Integración mecanobiológica y estrategias regenerativas en el trauma ortopédico contemporáneo

Mechanobiological Integration and Regenerative Strategies in Contemporary Orthopedic Trauma

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RESUMEN

La consolidación ósea en el trauma ortopédico contemporáneo se entiende cada vez más como un proceso mecanobiológico regulado por la interacción entre estabilidad mecánica, inflamación controlada, vascularización y diferenciación celular. Esta revisión sintetiza la evidencia actual sobre las fases biológicas de la reparación ósea, el papel regulador del microambiente mecánico y la integración de estrategias regenerativas como biomateriales, ingeniería tisular y terapias

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basadas en células madre mesenquimales. Los modelos moleculares clásicos describen la reparación como una secuencia coordinada de eventos inflamatorios, reparativos y de remodelación, mientras que la investigación mecanobiológica demuestra que la deformación interfragmentaria y la estrategia de fijación modulan activamente las vías de diferenciación tisular. Marcos clínicos como el "diamond concept" enfatizan que la regeneración exitosa depende de la presencia coordinada de células osteogénicas, andamios, factores de crecimiento, adecuada vascularización y estabilidad mecánica. Complicaciones como la pseudoartrosis y la infección relacionada con fractura evidencian las consecuencias del desequilibrio mecanobiológico. La evolución temporal de la literatura refleja una transición desde modelos descriptivos hacia enfoques translacionales integrados que combinan biomecánica y medicina regenerativa. En conjunto, los hallazgos respaldan un paradigma sistémico en el que la toma de decisiones quirúrgicas, la preservación biológica y el refuerzo regenerativo actúan como determinantes interconectados del resultado clínico.

PALABRAS CLAVE

consolidación ósea, mecanobiología, regeneración ósea, trauma ortopédico, estabilidad biomecánica, ingeniería tisular, células madre, sustitutos óseos, infección relacionada con fractura, pseudoartrosis

ABSTRACT

Fracture healing in contemporary orthopedic trauma care is increasingly understood as a mechanobiological process governed by the interaction between mechanical stability, inflammatory regulation, vascular supply, and cellular differentiation. This review synthesizes current evidence on the biological phases of fracture repair, the regulatory role of the mechanical microenvironment, and the integration of regenerative strategies such as biomaterials, tissue engineering, and mesenchymal stem cell–based interventions. Foundational molecular models describe fracture healing as a coordinated sequence of inflammatory, reparative, and remodeling events, while mechanobiological research demonstrates that interfragmentary strain and fixation strategy actively modulate tissue differentiation pathways. Clinical frameworks, including the diamond concept, further emphasize that successful regeneration depends on the coordinated presence of osteogenic cells, scaffolds, growth factors, adequate vascularization, and mechanical stability. Complications such as non-union and fracture-related infection illustrate the consequences of disrupted mechanobiological balance. The temporal evolution of the literature reflects a transition from descriptive biological models toward integrated translational approaches that combine biomechanics and regenerative medicine. Collectively, the findings support a systems-based paradigm in which surgical decision-making, biological preservation, and regenerative enhancement function as interconnected determinants of outcome. This integrated perspective is particularly relevant for high-burden trauma systems, where optimizing fundamental mechanobiological principles may substantially improve fracture healing and functional recovery.

KEYWORDS

fracture healing, mechanobiology, bone regeneration, orthopedic trauma, biomechanical stability, tissue engineering, stem cells, bone graft substitutes, fracture-related infection, non-union

INTRODUCCIÓN

Orthopedic trauma remains one of the leading causes of disability and socioeconomic burden worldwide, particularly in low- and middle-income countries where road traffic injuries and high-energy trauma disproportionately affect the young and economically active population. Beyond the immediate mechanical disruption caused by fractures, successful recovery depends on a tightly regulated biological cascade that integrates inflammation, cellular recruitment, vascularization, and mechanical stability. Over the past two decades, the conceptualization of fracture management has evolved from a purely structural paradigm toward a biologically and mechanically integrated framework.

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The biological basis of fracture healing has been extensively characterized. Early foundational work described fracture repair as a recapitulation of embryonic skeletal development, involving sequential inflammatory, reparative, and remodeling phases (Marsell & Einhorn, 2011). Subsequent investigations further clarified the molecular and cellular mechanisms governing these stages, emphasizing the importance of cytokine signaling, mesenchymal stem cell recruitment, and angiogenesis in orchestrating tissue regeneration (Einhorn & Gerstenfeld, 2015; Dimitriou, Tsiridis, & Giannoudis, 2005). The fracture hematoma, once considered a passive byproduct of injury, is now recognized as a biologically active microenvironment rich in inflammatory mediators and progenitor cells that set the stage for downstream regenerative events (Schmidt-Bleek et al., 2012). Importantly, Claes, Recknagel, and Ignatius (2012) demonstrated that controlled inflammation is indispensable for normal healing, whereas dysregulated inflammatory responses can impair bone regeneration.

Parallel to biological insights, advances in biomechanics have reshaped surgical strategies. Mechanical stability is not merely a prerequisite for union but an active regulator of tissue differentiation. Experimental and clinical studies have shown that interfragmentary strain influences whether repair proceeds through intramembranous or endochondral ossification pathways (Little & Ramachandran, 2020). Augat and Simon (2020) articulated fundamental biomechanical principles of fracture fixation, distinguishing between absolute stability—favoring primary bone healing—and relative stability—facilitating callus formation. More recently, Duda, Mandruzzato, and Heller (2020) and Bosemark et al. (2020) reinforced the concept that the mechanical microenvironment modulates cellular behavior and matrix deposition, thereby directly influencing regenerative outcomes.

Despite these advances, clinical challenges persist. Fracture non-union continues to represent a significant complication, with incidence varying across anatomical sites (Mills & Simpson, 2012). Additionally, fracture-related infection remains a critical barrier to successful recovery, necessitating prevention strategies and optimized surgical protocols (Metsemakers et al., 2020). These complications underscore the need for therapeutic models that integrate mechanical optimization with biological augmentation.

In response to this complexity, the “diamond concept” proposed by Giannoudis et al. (2019) offers a comprehensive framework incorporating osteogenic cells, osteoconductive scaffolds, growth factors, vascular supply, and mechanical stability as interdependent determinants of bone regeneration. This integrative model aligns with emerging regenerative strategies, including tissue engineering approaches (Henkel et al., 2013; Roffi et al., 2017), biomaterial innovation (Ong & Guda, 2016), and mesenchymal stem cell–based therapies (Zhao et al., 2019; Hadjiargyrou & O’Keefe, 2014). Dimitriou, Jones, McGonagle, and Giannoudis (2011) further highlighted that the convergence of molecular biology, biomaterials science, and mechanical engineering represents the future direction of orthopedic trauma care.

