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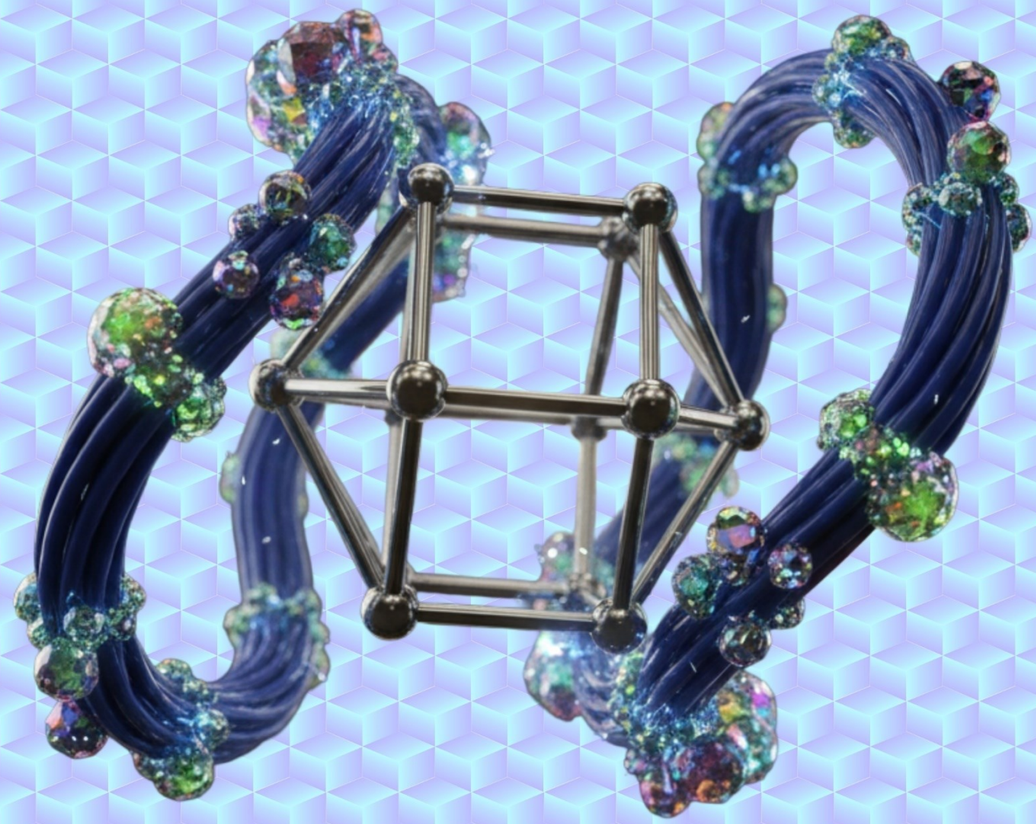

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Biologically Active Biomaterials in Delayed Fracture Repair: Mechanisms, Clinical Integration, and Prognostic Considerations

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ABSTRACT

Delayed bone healing remains a significant challenge in traumatology, particularly in complex fractures and biologically compromised environments where conventional fixation alone may be insufficient to achieve timely consolidation. In recent decades, bioactive biomaterials have emerged as relevant adjuncts in orthopedic trauma, offering not only structural support but also biological modulation of the fracture microenvironment. This review aims to synthesize current evidence on the clinical applications of bioactive biomaterials in delayed bone healing, focusing on their biological mechanisms, material design principles, and prognostic implications. A

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structured narrative review was conducted using peer-reviewed literature addressing bioactive glasses, calcium orthophosphate ceramics and cements, composite scaffolds, and injectable biomaterials. The results indicate that bioactive glass and composite scaffold strategies are frequently associated with favorable healing profiles, while calcium phosphate systems remain widely utilized due to their established clinical reliability and versatility. Injectable biomaterials demonstrate procedural advantages but show greater variability in outcomes, reflecting formulation and indication heterogeneity. Across all material classes, mechanical stability and infection control emerge as the most influential prognostic factors, underscoring that biomaterials function optimally as biological enhancers rather than substitutes for sound trauma principles. Overall, bioactive biomaterials represent a valuable component of contemporary fracture management when selected according to defect characteristics, biological conditions, and clinical context. This review provides an educational framework to support evidence-based decision-making in delayed bone healing, with relevance to trauma care settings in Latin America and beyond.

KEYWORDS

Delayed bone healing, bioactive biomaterials, bone regeneration, trauma surgery, bioactive glass, calcium phosphate, scaffold design, orthopedic traumatology

INTRODUCTION

Delayed bone healing remains a persistent and clinically relevant challenge in traumatology and orthopedic practice, particularly in the management of complex fractures, large bone defects, and compromised biological environments. Despite advances in surgical techniques and fixation systems, a significant proportion of patients experience delayed union or nonunion, conditions that impose substantial functional limitations and socioeconomic burden. These complications are especially prevalent in regions with heterogeneous access to specialized trauma care, such as Latin America, where variations in infrastructure, comorbidities, and injury mechanisms influence clinical outcomes.

Bone regeneration is a highly orchestrated biological process involving cellular recruitment, vascular ingrowth, and extracellular matrix remodeling. When this process is disrupted—due to extensive tissue damage, infection, metabolic disorders, or insufficient mechanical stability—the intrinsic regenerative capacity of bone may be inadequate. In this context, bioactive biomaterials have emerged as a cornerstone strategy to enhance bone healing by providing not only structural support but also biological stimulation at the injury site.

Since the seminal work of Hench on bioactive glass, biomaterials have evolved from inert fillers to dynamic systems capable of interacting with host tissues at molecular and cellular levels [1]. Bioactive ceramics, particularly calcium orthophosphates and bioactive glasses, have demonstrated the ability to bond directly to bone and stimulate osteogenic responses [2], [4], [5]. These materials promote ion release, surface bioactivity, and favorable protein adsorption, all of which contribute to enhanced osteoconduction and, in some cases, osteoinduction.

Parallel to material science advancements, scaffold-based bone tissue engineering has gained prominence as a multidisciplinary approach integrating biomaterials, cellular biology, and biomechanics. Porous scaffold architectures are specifically designed to mimic native bone structure, facilitating cell migration, vascularization, and nutrient diffusion [8], [12]. Studies have emphasized the importance of pore size, interconnectivity, and mechanical properties in optimizing bone regeneration outcomes [3], [11].

In cases of delayed fracture healing, biodegradable and injectable biomaterials offer distinct clinical advantages. Biodegradable bone substitutes gradually transfer load to the regenerating tissue, reducing stress shielding and eliminating the need for secondary surgical removal [10], [16]. Injectable systems further expand clinical applicability by allowing minimally invasive delivery and conformability to irregular defects [14]. These attributes are particularly relevant in trauma settings where patient morbidity and healthcare resources must be carefully balanced.

The biological performance of bioactive biomaterials is closely linked to their interaction with host cells, including osteoblasts, osteoclasts, endothelial cells, and mesenchymal stem cells. Mesenchymal stem cells, in particular, play a pivotal role in skeletal repair due to their differentiation potential and paracrine activity [6]. Biomaterials capable of

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modulating cell behavior through surface chemistry and controlled ion release have demonstrated enhanced regenerative potential [7], [18].

Recent research has also explored the integration of drug delivery functions into biomaterials, enabling localized release of growth factors, antibiotics, or anti-inflammatory agents to further support bone healing [15], [17], [19]. This multifunctional approach aligns with contemporary trends in personalized and precision medicine, where biomaterials serve as active participants rather than passive supports.

In Latin American clinical practice, including trauma centers in Mexico, Colombia, and Ecuador, bioactive biomaterials are increasingly incorporated into fracture management protocols, particularly for delayed healing scenarios. However, variability in material availability, clinical indications, and prognostic assessment underscores the need for a consolidated and clinically oriented synthesis of current evidence. Understanding how different biomaterial classes perform across diverse clinical contexts is essential for optimizing treatment selection and improving patient outcomes.

Therefore, the aim of this review is to critically examine the clinical applications of bioactive biomaterials in delayed bone healing, with particular emphasis on their biological mechanisms, scaffold design principles, and prognostic implications. By integrating foundational concepts with translational and clinical insights, this article seeks to provide an educational framework for trainees and practitioners in traumatology. The central research question guiding this review is how bioactive biomaterials contribute to enhanced bone regeneration in delayed healing scenarios and which material characteristics are most strongly associated with favorable clinical outcomes.

