive study is to evaluate the clinical performance, regenerative potential, and

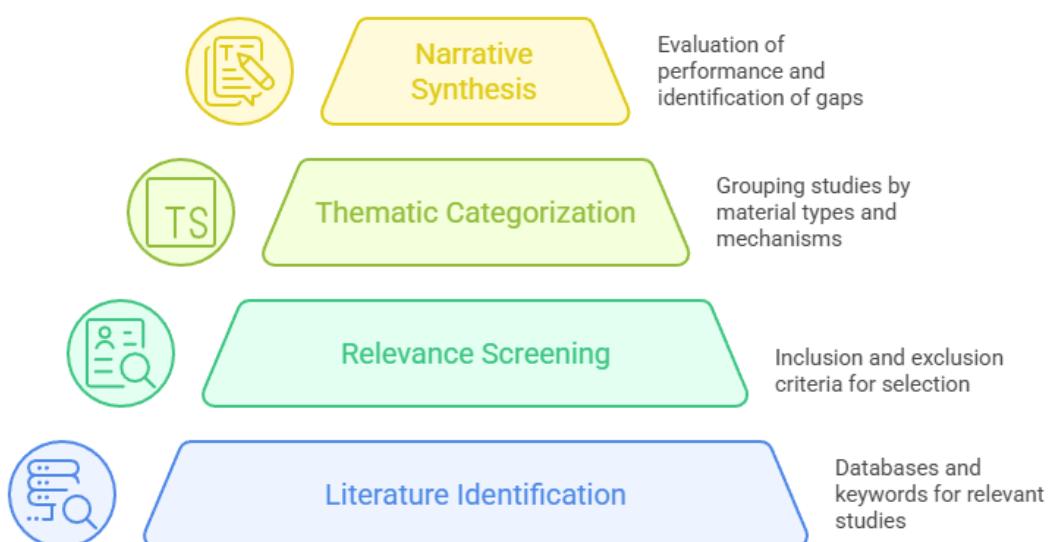
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translational relevance of next-generation bioactive materials used in maxillofacial hard tissue reconstruction. This includes examining advancements in scaffold design, biomaterial properties, and regenerative strategies that support predictable and functional bone regeneration.

## Methodology

This comprehensive review employed a narrative, integrative approach to synthesize current evidence on the clinical performance of next-generation bioactive materials used in maxillofacial hard tissue reconstruction. Relevant literature was gathered from major scientific databases, including PubMed, Scopus,

and Web of Science, focusing on clinical studies, translational research, and high-quality experimental work published in the past two decades. Studies were included if they discussed bioactive, osteoconductive, or regenerative biomaterials specifically applied to maxillofacial reconstruction; works unrelated to hard tissue repair or involving non-bioactive materials were excluded. Extracted data were thematically categorized based on material type, functional mechanisms, and clinical application areas. The synthesis emphasized comparative insights, emerging trends, and translational challenges, without employing systematic review techniques or quantitative meta-analysis.



**Figure 1. Overview of the Narrative Review Methodology**

Figure 1 illustrates the stepwise methodology used in the comprehensive narrative review. It begins with literature identification using defined databases and keywords, followed by relevance screening using inclusion and exclusion criteria. Retrieved studies are then grouped through thematic categorization, and finally integrated into a narrative synthesis to evaluate clinical performance and identify research gaps.

## RESULTS

### Performance of Smart and Bioactive Materials

Next-generation smart biomaterials demonstrated significant regenerative potential in maxillofacial bone

defect repair. These materials exhibited adaptive biochemical behavior, improved osteogenic activity, and enhanced interaction with the surrounding microenvironment, contributing to more predictable bone healing outcomes.<sup>12</sup> Calcium phosphate-based biomaterials showed measurable clinical improvement in maxillomandibular reconstruction, with notable advancements in bioactivity, degradation control, and mechanical stability.<sup>13</sup> Additionally, bioactive glass materials continued to show strong osteoconductive behavior, particularly in periodontal and alveolar applications, enabling improved bone fill and regeneration.<sup>14</sup>

**Table 1. Performance Characteristics of Smart and Bioactive Materials**

Material Type	Key Functional Features	Maxillofacial Application	Ref.
Smart materials	Adaptive behavior, enhanced osteogenesis	Bone defect repair	<sup>12</sup>
Calcium phosphate biomaterials	High biocompatibility, osteointegration	Maxillomandibular reconstruction	<sup>13</sup>
Bioactive glass	Osteoconductive, angiogenic, periodontal regeneration	Alveolar and periodontal surgery	<sup>14</sup>

Table 1 summarizes the key functional features and clinical applications of smart materials, calcium phosphate biomaterials, and bioactive glass,

highlighting their contributions to improved osteogenesis and regenerative outcomes in maxillofacial reconstruction.