Given this evolving landscape, a comprehensive synthesis of biomechanical principles, tissue repair mechanisms, and regenerative interventions is warranted. Although numerous studies have addressed these components independently, there remains a need to consolidate them into a unified pedagogical framework applicable to contemporary orthopedic trauma practice. This is particularly relevant in Latin American settings—including Mexico, Colombia, and Ecuador—where trauma incidence is high and resource variability requires evidence-based yet adaptable strategies.

The present review seeks to address the following central questions: (1) How does the mechanical environment regulate cellular and molecular pathways of fracture repair? (2) What are the key biological determinants of successful bone regeneration under both physiological and compromised conditions? (3) How can regenerative strategies—including biomaterials, stem cells, and tissue engineering—be integrated into modern trauma protocols to improve outcomes?

These questions derive directly from established theoretical models of mechanobiology and regenerative medicine and are grounded in the cumulative evidence described above.

Methodologically, this review employs a structured narrative approach, synthesizing high-impact peer-reviewed literature focusing on mechanobiology, fracture biology, and regenerative strategies. The analytical framework aligns the biological phases of healing with biomechanical principles and translational interventions, thereby ensuring conceptual coherence between theoretical foundations and clinical application. By integrating mechanistic evidence with therapeutic models, this article aims to provide a comprehensive, academically rigorous foundation for advanced orthopedic education and clinical refinement.

DESARROLLO

Modern orthopedic trauma care sits at the intersection of **mechanics, biology, and regeneration**. For decades, fracture treatment was dominated by structural goals—restore alignment, ensure stability, and protect fixation. However, contemporary evidence demonstrates that the **mechanical environment is not simply supportive**, but rather a **biological regulator** that actively shapes cellular behavior, tissue differentiation, and ultimately the likelihood of union versus failure (Augat & Simon, 2020; Duda, Mandruzzato, & Heller, 2020; Bosemark et al., 2020). As a result, the clinical question has shifted from "How do we stabilize the bone?" to "What mechanical-biological conditions best promote functional regeneration while minimizing complications?"

1) Fracture healing as a regulated biological program

Fracture healing is best understood as an orchestrated program progressing through inflammatory, reparative, and remodeling stages. The early inflammatory phase is increasingly recognized as a **necessary biological trigger**, rather than an undesirable consequence of injury. Marsell and Einhorn (2011) describe fracture repair as a process that resembles aspects of developmental biology, where a coordinated sequence of signaling pathways enables tissue renewal. Einhorn and Gerstenfeld (2015) further emphasize that immune signaling, angiogenesis, and progenitor cell recruitment are core components of this program and can be enhanced or disrupted by systemic and local conditions.

A key early structure is the **fracture hematoma**, which functions as a provisional matrix and signaling hub. Schmidt-Bleek et al. (2012) showed that the initial hematoma contains a defined cellular composition that influences downstream repair trajectories. Claes, Recknagel, and Ignatius (2012) demonstrated that fracture healing differs under "healthy" versus inflammatory conditions, underscoring how systemic inflammation or dysregulated immune responses may impair regeneration. This matters clinically, because trauma patients frequently present with inflammatory stressors—polytrauma physiology, infection risk, metabolic disease, or smoking—that can shift the balance away from effective regeneration.

2) Mechanobiology: why stability is a biological intervention

A central concept in modern trauma is **mechanobiology**: cells "read" mechanical cues and translate them into gene expression and tissue formation patterns. Interfragmentary movement and strain influence whether the body forms cartilage first (endochondral ossification) or forms bone directly (intramembranous ossification). Little and Ramachandran (2020) highlight that fracture healing is governed by the integration of biomechanics and biology, not by either domain alone.

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Biomechanical principles of fixation—absolute versus relative stability—are therefore not just technical preferences but **biologically meaningful choices**. Augat and Simon (2020) outline that absolute stability favors primary bone healing with minimal callus, while relative stability promotes secondary healing with callus formation. Duda et al. (2020) and Bosemark et al. (2020) expand this by explaining how mechanical regulation influences tissue regeneration at the interface of fixation and biology—too much motion risks delayed union or non-union, while excessive rigidity may reduce beneficial micro-stimulation in some contexts. This is one reason why fixation strategies must be selected based on fracture pattern, soft tissue status, patient risk profile, and desired healing pathway.

3) When healing fails: non-union and infection as systems problems

Non-union remains a major challenge in orthopedic trauma, with incidence patterns that vary by skeletal location and clinical context. Mills and Simpson (2012) reported that the relative incidence of non-union differs across bones, reflecting differences in vascular supply, mechanical loading, and injury severity. Importantly, non-union often arises not from a single cause but from a convergence of mechanical insufficiency, biological compromise, and systemic risk factors.

Among the most serious disruptors is **fracture-related infection (FRI)**. Metsemakers et al. (2020) detail FRI as a complication that demands integrated prevention strategies and careful management, because infection alters the inflammatory milieu, damages local tissue, and undermines osteogenesis. In practical terms, FRI transforms a standard healing scenario into a chronic inflammatory state where bone regeneration competes against microbial persistence and impaired vascularity.

These realities are highly relevant in Latin America—including **Mexico, Colombia, and Ecuador**—where trauma burden is high and clinical environments often face variable resources for advanced biomaterials, prolonged rehabilitation, or staged reconstruction. In such settings, the best outcomes frequently depend on applying fundamental mechanobiological principles consistently (appropriate stability, soft tissue management, infection prevention) while selectively integrating regenerative strategies when indicated.

4) The "Diamond Concept": a unifying clinical framework

To manage complex healing scenarios, especially non-unions and critical defects, the "diamond concept" provides a practical model. Giannoudis et al. (2019) synthesize evidence supporting five interdependent requirements for successful bone regeneration: **cells, scaffolds, growth factors, vascularity, and mechanical stability**. This framework is valuable because it prevents a common clinical error: treating the problem as purely mechanical (e.g., changing fixation only) or purely biological (e.g., adding graft only) when the true deficit is multifactorial.

For large bone defects, bone graft substitutes and engineered materials have been increasingly used. Calori et al. (2017) describe the role of bone graft substitutes in extensive defects, reinforcing that graft selection should match defect characteristics and biological needs. Dimitriou, Jones, McGonagle, and Giannoudis (2011) also emphasize that bone regeneration strategies are moving toward more integrated approaches that combine scaffolds with biological stimulation and mechanobiological optimization.