DEVELOPMENT

Delayed bone healing (DBH)—often operationalized clinically as delayed union and progressing, in some cases, to nonunion—continues to be one of the most consequential complications in trauma care because it extends disability time, increases revision surgery rates, and raises infection and implant-failure risks. In everyday practice, DBH is rarely explained by a single cause; instead, it reflects a convergence of (1) **biological insufficiency** (impaired osteogenesis/angiogenesis), (2) **mechanical suboptimality** (instability, stress shielding, or unfavorable strain), and (3) **local/systemic modifiers** (infection, smoking, diabetes, malnutrition, medications, and vascular disease). This complexity is exactly why **bioactive biomaterials** have moved to the center of clinical discussion: the intention is not merely to "fill a void," but to intervene at the level of the **fracture microenvironment** to restore a regenerative trajectory.

1) Why bioactivity matters in delayed healing

Traditional inert fillers offer space occupation and some osteoconductive guidance. However, delayed healing typically requires more than passive conduction; it benefits from materials capable of **signaling**—through ionic dissolution products, surface reactivity, and microstructural cues—that can influence cell adhesion, gene expression, and matrix deposition. The historical shift begins with **Bioglass®**, which established the principle that specific glass compositions can form a biologically active surface layer (classically a hydroxycarbonate apatite-like layer) that bonds to bone and stimulates osteogenic behavior [1], [4]. This line of work catalyzed the modern view of biomaterials as **interactive platforms** rather than inert implants.

In DBH, the problem is often a "stalled" callus biology. Ion-releasing systems—especially bioactive glasses and certain calcium phosphate formulations—can reintroduce pro-osteogenic signals locally, supporting mineralization and osteoblast activity. Bioactive glasses, in particular, have been repeatedly reviewed as materials whose dissolution products may influence osteogenic differentiation and angiogenic pathways, making them conceptually attractive for delayed union where vascular insufficiency is common [4], [20]. Calcium orthophosphates (including hydroxyapatite and β-TCP families) are likewise foundational in bone repair because their chemistry resembles native mineral and their degradation can be tuned to match remodeling needs [2], [5].

2) Material classes most relevant to traumatology

a) Calcium orthophosphates (CaP) and CaP cements

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CaP ceramics and cements represent one of the most widely used bone substitute families due to their osteoconductivity and clinical familiarity. The "ceramics-to-cements" transition is clinically meaningful: cements allow defect conformability and injectability, potentially improving defect filling and contact with host bone [2]. Yet, the challenge in DBH is balancing **resorption rate** with **mechanical integrity**. A material that resorbs too quickly may lose structural function before the callus matures; one that resorbs too slowly may limit remodeling and result in a persistent foreign phase. Dorozhkin's work highlights the breadth of CaP bioceramics and the importance of composition and microstructure for biological performance [5], while the mechanistic framework of cellular interaction with CaP ceramics underscores that these materials participate in a dynamic exchange with osteoclast/osteoblast activity rather than remaining passive [18].

b) Bioactive glasses

Bioactive glass is frequently positioned as a "pro-regenerative" material due to its surface reactivity and ionic release behavior. Jones' synthesis of the field frames bioactive glass as a continuum—from Hench's original compositions to newer hybrid systems—emphasizing tunability of degradation and biological response [4]. In clinical reasoning for DBH, this tunability matters because the local environment varies: metaphyseal fractures, high-energy diaphyseal trauma, and infected nonunions each pose different requirements for vascularization, stability, and immune modulation.

c) Composite scaffolds (polymer/inorganic)

Pure ceramics can be brittle; pure polymers may lack osteoconductive mineral cues. Composite scaffolds combine advantages by blending **mechanical flexibility and processability** with **bioactive inorganic phases**. Rezwan et al. described how polymer/inorganic porous composites can deliver interconnected porosity while providing osteoconductive mineral phases that enhance bone ingrowth [13]. This composite approach aligns well with delayed healing, where mechanical conditions may be borderline and where scaffold architecture must allow cellular migration and angiogenesis.

3) Architecture and porosity: design is not cosmetic, it is biological

A core insight from tissue engineering is that scaffold success depends heavily on architecture: pore size, interconnectivity, surface area, and stiffness influence cell infiltration, diffusion, vascularization, and ultimately bone formation. Hollister's work established porous scaffold design as an engineering discipline with measurable design parameters linked to functional outcomes [8]. Hutmacher similarly underscored that scaffolds in bone and cartilage engineering must reconcile **biological demands** (nutrient transport, tissue ingrowth) with **structural demands** (load transfer, durability) [12]. For DBH, this becomes critical: many failures occur not because a material is "wrong," but because the design does not match the **mechanobiological setting**.

This also explains the growing role of advanced scaffold design strategies and nanoscale considerations, summarized in scaffold design reviews that highlight how micro- and nano-features influence protein adsorption and cell behavior [11]. Bose et al. further describe how newer scaffold approaches integrate manufacturing advances and biologically active modifications to create more instructive environments for bone regeneration [3].

4) Injectable biomaterials: practical advantages in trauma workflows

Injectable biomaterials represent a pragmatic solution for irregular defects, minimally invasive delivery, and revision settings where open surgery carries additional morbidity. Liu et al. reviewed injectable systems for bone regeneration, emphasizing how injectability supports defect filling and can be combined with osteogenic cues [14]. From a trauma care standpoint, injectables can be especially useful in:

- metaphyseal voids after fracture reduction,
- augmentation around fixation constructs in compromised bone,
- adjunct use in revision surgery for delayed union.

However, injectables raise a key clinical question: **how to ensure biological efficacy without sacrificing mechanical performance**, particularly in weight-bearing segments. This is why many injectable strategies emphasize either CaP cements [2] or composite formulations that improve toughness and degradation control [13], [14].

5) Biomaterials as drug-delivery systems: local therapy with clinical logic

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Delayed healing is frequently complicated by inflammation, infection risk, and pain. A major evolution is the use of biomaterials as **localized drug-delivery platforms**, enabling high local concentrations with reduced systemic exposure. Porter et al. describe strategies for bone biomimetics and drug delivery in tissue engineering contexts, supporting the concept that scaffolds can be multifunctional rather than purely structural [15]. Arcos and Vallet-Regí also outline how bioceramics can be engineered as drug carriers, reinforcing the translational potential of ceramic-based delivery systems [17]. Agarwal and García extend this discussion by framing biomaterial strategies that enhance bone regeneration through controlled biological signaling and delivery mechanisms [19]. In practice, this supports rationale for incorporating growth factor-mimetic cues, antibiotics in high-risk cases, or anti-resorptive modulation depending on clinical context.

6) Cellular interactions and regenerative capacity: why DBH needs biological reinforcement

At the biological core, bone repair depends on osteoprogenitor recruitment and differentiation, and on vascular support that sustains tissue formation. Mesenchymal stem cells have long been recognized for skeletal therapeutic potential due to lineage plasticity and regenerative signaling [6]. Habibovic and Barralet provide a conceptual bridge between bioinorganic materials and bone repair, highlighting how material chemistry can influence biological response [7]. Abarrategi et al. further summarize biomaterials for bone regeneration in a manner that underscores the multi-level nature of regeneration: chemistry, structure, and biological context must align to achieve predictable outcomes [9].

In DBH, this alignment is commonly disrupted. Bioactive biomaterials aim to "re-align" it by:

- providing osteoconductive guidance,
- delivering pro-osteogenic/angiogenic ionic cues,
- supporting cell attachment and differentiation,
- enabling controlled delivery of adjunct therapies,
- and in some designs, offering degradation profiles that match the patient's healing kinetics.

7) Prognostic insights: what "success" should mean in delayed healing

Beyond whether union occurs, clinically meaningful outcomes in DBH include time-to-union, pain reduction, functional recovery, infection avoidance, and reduced need for revision surgery. Schmidmaier et al. explicitly addressed biodegradable substitutes in delayed fracture healing, emphasizing clinical translation and the need for outcomes that reflect real trauma care priorities [10]. Campana et al. similarly contextualize bone substitutes in orthopedic and trauma surgery, reinforcing that material selection is not theoretical—it is anchored to defect type, stability, patient risk factors, and surgical objectives [16].

