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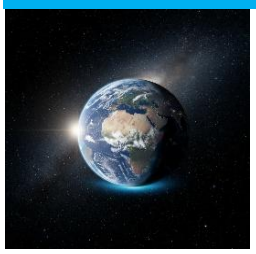

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The Impact of Supplementation and Adjuvant Pharmacotherapy on Bone Fracture Healing

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Abstract

Introduction and purpose: Bone fractures and healing complications, such as delayed union and non-union, present a substantial and growing global healthcare burden. While surgical fixation techniques have advanced significantly, optimizing the biological environment through targeted nutritional and pharmacological interventions remains critical for successful osteogenesis. This review aims to systematize the current knowledge regarding the impact of exogenous supplementation and adjuvant pharmacotherapy - ranging from basic nutrients to advanced biological drugs - on the bone fracture healing process.

A brief description of the state of knowledge: Based on a comprehensive literature search of major medical databases focusing on the last 15 years, the synthesis of clinical and preclinical data indicates that correcting baseline nutritional deficiencies (particularly protein, amino acids, and vitamin D3) is an essential prerequisite for adequate soft callus formation and subsequent mineralization. Structural components like chondroitin sulphate and collagen, alongside phytotherapeutics such as Cissus quadrangularis, provide significant early-stage support for endochondral ossification. Conversely, routine administration of non-steroidal anti-inflammatory drugs (NSAIDs) during the acute inflammatory phase should be approached with high caution due to their potential to significantly delay healing. In recalcitrant cases, advanced therapies like systemic teriparatide and locally applied bone morphogenetic proteins (BMPs) offer potent osteoinductive rescue strategies.

Summary (conclusions): A multifaceted approach that integrates early nutritional optimization, judicious analgesic management, and targeted osteoinductive pharmacotherapy is vital for enhancing physiological bone repair, reducing recovery time, and preventing severe non-union complications.

Keywords: bone fracture healing; delayed union; nutritional supplementation; osteoinductive pharmacotherapy; bone morphogenetic proteins; non-steroidal anti-inflammatory drugs (NSAIDs)

Introduction

Bone fractures currently constitute one of the most pressing challenges in modern trauma medicine, orthopaedics, and public health. According to the comprehensive epidemiological data presented in the Global Burden of Disease Study 2019 report, approximately 178 million

new fractures occur globally each year. This represents a increase of over 33% compared to 1990 [13]. The incidence of fractures in the general population is estimated at 1 in 100 people annually; however, in the era of globally aging populations, the risk of osteoporotic fractures is significantly higher, ranging from 13% to as much as 50% [25]. Furthermore, it is estimated that up to 455 million people live with the acute or chronic consequences of such injuries, which translates to 26 million Years Lived with Disability (YLDs) [13].

Despite the dynamic development of surgical techniques and the standardization of postoperative care, the bone healing process does not always proceed physiologically [4, 5]. The most severe biological complications of the healing process are delayed union and non-union. In the literature, it is assumed that these complications affect an average of 5% to 10% of all fractures, and as the overall number of injuries worldwide increases, the absolute number of patients suffering from healing disorders will grow proportionally [5, 25]. In high-risk groups-including malnourished or elderly patients, as well as those burdened with metabolic diseases-this percentage can be significantly higher [25].

Delayed union is characterized by a deceleration of the healing rate compared to the expected time for a given anatomical location and type of fracture. On the other hand, a non-union is defined as the complete and irreversible cessation of the repair process cascade, which clinically means there is no chance for union without additional medical intervention [4, 20]. The lack of union is a source of immense suffering for the patient, leading to chronic pain, loss of mobility, and disability [7]. From a systemic healthcare perspective, it generates the need for prolonged hospitalization and risky, extremely costly revision surgeries [10, 25].

