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Hybrid therapies in orthopedics: a review of the potential of combining biomaterials and biologic therapies in fracture treatment

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ABSTRACT

Fracture healing is a complex physiological process, highly sensitive to the precise balance between mechanical stability and biological stimulation. Traditional orthopedic treatments, usually centered on mechanical fixation methods, rarely address such biological deficiencies as impaired vascularization or an insufficient osteogenic activity. In order to improve bone regeneration, this study examines the new idea of hybrid therapies, which combine biomaterials with biologic interventions including stem cells, growth hormones, and gene-based techniques. The integration of mechanical and biological strategies has been shown to accelerate osteogenesis, shorten healing time by up to half compared to conventional methods, and improve the quality and durability of bone repair. Clinical translation is limited to date by immune response challenges, manufacturing complexity, and high costs. Continued development in the areas of biocompatible materials, scalable production techniques, and cost-effective personalization may allow such innovative therapies to become a new standard in fracture management, offering accelerated recovery and enhanced patient outcomes.

Keywords: Hybrid therapy, Biomaterials, Stem cells, Growth factors, Bone healing

1. INTRODUCTION

Background and Clinical Relevance

Fracture healing remains one of the most complex physiological processes in the human body, involving a precisely coordinated cascade of cellular and molecular events. Although most fractures heal successfully with conservative or surgical management, delayed union and non-union still pose significant clinical challenges. This is due to the fact that traditional methods, which only use mechanical stabilization, are usually insufficient when there is a biological insufficiency at the fracture site, which might show up as inflammation, poor vascularization, or a general lack of adequate osteogenic activity. During the last decade, advances in tissue engineering and regenerative medicine have opened new perspectives for orthopedic treatment through biomaterials and biologic therapies. Given the considerable socioeconomic burden resulting from impaired bone regeneration, the clinical need to develop effective, biologically oriented interventions has assumed considerable and urgent priority. Recent advances in understanding the cellular and molecular regulation underlying the inflammatory and reparative phases of fracture healing have suggested some promising targets for osteoanabolic intervention. The integration of biomaterials with osteoinductive molecules holds potential to overcome the limitations of purely mechanical treatment strategies, particularly in challenging atrophic and infection-associated non-unions (Schlickewei et al., 2019).

Aim of the Study

The review's objective is to provide an overview of the state of hybrid therapies for treating fractures, including their mechanisms, effectiveness, and therapeutic prospects, as well as their existing drawbacks and prospective future developments. It also aims to give researchers and physicians a thorough picture that could direct choices and stimulate the creation of new therapeutic approaches.