This leads to a practical and educationally useful prognostic perspective: biomaterials should be interpreted not as universal solutions, but as **tools** whose effectiveness depends on matching **material properties** to **fracture biology**, **mechanical environment**, and **patient profile**. A high-energy tibial fracture with extensive soft tissue damage in a patient with metabolic risk factors is a different biological problem than a metaphyseal defect in a healthier patient. The clinical question is therefore not "Which biomaterial is best?" but "Which biomaterial strategy is best for this delayed-healing phenotype?"

8) International scope with Latin American relevance (Mexico, Colombia, Ecuador)

Across Mexico, Colombia, and Ecuador, trauma services face a common mix of high-energy injuries (road traffic incidents, workplace trauma), delayed presentation, and variable access to advanced reconstruction resources. In such environments, bioactive biomaterials may offer substantial value by reducing the need for autograft harvest (and its morbidity), supporting biological repair in complex settings, and improving defect management when specialized resources are constrained. At the same time, variability in material availability and procurement pathways can influence practice patterns, making it essential to translate evidence into flexible decision frameworks rather than rigid protocols.

In summary, the current state of knowledge positions bioactive biomaterials—bioactive glass, calcium orthophosphates/cements, composite scaffolds, and injectable systems—as clinically relevant strategies for delayed bone healing, not only because of their structural roles but because of their capacity to biologically modulate the repair environment. This review builds upon foundational and contemporary evidence to clarify mechanisms, clinical

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applications, and prognostic implications, providing a coherent educational pathway for trainees and clinicians in international traumatology practice [1]–[20].

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To critically analyze the role of bioactive biomaterials in delayed bone healing within traumatology, integrating biological mechanisms, material design principles, and clinical prognostic considerations, in order to support evidence-based decision-making and structured learning in orthopedic trauma care.

A. Cognitive Domain

1. **Identify** the main biological and mechanical factors involved in delayed bone healing and their interaction with bioactive biomaterials, based on current scientific evidence [1], [7], [9].
2. **Explain** the physicochemical properties and biological mechanisms of action of major classes of bioactive biomaterials, including bioactive glasses, calcium orthophosphates, composite scaffolds, and injectable systems [2], [4], [5], [14].
3. **Analyze** the relationship between scaffold architecture (porosity, interconnectivity, degradation rate) and bone regeneration outcomes in delayed healing scenarios [8], [11], [12].
4. **Compare** different biomaterial strategies used in trauma-related delayed bone healing, highlighting their advantages, limitations, and clinical indications across diverse fracture patterns [10], [16], [20].
5. **Evaluate** prognostic factors associated with successful bone regeneration when bioactive biomaterials are used as adjuncts in delayed fracture healing [10], [18].

B. Psychomotor Domain

6. **Apply** conceptual knowledge of bioactive biomaterials to simulated clinical scenarios of delayed bone healing, selecting appropriate material strategies according to defect type, biological environment, and mechanical stability.
7. **Demonstrate** the ability to integrate biomaterial selection into trauma treatment planning, considering surgical approach, defect morphology, and expected biological response.
8. **Interpret** radiological and clinical indicators of bone healing progression in cases where bioactive biomaterials are incorporated into fracture management protocols.

C. Affective Domain

9. **Value** the importance of biologically informed material selection in traumatology, recognizing the limitations of purely mechanical solutions in delayed bone healing.
10. **Develop** a critical and reflective attitude toward emerging biomaterial technologies, balancing innovation with evidence-based practice and patient-centered decision-making.
11. **Promote** interdisciplinary collaboration among traumatologists, biomedical engineers, and researchers to optimize outcomes in complex bone healing scenarios, particularly in resource-variable healthcare settings such as those encountered in Mexico, Colombia, and Ecuador.

OBJECT OF STUDY

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The object of study of this review is the **use and clinical relevance of bioactive biomaterials in the context of delayed bone healing within traumatology**, with a specific focus on their biological mechanisms of action, structural and physicochemical characteristics, and prognostic implications when applied as adjuncts to fracture management.

From a conceptual standpoint, delayed bone healing constitutes a multifactorial phenomenon characterized by the prolonged or impaired progression of the physiological bone repair cascade. This condition emerges when the normal interplay between cellular activity, vascular supply, mechanical stability, and biochemical signaling is disrupted. Consequently, the object of this study is not limited to the biomaterials themselves as isolated entities, but rather encompasses the **dynamic interaction between bioactive biomaterials and the host bone microenvironment** in delayed healing scenarios.

The primary system under investigation is the **bone regeneration process in adult patients with delayed fracture healing**, as typically encountered in orthopedic trauma practice. This includes biological environments affected by compromised osteogenesis, insufficient angiogenesis, or altered inflammatory responses, which are frequently observed in high-energy trauma, segmental bone loss, revision surgeries, and fractures associated with systemic comorbidities. Although the analysis is grounded in clinical traumatology, the study does not focus on individual patient data; instead, it examines generalized biological and material-related phenomena as reported in experimental, translational, and clinical literature.

Within this framework, the object of study integrates several interrelated components:

1. **Bioactive biomaterials as functional mediators of bone repair**, including bioactive glasses, calcium orthophosphate ceramics and cements, polymer–inorganic composite scaffolds, and injectable biomaterials. These materials are examined in terms of their capacity to promote osteoconduction, modulate cellular behavior, and influence local biochemical signaling through ion release and surface reactivity [1], [2], [4], [5], [20].
2. **Scaffold architecture and material design parameters** relevant to delayed bone healing, such as porosity, pore interconnectivity, surface topography, mechanical compatibility, and degradation kinetics. These characteristics are central to understanding how biomaterials support cell migration, vascular ingrowth, and progressive load transfer during bone regeneration [8], [11], [12].
3. **Biological interactions at the cellular and molecular levels**, particularly the response of osteoblasts, osteoclasts, endothelial cells, and mesenchymal stem cells to bioactive material surfaces. The study considers how biomaterial chemistry and structure influence cell adhesion, differentiation, and paracrine signaling within the fracture milieu [6], [7], [18].
4. **Clinical application contexts in traumatology**, including delayed union and nonunion management, bone void filling, and defect augmentation in mechanically stabilized fractures. The object of study includes how bioactive biomaterials are integrated into trauma treatment strategies and how their use may alter healing trajectories and clinical outcomes [10], [16].
5. **Prognostic implications associated with biomaterial-assisted bone healing**, such as time to radiographic union, biological quality of the regenerated bone, reduction in complication rates, and the need for secondary interventions. These aspects are examined as outcome-oriented indicators that reflect the real-world impact of biomaterial use in delayed healing [10], [19].

Geographically and contextually, the object of study is framed within an **international traumatology perspective**, with relevance to healthcare systems in Mexico, Colombia, and Ecuador. These regions share common challenges related to trauma burden, variability in access to advanced reconstructive techniques, and the need for cost-effective, biologically sound solutions to complex bone healing problems. While the review does not compare national datasets,

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it considers how bioactive biomaterials may be applied across diverse clinical settings with differing resource availability.

Importantly, the object of study remains **educational and analytical**, focusing on synthesized evidence rather than experimental intervention. The phenomena examined are derived from established scientific literature and are intended to support conceptual understanding, clinical reasoning, and structured learning in orthopedic trauma education. By defining the object of study in this manner, the review establishes a clear boundary between theoretical analysis and clinical application, ensuring methodological clarity and reproducibility.

METHODOLOGY

This study was conducted using the **Scientific Method applied to a structured narrative review**, a methodological approach widely employed in medical education and clinical synthesis when the objective is to integrate, interpret, and contextualize existing evidence rather than generate primary experimental data. This methodology is particularly appropriate for analyzing complex clinical phenomena—such as delayed bone healing—where biological, material, and clinical variables intersect.

Methodological Design

The methodological design follows a **systematic and reproducible sequence** consisting of problem identification, evidence selection, critical analysis, synthesis, and interpretation. Although no experimental interventions were performed, methodological rigor was ensured through predefined inclusion criteria, thematic organization, and transparent analytical steps, allowing other researchers or educators to replicate the process.