Given the scale of this phenomenon and the social and economic costs resulting from prolonged treatment, the search for safe and effective methods to support the physiological process of bone healing, ranging from the correction of nutritional deficiencies to advanced pharmacotherapy stimulating matrix remodelling, has become one of the most important directions in contemporary orthopaedic research [25, 26].

Process of bone fracture healing is a very organised cascade of biological events, which leads to a reconstruction of original structure and bones' mechanical strength. The process can be divided into 3 main often overlapping stages: inflammatory, repair and remodelling [4, 5].

The inflammatory stage begins immediately after an injury along with the formation of a hematoma around the bony fragments. The hematoma serves as a temporary scaffold for immune system cells. These cells clear the fracture site and release specific growth factors and cytokines. These signals initiate the recruitment and proliferation of mesenchymal stem cells from the periosteum, endosteum, and bone marrow [4]. Endochondral ossification plays a key

role in the repair phase of bone fracture healing. In the initial phase, proliferating cells form a soft callus, composed mainly of cartilage and collagen fibres, which surrounds and secures the fracture gap. Then, due to the increased activity of osteoblasts and progressive mineralisation, the cartilage is replaced by a mineralised hard callus [5, 20]. The remodelling phase is the longest one, which can last from a few months up to several years. It requires the cooperation of osteoblasts and osteoclasts. During remodelling, the original and amorphous hard callus is slowly resorbed and replaced by fully mature and biomechanically tough bone. The ultimate microarchitecture of the bone is optimised and adjusted to the axial strain that the patient undergoes [4, 20].

Literature search methodology

In order to reliably and objectively gather scientific data, a comprehensive literature review was conducted based on systematic search principles. The process of collecting materials was carried out using renowned medical and scientific databases, such as PubMed (MEDLINE), Cochrane Library, EMBASE, and Google Scholar.

The search was primarily limited to publications from the last 15 years (2010–2025), including a few older, classic papers defining fundamental concepts in the biology of bone healing. To find relevant publications, the following keywords and their combinations using logical operators (AND, OR) were applied: “bone fracture healing”, “delayed union”, “non-union”, “fracture repair”, “supplementation”, “vitamin D”, “protein”, “collagen peptides”, “chondroitin sulphate”, “glucosamine”, “Cissus quadrangularis”, “BPC-157”, “teriparatide”, “bone morphogenetic proteins (BMP)”, “NSAIDs effect on bone healing”.

Articles meeting the following criteria were included in the review:

- Publications in the English language.
- Full-text papers subjected to a peer-review process.
- Studies evaluating the effect of exogenous supplementation or pharmacotherapy on the healing process following a fracture or in conditions of induced delayed union.
- Diverse study designs incorporating the highest level of medical evidence: meta-analyses, Cochrane systematic reviews, randomized placebo-controlled clinical trials (RCTs), and-due to the analysis of innovative peptides and substances in early testing phases (like BPC-157)-in vivo studies on animal models.

Studies not published in peer-reviewed journals, individual case reports (unless they concerned rare complications), and studies focusing exclusively on osteoporosis prevention that did not analyse the acute healing process after a fracture were excluded from the analysis.

To systematize the research strategy and define the exact scope of the review, the PICOS (Population, Intervention, Comparison, Outcomes, Study design) criteria were applied, which are summarized in the table below.

PICOS criterion	Description in the context of this review
P – population	• Patients with fresh bone fractures (treated conservatively and operatively). • Patients with healing complications (delayed union, non-union). • Animal models (rats, mice, rabbits) in preclinical and molecular studies analysing the biology of healing.
I – intervention	Supply of exogenous substances aimed at modulating the healing process, including: • Nutritional supplementation (vitamins D and C, protein, amino acids). • Structural compounds (collagen, glucosamine, chondroitin sulphate). • Phytotherapy and peptides (Cissus quadrangularis, BPC-157). • Advanced pharmacotherapy and biological drugs (Teriparatide, BMPs). • Exposure to COX inhibitors (NSAIDs).
C – comparison	• Control group receiving a placebo. • Group undergoing standard treatment without additional supplementation (Standard of Care). • Comparisons between specific doses or times of administration.
O – outcomes	Clinical and radiological endpoints: Time to achieve full union (clinical and on X-ray), incidence of complications (non-union), functional parameters, and pain reduction.