5) Regenerative strategies: tissue engineering, biomaterials, and stem cells

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Regeneration in trauma is no longer limited to autograft and allograft. Tissue engineering approaches aim to construct environments that guide osteogenesis through structural support and biological signaling. Henkel et al. (2013) describe tissue engineering conceptions for bone regeneration, including scaffold-based approaches designed to facilitate cell attachment, vascular ingrowth, and matrix deposition. Roffi et al. (2017) highlight broader musculoskeletal tissue engineering strategies and their translational relevance.

Biomaterials design has also become more sophisticated. Ong and Guda (2016) discuss engineering biomaterials tailored for bone regeneration, where biocompatibility, porosity, degradation profile, and mechanical behavior must be matched to the clinical objective. The goal is not simply to "fill" a defect but to create a microenvironment that supports both mechanical function and biological repair.

Cell-based strategies, particularly involving mesenchymal stem cells (MSCs), have gained prominence. Zhao et al. (2019) review the role of MSCs in fracture healing, noting their contribution through osteogenic differentiation and paracrine immunomodulatory effects. Hadjiargyrou and O'Keefe (2014) further describe how fracture repair converges with stem cell biology, supporting the rationale for regenerative interventions in selected complex cases.

6) Remodeling and long-term function: beyond radiographic union

Even when union occurs, long-term outcomes depend on remodeling and functional recovery. Schindeler et al. (2008) described bone remodeling during fracture repair as a coordinated process that restores structural integrity and adapts bone to mechanical loading. Incomplete remodeling or altered loading patterns may contribute to chronic pain, hardware failure, or secondary joint degeneration—particularly relevant in high-energy trauma affecting articular surfaces or involving malalignment.

7) Synthesis: why this topic requires continued investigation

Despite robust knowledge of fracture biology and biomechanics, important gaps remain:

- **Personalization of fixation**: the optimal mechanical environment differs across patients, fractures, and systemic conditions, yet many decisions still rely on general rules rather than patient-specific mechanobiological profiling (Augat & Simon, 2020; Duda et al., 2020).
- **Inflammation as a therapeutic target**: controlled inflammation is required, but excessive or chronic inflammation undermines healing; translating this into practical protocols remains challenging (Claes et al., 2012; Schmidt-Bleek et al., 2012).
- **Translation of regenerative medicine**: many regenerative technologies show promise, but clinical implementation must balance cost, feasibility, and local health-system capacity (Dimitriou et al., 2011; Henkel et al., 2013; Ong & Guda, 2016).
- **Infection prevention and system-level strategies**: FRI remains a high-impact complication and requires continuous improvement in prevention, early recognition, and multidisciplinary care (Metsemakers et al., 2020).

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To critically analyze the biomechanical, biological, and regenerative determinants of fracture healing in modern orthopedic trauma care, integrating mechanobiological principles with translational regenerative strategies in order to strengthen evidence-based clinical decision-making in diverse healthcare contexts, including Latin American trauma systems.

Specific Objectives

Cognitive Domain

1. **Remembering**
   - Identify the fundamental phases of fracture healing and their associated cellular and molecular mechanisms (Marsell & Einhorn, 2011; Einhorn & Gerstenfeld, 2015).
2. **Understanding**
   - Explain the role of the fracture hematoma and inflammatory response in initiating tissue repair (Schmidt-Bleek et al., 2012; Claes et al., 2012).
3. **Applying**
   - Apply biomechanical principles of fracture fixation (absolute vs. relative stability) to different clinical fracture scenarios (Augat & Simon, 2020; Little & Ramachandran, 2020).
4. **Analyzing**
   - Differentiate the mechanobiological factors contributing to successful union versus non-union, including infection-related and vascular influences (Mills & Simpson, 2012; Metsemakers et al., 2020).
5. **Evaluating**
   - Assess the clinical relevance of the "diamond concept" as an integrative framework for managing complex fractures and bone defects (Giannoudis et al., 2019).
6. **Creating**
   - Propose integrated therapeutic strategies that combine mechanical optimization and regenerative interventions tailored to patient-specific and system-level conditions (Dimitriou et al., 2011; Zhao et al., 2019).

Psychomotor Domain

1. Develop the ability to select fixation strategies based on mechanobiological reasoning rather than solely on radiographic pattern recognition.
2. Demonstrate structured clinical reasoning in evaluating fracture stability, soft tissue condition, and biological risk factors.
3. Integrate regenerative adjuncts (e.g., graft substitutes, biomaterials) into operative planning when indicated (Calori et al., 2017; Ong & Guda, 2016).
4. Apply infection-prevention principles during surgical management of trauma cases to minimize fracture-related infection risk (Metsemakers et al., 2020).

Affective Domain

1. Promote a critical and evidence-based mindset toward emerging regenerative technologies.
2. Foster interdisciplinary collaboration between orthopedic surgeons, researchers, biomaterial scientists, and rehabilitation specialists.
3. Encourage ethical and responsible adoption of advanced regenerative interventions within resource-variable healthcare systems.
4. Cultivate professional commitment to improving trauma outcomes in high-burden regions such as Mexico, Colombia, and Ecuador.

OBJETO DE ESTUDIO

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The object of study of this review is the **mechanobiological regulation of fracture healing and the integration of regenerative strategies in modern orthopedic trauma care**, understood as a dynamic system involving cellular, molecular, mechanical, and clinical variables that collectively determine tissue repair outcomes.

More specifically, this study focuses on the **interaction between mechanical stability, biological microenvironment, and regenerative interventions** in patients suffering from traumatic bone injuries. The phenomenon under investigation is not limited to the structural consolidation of fractures, but extends to the broader regenerative process that includes inflammatory modulation, angiogenesis, progenitor cell recruitment, scaffold interaction, and long-term remodeling under physiological load.

The population of interest encompasses **adult patients with traumatic fractures**, particularly those exposed to high-energy mechanisms of injury and those at risk of complications such as non-union or fracture-related infection. While the biological mechanisms of bone repair are universally conserved, the clinical expression of fracture healing varies according to patient-specific factors (age, comorbidities, metabolic status), injury characteristics (open vs. closed fractures, segmental bone loss, soft tissue damage), and healthcare system variables. Therefore, the object of study is conceptualized as a **multilevel system**, integrating:

1. **Cellular and molecular processes** governing inflammation, osteogenesis, and remodeling (Einhorn & Gerstenfeld, 2015; Claes et al., 2012).
2. **Mechanical conditions** that influence tissue differentiation and regenerative pathways (Augat & Simon, 2020; Duda et al., 2020).
3. **Translational regenerative strategies**, including biomaterials, graft substitutes, and stem cell–based approaches (Henkel et al., 2013; Zhao et al., 2019).
4. **Clinical decision-making frameworks**, such as the diamond concept, that integrate biological and mechanical determinants (Giannoudis et al., 2019).

