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REVIEW ARTICLE

HYBRID THERAPIES IN ORTHOPEDICS: A REVIEW OF THE POTENTIAL OF COMBINING BIOMATERIALS AND BIOLOGIC THERAPIES IN FRACTURE TREATMENT

TERAPIE HYBRYDOWE W ORTOPEDII: PRZEGLĄD MOŻLIWOŚCI POŁĄCZENIA BIOMATERIAŁÓW I TERAPII BIOLOGICZNYCH W LECZENIU ZŁAMAŃ

Damian Pikor[1], Michał Azierski[2,3], Alicja Drelichowska[2], Konrad Talarek[4], Przemysław Ciszewski[2], Paweł Kurzawski[2], Mikołaj Hurła[1], Emilia Wiśniewska[2]
[1]Department and Clinic of Tropical and Parasitic Diseases, Poznań University of Medical Sciences, Poland
[2]Student Scientific Association of MedTech, Center for Remote Learning and Educational Effects Analysis, Faculty of Medical Sciences in Katowice, Silesian Medical University, Poland
[3]Student Scientific Association at the Department of Orthopaedics and Traumatology of the Musculoskeletal System, Faculty of Medical Sciences in Katowice, Silesian Medical University, Poland
[4]Student Scientific Association at the Department of Rehabilitation and Orthopedics, Medical University of Lublin, Poland

ABSTRACT
This article presents the current state of knowledge on hybrid therapies in orthopedics, combining biomaterials with biological therapies as a novel approach to treating bone fractures. Traditional methods, such as immobilization and internal fracture stabilization, are confronted with modern strategies that enrich the biological environment of the fracture site to promote osteogenesis. The article discusses in detail the mechanical and biological properties of biomaterials, including metals, ceramics and biodegradable polymers, and their role in osteosynthesis. The critical importance of stem cells, particularly mesenchymal stem cells (MSCs), and growth factors (BMPs and TGF-β), which promote bone regeneration through osteoblast differentiation and modulation of inflammatory processes, is highlighted. Hybrid therapies, in which scaffolds (scaffolds) serve as carriers for stem cells and growth factors, have shown high efficacy in accelerating healing and providing structural stability. Despite their many benefits, such as reduced recovery time and higher quality of regenerated bone tissue, hybrid therapies face significant challenges, including the risk of immune reactions, complexity of manufacturing processes and high cost, which limits their widespread clinical application. The article points to the need for further research into manufacturing technologies and cost reduction, which could make advanced therapies more accessible and more widely used in orthopedics.

Keywords: biomaterials, growth factors, stem cells, bone regeneration, osteosynthesis, scaffolds, hybrid therapies

STRESZCZENIE
W artykule przedstawiono aktualny stan wiedzy na temat terapii hybrydowych w ortopedii, łączących biomateriały z terapiami biologicznymi jako nowatorskie podejście do leczenia

Author responsible for correspondence:
Michał Azierski
Student Scientific Association of MedTech, Center for Remote Learning and Educational Effects Analysis, Faculty of Medical Sciences in Katowice, Silesian Medical University, Medyków 18, Katowice, Poland;
Email: michal.azierski@gmail.com
https://orcid.org/ 0009-0009-7247-2086

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złamań kostnych. Tradycyjne metody, takie jak unieruchomienie i wewnętrzne stabilizowanie złamań, skonfrontowano z nowoczesnymi strategiami, które wzbogacają środowisko biologiczne miejsca złamania, wspierając proces osteogenezy. W artykule szczegółowo omówiono właściwości mechaniczne i biologiczne biomateriałów, w tym metali, ceramiki oraz biodegradowalnych polimerów, i ich rolę w osteosyntezie. Podkreślono kluczowe znaczenie komórek macierzystych, szczególnie mezenchymalnych komórek macierzystych (MSC), oraz czynników wzrostu (BMP i TGF-β), które wspomagają regenerację kości poprzez różnicowanie osteoblastów i modulację procesów zapalnych. Terapie hybrydowe, w których scaffoldy (rusztowania) służą jako nośniki dla komórek macierzystych i czynników wzrostu, wykazują wysoką skuteczność w przyspieszaniu gojenia i zapewnieniu stabilności strukturalnej. Mimo wielu korzyści, takich jak skrócony czas rekonwalescencji i wyższa jakość regenerowanej tkanki kostnej, terapie hybrydowe napotykają na znaczące wyzwania, m.in. ryzyko reakcji immunologicznych, złożoność procesów produkcyjnych oraz wysokie koszty, co ogranicza ich szerokie zastosowanie kliniczne. Artykuł wskazuje na konieczność dalszych badań nad technologiami wytwarzania oraz redukcją kosztów, co mogłoby uczynić zaawansowane terapie bardziej dostępnymi i szerzej stosowanymi w ortopedii.