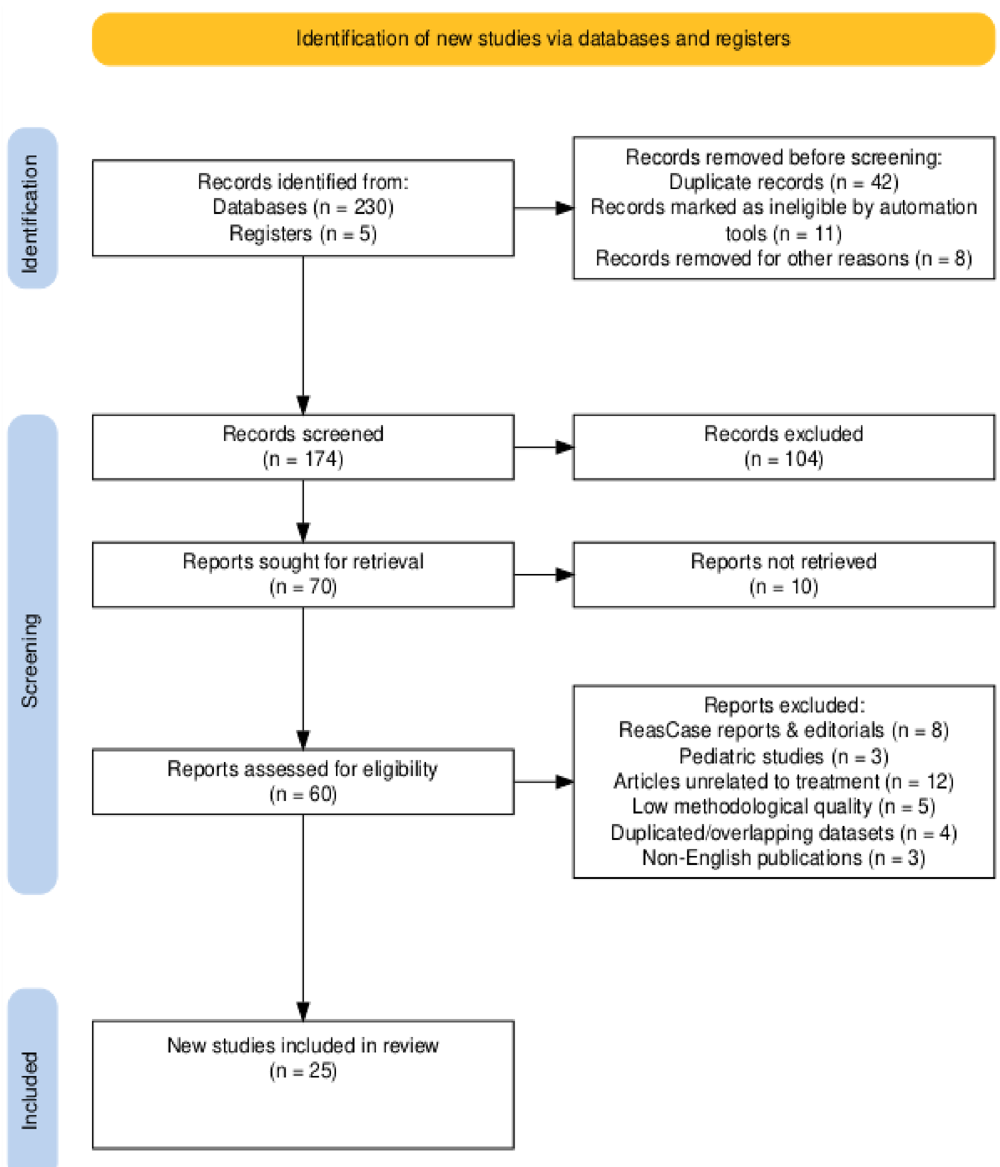

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process for this narrative review.

2. REVIEW METHODS

This narrative systematic review reviewed articles from January 2010 to June 2024, which were accessed through PubMed, Scopus, Web of Science, and Google Scholar. Keywords were terms that pertained to fracture healing, hybrid therapy, biomaterials, and biologic interventions, i.e., "mesenchymal stem cells," "growth factors," "biodegradable scaffolds," and "surface modification." Included studies were those that examined repair of fracture or bone regeneration in human subjects or pertinent preclinical models for the examination of combined or comparative use of biomaterials and biologic modalities. Included publications were original research articles, clinical trials, systematic reviews, and meta-analyses. Excluded were case reports, pediatric investigations, and non-orthopedic use. Following the exclusion of duplicates, 25 studies that met the specified criteria were qualitatively reviewed. The data extraction was based on study design, material or therapy type, and main outcomes of bone healing and osseointegration (Figure 1).

3. RESULTS & DISCUSSION

Types of Biomaterials in Osteosynthesis

Osteosynthesis is an internal bone fixation procedure that utilizes biomaterials to impart mechanical stability as well as encourage bone healing. The main biomaterials used in osteosynthesis are metals, ceramics, and biodegradable polymers. All of these materials possess different properties, both mechanical and biological, that determine their applications and limitations in orthopedic surgery (Schlickewei et al., 2019; Lackington and Thompson, 2020).