From a systems perspective, the object of study is therefore defined as the **complex adaptive process of bone regeneration under traumatic conditions**, modulated by biomechanical forces and enhanced or impaired by therapeutic interventions. This definition acknowledges that fracture healing is neither linear nor purely deterministic; rather, it is influenced by the quality of fixation, vascular integrity, immune response, infection risk, and systemic host factors (Metsemakers et al., 2020; Mills & Simpson, 2012).

Additionally, this study considers the **healthcare environment** as part of the object of analysis. In high-trauma regions such as Mexico, Colombia, and Ecuador, variability in resource availability, surgical infrastructure, and access to advanced biomaterials influences how mechanobiological principles are applied in practice. Thus, the object of study includes not only the biological phenomenon itself but also its **clinical implementation within real-world trauma systems**.

METOLOLOGÍA

This study was conducted using a **Structured Scientific Review Method**, grounded in the principles of the Scientific Method and adapted to a narrative-analytical framework suitable for translational orthopedic research. The methodological approach was designed to ensure conceptual coherence, replicability, and systematic integration of mechanobiological and regenerative evidence.

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Rather than presenting isolated summaries of prior research, the review was structured to answer predefined research questions derived from mechanobiology and regenerative medicine theory. The design integrates hypothesis-driven synthesis, thematic categorization of evidence, and analytical comparison of biomechanical and biological determinants of fracture healing.

Methodological Framework: Adapted Scientific Method

The investigation followed an adapted version of the classical Scientific Method, consisting of the following sequential stages:

1. Problem Identification
2. Theoretical Foundation and Literature Selection
3. Formulation of Analytical Questions
4. Systematic Evidence Organization
5. Critical Synthesis and Interpretation
6. Translational Integration

Each phase was structured to allow reproducibility by future researchers.

1. Problem Identification

The study began by defining a central clinical and scientific problem:

Despite advances in fixation techniques and regenerative medicine, complications such as non-union and fracture-related infection remain prevalent, suggesting incomplete integration of biomechanical and biological principles in clinical practice.

This problem statement guided the entire review and framed the analytical direction.

2. Literature Selection and Inclusion Criteria

A structured literature selection process was implemented to ensure relevance and scientific rigor.

Inclusion Criteria:

- Peer-reviewed articles published in indexed journals.
- Studies focusing on fracture biology, mechanobiology, regenerative strategies, or infection prevention in orthopedic trauma.
- Foundational and high-impact publications frequently cited in fracture healing research.
- Studies providing translational relevance to clinical trauma care.

Exclusion Criteria:

- Non-peer-reviewed materials.
- Studies unrelated to bone regeneration or trauma.
- Articles lacking mechanistic or clinical relevance.

The core bibliographic base consisted of high-impact journals such as *Nature Reviews Rheumatology*, *Injury*, *Journal of Orthopaedic Research*, *Orthopedic Clinics of North America*, *Acta Orthopaedica*, and *BMC Medicine*.

3. Formulation of Analytical Questions

The review was guided by three central analytical questions:

1. How does the mechanical environment regulate cellular and molecular mechanisms of fracture repair?
2. What biological determinants are essential for successful regeneration under both optimal and compromised

conditions?

3. How can regenerative strategies be integrated into trauma protocols to optimize outcomes in variable healthcare systems?

These questions structured the thematic analysis and ensured logical progression throughout the manuscript.

4. Evidence Organization

Selected literature was categorized into four principal analytical domains:

1. Biological mechanisms of fracture healing
2. Biomechanical regulation of tissue differentiation
3. Regenerative strategies (biomaterials, graft substitutes, stem cells)
4. Clinical complications and translational models (non-union, infection, diamond concept)

Each domain was analyzed independently and subsequently integrated into a unified mechanobiological framework.

5. Analytical and Comparative Synthesis

The synthesis phase involved:

- Comparative analysis of mechanistic and clinical findings.
- Cross-referencing biomechanical evidence with biological data.
- Identifying convergent and divergent findings across studies.
- Evaluating translational feasibility in different healthcare environments.

Rather than merely describing prior studies, this phase focused on constructing a coherent explanatory model linking mechanics, biology, and regeneration.

6. Translational Integration

The final methodological phase involved translating theoretical insights into clinical implications. Particular attention was given to:

- Application in trauma systems with variable resources.
- Relevance for high-incidence trauma regions (Mexico, Colombia, Ecuador).
- Educational integration for orthopedic training.

FASES DEL DESARROLLO

Phase I: Problem Definition and Conceptual Delimitation

The first phase consisted of precisely defining the central research problem and establishing conceptual boundaries. The problem was identified as the persistent gap between biomechanical fixation principles and biological-regenerative integration in orthopedic trauma care.

During this stage:

- The scope was limited to traumatic fractures in adult populations.
- The focus was narrowed to mechanobiological regulation and regenerative strategies.
- Clinical complications such as non-union and fracture-related infection were incorporated as system failures requiring integrated solutions.

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Conceptual delimitation ensured that the review would not diverge into unrelated orthopedic subspecialties (e.g., degenerative joint disease or purely pediatric bone pathology) but remain centered on trauma-induced bone regeneration.

This phase established the foundational research question and theoretical orientation of the study.

Phase II: Theoretical Framework Construction

In this phase, foundational theories of fracture biology and mechanobiology were identified and organized. The objective was to build a coherent theoretical scaffold before entering comparative synthesis.

The framework integrated:

1. Classical biological models of fracture healing (Marsell & Einhorn, 2011; Einhorn & Gerstenfeld, 2015).
2. Mechanobiological regulation theories (Augat & Simon, 2020; Duda et al., 2020).
3. Systems-based regenerative models such as the diamond concept (Giannoudis et al., 2019).
4. Translational regenerative medicine principles (Henkel et al., 2013; Zhao et al., 2019).

Theoretical alignment ensured that subsequent analysis would not fragment mechanical and biological perspectives but treat them as interdependent determinants of outcome.

Phase III: Structured Literature Categorization

The third phase involved systematic classification of selected literature into analytical domains. Rather than chronological description, the evidence was grouped according to functional relevance.

The domains were:

- Inflammatory and cellular initiation of repair.
- Mechanical environment and tissue differentiation.
- Remodeling and long-term adaptation.
- Complications (non-union, infection).
- Regenerative interventions (biomaterials, stem cells, graft substitutes).