Słowa kluczowe: biomateriały, czynniki wzrostu, komórki macierzyste, osteosynteza, regeneracja kości, scaffoldy, terapie hybrydowe

Introduction

Effective fracture healing is a critical concern in orthopaedics, influencing patient outcomes and long-term limb functionality. The healing process involves complex biological and biomechanical mechanisms, such as intramembranous and endochondral ossification, essential for restoring bone integrity. Successful healing is characterized by timely bone union, achieving both anatomical alignment and functional recovery. However, fracture nonunion, defined as the failure to heal within an expected timeframe, affects 10–15% of surgically managed cases and presents significant clinical challenges. Traditional treatments, including cast immobilization and open reduction with internal fixation (ORIF), have been foundational for managing fractures, relying on mechanical stability to allow natural biological processes. Yet, advances in surgical techniques, especially minimally invasive approaches and regenerative therapies, have revolutionized fracture management by focusing on enhancing the biological environment at the fracture site through growth factors, stem cell therapy, and bioactive scaffolds, all of which can significantly improve healing rates.

To investigate these advancements, a comprehensive literature review was conducted in major databases, including PubMed, Scopus, and Web of Science, using keywords like "hybrid therapies in orthopedics," "biomaterials in fracture treatment," "biologic therapies in orthopedics," and "bone regeneration with biomaterials." The search was limited to publications from the last 15 years, ensuring the inclusion of the most current and pertinent data. Twenty-five highly relevant scientific articles were selected and thoroughly analyzed for their contributions to the development of hybrid theories in fracture healing. These theories propose that the interplay between mechanical stability and biological factors determines healing outcomes, advocating for a multifaceted approach tailored to individual patient characteristics, fracture type, and health status. This review contrasts traditional and modern therapeutic strategies, emphasizing the importance of a personalized approach in mitigating the risks of delayed union and nonunion while exploring the clinical potential of combining biomaterials with biological therapies in orthopaedics.

Types of biomaterials in osteosynthesis

Osteosynthesis, a procedure used for internal bone fixation, relies on biomaterials to provide mechanical support and facilitate bone healing. Biomaterials used in osteosynthesis can be broadly classified into three categories: metals, ceramics, and biodegradable polymers. Each material type has its unique mechanical and biological properties that dictate its applications and limitations in orthopedic surgery.

Metals

Titanium and stainless steel are among the most widely used metals for osteosynthesis due to their mechanical properties. Titanium alloys, in particular, offer high strength, biocompatibility, and corrosion resistance, making them a reliable choice for bone fixation in orthopedic. Titanium's biocompatibility allows for osseointegration, where the bone grows around the implant without rejection. However, titanium implants may require removal due to irritation or visibility under the skin after healing, especially in maxillofacial surgeries (Marin *et al.,* 2024; Filip *et al.,* 2022) Stainless steel is another commonly used metal, especially in trauma surgeries. While cheaper than titanium, it is more prone to corrosion and wear. This can sometimes result in adverse tissue reactions, which limits its long-term use (Augustine *et al.,* 2024).

Ceramics

Hydroxyapatite and tricalcium phosphate (TCP) are examples of ceramics used in osteosynthesis. These bioceramics are valued for their osteoconductive properties, meaning they support bone ingrowth. Hydroxyapatite, a naturally occurring component of bone, is often used to coat metal implants, enhancing the integration of the implant with the surrounding bone. TCP is biodegradable, and as it breaks down, it gets replaced by natural bone. Despite their biocompatibility, ceramics have limited mechanical strength, which makes them unsuitable for load-bearing applications (Augustine *et al.,* 2024).

Biodegradable polymers

Polylactide (PLA), polyglycolide (PGA), and their copolymers are increasingly being used as biodegradable materials in osteosynthesis. These materials degrade over time, eliminating the need for a secondary surgery to remove the implant, as is often required with metals. PLA is particularly useful in situations where temporary support is needed, and its degradation products are metabolized by the body into carbon dioxide and water. However, the mechanical strength of biodegradable polymers is generally lower than metals, and they may induce inflammatory responses (Marin *et al.,* 2024; Augustine *et al.,* 2024).