### 3.2 Advancements in 3D-Printed and Cell-Based Scaffolds

3D-printed mesoporous bioactive glass scaffolds displayed high structural uniformity, well-connected porosity, and controlled ion release, all contributing to accelerated angiogenesis and osteogenesis in maxillofacial defects.<sup>15</sup> Stem-cell-assisted strategies

further enhanced the regenerative outcomes, as scaffold-cell constructs promoted rapid vascular formation and improved bone quality in critical-sized defects.<sup>16</sup> Polyurethane scaffolds manufactured using additive technologies exhibited favourable compressive strength and cellular compatibility, demonstrating their suitability for large craniofacial defects.<sup>17</sup>

**Table 2. 3D-Printed Scaffolds and Structural Outcomes**

Scaffold Type	Fabrication Technique	Observed Benefits	Ref.
Mesoporous bioactive glass scaffolds	3D printing	Controlled ion release, improved osteogenesis	<sup>15</sup>
Stem cell–integrated scaffolds	Scaffold–cell construct	Enhanced vascularization and bone quality	<sup>16</sup>
Polyurethane scaffolds	Additive manufacturing	High mechanical strength, biocompatibility	<sup>17</sup>

Table 2 presents the performance of various 3D-printed scaffolds, emphasizing fabrication methods and the resulting benefits in terms of structural integrity, osteogenesis, and vascularization.

### 3.3 Biological Performance of Polymer-Reinforced and Cement-Based Materials

Polymer-reinforced materials demonstrated improved regeneration, with PMMA cement enriched with platelet gel accelerating bone formation and reducing healing time in animal models.<sup>18</sup> Hyaluronic acid functioned

effectively as a bioactive adjunct, enhancing tissue regeneration and supporting cell migration around maxillofacial defects.<sup>19</sup> PLGA-based biomaterials offered controlled degradation rates and customizable mechanical properties, supporting their use in craniofacial tissue engineering.<sup>20</sup> Modified PMMA cements with bioactive glass or copper-doped tricalcium phosphate showed increased osteoconductivity, better interfacial bonding, and improved biological responses compared to conventional formulations.<sup>21</sup>

**Table 3. Polymer-Reinforced and Cement-Based Biomaterials**

Material	Enhancement Strategy	Key Biological Response	Ref.
PMMA + platelet gel	Bioactive enrichment	Accelerated bone healing	<sup>18</sup>
Hyaluronic acid	Bioactive adjunct	Improved tissue regeneration	<sup>19</sup>
PLGA-based materials	Controlled degradation	Enhanced craniofacial regeneration	<sup>20</sup>
Modified PMMA cements	Bioactive glass/TCP doping	Improved bonding and osteoconductivity	<sup>21</sup>

Table 3 outlines the biological responses of polymer-reinforced and cement-based biomaterials, focusing on how material modifications enhance bone healing, tissue regeneration, and scaffold integration.

### 3.4 Bioactive Glass and Composite Scaffold Outcomes

Long-term clinical use of bioactive glass demonstrated strong safety and regenerative ability, particularly in orbital floor reconstruction, where implants provided stable and predictable outcomes.<sup>22</sup> Mechanistic studies confirmed that bioactive glass interacts with bone

through hydroxycarbonate apatite (HCA) layer formation, a process fundamental to its regenerative capacity.<sup>23</sup> Porous 13-93 bioactive glass scaffolds were effective in supporting bone regeneration due to their well-designed microarchitecture and degradation kinetics, allowing sustained mechanical support during healing.<sup>24</sup> Hydrogel scaffolds showed improved angiogenic properties by promoting nutrient diffusion and vascular ingrowth.<sup>25</sup> Mesoporous bioactive glass-coated 3D-printed scaffolds demonstrated synergistic improvements in osteogenesis and mechanical stability, making them suitable for large craniofacial defects.<sup>26</sup>