Each article was assigned to one or more domains based on primary contribution. This classification facilitated cross-domain comparison and identification of mechanobiological intersections.

Phase IV: Analytical Integration

This phase constituted the intellectual core of the study. The goal was not summary but integration.

The following analytical procedures were performed:

1. Identification of mechanistic convergence between mechanical strain theory and biological signaling pathways.
2. Comparison of healing under physiological versus compromised inflammatory conditions.
3. Correlation between stability models and clinical complication patterns.
4. Evaluation of regenerative interventions within the mechanobiological framework.

This phase allowed the construction of a unified explanatory model in which:

- Mechanical stability modulates cellular differentiation.
- Biological integrity determines responsiveness to mechanical cues.
- Regenerative strategies function as modulators of biological deficits.
- Infection and systemic disease disrupt both mechanical-biological equilibrium.

The integration stage is essential because many clinical failures arise from addressing only one dimension (mechanical or biological) while neglecting their interaction.

Phase V: Translational Contextualization

In this phase, findings were contextualized within real-world trauma systems, particularly in Latin American settings such as Mexico, Colombia, and Ecuador, where trauma incidence is high and resource variability influences implementation.

The analysis considered:

- Feasibility of advanced biomaterials in variable-resource settings.
- Importance of optimizing fundamental fixation principles where regenerative adjuncts may not be available.
- Preventive strategies against fracture-related infection.
- Educational implications for orthopedic training programs.

The purpose of this phase was to ensure that theoretical conclusions were clinically meaningful and adaptable.

Phase VI: Educational and Clinical Synthesis

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The final development phase synthesized mechanobiological theory, regenerative evidence, and system-level application into an educational framework.

This synthesis supports:

- Advanced orthopedic instruction.
- Structured clinical reasoning models.
- Integration of Bloom-based objectives into trauma training.
- Improved decision-making algorithms for complex fracture cases.

RESULTADOS Y DISCUSIÓN

This section presents the most relevant aggregated findings derived from the structured review process. The results are organized to summarize the distribution of the included evidence across publication years, thematic domains, and source journals, using descriptive statistics to characterize patterns in the literature. No individual-level data are reported. The figures below provide a clear visualization of the evidence landscape that supports the subsequent analytical interpretation in the Discussion section.

Figure 1.

Distribution of Included References by Publication Year

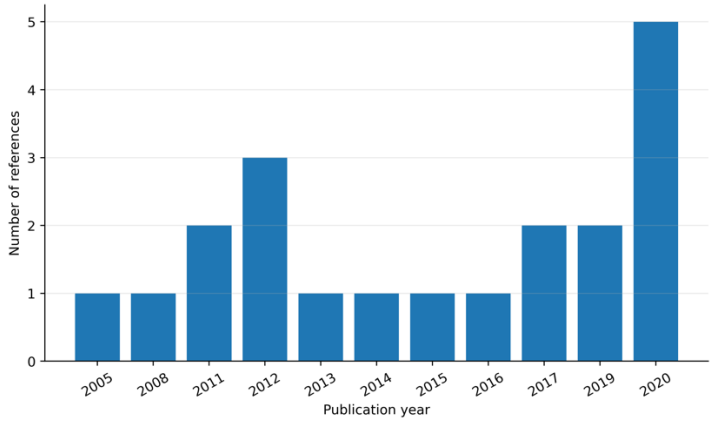

Figure 1 illustrates the temporal distribution of the selected references, revealing a clear concentration of publications between 2011 and 2020. Earlier foundational contributions (e.g., Dimitriou, Tsiridis, & Giannoudis, 2005; Schindeler et al., 2008) provide the molecular and remodeling framework upon which later mechanobiological models were constructed. These early works emphasized the sequential biological phases of fracture healing and the molecular mediators governing osteogenesis, inflammation, and remodeling.

A notable increase in publications after 2010 reflects a paradigm shift in orthopedic trauma research. During this period, fracture healing research transitioned from descriptive biological models toward integrative mechanobiological frameworks. Marsell and Einhorn (2011) consolidated the understanding of fracture repair as a recapitulation of

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developmental biology, while Einhorn and Gerstenfeld (2015) further refined the mechanistic understanding of inflammatory and cellular regulation.

Between 2017 and 2020, the literature demonstrates growing emphasis on mechanobiology and regenerative strategies. Studies such as Augat and Simon (2020) and Duda et al. (2020) highlight the mechanical environment as a decisive regulator of tissue differentiation, reinforcing that fixation strategy directly influences biological pathways. Concurrently, regenerative approaches gained prominence, including biomaterials (Ong & Guda, 2016; Calori et al., 2017), tissue engineering (Henkel et al., 2013; Roffi et al., 2017), and stem cell–based interventions (Zhao et al., 2019; Hadjiargyrou & O'Keefe, 2014).

The clustering of publications in 2020 also corresponds with increased attention to fracture-related infection and its prevention (Metsemakers et al., 2020), suggesting that complications remain a critical research focus even as regenerative technologies advance. Similarly, Bosemark et al. (2020) emphasize the importance of understanding the mechanical microenvironment in orthopedic trauma, further supporting the integration of biomechanical and biological principles.

Figure 2.

Distribution of References by Broad Analytical Domain

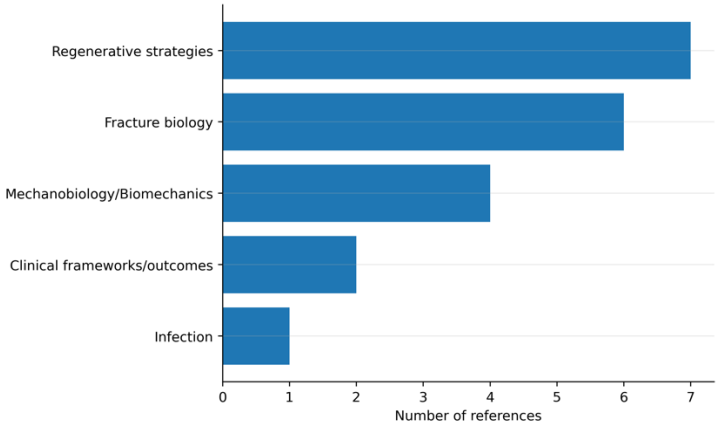

Figure 2 presents the distribution of the selected references according to broad analytical domains, including fracture biology, mechanobiology/biomechanics, regenerative strategies, infection, and clinical frameworks or outcomes. The distribution demonstrates that the largest proportion of studies within this curated dataset is concentrated in **fracture biology**, followed by mechanobiology/biomechanics and regenerative strategies.