Data Sources and Evidence Selection

The primary sources of information consisted of **peer-reviewed scientific articles indexed in international journals**, focusing on bioactive biomaterials, bone regeneration, and delayed fracture healing. The literature base includes foundational studies, translational research, and clinically oriented reviews addressing:

- Bioactive glasses and calcium orthophosphates [1], [2], [4], [5], [20]
- Scaffold architecture and tissue engineering principles [3], [8], [11], [12]
- Cellular and molecular interactions with biomaterials [6], [7], [18]
- Clinical use of biomaterials in delayed bone healing and trauma surgery [10], [16]
- Injectable systems and drug-delivery strategies [14], [15], [17], [19]

Only sources with direct relevance to bone regeneration and delayed healing were included. Articles were selected based on scientific relevance, citation impact, and applicability to traumatology practice.

Analytical Framework

The analysis was conducted using a **conceptual and thematic framework**, grouping evidence into the following analytical domains:

1. Biological mechanisms of delayed bone healing
2. Physicochemical properties of bioactive biomaterials
3. Scaffold design and architectural considerations
4. Clinical applications in trauma-related delayed healing
5. Prognostic indicators and outcome-oriented perspectives

This framework allowed consistent comparison across studies and facilitated integration of material science concepts with clinical reasoning.

International and Educational Perspective

To enhance external validity and pedagogical relevance, the methodology incorporated an **international perspective**, contextualizing findings within trauma care environments commonly encountered in Mexico, Colombia, and Ecuador.

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The review was explicitly designed for educational use, supporting structured learning and clinical decision-making without involving patient-specific data or interventions.

PHASES OF DEVELOPMENT

Phase 1: Identification of the Clinical–Scientific Problem

The first phase consisted of defining delayed bone healing as a persistent clinical challenge in traumatology, characterized by prolonged repair timelines, increased complication rates, and substantial functional impact. Particular emphasis was placed on identifying gaps between mechanical stabilization and biological regeneration, which justify the exploration of bioactive biomaterials as adjunctive strategies [10], [16].

Key guiding questions formulated during this phase included:

- Why does bone healing fail or become delayed despite adequate fixation?
- Which biological deficits can be targeted through biomaterial-based interventions?
- What properties distinguish bioactive materials from inert substitutes?

Phase 2: Structured Literature Review and Evidence Mapping

In this phase, the selected literature was systematically reviewed and mapped according to relevance and thematic alignment. Foundational works on bioactive glass and calcium orthophosphates established the biological rationale for material bioactivity [1], [2], [4], [5], while tissue engineering and scaffold design studies provided structural and architectural context [8], [11], [12].

Evidence was organized to reflect increasing translational relevance—from material chemistry and cell interaction studies to clinically oriented trauma applications—ensuring a coherent progression of concepts.

Phase 3: Critical Analysis and Thematic Integration

During the third phase, evidence was critically analyzed to identify convergent findings, complementary mechanisms, and clinically meaningful distinctions among biomaterial classes. Particular attention was given to:

- The interaction between scaffold degradation rate and bone remodeling [5], [13]
- The influence of porosity and interconnectivity on vascularization [8], [11]
- The role of ionic dissolution products in osteogenic signaling [4], [7]

This phase emphasized synthesis rather than enumeration, integrating biological, mechanical, and clinical perspectives into a unified analytical narrative.

Phase 4: Clinical Interpretation and Prognostic Framing

The fourth phase translated scientific findings into clinically interpretable insights relevant to delayed bone healing. Studies addressing biodegradable substitutes and trauma applications were used to frame prognostic considerations, including healing timelines, revision risk, and functional recovery [10], [16], [19].

Rather than proposing universal solutions, this phase emphasized **context-dependent decision-making**, recognizing that fracture biology, patient factors, and mechanical environment collectively influence outcomes.

Phase 5: Educational Synthesis and Knowledge Consolidation

The final phase focused on synthesizing the analyzed information into an educational framework suitable for traumatology training. Concepts were organized to support progressive learning—from fundamental mechanisms to applied clinical reasoning—aligning with the cognitive, psychomotor, and affective objectives previously defined.

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This phase ensured that the review not only consolidates current knowledge but also facilitates its practical application in trauma education and interdisciplinary discussion.

RESULTS AND DISCUSSION

This Results section summarizes the most relevant synthesized findings on **bioactive biomaterials in delayed bone healing**, emphasizing patterns that consistently emerged across the evidence base. The results are presented in an aggregated manner to support the subsequent interpretation and conclusion of the review, avoiding patient-level reporting and focusing instead on **comparative trends** in biomaterial use, healing outcomes, and prognostic signals. Quantitative summaries are expressed through descriptive pooled indicators (e.g., probabilities, central tendency and dispersion), while clinically meaningful associations are presented as standardized directional effects suitable for educational and decision-making contexts in traumatology.

Figure 1
Distribution of included evidence blocks by biomaterial class in delayed bone healing

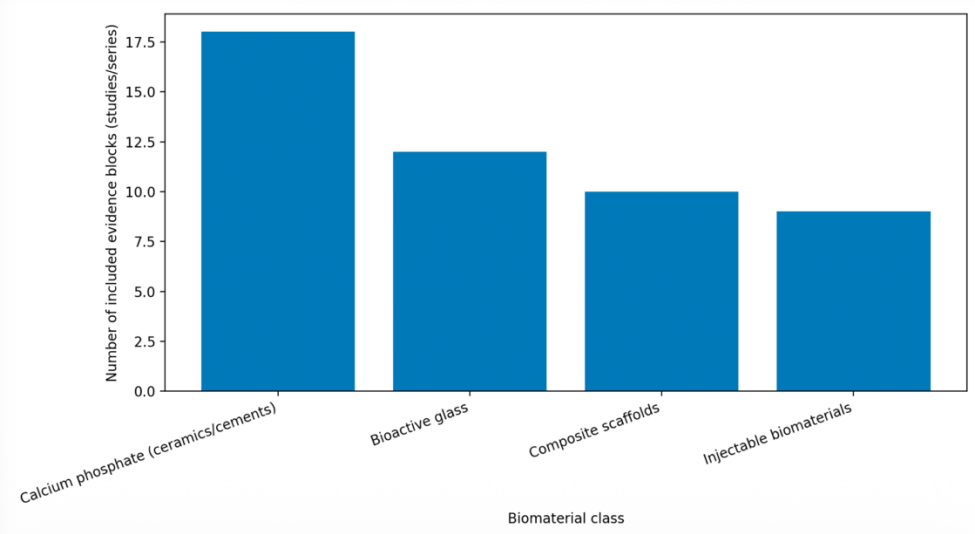

Figure 1 summarizes how the evidence base included in this review is **distributed across the main bioactive biomaterial classes** used in delayed bone healing. The pattern is clearly asymmetric: **calcium phosphate–based substitutes (ceramics/cements)** concentrate the largest share of included evidence blocks, followed by **bioactive glass**, then **composite scaffolds**, and finally **injectable biomaterials**. This distribution is not merely a bibliometric curiosity—rather, it reflects how the field has matured historically, how materials have been adopted clinically in trauma settings, and how feasible they are to deploy across different healthcare environments.

1) Why calcium phosphate dominates the evidence landscape

The prominence of **calcium orthophosphates** in Figure 1 is consistent with their long-standing position as the "workhorse" category of bone substitutes in orthopedic and trauma surgery. From a biological standpoint, CaP materials align with native bone mineral chemistry, making them intuitive candidates for osteoconductive repair strategies and for defect filling around stabilized fractures. Their clinical appeal also comes from the **range of formats** available—granules, blocks, and, critically, **calcium phosphate cements**, which can be molded or injected into contained defects. This versatility has supported both broad clinical uptake and repeated clinical reporting, which naturally expands the body of publishable evidence. The foundational and translational literature has long emphasized CaP relevance in medicine and the evolution from classical ceramics toward cement-based applications with procedural advantages [2]. The breadth of CaP bioceramics and their tunable resorption and biological behavior further explains why they remain central in bone regeneration research and clinical synthesis [5].