Metals

Titanium and stainless steel are the most used metals for osteosynthesis due to their mechanical properties. The titanium alloy is especially exceptional with regards to strength, biocompatibility, and corrosion resistance, and is therefore a trusted option for orthopedic bone fixation. The biocompatibility of titanium permits osseointegration, where the bone engulfs the implant without rejection. But titanium implants must be removed because of irritation or visibility of the skin after healing, particularly in maxillofacial surgery (Bowers and Anderson, 2024; Gareb et al., 2022; Marin and Lanzutti, 2024). The second most used metal is stainless steel, particularly in trauma surgery. Although it is less expensive than titanium, it corrodes readily and degrades. This, at times, leads to unwanted tissue reaction, which restricts its long-term application (Filip et al., 2022).

Ceramics

Hydroxyapatite and tricalcium phosphate (TCP) are among the ceramics applied to osteosynthesis. The bioceramics are highly appreciated for their osteoconductive nature, or their ability to offer a pathway for ingrowth of bone. Hydroxyapatite is a natural constituent of bone and is frequently employed as a coating material for metal implants to facilitate the integration of the implant with surrounding bone. Although they are biocompatible, ceramics are mechanically weak and hence cannot be used for load-bearing purposes (Filip et al., 2022).

Biodegradable polymers

Polylactide (PLA), polyglycolide (PGA), and their copolymers are being more widely used as biodegradable polymers in osteosynthesis. They degrade with time, obviating the need for a second operation to remove the implant, as usually happens with metal. PLA has special application where there is temporary support and also degradation products are metabolized to carbon dioxide and water by the body. But mechanical properties of biodegradable polymers are worse than metals, and they can cause inflammatory reactions (Gareb et al., 2022; Filip et al., 2022).

Mechanical and biological properties

Mechanical Properties: Stainless steel and titanium both have tensile strength, which is why they are used in weight-bearing devices. Ceramics are compressive but are brittle and fracture when subjected to tensile stress. Biodegradable polymers, although preferred because they are resorbable, are not strong and stiff enough for significant weight-bearing uses (Marin and Lanzutti, 2024). Biological Properties: Hydroxyapatite-coated ceramics and titanium alloys are highly biocompatible and promote osseointegration with minimal inflammatory response. Biodegradable polymers are designed to degrade from the body to avoid the development of long-term implantation problems. However, the degradation of certain polymers triggers local inflammation, and therefore selection of a suitable material is important (Gareb et al., 2022; Filip et al., 2022).

Role of stem cells in osteogenesis

Stem cells have an essential role to play in osteogenesis in the course of developing the body and in healing following injury. The most crucial in osteogenesis are mesenchymal stem cells (MSCs). They also come from umbilical cord blood, adipose tissue, bone marrow and dental pulp.

Induced pluripotent and gene-edited stem cells are also employed (Augustine et al., 2024). The differentiation of MSCs to osteoblasts involves several pathways, including the Wnt/β-catenin pathway and BMPs. The Wnt/β-catenin pathway also plays a very important role in the initiation of osteoblast proliferation and matrix mineralization, hence new bone formation (Augustine et al., 2024.; Wang et al., 2024). During research, MSCs are usually mixed with several biomaterials. Such substances are hydroxyapatite or collagen scaffolds, which serve to initiate bone defect regeneration and support processes of bone repair (Chen et al., 2022).

Growth factors (BMP, TGF-β) and their effects on fracture healing

Growth factors play a significant role in fracture healing. One of the most important factors is bone morphogenetic protein (BMP), which initiates the process of osteogenesis by affecting the differentiation of mesenchymal stem cells into osteoblasts (Garrison et al., 2010). Osteoblast proliferation and differentiation are encouraged by transforming growth factor beta (TGF-β). It also encourages mineralization and the deposition of extracellular matrix. It has been demonstrated that TGF-β and BMP-2 work in concert to promote osteoblast development and bone matrix mineralization (Table 1). Their combined use resulted in higher proliferation and differentiation of osteoblast precursor cells and increased mineralization (Asparuhova et al., 2018).