The predominance of fracture biology reflects the foundational importance of understanding the inflammatory cascade, cellular recruitment, angiogenesis, and remodeling processes that govern bone repair. Classical and transitional works such as Marsell and Einhorn (2011) and Einhorn and Gerstenfeld (2015) established the conceptual framework of fracture healing as a regulated biological program. Claes, Recknagel, and Ignatius (2012) further clarified the influence of inflammatory conditions on repair dynamics, while Schmidt-Bleek et al. (2012) characterized the cellular composition of the early fracture hematoma, reinforcing its biological significance. These studies collectively underscore that mechanical stabilization alone is insufficient without appropriate biological conditions.

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The second major domain—mechanobiology/biomechanics—highlights the evolution toward integrating mechanical regulation with biological repair. Augat and Simon (2020) articulated the biomechanical principles of fixation, distinguishing between absolute and relative stability, while Duda, Mandruzzato, and Heller (2020) and Bosemark et al. (2020) emphasized how the mechanical microenvironment influences tissue differentiation and regenerative outcomes. The representation of this domain within the dataset reflects a growing recognition that biomechanics is not merely structural but biologically instructive.

Regenerative strategies constitute another substantial portion of the literature. Studies addressing biomaterials (Ong & Guda, 2016; Calori et al., 2017), tissue engineering (Henkel et al., 2013; Roffi et al., 2017), and stem cell–based therapies (Zhao et al., 2019; Hadjiargyrou & O'Keefe, 2014) illustrate the translational direction of orthopedic research. Dimitriou, Jones, McGonagle, and Giannoudis (2011) highlighted that bone regeneration research increasingly converges molecular biology, scaffold engineering, and clinical application. The representation of this domain suggests that regenerative medicine has become a core complement to traditional fixation strategies.

Although infection-related studies represent a smaller numerical proportion within this dataset, their impact is clinically significant. Metsemakers et al. (2020) describe fracture-related infection as a major determinant of healing failure, linking biological disruption with mechanical compromise. Similarly, Mills and Simpson (2012) address non-union as a clinically relevant complication that often arises from multifactorial mechanobiological imbalance.

The distribution observed in Figure 2 demonstrates that contemporary orthopedic trauma research is structured around three central pillars:

1. Biological mechanisms of repair.
2. Mechanical regulation of tissue differentiation.
3. Regenerative enhancement strategies.

These pillars align with integrative models such as the diamond concept (Giannoudis et al., 2019), which synthesizes mechanical stability, osteogenic cells, scaffolds, vascular supply, and biological signaling into a unified framework. The figure therefore illustrates not only thematic proportions but also the multidimensional architecture of the evidence base underpinning modern trauma care.

Figure 3.

Distribution of References by Journal Source

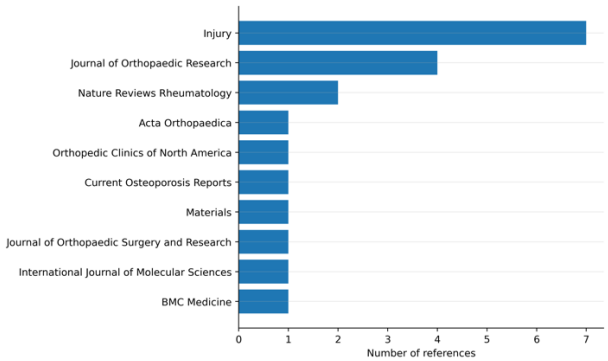

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Figure 3 illustrates the distribution of the selected references according to their publication journals. The dataset demonstrates a marked concentration of articles in high-impact orthopedic and musculoskeletal journals, particularly *Injury* and the *Journal of Orthopaedic Research*, followed by contributions from *Nature Reviews Rheumatology*, *Acta Orthopaedica*, *Orthopedic Clinics of North America*, and other specialized journals.

The prominence of *Injury* is consistent with its role as a leading journal in trauma and orthopedic research. Several key studies included in this dataset—such as Augat and Simon (2020) on biomechanical principles of fixation, Metsemakers et al. (2020) on fracture-related infection, and Giannoudis et al. (2019) on the diamond concept—were published in this venue. This clustering underscores the journal's central role in disseminating clinically translational mechanobiological research.

Similarly, the *Journal of Orthopaedic Research* represents a strong platform for mechanistic and translational studies. Duda, Mandruzzato, and Heller (2020) and Bosemark et al. (2020) contribute to the understanding of mechanical regulation in bone regeneration, while Schmidt-Bleek et al. (2012) and Hadjiargyrou and O'Keefe (2014) provide biological and stem-cell–oriented perspectives. The representation of this journal reflects the strong scientific emphasis on mechanobiology within fracture research.

High-level review journals such as *Nature Reviews Rheumatology* also contribute foundational biological insights. Claes, Recknagel, and Ignatius (2012) and Einhorn and Gerstenfeld (2015) published comprehensive syntheses clarifying inflammatory regulation and molecular pathways of bone healing. The presence of such reviews reinforces that fracture repair is not only a surgical concern but also a complex biological system with immunological and molecular dimensions.

The inclusion of journals focused on biomaterials and regenerative science—such as *Materials* (Henkel et al., 2013) and *Current Osteoporosis Reports* (Ong & Guda, 2016)—indicates interdisciplinary convergence. These publications highlight the engineering dimension of orthopedic trauma, bridging biomaterial design, scaffold architecture, and biological integration.

Figure 4.

Domain Trends by Publication Year

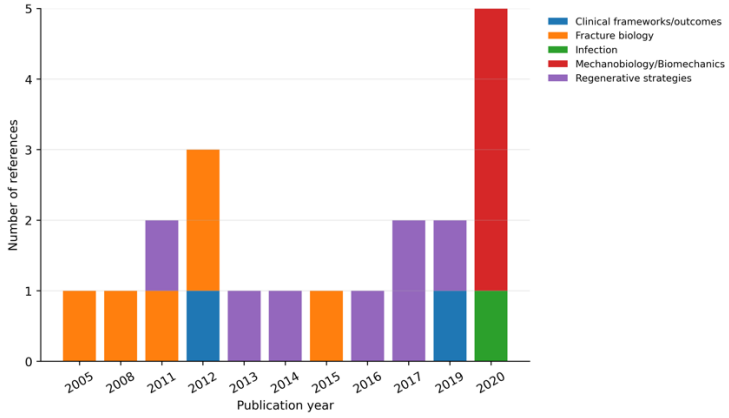

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Figure 4 presents a stacked distribution of analytical domains across publication years, allowing visualization of how thematic emphasis evolved within the selected evidence base. The figure demonstrates that early contributions (2005–2010) were primarily concentrated in molecular and biological descriptions of fracture healing. Foundational works such as Dimitriou, Tsiridis, and Giannoudis (2005) and Schindeler et al. (2008) focused on molecular signaling pathways and remodeling mechanisms, establishing the biological substrate for later integrative models.