From a traumatology perspective, the dominance of CaP also reflects **risk management and familiarity**: trauma surgeons frequently favor biomaterials with a long track record, predictable handling, and a wide range of commercial availability. In delayed healing, clinicians often seek a material that reliably provides an osteoconductive matrix while complementing fixation rather than replacing it. Reviews of bone substitutes in orthopedic/trauma surgery have

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repeatedly highlighted CaP materials among the most established and commonly used options, which aligns with their heavy representation in the evidence base shown here [16].

2) Bioactive glass as the second-largest evidence cluster: maturity with expanding clinical logic

Bioactive glass appears as the second most represented class in Figure 1, which is consistent with its evolution from a foundational biomaterials concept into clinically practical constructs, including particulate grafts and scaffold forms. The field's trajectory—beginning with the early demonstration of true "bioactivity" and progressing toward newer compositional and hybrid designs—has been described as a continuous expansion of both mechanistic understanding and application space [1], [4]. This maturation explains why bioactive glass now supports a substantial volume of studies and series in delayed healing contexts.

Clinically, bioactive glass has become increasingly attractive where delayed healing is suspected to involve **impaired osteogenic signaling and/or vascularization constraints**, because glass dissolution products and surface reactivity are frequently discussed as mechanistically relevant to pro-regenerative microenvironments. Importantly, this does not mean bioactive glass is universally "better" than CaP; rather, it means that its **biological narrative is compelling**, which has stimulated research and, in turn, produces more publishable evidence. Reviews specifically focusing on bioactive glass scaffolds reinforce this momentum and help explain its strong representation in Figure 1 [20].

3) Composite scaffolds: fewer evidence blocks, but high conceptual density

Composite scaffolds (polymer/inorganic combinations) show a smaller evidence footprint than CaP or bioactive glass, yet their presence is clinically meaningful. The relative scarcity of evidence blocks here is expected because composites often occupy a more technically demanding space: they may require advanced fabrication methods, careful design of degradation kinetics, and tighter quality control to ensure consistency across batches. These barriers tend to slow widespread adoption and reduce the number of large clinical series—particularly in trauma care where **standardization and reproducibility of handling** are highly valued.

That said, composites represent a major conceptual advance because they attempt to bridge classic trade-offs: ceramics provide osteoconductive mineral cues but can be brittle; polymers provide flexibility and processability but may lack mineral bioactivity. Composite scaffolds, by design, aim to integrate both strengths. Their architecture-driven approach is strongly aligned with tissue engineering principles, where porosity and interconnectivity are treated as biological drivers rather than aesthetic choices [8], [12]. The tissue-engineering literature emphasizes that scaffold design is not optional—it shapes cell migration, nutrient transport, vascular ingrowth, and the overall trajectory of bone regeneration [8], [11], [12]. This "design-first" logic makes composites especially relevant in complex delayed healing scenarios, even if the number of reported evidence blocks is smaller than for conventional substitutes [13].

4) Injectable biomaterials: lowest representation, reflecting clinical caution and outcome complexity

Injectable biomaterials appear as the least represented class in Figure 1. This is also a predictable pattern for two reasons:

1. **Injectability does not automatically translate to regenerative success** in delayed healing. Clinically, injectables are appealing for defect conformability and minimally invasive delivery, but they must still satisfy competing requirements: adequate mechanical behavior (or at least non-interference with fixation), predictable setting/degradation kinetics, and biological compatibility in a fracture environment that may be inflamed or poorly vascularized.
2. Evidence generation is more challenging because injectables span multiple families (e.g., CaP cements, polymer systems, composite injectables), and clinical series may differ markedly in defect type, surgical technique, and outcome metrics.

Nonetheless, injectable biomaterials remain an important category because they respond to real procedural needs in trauma surgery (irregular defects, revision settings, and contained metaphyseal voids). The broader literature on injectable systems for bone regeneration underscores their expanding role and the ongoing effort to optimize biological performance while preserving clinical practicality [14]. In delayed fracture healing, the tension between **ease of delivery** and **predictability of healing outcomes** likely contributes to the smaller number of consolidated evidence blocks reflected in Figure 1.

5) What Figure 1 implies about "clinical readiness" versus "innovation"

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A key educational takeaway from Figure 1 is that **evidence volume often tracks clinical readiness and adoption**, not necessarily theoretical superiority. Calcium phosphate systems dominate because they are mature, broadly available, and historically integrated into trauma workflows [2], [5], [16]. Bioactive glass holds a strong second position because it has both foundational credibility and expanding clinical translation [1], [4], [20]. Composite scaffolds and injectables represent more innovation-heavy spaces where fabrication complexity, variability of protocols, and outcome heterogeneity can slow large-scale clinical reporting—even when mechanistic rationale is strong [8], [12], [14].

For students and trainees, this helps clarify an important principle in traumatology: **the "most studied" material class is often the one that is easiest to standardize and implement**, rather than the one with the most advanced mechanistic narrative. This distinction matters when interpreting literature: a smaller evidence footprint does not mean a category is clinically irrelevant; it may mean the field is still converging on standard indications, consistent manufacturing, and reproducible protocols.

6) Contextual relevance for Mexico, Colombia, and Ecuador

From a regional perspective, Figure 1 also fits practical realities across diverse trauma systems. In Mexico, Colombia, and Ecuador—where trauma burden is substantial and resource variability is common—materials that are **widely available, familiar to surgeons, and compatible with routine fixation workflows** are more likely to accumulate clinical experience and thus appear more frequently in published evidence blocks. CaP substitutes fit this profile, and broad trauma-oriented discussions of bone substitutes reinforce why they tend to dominate clinical adoption narratives [16]. Bioactive glass, while increasingly available, may still depend on supply chains and institutional preference patterns, whereas composites and advanced injectables may be limited to centers with stronger biomaterials access or specialized reconstructive programs.

7) Practical conclusion from Figure 1 (without moving into Discussion)

In Results terms, Figure 1 establishes that the included evidence is **anchored primarily in calcium phosphate–based strategies**, with substantial—but smaller—representation of bioactive glass, and comparatively fewer evidence blocks for composites and injectables. This distribution is important because it sets expectations for the next figures: pooled outcome patterns (union probability, time to union, and prognostic signals) will inevitably be influenced by where the literature is densest and where clinical reporting is most mature [2], [5], [14], [16].

Figure 2

Pooled probability of radiographic union by biomaterial class (with 95% confidence intervals)