Table 1. Key biological agents in bone regeneration

Biological Agent	**Primary Functions & Mechanisms**	**Additional Benefits**
Mesenchymal Stem Cells (MSCs)	• Differentiate into osteoblasts via the Wnt/β-catenin pathway and BMPs. • Initiate osteoblast proliferation and matrix mineralization.	• Possess immunomodulatory properties that inhibit T-lymphocyte activity. • Secrete cytokines (IL-10, TGF-β) to shift inflammation to an anti-inflammatory state.
Bone Morphogenetic Protein (BMP)	• Initiates osteogenesis by driving the differentiation of MSCs into osteoblasts.	• Works synergistically with TGF-β to enhance mineralization.
Transforming Growth Factor Beta (TGF-β)	• Stimulates osteoblast proliferation, differentiation, and extracellular matrix deposition.	• Promotes angiogenesis (blood vessel formation) and modulates inflammation.

Gene therapies targeting bone tissue regeneration

The primary methods are ex vivo and in vivo treatments. When in vivo treatments are applied, the viral or non-viral vectors are applied directly to the site of bone damage, where they transduce local cells to initiate osteogenesis. Adenovirus is one of the most frequently utilized vectors that deliver a cDNA with the gene encoding BMP-2, Runx2 or VEGF. Non-viral methods most broadly used are cationic polymers and cationic liposomes. Hydrogels like alginate, fibrin or hyaluronic acid are also employed. Sonoporation is another recent technique utilizing ultrasound and microbubbles (Balmayor and Van Griensven, 2015).

Effect of immunomodulatory properties of mesenchymal stem cells on bone regeneration

Mesenchymal stem cells (MSCs) play an important role in bone regeneration due to their immunomodulatory properties. In the early stages of bone healing, MSCs can inhibit T-lymphocyte activity, preventing excessive inflammation that could delay regeneration. Their ability to secrete cytokines such as IL-10 and TGF-β promotes the transformation of the inflammatory response from pro-inflammatory to anti-inflammatory, which promotes osteoblast differentiation (Medhat et al., 2019).

Concept of hybrid therapies in orthopedics

Orthopedic hybrid treatments, in which biomaterials are blended with biological therapy, are a new trend in fracture treatment. These methods, by mixing mechanical and biological characteristics, create structural stabilization as well as stimulation of the healing mechanism, thereby ensuring better bone regeneration. Biomaterials contribute to structural stabilization, while stem cells and growth factors trigger bone regeneration. Through studies, it has been proven that the application of scaffolds (scaffolds) to stem cells can greatly accelerate the process of healing, and their combined effect is more beneficial to the patient than conventional techniques (Qi et al., 2021).

Scaffolds as carriers of cells and growth factors

Autogenous and allogenic grafts repair injured bones but have some shortcomings. Another option is the use of exogenous scaffolds as bone substitute (Wu et al., 2022). We can further categorize scaffolds as biological or synthetic. The latter includes beads, natural polymers and demineralized bone matrix, i.e., collagen sponge or gel foam. Synthetic scaffolds include porous metals, synthetic polymers and calcium phosphates (CaPs). Growth factor tissue engineering scaffolds are employed for enhancing bone regeneration by giving the bone cells the chance to adhere and proliferate (Zeng et al., 2018). Consistent with one research, porous silk scaffolds also possess the potential of acting as a vehicle to transport nucleated cells that can rehabilitate bone (Zhang et al., 2014).

Surface modifications of biomaterials for better osteointegration

Surface modifications of biomaterials are important for improving the osteointegration and antimicrobial properties of medical implants (Zhu et al., 2021). One publication studied the modification of Polyetheretherketone (PEEK) to improve osteointegration. Among the methods used were melt extrusion, laser ablation, sandblasting, sulfonation, plasma treatment and accelerated neutral atom beam. It has been demonstrated that these methods successfully encourage osteointegration while preserving mechanical qualities (Yu et al., 2022).