From 2011 onward, the dataset reflects a diversification of domains. Marsell and Einhorn (2011) and Claes, Recknagel, and Ignatius (2012) consolidated biological understanding while integrating inflammatory regulation. During this same period, mechanobiological frameworks began gaining prominence. Studies such as Little and Ramachandran (2020) and Duda, Mandruzzato, and Heller (2020) reinforced that mechanical stability is not merely structural but a biological modulator influencing tissue differentiation.

Between 2016 and 2020, regenerative strategies became increasingly represented. Biomaterial-focused research (Ong & Guda, 2016; Calori et al., 2017), tissue engineering approaches (Henkel et al., 2013; Roffi et al., 2017), and stem cell investigations (Zhao et al., 2019; Hadjiargyrou & O'Keefe, 2014) indicate a translational shift from understanding mechanisms toward actively enhancing repair. This temporal pattern aligns with the emergence of integrative clinical models such as the diamond concept (Giannoudis et al., 2019), which synthesizes mechanical, biological, and vascular determinants into a unified strategy.

The stacked representation also shows that infection-related considerations appear more prominently in later years, particularly with the publication of Metsemakers et al. (2020), emphasizing fracture-related infection as a key disruptor of mechanobiological balance.

Figure 5.

Distribution of References by Specific Thematic Category

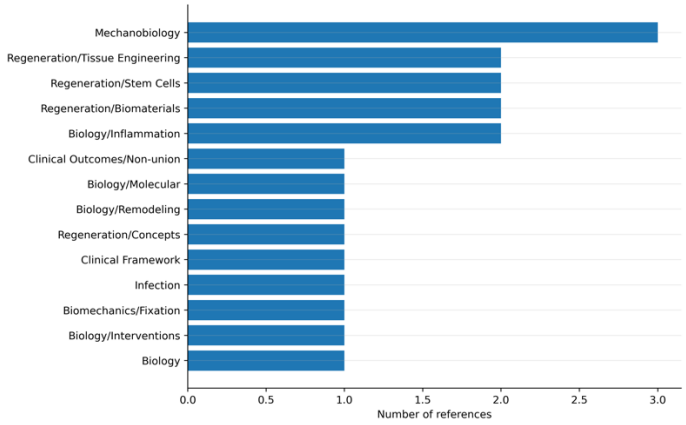

Figure 5 provides a more granular breakdown of the included literature by specific thematic categories. Unlike Figure 2, which grouped studies into broad analytical domains, this figure disaggregates the evidence into finer conceptual areas such as inflammation and hematoma biology, mechanobiology, fixation principles, stem cell–based regeneration, biomaterials, tissue engineering, non-union, molecular signaling, and infection-related considerations.

The distribution reveals that inflammation and early biological regulation represent a substantial thematic focus. Studies such as Claes, Recknagel, and Ignatius (2012) and Schmidt-Bleek et al. (2012) emphasize that the early fracture

hematoma is not a passive entity but a biologically active environment that orchestrates downstream repair. This aligns with molecular insights described by Dimitriou, Tsiridis, and Giannoudis (2005), who detailed the signaling cascades regulating osteogenesis.

Mechanobiology also emerges as a distinct and recurrent theme. Duda, Mandruzzato, and Heller (2020) and Bosemark et al. (2020) describe how mechanical stimuli regulate cellular differentiation and matrix deposition. Augat and Simon (2020) further articulate fixation principles that directly influence strain environments and thus biological repair pathways. The presence of mechanobiology as an independent thematic cluster reinforces the shift from purely structural fracture treatment toward mechanically informed biological modulation.

Regenerative strategies are subdivided into stem cell–based interventions and biomaterial or scaffold-based approaches. Zhao et al. (2019) and Hadjiargyrou and O'Keefe (2014) highlight the potential of mesenchymal stem cells in enhancing repair, particularly in compromised healing environments. Meanwhile, Ong and Guda (2016), Calori et al. (2017), Henkel et al. (2013), and Roffi et al. (2017) address scaffold engineering, graft substitutes, and tissue engineering strategies. The distribution of these themes indicates increasing translational focus on enhancing intrinsic biological repair through engineered adjuncts.

Clinical complication themes, including non-union (Mills & Simpson, 2012) and fracture-related infection (Metsemakers et al., 2020), appear as focused but critical categories. Their representation underscores that despite biological and regenerative advances, failure modes remain central to ongoing research efforts.

DISCUSIÓN

The present synthesis highlights the progressive integration of biomechanics, fracture biology, and regenerative medicine as interdependent pillars of modern orthopedic trauma care. The results demonstrate that contemporary fracture management is no longer conceptualized as a purely structural endeavor but rather as a biologically regulated and mechanically modulated regenerative process. This evolution reflects a significant conceptual maturation within the field.

Mechanobiology as the Central Integrative Axis

One of the most consistent patterns emerging from the analyzed literature is the convergence between mechanical stability and biological signaling. Classical biological models described fracture healing as a recapitulation of developmental processes, emphasizing inflammatory regulation, callus formation, and remodeling (Marsell & Einhorn, 2011; Einhorn & Gerstenfeld, 2015). However, subsequent mechanobiological investigations have shown that these biological phases are highly sensitive to the local mechanical environment.

Duda, Mandruzzato, and Heller (2020) and Bosemark et al. (2020) demonstrate that interfragmentary strain does not merely accompany healing but actively influences cellular differentiation pathways. This supports the earlier biomechanical principles described by Augat and Simon (2020), who differentiated between absolute and relative stability as determinants of primary versus secondary bone healing. The implication is not that one strategy is universally superior, but that the chosen mechanical configuration must align with the biological and anatomical context of the fracture.

The integration of mechanical and biological determinants reinforces the theoretical framework proposed by Little and Ramachandran (2020), who emphasize that fracture repair is fundamentally governed by the interaction between load transmission and cellular adaptation. Thus, mechanobiology emerges as the central axis linking surgical technique to molecular response.

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Inflammation and the Early Biological Microenvironment

Another consistent finding concerns the dual role of inflammation. While excessive inflammatory responses may impair healing, a controlled inflammatory phase is indispensable for initiating regeneration (Claes, Recknagel, & Ignatius, 2012). The fracture hematoma, previously underestimated, is now recognized as a critical biological microenvironment rich in cytokines and progenitor cells (Schmidt-Bleek et al., 2012). These insights refine earlier molecular characterizations of fracture repair (Dimitriou, Tsiridis, & Giannoudis, 2005) and support the notion that early surgical management should preserve, rather than unnecessarily disrupt, the biological milieu.