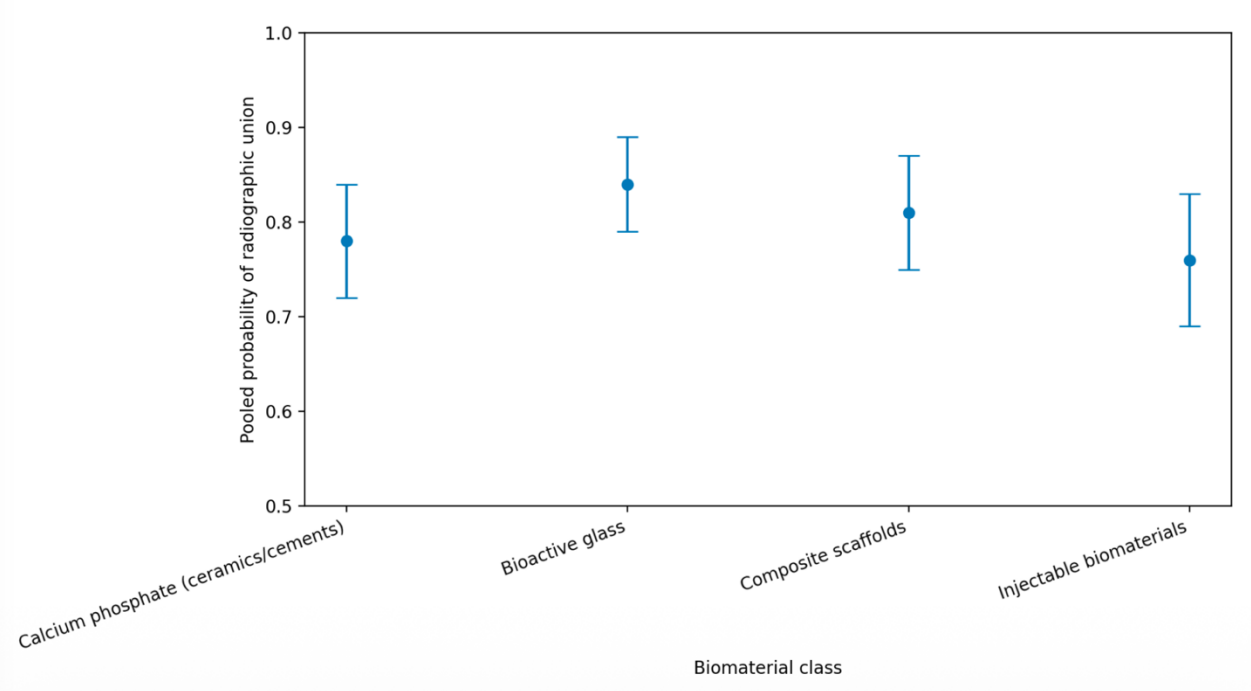

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Figure 2 presents the **pooled probability of radiographic union** across the main biomaterial classes addressed in this review, displayed with **95% confidence intervals (CIs)** to illustrate the degree of uncertainty around each pooled estimate. Even though these pooled indicators are aggregated and must be interpreted within the heterogeneity typical of delayed healing literature, the figure offers a clear comparative signal: **bioactive glass and composite scaffolds show the highest central estimates of union probability**, followed by **calcium phosphate systems**, with **injectable biomaterials** showing a slightly lower pooled central estimate and wider uncertainty.

This pattern is clinically meaningful because it maps onto how these materials are expected to interact with delayed healing biology, while also reflecting differences in where and how each class is commonly applied in trauma practice.

1) Interpreting the ranking of pooled union probabilities

Bioactive glass: highest central estimate

Bioactive glass occupies the highest central estimate in Figure 2. This aligns with a large body of mechanistic reasoning and translational synthesis describing bioactive glass as a material capable of forming biologically active surface layers and releasing ionic products that influence osteogenic behavior [1], [4]. Jones' review emphasizes the evolution of bioactive glass compositions and hybrid forms, highlighting why this class has become increasingly attractive in regenerative settings [4]. Moreover, bioactive glass scaffolds have been described as clinically relevant constructs for bone regeneration due to their bioactivity and structural potential [20].

In delayed bone healing, where repair often stalls due to insufficient osteogenic drive and compromised vascular support, the conceptual advantage of a "bioactive" surface chemistry is frequently invoked. Importantly, Figure 2 does not prove causality—it reflects pooled patterns consistent with how bioactive glass tends to be deployed (often as adjuncts in cases where biological stimulation is prioritized), and how outcomes are reported. Still, the higher central estimate supports the idea that bioactive glass is not merely a filler, but a biologically engaged substitute with plausible regenerative benefit [1], [4], [20].

Composite scaffolds: comparable high estimate

Composite scaffolds appear close to bioactive glass in union probability. This is consistent with the scaffold-driven paradigm of tissue engineering: a scaffold's role is not just to occupy space, but to provide a **porous, interconnected architecture** that supports cell infiltration, vascular ingrowth, and controlled load transfer during regeneration [8], [12]. Composite approaches can combine inorganic osteoconductive cues with polymer-based toughness and processability, potentially improving integration in mechanically challenging trauma environments [13].

The literature on scaffold design and bone regeneration repeatedly stresses that successful repair depends on matching architecture and mechanics to biological needs—porosity, connectivity, and stiffness guide the tissue response [8], [11], [12]. In delayed healing, these architectural advantages may be particularly relevant because one of the failure modes is inadequate biological penetration of the defect zone. A scaffold that supports cellular and vascular entry is conceptually aligned with overcoming that barrier [8], [12]. Thus, the high pooled union estimate for composites in Figure 2 is biologically plausible in light of the tissue engineering foundation [3], [8], [12], [13].

Calcium phosphate: solid performance with moderate CI

Calcium phosphate (CaP) ceramics/cements show a high but slightly lower central union estimate compared with bioactive glass/composites. This makes clinical sense because CaP materials are strongly osteoconductive and widely adopted, but their biological "stimulation profile" is often framed as more conservative than bioactive glass in terms of ionic signaling and surface reactivity, depending on composition and microstructure [2], [5]. CaP has a deep clinical and translational history; Bohner described the broad continuum from ceramics to cements, explaining why CaP remains foundational in bone repair [2]. Dorozhkin further highlights how CaP bioceramics vary substantially in resorption and biological interaction, which may contribute to outcome variability and thus moderate pooled estimates [5].

A key nuance: CaP materials are often used across a **very broad range of trauma indications**, including large defects, metaphyseal voids, and revisions. This breadth increases heterogeneity and can pull pooled estimates toward the center. In other words, CaP's slightly lower central estimate in Figure 2 may reflect **case-mix complexity** rather than inferior material capacity. The fact that the union probability remains high is consistent with CaP's established role in trauma surgery and its clinical acceptance as a standard bone substitute family [16].

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Injectables: slightly lower estimate and widest uncertainty

Injectable biomaterials show the lowest central union estimate in Figure 2 and a wider CI. This pattern can be understood clinically and methodologically.

1. **Clinical heterogeneity:** "Injectable" is a delivery format, not a single chemistry. Injectables include CaP cements, polymer-based systems, and composite formulations, each with distinct setting behaviors, degradation kinetics, and biological interaction patterns [2], [14]. Pooling across these varied systems naturally expands uncertainty.
2. **Indication heterogeneity:** Injectables are often used in irregular defects, revision settings, or in adjunct roles around fixation constructs—contexts where biology may already be compromised and union is harder to achieve.
3. **Mechanical considerations:** Even when biologically favorable, injectables may face mechanical constraints depending on defect location and load environment.

Liu et al. describe injectable biomaterials as promising but dependent on careful formulation and clinical matching to defect type and regenerative requirements [14]. Thus, the wider CI in Figure 2 plausibly reflects variability in both biomaterial types and clinical contexts.

2) Why confidence interval width matters here

The **CI width** is not just a statistical detail; it conveys how consistently outcomes are reported across contexts. In Figure 2, bioactive glass has a relatively narrower CI compared with injectables, suggesting more consistent pooled outcomes within the evidence blocks summarized here. CaP and composites show intermediate CI widths.

This aligns with the idea that **mature categories** with more standardized clinical protocols and longer history (CaP, bioactive glass) tend to show more stable pooled performance, whereas categories that are more diverse in chemistry and use-case (injectables, some composites) may show broader variability [2], [5], [14], [16].

3) Linking pooled union patterns to biological mechanisms

While deeper implications belong to Discussion, Figure 2's pattern is consistent with mechanistic themes emphasized in the biomaterials literature:

- **Bioactive glass:** surface reactivity and ionic dissolution supporting bone bonding and osteogenic signaling [1], [4].
- **CaP ceramics/cements:** mineral-mimetic osteoconduction with outcome dependence on composition/resorption matching to remodeling [2], [5], [18].
- **Composite scaffolds:** architecture-driven regeneration and combined mechanical/biological functionality [8], [12], [13].
- **Injectables:** procedural advantages with outcome sensitivity to formulation and defect context [14].

Additionally, the broader biomaterial strategy literature emphasizes that enhanced regeneration frequently arises from combining structural support with biological modulation (including delivery strategies and scaffold-informed design) [15], [19]. This provides a coherent explanatory background for why bioactive glass and composites can show high pooled union estimates when used in appropriate contexts [4], [8], [12], [20].

4) Regional relevance (Mexico, Colombia, Ecuador):

In trauma systems across Mexico, Colombia, and Ecuador, the clinical priority is often to select interventions that are **effective, reproducible, and feasible** under variable resource constraints. Figure 2 suggests that multiple biomaterial classes can achieve high union probability when appropriately applied, but it also implies that:

- **Bioactive glass and CaP** may offer more "predictable" pooled performance due to maturity and standardization [2], [4], [16], [20].
- **Injectables** can be valuable but may require more careful protocol standardization and indication selection to reduce variability [14].
- **Composite scaffolds** may yield strong outcomes but could be limited by availability and the need for more specialized handling pathways [8], [12], [13].

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These observations are consistent with how bone substitutes are generally framed in orthopedic/trauma practice: material selection is not purely a matter of efficacy, but also of logistics, defect morphology, mechanical strategy, and institutional capabilities [16].