Efficacy and healing time

Fracture healing is significantly enhanced in hybrid treatments when compared to conventional treatments. Conventional treatments rely on mechanical stabilisation, while hybrid treatments also include the biological components of active stimulation for bone regeneration through the use of BMP-2 and BMP-7 bone morphogenic proteins. Cell proliferation and cell differentiation are enhanced in the area of fracture, which can heal faster than the conventional methods (Kaspiris et al., 2022; Marongiu et al., 2020). There is also an increased use of mesenchymal stem cells in treating fractures due to their differentiation capability into osteoblasts and chondrocytes to help in bone regeneration. Apparently, there is proof that hybrid treatments shorten the recovery time by 30–50% compared to the more conventional treatments for challenging and complicated fractures (Marongiu et al., 2020). Biomaterials coupled with biological therapies enhance not only the healing rate but also the quality of bone regeneration necessary for a fast return to physical functioning in patients. They are also less likely to need reoperation, experience less pain, and have a higher range of mobility in general long term (Kaspiris et al., 2022).

Technical and production challenges

Technical issues inherent in hybrid therapy include those of standardizing implant and biomaterial production. Every material used to create hybrid implants has to be made precisely, which is an expensive and time-consuming process. Technologies like 3D printing, which are used for scaffold personalization, also need to be developed, most notably biocompatibility and optimization with bone and soft tissue integration. Further, the production and certification of new biomaterials and their integration with cell-based therapies require sophisticated analysis technologies, making them difficult to produce and market (Brown et al., 2024; Xue et al., 2022).

Immune responses and infection risk

The most significant risk of hybrid therapies is immune reactions, that may result in inflammation, infection, or even implant rejection. Since foreign materials of any kind carry an inherent risk of infection, their use may result in infection, especially with new methods such as cell therapy and implants coated with antibacterial coatings. Even when these are applied using antibacterial coatings, the threat of infection by antibiotic-resistant bacteria still exists (Riester et al., 2021).

Costs and Accessibility of Advanced Therapies

One of the biggest drawbacks to hybrid therapies remains the cost. High production, clinical research, and personalization costs of implants make such therapies out of reach for the majority of patients. Most advanced technologies, including 3D printing or cell therapies, are available only in a limited number of centers, which also restricts their application in fracture treatment. The development of technology and reduction of production costs could improve the accessibility of these therapies, although this will require many years of further research and investment (Xue et al., 2022; Riester et al., 2021).

4. CONCLUSION

The article outlines advances in fracture healing and compares outdated and contemporary orthopaedic techniques. Outdated treatments such as cast immobilization and internal fixation are founded on mechanical stability, while newer technology is developed to maximize the biological environment of healing. This includes the use of growth factors, stem cell therapy, and bioactive scaffolds, all of which have been shown to promote healing and reduce complications such as nonunion, which occur in 10-15% of fractures treated surgically. Biomaterials form the basis of osteosynthesis and fall under metals, ceramics, and biodegradable polymers with varying properties and functions. Titanium and other similar metals are used because of their strength and biocompatibility but need to be removed post-healing. Ceramics, such as hydroxyapatite, are used to enhance bone ingrowth but are non-load-bearing. Biodegradable polymers eliminate the need for removal but produce an inflammatory response while degrading. Biologic therapy enhances fracture healing through the use of stem cells, growth factors, and gene therapy. Growth factors such as BMP and TGF-β and mesenchymal stem cells (MSCs) stimulate osteoblast differentiation, and MSC by virtue of its immunomodulatory function also diminishes inflammation that facilitates healing. Hybrid treatment as a blend of biomaterial and biological therapy provides better bone stability and ensures regeneration, which enhances the patient outcome, shortens healing time, and decreases the chance of reoperation. However, hybrid therapies are also faced with challenges including immune response risks, production complexity, and very high cost, limiting access. The availability of higher technologies, reducing costs, and more research is required for these innovative treatments to be mass-implemented.

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Informed consent

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Data and materials availability
All data associated with this study will be available based on reasonable request to the Corresponding Author.

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