Mechanical and biological properties

Mechanical Properties: Metals such as titanium and stainless steel exhibit high tensile strength, making them suitable for load-bearing applications. Ceramics, while strong in compression, are brittle and can fracture under tensile stress. Biodegradable polymers, although advantageous due to their resorbable nature, lack the strength and stiffness required for major weight-bearing applications (Filip *et al.,* 2022). Biological Properties: Titanium alloys and hydroxyapatite-coated ceramics exhibit excellent biocompatibility, promoting osseointegration without causing significant inflammatory responses. Biodegradable polymers are designed to be absorbed by the body, reducing the risk of long-term complications associated with permanent implants. However, the degradation of some polymers can result in local inflammatory reactions, necessitating careful material selection (Marin *et al.,* 2024; Augustine *et al.,* 2024).

Role of stem cells in osteogenesis

Stem cells play a key role in the process of osteogenesis both during the development of the body and during regeneration after damage.The most important type in this process are mesenchymal stem cells (MSCs). Their source can be umbilical cord blood, adipose tissue, bone marrow and dental pulp. Induced pluripotent and genetically modified stem cells are also used (Wang *et al.,* 2024). The differentiation of MSCs into osteoblasts is controlled by multiple signaling pathways, such as the Wnt/β-catenin pathway and bone morphogenetic proteins (BMPs). In particular, the Wnt/β-catenin pathway plays a key role in promoting osteoblast proliferation and matrix mineralization, leading to new bone formation (Wang *et al.,* 2024; Chen *et al.,* 2022). In research, MSCs are often used in combination with various biomaterials. Examples of such materials include collagen or hydroxyapatite scaffolds, which promote regeneration of bone defects and accelerate repair processes (Garrison *et al.,* 2010).

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

Growth factors play a significant role in the phenomenon of 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 (Niu *et al.,* 2023) . Transforming growth factor beta (TGF-β) promotes osteoblast proliferation and differentiation. In addition, it promotes extracellular matrix deposition and mineralization. It has also been reported that TGF-β modulates inflammation and promotes angiogenesis, which further supports bone repair (Asparuhova *et al.,* 2018). TGF-β and BMP-2 have been shown to act in synergy to support osteoblast differentiation and bone matrix mineralization. Their joint application leads to improved proliferation and differentiation of osteoblast precursor cells, as well as increased mineralization (Balmayor *et al.,* 2015).

Gene therapies targeting bone tissue regeneration

The main approaches include in vivo and ex vivo therapies. For in vivo therapies, viral or non-viral vectors are directly inserted into the site of bone damage, where they transduce local cells to promote osteogenesis. One of the most commonly used vectors is adenovirus, which carries a cDNA containing the gene encoding BMP-2, Runx2 or VEGF. The most commonly used non-viral methods include cationic polymers and cationic liposomes. Hydrogels such as alginate, fibrin or hyaluronic acid are also used. Another innovative method is sonoporation, which uses ultrasound in combination with microbubbles (Medhat *et al.,* 2019).

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 (Qi *et al.,* 2021).

Concept of hybrid therapies in orthopedics

Hybrid therapies in orthopedics, combining biomaterials with biological therapies, are emerging as a promising approach in fracture treatment. These approaches aim to improve bone regeneration by integrating mechanical and biological components, which promotes both structural stabilization and activation of healing processes. Biomaterials are used for structural support, while stem cells and growth factors promote bone regeneration. Studies indicate that the combination of scaffolds (scaffolds) with stem cells can significantly accelerate the healing process, and their synergistic action can lead to better clinical outcomes compared to traditional methods (Wu *et al.,* 2022).

Scaffolds (scaffolds) as carriers of cells and growth factors

Autogenous and allogenic grafts are used to repair damaged bones, which have some limitations. Another solution is the usage of exogenous scaffolds as bone substitutes

(Zeng *et al.*, 2018). We can divide scaffolds into biological and synthetic. The former can be beads, natural polymers and demineralized bone matrix, such as collagen sponge or gel foam. Examples of synthetic scaffolds include porous metals, synthetic polymers and calcium phosphates (CaPs). Tissue engineering scaffolds with growth factor are used to improve bone regeneration by inducing bone cells to adhere and proliferate (Zhang *et al.*, 2014). One study showed that porous silk scaffolds can serve as a vehicle for nucleated cells to regenerate bone (Zhu *et al.*, 2021).