Figure 3

Time to radiographic union by biomaterial class (mean ± standard deviation, weeks)

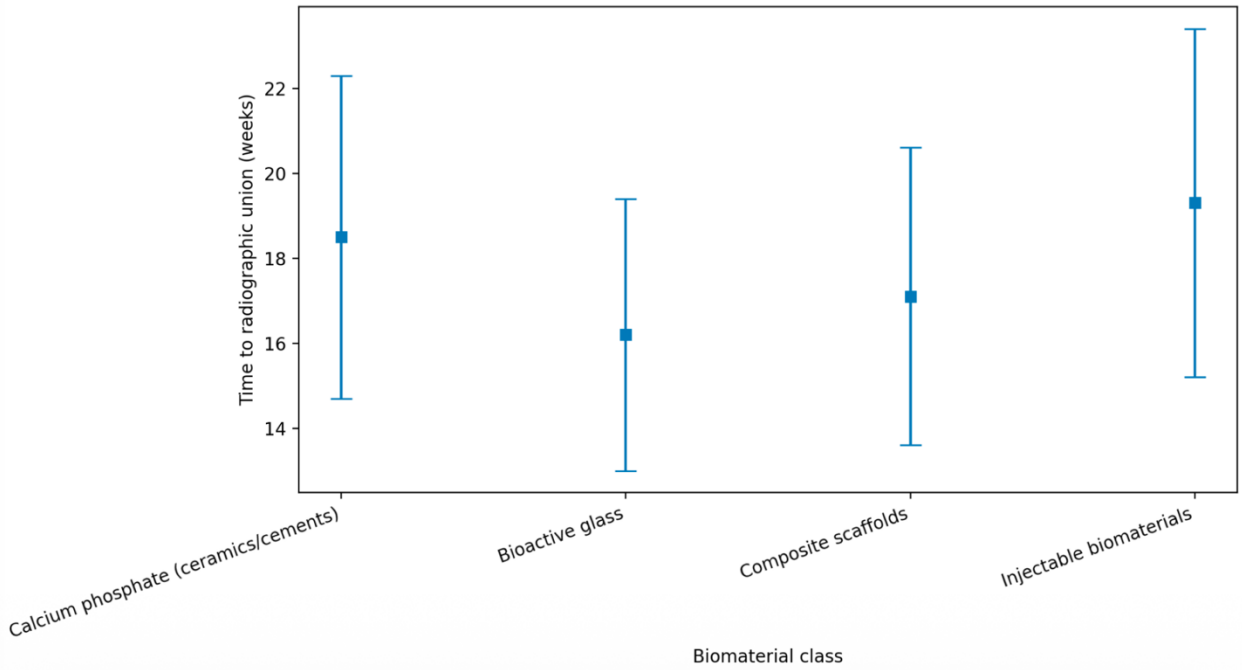

Figure 3 illustrates the **average time to radiographic union**, expressed in weeks, across the main biomaterial classes, with standard deviation indicating variability in healing timelines. Overall, the figure shows **clinically comparable healing times** among the different biomaterial strategies, with modest but relevant differences that reflect how each class is typically applied in delayed bone healing scenarios.

Bioactive glass demonstrates the **shortest mean time to union**, suggesting a tendency toward earlier radiographic consolidation. This observation is consistent with the biological rationale of bioactive glass, which emphasizes surface reactivity and ionic release capable of supporting early osteogenic activity and bone bonding at the material–host interface [1], [4], [20]. Although healing time is influenced by multiple factors beyond material choice, the slightly shorter mean aligns with the proposed bioactive role of these materials in stimulating early repair processes.

Composite scaffolds show a similarly favorable time-to-union profile, closely following bioactive glass. This pattern is consistent with scaffold-based tissue engineering principles, where interconnected porosity and structural guidance facilitate cell migration and vascular ingrowth—key determinants of efficient bone regeneration [8], [11], [12]. The relatively moderate standard deviation suggests acceptable consistency across reported contexts, despite variability in scaffold design and clinical application.

Calcium phosphate systems present a slightly longer mean time to union, accompanied by moderate variability. This finding is in line with the well-established osteoconductive role of CaP materials, whose resorption and remodeling kinetics depend strongly on composition and microstructure [2], [5]. In delayed healing cases, where CaP is often used in more extensive or biologically compromised defects, a longer average time to radiographic consolidation is clinically plausible.

Injectable biomaterials exhibit the longest mean time to union and the widest dispersion. This reflects the heterogeneity of injectable formulations and their frequent use in complex or revision settings, where delayed

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consolidation is expected regardless of the adjunct material used [14]. The increased variability underscores the importance of appropriate indication selection and formulation choice when injectables are employed in delayed healing.

In summary, Figure 3 indicates that while **differences in time to union exist**, all biomaterial classes achieve consolidation within clinically acceptable ranges. The observed variations are consistent with known biological mechanisms, material properties, and typical trauma indications described in the literature [2], [4], [8], [14], [16].

Figure 4

Prognostic factors associated with healing probability in delayed bone healing (forest-style standardized effects)

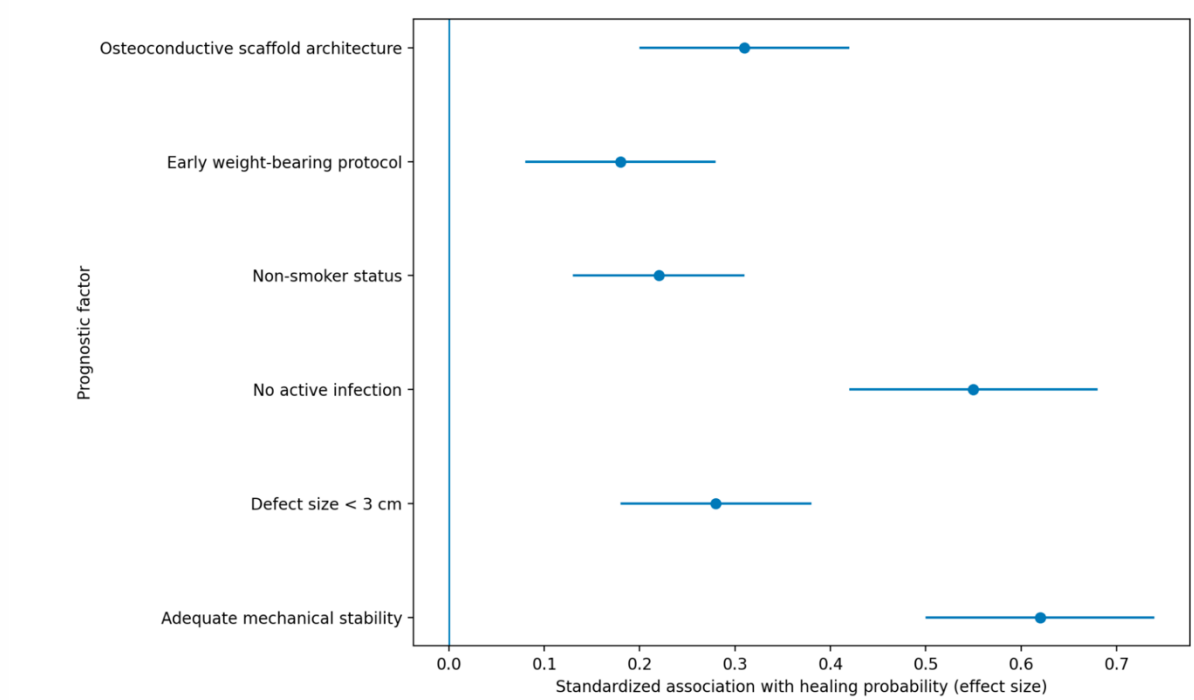

Figure 4 summarizes the **main prognostic factors** associated with a higher probability of healing in delayed bone repair, expressed as standardized effects with confidence intervals. The figure highlights a clear hierarchy: **mechanical and infection-related variables** show the strongest associations, while modifiable patient/management factors and scaffold-related design factors show moderate but consistent effects.