	Biological endpoints: Quality and volume of the forming callus, bone mineral density (BMD) of the new bone, biomechanical strength, and levels of bone formation markers (e.g., alkaline phosphatase - ALP).
S – study design	The review included a broad spectrum of study designs to capture both mechanistic and clinical insights. Eligible designs comprised in vitro and in vivo animal models (preclinical studies), randomized controlled trials (RCTs), prospective and retrospective clinical cohorts, systematic reviews, meta-analyses, and comprehensive narrative reviews published in peer-reviewed journals.

Utilisation of artificial intelligence (AI)

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process. Following AI tools were used: Google Gemini, NotebookLM.

Nutritional and Structural Foundations

Protein and Specific Amino Acids Adequate nutritional status is a fundamental prerequisite for physiological fracture healing. Malnutrition, particularly protein deficiency, is a significant risk factor for delayed union, prolonged hospitalization, and increased complication rates, especially in elderly patients sustaining hip fractures [2, 25]. Since the organic bone matrix is predominantly composed of protein, an adequate supply of amino acids is crucial for callus formation. Specific amino acids, such as arginine and citrulline, play pivotal roles in the repair cascade; they serve as precursors for nitric oxide (NO) synthesis, which is essential for local angiogenesis, adequate blood flow, and the stimulation of osteoblast proliferation at the fracture site [21, 25]. Evidence suggests that targeted supplementation with protein and arginine-fortified formulations can accelerate the healing process and enhance the biomechanical strength of the forming bone [21].

Vitamin D3 and Calcium Hypovitaminosis D is highly prevalent among orthopaedic trauma patients and is increasingly recognized as a major factor contributing to impaired bone regeneration and non-union development [12, 19]. Vitamin D3 is integral not only to systemic calcium and phosphate homeostasis but also exerts direct cellular effects by promoting osteoblast differentiation and facilitating the rapid mineralization of the cartilaginous soft callus [18, 23]. Systematic reviews and clinical trials indicate that early and targeted supplementation of vitamin D3 and calcium-particularly in elderly individuals or those with documented pre-existing deficiencies-can significantly improve the bone mineral density (BMD) of the newly formed callus and improve both clinical and radiological union rates [9, 12, 19, 23].

Vitamin C and Minerals Vitamin C (ascorbic acid) functions as an indispensable enzymatic cofactor in the biosynthesis of collagen, which forms the primary structural framework of the bone matrix [8]. Specifically, it is required for the hydroxylation of proline and lysine residues, a process that cross-links collagen fibres and provides the necessary tensile strength to the healing tissue [8]. Furthermore, due to its potent antioxidant properties, vitamin C helps mitigate excessive oxidative stress and modulates the local inflammatory response during the acute phase of fracture healing [3, 8]. Recent literature confirms that adequate ascorbic acid supplementation can accelerate the early phases of soft tissue repair and endochondral ossification, thereby promoting the formation of a robust extracellular matrix [3, 8].

The Role of Bone Matrix Components: Collagen, Chondroitin Sulphate, and Glucosamine

Collagen serves as the primary structural scaffold for both cartilage and bone tissue. During the physiological healing process, the composition of the extracellular matrix dynamically changes; the early soft callus is predominantly composed of type III collagen, which is subsequently resorbed and replaced by mature type I collagen during the hard callus and remodelling phases. Studies indicate that oral supplementation with collagen peptides, often fortified with specific amino acids like arginine, can significantly accelerate the fracture healing process and improve the mechanical strength of the newly formed tissue [15, 21]. However, the application of collagen in surgical settings presents a complex biological challenge. While collagen type I is frequently used as a biomaterial scaffold in orthopaedic research and surgery, preclinical models have demonstrated that the application of isolated, pure collagen I scaffolds without additional osteogenic stimulators can paradoxically delay fracture healing. The immune system

and local cells may react to the pure scaffold in a way that impedes the natural progression of endochondral ossification [22].