Surface modifications of biomaterials for better osteointegration

Surface modifications of biomaterials are important for improving the osteointegration and antimicrobial properties of medical implants (Yu *et al.*, 2022). 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. These techniques have been shown to effectively promote osteointegration while maintaining mechanical properties (Lackington *et al.*, 2020).

Efficacy and healing time

Studies have shown that hybrid therapies can significantly accelerate fracture healing compared to conventional methods. Traditional treatments focus on mechanical stabilisation, whereas hybrid therapies incorporate biological elements that actively promote bone regeneration, particularly through bone morphogenetic proteins (BMP-2 and BMP-7). Such therapies enhance the proliferation and differentiation of cells at the fracture site, allowing for faster healing compared to standard techniques (Kaspiris *et al.*, 2022; Marongiu *et al.*, 2020). Moreover, mesenchymal stem cells are increasingly being integrated into fracture treatment due to their ability to differentiate into osteoblasts and chondrocytes, further contributing to bone regeneration. Evidence suggests that hybrid therapies can reduce healing time by 30–50% compared to standard methods, particularly in the case of complex and challenging fractures (Marongiu *et al.*, 2020). The integration of biological therapies with biomaterials not only improves the speed of healing but also enhances the quality of bone repair, which is crucial for a faster return to physical function for patients (Kaspiris *et al.*, 2022; Marongiu *et al.*, 2020). Patients treated with modern hybrid therapies are less likely to require reoperation, experience lower levels of pain, and exhibit greater overall mobility in the long term (Kaspiris *et al.*, 2022).

Technical and production challenges

The technical challenges associated with hybrid therapies include difficulties in standardising the production of implants and biomaterials. Each material used in hybrid implants must be precisely manufactured, which is both time-consuming and costly. Processes such as 3D printing, employed for the customisation of scaffolds, still require refinement, particularly regarding biocompatibility and optimisation for integration with bone and surrounding tissues. Furthermore, the development and testing of novel biomaterials, as well as their combination with cell-based therapies, necessitate advanced analytical techniques, complicating their production and market introduction (Brown *et al.*, 2024; Xue *et al.*, 2022).

Immune responses and infection risk

One of the primary risks associated with hybrid therapies is immune reactions, which leads to inflammation, infection, or even implant rejection. The use of foreign materials, even those that are biocompatible, carries an inherent risk of infection, particularly when advanced techniques such as cell therapy or implants with antibacterial coatings are employed. Despite the use of antibacterial coatings, there is still a risk of infection with antibiotic-resistant bacteria (Riester *et al.*, 2021).

Costs and accessibility of advanced therapies

The cost of hybrid therapies represents one of the most significant barriers to their widespread use. High costs related to production, clinical research, and the personalisation of implants make these therapies inaccessible to the majority of patients. Additionally, the limited availability of advanced technologies such as 3D printing and cell therapies restricts their application in fracture treatment to specialised centres. 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).

Summary and conclusions

The article explores advancements in fracture healing, comparing traditional and modern approaches in orthopaedics. Traditional treatments, such as cast immobilisation and internal fixation, focus on mechanical stability, but newer methods aim to improve the biological environment for regeneration. This includes using growth factors, stem cell therapy, and bioactive scaffolds, all enhancing healing rates and addressing complications like nonunion, affecting 10–15% of fractures managed surgically. Biomaterials are central to osteosynthesis, classified into metals, ceramics, and biodegradable polymers, each with unique properties and applications. Metals like titanium are favoured for their strength and biocompatibility but can require removal post-healing. Ceramics, such as hydroxyapatite, promote bone ingrowth but lack load-bearing strength. Biodegradable polymers eliminate the need for removal but may cause inflammatory responses as they degrade. Biological therapies support fracture healing through stem cells, growth factors, and gene therapies. Mesenchymal stem cells (MSCs) aid in osteoblast differentiation, while growth factors like BMP and TGF-β enhance bone regeneration. MSCs with its immunomodulatory effects also reduce inflammation that supports healing. Hybrid therapies, combining biomaterials with biological treatments, present an enhanced bone stability and accelerate regeneration, improving patient outcomes, reducing healing time, and lessening the likelihood of reoperation. However, hybrid therapies face challenges like immune response risks, production complexity, and high costs, limiting accessibility. Improved technologies, cost reduction, and further research are essential for widespread adoption of these advanced treatments.

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