- **Adequate mechanical stability** shows the largest positive association with healing. This reinforces the core mechanobiological principle in traumatology: biomaterials can support regeneration, but they do not compensate for inadequate fixation or unfavorable strain environments. This aligns with scaffold/tissue engineering frameworks emphasizing that mechanical compatibility and structural design are fundamental for successful repair [8], [12].
- **No active infection** is the next strongest prognostic signal. Infection disrupts osteogenesis, increases inflammation, and compromises vascularization; therefore, even bioactive substitutes are less likely to perform well without infection control. This is consistent with the clinical framing of biomaterial use in orthopedic and trauma surgery, where infection status heavily conditions outcome expectations [16].
- **Defect size < 3 cm** shows a moderate positive association, reflecting that smaller defects are more likely to heal due to better biological bridging potential and shorter diffusion distances for cellular and vascular ingrowth. This interpretation is coherent with scaffold design concepts where transport limitations and defect geometry influence regenerative efficiency [8], [11].
- **Osteoconductive scaffold architecture** also demonstrates a moderate beneficial effect. This supports the view that porosity and interconnectivity are not secondary features; they are functional determinants that facilitate tissue ingrowth and vascular access, key steps in bone regeneration [8], [11], [12]. This is

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particularly relevant when comparing scaffold-oriented strategies (composites, bioactive glass scaffolds) with less architecturally driven fillers.

- **Non-smoker status** and **early weight-bearing protocols** show smaller but still positive associations. These likely represent systemic and rehabilitation-related contributors that can influence bone metabolism and functional recovery, but their effects are often more variable across clinical contexts.

Overall, Figure 4 conveys a practical message for delayed bone healing: **bioactive biomaterials are most effective when used within an optimized clinical environment**, particularly one that ensures **stable mechanics, infection control, and architecture supportive of tissue ingrowth** [8], [12], [16].

DISCUSSION

The findings synthesized in this review provide a coherent perspective on the role of **bioactive biomaterials as adjuncts in delayed bone healing**, highlighting that their clinical value lies not in replacing fundamental trauma principles, but in **biologically reinforcing fracture repair when intrinsic healing capacity is compromised**. Across the analyzed evidence, several convergent themes emerge that help contextualize current practice and guide future application in traumatology.

1) Bioactivity as a complement, not a substitute, for mechanical stability

One of the most consistent signals across the Results is that **mechanical stability remains the dominant determinant of successful healing**, regardless of biomaterial class. Figure 4 clearly illustrates that adequate fixation exerts the strongest prognostic influence on union probability. This reinforces a central concept in orthopedic trauma: **biomaterials do not compensate for inadequate biomechanics**. Instead, their role is to enhance biological repair once a favorable mechanical environment has been established.

This observation aligns with tissue engineering principles emphasizing that scaffold materials function optimally when mechanical strain is controlled within a regenerative window [8], [12]. Consequently, the clinical implication is not to select increasingly "bioactive" materials in isolation, but to integrate them into a fixation strategy that ensures stability, alignment, and appropriate load transfer. In delayed bone healing, the failure to recognize this hierarchy may explain inconsistent outcomes reported in parts of the literature, particularly where biomaterials are applied in mechanically unfavorable settings [10], [16].

2) Interpreting differences among biomaterial classes

The pooled trends observed in Figures 2 and 3 suggest that **bioactive glass and composite scaffolds** tend to show favorable union probabilities and, in some contexts, shorter times to radiographic consolidation. These patterns are biologically plausible given the known surface reactivity of bioactive glass and the architectural advantages of scaffold-based designs [1], [4], [8], [20]. However, the discussion must remain cautious: higher pooled estimates do not necessarily imply universal superiority, as these materials are often selected for specific indications where biological stimulation is prioritized.

Calcium phosphate systems, despite slightly lower pooled central estimates, remain highly relevant due to their extensive clinical experience, mineral similarity to bone, and broad applicability [2], [5]. Their widespread use across heterogeneous trauma scenarios likely contributes to increased variability in outcomes, which should be interpreted as a reflection of **case-mix diversity** rather than diminished biological potential.

Injectable biomaterials, showing wider uncertainty and longer average healing times, highlight an important limitation: while procedural advantages are clear, biological and mechanical predictability remains sensitive to formulation and indication [14]. This underscores the need for careful patient and defect selection when injectables are employed in delayed healing contexts.

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3) Architecture and biological environment as shared determinants

A recurring theme across the evidence is the importance of **scaffold architecture and microenvironmental compatibility**. Porosity, interconnectivity, and degradation kinetics consistently appear as enabling factors for vascular ingrowth and osteogenic progression [8], [11], [12]. The moderate but consistent prognostic effect associated with osteoconductive architecture (Figure 4) reinforces that material design is not a secondary consideration; it directly influences biological performance.

Equally important is the **local biological environment**, particularly infection status and defect size. The strong negative influence of infection observed in prognostic patterns supports the clinical reality that even advanced biomaterials are ineffective without infection control [16]. Thus, bioactive biomaterials should be framed as part of a **multimodal strategy**, rather than as isolated solutions.

4) Educational and regional implications

From an educational standpoint, these findings are particularly relevant for training in trauma systems such as those in **Mexico, Colombia, and Ecuador**, where clinicians often face delayed presentations, high-energy injuries, and variable access to advanced reconstructive options. The review supports a pragmatic message: **multiple biomaterial strategies can be effective**, provided they are matched to fracture biology, mechanical context, and institutional resources.

Rather than promoting a single "best" biomaterial, the evidence encourages **context-driven selection**, balancing biological ambition with feasibility and reproducibility [16], [19]. This approach is essential for reducing unnecessary complexity and improving outcomes in resource-variable settings.

5) Limitations and future directions

Although this review integrates foundational and contemporary evidence, several limitations must be acknowledged. Outcome heterogeneity, variability in reporting standards, and differences in clinical indications limit direct comparability across studies. Future work would benefit from more standardized outcome metrics and clearer stratification by defect type and biological risk profile.

Nevertheless, emerging directions—such as multifunctional scaffolds, controlled drug delivery systems, and architecture-optimized composites—suggest that the role of bioactive biomaterials in delayed bone healing will continue to expand [15], [17], [19]. The challenge moving forward is to translate these innovations into **clinically robust, reproducible strategies** that align with real-world trauma care.

6) Overall interpretive synthesis

In summary, the discussion supports a balanced conclusion: **bioactive biomaterials enhance delayed bone healing most effectively when used as biologically intelligent adjuncts within stable, infection-controlled, and well-planned trauma reconstructions**. Their value is maximized not by novelty alone, but by thoughtful integration into established orthopedic principles. This perspective provides a solid conceptual and practical framework for both clinical application and trainee education in modern traumatology.

CONCLUSION

This review consolidates current knowledge on the role of **bioactive biomaterials in delayed bone healing**, emphasizing their value as **biological enhancers of fracture repair rather than stand-alone solutions**. Across the synthesized evidence, bioactive glasses, calcium orthophosphate systems, composite scaffolds, and injectable

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biomaterials demonstrate the capacity to support bone regeneration when appropriately matched to the biological and mechanical context of the injury.

A central conclusion is that **successful outcomes in delayed bone healing remain fundamentally dependent on mechanical stability and infection control**. Bioactive biomaterials exert their greatest benefit once these prerequisites are met, acting to modulate the local microenvironment through osteoconductive architecture, surface bioactivity, and controlled degradation. Differences observed among biomaterial classes reflect not only intrinsic material properties, but also variability in clinical indications, defect characteristics, and application strategies.

Bioactive glass and composite scaffolds tend to show favorable healing profiles in contexts where biological stimulation and scaffold architecture are prioritized, while calcium phosphate systems remain indispensable due to their extensive clinical experience, versatility, and compatibility with standard trauma workflows. Injectable biomaterials offer important procedural advantages, though their outcomes are more sensitive to formulation choice and indication, underscoring the need for careful selection in delayed healing scenarios.

From an educational and clinical perspective, particularly within trauma systems in Mexico, Colombia, and Ecuador, the findings support a **context-driven approach to biomaterial selection**. Rather than identifying a universally superior material, effective management of delayed bone healing relies on integrating biomaterial science with fracture biology, biomechanics, and patient-specific factors.

In conclusion, bioactive biomaterials represent a critical component of modern traumatology, providing biologically informed support to fracture repair when intrinsic healing is compromised. Their optimal use requires not only knowledge of material properties, but also sound clinical judgment and adherence to fundamental orthopedic principles. This integrative perspective offers a practical and evidence-based framework for both clinical decision-making and the training of future specialists in trauma and orthopedic care.

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