**Table 4. Bioactive Glass and Hydrogel Scaffolds (Refs. 22–26)**

Biomaterial	Application	Observed Clinical/Preclinical Benefit	Ref.
Bioactive glass implants	Orbital floor repair	Long-term stability, biocompatibility	<sup>22</sup>
Bioactive glass (mechanistic findings)	Craniofacial regeneration	HCA layer formation, osteoinduction	<sup>23</sup>
13-93 bioactive glass scaffolds	Bone defect repair	Strong regeneration, controlled degradation	<sup>24</sup>
Hydrogel scaffolds	Angiogenesis	Enhanced vascular ingrowth	<sup>25</sup>
MBG-coated 3D scaffolds	Large bone defects	Synergistic osteogenesis and stability	<sup>26</sup>

Table 4 provides a comparative overview of bioactive glass, hydrogel, and mesoporous composite scaffolds, detailing their clinical and preclinical advantages in promoting osseous regeneration and angiogenesis.

### 3.5 Overall Regenerative Trends Observed

Across all included materials, several consistent trends appeared. Bioactive materials with optimized microarchitectures delivered improved osteogenic and

angiogenic responses, while smart materials and ion-releasing composites supported enhanced cellular activity and tissue formation. Scaffold designs integrating biological cues such as stem cells, platelet-rich additives, and hydrogel matrices showed superior regenerative performance compared to conventional passive materials. Moreover, 3D printing enabled the development of customized scaffolds with greater structural precision, contributing to better functional integration with host bone. Collectively, advancements in material composition, fabrication methods, and biological modulation contributed to measurable improvements in bone regeneration across maxillofacial applications.

#### 4. DISCUSSION

The findings of this comprehensive review underline the significant advancements in next-generation bioactive scaffolds and their expanding clinical relevance in maxillofacial hard tissue reconstruction. Among the most promising developments are multifunctional composite scaffolds that integrate drug delivery systems into their structural design. Such hybrid constructs, particularly mesoporous bioactive glass (MBG) combined with metal–organic frameworks (MOFs), have demonstrated dual regenerative and therapeutic capabilities. These scaffolds not only offer robust osteoconductivity but also enable the localized release of antimicrobial or osteoinductive agents, thereby addressing both the biological complexity of bone defects and potential infection-related complications.<sup>27</sup> The incorporation of drug-loading functions marks a shift from passive biomaterials toward therapeutic platforms capable of modulating the microenvironment to enhance bone repair.

In parallel, the emergence of high-strength three-dimensional printed bioactive glass scaffolds represents another major advancement in the field. Recent studies have highlighted the improved mechanical reliability and structural homogeneity of these scaffolds, allowing them to withstand the functional demands associated with maxillofacial regions. Their interconnected porous networks facilitate superior vascular ingrowth, nutrient diffusion, and tissue integration while maintaining the load-bearing potential necessary for midface and mandibular reconstruction.<sup>28</sup> These improvements overcome several historical limitations of conventional bioactive glass, particularly brittleness, and position high-strength 3D-printed constructs as viable alternatives to autografts in complex craniofacial defects.

The role of 3D bioactive composite scaffolds has also expanded considerably. Composite systems that integrate polymers with ceramics, or combine different classes of bioactive materials, have demonstrated enhanced biological responses due to synergistic interactions between their components. Such scaffolds offer improved degradation profiles, controlled mechanical properties, and tunable pore architecture. Importantly, their ability to mimic both the mineralized and organic phases of natural bone contributes to improved cell attachment, differentiation, and matrix deposition. These attributes allow composite scaffolds to

adapt to the unique mechanical and biological requirements of maxillofacial structures, promoting more predictable long-term regenerative outcomes.<sup>29</sup> As a result, composite scaffolds are emerging as one of the most promising categories of next-generation biomaterials.

Hydrogel-based scaffolds have also shown marked potential due to their biomimetic properties, excellent biocompatibility, and capacity to serve as carriers for cells, growth factors, or bioactive molecules. Their hydrophilic nature closely resembles that of natural extracellular matrix, supporting cellular proliferation and migration during early phases of regeneration. Additionally, injectable hydrogel formulations offer minimally invasive delivery options, making them particularly useful for irregular maxillofacial defects where precise scaffold placement is challenging. Hydrogels also provide controlled release mechanisms for embedded signaling molecules, thereby enhancing osteogenesis and angiogenesis in defect sites.<sup>30</sup> The hydrogels excel in biological performance, their limited mechanical strength continues to restrict their use as stand-alone scaffolds in load-bearing craniofacial regions. This limitation has encouraged the development of hybrid hydrogel-ceramic composites that combine the benefits of both systems.