Since secondary fracture healing relies heavily on endochondral ossification, the cartilaginous soft callus phase is critical for successful union. Chondroitin sulphate, a major glycosaminoglycan of the extracellular matrix, accumulates rapidly during this phase. Animal models have revealed that chondroitin sulphate, operating synergistically with small leucine-rich proteoglycans like biglycan, plays a pivotal role in retaining bound water within the bone matrix. This mechanism drastically improves the biomechanical toughness and elasticity of the forming bone, making the callus less brittle and more resistant to mechanical stress [17]. Additionally, clinical evidence supports the use of structural components such as glucosamine combined with sodium hyaluronate. In patients with compromised bone quality (e.g., osteoporosis complicated by osteoarthritis), this combination has been shown to significantly improve joint function, reduce pain, and positively influence bone metabolic markers, including type I collagen cross-linked C-telopeptide (CTX-1) and bone gla protein (BGP) [31]. By actively stimulating the early cartilaginous framework, these structural components provide a robust foundation for subsequent mineralization.

Phytotherapy and Innovative Peptides in Orthopaedics

Cissus quadrangularis (CQ) is a plant that has been used in traditional medicine for centuries, often referred to as a "bone setter". Contemporary clinical studies confirm its potent osteogenic properties. Extracts of CQ have been shown to contain high concentrations of vitamin C, calcium, and substances with anabolic effects that stimulate the early stages of callus formation [6, 28]. In studies on patients with maxillofacial fractures, oral CQ supplementation significantly accelerated bone union, reduced pain, and shortened healing time compared to the control group [6, 28]. Furthermore, research demonstrates that CQ strongly stimulates the expression of osteopontin - a key extracellular matrix protein involved in mineralization, neovascularization, and the early remodelling of the bone scar [28]. In more recent clinical trials, it has also been observed that preparations based on Cissus quadrangularis serve as an effective and safe alternative to support osteosynthesis, promoting healing processes without adverse side effects [14].

In recent years, the experimental peptide BPC-157 (Body Protection Compound-157) has sparked immense interest in the fields of sports medicine and orthopaedics. It is a synthetic, 15-amino acid fragment of a protein naturally found in human gastric juice, which exhibits extraordinarily strong regenerative properties for musculoskeletal tissues [24, 29]. Preclinical

studies in animal models demonstrate that the administration of BPC-157 accelerates the healing of both soft tissues and bone, including in challenging segmental defect models, where it stimulated the formation of mature lamellar bone instead of fibrous tissue [29]. The primary mechanism of action of this peptide relies on the potent stimulation of angiogenesis-a critical process for restoring blood supply in the ischemic fracture site-and the promotion of the survival and proliferation of local cells (e.g., fibroblasts and osteoblasts) [24, 29]. Despite highly promising in vivo results, the use of BPC-157 in humans remains controversial. There is currently a lack of rigorous, randomized clinical trials on patients, which means this substance is not officially approved for the treatment of injuries and is currently on the World Anti-Doping Agency (WADA) prohibited list [24, 29].

Advanced Adjuvant Pharmacotherapy: Osteoinductive Agents

Teriparatide, a synthetic analogue of the human parathyroid hormone (fraction 1-34), has emerged as a potent systemic anabolic agent in orthopaedic trauma management. While its primary regulatory approval is for the treatment of high-risk osteoporosis, its off-label use for addressing delayed union and non-union has gained significant scientific support [7, 16, 27]. Unlike continuous PTH elevation, which is catabolic, the intermittent administration of teriparatide stimulates osteoblast activity, increases the osteoblast lifespan by reducing apoptosis, and enhances the recruitment of mesenchymal stem cells to the fracture site [7, 16, 27]. Systematic reviews and meta-analyses indicate that teriparatide significantly improves clinical and radiological union rates in complex cases, including hip fractures and bisphosphonate-associated atypical femoral fractures [16, 27]. Notably, clinical trials have also compared its efficacy to traditional phytotherapeutic agents, demonstrating that teriparatide provides superior outcomes in terms of bite force and serum alkaline phosphatase (ALP) levels in maxillofacial trauma recovery [14].