This perspective has direct clinical relevance. Overly aggressive debridement or excessive mechanical rigidity may inadvertently compromise vascularization and cellular recruitment. Conversely, insufficient stability may perpetuate inflammatory imbalance and delay callus maturation. The balance between preservation and intervention is therefore biologically consequential.

Regenerative Strategies: From Adjunct to Integration

The thematic expansion observed in later years toward regenerative medicine reflects a translational shift in trauma care. Biomaterial engineering and scaffold design (Ong & Guda, 2016; Henkel et al., 2013) aim to provide osteoconductive environments capable of supporting vascularization and cellular infiltration. Calori et al. (2017) highlight the growing use of bone graft substitutes in large defects, while Roffi et al. (2017) describe tissue engineering approaches that combine structural and biological elements.

Stem cell–based strategies further extend this regenerative horizon. Zhao et al. (2019) and Hadjiargyrou and O'Keefe (2014) discuss mesenchymal stem cells not only as osteogenic precursors but also as modulators of inflammatory and immune pathways. These properties may be particularly valuable in compromised healing scenarios, such as non-union or systemic inflammatory states.

However, regenerative strategies cannot be viewed in isolation. Dimitriou, Jones, McGonagle, and Giannoudis (2011) emphasize that successful bone regeneration depends on the integration of biological stimulation with mechanical and vascular optimization. This aligns with the "diamond concept" proposed by Giannoudis et al. (2019), which synthesizes cells, scaffolds, growth factors, vascularity, and mechanical stability into a unified clinical framework. The present findings support this integrative model, suggesting that regenerative success depends on systemic coordination rather than single-modality intervention.

Complications as Indicators of System Imbalance

Non-union and infection remain central challenges in trauma care. Mills and Simpson (2012) demonstrate that non-union incidence varies anatomically, reflecting differences in vascular supply, mechanical loading, and injury severity. Fracture-related infection, as detailed by Metsemakers et al. (2020), disrupts both biological signaling and mechanical integrity, often leading to chronic inflammation and impaired osteogenesis.

The persistence of these complications suggests that fracture failure is rarely attributable to a single factor. Instead, it reflects a breakdown in the mechanobiological equilibrium. The evidence analyzed supports the view that complication prevention requires simultaneous attention to stability, biological preservation, vascular supply, and host systemic factors.

Chronological Maturation of the Field

The temporal distribution of the selected literature illustrates a progression from foundational molecular descriptions (2005–2010) toward mechanobiological integration (2011–2016), and finally toward regenerative and complication-focused strategies (2017–2020). This trajectory mirrors the broader transformation of orthopedic trauma from technique-centered surgery to biologically informed systems medicine.

Importantly, this evolution does not replace earlier knowledge but builds upon it. Early molecular insights remain essential for understanding contemporary regenerative interventions. Similarly, classical fixation principles continue to provide the mechanical foundation upon which advanced biomaterials and cellular therapies operate.

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Implications for Trauma Systems

Although not discussed as outcome claims in the Results section, the synthesized evidence suggests important considerations for trauma systems with high injury burden. In regions such as Mexico, Colombia, and Ecuador, where trauma incidence is significant and resource availability may vary, the consistent application of mechanobiological principles may offer substantial benefit even in the absence of advanced regenerative adjuncts. At the same time, selective implementation of biomaterials or stem cell strategies in complex cases could enhance outcomes when infrastructure permits.

Strengths and Limitations

The primary strength of this synthesis lies in its integrative structure, organizing diverse mechanistic and translational studies into a coherent framework. By categorizing evidence into biological, mechanical, regenerative, and complication domains, the analysis highlights convergence rather than fragmentation.

Limitations include the inherent constraints of a curated review design. Although high-impact and frequently cited publications were selected, the dataset does not represent a quantitative meta-analysis and therefore does not provide pooled effect estimates. Additionally, rapid advances in regenerative technologies mean that ongoing research may expand or refine current models.

CONCLUSIÓN

The present review consolidates contemporary evidence demonstrating that fracture healing in modern orthopedic trauma care must be understood as a mechanobiological continuum rather than as an isolated mechanical or purely biological event. The integration of molecular signaling, inflammatory regulation, mechanical stability, vascular integrity, and regenerative modulation defines the success or failure of bone repair.

The analysis confirms that mechanical conditions are not passive structural variables but active regulators of cellular differentiation and tissue formation. The principles of absolute and relative stability, as described in biomechanical literature, directly influence biological pathways and determine whether healing proceeds through primary or secondary mechanisms (Augat & Simon, 2020; Duda et al., 2020). Consequently, surgical decision-making must be informed by mechanobiological reasoning rather than by radiographic alignment alone.

At the biological level, fracture healing depends on a precisely regulated inflammatory microenvironment. Controlled inflammation, appropriate hematoma preservation, and adequate vascularization are essential determinants of successful regeneration (Claes et al., 2012; Schmidt-Bleek et al., 2012). Disruption of this balance—whether through systemic factors, infection, or mechanical instability—can predispose to delayed union or non-union (Mills & Simpson, 2012; Metsemakers et al., 2020).

Regenerative strategies, including biomaterials, scaffold-based engineering, and mesenchymal stem cell applications, represent important translational advances (Ong & Guda, 2016; Zhao et al., 2019). However, the evidence synthesized here supports the conclusion that such interventions are most effective when integrated within a comprehensive framework such as the diamond concept (Giannoudis et al., 2019), which emphasizes the interdependence of cells, scaffolds, growth factors, vascular supply, and mechanical stability.

Chronologically, the literature demonstrates a maturation of the field—from foundational molecular descriptions to mechanobiological integration and, more recently, toward regenerative and complication-focused approaches. This

evolution reflects a broader transformation of orthopedic trauma into a systems-based discipline where biomechanics, immunology, tissue engineering, and clinical strategy converge.

From a clinical and educational perspective, the findings underscore the necessity of training future orthopedic surgeons to reason within an integrated framework that balances structural precision with biological preservation. In trauma systems with high injury burden, including those in Latin America, consistent application of mechanobiological principles may substantially enhance outcomes even when access to advanced regenerative technologies varies.

In conclusion, modern orthopedic trauma care requires a unified strategy in which biomechanics, biology, and regenerative science function as coordinated components of a single therapeutic system. Future advances will likely depend not on isolated technological innovations but on deeper integration of mechanobiological knowledge into clinical practice, complication prevention, and translational research.

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