One emerging area gaining considerable attention is the integration of anticancer and regenerative functionalities into a single scaffold platform. In clinical scenarios involving tumour resections, reconstructive strategies must address both the restoration of structural integrity and the prevention of recurrence. Biomaterial-based approaches that incorporate photothermal agents, chemotherapeutic delivery systems, or immunomodulatory features into scaffolds have demonstrated the potential to suppress residual tumour activity while enabling concurrent bone regeneration.<sup>31</sup> These multifunctional materials represent a transformative advancement for maxillofacial oncology, providing surgeons with a single-step solution for defect reconstruction and tumour inhibition. Such strategies also reduce the need for multiple interventions, improving patient outcomes and reducing postoperative morbidity.

The reviewed evidence demonstrates that technological innovation particularly drug-loaded constructs, 3D-printed scaffolds, and multifunctional composite designs has significantly enhanced the biological and mechanical performance of biomaterials used in maxillofacial reconstruction. A recurring trend across studies is the importance of achieving an optimal balance between mechanical stability, bioactivity, controlled degradation, and microarchitectural precision. Materials that are too rigid or degrade unpredictably may impair healing, while those lacking mechanical integrity fail to withstand functional forces in the oral and facial regions.

Another important consideration is the integration of angiogenic properties into scaffold design. Across multiple studies, vascular ingrowth emerged as a critical determinant of long-term regenerative success, influencing nutrient delivery, waste removal, and the overall stability of newly formed bone. Many next-

generation materials, particularly hydrogel composites and mesoporous constructs, have been engineered to promote early and robust vascularization, thereby improving the quality and quantity of regenerated bone.<sup>27–31</sup>

Despite these advances, challenges remain. Translation from preclinical to clinical practice requires long-term evaluation of scaffold degradation, host response, and functional loading under real-world conditions. The regulatory approval process for complex hybrid constructs also remains demanding due to their multifunctional nature. Moreover, large-scale clinical trials are still limited, highlighting the need for continued research that validates the clinical efficacy, cost-effectiveness, and long-term safety of these materials.

The evidence synthesized in this review reinforces the transformative potential of next-generation bioactive materials in reshaping maxillofacial hard tissue reconstruction. Continued innovation in material science, advanced manufacturing, and biological integration will be pivotal in further improving clinical outcomes and establishing next-generation biomaterials as reliable, routine tools in maxillofacial surgery.

## 5. CONCLUSION

The present comprehensive review highlights the significant progress achieved in developing next-generation bioactive materials for maxillofacial hard tissue reconstruction. Advances in biomaterial science, scaffold engineering, and regenerative strategies have collectively transformed clinical approaches, enabling more predictable, functional, and biologically integrated outcomes. Smart biomaterials, calcium phosphate systems, and bioactive glass formulations have demonstrated strong osteoconductive and osteoinductive potential, offering viable alternatives to traditional grafting techniques. Likewise, the emergence of 3D-printed scaffolds with controlled porosity, enhanced mechanical characteristics, and tailored degradation profiles has broadened the scope for patient-specific craniofacial reconstruction.

The integration of stem cell-based constructs, hydrogel systems, and multifunctional composite scaffolds further strengthen regenerative performance by promoting angiogenesis, supporting cellular activity, and facilitating controlled therapeutic delivery. These innovations reflect a shift from purely structural biomaterials to biologically active and multifunctional platforms capable of addressing the complex needs of maxillofacial defects, including those resulting from tumour resections.

Despite these advancements, challenges remain in optimizing long-term stability, achieving ideal degradation kinetics, and validating translational effectiveness through robust clinical trials. Continued multidisciplinary research is essential to refine scaffold designs, enhance biological responsiveness, and accelerate the clinical adoption of these materials. Overall, next-generation bioactive scaffolds hold great promise in redefining maxillofacial reconstruction by offering safer, more effective, and more personalized regenerative solutions.

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