Bone Morphogenetic Proteins (BMPs), members of the transforming growth factor-beta (TGF-ß) superfamily, represent the most advanced locally applied osteoinductive therapies currently available [26]. These proteins act by inducing the differentiation of undifferentiated mesenchymal cells into mature osteoblasts, effectively "kick-starting" the regenerative cascade in biologically compromised environments [10, 26]. Recombinant human BMP-2 (rhBMP-2) has shown exceptional success rates in the treatment of resistant long-bone non-unions, particularly in the tibia, with union rates reported as high as 89% in specific clinical cohorts [10]. However, the use of BMPs remains a subject of clinical debate due to high procedural costs and potential complications. According to Cochrane systematic reviews, while BMPs can be as effective as autologous bone grafting in promoting union for open tibial fractures, they

must be used judiciously, weighing their osteoinductive potency against the risk of local adverse reactions and the economic burden on the healthcare system [11, 26].

Pharmacological Factors Inhibiting Bone Union

The inflammatory phase is a critical, initial stage of physiological fracture healing, essential for stem cell recruitment, angiogenesis, and the initiation of the repair process cascade [4]. Prostaglandins (particularly PGE2), whose local synthesis is directly regulated by cyclooxygenase isoenzymes (COX-1 and COX-2), play a key role in bone metabolism and osteoblast activation [30]. Non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the activity of these enzymes, which effectively reduces pain and swelling but simultaneously drastically decreases prostaglandin concentrations at the injury site. Due to this mechanism of action, both in vitro studies and numerous animal models have convincingly demonstrated that exposure to NSAIDs can delay or even completely inhibit bone union [1, 30].

Although evidence from preclinical studies is highly consistent, translating these conclusions to the ultimate outcomes of trauma treatment in humans remains a topic of debate in the orthopaedic community. The most recent comprehensive meta-analyses, including those based on randomized clinical trials, indicate that the overall impact of NSAIDs on healing largely depends on the duration of exposure and the dose. While very short-term use of these medications for immediate post-operative acute pain control may not permanently disrupt union, chronic administration of NSAIDs clearly and statistically significantly increases the risk of delayed union and the development of non-unions [1, 30]. For this reason, modern clinical practice recommends great caution and the intentional avoidance of routine administration of COX-inhibiting drugs during the first weeks following a fracture, treating it as a key, modifiable risk factor - especially in patients with additional comorbidities [30].

Discussion

The complex nature of bone fracture healing necessitates a multifaceted approach that extends beyond mechanical stabilization to include biological and metabolic support. As demonstrated in this review, the physiological process of bone regeneration is highly dependent on a synergistic interaction between fundamental nutritional building blocks and advanced osteoinductive signals. The clinical efficacy of isolated nutrient supplementation is often limited; however, correcting multiple deficiencies simultaneously - such as combining adequate protein intake with vitamin D3 and calcium - creates an optimal biological foundation for callus formation and subsequent mineralization [2, 12, 25]. Ensuring this baseline nutritional adequacy is especially critical in high-risk groups, such as the elderly or malnourished, where

the lack of raw materials for the extracellular matrix directly correlates with non-union development [25].

A significant challenge in contemporary orthopaedic research remains the translational barrier between preclinical models and human clinical practice. Numerous experimental interventions, such as pure collagen type I scaffolds or the synthetic peptide BPC-157, have demonstrated remarkable angiogenic and osteogenic properties in highly controlled in vivo animal models (e.g., rodents and rabbits) [22, 24, 29]. However, the immense biological complexity and rapidity of human fracture healing, combined with the heterogeneity of patient populations regarding age, metabolic comorbidities, and biomechanical loading, often yield less predictable outcomes in human trials [4, 22]. For instance, while certain biomaterials perform exceptionally well in mice, their unguided application in human surgery may inadvertently trigger immune responses that delay endochondral ossification [22].

Furthermore, despite the growing body of evidence supporting both nutritional supplementation and adjuvant pharmacotherapy, there is a distinct lack of standardized clinical guidelines regarding their implementation in acute trauma care [5, 9]. The decision-making process is further complicated when considering pharmacological agents that inhibit healing. While the detrimental impact of NSAIDs on the early inflammatory phase of bone union is well-documented in basic science, clinical consensus on their absolute contraindication remains highly debated, highlighting the difficult balance between effective postoperative pain management and the preservation of the physiological healing cascade [1, 30]. Consequently, while potent osteoinductive drugs like teriparatide and BMPs offer promising rescue strategies for delayed unions, their high costs and potential adverse effects underline the necessity for establishing definitive, evidence-based protocols that prioritize early, safe, and easily accessible nutritional and structural interventions [7, 11].

Conclusions

Based on the comprehensive review of the current literature regarding the biological and clinical aspects of bone fracture healing, the following key conclusions can be drawn for clinical practice and future research:

- Nutritional Optimization is a Mandatory Foundation: The correction of foundational nutritional deficiencies - particularly regarding protein, specific amino acids (such as arginine), and vitamin D3 - is not merely an optional adjunct but a mandatory first step

in trauma management. Securing this baseline optimizes the systemic and local biochemical environment required for successful osteogenesis [12, 25].

- Matrix Components Support the Early Callus: Structural compounds, such as chondroitin sulphate and glucosamine, provide valuable biological support primarily during the early stages of endochondral ossification. Their accumulation improves the water retention and mechanical toughness of the cartilaginous soft callus, preparing it for subsequent mineralization [17, 31].

- Phytotherapy Shows a Promising Clinical Profile: Phytotherapeutic interventions, most notably Cissus quadrangularis, demonstrate a robust, proven, and safe clinical profile. They effectively accelerate early osteogenesis, enhance extracellular matrix protein expression (e.g., osteopontin), and help reduce postoperative pain, serving as a highly viable adjunct to standard surgical osteosynthesis [6, 14, 28].

- Caution with Early NSAID Administration: Clinicians must exercise strict caution regarding the administration of non-steroidal anti-inflammatory drugs (NSAIDs) during the acute inflammatory phase of fracture healing. While short-term use may be necessary for acute pain control, prolonged exposure significantly suppresses local prostaglandin synthesis and increases the risk of delayed union and non-union [1, 30].

- Potent Rescue Therapies Exist for Recalcitrant Cases: In the event of an established non-union or a highly compromised biological environment (such as in severe osteoporotic fractures), modern medicine possesses powerful osteoinductive tools. Advanced therapies, including systemic teriparatide and locally applied bone morphogenetic proteins (BMPs), serve as highly effective rescue interventions capable of re-initiating the arrested regenerative cascade [7, 10, 16].

Disclosure

Author's contribution :
Conceptualization: B.M. and A.Ś
Methodology: B.M. and K.A.
Software: B.M. and N.J.
Validation: W.F. and M.K.
Formal analysis: B.B. and N.T.
Investigation: K.M. and A.Ś. and K.A.
Resources: M.K and B.B
Data curation: B.M and W.F and A.Ś and K.M and J.B.

Writing - original draft preparation: N.J. and B.B and M.K.
Writing - review and editing: B.M and A.Ś.
Visualization: B.B. and J.B.
Supervision: B.M and A.Ś
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In preparing this work, the authors used Google Gemini and NotebookLM for the purpose of assisting with grammar and readability. After using this tool/service, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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